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Free energy of the edge of an open lipid bilayer based on the interactions of its constituent molecules

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ABSTRACT

Lipid bilayers are the fundamental constituents of the walls of most living cells and lipid vesicles, giving them shape and compartment. The formation and growing of pores in a lipid bilayer have attracted considerable attention from an energetic point of view in recent years. Such pores permit targeted delivery of drugs and genes to the cell, and regulate the concentration of various molecules within the cell. The formation of such pores is caused by various reasons such as changes in cell environment, mechanical stress or thermal fluctuations. Understanding the energy and elastic behaviour of a lipid-bilayer edge is crucial for controlling the formation and growth of such pores. In the present work, the interactions in the molecular level are used to obtain the free energy of the edge of an open lipid bilayer. The resulted free-energy density includes terms associated with flexural and torsional energies of the edge, in addition to a line-tension contribution. The line tension, elastic moduli, and spontaneous normal and geodesic curvatures of the edge are obtained as functions of molecular distribution, molecular dimensions, cutoff distance, and the interaction strength. These parameters are further analyzed by implementing a soft-core interaction potential in the microphysical model. The dependence of the elastic free-energy of the edge to the size of the pore is reinvestigated through an illustrative example, and the results are found to be in agreement with the previous observations.

1. Introduction

A phospholipid molecule consists of a hydrophilic head and two hydrophobic fatty-acid tails [1]. When suspended in an aqueous solution at sufficient concentrations, phospholipid molecules self-assemble into structures such as lipid bilayers, in order to shield the tail groups from the solvent [2,3]. Lipid bilayers are the main constituents of cell membrane in most living organisms, as well as model membranes such as liposomes [4]. They provide the cell and its substructures with compartment and shape, and further, function as barriers for water-soluble molecules such as water, ions, and proteins [5,6]. Lipid bilayers are composed of two adjacent leaflets of phospholipid molecules oriented transversely and set tail-to-tail.

Forming of open edges in lipid membranes results in the exposure of the tail groups at the edge to water [4], which is energetically unfavourable. As a result, phospholipid molecules rapidly rearrange around the exposed edge, forming a semicylindrical rim along it. This rearrangement is the source of a line energy at the edge. In order to eliminate this edge energy, lipid bilayers commonly tend to form closed structures such as spheroids [7]. Nevertheless, they can transiently open due to various stimuli such as mechanical stresses and thermal instabilities. The formation of these transient pores is essential for regulation of PH, transmembrane electrochemical potential, and concentrations of different molecules in the cell [5]. Additionally, transient open membranes are formed during electro-formation [8]. More recently, stabilizing pores and control over their size have been pursued by means of electric fields [9], sonication [10], and use of edge-active chemical agents [11]. The rapid progress in these techniques has attracted increasing attention to the study of the open lipid bilayers, including molecular dynamic simulations, as well as continuum mechanical treatment and numerical investigations of the equilibrium configurations [12,13].

Theoretical studies of the equilibrium and stability of pored membranes have mainly relied on constitutive assumptions for the edge, which neglect its flexural and torsional elasticity. For instance, Boal and Rao [14], Capovilla et al. [15], and Tu and Ou-Yang [16,17] considered the edge energy of an open lipid bilayer as a given constant. Tu and Ou-Yang [18] considered dependence of the edge energy on its geometry, namely geodesic and normal curvatures. Nevertheless, their assumptions on the form of the line energy have not been precisely justified.

May [19] obtained the line energy of a lipid bilayer edge through optimization of the lipid packing at the vicinity of the edge. He modeled the edge as a semicylindrical micelle, and took the free energy per molecule to depend upon the chain length of

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the molecules, their cross-sectional area, and the strength of the interactions of the molecules with each other and with the surrounding solution. Although successful in obtaining the line tension that framework did not capture the bending and torsional energetics of the edge. The gap in the literature to successfully relate the macro-scale edge energy to its microstructure has motivated the current study.

The interactions between the constituent molecules of a material may be used to obtain the free-energy density function of that material. For instance, Keller and Merchant [20] have employed such a microphysical approach to extract the internal energy, surface tension, and bending energy of a liquid surface and to relate its bending rigidity to the molecular density and interaction potential. In a recent application of the work of Keller and Merchant [20], the Canham–Helfrich free-energy density for a lipid vesicle was derived based on microphysical considerations [21]. Using the same approach, a model for the elastic free-energy of wormlike micelles was derived [22]. In doing so, the surfactant molecules comprising the wormlike micelle were assumed to have constant length, and thus, were modeled by one-dimensional rigid rods. The resulted expression for the free energy was found to be quadratic in the curvature and torsion of the centerline of the micelle [22].

The current study adopts the microphysical approach of Keller and Merchant [20] to investigate the elastic behaviour of the edge of a lipid bilayer. Following May [19] and motivated by previous studies [23–26], the edge is modeled as a semicylindrical surface. In addition, the phospholipid molecules comprising the edge are modeled as one-dimensional rigid rods of constant length, oriented perpendicular to the centerline of the edge. The applied framework enables us to extract the form of the free energy and the flexural and torsional moduli of the edge, based on the intermolecular energetic interaction between phospholipid molecules.

To find the free-energy density of the edge at a position $\boldsymbol{x}$, we account for the interactions between all phospholipid molecules on the edge within a cutoff distance δ from the molecules at $\boldsymbol{x}$. We assume that the phospholipid molecules are perpendicular to the centerline of the edge. Our derivation relies on Taylor series expansions with respect to a dimensionless parameter $\varrho := \delta/\ell \ll 1$, where ℓ is a characteristic size parameter of the edge, such as its length. For ℓ taken as the length of the edge (or equivalently, the perimeter of a pore), it can be related to the thickness or the length of the constituent molecules, if the density of the molecules along the edge and their aspect ratios are provided. The net free-energy of the edge results from integrating the free-energy density ϕ over the centerline of the edge.

The paper is structured as follows. In Section 2, required mathematical definitions are presented. Modeling assumptions for the edge of an open lipid bilayer are synopsized in Section 3. Section 4 is concerned with the derivation of the free-energy density of such an edge. In Section 5, the consequences of choosing a spheroidal-particle potential (Berne and Pechukas [27] and Gay and Berne [28]) are considered to obtain the material parameters present in the derived model. As an illustrative example, a simplified model for a pore on a lipid bilayer is given in Section 6, and the parameters obtained in Section 5 are used to find the free-energy of the pore as a function of its size. Finally, the key findings of the study are summarized and discussed in Section 7. Details of the various derivations are provided in the Appendix.

2. Differential geometry of the bounding curve of a surface

Consider a smooth, orientable, open surface $\mathcal{S}$ representing the open lipid bilayer, with boundary $\mathcal{C} = \partial\mathcal{S}$, as depicted schematically in Fig. 1. Let

$$\mathcal{C} = \{\boldsymbol{x} : \boldsymbol{x} = \boldsymbol{x}(s), 0 \le s \le L\}, \tag{1}$$

denote the arclength parametrization of the closed boundary curve $\mathcal{C}$. On denoting the differentiation with respect to the arclength s by a superposed dot, it follows that $|\dot{\boldsymbol{x}}| = 1$, and thus,

$$\dot{\boldsymbol{x}} \cdot \ddot{\boldsymbol{x}} = 0 \quad \text{and} \quad |\dot{\boldsymbol{x}} \times \ddot{\boldsymbol{x}}| = |\ddot{\boldsymbol{x}}|. \tag{2}$$

The unit tangent of $\mathcal{C}$ is introduced, in terms of the arclength parametrization $\boldsymbol{x}$, by

$$\mathbf{t} := \dot{\boldsymbol{x}}. \tag{3}$$

Since the unit tangent $\mathbf{t}$ has a constant length, its arclength derivative $\dot{\mathbf{t}} = \mathrm{d}\mathbf{t}/\mathrm{d}s$ is perpendicular to it, and thus, perpendicular to the curve $\mathcal{C}$. The orientation of $\dot{\mathbf{t}}$ is called the unit normal of $\mathcal{C}$, and is denoted by $\mathbf{N}$. The curvature vector $\boldsymbol{\kappa}$ at any point of $\mathcal{C}$ is then defined by the arclength derivative of the unit tangent $\mathbf{t}$ as

$$\boldsymbol{\kappa} := \dot{\mathbf{t}} = \kappa \mathbf{N}, \tag{4}$$

where κ denotes the magnitude of the curvature of $\mathcal{C}$ at that point, which is given in terms of the arclength parametrization $\boldsymbol{x}$ by

$$\kappa = |\dot{\boldsymbol{x}} \times \ddot{\boldsymbol{x}}| = |\ddot{\boldsymbol{x}}|. \tag{5}$$

For an arbitrary point on curve $\mathcal{C}$ at which $\kappa \neq 0$, the unit binormal vector is defined by $\mathbf{B} = \mathbf{t} \times \mathbf{N}$. The unit tangent $\mathbf{t}$, unit normal $\mathbf{N}$, and unit binormal $\mathbf{B}$ at each point of $\mathcal{C}$, form the Frenet frame $\{\mathbf{t}, \mathbf{N}, \mathbf{B}\}$ at that point.

The torsion τ of $\mathcal{C}$ is defined by $\dot{\mathbf{B}} = -\tau \mathbf{N}$, and is expressed in terms of the arclength parametrization $\boldsymbol{x}$ as

$$\tau = \frac{\dot{\boldsymbol{x}} \cdot (\ddot{\boldsymbol{x}} \times \dddot{\boldsymbol{x}})}{|\ddot{\boldsymbol{x}}|^2}. \tag{6}$$

The torsion τ of $\mathcal{C}$ describes the tendency of the curve $\mathcal{C}$ to move out of its osculating plane at a given point, or, equivalently, it measures the turnaround of the unit binormal $\mathbf{B}$ of $\mathcal{C}$ at a given point. In general, a space curve is determined up to a rigid translation, by its two locally invariant quantities: the curvature κ and torsion τ, both in terms of the arclength parameter s.

On the boundary curve $\mathcal{C}$ of the surface $\mathcal{S}$, the unit normal to the surface is denoted by $\boldsymbol{n}$. Also, since $\dot{\boldsymbol{x}}$ is a unimodular vector, its arclength derivative $\ddot{\boldsymbol{x}}$ is perpendicular to $\dot{\boldsymbol{x}}$, and thus, can be considered as a linear combination

$$\ddot{\boldsymbol{x}} = \kappa_n \boldsymbol{n} + \kappa_g \boldsymbol{n} \times \dot{\boldsymbol{x}}, \tag{7}$$

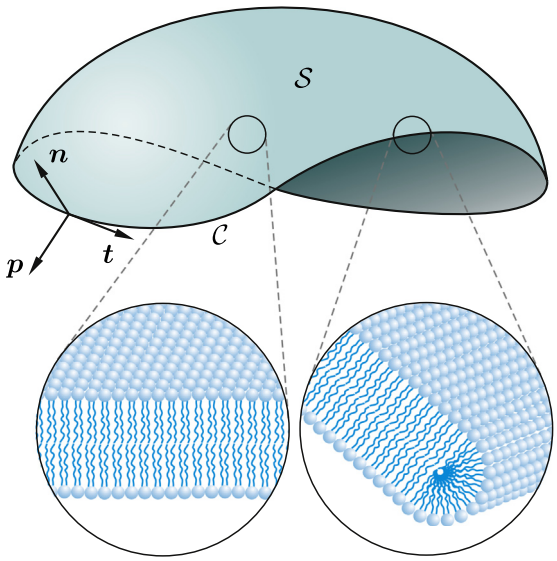

Fig. 1. Mathematical identification of an open lipid bilayer as an open surface $\mathcal{S}$ with boundary $\mathcal{C} = \partial\mathcal{S}$ on which a Darboux frame has been shown. Also the schematic arrangements of phospholipid molecules in an interior point on $\mathcal{S}$ and at the vicinity of the edge $\mathcal{C}$ are depicted at a point.