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Line active molecules promote inhomogeneous structures in membranes: Theory, simulations and experiments

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ABSTRACT

We review recent theoretical efforts that predict how line-active molecules can promote lateral heterogeneities (or domains) in model membranes. This fundamental understanding may be relevant to membrane composition in living cells, where it is thought that small domains, called lipid rafts, are necessary for the cells to be functional. The theoretical work reviewed here ranges in scale from coarse grained continuum models to nearly atomistic models. The effect of line active molecules on domain sizes and shapes in the phase separated regime or on fluctuation length scales and lifetimes in the single phase, mixed regime, of the membrane is discussed. Recent experimental studies on model membranes that include line active molecules are also presented together with some comparisons with the theoretical predictions.

Contents

1. Introduction

The lateral organization of multi-component model membranes has been the focus of numerous investigations for two decades. Under some conditions, these components can self-assemble into domains of finite sizes (much smaller than the overall size of the membrane). However, finite size domains are not consistent with typical equilibrium phase behavior of mixtures in which the components either uniformly mix or macroscopically phase separate (domains of the order of the membrane size). Understanding how such finite domains arise is a key challenge to a physical understanding of the "lipid raft" hypothesis in real cells which postulates that nanoscale lateral heterogeneities of cholesterol and sphingolipids in the plasma membrane are necessary for the cells to be functional [1,2]. Examples of functions whose postulated mechanism utilizes lipid rafts include protein membrane sorting and cell signaling [1,3,4].

So far, the evidence for rafts in biological cells comes from indirect observations; the rafts are too small to be resolved with the most powerful microscopes. In several studies, cell membrane domains enriched in cholesterol were discovered to resist detergent extraction (see [1,2,5] and references therein). In others, Förster Resonance Energy Transfer studies of fluorescent proteins revealed that they tend to aggregate in small domains; an effect attributed to their favorable partitioning in rafts (see [6] and references therein). These two indirect

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observations are perhaps the most common, but other techniques have also been used [2]. From the compilation of various experimental results on plasma membranes, rafts are now believed to have sizes of the order of 10–100 nm [6].

The study of model membranes provides useful information regarding the interactions among membrane constituents since they are not subject to other types of interactions present in real cells (i.e. coupling with the cytoskeleton and/or active processes). One useful approach measures the properties of self-assembled giant unilamellar vesicles (GUVs) or suspended bilayers whose lipid composition can either be controlled [7–13] or extracted from cell membranes [7,14,15].

In parallel to those experimental studies, several theoretical models for the formation and stability of small (of the order of estimated raft sizes) domains have been proposed. One class of models is based on line active molecules or "linactants". The term linactant (2D analogs of surfactants) was first proposed in a recent study [16] that demonstrated how specifically designed non-lipid molecules can reduce the line tension between domains in monolayers. The linactant molecule has a lower free-energy when it resides at an interface compared to its free energy in either of the bulk phases. Hence, with linactants, a membrane can adopt equilibrium, locally phase separated, conformations with finite size domains that are stable despite their much larger total interfacial length. This short review focuses on related models applied to lipid mixtures. We highlight studies that indicate how lipid linactants can promote inhomogeneous structures in mixed membranes. Due to the simplicity of these theories, a comparison with experimental data obtained on model membranes (rather than real cells) is more appropriate. Other types of mechanisms for lateral heterogeneity have also been proposed. Some are based on the coupling between the membrane curvature and the lipid composition [17–20], the interleaflet couplings [21,22,20], the height mismatch between domains [23,24,19] and electrostatic interactions [25,26]. In biological cells, the interactions between lipids and proteins [27–29] can also favor small domains as do cell–cell adhesion [23]. Of course, the role of line active molecules on the generic stability of nanodomains does not exclude any of these mechanisms which may have equally important roles. We direct readers interested in these mechanisms to the appropriate references and to the review paper by Komura and Andelman that appears in this special issue.

The paper is organized as follows. In Section 2, we outline the basic features of model membrane phase diagrams and highlight the relevance to lipid rafts. Section 3 is the main part of the paper. It reviews recent theoretical models that include line active molecules that can provide a mechanism for lateral heterogeneities in membranes. Section 3.1 focuses on coarse-grained theoretical views of lipid membranes where the natural amphiphile is a hybrid lipid while Section 3.2 focuses on more microscopic models based on molecular dynamics simulations that incorporate hybrid lipids and other line active molecules. Section 3.3 discusses the role of line active lipids in increasing the probability of small scale fluctuations of the lipids in the uniformly mixed phase of the membrane, even near the critical point, where normally large scale fluctuations are most probable. As we will show, composition fluctuations are also predicted to have longer lifetimes in the presence of linactants. A review of experimental studies that focus on model membranes that comprise linactants is presented in Section 4 and Section 5 concludes the paper with final remarks.

2. Phase diagram of model membranes

The role that linactants play in the lateral organization of model membranes is usually understood in terms of the phase behavior of the membrane. In its simplest description, the membrane is treated as a binary mixture in 2D. The lipids that tend to phase separate at low temperatures are classified as A and B and they have unfavorable nearest-neighbor interactions (in principle, A and B can both describe more than one type of lipids). In such a two-component mixture, the mean-field membrane free-energy per molecule can be written as (for example, see Refs. [30,31]),

$$\frac{F}{k_b} = T[\phi\log\phi + (1-\phi)\log(1-\phi)] + 2J\phi(1-\phi), \tag{1}$$

where the first term is the entropy of mixing of the two components, ϕ is the fraction of class A lipid molecules ($(1-\phi)$ is the fraction of class B), $J(>0)$ is the energy cost associated with nearest-neighbor A and B pairs, k_B is Boltzmann's constant and T is the temperature. Fig. 1 shows the mixing temperature, $T_m(\phi)$, of the membrane as a function of the composition that results from this binary mixture model. For $T > T_m(\phi)$ the membrane is in the single phase; the system is uniform on average and lipid components A and B are mixed. Lowering the temperature in the region $T < T_m(\phi)$ gives rise to coexisting regions enriched (depleted) in $A(B)$ and depleted (enriched) in $B(A)$; the system phase separates. In this simplified picture, the maximum mixing temperature defines a critical point, $T_c = T_m(\phi = 1/2)$.

The phase diagram of real model membranes is much richer than the simple binary mixture diagram shown in Fig. 1 since they usually contain saturated lipids (characterized by hydrocarbon chains that have no double bonds, see Fig. 2A), unsaturated lipids (where both chains have double bonds, see Fig. 2A) and cholesterol. Moreover, the lipid molecules have chain conformational degrees of freedom (and possibly, orientational degrees of freedom in addition to the local composition degree of freedom) that contribute to the phase behavior. In fact, the phase separated regime can be subdivided into numerous phases that display different degrees of order. For a review of the typical phases observed in model membranes, see Refs. [32,33]. In summary, the liquid-disordered phase, L_d or L_α, is usually found at high temperatures and/or large cholesterol fraction. In that phase, the lipid chains are disordered and the lipid translational motion is rapid (characterized by a large diffusion coefficient, $D \approx 1\ \mu m^2/s$). In decreasing order of fluidity, the liquid-ordered, L_o, phase follows. There, the lipid chains are ordered (straight), but lipid diffusion is still rapid ($D \approx 1\ \mu m^2/s$). Next is the gel phase (the gel phase can often be found by reducing the temperature and/or decreasing the cholesterol content), L_β, where the chains are ordered and lipid diffusion is slow ($D \approx 10^{-3}\ \mu m^2/s$). The nomenclature for these various phases is the one proposed in Refs. [32,33], but there are papers that use a different one. Note that crystalline phases have been observed in monolayers made of cholesterol and ceramides [34], but the crystal order was maintained over short distances only ($\approx$10 nm). Recall that long-range order is strictly forbidden in 2D by the Mermin–Wagner theorem [35] (also see Section 6.1 in Ref. [30]). Each of these phases can be observed in specific composition and temperature ranges. In particular, the liquid ordered phase is often called the lipid raft phase since it requires (and it is enriched in) cholesterol and saturated lipids which dominate the composition of detergent

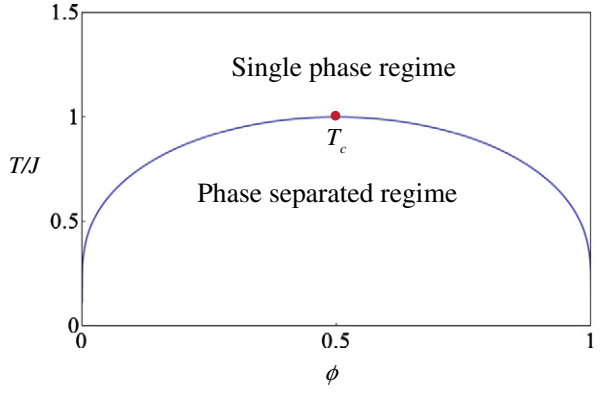

Fig. 1. The mixing temperature, $T_m(\phi)$ for a binary mixture as a function of the composition, ϕ. T_c indicates the position of the critical point.