Extreme Mechanics Letters 18 (2018) 29–35

Contents lists available at ScienceDirect

Extreme Mechanics Letters

journal homepage: www.elsevier.com/locate/eml

A method to compute elastic and entropic interactions of membrane inclusions

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ARTICLE INFO

Article history:
Received 10 July 2017
Received in revised form 23 October 2017
Accepted 31 October 2017
Available online 10 November 2017

Keywords:
Membrane inclusions
Elastic plate model
Lipid bilayer
Entropic forces

ABSTRACT

Curvature mediated elastic interactions between inclusions in lipid membranes have been analyzed using both theoretical and computational methods. Entropic corrections to these interactions have also been studied. Here we show that elastic and entropic forces between inclusions in membranes can compete under certain conditions to a yield a maximum in the free energy at a critical separation. If the distance between the inclusions is less than this critical separation then entropic interactions dominate and there is an attractive force between them, while if the distance is more than the critical separation then elastic interactions dominate and there is a repulsive force between them. We assume the inclusions to be rigid and use a previously developed semi-analytic method based on Gaussian integrals to compute the free energy of a membrane with inclusions. We show that the critical separation between inclusions decreases with increasing bending modulus and with increasing tension. We also compute the projected area of a membrane with rigid inclusions under tension and find that the trend of the effective bending modulus as a function of area fraction occupied by inclusions is in agreement with earlier results. Our technique can be extended to account for entropic effects in other methods which rely on quadratic energies to study the interactions of inclusions in membranes.

1. Introduction

In mechanics, the forces of interaction between defects in an elastic body are well understood. For example, two screw dislocations with Burger's vectors b and b' at a distance r from each other interact with a force per unit length f of magnitude $f = \mu bb'/(2\pi r)$ where μ is the shear modulus of the solid. This interaction force arises because the defects produce elastic fields around them which can overlap. The interaction between the defects could be attractive or repulsive depending on whether the total elastic energy of the solid decreases or increases due to the overlapping of stress and strain fields produced by the defects [1]. Interactions between defects in an elastic solid can also arise due to entropic effects. For example, the equilibrium concentration of vacancies in a solid is a result of the competition between the elastic energy and the entropy of the vacancies. The elastic part of the free energy of the solid, U_{el}, increases if the vacancy concentration increases because the vacancies create elastic fields around them that store energy. On the other hand, the entropic part of the free energy of the solid $U_{en} = -TS \approx -T(c\log c + (1-c)\log(1-c))$ decreases as the vacancy concentration c increases, for $c \ll 1$. This competition gives rise to a non-zero vacancy concentration at which the free energy is a minimum [2]. In a similar vein, the chemical force on a dislocation has its origins in the entropy of vacancies [1]. The physics of elastic and entropic interactions described above is applicable to any kind of defect of in an elastic material. Since lipid membranes can be modeled as elastic continua we will apply concepts similar to those described above to inclusions, such as proteins, in them.

If two similar proteins bind to a lipid bilayer separated by a distance r then the elastic deformation field around one of them can produce a repulsive force on the other one [3]. The potential of this force decays as $1/r^4$ as has been deduced from studies of proteins interacting through elastic deformations of a lipid bilayer [4–10]. Lipid membranes also fluctuate due to Brownian motion. This results in an attractive entropic force between two similar proteins [4,6]. The competition between attractive and repulsive forces can lead to self-assembly of proteins on a lipid bilayer membrane [11,12]. This sort of self-assembly determines the shape of a cell membrane and plays a role in endo- and exo-cytosis by the formation of localized invaginations or buds. Bud formation is exactly what happens when capsid proteins of viruses, like HIV and influenza, land on lipid membranes and self-assemble [4]. Similarly, the protein endophilin clusters together on lipid membranes and causes the formation of cylindrical tubules, and thus, it plays a role in membrane trafficking events in a cell [13]. The early stages of self-assembly of certain amyloid forming proteins (which cause

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https://doi.org/10.1016/j.eml.2017.10.003
2352-4316/

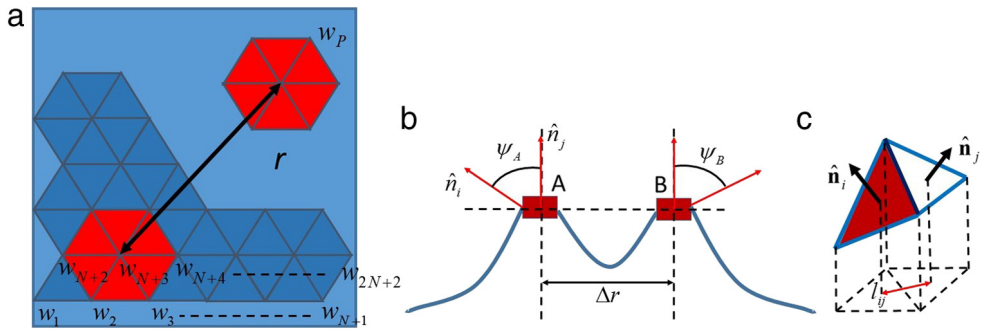

Fig. 1. (a) Equilateral triangle element discretization scheme of a square membrane. The inclusions are represented by red hexagons consisting of many triangle elements. We keep the element size fixed, so the number of triangle elements in an inclusion depends on the size of the inclusion. (b) The equilibrium shape of a membrane with two proteins embedded in it and separated by a distance Δr. The proteins are rigid cylinders which enforce contact angles ψ_A and ψ_B with respect to the adjacent membrane. In section 3.1, we will fix these angles to a given value as an enforced boundary condition. (c) Unit normal vectors $\hat{n}_i$ and $\hat{n}_j$ of two elements sharing one inclusion–membrane boundary edge. l_{ij} is the reference length between the center of these two triangle elements. The red triangle belongs to the inclusion. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Alzheimer's and Parkinson's diseases) also involves self-assembly of monomers on a lipid membrane [14]. Since self-assembly often involves many more than two proteins, the interactions between many proteins on a membrane have been studied and it has been learned that pair-wise expressions are not sufficient to describe these many body interactions [5]. However, most analytic studies of these many body interactions account for membrane bending deformations only. The entropic component of the interactions has been studied recently using simulations and a sophisticated field theory [6,7]. The field theory relies on the idea that the height fluctuations of the membrane are small, so the bending energy can be written as a quadratic form. This leads to Gaussian path integrals that can be evaluated analytically, but not without difficulty [6].

Our overarching goal here is to study elastic and entropic forces between many inclusions on lipid membranes using computational methods based on Gaussian integrals. Although mechanical and thermodynamic properties of lipid membranes, including how inclusions (such as, proteins) effect the overall membrane behavior, have been quantitatively studied using experimental, theoretical and computational methods [15–22], it is not always possible to design an experiment for large scale problems involving membrane protein interactions; on the other hand, the sample scale is too large for molecular simulations. To overcome these difficulties, researchers have turned to continuum modeling and associated computational methods [23] to study large scale (more than several microns) problems involving protein interactions on membranes. Unlike molecular simulation (such as, Monte Carlo and Molecular Dynamics based studies [21,22]) these continuum methods do not include Brownian fluctuations. Our technique described below can potentially be combined with continuum computational methods to account for entropic effects arising from Brownian fluctuations.

2. Theory

2.1. Semi-analytic method to compute membrane free energy

The thermodynamic properties of a fluctuating lipid membrane have been studied by starting from an energy expression [24,25]:

$$E_b = \int_0^L \int_0^L \mathrm{dxdy} \left\{ \frac{K_b}{2} \left(w_{,xx} + w_{,yy} \right)^2 + \frac{F}{2} (w_{,x}^2 + w_{,y}^2) \right\}. \tag{1}$$

Here, L is the side of a square membrane, K_b is the bending modulus, and F is the externally applied isotropic tension. The variable $w(x, y)$ in the expression above is the out-plane deflection of the neutral plane. We assume that the deformation is relatively small such that there are no overhangs in the membrane, and thus the displacement of each point is written as a function of the in-plane coordinate (x, y). We discretize the membrane into approximately $Q = 4N^2/\sqrt{3}$ equilateral triangle elements of side l as shown in Fig. 1(a) (so that $N = L/l$), similar to many Monte Carlo simulations on other fluid and solid membranes [26,27]. But, in contrast to the Monte Carlo simulations we will compute the partition function analytically. The key idea is to express the membrane energy quadratically as a function of approximately $P \approx 2N(N+1)/\sqrt{3}$ node variables w_i, $i = 1..P$ as in [24,25]:

$$\begin{aligned} E =& \frac{4K_bA_e}{3l^4} \sum_{(i,j)} \left(w_i + w_j - w_k - w_l \right)^2 \\ &+ \frac{FA_e}{3l^2} \sum \left[(w_r - w_s)^2 + (w_s - w_t)^2 + (w_t - w_r)^2 \right]. \end{aligned} \tag{2}$$

Here the summation in the bending energy term runs over all the adjacent triangle element pairs that share one edge linked by nodes i, j, with k, l, being the other two nodes of these two elements. The summation in the potential energy of the tension F runs over all the triangle elements. The subscripts r, s, t denote the nodes of one triangle in the second sum. $A_e = L^2/Q$ is the reference area of one triangle. Since the energy expression is quadratic, we can define a stiffness matrix $\mathbf{M}$ such that $E = \mathbf{wMw}^{\mathrm{T}}$, where the vector $\mathbf{w} = [w_1, w_2, \ldots, w_P]$ contains all the node displacements. Recall that $\mathbf{M}$ is a function of K_b, F, L, l. In statistical mechanics, $\frac{1}{Z} \exp(-E/k_BT)$ is the probability of finding a system in a given state of energy E, where k_B is the Boltzmann constant, T is the absolute temperature and Z is the partition function. Next, we are going to compute the partition function Z by carrying out the integration of $\exp(-E/k_BT)$ over all possible states of the system as in [28–31]. The partition function Z scales inversely with the square root of the determinant of $\mathbf{M}$, as

$$Z = \sqrt{\frac{(2\pi k_BT)^P}{\det \mathbf{M}}}. \tag{3}$$

The Gibbs free energy $G(F, T)$ of the membrane is related to the partition function Z as $G = -k_BT \ln Z$, and hence the projected area, entropy and other thermal quantities can be computed by differentiating $G(F, T)$. We computed the projected area and entropy of the membrane as a function of T, K_b and F using the method above in [24] and recovered results from well-known analytic expressions for the projected area [18] and entropy in the limit as l became small. For $L = 1\ \mu\mathrm{m}$ and $0.01\ \mathrm{pN/nm} \leq F \leq 1\ \mathrm{pN/nm}$, $l = 2.5$ nm resulted in excellent agreement with the known analytic formula for projected area and entropy. Thus, we have the capability to capture elastic and entropic effects in fluctuating membranes.