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# Geodesic curvature driven surface microdomain formation

Melissa R. Adkins, Y. C. Zhou *

*Department of Mathematics, Colorado State University, Fort Collins, CO 80523-1874, United States*

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ABSTRACT

Lipid bilayer membranes are not uniform and clusters of lipids in a more ordered state exist within the generally disorder lipid milieu of the membrane. These clusters of ordered lipids microdomains are now referred to as lipid rafts. Recent reports attribute the formation of these microdomains to the geometrical and molecular mechanical mismatch of lipids of different species on the boundary. Here we introduce the geodesic curvature to characterize the geometry of the domain boundary, and develop a geodesic curvature energy model to describe the formation of these microdomains as a result of energy minimization. Our model accepts the intrinsic geodesic curvature of any binary lipid mixture as an input, and will produce microdomains of the given geodesic curvature as demonstrated by three sets of numerical simulations. Our results are in contrast to the surface phase separation predicted by the classical surface Cahn–Hilliard equation, which tends to generate large domains as a result of the minimizing line tension. Our model provides a direct and quantified description of the structure inhomogeneity of lipid bilayer membrane, and can be coupled to the investigations of biological processes on membranes for which such inhomogeneity plays essential roles.



## 1. Introduction

This work is motivated by the formation of lipid rafts in lipid membranes. Lipid bilayer membranes are of utmost importance for the survival of cells. They separate the interior of cells from the extracellular environment and compartmentalize subcellular organelles so that suitable micro-environment can be maintained in the enclosed domains for various vital biochemical and biophysical reactions. They are material basis for morphological changes such as budding, tubulation, fission and fussion that occur during cell division, biological reproduction, and intracellular membrane trafficking. They also provide a physical platform to store and transduce energy as electrochemical gradients, to segregate or disperse particular membrane proteins, and to act as messengers in signal transduction and molecular recognition processes [1]. While most of these functionalities depend on the fluidity of the lipids and thereby the free diffusion of lipids and proteins in the bilayer, accumulated evidences show that lipids and proteins on bilayer membranes segregates into discrete domains of distinct composition and various sizes [2–7]. The domain boundaries can appear as the barriers of free lateral diffusion of lipids and proteins, as the measured lateral diffusion coefficients of lipids and proteins *in vivo* are less than the measured coefficients in artificial pure bilayer by more than one order of magnitude [5,8]. Inside the domains and on the domain boundaries particular proteins may aggregate, to cause various membrane curvature as the consequence of the modification of local membrane composition [9–11] or to complete specific signal transduction [12–15]. Some of these domains are transient,

* Corresponding author.
*E-mail address:* yzhou@math.colostate.edu (Y.C. Zhou).

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with a duration ranging from seconds to minutes, some can persist for the entire life of the cell, and the domains themselves can diffuse on the membrane surface as well [16]. The composition, location, size, configuration, duration of these domains and the dynamics of these characteristics are of functional and structural significance to the associated biological processes. Efforts integrating direct microscopic measurements, biophysical modeling, and computational simulations have been invested to elucidate the underlying physics of the dynamics of these lipid domains and predict their biological consequences [17–19]. Before introducing our approach based on the geodesic curvature energy of the lipid domain boundaries we first review four most representative theoretical studies on the dynamics of lipid domains.

Lipid domains may appear as a result of lipid phase separation caused by distinct spontaneous curvatures. When bilayer membranes have multiple lipid species of distinct spontaneous curvatures, individual lipid species may be localized to regions where the local mean curvatures best approximate the corresponding spontaneous curvatures of the residing lipid species [20]. Wang and Du formalized this reasoning by summing up the classical Canham–Evans–Helfrich energy [21–23] for each individual lipid species and the line tension energy to generate a multi-component lipid membrane model [24]. By representing the membrane bending energy using the phase field formulation, they have obtained rich patterns of membrane morphology and the generation of lipid membrane domains of different mean curvatures, where lipid species of the approximate spontaneous curvatures are concentrated. This model was also extended to simulate the open membrane thanks to the line tension energy, and the closing of membrane pores was simulated corresponding to the vanishing linear tension energy. These permanent domains have sizes that are determined by local mean curvatures of the membrane necks or bumps. These sizes in general do not match the measured sizes of mobile lipid rafts [25,17].

The classical phase separation model based on the Ginzburg–Landau (GL) free energy could also be directly applied on a membrane surface to generate surface phase separation, and the results can be related to the lipid domains. A surface Cahn–Hilliard equation can be derived for the gradient flow of the GL free energy, and the numerical simulations will produce large separated domains as a result of the coarsening dynamics [26]. In order to generate small domains at spatial and temporal scales comparable to experimental results, Camley and Brown couples the GL free energy for quasi two-dimensional binary lipids mixtures to the random hydrodynamics and thermal fluctuations [27,28]. The random in-plane velocity field of the membrane is given by Saffman–Delbruck hydrodynamic model [29]. This velocity field is added to the Cahn–Hilliard equation for the gradient flow of the GL free energy to produce an advection–diffusion equation, above which a Gaussian white noise is added, modeling the thermal fluctuation as a random source to the order parameter. Complete phase separation shall occur as the result of a sequence of coarsening dynamics when the GL free energy is minimized, while the domain boundaries flicker as a result of random hydrodynamic and thermal perturbations, with a flickering magnitude depending on the competing between the random perturbation and the persisting linear tension. Under high line tension small domains will merge to form large separated domain, but small domains under a critical size could remain separated for a long time during the course of coarsening if the line tension is not large enough to suppress the random perturbation, giving rise to lasting microdomains. Various dynamical scaling rates were summarized to related the microdomain size and the time when the domain size is far way from the Saffman–Delbruck length $L_{sd}$ determined by the relative viscosity of the lipid membrane with respect to the surrounding fluid field. This approach has been recently extended to model multicomponent membranes with embedded proteins [30,31].

It is also possible to simulate lipid microdomains in the deterministic setting. Arguing that lipid rafts are microdomains of lipids compactly organized around embedded protein receptors, Witkowski, Backofen and Voigt proposed to supplement the classical Ginzburg–Landau free energy with Gaussian potentials localized at specified positions where the membrane proteins are supposed to be embedded [32]. By specifying the center and modulation of these external potentials they were able to produce lipid microdomains of arbitrary size at arbitrary position. Coarsening dynamics were reproduced by solving the Cahn–Hilliard equation for the gradient flow of the total energy, and a scaling law was deduced for the growth of the microdomains. In contrast to the above approaches, one is not able to drive the lateral diffusion coefficient of the microdomains as their positions are specified in the construction of the free energy. In general this model lacks a biophysical interpretation of the external potential and the related parameters that could justify the striking generation of lipid microdomains in the absence of line tension.

In addition to the above continuum approaches, particle-based discrete methods have also been developed to simulate the lipid microdomains. Molecular dynamics simulations, fully atomic or coarse grained, as reviewed in [33,34], have been able to generate lipid membrane domains that could interpret some experiments on complex model membranes. Two discrete methods that gives particular valuable insight into the structure and dynamics of lipid microdomains are dynamical triangulation Monte Carlo (DTMC) [35] and dispersive particle dynamics (DPD) [36,37]. DTMC neglects the solvent hydrodynamics and approximate a bilayer membrane as a randomly triangulated sheet. Each vertex is described by a three-dimensional position vector, and all vertices are connected by flexible tethers, which flip during the course of dynamical triangulation to simulate phase segregation. DPD adopts a coarse-grained representation of amphiphilic lipids as connected head (H) and tail ($C_n$) beads, with an variable number of tail beads. The geometric and molecular mechanics representations of lipids in DPD differ from the coarse-grained molecular dynamics simulations (those based on the MARTINI force field [38,39], for example) in that all beads are soft with interaction defined by effective forces that reproduce the hydrodynamic behavior of fluid bilayer membrane rather than the classical intermolecular interactions. DPD allows asymmetric lipid composition in the two leaflets, where different lateral sizes of the lipid domains can be simulated. While DPD can simulate the membrane properties to length and time scales that are unattainable by MD and coarse-grained MD simulations, there still