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On the mechanics of lipid membranes: budding formation, diffusion of transmembrane proteins and line tension

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ABSTRACT

We study the formation of membrane budding in model lipid bilayers with the budding assumed to be driven by means of diffusion of trans-membrane proteins over a composite membrane surface. The theoretical model for the lipid membrane incorporates a modified Helfrich-type formulation as a special case. In addition, a spontaneous curvature is introduced into the model in order to accommodate the effect of the non-uniformly distributed proteins in the bending response of the membrane. Further, we discuss the effects of line tension on the budding of the membrane, and the necessary adjustments to the boundary conditions. The resulting shape equation is solved numerically for the parametric representation of the surface which has one to one correspondence to the membrane surface in consideration. Our numerical results successfully predict the vesicle formation phenomenon on a flat lipid membrane surface, since the present analysis is not restricted to the conventional Monge representation often adopted to the problems of these kind for the obvious computational simplicity, despite it's limited capability on describing the deformed configuration of membranes. In addition, we show that line tension at the interface of the protein concentrated domain makes a significant contribution to the budding formation of membranes.

1. INTRODUCTION

Helfrich energy potential (also often referred as Helfrich model (Helfrich 1973)) based on 2D liquid crystal theory has become one of the most influential models in lipid membrane study for their simplicity and applicability. The fundamental premise of the model is that the lipid membrane can be regarded as an ideally thin film so that the stored energy during the membrane deformations is compatible to the change of curvatures of the membrane. Despite of the extensive use of the model, it's application to the actual predictions of the membranes' responses (morphological transitions, in particular) are limited to the relatively simple deformations of the membrane (e.g.

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substrate interaction and boundary excitations). This is mainly attributed by the fact that Helfrich model accounts only the variations of Mean and Gaussian curvatures. In addition the adopted surface representation is limited to the normal deformation of membranes (Monge representation) for the obvious simplicity in the corresponding analysis.

In the present study, motivated by the work in (Agrawal 2011), we present modified local form of the Helfrich energy-type formulation that can predict highly complex behaviors of membranes such as budding and vesicle formations. The modified model is capable of reflecting the effect of protein diffusion and local curvature change of the membrane. A spontaneous curvature description is introduced into the model in order to accommodate the effect of the non-uniformly distributed proteins in the bending response of the membrane. In particular, the description of the shape equation is based on a parametric representation of the surface (not limited within the Monge representation) and hence applicable for general membrane geometries. The proposed model successfully predicts the vesicle formation phenomenon on a flat lipid membrane surface. We also demonstrate that the corresponding deformations are energetically favourable and therefore stable.

2. VARIATIONAL FORMULATION

The present model is the extension of the model in (Agrawal 2011) accounting for the diffusion of trans-membrane proteins domain on the membrane surface and the line tension on the boundary of interest. Within which, the areal energy density distribution of the lipid membrane can be claimed as a natural extension of the Helfrich energy (Helfrich 1973) potential and is necessarily assumed of the form

$$W(H,K,\sigma;\theta^{\alpha}) = \eta(\sigma) + k(\sigma)[H - C(\sigma)]^2 + \bar{k}(\sigma)K, \tag{1}$$

where $\sigma(\theta^{\alpha},t)$ is the areal concentration of proteins on the membrane surface and $k(\sigma)$ and $\bar{k}(\sigma)$ are bending rigidity pertaining to non-uniform properties of the limpid membrane. H and K are well know mean and Gaussian curvatures of surfaces given by

$$H = \frac{1}{2}(\kappa_v + \kappa_t),\ K = \kappa_v - \kappa_t - \tau^2 \tag{2}$$

where $\boldsymbol{v}$ and $\boldsymbol{t} = \boldsymbol{n} \times \boldsymbol{v}$ refer to the exterior unit normal and unit tangent to a differentiable surface boundary ∂w. κ_v and κ_t are the normal curvatures and τ is the corresponding twist. The space parametric vector $\boldsymbol{r}(\theta^{\alpha})$ has one to one correspondence to the membrane surface. Here $\boldsymbol{a_\alpha} = \boldsymbol{r}_{,\boldsymbol{\alpha}}$ forms natural basis of curvilinear coordinate inducing the surface matric $a_{\alpha\beta} = \boldsymbol{a_\alpha} \cdot \boldsymbol{a_\beta}$ and dual matric components $a^{\alpha\beta}$. The local curvature of the membrane is then given by (Sokolnikoff (1951) $\boldsymbol{b} = b_{\alpha\beta}\boldsymbol{a^\alpha} \otimes \boldsymbol{a^\beta}$, where $b_{\alpha\beta} = \boldsymbol{n} \cdot \boldsymbol{r_{\alpha\beta}}$ is the coefficient of second fundamental form with $\boldsymbol{n} = (\boldsymbol{a_1} \times \boldsymbol{a_2}/|\boldsymbol{a_1} \times \boldsymbol{a_2}|$ is the local surface normal. Lastly, Greek indices take the value 1 and 2. The contravariant cofactor of the curvature is then defined by

$$\tilde{b}^{\alpha\beta} = 2Ha^{\alpha\beta} - b^{\alpha\beta} \tag{3}$$

where $b^{\alpha\beta}$ is the inverse of $b_{\alpha\beta}$. In the present study, the spontaneous curvature $C(\sigma)$ is introduced to accommodate the effects of non-uniformly distributed proteins on the corresponding membrane field. A simple expression of $C(\sigma)$ ensuring bilayer symmetry in the absence of protein is given by (Agrawal 2011) $C(\sigma) = (\mu\varphi)\sigma$, where $\mu\varphi$ is a constant of proportionality. Here μ is a positive constant and φ is the angle induced by the meridian of the cone with local surface normal $\boldsymbol{n}$. Consequently, the total potential energy of the deformed surface can be expressed as

$$E = \int_w W(H, K, \sigma; \theta^\alpha)\, da + \int_{\partial w} \gamma\, ds, \tag{4}$$

where γ is the acting line tension per unit length. To accommodate incompressibility, we consider the following augmented energy functional (Agrawal and Steigmann (2009))

$$E^* = \int_\Omega J[W(H, K, \sigma; \theta^\alpha) - \lambda(J-1)]\, da + \int_{\partial w} \gamma\, ds, \quad \because JdA = da, \tag{5}$$

where $\lambda(\theta^\alpha)$ is a Lagrange-multiplier field. J is the local areal stretch from a fixed reference (Ω) to the deformed surface (w) defined as $J = \sqrt{a/A}$.
Here a and A are the corresponding areas of w and Ω, respectively.

The equilibrium state of the membrane can be derived through the variation of the energy. To compute energy variation, it is necessary to evaluate the variational derivatives of J, H and K induced by the virtual displacement $\boldsymbol{u}(\theta^\alpha) = \dot{\boldsymbol{r}}$.
Here superscript "$\cdot$ " is small deformations (virtual displacements) of the membrane which here simply indicated by the derivative with respect to a parameter ϵ (e.g. $(*) = \partial(*)/\partial\epsilon$). In addition, the dot notation states the derivatives at a fixed value of parameter associated with the particular equilibrium state considered (here we set $\epsilon = 0$). Therefore, $\boldsymbol{u}(\theta^\alpha) = \frac{\partial}{\partial\epsilon}\boldsymbol{r}(\theta^\alpha; \epsilon)|_{\epsilon=0}$**.** The same meaning applies to any variables bearing a superposed dot ($\dot{H} = \frac{\partial}{\partial\epsilon} H(\theta^\alpha; \epsilon)|_{\epsilon=0}, etc$ ...).
In order to evaluate total energy variation of membranes, it is essential to account both tangential and normal variations u^α and u. This can be done by decomposing the virtual displacement into the normal and tangential components as $\boldsymbol{u} = u^\alpha \boldsymbol{a}_\alpha + u\boldsymbol{n}$**.**

Thus, the induced energy variation is obtained by

$$\frac{d}{dt}\dot{E} = \int_w \left[\dot{W} + \frac{\dot{J}(W+\lambda)}{J} + \lambda(1 \dot{-} J^{-1}\right] da + \int_{\partial w} \gamma\, (\dot{ds}), \tag{6}$$

where

$$W_H \dot{H} + W_K \dot{K} + W_\sigma \dot{\sigma}. \tag{7}$$

The explicit formulas for the variational derivatives of H and K are given in (Steigmann 2003). Therefore the corresponding shape equation can be obtained as

$$k\Delta(H-C) + 2k(H-C)(2H^2 - K) - 2H[(\alpha\sigma - \beta)^2 + k(H-C)^2] - 2\lambda H = P, \tag{8}$$

and the corresponding Lagrange multiplier ca be written as

$$\nabla\lambda = 2k[k\mu\varphi(H-C) - \alpha(\alpha\sigma - \beta)\nabla\sigma. \tag{9}$$

The associated boundary conditions are also given by

$$M = k(K - C),\ f_v = (\alpha\sigma - \beta)^2 + \lambda - \kappa_v M + c_g\gamma, \tag{10}$$

and

$$f_t = \tau M, f_n = (\tau M)' - M_{,v} + c_{,n}\gamma. \tag{11}$$

Due to the space limitation, we intentionally omit discussions regarding protein diffusion and parametric surface representation. Eqs (10-14) are highly nonlinear coupled two-point boundary valued Partial Differential Equations (PDEs) in nature. The solution can be obtained numerically using commercial packages (e.g. Matlab, COMSOL etc...).

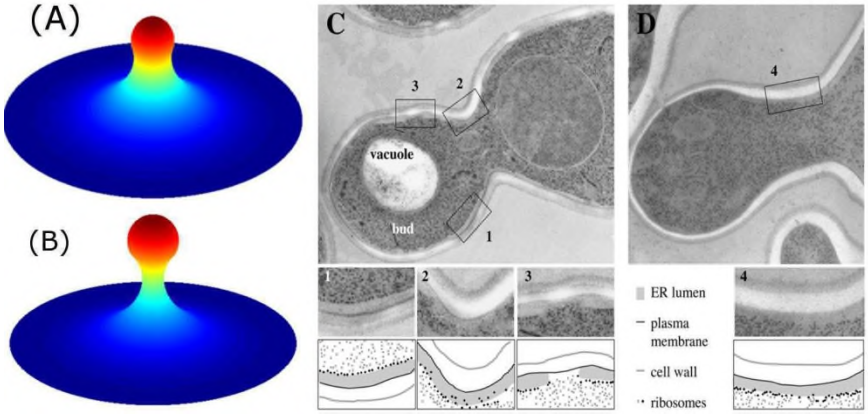

Fig. 1 Sequence of the budding formations (A, B) / (C, D) budding of sh1Δ mutant cell

3. CONCLUSIONS

We proposed a continuum based model describing budding formation of lipid membranes induced by the surface diffusion of proteins and acting line tension on the membrane. The proposed model successfully predicts budding and vesicle formation of membranes when necessary boundary conditions are applied. We also found that a sufficient amount of line tension is a dominant factor for the membrane in forming budding and/or vesicle.

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