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CURVATURE-DRIVEN MOLECULAR FLOW ON MEMBRANE SURFACE*

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Abstract

This work presents a mathematical model for the localization of multiple species of diffusion molecules on membrane surfaces. Morphological change of bilayer membrane *in vivo* is generally modulated by proteins. Most of these modulations are associated with the localization of related proteins in the crowded lipid environments. We start with the energetic description of the distributions of molecules on curved membrane surface, and define the spontaneous curvature of bilayer membrane as a function of the molecule concentrations on membrane surfaces. A drift-diffusion equation governs the gradient flow of the surface molecule concentrations. We recast the energetic formulation and the related governing equations by using an Eulerian phase field description to define membrane morphology. Computational simulations with the proposed mathematical model and related numerical techniques predict (i) the molecular localization on static membrane surfaces at locations with preferred mean curvatures, and (ii) the generation of preferred mean curvature which in turn drives the molecular localization.

Keywords

lipid bilayer membrane; protein localization; mean curvature; energy potential

AMS subject classifications

35Q92; 92C40; 65M70

1. Introduction

This paper concerns the derivation of a curvature-driven transport equation for membrane bound proteins. Experiments suggest that diffusive proteins within lipid membranes play a significant role in producing and regulating membrane curvature [4, 50, 3, 9, 31, 40, 23, 36, 26]. We capture a major class of these effects in our model, which couples the lateral protein

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diffusion with the dynamic membrane in which these proteins are attached (embedded, inserted, or tethered).

Approximately 30–90% of all membrane proteins can diffuse along the membrane [18, 24]. In addition, proteins induce various curvatures to the membrane they attach. A few mechanisms of protein induced curvature are summarized as follows. Rigid proteins such as those in the BAR (Bin/Amphiphysin/Rvs) domain family can act as a scaffold to the membrane. These proteins have an intrinsic curvature and, upon attachment, the membrane bends to match the protein curvature. In a similar fashion, several proteins can oligomerize to create a rigid shape and bend the membrane. Protein coats such as clathrin, COPI (COat Protein I) and COPII (COat Protein II) are examples of this type. Another type of protein induced membrane curvature is through protein insertion. Membrane curvature is induced when there is a difference between the length of the hydrophobic region of a membrane protein and the thickness of the hydrophobic core of the lipid bilayer in which it is embedded [31]. Epsin proteins do this by forming an α -helix upon binding to the membrane, and this helix, known as H0, inserts itself into the membrane [4]. Moreover, local protein crowding of peripheral proteins can cause membrane bending by creating an asymmetry of the monolayer areas and thereby curling the membrane away from the side where the crowding occurs. This effect is experimentally demonstrated in [40]. Further illustrating the importance of proteins in membranes, Schmidt *et. al.* showed that the M2 protein plays an essential role in generating regions of high curvature in the influenza A virus membrane [35]. This specific type of proteins accumulates in regions of negative Gaussian curvature and can generate curvature in the membrane itself, creating a positive feedback loop and allowing the replicated virus to be wrapped and released from the infected cells. Similar negative Gaussian curvature is also found at the vesicle bud necks where ESCRT (Endosomal Sorting Complex Required for Transport) proteins are localized [34]. We finally note that all endocytosis and exocytosis processes are promoted in one way or another by proteins. Therefore, any viral replication process requires proteins. Antagonizing these curvature effects of proteins may be a viable antiviral strategy [35]. This motivates the necessity for a model coupling membrane shape and protein localization.

The classical mechanical bending energy of a bilayer membrane, given by Canham [7], Helfrich, [22], and Evans [17] depends only upon the membrane curvature. However, when a force that produces a topological change to the membrane surface, such as those induced by proteins, this so-called sharp-interface model fails, since a change to the topology creates a discontinuity in the energy functional. In addition, a change in topology requires a discontinuous surface for a moment, which is impossible to model using an explicit parameterization of the surface. An effective way to treat topological changes is to track the surface implicitly as a level set of a three-dimensional function. Phase field method is such an implicit and diffuse-interface method, and it has been very successful in modeling membrane dynamics [12, 13, 43]. In a phase field method the membrane is defined by a level set of a phase field function, ϕ , and the motion of the membrane is governed by gradient flow of the energy functional, ensuring a decrease in energy in time. Since the membrane is never explicitly tracked, topological changes can occur. This approach has the obvious advantage over sharp interface models since it provides a way to describe topological changes to the membrane. However, a disadvantage of this method is that it is

difficult for this method to describe local forces on the membrane. If local forces need to be modeled, one should use the sharp-interface method. Furthermore, this method requires solving a higher dimensional system, since the energy functional is computed over the entire space $\Omega \subset \mathbb{R}^3$ rather than just a 2-manifold Γ embedded $\mathbb{R}^3$. This is the price we must pay to describe membrane merging and separating.

We need to use a phase field approach to model the dynamics of the membrane surface when membranes merge and separate. We must also include the activity of proteins in our phase field model. Du *et. al.* have successfully used a phase field approach to track multiple lipid species by using two phase functions [44]. The phase functions are orthogonal and their intersections define the separation of the two lipid species. They have been able to reproduce numerous vesicle shapes which match experimental results [5]. However, we argue that a phase field approach should not be used to track the dynamics of the diffusive membrane proteins. Lipid species may arrange themselves into distinct phases, but proteins do not necessarily form separate phases [24, 37]. Therefore, a dual phase field model cannot account for the effect of diffusive proteins in lipid membranes. We describe the proteins as diffusive particles governed by the advection-diffusion equation. A continuum model for the diffusion of proteins is physically justifiable by the relative length scales of the proteins embedded in the membrane, which are typically 4–5nm. thick, to the cell, which can be up to 100 μm in diameter [27]. (In the aforementioned virus replication example, the spherical virions produced from the budding are typically 100nm in diameter [33].) At such length scales, we may consider the proteins as diffusive particles that are attracted toward regions of specific membrane curvature. Therefore, the membrane proteins follow an equation similar to the usual drift-diffusion equation. The difference between this diffusion equation and the usual drift-diffusion equation is that the flux is proportional to a diffusion potential which is governed by the curvature energy of the membrane. That is, it is the curvature of the membrane responsible for the ‘drift’ of the proteins.

The diffusion of the proteins occurs only on the membrane surface, which is implicitly defined in a phase-field framework. Various techniques have been established for solving partial differential equations (PDEs) on surfaces, and we provide a brief overview here. Dziuk used finite element methods to solve elliptic partial differential equations on stationary surfaces [14]. This work was expanded by Elliott to parabolic equations on dynamic surfaces [16], and was extended even further by Deckelnick and Heine who solve the elliptic surface PDE on a narrow band around the surface [10]. Other approaches for PDEs on surfaces include [43, 21, 1, 46, 29] and references therein.

In all of these approaches, mesh refinement is required to accurately resolve the numerical solution. Therefore, these methods are suitable for stationary surfaces, but mesh refinement for dynamic surfaces can be a significant computational challenge. For this reason, we use the Fourier spectral method to solve the diffusion equation. This method is also available to solve the phase field equations [12, 13, 44, 43], giving a consistent solution procedure. Fourier methods exhibit exponential convergence, meaning that the error decreases faster than any power of the grid size [42]. Therefore, local mesh refinement near the interface is less important in Fourier (global) approaches than finite element and finite difference (local)

approaches. With this consistent framework, we may simultaneously solve for the shape of the membrane and the dynamics of the diffusive proteins in the membrane.

This paper is organized as follows. In Section 2, we first define the total energy in the Lagrangian formulation. The molecule concentration dependent spontaneous curvature is introduced to the bending energy of the bilayer membrane. The transport equation for diffusive molecules is derived as the gradient flow of the total energy. We then introduce the phase field function with which the Eulerian formulation of the total energy is presented. In Section 3 we are concentrated in the derivation of the transport equation in the entire domain but practically restricted to a small neighborhood near the implicitly defined membrane surface. This equation appears as the drift-diffusion equation in its essential nature. Then in Section 4 we outline present the results of computational simulations using the developed mathematical model and sketched numerical methods. Depending on the input parameters, diffusive proteins exhibit various curvature preferences on the surface of a torus. We draw conclusions and indicate further extension of the model in the final section 5.

2. Energy formulation

We model an enclosed bilayer membrane as a structureless surface Γ contained in a three-dimensional domain $\Omega \in \mathbb{R}^3$. The membrane Γ separates Ω into two subdomains, one inside the membrane and the other outside. On the membrane there distribute $m + 1$ distinct lipid species with concentrations ρ_l^{lip} , $l = 0, \dots, m$, and a single diffusive membrane protein with concentration ρ^{pro} . Throughout our notation, we use subscripts to denote the species number and superscripts to denote the species type. We consider only one protein species in this work, while the model can easily be extended to multiple protein species. The total energy of the system is composed of the membrane bending energy E_{mem} that includes the effects of the multiple lipid and protein species and the entropic energy E_{ent} for the distributions of lipids and proteins:

$$E_{\text{tot}} = E_{\text{mem}} + E_{\text{ent}}. \quad (2.1)$$

The exact representation of the total energy depends on the representation of the membrane Γ , which can be given explicitly as a parameterized three-dimensional surface or implicitly as a level set of a three-dimensional function that is defined in the entire domain Ω . The corresponding energy formulations using the explicitly and implicitly represented surfaces will be referred to as the Lagrangian and Eulerian formulations, respectively. The Lagrangian formulation is a direct mathematical description of the energetic nature of the interacted protein-membrane system. However, numerical implementations of this formulation in tracing the dynamics of the membrane suffers from the geometrical singularities that may arise when there is a topological change in membrane morphology. For this reason we will adopt Eulerian formulation of the membrane morphology in computational implementation. We shall first introduce the total energy using the Lagrangian formulation and then translate it into the Eulerian formulation for ease of exposition.

2.1. Lagrangian Formulation

The Lagrangian form of the membrane energy E_{mem} is the Canham-Helfrich-Evans membrane energy derived from fundamental physical principles [22, 20]:

$$E_{\text{mem}} = \int_{\Gamma} k(H - C_0)^2 ds, \quad (2.2)$$

where H is the mean curvature of the membrane Γ , C_0 is the spontaneous curvature of the membrane, and k is the bending modulus. We note that the above equation neglects surface tension and stretching rigidity. The surface tension is constant in vesicles with fixed surface area giving justification of our simplification [13]. We refer the reader to [12] for adding stretching rigidity to (2.2). The spontaneous curvature is an intrinsic property of the lipid composition of membrane [19], and when proteins are induced in the bilayer, it should depend on the protein structure and distribution as well [39, 4]. We are motivated by this biophysical nature to model the membrane spontaneous as a local parameter that depends on the surface concentrations of lipids and proteins. Each lipid species l has its intrinsic spontaneous curvature, denoted C_0^l . Furthermore, proteins can induce membrane curvature when embedded in a membrane, and a corresponding spontaneous curvature of the protein C_0^{pro} can be measured [6]. We define $C_0(\rho_l^{\text{lip}}, \rho^{\text{pro}})$ as the average of the spontaneous curvatures of all the contributing species weighted by their respective fractions of surface coverage:

$$C_0 = \sqrt{2} \left(\frac{\sum_{l=0}^m C_0^l (a_l^{\text{lip}})^2 \rho_l^{\text{lip}} + C_0^{\text{pro}} (a^{\text{pro}})^2 \rho^{\text{pro}}}{\sum_{l=0}^m (a_l^{\text{lip}})^2 \rho_l^{\text{lip}} + (a^{\text{pro}})^2 \rho^{\text{pro}}} \right), \quad (2.3)$$

where the spontaneous curvatures C_0^l and C_0^{pro} are constants pertaining to the lipid and protein structures. Similar model was used for computing the spontaneous curvatures of lipid mixtures [48]. The constants a_l^{lip} are the effective sizes of lipids for $l = 1, \dots, m$. Each lipid is modeled as a hard disk occupying some surface area in the membrane, hence we take $(a_l^{\text{lip}})^2$ for an effective surface area, which is measurable [28]. Similarly, the constant a^{pro} is the effective size of the protein embedded in the membrane, occupying an effective surface area $(a^{\text{pro}})^2$. The concentration of particles on the membrane cannot exceed the available total surface space, so the concentrations must satisfy the saturation condition

$$\sum_{l=0}^m (a_l^{\text{lip}})^2 \rho_l^{\text{lip}} + (a^{\text{pro}})^2 \rho^{\text{pro}} = 1. \quad (2.4)$$

With this condition (2.4) the spontaneous curvature defined by (2.3) can be simplified to be

$$C_0 = \sqrt{2} \left(\sum_{l=0}^m C_0^l (a_l^{\text{lip}})^2 \rho_l^{\text{lip}} + C_0^{\text{pro}} (a^{\text{pro}})^2 \rho^{\text{pro}} \right). \quad (2.5)$$

The entropic energy for the membrane with embedded proteins is defined following the Boltzmann relation by

$$E_{\text{ent}} = \frac{1}{\beta} \int_{\Gamma} \left(\sum_{l=0}^m \rho_l^{\text{lip}} \left[\ln \left(\rho_l^{\text{lip}} (a_l^{\text{lip}})^2 \right) - 1 \right] + \rho^{\text{pro}} \left[\ln \left(\rho^{\text{pro}} (a^{\text{pro}})^2 \right) - 1 \right] \right) ds, \quad (2.6)$$

where $\beta = 1/(k_B T)$ is the inverse thermal energy [49].

The variation of the surface concentration of lipids and proteins follows the general mass conservation law. It reads for a general concentration ρ on Γ that [41, 15]

$$\frac{D\rho}{Dt} + (\nabla_s \cdot \mathbf{v})\rho = -\nabla_s \cdot \mathbf{J}, \quad (2.7)$$

if the surface Γ evolves only in its normal direction at a velocity $\mathbf{v} \cdot \mathbf{n}$, where D/Dt is the advective surface material derivative, $\mathbf{v}$ is a divergence-free velocity field in Ω , ∇_s is the surface divergence, and $\mathbf{J}$ is the flux vector on surface. Divergence-free velocity field is what the membrane experiences since the fluid in which it is immersed is incompressible. We note that the surface advection-diffusion equation of the form

$$\frac{\partial \rho}{\partial t} + \mathbf{v} \cdot \nabla_s \rho = -\nabla_s \cdot \mathbf{J}$$

is less relevant to the transport of lipids or proteins on membrane surface, because it assumes a steady surface in a velocity field $\mathbf{v}$ thereby $\mathbf{v} \cdot \mathbf{n} = 0$ and $\nabla \cdot \mathbf{v} = \nabla_s \cdot \mathbf{v}$. A constitutive relation for the flux is given by the Nernst-Planck formula as an extension of Fick's first law,

$$\mathbf{J} = -D_{\Gamma} \beta \rho \nabla_s \mu, \quad (2.8)$$

where μ is the diffusion potential, D_{Γ} is the (constant) lateral diffusion coefficient [2, 32], and ∇_s is the surface gradient [49]. The diffusion potential μ is defined as the variation of the total energy with respect to the corresponding surface concentration:

$$\mu_l^{\text{lip}} = \frac{\delta E_{\text{tot}}}{\delta \rho_l^{\text{lip}}} = \frac{\delta E_{\text{mem}}}{\delta \rho_l^{\text{lip}}} + \frac{\delta E_{\text{ent}}}{\delta \rho_l^{\text{lip}}}, \quad l=1, \dots, m; \quad (2.9)$$

$$\mu^{\text{pro}} = \frac{\delta E_{\text{tot}}}{\delta \rho^{\text{pro}}} = \frac{\delta E_{\text{mem}}}{\delta \rho^{\text{pro}}} + \frac{\delta E_{\text{ent}}}{\delta \rho^{\text{pro}}}. \quad (2.10)$$

It is not necessary to solve a PDE for the concentration of the 0^{th} species of lipids thanks to the saturation condition (2.4). For the computation of the entropic portion of the diffusion potentials, we solve (2.4) for $\rho_0^{\text{lip}} (a_0^{\text{lip}})^2$ and substitute in the entropic energy (2.6) to obtain an form facilitating differentiation. We shall have

$$\begin{aligned} E_{\text{ent}} = & \frac{1}{\beta} \int_{\Gamma} \left(\frac{1}{(a_0^{\text{lip}})^2} \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{l=1}^m \rho_l^{\text{lip}} (a_l^{\text{lip}})^2 \right) \right. \\ & \times \left[\ln \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{l=1}^m \rho_l^{\text{lip}} (a_l^{\text{lip}})^2 \right) - 1 \right] + \\ & \left. + \sum_{l=1}^m \rho_l^{\text{lip}} \left[\ln \left(\rho_l^{\text{lip}} (a_l^{\text{lip}})^2 \right) - 1 \right] + \rho^{\text{pro}} \left[\ln \left(\rho^{\text{pro}} (a^{\text{pro}})^2 \right) - 1 \right] \right) ds \end{aligned} \quad (2.11)$$

for the l^{th} lipid species, $1 \leq l \leq m$. Its derivative is

$$\begin{aligned} \frac{\delta E_{\text{ent}}}{\delta \rho_l^{\text{lip}}} = & \frac{1}{\beta} \left(\frac{1}{(a_0^{\text{lip}})^2} \left(- (a_l^{\text{lip}})^2 \right) \left[\ln \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2 \right) - 1 \right] \right. \\ & + \frac{1}{(a_0^{\text{lip}})^2} \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2 \right) \left[\frac{- (a_l^{\text{lip}})^2}{1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2} \right] \\ & \left. + \left[\ln(\rho_l^{\text{lip}} (a_l^{\text{lip}})^2) - 1 \right] + \rho_l^{\text{lip}} \frac{(a_l^{\text{lip}})^2}{\rho_l^{\text{lip}} (a_l^{\text{lip}})^2} \right) \\ = & \frac{1}{\beta} \left(\frac{- (a_l^{\text{lip}})^2}{(a_0^{\text{lip}})^2} \ln \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2 \right) + \ln(\rho_l^{\text{lip}} (a_l^{\text{lip}})^2) \right). \end{aligned} \quad (2.12)$$

The entropic portion of the diffusion potential for the protein species is computed similarly.

The curvature-driven portion of the diffusion potential is defined as the variation of the membrane energy with respect to the concentrations. Using the Lagrangian formulation given in Eq.(2.2), we compute the variation to be

$$\frac{\delta E_{\text{mem}}}{\delta \rho_t^{\text{lip}}} = 2\sqrt{2}k(C_0 - H) \frac{\partial C_0}{\partial \rho_t^{\text{lip}}} = 2kC_0^l (a_t^{\text{lip}})^2 (C_0 - H), \quad (2.13)$$

$$\frac{\delta E_{\text{mem}}}{\delta \rho^{\text{pro}}} = 2\sqrt{2}k(C_0 - H) \frac{\partial C_0}{\partial \rho^{\text{pro}}} = 2kC_0^l (a_t^{\text{pro}})^2 (C_0 - H). \quad (2.14)$$

The full potential for the individual species of lipids is then given by combining Eqs.(2.12–2.13),

$$\mu_t^{\text{lip}} = \frac{1}{\beta} \left[\frac{-(a_t^{\text{lip}})^2}{(a_0^{\text{lip}})^2} \ln \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2 \right) + \ln(\rho_t^{\text{lip}} (a_t^{\text{lip}})^2) \right] + 2\sqrt{2}C_0^l (a_t^{\text{lip}})^2 (C_0 - H) \quad (2.15)$$

and the transport equation can be obtained by using this full diffusion potential to the prototype equation (2.7). The transport equation for proteins can be obtained similarly.

2.2. Eulerian Formulation

We anticipate that the molecular localization model being developed here can be finally coupled to dynamic morphological change of membrane where the position of membrane surface Γ is unknown *a priori*. For that purpose it is desirable to replace the above Lagrangian formulation with an alternative formulation that is independent of the parameterization of the surface Γ . Here we recast the energy functional in an Eulerian formulation using a smooth phase field function ϕ . The zero level set of ϕ separates Ω into two subdomains, Ω_i in the interior of Γ and Ω_e to the exterior of Γ . In other words, the set $\{x: \phi(x) = 0\}$ represents the membrane Γ , the set $\{x: \phi(x) > 0\}$ represents the domain inside the membrane, $x \in \Omega_i$, and the set $\{x: \phi(x) < 0\}$ represents the domain outside the membrane, $x \in \Omega_e$. These properties are illustrated in Figure 2.1.

We initiate the phase field function using

$$\phi(x) = \tanh \left(\frac{d(x)}{\sqrt{2}\varepsilon} \right). \quad (2.16)$$

The function $d(x)$ is the signed distance for any point $x \in \Omega$ to the surface Γ . It has the properties that $d(x) = 0$ for $x \in \Gamma$, $d(x) > 0$ for $x \in \Omega_i$ and $d(x) < 0$ for $x \in \Omega_e$. The parameter $0 < \varepsilon \ll 1$ adjusts the transition width of ϕ in the vicinity of the membrane. The dilation $1/(\sqrt{2}\varepsilon)$ for small ε gives ϕ a steep sigmoid shape. The sharp-interface is recovered in the limit as $\varepsilon \rightarrow 0$. Additional reasoning for the choice of $\tanh(\cdot)$ can be found in [13].

The equivalent Eulerian form of the membrane energy E_{mem} is given by

$$E_{\text{mem}} = \int_{\Omega} \frac{\varepsilon}{2} \left| \Delta \phi - \frac{1}{\varepsilon^2} (\phi^2 - 1) (\phi + C_0(\rho_l^{\text{lip}}, \rho^{\text{pro}}) \varepsilon) \right|^2 dx, \quad (2.17)$$

where C_0 is the spontaneous curvature of the membrane as defined in (2.3), accounting for the dependence of membrane curvature energy on the local concentrations of lipids and proteins. If we substitute (2.16) into (2.17) with the above-defined phase field function and take the limit $\varepsilon \rightarrow 0$, the Lagrangian formulation (2.2) will be recovered [11]. The scaling by $\sqrt{2}$ appears from this derivation of the equivalence to the two-dimensional energy in the sharp interface limit.

In addition to the Eulerian formulation for the bending energy, we define the following area and volume constraints. The volume constraint is given by

$$V(\phi) = \int_{\Omega} \phi(x) dx. \quad (2.18)$$

Notice that the integral defined by (2.18) gives

$$\int_{\Omega} \phi dx = \int_{\Omega_i} \phi dx + \int_{\Omega_e} \phi dx \xrightarrow{\varepsilon \rightarrow 0} \int_{\Omega_i} 1 dx + \int_{\Omega_e} -1 dx.$$

That is, $V(\phi)$ approaches the difference between the interior and exterior volumes. The surface area constraint is defined by

$$A(\phi) = \int_{\Omega} \left(\frac{\varepsilon}{2} |\nabla \phi|^2 + \frac{1}{4\varepsilon} (\phi^2 - 1)^2 \right) dx. \quad (2.19)$$

For small ε , the integrand of (2.19) is significant only near the interface Γ , and as $\varepsilon \rightarrow 0$, we have $A(\phi) \rightarrow 2\sqrt{2}/3$. These constraints will be used to ensure the conservation of the membrane surface area and its enclosed volume when we solve the PDE for the gradient flow of E_{mem} to evolve the phase field function ϕ [11]. The other component of total energy, E_{ent} (c.f. Eq.(3.1 below), is independent of ϕ and thus does not directly constitute this evolution equation for ϕ . This PDE for ϕ has a spatial dependent spontaneous curvature C_0 .

which will be updated when the local molecular concentrations are updated following the transport equations to be derived below.

3. Curvature-driven Transport

We proceed to the treatment of the diffusive lipids and proteins with the new Eulerian formulation of total energy. While the diffusion occurs on the membrane where $\phi = 0$, solving diffusion equations on the surface involves surface mesh generation, mesh deformation, and re-meshing if there is a large deformation or topological change to the membrane surface during the evolution of the phase field function ϕ . We choose to extend the diffusion domain from Γ to the entire Ω , practically concentrated in the neighborhood of Γ following the evolution of ϕ , to avoid the treatment of a surface mesh. Consequently, the Lagrangian formulation of the entropic energy in (2.6) need to be replaced by the following Eulerian formulation

$$E_{\text{ent}} = \frac{1}{\beta} \int_{\Omega} \left(\sum_{l=0}^m \rho_l^{\text{lip}} \left[\ln \left(\rho_l^{\text{lip}} (a_l^{\text{lip}})^2 \right) - 1 \right] + \rho^{\text{pro}} \left[\ln \left(\rho^{\text{pro}} (a^{\text{pro}})^2 \right) - 1 \right] \right) dx. \quad (3.1)$$

This formulation indicates that the surface distributions of lipids and proteins need to be replaced by volume distributions. The initial volume distribution can be obtained by extending the surface distribution $f(s)$, $s \in \Gamma$ to a function $f_{\Omega}(x)$ in Ω such that

$$f(s) = \int_{-L}^L f_{\Omega}(s + l \cdot \mathbf{n}) \delta_{\Gamma} dl, \quad (3.2)$$

where a surface delta function δ_{Γ} is introduced to restrict the volume concentration is essentially concentrated in the neighborhood of width $2L$ symmetrically located on the surface Γ . There are many choices to use for the surface delta function. A catalog of possibilities is found in [25]. A good choice must maintain the property that $\int_{\Omega} \delta_{\Gamma} dx \propto \text{area}(\Gamma)$ similar to the area constraint (2.19). It is also convenient to choose a function without the use of $|\nabla \phi|$ for the sake of the simplicity of the variation computations with respect to ϕ (which is useful for computing the shape equation of the membrane [13]). We choose the following function for numerical reasons,

$$\delta_{\Gamma} = \begin{cases} \tanh(10(\phi+1)), & -1 \leq \phi \leq 0; \\ -\tanh(10(\phi-1)), & 0 \leq \phi \leq 1. \end{cases} \quad (3.3)$$

Note that this function is continuous at $\phi = 0$; however, it does not have a continuous derivative. This effect is negligible, since $\text{sech}^2(D) \rightarrow -\text{sech}^2(-D)$ as $D \rightarrow \infty$, and $D = 10$ is large enough at which the first derivative of δ_{Γ} is numerically continuous.

The Eulerian formulation of the membrane curvature energy involves the concentrations of lipids and proteins so it is mathematically possible to compute the variations of this energy with respect to these concentrations. This variation is defined everywhere in Ω , although it is the membrane curvature at the zero level set of the phase field function that is relevant to the molecular localization. Consequently, rather than computing a new variation directly from (2.17), it is simpler to use the variations (2.13)–(2.14) and replace the membrane mean curvature H by a function of the phase field function. An H expression consistent with the above definition of phase field function is given as [11]

$$H = \frac{\sqrt{2}\varepsilon}{2(\phi^2 - 1)} \left(\Delta\phi - \frac{1}{\varepsilon^2} \phi(\phi^2 - 1) \right). \quad (3.4)$$

Again, this expression is only valid near the level set $\phi = 0$ where the membrane surface is actually defined. Therefore, we restrict the mean curvature with a surface delta function so that it is only computed on (a narrow band around) the surface. The computation of H at other level sets of ϕ is extremely temperamental and introduces great numerical difficulties. Using this phase field approximation to the mean curvature in (3.4) we will get an Eulerian formulation of the membrane curvature energy with respect to the lipid concentrations:

$$\frac{\delta E_{\text{mem}}}{\delta \rho_l^{\text{lip}}} \sim 2\sqrt{2}C_0^l (a_l^{\text{lip}})^2 \left(C_0 - \frac{\varepsilon}{\sqrt{2}(\phi^2 - 1)} \left(\Delta\phi - \frac{1}{\varepsilon^2} \phi(\phi^2 - 1) \right) \delta_\Gamma \right). \quad (3.5)$$

Note that the diffusion potential for the lipids is defined over all of Ω , but is nonzero only near the membrane Γ . The concentrations are initially distributed on the membrane only, and it is clear in Eq. (3.10) below that the flux is restricted to the membrane only, hence these terms remain zero away from Γ . This is also the case for the spontaneous curvature C_0 , since it depends upon the concentrations. However, the mean curvature (3.4) may be nonzero away from Γ , since this computation depends upon ϕ , yet the expression is only relevant for the level set $\phi = 0$ as we are using only the mean curvature at $\phi = 0$ to drive the transport of lipids and proteins. For this reason, a surface delta function is applied to this term only to avoid irrelevant mean curvatures away from the zero level set.

The full diffusion potential for the lipid species in the context of the phase field is now given by combining (2.12) and (3.5),

$$\begin{aligned} \mu_l^{\text{lip}} = & \frac{1}{\beta} \left[\frac{-(a_l^{\text{lip}})^2}{(a_0^{\text{lip}})^2} \ln \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2 \right) + \ln(\rho_l^{\text{lip}} (a_l^{\text{lip}})^2) \right] \\ & + 2\sqrt{2}C_0^l (a_l^{\text{lip}})^2 \left(C_0 - \frac{\varepsilon}{\sqrt{2}(\phi^2 - 1)} \left(\Delta\phi - \frac{1}{\varepsilon^2} \phi(\phi^2 - 1) \right) \delta_\Gamma \right). \end{aligned} \quad (3.6)$$

The protein diffusion potential is computed similarly as

$$\begin{aligned} \mu^{\text{pro}} = & \frac{1}{\beta} \left[\frac{-(a^{\text{pro}})^2}{(a_0^{\text{lip}})^2} \ln \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2 \right) + \ln(\rho^{\text{pro}} (a^{\text{pro}})^2) \right] \\ & + 2\sqrt{2} C_0^{\text{pro}} (a^{\text{pro}})^2 \left(C_0 - \frac{\varepsilon}{\sqrt{2}(\phi^2 - 1)} \left(\Delta\phi - \frac{1}{\varepsilon^2} \phi(\phi^2 - 1) \right) \delta_\Gamma \right). \end{aligned} \quad (3.7)$$

3.1. Surface velocity

The fact that the surface deformation is driven by energy minimization implies that any component of the velocity that is tangential to the surface will cost extra energy for the deformation. In other words, a velocity field given by the evolution of the phase field function and consistent with the minimization of the total energy must be normal to the zero level set of ϕ . With these justifications, we will derive a velocity field from the evolving phase field function using [30]

$$\mathbf{v}_n = \mathbf{n} \cdot \frac{d\mathbf{x}}{dt} = \frac{\nabla\phi}{|\nabla\phi|} \frac{d\mathbf{x}}{dt} = -\frac{\phi_t}{|\nabla\phi|}. \quad (3.8)$$

3.2. Curvature-driven transport equation

With the extension of the lipid and protein concentrations from the surface to domain, their transport can not be described by the surface equation (2.7). Rather, it will be governed by following general transport equation defined in the entire Ω :

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\mathbf{v}\rho) = -\nabla \cdot \mathbf{J}, \quad (3.9)$$

with the flux vector being defined now by

$$\mathbf{J} = -D_\Omega \delta_\Gamma \beta \rho \nabla \mu, \quad (3.10)$$

where D_Ω is the volume diffusion coefficient, which can be inversely determined by using the measured lateral diffusion coefficients of lipids or proteins and a relation modeling Eq. (3.2): $D_\Gamma = D_\Omega \int_{-L}^L \delta_\Gamma dl$. We do not assume the velocity field given by the evolving phase field ϕ is divergence free.

We are now in a position to rearrange the diffusion equation (3.9) with individual terms computed above. We define

$$L^{\text{lip}}(\rho_l^{\text{lip}}) = \ln(\rho_l^{\text{lip}} (a_l^{\text{lip}})^2), \quad (3.11)$$

$$R^{\text{lip}}(\rho_l^{\text{lip}}, \rho^{\text{pro}}) = \frac{-(a_l^{\text{lip}})^2}{(a_0^{\text{lip}})^2} \ln \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2 \right), \quad (3.12)$$

$$L^{\text{pro}}(\rho^{\text{pro}}) = \ln(\rho^{\text{pro}} (a^{\text{pro}})^2), \quad (3.13)$$

$$R^{\text{pro}}(\rho_l^{\text{lip}}, \rho^{\text{pro}}) = \frac{-(a^{\text{pro}})^2}{(a_0^{\text{lip}})^2} \ln \left(1 - \rho^{\text{pro}} (a^{\text{pro}})^2 - \sum_{j=1}^m \rho_j^{\text{lip}} (a_j^{\text{lip}})^2 \right), \quad (3.14)$$

$$P(\phi, \rho_l^{\text{lip}}, \rho^{\text{pro}}) = \left(C_0(\rho_l^{\text{lip}}, \rho^{\text{pro}}) - \frac{\varepsilon}{\sqrt{2}(\phi^2 - 1)} \left(\Delta \phi - \frac{1}{\varepsilon^2} \phi(\phi^2 - 1) \right) \delta_\Gamma \right). \quad (3.15)$$

The notation is indicative of leading order terms for the lipids and proteins (L), remaining terms corresponding to the size restrictions (R), and a term corresponding to the curvature determined by the phase field function (P). Using (3.11)–(3.15) and suppressing the notation describing each function's independent variables, the diffusion potentials (3.6) and (3.7) become

$$\mu_l^{\text{lip}} = \frac{1}{\beta} (L^{\text{lip}} + R^{\text{lip}}) + 2\sqrt{2}C_0^l (a_l^{\text{lip}})^2 P, \quad (3.16)$$

$$\mu^{\text{pro}} = \frac{1}{\beta} (L^{\text{pro}} + R^{\text{pro}}) + 2\sqrt{2}C_0^{\text{pro}} (a^{\text{pro}})^2 P. \quad (3.17)$$

Then, to compute the flux (3.10) we have

$$\nabla \mu_l^{\text{lip}} = \frac{1}{\beta} (\nabla L^{\text{lip}} + \nabla R^{\text{lip}}) + 2\sqrt{2}C_0^l (a_l^{\text{lip}})^2 \nabla P, \quad (3.18)$$

$$\nabla \mu^{\text{pro}} = \frac{1}{\beta} (\nabla L^{\text{pro}} + \nabla R^{\text{pro}}) + 2\sqrt{2} C_0^{\text{pro}} (a^{\text{pro}})^2 \nabla P, \quad (3.19)$$

where we note the derivatives of the leading terms are simply

$$\nabla L^{\text{lip}} = \frac{\nabla \rho_l^{\text{lip}}}{\rho_l^{\text{lip}}}, \quad (3.20)$$

$$\nabla L^{\text{pro}} = \frac{\nabla \rho^{\text{pro}}}{\rho^{\text{pro}}}. \quad (3.21)$$

Also define

$$M_l^{\text{lip}} = 2\beta C_0^l (a_l^{\text{lip}})^2, \quad (3.22)$$

$$M^{\text{pro}} = 2\beta C_0^{\text{pro}} (a^{\text{pro}})^2. \quad (3.23)$$

Using these variables, the diffusion equation (3.9) for each species becomes

$$\frac{\partial \rho_l^{\text{lip}}}{\partial t} + \nabla \cdot (v \rho_l^{\text{lip}}) = D_l^{\text{lip}} \nabla \cdot \left\{ \delta_\Gamma \nabla \rho_l^{\text{lip}} + \delta_\Gamma \rho_l^{\text{lip}} \nabla R^{\text{lip}} + M_l^{\text{lip}} \delta_\Gamma \rho_l^{\text{lip}} \nabla P \right\}, \quad (3.24)$$

$$\frac{\partial \rho^{\text{pro}}}{\partial t} + \nabla \cdot (v \rho^{\text{pro}}) = D^{\text{pro}} \nabla \cdot \left\{ \delta_\Gamma \nabla \rho^{\text{pro}} + \delta_\Gamma \rho^{\text{pro}} \nabla R^{\text{pro}} + M^{\text{pro}} \delta_\Gamma \rho^{\text{pro}} \nabla P \right\}. \quad (3.25)$$

The equations above take the form of the drift-diffusion equation. If we neglect the size effect terms involving R , and consider the equation on a stationary membrane ($v = 0$), the equations will take the form

$$\frac{\partial \rho}{\partial t} = D \nabla \cdot (\delta_\Gamma \nabla \rho + M \delta_\Gamma \rho \nabla (C_0 - H \delta_\Gamma)). \quad (3.26)$$

If we use the surface operator, the use of delta functions can be absorbed, giving rise to

$$\frac{\partial \rho}{\partial t} = D \nabla_s \cdot (\nabla_s \rho + M \rho \nabla_s (C_0 - H)). \quad (3.27)$$

The second term in the above two equation shows that the drift of the diffusive species is due to the difference in the actual membrane curvature and the spontaneous curvature of the membrane $C_0 - H$. It is this term that drives the localization of lipids and proteins to the position on membrane surface where the preferred mean curvature is observed.

3.3. Analytical solution to steady state surface diffusion

The steady state drift-diffusion equation has an analytical solution. Using the Slotboom variable $u = \rho e^{M(C_0 - H)}$ [38], one can obtain the steady state form of (3.27)

$$0 = \nabla_s \cdot (e^{-M(C_0 - H)} \nabla_s u), \quad (3.28)$$

which admits a general solution

$$\rho = c e^{-M(C_0 - H)}, \quad (3.29)$$

where c is some constant. The integration of the lipid concentration over the membrane Γ gives the total number of lipids on a leaflet, a conserved quantity,

$$T = \int_{\Gamma} \rho \, dS = \int_{\Gamma} c e^{-M(C_0 - H)} \, dS. \quad (3.30)$$

Factor the constant c out of the integral and solve to get

$$c = \frac{T}{\int_{\Gamma} e^{-M(C_0 - H)} \, dS}. \quad (3.31)$$

Plugging (3.31) back into (3.29), we have the analytical solution to the steady state of (3.27),

$$\rho[\Gamma] = \frac{T e^{-M(C_0 - H)}}{\int_{\Gamma} e^{-M(C_0 - H)} \, dS}. \quad (3.32)$$

4. Computational Simulations

In the computational simulations, we solve the diffusion equations (3.25) numerically for two competing species, one diffusive proteins, the other background lipids. By using a two-species model, we only need to solve one governing equation, since the concentration of the second (background) species can be computed directly from the concentration of the diffusive species according to saturation condition (2.4). To further focus on the curvature induced molecular localization, we neglect the correction terms in the equation accounting for the size effects of molecules (R in Eq.(3.12)). When dynamic membrane morphology is coupled, evolution of membrane phase field function is tracked following the approach in [13]. All PDEs are solved using Fourier spectral method. For drift-diffusion equation, a proper transformation is needed so the variable diffusion coefficient caused by the surface delta function can be efficiently treated before applying a Fourier transform [8, 42]. The detailed numerical procedure will be described in a future article. In all the simulations presented here we consistently choose $\varepsilon = 0.1$.

4.1. Molecular flow on static surface

Here we choose a torus as a test surface for that it has regions of positive curvature and regions of negative curvature which we can analytically compute to test the curvature preference of diffusive proteins. The torus surface is defined by

$$\left(r_M - \sqrt{x^2 + y^2}\right)^2 + z^2 = r_m^2, \quad (4.1)$$

where r_M and r_m are the major and minor radii, respectively. The torus can also be parameterized using the poloidal angle θ and the toroidal angle ψ ,

$$\mathbf{x} = \begin{pmatrix} (r_M + r_m \cos \theta) \cos \psi \\ (r_M + r_m \cos \theta) \sin \psi \\ r_m \sin \theta \end{pmatrix}, \quad (4.2)$$

where $0 \leq \theta, \psi < 2\pi$. We consider a ring torus (i.e., $r_M > r_m$), with $r_M = 2.0$ and $r_m = 1.1$, and solve the diffusion equation over a grid of $[-4, 4]^3$, with a $128 \times 128 \times 128$ uniform mesh.

The initial concentration of diffusive proteins is chosen to be localized along the ring around the positive x -axis, smoothly distributed along the surface and smoothly distributed from the surface to the bulk,

$$\rho(x, y, z, 0) = S \cdot \exp \left(-\sqrt{(x-r_M)^2 + y^2 + z^2} \right) \cdot \exp \left(-2 \left(r_m - \sqrt{(x-c_x)^2 + (y-c_y)^2 + z^2} \right) \right), \quad (4.3)$$

where the point $(c_x, c_y, 0)$ is the center of the torus tube at a given angle ψ , and the scaling constant S is chosen so that the maximum of the concentration is 1 on the torus surface.

The profile of the delta function given by Eq.(3.3) for the torus is shown in Figure 4.1. The one-dimensional cross section of the delta function as seen in Figure 4.1 shows that the surface is well resolved on the $y = z = 0$ cross section. That is, there is a clear transition from the outside to the inside of each ring, and the delta function settles to zero in the empty space.

Analytically, the mean curvature of a torus is given by

$$H_{torus} = \frac{r_M + 2r_m \cos \theta}{2r_m(r_M + r_m \cos \theta)}. \quad (4.4)$$

At the outer ring of the torus, $\theta = 0$. Therefore the mean curvature is $H_{torus} \approx 0.6158$. At the inner ring of the torus, $\theta = \pi$, and $H_{torus} \approx -0.1010$. An one-dimensional cross section of the numerical mean curvature is shown in Figure 4.2. The plot matches the analytical values at the positions of the inner and outer rings well.

To drive the diffusive species to the outer ring and the background to the inner ring, we set the spontaneous curvatures $C_0^{\text{pro}} = 0.5$ and $C_0^{\text{lip}} = -0.1$. The numerical solution to the curvature-driven diffusion equation with these spontaneous curvatures is presented in Figure 4.3. The curvature preference of the diffusive proteins toward the outer regions can be clearly seen in this figure. Reversing the curvature preference, we now solve the equation with the diffusive proteins $C_0^{\text{pro}} = -0.1$ and the background lipids $C_0^{\text{lip}} = 0.5$. This is more like the motivating application of the M2 proteins, which prefer regions of negative curvature. The plots of the concentration with these curvature preferences together with the corresponding cross sections are shown in Figure 4.4. The curvature preference toward the inner ring of the torus is clearly illustrated.

4.2. Molecular flow on dynamic surface

To couple the molecular flow and dynamic membrane morphology we consider in a $[-\pi, \pi]^3$ domain a membrane whose initial surface is given by

$$z(x, y) = h \exp(-k(x^2 + y^2)) + z_0$$

where we choose $h = 0.5$, $h = 2$ and $z_0 = 0.5$. The phase field initialized using the signed distance function with respect to this surface is not periodic in z -direction, and we symmetrically extended the domain so that the Fourier spectral method can be applied, c.f. Fig. 4.6. The molecular concentration is initially clustered at on membrane surface at $(x_1, y_1) = (-1, 0)$ and $(x_2, y_2) = (1, 0)$, such that

$$\rho(x, y, z, 0) = S \cdot \exp(-2 \min(r_1, r_2)) \exp(-2d), \quad (4.5)$$

where $r_i = \sqrt{(x-x_i)^2 + y^2 + (z-1-h)^2}$ for $i = 1, 2$, and d is the signed distance function of (x, y, z) to the initial membrane surface. The symmetric initialization of $\rho(x, y, z, t)$ is to ensure that the molecular concentration is periodic in x and y directions over the evolution. We set the spontaneous curvatures of diffusive proteins and background lipids as $C_0^{\text{pro}} = -0.5$ and $C_0^{\text{lip}} = 0$, respectively. Initial and final membrane surfaces are shown in Fig. 4.5, and the evolution of the membrane morphology is illustrated using the cross-section of the phase field function in Fig. 4.6. As proteins are diffusing from their initial clusters to surround, negative curvature is accumulating at the bottom of the bump (Fig. 4.6, Row 3, middle chart). This negative curvature guides the transport of proteins along the bottom of the bud (Fig. 4.6, Row 1, middle and right charts). The localization of the proteins with negative spontaneous curvature further promotes the negative curvature of the membrane ((Fig. 4.6, Row 4), which in turn favors the localization of the proteins along the bottom of the bud ((Fig. 4.6, Row 2). The positive coupling between molecular localization and membrane curvature generation describes the minimizing of total total energy in Eq.(2.1) though the evolution of molecular concentration ρ^{pro} and phase field function ϕ .

5. Conclusions and future work

In this paper, we have modeled the curvature preference of diffusion molecules in bilayer membranes using an energetic variational principle [47, 45]. We introduced an molecule concentration dependent spontaneous curvature in defining the bending energy of the bilayer membrane. This bending energy and the entropic energy of molecules distributions consist the total energy of the interacted protein-membrane system. The transport of molecules on membrane surfaces follows the gradient flow of this total energy. We derived a drift-diffusion equation for the gradient flow, where the difference between the local membrane curvature and the molecule concentration dependent local spontaneous curvature appears as a drift potential, a feature models the biophysics of molecular localization on membrane surfaces. This localization is further confirmed by the numerical solutions of the drift-diffusion equation on torus. These solutions simulate the localization toward the inner and outer rings, corresponding to the different intrinsic curvatures of the diffusive molecules. Simulations on dynamic surfaces show that the spontaneous curvature of proteins will promote the budding of the membrane. Meanwhile, the generated negative mean curvature will guide the molecular flow along the bottom of the bud, presenting a positive feedback as modelled by the minimizing of the total energy.

Various extensions to the curvature-driven model presented can be made. First, the model can be coupled to the evolution of the phase field function so the localization on moving membrane surfaces can be simulated. This can be achieved by coupling the mean curvature drift-diffusion equation to gradient flow of the phase field function [13]. Second, we presented numerical results for a single diffusive species, but the model allows for multiple diffusive species. The growth of the computational cost is linear with each additional species, since each additional diffusive species requires solving one additional diffusion equation. In addition, we can also consider spatially variable diffusion coefficients, electrostatics of the charged molecules, and the finite size effects (R) in our numerical results [49]. By including these effects the simulations can be made more realistic and results can be predictive in quantitatively accessing the capability of specific proteins and their mutations in modulating membrane curvatures.

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Fig. 2.1.
Properties of phase function ϕ within the domain Ω .

Fig. 4.1.

Profile of delta function for the torus with radii $r_M = 2.0$ and $r_m = 1.1$ on a $128 \times 128 \times 128$ uniform mesh. Left: One-dimensional profile ($y = z = 0$) of delta function across the x grid points. Right: Two-dimensional profile ($y = 0$) across x and z grid points.

Fig. 4.2.

Mean curvature of a torus with $128 \times 128 \times 128$ mesh. Top: One-dimensional profile ($y = z = 0$) of a (simpler) delta function used to restrict mean curvature (3.4) to the surface.

Bottom: One-dimensional profile of numerical mean curvature of torus. Note the match to the analytical values of 0.6 and -0.1 .

Fig. 4.3.

Concentration of diffusive proteins with curvature preference on the torus using $128 \times 128 \times 128$ mesh. The diffusive proteins prefer the curvature $C_0^{\text{pro}} = 0.5$ (located on the outer ring) and the background lipid species prefer the curvature $C_0^{\text{lip}} = -0.1$ (located on the inner ring). Times shown are $t = 0, 0.1, 0.25, 0.5, 1.0$, and 5.0 . The color is scaled by the maximum concentration in each plot.

Fig. 4.4.

Concentration of diffusive proteins with curvature preference on the torus using $128 \times 128 \times 128$ mesh. The diffusive proteins prefer the curvature $C_0^{\text{pro}} = -0.1$ (located on the inner ring) and the background lipid species prefer the curvature $C_0^{\text{lip}} = 0.5$ (located on the outer ring). Times shown are $t = 0, 0.1, 0.25, 0.5, 1.0$, and 5.0 . The color is scaled by the maximum concentration in each plot.

Fig. 4.5.
Initial (left, $t = 0$) and equilibrium (right $t = 8$) membrane surfaces.

Fig. 4.6. Concentration of diffusive proteins (Row 1 and 2) on evolving membrane surface (Row 3 and 4) in a $[-\pi, \pi]^3$ domain with $64 \times 64 \times 64$ uniform mesh. The diffusive proteins prefer a negative curvature $C_0^{\text{pro}} = -0.5$ and the background lipids prefer the curvature $C_0^{\text{lip}} = 0.0$. Times shown are $t = 0, 0.2, 0.5, 1.0, 5.0$, and 8.0 . The membrane surface is shown as the cross-section of the phase field function ϕ at plane $y = 0$.