

## PROJECT SUMMARY

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### Overview:

This proposal aims to advance the mathematical modeling of the collective dynamics of amphiphilic particles, with main focuses on their self-assembly, fusion and fission of amphiphilic bilayer membranes, and optimal shape designs for specific functions. The self-assembly of amphiphilic molecules (such as lipids) in solvents has inspired fabrication of amphiphilic nanoparticles that spontaneously aggregate to form building blocks (such as bilayers or micelles) for smart materials. To better design these building blocks for precise smart material fabrication, it is imperative to quantify the physical processes that underpin the collective dynamics of amphiphilic particles, and how their interactions affect the fusion and fission of bilayers amphiphilic particles. Novel mathematics (PI-Ryham), multiscale physical models (PI-Young) and fast numerical schemes (co-PI Jiang) will be developed to quantitatively describe the collective hydrodynamics of amphiphilic particles. The PIs hypothesize that hydrophobic interactions give rise to several mechanical properties of the amphiphilic bilayer. The proposed mathematics establishes a platform for efficiently simulating the collective amphiphilic dynamics at large scales to allow for direct comparison with pre-existing theory and experimental measurements.

### Intellectual Merit:

A central theme of the project is the mathematical development and analysis of the physical model for interaction between many amphiphilic particles. The model formulates the interaction potential through a screened Laplace equation boundary value problem possessing the physical properties, like non-additivity and long-range decay, of realistic hydrophobic attraction. Colloidal systems collectively self-assemble into bilayer morphologies, and we analyze the elastic properties of these amphiphilic particle assemblies. This allows us to interpret the Helfrich free energy in terms of specific molecular characteristics, and broadens the possible morphological transitions beyond what was capable by current methods. We extend the capabilities of the quadrature by expansion method from the theory of boundary integral equations to perform large particle number simulations in three dimensions with collisions. Results from these computations will be used to compare collective amphiphilic behavior against experiment, and study the optimal design of functional materials.

### Broader Impacts:

The proposed mathematical analysis and modeling will provide a transformative understanding of the collective dynamics of amphiphilic particles such as (1) their self-assembly into micelles and bilayers, and (2) the interaction between these building blocks. Amphiphilic Janus particles have gained increasing popularity for fabrication of smart materials. The proposed hybrid continuum model, mathematical analysis and numerical algorithms will have transformative impact on precision design for specific mechanical properties of materials made of amphiphilic nanoparticles. An important component of this proposal is the interdisciplinary education and training of both undergraduate and graduate students. The combination of mathematical modeling, analysis and scientific computing in this project provides a compelling example of the importance of mathematics in biophysics and engineering applications. The concepts and methods described here go beyond the context of amphiphilic particles and lipid molecules. They extend to other problems featuring microscopic phase separation that leads to formation of mesoscopic domains. This situation arises, for example, in biological development in systems biology. The methods developed here have the potential to impact those and other related areas in biomedicine and biotechnology.

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# **Collaborative Research: Mathematical modeling and coarse-grained simulations of self-assembly of amphiphilic Janus particles in a solvent**

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*Shidong Jiang (co-PI, NJIT) and Yuan-Nan Young (PI, NJIT)*

## **1 Background**

### **1.1 Hydrophobic Forces**

The hydrophobic force is a ubiquitous molecular interaction in biology [93]. The word hydrophobic (water fearing) derives from the low solubility of oil (hydrocarbon solute) in water and vice versa. It causes hydrophobic moieties to aggregate and cluster, is responsible for the adhesion between hydrophobic surfaces [52], large contact angles on a dewetting surface [8, 178], accumulation of particles along interfaces [125, 126], formation of micelles and bilayers [95], and protein folding and membrane insertion [106].

Lipids are amphiphilic molecules whose structure possesses both hydrophobic and hydrophilic parts. The amphiphilic property is what allows lipids to form the membranes and compartments of living cells [95]. More specifically, a lipid consists of an elongated hydrocarbon tail that is hydrophobic, attached to a polar head that is hydrophilic. To shield the hydrophobic tails from water, lipids self-assemble into micelles and bilayers. A micelle is a spherical arrangement of lipids with tails terminating at the micelle center. A bilayer consists of two layers of lipids called monolayers, where the lipid tails point from the monolayer surface into the bilayer core.

The mathematical modeling of a biological membrane is a challenging problem in applied mathematics. Bilayers are elastic and resist deformations like bending, twisting, and stretching. Their elastic deformations are well described by the theory of liquid crystals [6]. Lipid bilayer membranes can also be fluidic, and the lateral translation of lipids (or any membrane bound proteins) couples nonlocally to the motion of the aqueous environment [144, 157, 158, 190].

There are two prevailing approaches in membrane modeling, and each has its advantages and disadvantages. Molecular dynamics (MD) is to date the only tool capable of resolving granular biological details. The computational cost of MD, however, grows with the sixth power of the sample diameter and so simulations are severely limited to small system sizes and short time scales [42]. The other approach, continuum mechanics, assumes smooth surfaces and can therefore model realistic systems over physical times. But continuum description of a biological membrane ignores the granularity of lipid molecules, and thus requires some assumptions when a membrane ruptures or when two membranes fuse [36].

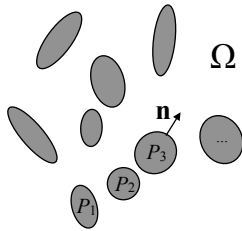
Recently the PIs developed a mathematical model called the hydrophobic attraction potential (HAP) [64]. This model addresses the major shortcomings of MD and continuum approaches, and will hopefully offer an alternative modeling methodology that leads to new mathematical ideas and is both physically accurate and computationally practical.

The hydrophobic force arises when polar solvent molecules come in contact with a non-polar substance, such as hydrocarbon or vapor. In a polar solvent (like water), the dipole-dipole interaction between solvent molecules form a loosely structured hydrogen-bond network where each solvent molecule shares bonds with neighboring molecules at any given time [93]. In the presence of a non-polar solvent molecule loses the ability to form hydrogen bonds in one direction. The decrease in the number of hydrogen bonds causes a reorientation, or structural change, in the surrounding water that is energetically very unfavorable [21].

The substantial free energy for placing hydrophobic substances in contact with water is roughly proportional to the surface area of the contact region. As a result, hydrocarbon solutes have a large interfacial tension and try to minimize their surface area when in water. At the microscopic level, however, the hydrophobic force is a long-range, surface interaction. This means that two hydrophobic surfaces, separated by water over some distance, experience an attractive force [80, 135, 145]. Measurements show that the hydrophobic force decays exponentially with a decay length like 1 nm [38, 94, 131, 138]. It is also known that the interaction is not pairwise additive, meaning that the force between any two hydrophobic objects is altered by the presence of a third object.

As a summary of its mathematical properties, the hydrophobic force is a non-additive, exponentially decaying surface force that possesses a separation of length scales. These properties suggest a boundary value problem formulation of the hydrophobic force. The non-additivity of the hydrophobic force has to do with the fact that there is no superposition principle for including subdomains in boundary value problems. The exponential decay is a property of a second order elliptic partial differential equation (PDE). Finally, the separation of scales come from boundary layers, where the energy of the boundary layer in the zero-thickness limit corresponds to macroscopic interfacial tension. Overlapping boundary layers correspond to microscopic hydrophobic attraction, and the boundary layer thickness corresponds to the decay length of attraction.

## 1.2 Hydrophobic Attraction Potential (HAP)



**Figure 1.** The exterior domain  $\Omega$  is the solvent region surrounding a number of rigid particles  $P_1, P_2, P_3, \dots$ . The surface  $S$  is the solvent-particle interface, indicated by the unit normal  $\mathbf{n}$ .

Based on the physical origin of hydrophobicity, we have devised a functional, called the hydrophobic attraction potential (HAP), to model hydrophobic forces [65]. The motivation for HAP concept stemmed from the lead PI's earlier work on the problem of energy barriers in membrane fusion [162, 175]. There, the lead PI and collaborators resolved the long-standing issue of accounting for the energy of a fissure surface during topological transitions, by applying a squared gradient mathematical theory for hydrophobic attraction between planar surfaces [55, 135, 138, 143] to monolayer fissures. Based on the PI Young's coarse-grained membrane modeling work [63], the investigators initiated a collaboration to create a gradient theory for arbitrary collections of hydrophobic and amphiphilic particles. This new method eliminates the costly calculation of water by treating the solvent implicitly, and avoids complicated re-meshing schemes of continuum approaches by utilizing a particle-based representation.

To define HAP, consider a region  $\Omega \subset \mathbb{R}^3$  modeling the solvent surrounding a number of particles (Figure 1). As stated earlier, the HAP must be an energy of the shape of the region because hydrophobic attraction is non-additive. The boundary of the region is the water-particle interface and some parts of this surface are hydrophobic while others are hydrophilic. Monte Carlo simulations show that water changes structure at hydrophobic interfaces [104, 136, 194]. Due to rapid fluctuation in the hydrogen bond network, restructuring at the interface extends into bulk water. This motivates the following definition for the HAP of the particles:

$$\Phi = \gamma \iiint_{\Omega} \rho |\nabla u|^2 + \rho^{-1} u^2 dx dy dz, \quad (1)$$

where  $u$  is the unique solution of screened Laplace equation boundary value problem

$$-\rho^2 \Delta u + u = 0 \in \Omega, \quad u = f \text{ on } \partial\Omega, \quad u(x) \rightarrow 0 \text{ as } x \rightarrow \infty. \quad (2)$$

The scalar function  $u(x)$  is called the water activity. Its boundary values  $f$  define the degree of hydrophobicity of the water-particle interface. The value 1 represents a completely hydrophobic interface, where water has lost rotational freedom. Conversely, the boundary value 0 corresponds to a polar surface where water has the same rotational freedom as in bulk water. The parameter  $\rho$  is the decay length of attraction, around 1 nm, and the parameter  $\gamma$  is the interfacial tension [93]. The parameters  $\rho$  and  $\gamma$  contain information about the quality of the solvent [44].

From a phenomenological perspective, (1–2) is an appropriate model of hydrophobic attraction. Specifically, using boundary layer analysis, it is possible to show that  $\Phi$  converges to a surface energy in the zero-decay length limit [124, 130, 183]. For non-zero decay lengths, solutions of (2) yield an attractive interaction, e.g. between hydrophobic parallel disks separated by water [55]. Also, we have demonstrated with simulation that the forces derived from HAP theory are non-additive, and even deviate significantly from a pairwise potential [65, 145].

## 2 Previous Results by the PIs

In our paper [65], we developed the model (1–2) to quantify the macroscopic assembly and mechanics of a lipid bilayer membrane in solvents. To define the particle dynamics, we considered the exterior domain  $\Omega$  for a finite number of disjoint, rigid and closed particles  $P_1, P_2, \dots, P_n$ , each with Lipschitz boundary, and boundary data  $f$  in the Sobolev space  $H^1(\Omega)$ . For any fixed configuration, the functional (1) has a unique minimizer  $u$  among all  $u - f$  with vanishing trace. This minimizer is a solution to (2). Conversely, from maximum principles and energy estimates, any solution of (2) is the minimizer of (1), and this supplies  $\Phi$  with a well-defined value.

The main analytical tool of our manuscript is a formula for the first variation of  $\Phi$  [11, 77, 179]. This first variation is a symmetric, rank-two tensor called the hydrophobic stress;

$$\boldsymbol{\sigma}_{\text{hydro}} = \gamma \rho^{-1} u^2 I + 2\rho \gamma \left( \frac{1}{2} |\nabla u|^2 I - \nabla u \nabla u^T \right). \quad (3)$$

To obtain (3), we observe that the potential  $\Phi$  is a function of the particle position and orientations. This is because the particle configuration defines the shape of  $\Omega$  and the boundary data  $f$ . Taking the derivative of (1) with respect to particle configurations, and using the boundary value problem (2) in a critical way leads to the surface term (3). By integrating the hydrophobic stress over the surface of particle  $P_i$ , we obtaining the hydrophobic force and torque on each particle

$$\mathbf{F}_i = \iint_{\partial P_i} \boldsymbol{\sigma}_{\text{hydro}} \cdot \mathbf{n} dS, \quad \mathbf{T}_i = \iint_{\partial P_i} \mathbf{x} \times (\boldsymbol{\sigma}_{\text{hydro}} \cdot \mathbf{n}) dS. \quad (4)$$

We verified that this system is force and torque free. To supply viscous dissipation, we incorporated the mobility problem in Stokes flow to obtain the rigid body motions;

$$\begin{aligned} -\mu \Delta \mathbf{u} + \nabla p &= 0, \quad \text{in } \Omega, & \nabla \cdot \mathbf{u} &= 0, \quad \text{in } \Omega, \\ \mathbf{u}(\mathbf{x}) &\rightarrow 0 \quad \text{as } |\mathbf{x}| \rightarrow \infty, & \mathbf{u}(\mathbf{x})|_{\partial P_i} &= \mathbf{v}_i + \boldsymbol{\omega}_i \times (\mathbf{x} - \mathbf{a}_i), \\ \int_{\partial P_i} \boldsymbol{\sigma} \cdot \mathbf{n} dS &= -\mathbf{F}_i, & \int_{\partial P_i} (\mathbf{x} - \mathbf{a}_i) \times (\boldsymbol{\sigma} \cdot \mathbf{n}) dS &= -\mathbf{T}_i. \end{aligned} \quad (5)$$

Here  $\mu$  is the fluid viscosity and the first two equations state that the fluid motion is a divergence-free Stokes flow; the third equation specifies the fluid velocity at infinity; the fourth equation enforces a rigid body motion constraint on each particle, where  $\mathbf{v}_i$  and  $\boldsymbol{\omega}_i$  are unknown translation and angular velocities of the  $i$ -th particle and  $\mathbf{a}_i$  is the center of mass of  $P_i$ ; the last two equations state that the net forces and torques on each particle are given by the quantities  $\mathbf{F}_i$  and  $\mathbf{T}_i$  from (4), and  $\boldsymbol{\sigma}$  is the fluid shear stress.

The time integration of particle configurations goes as follows: **(i)** solve the BVP (2) for the screened Laplace equation, **(ii)** determine the rigid body forces and torques (4), **(iii)** solve the Stokes mobility problem (5) for rigid body motion, **(iv)** update the particle configuration. §4.2, addresses the numerical challenges in evaluating (3) and how these challenges are overcome.

Our simulations used Janus particles to model lipid amphiphiles. Janus particles are a popular tool in material science and physics for creating functional materials [125, 126]. This topic is the basis of Specific Aim 3. Janus particles are typically spherical with a biphasic material label on either hemisphere, endowing the particle with a directional order. We considered a two-dimensional system, and represented an elongated lipid by elliptical particles with hydrophobic and hydrophilic labels along the ellipse’s long axis.

Under the hydrophobic force, and with an excluded volume to prevent collisions, the Janus particles spontaneously merge and realign to form bilayers. This occurs only as a result of energy minimization and does not require artificial inputs. To our knowledge, this is the first demonstration of bilayer self-assembly by a continuum hydrophobic interaction model [23, 28, 56, 156, 202].

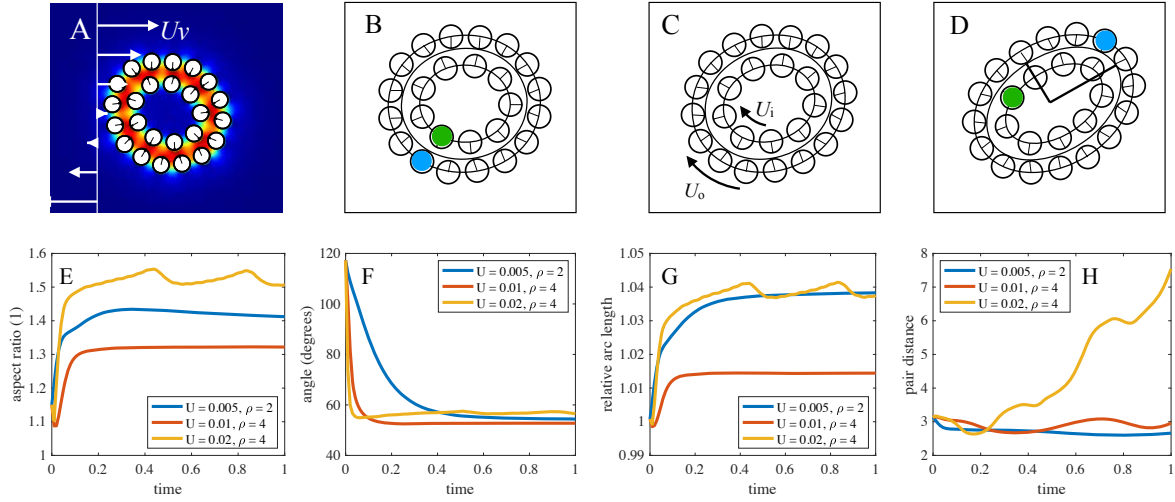
It is worth emphasizing that the model uses only a few parameters; interfacial tension, decay length, repulsion strength and particle shape. For example, an elastic modulus for stretching a vesicle derived from micropipette manipulation directly calibrate our interfacial tension parameter. MD simulators have also made measurements and lately there is better and better agreement with reality. But even the simplest coarse grained models based on pair potentials for lipids has many more parameters [194, 202] .

As a proof of concept, our work has already tested for elastic energies for bending, stretching and tilt of the bilayer assembly. Extracting coefficients from the HAP simulations showed strikingly positive agreement with experimentally determined values [65]. Encouraged by these results and the hydrodynamic simulations of the bilayer assembly, the PIs propose to further extend the HAP model and the numerical schemes (see §4) to make direct comparison with experiments, the continuum liquid crystal results and MD simulations results, to establish that the HAP model has the capability and adaptivity to model phenomena across length scales and time scales.

### 3 Preliminary Work on Two-dimensional Vesicle Hydrodynamics in Shear Flow

Over the past decades, researchers have used a number of mathematical tools to model vesicles in shear flow, including phase field [19, 47], level set [45], boundary integral [169, 195] and immersed boundary approaches [92, 111, 112]. All these approaches assume a mathematical surface, whether implicitly or explicitly, and define an elastic bending energy of the surface. The vesicle obeys fluid transport and in turn the fluid balances shear stress with the vesicle’s bending force.

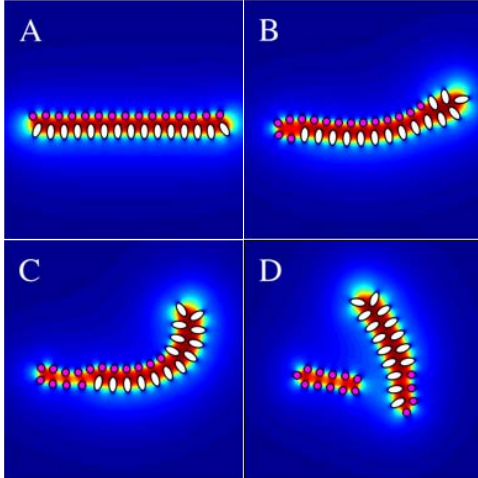
Our HAP approach differs from prior methods in a number of respects. First, we do not assume a surface. Rather, we more fundamentally consider a collection of amphiphilic particles. The collection of amphiphiles minimize hydrophobic interactions by sequestering hydrophobic tails in the form of a bilayer, and the particles’ excess free energy gives rise to an elastic bilayer energy.



**Figure 2.** (A) A vesicle formed by amphiphilic particles in shear flow, and the tank-treading motion (B)–(D). The separation of particle pairs in (B) and (C) illustrate inter-leaflet slip. (E) – (G) Tank-treading reaches a steady state in elliptical aspect ratio, major-axis angle, and circumference.

The second difference lies in the fluid-interface coupling. Here, the associated mobility problem (5) is more complicated than dealing with a stress boundary condition or diffusive surface force, because the fluid velocity must be that of a rigid body motion at the particle surfaces.

To implement a vesicle in shear flow in the context of hydrophobic potentials and mobility problem, we consider a shear flow  $\mathbf{u}_\infty = Uy\mathbf{i}_x$  in the direction of the  $x$ -axis (Figure 2A). This field satisfies the linear Stokes system but does not give rise to a rigid motion at the particle interfaces. To have a rigid motion, we change variables  $\mathbf{u} = \tilde{\mathbf{u}} + \mathbf{u}_\infty$  and for the new field  $\tilde{\mathbf{u}}$  vanishing at infinity we let  $\tilde{\mathbf{u}}|_{\partial P_i} = \mathbf{v}_i + \boldsymbol{\omega}_i \times (\mathbf{x} - \mathbf{a}_i)$  where  $(\mathbf{v}_i, \boldsymbol{\omega}_i)$  are the unknown translation and angular velocities of the  $i$ th particle  $P_i$ .



**Figure 3.** An initial assembly of small and large particles spontaneous segregates into two smaller bodies.

The HAP simulations show vesicle tank-treading. Under the external shear flow, the initially circular vesicle rotates in the clockwise direction. As the rate of rotation increases, the vesicle approaches a steadily tank-treading ellipse. In Figure 2B-D, the solid curves are ellipses fit to the particle centers and midplane respectively. In the non-dimensionalized system, the particles have diameter 2, on the order of  $\rho$ , and the vesicle diameter is about 14. Figure 2E shows the aspect ratio of the major to minor axes reaching an equilibrium value in the red and blue curves, yet oscillating in the high-shear rate (yellow) curve. The tank-treading vesicle elongates and becomes more horizontal with an increase in flow rate or with a decrease in stiffness (effected by decreasing  $\rho = 4$  to  $\rho = 2$ ).

For large shear flow rates, there is an increase in arc length. Here arc length refers to the the mid-plane circumference. Thus, some of the external force is going into



stretching the vesicle—the other part is going into bending and viscous dissipation. From our experiments, we find that the vesicle ruptures once stretching exceeds about 5 % (see Figure 4). Finally, movies of the tank-treading motion show a slip velocity between the outer and inner leaflets Figure 2G. We have illustrated this by tracking the distance between two reference particles in the inner and outer leaflet (Figure 2B & D, green and blue particles). With moderate shear rates or greater adhesion, the particle pair moves in tandem (in Figure 2H, blue and red curves, their distance is more or less constant). For a large shear rate, the particle separates as the two leaflets slide against one another.

There are a number of advantages to using our particle based approach. For one, the HAP theory automatically accounts for the existence of multiple phases. For example, we can vary lipid length, spontaneous curvature and bending rigidity by introducing differentiating particle shapes and hydrophobic boundary conditions (Figure 3). Continuum theory deals with multiple phases through additional surface densities that must then satisfy specialized transport equations [134, 146]. As illustrated in Figure 2, the particle based approach supports inter-leaflet slip, and this can be used to determine inter-leaflet and in-plane shear viscosities.

The ability to form discontinuities is perhaps the HAP method’s greatest strength. Indeed, a strong, extensional shear flow must cause membrane rupture since the energy of stretching must exceed the pore nucleation and widening barriers for sufficiently large flow strengths. Some disadvantages are that the hydrophobic interaction does not constrain vesicle volume. Instead, changes in volume are rate limited by inter-particle spacing, which may be undesirable in case of a mathematically strict volume constraint.

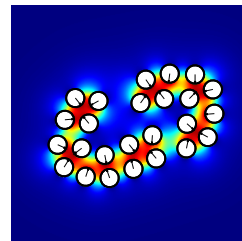
In recent years, researchers have developed a number of numerical methods for calculating energy minimizing steady equilibrium shapes of lipid bilayer membranes, vesicles and red blood cells. These approaches range from the finite element method [15, 163, 175, 188], phase field method [46, 49, 82] to immersed boundary method [90, 91, 110]. PI Ryham and collaborators led in part the development of phase field functionals of membrane elastic energy and approaches to coupling membrane elasticity to fluids [48–51].

## 4 Proposed Research

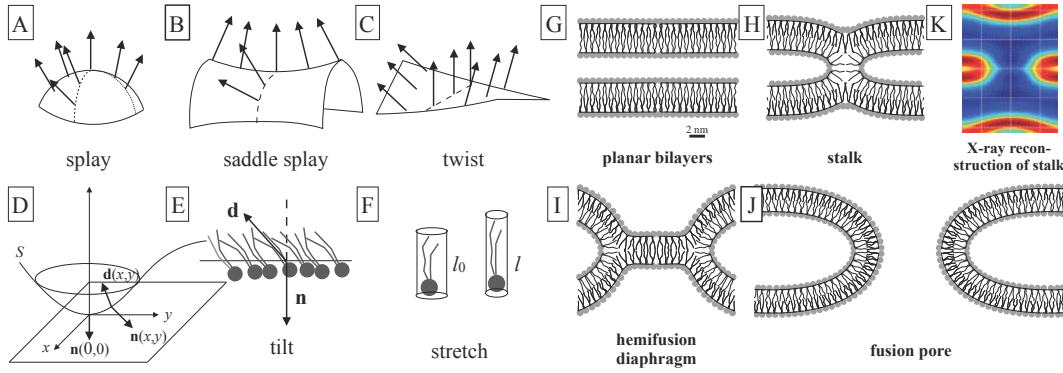
The goal of the proposed research is to develop fast, high-order-accurate, parallel numerical algorithms for large-scale simulations of the collective hydrodynamics of amphiphilic particles in a viscous solvent. We have demonstrated that our potential theory approach can efficiently simulate self-assembly of amphiphilic particles into two-dimensional micelles, bilayer membranes, and vesicles [65]. While these results show great potentials in simulating the collective hydrodynamics of amphiphilic particles and reproducing mechanical properties of their bilayer assembly, several outstanding issues need to be addressed for such approach to be efficiently applied to three-dimensional collective hydrodynamics of amphiphilic particles.

### 4.1 Specific Aim 1: Elastic properties of amphiphile ensembles

We conjecture that once assembled, the bilayer shapes possess some or all of the mechanical properties of bilayers from continuum theory.



**Figure 4.** Rupture of tank-treading vesicle under strong shear flow.



**Figure 5.** (A–C) The splay ( $\text{Div } \mathbf{d}$ ), saddle splay ( $\det D$ ) and twist ( $\text{Curl } \mathbf{d}$ ) elastic distortions of a monolayer. (D) The monolayer neutral surface  $\Sigma$ , director  $\mathbf{d}$  and unit normal  $\mathbf{n}$  in local coordinates. (E–F) Lipids are able to tilt from the surface normal, and stretch. (H–J) Intermediates of membrane fusion and (K) experimental image of a stalk [1].

The mechanical properties of bilayer are characterized by the Helfrich Hamiltonian;

$$\int_{\Sigma} \frac{1}{2} k_B \left[ (\text{Div } \mathbf{d} + k_0)^2 - k_0^2 \right] + \frac{1}{2} k_T (\text{Curl } \mathbf{d})^2 + k_G \det D \, dA. \quad (6)$$

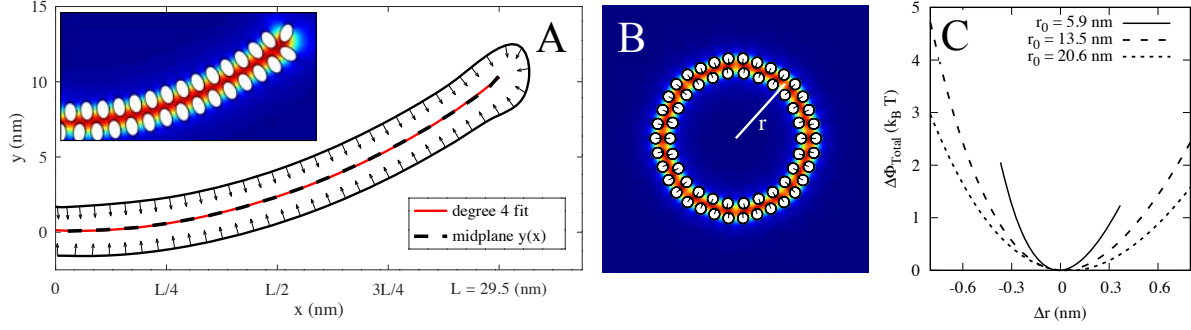
This hamiltonian is the energy functional for one monolayer, represented by a smooth surface  $\Sigma$  and director field  $\mathbf{d}$  [79, 83, 96]. The surface  $\Sigma$  coincides with the monolayer neutral surface. The unit length director  $\mathbf{d}$  tracks lipid orientations and points from the lipid head toward the lipid tail [113, 114]. In a bilayer, the energy is the sum of the two monolayer energies.

The form of the elastic energy density (6) is the same as the Oseen-Frank energy density for nematic liquid crystals [6, 192]. In fact, a lipid monolayer acts as one layer in a smectic phase [96, 142, 171]. The constants  $k_B$ ,  $k_T$  and  $k_G$  play the same role as the Frank constants  $K_1$ ,  $K_2$  and  $K_{24}$  liquid crystal theory. The Helfrich hamiltonian derives from the assumption of a quadratic energy density in the director surface gradient  $[D]_{ij} = \frac{\partial \mathbf{d}}{\partial \tau_i} \cdot \tau_j$ ,  $i, j = 1, 2$ , where  $\tau_1$  and  $\tau_2$  are orthogonal tangent vectors. Thus, the director gradients in (6) couple to surface geometry. Symmetries with respect to mirror reflection and in-plane rotation require that the energy come from *splay* ( $\text{Div } \mathbf{d}$ ), *twist* ( $\text{Curl } \mathbf{d}$ ) or *saddle-splay* ( $\det D$ ) distortions, where Div and Curl are the surface divergence and curl operators, respectively (Figure 5A–C). The associated elastic coefficients are the *bending modulus*  $k_B$ , *twist modulus*  $k_T$  and *saddle-splay modulus*  $k_G$ .

The *spontaneous curvature*  $k_0$  depends on lipid composition and determines the preferred lipid splay, [118, 173]. Figure 5A illustrates positive splay. The lipid DSPC, for instance, has  $k_0 = -0.1 \text{ nm}^{-1}$  and these lipids would line the inner monolayer of a spherical liposome, because the addition of a positive splay  $\text{Div } \mathbf{d}$  in (6) to the negative spontaneous curvature  $k_0$  leads to lower energy [107, 116, 173, 181]. The subtraction of  $k_0^2$  makes the energy distortion free<sup>1</sup>.

The Helfrich hamiltonian is widely used to determine energy barriers of fusion between lipid bilayer membranes [36]. PI Ryham and collaborators calculated, for the first time in continuum theory, a least energy path for transitions between planar bilayers, a membrane stalk, hemifusion

<sup>1</sup>The “bend” distortion from nematics is not present in monolayers since the directors have no dependence in the normal direction, *i.e.* the Frank “bend” constant  $K_3$  should not be confused with the *bending modulus*  $k_B$ . There is also no “spontaneous twist” in monolayers due to invariance under mirror reflection.

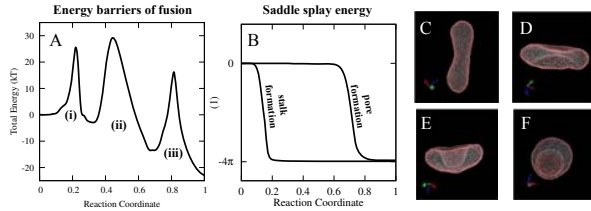


**Figure 6.** (A) A partially clamped bilayer with mid-plane (dashed curve) under uniform load. The quartic fit comes from continuum theory. (B) A circular vesicle at equilibrium. (C) The area modulus derives from convexity in energy as a function of radius.

diaphragm and the fusion pore [174, 175]. These studies found that each of the transitions required on the order of 30  $k_B T$  (Figure 7A), a result that is in agreement with barrier heights derived by recent molecular dynamics and experimental studies [58]. (Throughout the proposal,  $k_B T = 4.11 \times 10^{-21}$  J.)

#### 4.1.1 Evidence for elastic properties

We tested for elastic properties by subjecting two-dimensional bilayer morphologies to external loads [65], using realistic values for phospholipid length [22], the screening length  $\rho = 2.5$  nm [55, 95, 131, 161, 191] and interfacial tension  $\gamma = 4.1$  pN nm $^{-1}$  [67, 121, 165]. We first considered a planar bilayer subject to a uniform vertical load on the particle centers (Figure 6). The bilayer is clamped and horizontal at one end and the restoring force in the free part of the bilayer opposes the load. Twist and saddle splay are both zero, singling out splay as the only distortion. Since deformations are small (6), it is possible to solve the bilayer loading in closed form. This analytical solution (red curve) basically overlaps the midplane of the particle based solution (Figure 6A).



**Figure 7.** (A) Energy barriers for stalk formation (i), hemifusion diaphragm expansion (ii) and pore formation (iii). (B) Saddle-splay energy for each change in *monolayer* topology calculated in [175]. (C)–(F): Shape transition of vesicle at different values of volume to area ratio from coarse-grained simulations of lipid bilayer membranes [62].

Manipulation experiments give a monolayer area modulus in the range 30 – 40  $k_B T$  nm $^{-2}$  [149, 150]. To measure an area modulus, we stretched a circular vesicle, modeling the cross-section of a bilayer tube (Figure 6B & C). This procedure gave a monolayer area modulus  $34 \pm 2$   $k_B T$  nm $^{-2}$ , independently of the vesicle size, which is also remarkably close to the experimental value.

The successful outcomes of our preliminary tests suggest that the HAP particle configurations

Experimental measurements have accurately determined the bending modulus for several lipid types, with typical values lying around 10  $k_B T$  [96, 151, 152, 196]. By comparing with the exact solution, we derived a bending modulus in the range 8.51 – 13.54  $k_B T$ , which is in excellent agreement with the experimentally derived value, especially considering how few parameters the HAP formalism involves.

We also considered the stretching deformation [65]. Stretching occurs whenever there is an excess monolayer area, and it is energetically costly since it exposes hydrocarbon tails to water.

do behave like an elastic material. To validate our conjecture, we must consider ways to isolate or partially isolate the remaining distortions. The twist deformation, for example, has a modulus in the range of 1 to 2  $k_B T$  as evaluated by molecular dynamics [129]. But twist is mathematically zero in our two-dimensional monolayers, and so we require a computationally efficient means for evaluating the boundary integral equations in a collection of three-dimensional particles. Specific Aim 2 discusses some of the outstanding implementation issues.

Our eventual three-dimensional calculations must also consider the saddle-splay distortion, and the calculations may help resolve some well-known issues in the theory [191]. Theoretical analysis of lipid phase transitions predict a negative saddle-splay modulus around  $-8 k_B T$  [185, 186]. This value, however, predicts an energy barrier for monolayer fusion on the order of 200  $k_B T$ , which runs counter to the value 30  $k_B T$  estimated in experiments [58, 175, 192]. We expect the particle-based approach can shed light on this inconsistency.

## **4.2 Specific Aim 2: Efficient high-order numerical algorithm for large-scale simulation of the HAP model**

### **4.2.1 Overview of the potential theory and boundary integral equation methods**

The HAP model requires solving the exterior Dirichlet problem of the screened Laplace equation and the mobility problem of the Stokes flow at each time step. Standard numerical methods such as finite difference and finite element methods have to truncate the infinite domain to a finite computational domain by imposing certain artificial boundary conditions on the truncated domain and need the discretization of the whole volume of the truncated domain. The artificial boundary conditions are very often inexact, introducing another layer of approximation that lowers the accuracy of the solution. The discretization of the whole volume is very expensive for three dimensional problems, leading to excessively large number of unknowns in the linear system. Furthermore, it is rather difficult to obtain high-order discretization when the boundary surfaces are irregular.

Potential theory and boundary integral equation (BIE) methods remove the aforementioned obstacles in a very elegant way. The starting point is that for constant-coefficient PDEs the fundamental solutions, i.e., the Green's functions, are readily available. This allows us to represent the solution via the so-called layer potentials that are the convolution integrals of a kernel and an unknown density only on the boundary. The kernel is a linear combination of the Green's function and its derivatives, which ensures that the representation satisfies the underlying PDE and the condition at infinity automatically. And the boundary condition at the material interfaces together with the jump relation of the layer potential leads to a boundary integral equation for the unknown density.

The BIE method removes the need of imposing artificial boundary conditions for exterior problems and reduces the dimension of the problem by one, leading to optimal number of unknowns in the solve phase. Very often, one is able to construct the so-called *second kind integral equation* (SKIE) formulation for these problems, where the operator is a sum of the identity operator and a compact operator. It is well-known that the condition number of the resulting linear system for SKIEs is *independent* of the mesh size  $h$  or equivalently, the number of discretization points. This leads to a constant number of iterations when iterative solvers are applied to solve the resulting linear system. It further improves the accuracy of the solution as the relative error of solution will never increase as the number of total discretization points increases. On the other hand, the condition number of the linear system from finite difference and finite element methods generally

increases as a power function of the total number of discretization points, with the exact power depending on the underlying spatial dimension and the highest order of the differential operator in the PDE. This leads to an increase in the number of iterations (and hence the total computational cost) and an increase in the relative error of the solution as the number of discretization points increases.

The discretization of the integral operator often leads to a dense matrix, while finite difference/finite element methods result in sparse matrices, making matrix-vector product much cheaper to compute. However, since the invention of the original fast multipole method (FMM)[73], there have been many fast algorithms [32, 35, 57, 69, 74, 209, 213] that reduce the cost of matrix-vector product to linear ( $O(N)$ ) or quasilinear complexity ( $O(N \log^k N)$ ) for dense matrices resulting from the BIE discretization. Fast direct solvers have also been developed recently [24, 68, 75, 87–89, 117, 139–141, 147, 148]. The development of these fast algorithms have removed a huge hurdle for the use of boundary integral equations, making the BIE method the method of choice for constant-coefficient PDEs with linear boundary conditions. For the exterior Dirichlet problem of the screened Laplace equation, the SKIE formulation in our previous work [65] can be readily extended to the 3D case. For the mobility problem of the Stokes flow in three dimensions that takes the hydrodynamic effect into account, an SKIE formulation can be found in [167].

#### 4.2.2 High-order discretization of surface integrals in three dimensions

The practical application of integral equation methods requires the accurate evaluation of boundary integrals with singular, weakly singular or nearly singular kernels. There are many numerical quadrature schemes for dealing with line integrals in two dimensions [5, 16, 17, 27, 30, 31, 40, 53, 71, 72, 78, 81, 84–86, 97, 108, 109, 119, 133, 137, 180, 180, 184, 208, 210] and some of them are extremely efficient and can achieve arbitrary high order.

The high-order quadrature rules for the evaluation of surface integrals in three dimensions, however, are much less developed than the line integrals in two dimensions. For example, there are no Gaussian quadratures for integrating polynomials on a flat triangle, even though efficient quadratures [197, 205] have been developed recently for such purpose. For weakly singular or singular integrals, [25, 26] constructed high-order quadratures for surface integrals on a general triangle, while [70] presented a fast algorithm for integrating  $1/r$ -type singular integrals for surfaces that are homeomorphic to a sphere. We plan to study the so-called quadrature by expansion (QBX) scheme [54, 115] for the evaluation of both singular and near-singular surface integrals encountered in the discretization of BIEs in three dimensions. Conceptually, the idea of the QBX to evaluate singular, hypersingular and near singular integrals on smooth surfaces is straightforward. That is, the surface is discretized into smooth triangles and smooth high-order quadratures are applied to evaluate the expansion coefficients on all source triangles with the QBX expansion center placed at a point off the surface. One may then form a suitable expansion (for example, a Taylor expansion) around that center and evaluate this expansion back at the target point on the surface (or close to the surface in the near singular case). Compared to the competing aforementioned quadrature schemes, the QBX quadrature is attractive because it offers a clear path for being extended to: **(1)** handle any singularity, including hypersingular operators, **(2)** be usable with any high-order surface discretization, **(3)** generate well-conditioned discrete operators to which iterative methods such as GMRES [176] can be applied in a black-box fashion, **(4)** integrate well with fast algorithms such as the FMM.

In practice, there are still many issues that need to be resolved. For example, there are now many variants of QBX including global and local QBX [115, 168], the target-specific QBX [187], kernel-independent QBX [170], and quadrature by two expansions [43]. The coupling of the QBX and the FMM may also lead to certain instability issues which may require some changes in the fast multipole method [198]. Similar to other quadrature methods, there have been extensive study on the QBX methods in two dimensions, while its three dimension version [2, 187, 199, 200] has not been fully studied and the implementation is even more scarce. We plan to investigate the accuracy and the convergence order of the various QBX schemes mentioned above, its coupling with the FMM, parallel implementation issues for large-scale problems, and the application to our target problems.

#### 4.2.3 A hybrid method for close-to-touching Janus particles

The HAP model for membranes will inevitably lead to the case where some Janus particles will be very close to each other. Even though QBX can handle such case accurately, it may lead to excessively large number of unknowns in order to resolve the unknown densities at those close-to-touching points. In [66], a hybrid scheme is developed to treat the close-to-touching spheres for the interface problem of the Laplace equation. The key idea is to combine the analytic image method and spectrally accurate method of moments, where the analytic image method will capture the most singular part of the unknown density at the close-to-touching points. With the aid of the FMM, the scheme achieves linear complexity with much less number of unknowns on the material interfaces. We plan to study the hybrid scheme to treat the close-to-touching case for both the screened Laplace equation and the mobility problem to further improve the efficiency of the numerical algorithm for the HAP model.

#### 4.2.4 Other numerical issues

Another outstanding numerical issue pertaining to simulating the self-assembly of amphiphilic particles (such as lipid macromolecules) in a viscous solvent is the collision between amphiphilic particles. The hydrophobic attraction potential drives the amphiphilic particles to move towards each other so to minimize exposure to the solvent. Under such attraction force the fluid is being squeezed out as particles move toward each other, and the amphiphilic particles can come into physical contact in finite time. Such particle collisions in a dense rigid body suspension is a great challenge and can be a bottleneck in large-scale simulations. In our previous work a Leonard-Jones potential is used to keep the particles from overlapping [65]. Such steep steric interaction at short ranges introduces great numerical stiffness that limit the time step size.

Yan *et al.* proposed a collision-resolution algorithm within the framework of boundary integral methods to resolve the non-smooth many-body dynamics due to collisions by formulating the particle collision process as a linear complementarity problem with geometric ‘non-overlapping’ constraint [206]. We propose to treat the particle collisions based on Yan *et al.*’s work after the first two goals (see above) are achieved. A potential complication in combining the algorithms for particle collision into our QBX integral formulation is the computational cost for the QBX to refine meshes on particles in collision.

Once the collision-resolution algorithm is implemented, we will check the computing performance first before we embark on incorporating fluctuating hydrodynamics [13, 14], which might be important even at the scales of the amphiphilic particle size in some cases. We propose to extend the high-order time-integration scheme for a stochastic differential equation [59] to this system.

### 4.3 Specific Aim 3: Functional Materials

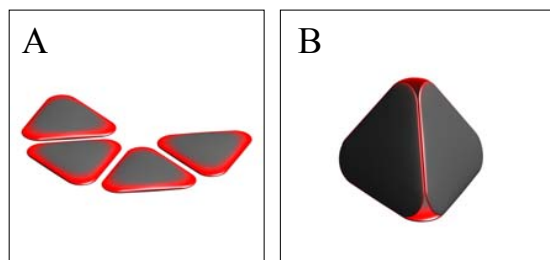
Over the past decade, there has been an explosion of interest in the fabrication of complex microscopic three-dimensional structures [37]. These fabrication processes utilize the fact that at small scales, capillary forces dominate van der Waals interactions and thermal noise [214], enabling the coordinated movement and binding of material subunits. Two prominent fabrication techniques are capillary origami [128, 160, 172] and colloidal self-assembly [39, 189]. Capillary origami uses principles of elastocapillarity wherein elastic solids deform under surface tension [20, 193]. In self-assembly of colloids, particles exhibit similar thermodynamic behavior of molecular systems, except that the behavior occurs over observable, long time scales [214].

There is inherent intellectual value in fabricating novel three dimensional structures: Living cells construct biological molecules like proteins, membranes and viral capsids using hierarchical assembly [204]. At the same time, elastocapillarity and colloidal self-assembly supply model systems for biological processes, like vesicle adhesion and membrane bound protein interaction [39], the hydro-polar model of protein folding [123, 160] and viral capsid assembly and [33]. Capillarity can serve as a model for the lock and key mechanism binding between the active site of an enzyme and a substrate molecule [7], or treating viruses like adhered particles [3, 4, 41], or studying decorated vesicles [9, 10, 203]. Although challenging, mathematically analyzing these model systems gives deep insight into biological structure and function.

The HAP theory is ideally suited to the problem of creating microstructures through capillary action. Specifically, the modeling application considers the assembly of polyhedra from smaller subunits. Our developments, which include viscous interactions, thermal fluctuation, and a long range description of capillarity, will pave the way for dynamical understanding to organizational principles in viral capsid formation, for instance [33, 166].

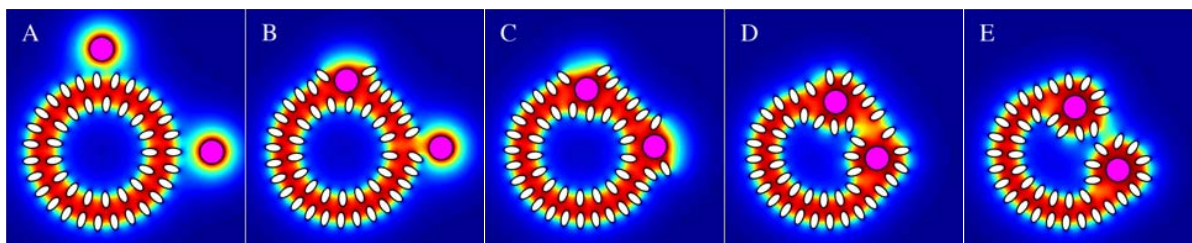
In order to illustrate the novelty of our approach, it is helpful to first describe how current experimental and mathematical techniques deal with polyhedral assembly. Capillary origami uses lithography to etch faces out of a thin, elastic sheet [160, 172]. The collection of faces form a so-called net, and this net self-folds into a three-dimensional polyhedron (Figure 8). The motivation is to create micro containers to mimic protein folding [172]. Prediction of geometric structure from its subunits is non-trivial. That is because the final morphology depends on the net structure, physical interactions, and the surrounding media, and researchers have formulated optimality criteria for these nets [7, 160].

The experimental shapes are hundreds of microns in diameter. Thus, as a key distinction with HAP approach, the driving force for folding in capillary origami and related processes comes from surface energy of the hinges (e.g. soldered hinges that supply a surface tension once the system is heated). Mathematicians have numerically and analytically described the behavior of these surface tension driven hinges [20, 29, 164], making it possible to simulate the mechanical problem, in principle, using slender body theory for plates.



**Figure 8.** Illustration of self-assembly of hydrophobically labeled faces. The thick triangles have a rim-hydrophobic label on one side, and are hydrophilic on the other side. These shapes would potentially aggregate into a tetrahedral container.





**Figure 9.** (A)–(D) shows the spontaneous insertion of two hydrophobic particles into a vesicle bilayer. The driving force is long-range interaction between the hydrophobic, magenta particles and the bilayer core. The particle entrainment cause the vesicle to break apart, analogously to surfactant induced lysis.

To study this problem using HAP theory, we form a collection of thin, prism-like particles in Figure 8. Each of these particles serves as a face in the final morphology. The edges of the prisms are labeled hydrophobic according to the boundary condition in the screened Laplace equation boundary value problem. This way, the edges coalesce, forming the desired structures. Furthermore, by manipulating the boundary condition in HAP, it is possible to have faces attach and detach with precision, and form a net or other structures if so desired. Our HAP theory therefore generalizes submillimeter theoretical and experimental work to the micron and nanometer sizes.

Finally, further applications of our modeling approach include colloidal interaction on interfaces. Here, the experimental setups use Janus particles to model, for example, membrane bound proteins [120, 127, 214]. The idea of an amphiphilic Janus particle was introduced by P. G. de Gennes in 1991 [214]. The Investigators have significant experience as Janus particles figure heavily into our particle based description of bilayers, and can adjust our modeling approach to account for proteins. This is done by consider mixtures, consisting of many (hundreds to thousands) long, elongated amphiphilic particles for the lipid phase. Larger particles with hydrophobic patches or stripes model the proteins [105].

The distinction between macroscopic capillarity and microscopic hydrophobic force are relevant here as well. Prior models use surface energies to account for interaction between particles in an interface [39]. However, this may be missing important physics, and here our modeling approach has the advantage in that protein insertion, for instance, is a self-consistent consequence of the formulation, versus an assumption imposed by boundary conditions. The simulations will enable us address important biological questions on how a collection of interface bound colloids interact [177, 207], and how configurations dictate macroscopic surface properties and sense background curvature [34, 132, 182].

## 5 Broader Impacts of the Proposed Work

The proposed mathematical analysis and modeling will provide a transformative understanding of the collective dynamics of amphiphilic particles such as (1) their self-assembly into micelles and bilayers, and (2) the interaction between these building blocks. Amphiphilic Janus particles have gained increasing popularity for fabrication of smart materials. The proposed hybrid continuum model, mathematical analysis and numerical algorithms will have transformative impact on precision design for specific mechanical properties of materials made of amphiphilic nanoparticles. An important component of this proposal is the interdisciplinary education and training of both undergraduate and graduate students. The combination of mathematical modeling, analysis and



scientific computing in this project provides a compelling example of the importance of mathematics in biophysics and engineering applications. The concepts and methods described here go beyond the context of amphiphilic particles and lipid molecules. They extend to other problems featuring microscopic phase separation that leads to formation of mesoscopic domains. This situation arises, for example, in biological development in systems biology. The methods developed here have the potential to impact those and other related areas in biomedicine and biotechnology.

### 5.1 Educational Impacts

The proposed research will have immediate impact on undergraduate and graduate education. At the undergraduate level, the project will involve and support undergraduate researcher from Fordham University. The supported summer researchers will gain valuable first-hand experience in inherently interdisciplinary, mathematical fluid modeling and computation. We will incorporate research into teaching, especially in differential equation and programming courses.

Over the past eight years, PI Ryham has included many undergraduates in the execution of research initiatives, coauthoring publications. He has a track record for supporting underrepresented groups, being called on by the Collegiate Science and Technology Entry Program (CSTEP) to make opportunities for promising students, for example. He has mentored two Clare Boothe Luce Scholars, one a U.S. Marine Corp veteran, and a high school student in the NYU GSTEM program.

The PIs will capitalize on the synergy between NJIT's doctoral program in Mathematical Sciences and Fordham's undergraduate focus in the Department of Mathematics. Promising, young undergraduate scientists from the Bronx community will find a natural pipeline into graduate studies through working directly or indirectly on this project. On the graduate-level education, PI Young and co-PI Jiang expect to train and support a PhD student, Yuexin Liu (who is in her third-year at NJIT) for two more years. Yuexin Liu has past experiences in the undergraduate training program at NJIT, and will train an undergraduate intern. The PIs will foster vertical integration between the senior personnel, their collaborators, postdocs, doctoral and Bachelor students, enhancing the learning environment.

## 6 Intellectual Merit

A central theme of the project is the mathematical development and analysis of the physical model for interaction between many amphiphilic particles. The model formulates the interaction potential through a screened Laplace equation boundary value problem possessing the physical properties like non-additivity and decay of realistic hydrophobic attraction. Colloidal systems collectively self-assemble into bilayer morphologies, and we analyze the elastic properties of these amphiphilic particle ensembles. This allows us to interpret the Helfrich free energy in terms of hydrophobic interactions and specific molecular characteristics. We extend the capabilities of the boundary integral equation quadrature by expansion method to perform large particle number simulations in three dimensions with collisions. Results from these computations will be used to compare collective amphiphilic against experiment, and study the optimal design of three-dimensional functional materials.

## 7 Relevant Results from Prior NSF Support

**Rolf Ryham:** no prior NSF support.

**Yuan-Nan Young:** *NSF-DMS-1222550, Mathematical and experimental study of lipid bilayer shape and dynamics mediated by surfactants and proteins*, \$212,603, 9/15/2012 - 08/31/2016 (with

no-cost extension), PI. *Intellectual merit:* The focus of this grant is modeling the interaction between a pure lipid bilayer membrane (LBM) with surfactant, cholesterol and protein.

*Broader impacts:* One PhD student (Szu-Pei Fu) was funded to work with YNY, and work has resulted in seven papers [60, 153–155, 159, 211, 212]. YNY has been actively involved with promotion of underrepresented students at NJIT. The other PhD student (Herve Nganguia) is African. YNY has taught a broad spectrum of courses in fluid mechanics and applied math modeling.

**Shidong Jiang:** *NSF DMS-1418918, Efficient High-Order Parallel Algorithms for Large-Scale Photonics Simulation*, \$150,000, 08/15/2014 - 06/30/2017, PI. *Intellectual merit:* The goal of the proposed research is to develop *robust, high-order numerical methods* and *efficient parallel algorithms* to achieve greater accuracy and larger scale for photonics simulation.

*Broader impacts:* During the funded period, the PI has published or submitted twelve papers to refereed international journals [12, 18, 61, 66, 76, 98–103, 122], and presented the research results at many institutions and international conferences/workshops to disseminate research results. On the education side, the PI has supervised two students - Shaobo Wang [101, 201] and Szu-Pei Fu [61, 65] (co-advised with Yuan-Nan Young), with the partial support of the grant.

## 8 Project Management, Collaboration Plan, and Schedules of Research Tasks

**Project management:** The success of the proposed research requires complementary expertise and collaborative efforts in physics, applied mathematics, algorithms and computing. Ryham has been working on mathematical modeling with a strong analytical background. Young has been working on many areas of computational fluid dynamics and applications to math biology for many years. Jiang has been working on integral equation methods, fast algorithms, and their applications to computational electromagnetics and fluid dynamics for many years. Their recent collaborative work on the HAP model in two dimensions has provided a solid foundation on the proposed research.

**Collaboration plan:** The management responsibility of this collaborative research will reside with the lead PI (Ryham) for this endeavor. The research work is structured to meet the tasks discussed in Sec. 4. The PIs, their postdoc and students will meet frequently in person. The PIs will share software packages, paper sources, and references on a common Git repository. The resulting software packages will be posted on the Github software repository.

**Research Schedule:** The detailed schedule for the proposed work is shown in Fig. 10.

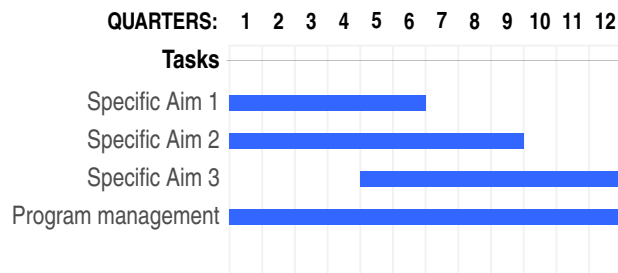


Figure 10. Schedule for the proposed work, measured in quarters from the beginning of the project.