Phase field calculus, curvature-dependent energies, and vesicle membranes*

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Abstract

Lipid bilayer vesicles are membranes formed spontaneously in aqueous environment under suitable conditions. They have been extensively studied in the literature as a simple model of cell membranes. In this work, we discuss some recent development in the phase field modeling and simulations of vesicles. We describe how the equilibrium and dynamic properties of the vesicles can be effectively described by the phase field calculus which is a natural translation of the energy variations with respect to the vesicle geometry to the variations of the corresponding diffuse interfacial energy with respect to the phase field functions. We also illustrate how phase field techniques can be generalized to model a multi-component vesicle, a vesicle interacting with a surrounding fluid and the adhesion of a vesicle to a substrate.

Keywords: Diffuse interface, phase field, curvature, vesicle deformation, vesicle fluid interaction, vesicle substrate adhesion

1 Overview

Interfaces and defects are ubiquitous in nature and they may take on different forms in different materials and can be studied on different spatial and time scales. One of the popular approaches used to study interfaces and defects on the continuum level is the general Landau formalism [85] where the physical state is described by one (or more) smoothly defined order parameter(s) ψ which takes on nearly constant values except in a thin layer or small neighborhood surrounding the interfaces and defects, together with a governing free energy $E = E(\psi)$ which incorporates the relevant physics. Such a formalism dates back to the work of van der Walls in 1893 on the gas-liquid interface, and over the years, it has been successfully applied to study many problems that involve various interfaces, defects and phase transitions. The formalism is now commonly called a phase field or diffuse interface approach (two terms that we use interchangeably in this paper). Examples of this formalism include celebrated works like the Cahn-Hilliard diffuse interface theory of phase transition [17, 28], and the Ginzburg-Landau model of superconductivity [38, 124], as well as more recent high-order extensions such as the phase field crystal models [52] and

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phase field models of fluid vesicle membranes [44]. The latter is the focus of this review. We begin with a brief introduction to the background of vesicle membrane modeling and the geometric and analytic ingredients in the phase field calculus. We then discuss the phase field modeling and simulations of single component equilibrium vesicles, followed by the extension to multi-component vesicles. Afterwards, we present phase field models for vesicle-fluid hydrodynamic interactions and vesicle-substrate interactions. Issues related to the topological transformations of vesicles and the Gaussian curvature contributions are also explored. There are surely more works on the phase field modeling of vesicle membrane yet to be carried out, in order to provide more quantitative validations of the models and to develop more effective and predictive simulation tools for practical applications; some of these important issues and related questions are discussed in the final section of this paper.

In this exposition, while we attempt to include the significant contributions from different groups, it should be said that the works discussed here are certainly more biased towards those we are more closely involved in. Indeed, even though the subject of phase field modeling and simulation of vesicle membranes is relatively new, it has been attracting more and more attention in recent years and this review provides at best a partial account. We refer to [2, 8, 18, 19, 20, 21, 27, 40, 41, 42, 43, 44, 45, 47, 48, 50, 51, 53, 61, 62, 63, 66, 72, 73, 77, 78, 89, 90, 120, 132] for more details on relevant studies and additional references.

2 Phase field calculus and diffuse interface modeling

A well known example of the diffuse interface (phase field) approach is the diffuse interface description of material interfaces developed by Cahn and Hilliard [17] for phase transition problems. We refer to [3, 28, 54, 121] for related reviews.

In a typical diffuse interface description of a material interface, a smoothly defined phase field function (or order parameter) ψ is used which takes on two nearly constant values, say ± 1 for illustration, away from the interface on its two different sides, and exhibits a smooth but more significant variation within a thin *diffuse transition layer* containing the the interface. The thickness of the transition layer is typically characterized by a small positive parameter ϵ) and the surface Γ is recovered as a particular level set of ψ, say $\{\psi(x) = 0\}$, see Figure 1.

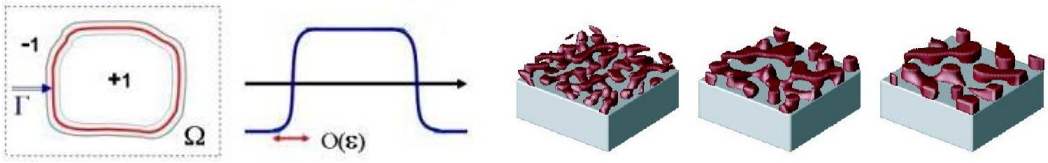

Figure 1: An interface Γ with a *thin* diffuse interface layer, a typical one-dimensional phase field profile, and a phase field simulation of thin film microstructures on a substrate [134].

To construct a diffuse interface or phase field model of the interface, a key question to be answered would be: how can one use such a function ψ to represent the geometric features and physical properties associated with the interface Γ? Let us consider the geometric features for the moment, and in the simplest case, they may involve the enclosed volume of the interface and possibly the surface area. For the phase field descriptions of such quantities, the answers are well-known [17]. For example, as $\epsilon \to 0$, the functional

$$\mathcal{E}_\epsilon(\psi) = \int_\Omega \left(\frac{\epsilon}{2} |\nabla \psi|^2 + \frac{1}{4\epsilon} (|\psi|^2 - 1)^2 \right) d\Omega \tag{1}$$

approaches to a constant multiple of the surface area of Γ (in the sense of Γ-convergence) [16, 56, 96]. Contributions of other energies may also be incorporated, such as the anisotropic interfacial energy and the bulk misfit elastic energy [79, 137]. It is then of both theoretical and practical interests to study the structures of phase field functions which minimize the various forms of the energy functionals under different constraints, and/or their dynamic behavior as they evolve in time via some forms of a gradient system (that is, steepest-descent dynamics) of the energy or through the interaction with other external systems. The equilibrium phase field function is determined by the Euler-Lagrange equation of (1) and in the unconstrained case, it leads to

$$\delta\mathcal{E}_\epsilon(\psi) = -\Delta\psi + \frac{1}{\epsilon^2}(|\psi|^2 - 1)\psi = 0\,, \tag{2}$$

where $\delta\mathcal{E}_\epsilon(\psi)$ denotes the variation of the energy with respect to the function ψ. Meanwhile, well-known representatives of the associated dynamics include the Allen-Cahn (Ginzburg-Landau) equation,

$$\eta\psi_t = \Delta\psi - \frac{1}{\epsilon^2}(|\psi|^2 - 1)\psi \tag{3}$$

for a time relaxation parameter η, and the Cahn-Hilliard equation:

$$\eta\psi_t = -\Delta\Big(\Delta\psi - \frac{1}{\epsilon^2}(|\psi|^2 - 1)\psi\Big)\,, \tag{4}$$

as well as hydrodynamic systems of coupled phase-field Navier-Stokes equations [71, 47]. In application, these diffuse interface (phase field) models represent various different dynamics, for example, the Allen-Cahn equation can be used to describe the order-disorder kinetics or so-called Model-A dynamics of a non-conserved variable, while the Cahn-Hilliard equation can describe the kinetics of spinodal decomposition and it is also called Model-B dynamics of a conserved variable [68].

There have been many works in the last fifty years related to the various extensions of diffuse interface theory and their applications. We again refer to the reviews cited earlier for surveys on many of these studies.

Recently, the phase field diffuse interface framework has also been extended to model interfaces governed by curvature dependent energies, such as the lipid bilayer vesicles which are basic models of cell membranes. Cellular membranes change conformation in striking ways during many important biological processes as movement, division, and vesicle trafficking [91, 92]. A crucial feature describing such changes is given by the membrane curvature which is now viewed as an active means to create membrane domains and to help inducing biological signaling [92]. Given the fluid-like behavior vesicle membranes, an important energetic term entering a continnum mechanics description of a vesicle surface is the bending elastic energy, formulated by by Canham, Evans and Helfrich [22, 67, 88, 103] as:

$$\mathcal{E}_H = \int_\Gamma \Big(\frac{b}{2}(H - c_0)^2 + cK + \sigma\Big)\, ds, \tag{5}$$

where Γ is the surface representation of the vesicle, σ denotes the surface tension, b and c are the bending rigidities which are usually on the order of some tens of k_BT for phospholipid bilayers, H and K are the the mean and Gaussian curvatures of the surface Γ, and c_0 is the spontaneous curvature (which may also be modeled by the area difference elasticity) [43, 95].

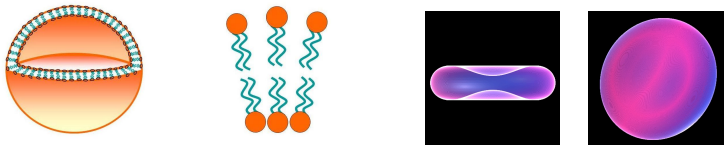

Figure 2: A bilayer vesicle assembled by amphiphilic molecules, and a computed equilibrium vesicle configuration in the shape of a discocytes [44].

As a simple illustration, let us take the case $c_0 = c = 0$ in (5) and consider only the contribution of the mean curvature energy term:

$$\mathcal{E}_b = \int_\Gamma H^2 \, ds \,. \tag{6}$$

Rather than using a coarse-grained MD approach [31, 32, 93, 100] or taking an explicit sharp interface geometric description [10, 12, 57, 103, 129], following the Landau formalism, we developed a phase-field/diffuse-interface bending energy model in [44] by exploring the intrinsic connections between the *geometric calculus* and the corresponding *phase field calculus*. We note that the Ginzburg-Landau formalism has been used to study the properties of lipid bilayers in many contexts, see for example, [64]. Our focus here is on its application to the curvature dependent energies.

Our starting point is the well-known connection between the energy functional $\mathcal{E}_\epsilon$ in (1) and the interfacial area/surface tension in the sharp interface limit, that is, as $\epsilon \to 0$. Moreover, we also know that geometrically, the variation of interfacial area is related to the mean curvature of the surface [16, 29, 56, 96]. Thus, motivated by the following diagram:

$$\begin{array}{ccc} E(\psi) = \displaystyle\int_\Omega \Big(\frac{\epsilon}{2}|\nabla\psi|^2 + \frac{1}{4\epsilon}(|\psi|^2-1)^2\Big) d\Omega & \xrightarrow[\epsilon\to 0]{\Gamma\text{–convergence}} & \text{Surface area } \; B = \displaystyle\int_\Gamma d\,\Gamma \\ \text{variation}\big\downarrow \text{ of } \psi & & \text{variation}\big\downarrow \text{ of } \Gamma \\ \dfrac{\delta E}{\delta \psi} = -\epsilon\Delta\psi + \dfrac{1}{\epsilon}(|\psi|^2-1)\psi & \xrightarrow[\epsilon\to 0]{\text{at } \{\psi=0\}\to\Gamma} & \text{Mean Curvature } \; \frac{\delta B}{\delta \Gamma}\cdot\vec{n} = H \end{array}$$

that reveals the connection between the geometric and the phase field descriptions, it is plausible that the functional

$$\mathcal{E}^b_\epsilon(\psi) = \frac{b}{2\epsilon}\int_\Omega \left(\epsilon\Delta\psi + \frac{1}{\epsilon}\psi(1-\psi^2)\right)^2 \, d\mathbf{x} \tag{7}$$

is consistent to (6) as $\epsilon \to 0$ (up to a constant multiple $4\sqrt{2}/3$ [42, 104], which is neglected here for simplicity). We note that the Gaussian curvature term in (5) is related to the Euler number whose diffuse interface formulation [46] will be discussed later.

The variational problem of minimizing the phase field bending energy (7) is first described in [44], which is another variant of the Ginzburg-Landau formalism. Based on the analysis in [42, 104, 130], we also have the following diagram in connection with the sharp

interface limit:

$$\mathcal{E}_\epsilon^b(\psi) = \frac{1}{\epsilon}\int_\Omega \left(\epsilon\Delta\psi + \frac{1}{\epsilon}\psi(1-\psi^2)\right)^2 d\Omega \quad \xrightarrow[\epsilon\to 0]{\Gamma-\text{conv.}} \quad \text{Bending energy } \mathcal{E}^b = \int_\Gamma H^2 d\Gamma$$

$$\text{variation}\downarrow \text{ of } \psi \qquad\qquad \text{variation}\downarrow \text{ of } \Gamma$$

$$\begin{array}{l}\delta\mathcal{E}_\epsilon^b(\psi) = \epsilon\triangle f - \frac{1}{\epsilon}(3\psi^2-1)]f \\ \text{where } f = \triangle\psi - \frac{1}{\epsilon^2}(\psi^2-1)\phi\end{array} \quad \xrightarrow[\epsilon\to 0]{\text{at } \{\psi=0\}\to\Gamma} \quad \begin{array}{c}\text{Willmore stress} \\ \frac{\delta\mathcal{E}^b}{\delta\Gamma}\cdot\vec{n} = -\Delta_\Gamma H - 2H(H^2-K)\,.\end{array}$$

One may find detailed calculations on the sharp interface limit of the variational derivatives of the phase field bending energy functional in [130]. The diagram is another successful illustration of the consistency between the *geometric calculus* and the *phase field calculus* which puts the phase field bending energy functional (7) on a solid mathematical foundation.

Given the natural derivation of the phase field energy functional (7), it is no surprise that it has been used in other areas of studies as well. For example, a two dimensional version of the functional has been previously adopted for image analysis applications [25] which traced it back to a conjecture of DeGiorgi [35]. We note also that, there have also been a number of studies on phase field or Ginzburg-Landau type models for nearly flat bilayers where the energy functionals can be viewed as a combination of the energy (1) with a linearization of (7) [64, 105].

3 Equilibrium configurations of single component vesicles

Based on the bending elasticity model, the equilibrium shape of a single component vesicle can be obtained by minimizing (5) subject to a fixed surface area and enclosed volume [103, 111]. Numerical simulations based on minimizing the phase field bending elastic energy (7) have been given in [44, 45], subject to a given surface area imposed by a prescribed value of $B(\psi)$ and a given volume imposed by a prescribed value of the integral of ψ. In the phase field simulations, the interfacial width was taken to be sufficiently small so that the consistency between the computed results based on the phase field models and that based the sharp interface descriptions can be numerically confirmed. The equilibrium shapes are obtained through a gradient flow dynamics associated with the energy (7) subject to both volume and surface area constraints.

A number of well-known equilibrium configurations have been obtained along with a detailed energy bifurcation diagram, see figure 3 for plots of the discocytes and stomacytes. Among the various other computational findings, one that is of particular interest is the phase field simulation which reproduces the non-axisymmetric equilibrium shapes such as the one shown in figure 4, which has been previously studied in [60, 74, 108]. Also shown in the figure is an equilibrium vesicle shape with a high genus, which is easily obtained in the phase field setting since the implicit surface representation allows the simulation of interfaces with different topological structures.

The effect of the spontaneous curvature [113] has been examined within the phase field context as well in [43]. In particular, with c_0 being spatially inhomogeneous, an example with a nonzero spontaneous curvature near two opposite ends of the vesicle is also shown in figure 3. The phase field simulations of the equilibrium shapes provide further evidence to the effectiveness of the diffuse interface modeling approach.

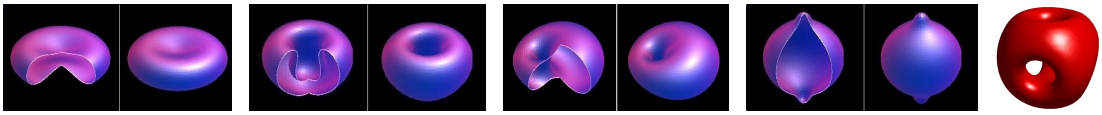

Figure 3: Equilibrium shapes of vesicles: discocytes, stomacytes, non-axisymmetric torus, a vesicle with inhomogeneous spontaneous curvature and a high-genus surface.

Since [44], there have been other studies that were based on the formulation (7) for modeling vesicle bending elastic energy. For example, it has been used in [18] to study both the equilibrium and dynamic shapes of vesicles, much in the same spirit as [44] and [43], but with a local surface area conservation constraint rather than the global constraint adopted by [44]. It is known that for the computation of equilibrium vesicle shapes, the local and global area constraints are in fact equivalent based on the Euler-Lagrange equations for both formulations.

4 Multicomponent vesicles and vesicles with free edges

In recent experimental studies, multi-component vesicles with different lipid molecule compositions (and phases) have been shown to display complex morphology involving microdomains [6, 98]. There is strong evidence suggesting that phase segregation and interaction contribute critically to the membrane signaling, trafficking and sorting processes [119]. Equilibrium shapes of a multi-component vesicle are often described by minimizing an energy that includes elastic bending energy of the membrane and the line tension energy at the interface between the components or a mixing energy [2, 27, 66, 73, 75, 78, 83, 122]. The mixing energy was often given by a natural Ginzburg-Landau free energy expansion with respect to a local composition fluctuation profile, which is like a phase field variable. The strong segregation limit of such a mixing energy is consistent with the formulation given by the line energy. In the last few years, there have also been new studies on the use of phase field models to simulate multicomponent vesicles and the phase separation process [53, 62, 89, 120, 132].

In the phase field model presented in [132] for a two-component vesicle, a pair of phase field functions (ϕ, ψ) was introduced so that one of them would identify the vesicle surface while the other would signify the different phases, which is in the same spirit as level set description of an object with codimension 2 [15]. The equilibrium configurations can be computed by minimizing the total energy subject to a prescribed total volume and the areas (total compositions) of individual components. A number of simulations were performed in [132] to match with the experimental findings reported [6] and to provide numerical evidence for the equilibrium properties of such configurations.

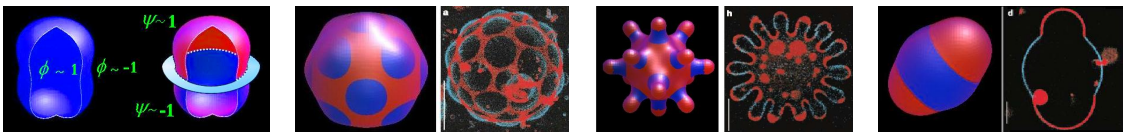

Figure 4: A pair of phase field functions can simultaneously determine both the vesicle surface and the two different phases, and comparisons of some phase field simulation of a twocomponent vesicle in [132] with the experimental observations in [6].

Rather than taking the phase field descriptions of both the vesicle and the individual phases, phase field or Ginzburg-Landau type models have been developed in [2, 27, 73, 78,

93, 123, 122] and also [53, 62, 89, 120] based on a sharp-interface geometric description of the vesicle but with a diffuse interface (phase field) representation of the individual phases. Many interesting results have been obtained. For example, a number of three dimensional equilibrium patterns were provided in [73] for a constant bending rigidity but a composition dependent spontaneous curvature. Working with a near planar geometry, [62] examined the morphological evolution and stability of lipid membranes initialized in a variety of compositional and geometric configurations, and it was also observed that rigid topographical surface patterns have a strong effect on the phase separation and compositional evolution in these systems. Based on two dimensional simulations, it was found in [89] that due to the differences between the spontaneous curvatures and the bending rigidities, the formation of buds, asymmetric vesicle shapes and vesicle fission can take place in two-component vesicles. There are also theoretical analysis available, for instance, careful asymptotic analysis in the sharp interface limit of such type of models has been performed in [53].

It was noted that the phase field method developed in [132] for two-component closed vesicles can be readily applied to model and simulate a single component open vesicle which has been an experimentally and analytically studied subject [24, 107, 125, 126, 128, 133]. A key idea is to include a ghost component which seals the open vesicle, but does not contribute to the total energy. In [132], taking advantage of the effective handling of topological changes by the phase field approach, a number of simulated equilibrium shapes of open vesicles were provided along with comparisons with some experimentally observed shapes.

Figure 5: Comparisons of simulated open vesicles [132] with that observed in experiments in [107] and a sequence of equilibrium shapes showing the closing of the vesicle with increasing line tension.

5 Dynamics of vesicles

The study of the vesicle dynamics has been of much theoretical and practical interests [1, 7, 70, 76, 82, 83, 86, 94, 100, 101, 112]. Naturally, the study of the corresponding phase field models has also attracted the most attention of the community, see [8, 18, 40, 41, 47, 61, 72, 77] on works related to mostly single-component vesicles and [62, 89, 120] for the dynamics of two-component vesicles. As the latter has been discussed in the previous section, we focus on the single-component case here.

The hydrodynamic model developed and analyzed in [41, 47] is of a phase-field Navier-Stokes type, similar to that developed in [14, 71, 87, 135], but with the phase field surface tension energy replaced by the phase field bending elasticity energy:

$$\begin{cases} u_t + u \cdot \nabla u = \mu \triangle u + \nabla p + \delta \mathcal{E}_\epsilon^b(\psi) \nabla \psi \ , \\ \psi_t + u \cdot \nabla \psi = -\gamma A^2 \delta \mathcal{E}_\epsilon^b(\psi) \ , \\ \nabla \cdot u = 0 \ . \end{cases} \tag{8}$$

For convenience, here $\delta \mathcal{E}_\epsilon^b(\psi)$ denotes the variation of the phase field bending elastic energy described earlier, u is the fluid velocity, p is the pressure, γ is a damping parameter which is zero for the pure transport corresponding to a no-slip boundary condition or it can be taken

to be a small positive number with $A^2 = I$ for a nonconserved Allen-Cahn type dynamics or $A^2 = -\Delta$ for a conversed Cahn-Hilliard type dynamics. The system of equations (8) can be derived either from the principle of virtual work or from the least action principle [41, 47]. In the case $\gamma > 0$, the damping term can help stabilizing the numerical simulations [47]. To preserve the volume and surface area constraints, in [41, 47], both Lagrange multiplier and penalty formulations have been suggested.

An immediate consequence of the model derivation given in [41, 47] is that the system (8) enjoys the energy dissipation law given by

$$\frac{d}{dt}\Big(\frac{1}{2}\int_\Omega |u|^2\, d\Omega + \mathcal{E}_\epsilon(\psi)\Big) = -\int_\Omega \Big(\mu|\nabla u|^2 + \gamma|A\delta\mathcal{E}_\epsilon^b(\psi)|^2\Big)\, d\Omega. \tag{9}$$

which, for $\gamma = 0$, is the phase field analog of energy dissipation law in the sharp interface limit:

$$\frac{d}{dt}\left(\frac{1}{2}\int_\Omega |u|^2\, d\Omega + \int_\Gamma kH^2 d\Gamma\right) = -\mu\int_\Omega |\nabla u|^2\, d\Omega.$$

The consistency of the two energy laws has been rigorously established in [47]. Moreover, as $\epsilon \to 0$, it was shown that the term $\delta\mathcal{E}_\epsilon^b(\psi)\nabla\psi$ approaches to the Willmore stress [47]. Preliminary numerical simulations of initially resting vesicles and subsequently transported in a background fluid were presented in [47], see Figure 6 for an illustration. Notice that while topological changes have taken place, the total volume and the surface area has remained constant, so has the Euler number which accounts for the energy contribution from the change in the Gaussian curvature. More numerical studies remain to be carried out, especially in complex flow situations and with a dynamic change in the contribution of Gaussian curvature energy.

Figure 6: An elliptical shaped vesicle is flushed by a fluid jet [47].

Phase field models of vesicles dynamics have also been studied in [18, 19, 20, 21] based on the basic dynamic equations in [18] which is a gradient flow of the phase field energy functional (7). Interesting phenomena involving pearling instabilities and polymer-induced tubulations have been studied. We note that such a gradient dynamic system can also be treated as a special case of the system (8) with $u = 0$ and $A^2 = -\Delta$:

$$\psi_t = \Delta\Big(\epsilon\triangle f - \frac{1}{\epsilon}(3\phi^2 - 1)]f\Big) \;\text{ with }\; f = \triangle\phi - \frac{1}{\epsilon^2}(\phi^2 - 1)\phi\,,$$

which is the H^{-1} gradient flow, or more commonly called the conserved Cahn-Hilliard type dynamics, of the energy functional (7). Following (9), it has a specialized energy dissipation law:

$$\frac{d}{dt}\mathcal{E}_\epsilon(\psi) = -\gamma\int_\Omega |\nabla\delta\mathcal{E}_\epsilon^b(\psi)|^2\, d\Omega = -\gamma\int_\Omega |(-\Delta)^{-1/2}\psi_t|^2\, d\Omega\,.$$

A hydrodynamic phase field model has also been used in [8, 9, 77] with a different phase field formulation. Though named an advected-field approach, the work [9] appears to be the earliest attempt to develop a phase field type hydrodynamic model for vesicles. While there

is no explicit formulation of the phase field bending elastic energy there, the vesicle motion was represented by the advection of the phase field function (with additional damping) and a method was proposed in the two dimensional setting to compute the stress due to the variation of the bending energy. Such a stress calculation is more involved than the Willmore stress formula associated with the phase field elastic bending energy (7). Later in [72], a thermodynamic phase field model was derived for the hydrodynamics of vesicles under the assumption of local membrane incompressibility. An extensive list of simulations have been performed in [8, 9, 77] to study the various motions of the vesicles in a flow environment, including the tank-treading, tumbling, vacillating and breathing modes. More recently, the work of [61] offered a very general derivation of the so called thermodynamically consistent phase field models that covered both the approaches used in [41, 47] and [8, 72, 77].

To model the interactions of an immersed interface in a fluid environment subject to fluctuation forces, a number of approaches have been developed in recent years such as the discrete particle based Brownian dynamics [101], Stokesian dynamics [13] and dissipative particle dynamics [69], interfacial Langevin equations [80], and the stochastic immersed boundary methods [5]. Within the diffuse interface framework, we derived a stochastic implicit interface model (SIIM) for an immersed interface in an incompressible viscous fluid subject to fluctuating forces[39, 40]. For example, for an incompressible viscous fluid in the low Reynolds number regime, if we let u be the fluid velocity, p the pressure, and ψ the phase field function for the immersed interface, then one particular form of the SIIM is given by

$$\begin{cases} u_t - \mu\triangle u + \nabla p = \zeta * (\delta\mathcal{E}_\epsilon^b\psi)\nabla\psi) + F + \dot{f}, \\ \nabla\cdot u = 0\ , \\ \psi_t + (\zeta * u)\cdot\nabla\psi = 0\ , \end{cases}$$

Here, ζ is a spatial averaging kernel which is often used immersed boundary methods, with $*$ denoting the spatial convolution, F is a deterministic body force and $\dot{f}$ is a stochastic force whose particular form obeys the fluctuation dissipation theorem. The deterministic version of the coupled equations is consistent with the least action principle [14]. The energy functional $E = E(\psi)$ can take on a diffuse interface form like (1) or (7) or take on the form used in level-set methods like those given in [26, 33, 102, 117].

6 Vesicle substrate adhesion

Adhesion is a key mechanism for the survival of many cells and organism and it occurs ubiquitously in nature. It is now established that the stem cells differentiate into various cell types including neurons, myoblasts, and osteoblasts depending on the stiffness of the elastic substrate that they adhere to [55]. While the cytoskeletal network within the cell provides the key mechanism for the adhesion to a substrate and sense the stiffness of the substrates [99, 106], investigations also revealed the important role played by cell membranes [115]. Recently, we also extended the phase field bending energy model to account for the interaction of the vesicles with both flat and curved substrates. For a single component vesicle interacting with a substrate Γ_s through an adhesion potential $W = W(\mathbf{x})$ which is a function of the distance between a point $\mathbf{x}$ on the vesicle to the substrate, the total phase field energy then becomes:

$$\mathcal{E}_a(\psi) = \int_\Omega \epsilon\Big[\Big(\Delta\psi - \frac{1}{\epsilon^2}(\psi^2-1)\,\psi\Big)^2 - W(\mathbf{x})\frac{(\phi^2-1)^2}{\epsilon} + G\frac{1-\psi}{2}x_3\Big]d\Omega\ , \quad (10)$$

where G is the gravity constant. A number of different choices of the adhesion potential $W = W(\mathbf{x})$ has been used, including a Gaussian potential and a Leonard-Jones type potential. The phase field formulation is based on sharp interface versions used in many existing studies of vesicle-substrate adhesions, see for example [23, 114, 118]. In the limit when the bending effect becomes negligible the overall vesicle shape approaches to the limiting profile given by the Laplace-Young equation for a soap film with a nonzero contact angle which gives unbounded bending energy. With small but non-zero bending, a boundary layer develops near the contact point where the curvature changes rapidly [34].

To validate the model, in [136], the results of phase field simulations were compared with that obtained by the sharp interface computation. The effect of the substrate curvature on bounding and unbounding transitions has been discussed, similar to the study in [114]. We also used a Gaussian adhesion potential coupled with the gravitational effect to study the interplay between the gravity and the adhesion, which is a subject previously examined in [81]. The phase field numerical simulations presented in Figure 7 show that the gravity pushes down the vesicles to the bottom substrate while stronger adhesion leads to more visible protrusions.

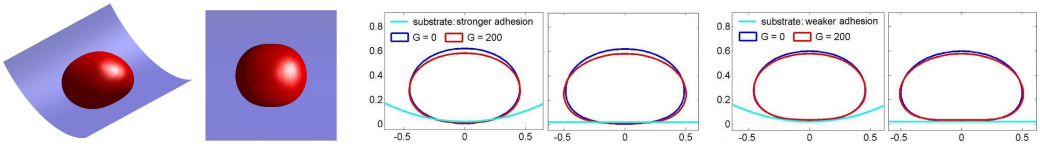

Figure 7: A vesicle adhered to a cylindrical substrate: the three dimensional view (left) and the showing of different cross sections with and without the gravitational effect and subject to stronger and weaker adhesion (right) [136].

In another related work, we studied the effect of adhesion on the phase separation process [138] by extending a phase field formulation for a two-component vesicle [2, 78] to include the effect of an adhesion potential between the vesicle and a substrate. The total energy is of the form

$$E(\eta) = \int_\Gamma \left\{ \frac{b(\eta)}{2}[H - c_0(\eta)]^2 + \sigma_l[\frac{\epsilon}{2}|\nabla_\Gamma \eta|^2 + \frac{1}{4\epsilon}(\eta^2 - 1)^2] \ - w(\eta)P(\mathbf{x}) \right\} \, \mathrm{d}\mathbf{x}$$

with $\eta = \eta(\mathbf{x})$ being the phase field function, ϵ the interfacial width parameter, σ_l a line tension constant, and $P = P(\mathbf{x})$ an adhesion potential as a function of the distance from $\mathbf{x} \in \Gamma$ to the substrate, so that the values of $b(\eta)$, $c_0(\eta)$ and $w(\eta)$ at $\eta = \pm 1$ give, respectively, the values of the bending moduli, spontaneous curvatures and the adhesion coefficients corresponding to the two different phases. Though the formulation remains valid in general, to simplify the computation, we only conducted numerical simulations in the case that both the vesicle membrane and the substrate are axisymmetric in three dimensions. Not only a number of typical profiles were found for equilibrium two-component axis-symmetric vesicles subject to adhesion, numerical experiments have also been conducted in [138] to support the observation of [65] that the adhesion may promote the phase separation of a multi-component membrane.

7 Gaussian curvature, Euler number and Topological transformation

In the Helfrich formulation of the bending elastic energy (5), there is a contribution coming from the Gaussian curvature which is viewed as very important factor in a number of biological processes such as vesicle fusion [116].

For constant Gaussian bending modulus, it is well known that the resulting term is a topological quantity related to the Euler number of the vesicle surface. It is perhaps an intriguing statement that phase field method is not only capable of dealing with complex topological changes of the interfaces given the implicit surface representation, but it is also possible to effectively retrieve topological information from the phase field formulations. This is largely based on the framework of phase field calculus: one can derive a counterpart of the Gauss-Bonnet theorem for surfaces in terms of phase field functions. A perhaps pioneering work in this regard is given in [46] where integral formulae have been presented to show that one can reliably post-process the phase field solutions to recover the so-called phase field Euler number, an approximation to the conventional Euler number of the interface under consideration.

To give an example, we consider a typical phase field function $\psi = \psi(x)$ in the three dimensional space with $\Omega_c = \{x \mid -c < \psi(x) < c\}$ containing level surfaces of similar topology for a suitable parameter c. By defining

$$M(x)_{ij} = \frac{1}{\sqrt{2\pi c|\nabla\psi|}}\left(\nabla_i\nabla_j\psi - \frac{\nabla|\nabla\psi|^2\cdot\nabla\psi}{2|\nabla\psi|^4}\nabla_i\psi\nabla_j\psi\right), \text{ and } G_e = \int_{\Omega_c}\Lambda(M(x))dx \tag{11}$$

with $\Lambda(M)$ being the trace of $(Adj(M))$ which is the adjoint matrix of M. Computationally, it was shown that G_e gives a good approximation to the conventional Euler number in the sharp interface limit. A numerical example is given in Figure 8. The notable changes of computed phase field Euler numbers occur while the vesicles are going through topological transformations. The fractional number values of the Euler number also signify the formation of self-intersecting surface singularities during the merging process even though the phase field function remains smooth during the whole simulation. Recently, we also considered simplified algorithms to retrieve topological information directly from the implicit diffuse interface description [48].

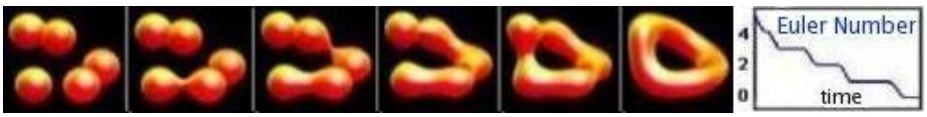

Figure 8: A phase field simulation of a few spherical like vesicles merge into a single vesicle through topological transformation, and the corresponding phase field Euler number computed on-the-fly [46].

8 Conclusions

In this brief review, we discussed how the ideas of phase field calculus can be used as an analog of the standard geometric calculus to develop reliable phase field models for interfaces governed by curvature dependent energies. A particular motivation is the study of the bending elastic energy model for vesicle membranes. Our focus here has been on

the most basic modeling issues and its several applications. There are obviously many important issues that we have not addressed here.

First of all, in applications of the diffuse interface framework, the studies are mostly carried out through numerical simulations [28, 121]. Since a diffuse interface model often gives a single set of equations with regular/smooth solutions in the computational domain, the initial code development is relatively easier, in comparison with its sharp interface counterpart. Yet, the solutions may display large gradients in narrow interfacial regions which raise tremendous challenges to numerical analysts in differentiating and balancing both the modeling and numerical errors [49]. The effectiveness of phase field simulations rely on efficient numerical methods that can resolve the phase field function and other related physical variables. For much of the phase field simulations we have performed, we have utilized both finite element methods and the Fourier spectral methods. The former can work for more general geometry and with more general boundary conditions while the latter is particularly effective for cubic domains with periodic boundary conditions and for simulations that approach the sharp interface limit [131]. We refer to [50, 51, 131, 132] for the implementation and theoretical analysis of these numerical methods, along with their adaptive implementations. With the Moving Mesh Fourier Spectral methods [58, 59], the implementation can offer anisotropic adaptivity which also significantly improves the computational efficiency and stability. For the phase field bending elasticity models, it has also been demonstrated that with isotropic adaptive finite element based on local mesh refinement and coarsening governed by rigorous residual-based *a posteriori* error estimators, the computational cost of a typical three dimensional phase field simulations can be proportional to that of $O(\epsilon^{-2})$ where ϵ is the interfacial width parameter. In comparison, the computational cost on a uniform mesh would be at least of the order $O(\epsilon^{-3})$ [50]. We refer to [50, 58, 59] for more detailed discussions and extensive lists of references on the adaptive methods for phase field simulations. A challenging issue requiring much investigation is the development of efficient anisotropic three dimensional finite element methods for phase field simulations. Meanwhile, quantitative validation of phase field simulations is obviously another important issue that needs to be seriously addressed.

Furthermore, we note that the successful applications of the phase field approach can be expedited with the development of reliable and adaptive methods for not only the numerical solutions but also the information processing from the large scale simulations such as the retrieval of the hidden topological structures and other important statistics. The phase field Euler number provides an example to the fact that it is constructive sometimes to take a contrarian view: while the diffuse interface approach is known to be insensitive to topological changes of the underlying interface, topological features of the interface can be important information for the underlying physical or biological processes which should not be missed. In the phase field community, there have been studies of the topological structures simulated by phase field methods and commonly, they are done by analyzing the reconstructed images of implicitly captured interfaces [84]. The study in [46] shows that it is possible to perform some of these tasks directly from phase field simulations through a numerical integration. Indeed, in the application of phase field modeling to multiphysics, multiscale study of many physical and biological processes, extracting statistics on the interfaces is often a more important task than simply re-constructing their detailed geometric structures. Such a trend reflects the nature of integrated, adaptive and intelligent scientific computation [37].

Finally, on the application of phase field models to the study of vesicles, there are also additional works such as [63] which incorporated the effect of the electromagnetic interactions. While we have discussed phase field models for both the vesicle dynamics and

the vesicle-substrate adhesions, we have not combined them for the study of the dynamic vesicle-substrate interactions in a moving fluid environment. This is certainly a very interesting and challenging topic for future research. There are naturally many other interesting issues related to vesicles where the phase field formulation can become useful such as the study the vesicle fusion due to virus entry [30] and vesicle-mediated particle interactions [31, 97]. Many ideas presented here can also find applications to other related problems. Moreover, the popularity and the amazing *unreasonable effectiveness* (borrowing the words of [4]) of the phase field methods in various applications also signify the need for further mathematical analysis and computational studies.

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