

Collaborative Research: Mathematical modeling and simulation of self-assembling amphiphilic particles in solvent

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1 Background

The goal of this collaborative proposal is to use mathematical modeling and numerical simulations to investigate the dynamic self-assembly of amphiphilic particles interacting via hydrophobic forces in solvent. Amphiphilic particles (such as lipid molecules) possess both hydrophobic and hydrophilic structures. In a viscous solvent they self-assemble into meso-/macroscopic structures (such as micelles and bilayers of lipids) to shield their hydrophobic parts from contact with the solvent (water) molecules. Such self-assembly of amphiphiles via hydrophobic forces is ubiquitous in biology and biophysics [93], and has been a major source of nonspecific interactions between nanoparticles in soft matter [4, 182, 213].

The substantial free energy for placing hydrophobic substances in contact with water is roughly proportional to the surface area of the contact region [15]. At the microscopic level, 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, 130, 142]. Measurements show that the hydrophobic force decays exponentially with a decay length on the order of 1 nm [34, 94, 124, 135]. Additionally, the interaction is not pairwise additive, meaning that the force between any two hydrophobic objects is altered by the presence of a third object, hydrophobic or otherwise [197].

Recently, PIs RR and YNY developed a mathematical model, called the hydrophobic attraction potential (HAP) model [67], that is based on the physical origin of hydrophobicity. This model addresses the major shortcomings of molecular dynamics (MD) and continuum approaches. Based on preliminary results (§5), the PIs propose to extend this HAP model to offer an alternative modeling methodology that leads to new mathematical ideas and is both physically accurate and computationally practical. The proposed research aims to provide fundamental understanding of the self-assembly dynamics of amphiphilic particles. These results will facilitate optimal design of smart materials by tuning the geometry and properties of the amphiphilic particles.

1.1 Hydrophobic Attraction Potential (HAP)

The motivation for the HAP concept stemmed from PI RR's work concerning energy barriers in membrane fusion [32, 180]. By applying a mathematical, squared-gradient theory for hydrophobic attraction between planar surfaces [54, 130, 135, 141], PI RR and collaborators resolved the long-standing issue of accounting for the energy of a monolayer fissure surface during topological transitions. Based on PI RR and YNY's coarse-grained membrane modeling work [66], the investigators devised a gradient theory for arbitrary collections of hydrophobic and amphiphilic particles. As a new method, HAP eliminates the costly calculation of water by treating the solvent implicitly, is capable of representing biologically-relevant morphologies, and avoids complicated re-meshing schemes of continuum approaches by utilizing a particle-based representation.

To define HAP, consider a collection of particles suspended in a solvent. The region $\Omega \subset \mathbb{R}^3$ models the solvent phase (Figure 1). The boundary of the region is the union of water-particle

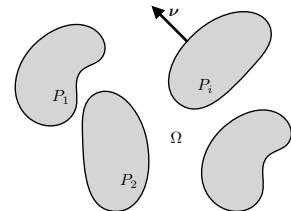


Figure 1. A collection of rigid particles: P_1 , P_2 , P_3, \dots . The exterior domain Ω represents the solvent.

interfaces with unit normal $\boldsymbol{\nu}$. Some parts of this interface are hydrophobic while others are hydrophilic. Hydrophobic interfaces disturb the hydrogen bond structure of water [99, 132, 206] and this disturbance comes with an energetic penalty that is proportional to interfacial area. There is an additional decay length, due to rapid fluctuation in the hydrogen bond network, describing how far the restructuring extends into bulk water.

The above considerations motivate the following definition for HAP:

$$\Phi = \gamma \int_{\Omega} \rho |\nabla u|^2 + \rho^{-1} u^2 \, dV. \quad (1)$$

The integrand contains the decay length ρ and a dimensionless scalar function $u(\mathbf{x})$ called the water activity. The integrand has units of an inverse length, so the volume integral has units of area. Multiplication by interfacial tension γ makes Φ an energy.

To establish an attraction between interfaces, the water activity is not arbitrary but rather is the solution of the screened Laplace equation boundary value problem

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

The boundary values f define the degree of hydrophobicity of the water-particle interface: $f = 1$ describes a hydrophobic interface, and $f = 0$ describes a hydrophilic interface. Thus, f encodes information about the particles, and the parameters ρ and γ encode information about the quality of the solvent [41, 93]. In the figures throughout the proposal, red is for $u = 1$ and blue is for $u = 0$. In practice, we integrate (1) by parts and use (2) to obtain

$$\Phi = -\gamma \int_{\partial\Omega} \rho u \nabla u \cdot \boldsymbol{\nu} \, dS, \quad (3)$$

thereby avoiding volume integral calculations.

The equations (1) and (2) possess a number of mathematical properties that mirror the phenomenological characteristics of hydrophobic attraction. Specifically, solutions of (2) yield an attractive force between hydrophobic bodies separated by water, and this attraction decreases exponentially with the distance of separation [54]. Using boundary layer analysis, the HAP converges to a surface energy in the zero-decay length limit [117, 123, 190]. Finally, we have demonstrated that the forces derived from HAP theory are non-additive [67, 142].

To define the particle dynamics, let P_1, P_2, \dots, P_N be a finite collection of disjoint, rigid, and closed particles each with a Lipschitz boundary. Assume that the label f is an element of the Sobolev space $H^1(\Omega)$. The functional (1) has a minimizer among all functions u equaling f on the boundary in the sense of trace. Conversely, from maximum principles and energy estimates, the solution of (2) is unique and minimizes (1). Taking the first variation of (1), i.e. the derivative with respect to the domain [7, 77, 183], yields a symmetric, rank-two tensor called the hydrophobic stress (equation (2.3) in [67]):

$$\boldsymbol{\sigma}_{\text{hydro}} = \gamma \rho^{-1} u^2 I + 2\rho\gamma \left(\frac{1}{2} |\nabla u|^2 I - \nabla u \nabla u^T \right). \quad (4)$$

Integrating the hydrophobic stress over the surface of particle P_i reveals the hydrophobic force, and torque on each particle

$$\mathbf{F}_{\text{hydro},i} = \int_{\partial P_i} \boldsymbol{\sigma}_{\text{hydro}} \cdot \boldsymbol{\nu} \, dS, \quad \mathbf{G}_{\text{hydro},i} = \int_{\partial P_i} (\mathbf{x} - \mathbf{a}_i) \times (\boldsymbol{\sigma}_{\text{hydro}} \cdot \boldsymbol{\nu}) \, dS, \quad (5)$$

relative to the center of mass \mathbf{a}_i . This system is force- and torque-free (§4.2). To avoid particle collisions, we define an excluded volume potential Φ_{repul} that diverges whenever tubular neighborhoods of adjacent particles overlap. The total potential, force, and torque are then

$$\Phi = \Phi_{\text{hydro}} + \Phi_{\text{repul}}, \quad \mathbf{F}_i = \mathbf{F}_{\text{hydro},i} + \mathbf{F}_{\text{repul},i}, \quad \mathbf{G}_i = \mathbf{G}_{\text{hydro},i} + \mathbf{G}_{\text{repul},i}. \quad (6)$$

To supply viscous dissipation, we incorporate the mobility problem flow for a rigid body suspension in Stokes flow:

$$\begin{aligned} -\mu\Delta\mathbf{u} + \nabla p &= 0, \quad \mathbf{x} \in \Omega, \quad \nabla \cdot \mathbf{u} = 0, \quad \mathbf{x} \in \Omega, \\ \mathbf{u}(\mathbf{x}) &\rightarrow 0 \quad \text{as } |\mathbf{x}| \rightarrow \infty, \quad \mathbf{u}(\mathbf{x})|_{\partial P_i} = \mathbf{v}_i + \boldsymbol{\omega}_i \times (\mathbf{x} - \mathbf{a}_i), \\ \int_{\partial P_i} \boldsymbol{\sigma} \cdot \mathbf{n} dS &= -\mathbf{F}_i, \quad \int_{\partial P_i} (\mathbf{x} - \mathbf{a}_i) \times (\boldsymbol{\sigma} \cdot \mathbf{n}) dS = -\mathbf{G}_i. \end{aligned} \quad (7)$$

Here, μ is the fluid viscosity; the first two equations state that the fluid motion is a divergence-free Stokes flow; the third equation specifies that the fluid velocity vanishes at infinity; the fourth equation enforces a rigid body motion on each particle, where \mathbf{v}_i and $\boldsymbol{\omega}_i$ are unknown translation and angular velocities; and the last two equations state that the net viscous forces and torques with fluid shear stress $\boldsymbol{\sigma}$ balance (6).

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 (5), (iii) solve the Stokes mobility problem (7) for the rigid body motions, and (iv) update the particle configuration. Numerical challenges and how these challenges are overcome are described in §4.2.

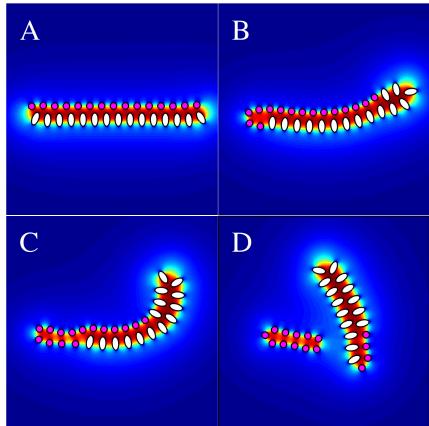


Figure 2. An initial assembly of small and large particles spontaneously segregates into two smaller bodies.

The HAP formulation is, to our knowledge, the first demonstration of bilayer self-assembly by a continuum-based interaction model [17, 19, 57, 154, 211]. Our simulations use Janus particles to model lipid amphiphiles which are popular in material science and physics for creating functional materials [118, 119]. Janus particles are typically spherical with a biphasic material label on either hemisphere, endowing the particle with a directional order. We model an elongated lipid by elliptical particles with the hydrophobic label defined along the ellipse's axis. Under the hydrophobic force, with excluded volume, 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.

It is worth emphasizing that the HAP model uses only a few parameters: interfacial tension, decay length, repulsion strength, and particle shape. For example, an elastic modulus for stretching a vesicle from micropipette manipulation calibrates our interfacial tension parameter. This is in direct contrast with pair-potential-based approaches in MD simulations and coarse-grained models where many more parameters are required [206, 211].

Over the past decades, researchers have used a number of mathematical tools to simulate vesicles in a shear flow, including lattice Boltzmann [101], coarse-grained Brownian dynamics [155], phase field [14, 44], level set [42], boundary integral [173, 207], and immersed boundary approaches [91, 104, 105]. Most of these approaches assume a mathematical surface, whether implicitly or explicitly,

and define an elastic bending energy of the surface. These vesicle studies built off 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 [12, 161, 180, 199], phase field [43, 46, 82], and immersed boundary methods [89, 90, 104]. PI RR and collaborators led in part the development of phase field functionals of membrane elastic energy and approaches to coupling membrane elasticity to fluids [45–48].

Our HAP approach differs from these prior methods in a number of respects. First, we do not assume a surface. Rather, we assume 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. The second difference lies in the fluid-interface coupling. Here, the associated mobility problem (7) is more complicated than dealing with a stress boundary condition or diffusive surface force because the fluid velocities are for individual rigid body motions at each particle surfaces. Finally, the HAP model directly addresses the existence of multiple phases. We can vary lipid length, spontaneous curvature, and bending rigidity by introducing different particle shapes and hydrophobic boundary conditions (Figure 2). In contrast, continuum theory deals with multiple phases through additional surface densities that must satisfy specialized transport equations [127, 143].

The greatest strength of using the HAP to model a lipid bilayer membrane is the ability to form discontinuities (interfacial singularities) from first physical principles without any artificial manipulation to rearrange the interface (Figures 2 and 3). For example, using the HAP model to simulate a vesicle under a shear flow that is strong enough to cause the vesicle membrane to rupture (see §5), we expect the HAP model to capture the reorganization of lipid molecules on the scales of membrane thickness (~ 5 nm), which is a nearly impossible task using phase-field or immersed boundary methods without extreme refinement around the membrane and artificial treatment of reconnection during the topological change of an interface [24, 36, 37, 59, 111, 122].

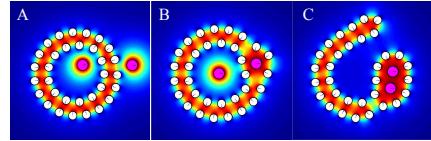


Figure 3. Two hydrophobic particles enter and then lyse the circular bilayer.

2 Broader Impacts

This project aims to advance the mathematical modeling of collective dynamics of amphiphilic particles. The simulations use a new, yet intuitive, approach that can account for important and complex systems that are out of reach in computational material science. These complex systems include fusion and fission of amphiphilic bilayer membranes and optimal shape design in metamaterials. The development of three-dimensional models describing colloidal systems could be transformative in biomedicine and material science. The research draws from expertise in scientific computing, physics of fluids, and mathematics. The mathematical component incorporates leading techniques from geometric analysis and gives deep insight into fundamental material science. The project offers undergraduates in a socially impactful manner the opportunity to do research and train with graduate and postdoctoral personnel. It incorporates research in the classroom, and with its combination of mathematical modeling, analysis, and scientific computing, the project highlights the importance of mathematics and computation to all areas of science and engineering.

2.1 Educational Impacts

The topics of this proposal have application in robotics, machine learning, and engineering. To foster training in mathematical sciences, the project will include undergraduate researchers (URs). The proposal supports one UR per year from the lead institution, and will include one or two additional URs from actively supported in-house programs.

The URs will work as a team for eight weeks in the summer. They will collaborate directly with the senior personnel, have tutorials in topics such as numerical quadrature and integral equations, and train in mathematical writing and presentation. To maximize vertical integration, and to the extent possible, the PIs and personnel will travel to New York for one or two weeks  the summers. Fordham University recently constructed a seminar/collaboration space specifically for collaborative research, and the URs will have office space with desks there.

As a requirement, the URs will write quality summary reports and give presentations at the their respective research symposia. The work will be considered  access if the URs also participate in a national conference. The best possible outcome  if URs coauthor a publication.

There are two ways the proposal will meaningfully engage the community.  To be more impactful, students from the Bronx High School of Science (PI RR) and Newark Science Park High School (PI YNY) will be encouraged to join the research team. PI BQ will work with undergraduate and high school students through the Undergraduate Research Opportunity Program and Young Scholar's Program, as he has done in the past. Secondly, the PIs will prioritize students who would most benefit from the grant activity.  These include students from underrepresented groups, and we specifically target students whose socio-economic background prevents them  from participating in out-of-state research experiences.

Finally, we will create several modules to include in our courses. These modules will introduce topics from numerical linear algebra and optimization, and be based on the ideas of the proposal. Additionally, we and our UR collaborators will give remote, guest lectures in each others' courses and undergraduate seminars.

3 Intellectual Merit

The purpose of this research is to reach interesting physical phenomena with less computational cost than molecular dynamics, and account for more general features that continuum theory misses. The main ingredient is defining a nonlocal interaction through the solution of an elliptic boundary value problem that has the phenomenological characteristics of long-range hydrophobic attraction. It turns out that this minimal model gives rise to rich phenomena for Janus particle aggregates and correctly predicts elastic properties of bilayer. The technical research tasks include quantifying collective properties of amphiphilic ensembles, mathematical analysis of continuum elastic energies, efficient, high-order numerical algorithms for large-scale simulations, and incorporating external fields through electric charge. Lastly, the proposal extends the results using three-dimensional boundary integral formulations.

4 Proposed Research

We have demonstrated that our hydrophobic attraction with repulsion potential (HAP) approach efficiently simulates self-assembly of amphiphilic particles into two-dimensional micelles, bilayer membranes, and vesicles [67] and recreates the tank-treading phenomenon in external shear flows [64]. While the results show great promise in the field of collective body hydrodynamics, several outstanding issues need to be addressed. These include a thorough analysis of elastic properties of

our coarse-grained bilayers and efficiently simulating three-dimensional collective hydrodynamics of amphiphilic particles. We must also incorporate electric charge and account for how external fields control particle self-assembly.

4.1 Specific Aim 1: Measuring material properties of amphiphile self-assembly

The goal of Specific Aim 1 is to characterize the material properties of many-body, self-assembled amphiphiles. For amphiphiles assembled into bilayers, these properties are described by membrane continuum mechanics. Our goal is to map the parameters of the particle-based model onto the elastic moduli from continuum theory. Results from this goal will facilitate simulators to use the hydrophobic attraction force calculations to model bilayers with specific composition. These calculations have provably less computational complexity than those of molecular dynamics simulations and possess the molecular granularity lacking from continuum models.

Hamm and Kozlov (HK) pioneered the modern theory of membrane continuum mechanics [79], and their theory is widely used to describe biological phenomena, including fission [63, 128, 139], fusion [1, 30, 110, 114], poration [68], phase boundaries, and interaction with inclusions [163, 181, 189]. These phenomena require resolution of the internal structure of the membrane. Recently, there has been a revival of interest in the HK theory as the quadratic assumption for the elasticity energy density has caused researchers to question the applicability of the theory for large curvatures [6, 22].

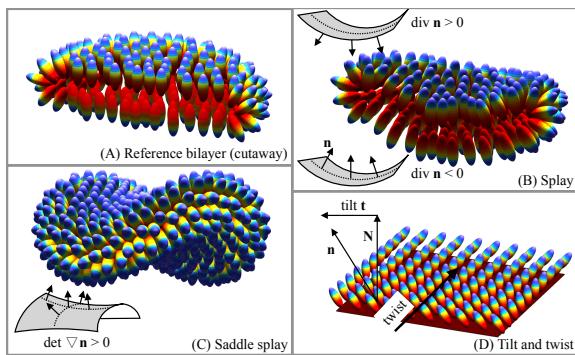


Figure 4. Sketch of the HK membrane model [79].

splay ($\text{div } \mathbf{n}$), twist ($\text{curl } \mathbf{n}$), saddle splay ($\det \nabla \mathbf{n}$), and tilt $\mathbf{t} = \mathbf{n}/(\mathbf{N} \cdot \mathbf{n}) - \mathbf{N}$ where \mathbf{N} is the unit surface normal;

$$\mathcal{W} \equiv \int_{\Sigma} \frac{1}{2} k_B [(\text{div } \mathbf{n} + k_0)^2 - k_0^2] + \frac{1}{2} k_T (\text{curl } \mathbf{n})^2 + k_G \det \nabla \mathbf{n} + \frac{1}{2} k_\theta |\mathbf{t}|^2 dA. \quad (8)$$

Here, the deformations come with elastic coefficients: the bending modulus k_B , twist modulus k_T , saddle-splay modulus k_G , and tilt modulus k_θ . The parameter k_0 is the spontaneous curvature and determines the preferred lipid splay [109, 177].

Although the HK elastic theory assumes small deformations, Galimzyanov *et al.* [69] have shown that energies derived from molecular dynamics and those derived from (8) are in agreement, even when curvatures are large. Under spatial scales much larger than the membrane thickness, membrane energy is well-characterized by the Canham-Helfrich energy used throughout the fluid-structure literature [48, 90, 91, 104, 127, 166, 169]. The Canham-Helfrich energy is actually a special case of (8) obtained by setting $\mathbf{n} = \pm \mathbf{N}$ (the \pm depending on orientation) and collapsing both monolayers onto the membrane midplane.

This proposal will develop much-needed mathematical analysis to resolve these controversies due to the assumptions in the HK theory.

The HK framework assumes a three-dimensional lipid monolayer where the internal structure consists of straight fibers that represent elongated hydrocarbon chains. The elastic energy density \mathcal{W} is quadratic in the Green-Lagrange strain tensor for this striated, internal structure. This energy density decomposes into four, fundamental, and independent deformations (Figure 4):

4.1.1 Simulations of the HAP model to estimate elastic moduli and energy

We propose to (i) determine the value of effective elastic moduli k_B , k_T , k_G , and k_θ and then (ii) understand how the model parameters ρ , γ , and the particle shape map onto elastic moduli. An accurate and robust way to measure material properties is to track the evolution of the bilayer as it relaxes from an initially non-equilibrium configuration [22]. Figure 5 shows an example where the initial configuration of a bilayer patch containing the splay deformation without any other components (saddle splay, twist and tilt). As the bent membrane flattens, both the self-interaction energy Φ and the elastic energy \mathcal{W} decrease, and because the saddle splay, twist, and tilt stay zero, the slope gives the bending modulus in this case.

Here we start with a particle-based bilayer in a specific non-equilibrium shape that involves only one of the components of the displacement in Figure 4, and then evolve the particle system according to the time integration for (7). Because elastic properties are independent of dissipation, we can forgo solving for fluid velocity and set the translational velocity and angular velocity directly proportional to the force and torque, respectively.

This yields a dissipation of the total potential (6), which stabilizes the evolving bilayer shape. Therefore, we reconstruct an evolving monolayer dividing surface Σ and director field \mathbf{n} by interpolating the particle centers and orientations. Using (8), we calculate a continuum energy \mathcal{W} from the interpolated shapes.

We propose to conduct calculations similar to the example of Figure 5 for other elastic moduli such as the effective twist modulus k_T . Molecular dynamics investigations find a twist modulus about $1 \text{ k}_\text{B}\text{T}$ [121], and here, the specific non-equilibrium shape consists of a single layer of amphiphilic particles on a hydrophobic substrate as illustrated by Figure 4D. Having a nonzero twist requires nonzero tilt because the surface gradient of the lipid director equals the second fundamental form whenever tilt is zero locally. The twist deformation is a fully three-dimensional deformation. §4.3 addresses outstanding implementation issues like three-dimensional boundary integral equation solvers.

The gradient descent technique is ineffective for measuring the saddle splay modulus k_G because the saddle splay energy is largely invariant under shape changes. To evaluate k_G , we will combine the present particle simulations with the string method from PI RR's work on membrane fusion [180]. The string method is a numerical scheme that finds least energy pathways separating energy basins [52]. In the simplified Canham-Helfrich formulation, saddle splay energy is an exact indicator of topological transitions, thanks to the Gauss-Bonnet theorem [202]. More generally, PI RR has shown that saddle splay acts as a topological indicator even in the presence of nonzero tilt [180]. As a result, saddle splay can be quantified from the transition energies of a least energy path of pore formation (Figure 6).

The field of membrane continuum mechanics still lacks consensus as to whether HK energy is the appropriate functional for bilayer energy. (i) Researchers have assumed that $k_T = 0$ to effect lateral fluidity in membranes [69, 79, 164, 202]. A value $k_T = 0$, however, makes (8) a

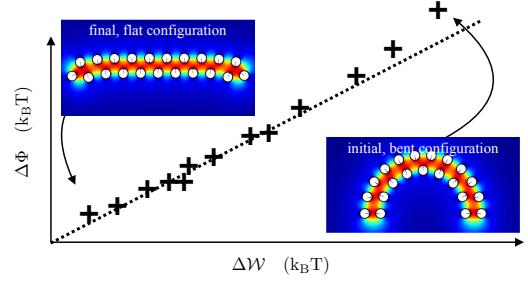


Figure 5. Example of computing bending modulus of a lipid bilayer from particle simulation.

noncoercive functional. (ii) Recently, [202] derived a tilt curvature term that was neglected from the HK analysis [79]. Later, [69] and [164] independently identified an inconsistency in the argument used by [202] arising from a transversal tilt invariance assumption. In [180], PI RR and collaborators showed that the tilt vector leads to unphysical cusps depending on how one accounts for membrane thickness. (iii) Theoretical analysis of lipid phase transitions predict a negative saddle-splay modulus around $-8 \text{ k}_\text{B}T$ [194, 195] that gives rise to a larger energy barrier for monolayer fusion than is found by experiments [62, 202, 204].

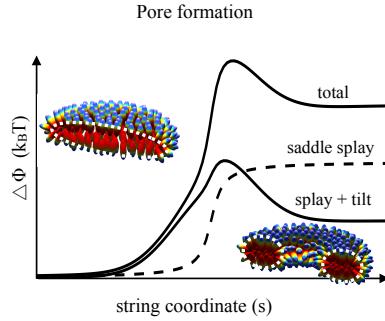


Figure 6. Example of determining the saddle splay modulus.

Steiner-type polynomial in $\text{div } \mathbf{n}$ and $\det \nabla \mathbf{n}$ [58]. In contrast, the works [69, 79, 164, 202] utilize an approximate identity for incompressibility as a base, so we can considerably improve upon the analysis of monolayer energy.

4.1.2 Analysis of the HAP model in terms of the HK functional

The HK functional (σ) has had tremendous impact in understanding biological membranes, but has received little attention in terms of mathematical analysis. In the calculus of variations, the principal question is whether a minimizer of an energy functional exists. In the case of (8), the answer is presently unknown. With regard to the simpler Canham-Helfrich energy, [198] proved the existence of minimizing surfaces without boundary, and [175] proved the well-posedness of a spatially periodic, time-dependent elastic interface problem. An analytical challenge for the HK functional (8) is that surface-director coupling makes it possible to have bounded energy monolayers with corners, and such pathological examples must be ruled out before carrying over the arguments for the Canham-Helfrich functional to the present setting.

Our goal here is to develop tools that can explain functionals like (8) from first principles in terms of HAP. The papers [24, 187, 188] give statistical mechanical/mean field derivations of the Canham-Helfrich energy from a pair-potential for rod-like molecules, but do not include tilt, which is an indispensable deformation at biological scales. To make progress, we must first understand how the HAP functional behaves under various limits.

We first consider HAP in the limit of vanishing screening length. As a concrete model problem, we consider a collection of colloidal polyhedral where the binding energy of this system can be described by a discrete, lower semicontinuous functional Φ_0 whose value is the total surface area of the polyhedra minus two times the area of any overlapping faces. We conjecture that the Φ energy Γ -converges to Φ_0 [146], meaning that any cluster points of minimizers of Φ converge to a minimum of Φ_0 in the limit $\rho \rightarrow 0$. To address this conjecture, we employ boundary layer analysis for the screened Laplace equation [117, 117, 123, 178, 190]. The technique of Γ -convergence is a

The form of the elastic energy density (8) is the same as the Oseen-Frank energy density for nematic liquid crystals [5, 83, 204]. In fact, a lipid monolayer acts as one layer in a smectic phase [96, 138, 174]. Based on this observation, we propose to examine the HK analysis to resolve the aforementioned inconsistencies. We will expand the strain tensor in terms of a plane perpendicular to \mathbf{n} (instead of the monolayer tangent plane as done in the past works) so that the gradient terms in the elastic energy completely decouple. Using this expansion we prove an exact identity that gives the incompressibility condition by a Steiner-type polynomial in $\text{div } \mathbf{n}$ and $\det \nabla \mathbf{n}$ [58].

powerful tool for numerical approximations and with it we can help explain unexpected phenomena like hierarchical self-assembly in colloidal systems [131].

4.2 Specific Aim 2: Efficient, high-order methods for large-scale simulations

Over the past decade, there has been an explosion of interest in small-scale processes that utilize capillary forces and van der Waals interactions to coordinate movement and bind microscopic components in solvent [159, 200, 222]. Additionally, hydrodynamic interactions are central to fabricating complex, three-dimensional microstructures [33, 38, 120, 176]. Hydrodynamic effects cannot be ignored since they, like for the rates of biological functions like pore dynamics [179], set the rate of dissipation. In Specific Aim 2, we propose to develop efficient high-order numerical methods to simulate dynamic assembly of particles under HAP potential in a viscous solvent. As described in (7) and illustrated in Figure 7, the solvent phase is modeled by the Stokes equations for an incompressible, viscous fluid, and these equations are coupled to the screened-Laplace equation (2) through viscous and hydrophobic stress balance.

The HAP model requires solving exterior Dirichlet problems for the screened Laplace equation and the Stokes mobility problem at each time step in complex domains such as in Figure 1. If discretizing these equations with stencil-based numerical methods, the computational domain must be truncated, the fluid volume must be discretized, and artificial boundary conditions must be imposed. The artificial boundary conditions introduce additional error, and discretizing the volume results in an excessively large system of equations. Moreover, it is difficult to obtain high-order discretizations when the boundary surfaces are irregular. Alternatively, since we are solving constant-coefficient linear elliptic partial differential equations (PDEs), the solutions can be represented with layer potentials

$$u(\mathbf{x}) = \mathcal{K}[\sigma](\mathbf{x}) = \int_{\partial\Omega} K(\mathbf{x}, \mathbf{y})\sigma(\mathbf{y}) dS, \quad (9)$$

where σ is an unknown density function, and $K(\mathbf{x}, \mathbf{y})$ is a derivative of the fundamental solution of the PDE. By matching the prescribed boundary condition at $\mathbf{x}_0 \in \partial\Omega$ with the limit of equation (9) as $\mathbf{x} \rightarrow \mathbf{x}_0$, a boundary integral equation (BIE) for the density function is formed.

Numerical methods to solve BIEs have several advantages over their PDE-based counterpart: by construction, the layer potential (9) satisfies far-field conditions; only $\partial\Omega$ needs to be discretized; carefully chosen kernels $K(\mathbf{x}, \mathbf{y})$ result in a well-conditioned linear system that is solved with a mesh-independent number of GMRES iterations; and high-order or spectral accuracy is attainable with appropriate quadrature methods. PI RR and YNY's previous work [67] demonstrated that BIEs are a powerful tool to simulate two-dimensional suspensions of amphiphilic particles. In addition to improving two-dimensional simulations, the present proposal extends the results to

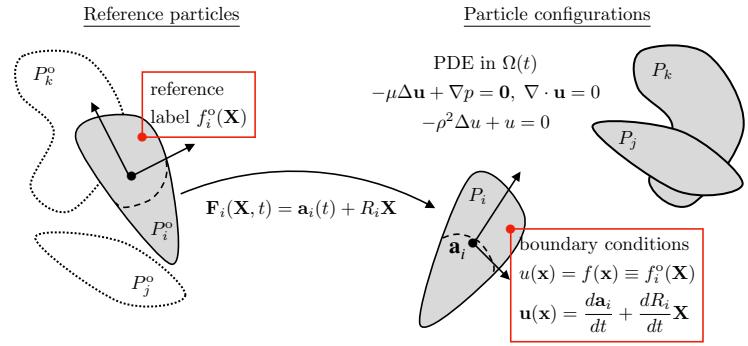


Figure 7. A collection of 3D amphiphilic particles suspended in a solvent. The solvent velocity satisfies the Stokes equations, and the hydrophobic forces depend on the solvent activity that satisfies the screened Laplace equation. The geometry is updated by solving the mobility problem.

three dimensions using a three-dimensional BIE formulation of the screened Laplace equation [218] and a well-conditioned BIE formulation of the mobility problem [170, 171].

Significant challenges to solving BIEs include solving dense linear systems, developing preconditioning strategies, and developing quadrature methods for nearly-singular integrands. These challenges are described in §4.2.1. However, numerical errors can still lead to unphysical contact between bodies. We propose two algorithms to avoid contact in §4.2.2. An identity to accurately compute the hydrophobic stress is in §4.2.3. Then, proposed work for well-conditioned BIE formulations of fluctuating hydrodynamics are described in §4.2.4.

4.2.1 Numerical issues

Discretizations of carefully chosen BIEs can be solved with a mesh-independent number of GMRES iterations [25]. Therefore, the required CPU time is proportional to the cost of a matrix-vector multiplication that can be performed in optimal or near-optimal time with the fast multipole method (FMM) [74] and its extensions [26, 29, 61, 72, 75, 217, 221]. PI BQ is experienced with applying FMMs for the Stokes equation [23, 166] and the screened Laplace equation [113, 165]. Alternatively, fast direct solvers avoid iteration [71, 76, 87, 88, 107, 136, 137, 144, 145], but often require a large amount of computational overhead, and this makes them less practical for problems with moving geometries. Alternatively, fast direct solver techniques can be used to develop efficient preconditioning strategies such as the inverse Fast Multipole Method (IFMM) [35]. PI BQ used the IFMM to precondition Stokes equations [168]. A suite of other preconditioners including sparse approximate inverses [28] and multigrid [86, 184] will be investigated.

Nearly touching bodies is ubiquitous in self-assembly of amphiphilic particles, and this results in nearly-singular integrands. Quadrature methods for these integrands have received a lot of attention in two and three dimensions [2, 3, 11, 13, 18, 20, 21, 39, 40, 49, 53, 73, 78, 84, 85, 98, 102, 103, 106, 133, 172, 185, 185, 193, 196, 210, 216, 218]. The trapezoid rule is the workhorse for two-dimensional BIEs since it achieves spectral accuracy when integrands are not nearly-singular [205]. To address nearly-singular integrands of two-dimensional BIEs, we will use a *barycentric quadrature rule* that only requires a slight modification of the trapezoid rule [92]. In its current form, this method requires the layer potential to satisfy Laplace or Stokes equations [10, 31], but the PIs will extend the method to layer potentials for the screened Laplace equation. This will be done by recognizing that the fundamental solution of the screened Laplace equation can be decomposed as $K(\mathbf{x}, \mathbf{y}) = K_1(\mathbf{x}, \mathbf{y}) + K_2(\mathbf{x}, \mathbf{y})$, where $K_1(\mathbf{x}, \mathbf{y}) = -\log |\mathbf{x} - \mathbf{y}|$ and $K_2(\mathbf{x}, \mathbf{y}) = K(\mathbf{x}, \mathbf{y}) + \log |\mathbf{x} - \mathbf{y}|$. Then, layer potentials involving $K_1(\mathbf{x}, \mathbf{y})$ can be accurately computed with the barycentric quadrature rule [92], and layer potentials involving $K_2(\mathbf{x}, \mathbf{y})$ can be accurately computed with the trapezoid rule since the kernel is bounded for all \mathbf{x} and \mathbf{y} . The proposed method is demonstrated in Figure 8, where the amplitude of the Fourier modes of $K(\mathbf{x}_0, \mathbf{y})$ and $K_2(\mathbf{x}_0, \mathbf{y})$ are plotted. The quadrature error of the trapezoid rule

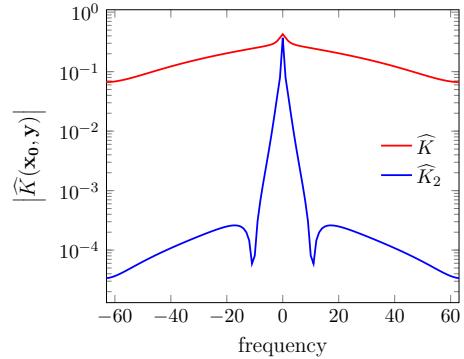


Figure 8. The Fourier modes of $K(\mathbf{x}_0, \mathbf{y})$ and $K_2(\mathbf{x}_0, \mathbf{y})$ where $|\mathbf{x}_0| = 0.99$, $\mathbf{y} \in \partial\Omega$, and Ω is the unit disk. The trapezoid rule applied to the red integrand has large amounts of error, but the trapezoid rule is much more accurate when applied to the blue integrand. Since the difference between the red and blue curves can be accurately computed with the barycentric quadrature rule, the quadrature error applied to layer potentials for the screened Laplace equation will be uniformly bounded in Ω .

is the sum of the unresolved Fourier modes.

4.2.2 Eliminating contact with adaptive time stepping and repulsion

A numerical issue when simulating the self-assembly of amphiphilic particles is avoiding particle collision. The hydrophobic attraction potential drives the amphiphilic particles towards one another and this leads to physical contact in finite time. Such particle collisions in a dense, rigid-body suspension are a great challenge and can be a bottleneck in large-scale simulations. We propose two algorithms to remedy this computational challenge: high-order adaptive time stepping and repulsion forces.

PI BQ developed a high-order adaptive time stepping method for hydrodynamic suspensions [167], and it has served as a robust method to simulate processes including mixing and adhesion in suspensions [100, 169]. The method uses a single-step, high-order time stepping method and a computationally cheap estimate of the error. The proposed work will use a spectral deferred correction method [51] since it iteratively applies a low-order, single-step method to achieve high-order accuracy. To estimate the error, at each time step, we will compute the total force and torque of the system which is computationally cheap and physically zero. PI BQ's experience is that error estimates based on physical constraints such as force- and torque-free conditions appropriately determine how the time step should be adjusted so that the dynamics are resolved without the computational expense of techniques such as embedded Runge-Kutta methods, step-doubling, and Richardson extrapolation.

Our previous work avoided particle contact through Lennard-Jones body forces [67]. Such steep, short-range, steric interactions introduce numerical stiffness and limit the time step size. To remove this stiffness, we propose a geometry-based contact method [81]. This method has been applied to vesicle suspensions [129] and to rigid body suspensions in two dimensions [23] and three dimensions [214]. These methods determine repulsion force by solving a non-linear complementarity problem with a geometric constraint that the configuration is non-overlapping. In this manner, contact is avoided without the excessively small time steps required by stiff Lennard-Jones forces.

4.2.3 Novel reciprocal identities

The force and torque formulas (5) use the hydrophobic stress along the particle boundaries. Unfortunately, layer potentials for ∇u involve hyper-singular integrals and this introduces large amounts of quadrature error on the particle boundaries (Figure 9). Therefore, it is useful to devise reciprocal identities for the force and torque on body i that do not require integration along body i . One identity, that we have proved, is

$$\mathbf{F}_{\text{hydro},i} = \sum_{j \neq i} \int_{\partial P_i} [\boldsymbol{\sigma}_{ij} + \boldsymbol{\sigma}_{ji}] \boldsymbol{\nu} \, dS, \quad \mathbf{G}_{\text{hydro},i} = \sum_{j \neq i} \int_{\partial P_i} (\mathbf{x} - \mathbf{a}_i) \times [\boldsymbol{\sigma}_{ij} + \boldsymbol{\sigma}_{ji}] \boldsymbol{\nu} \, dS, \quad (10)$$

for $i = 1, \dots, N$. Here, u_i is the solution of the screened Laplace equation when only the contribution from particle i is considered and $\boldsymbol{\sigma}_{ij} = \rho^{-1} u_i u_j \mathbf{I} + \rho ((\nabla u_i \cdot \nabla u_j) \mathbf{I} - 2 \nabla u_i \otimes \nabla u_j)$. Equation (10) does not require knowledge of ∇u on particle boundary i , and this is enormously beneficial for calculating the hydrophobic force and torque.

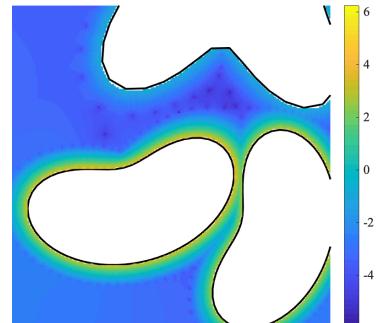


Figure 9. The false color map shows how numerical quadrature of layer potentials loses accuracy near the particle boundaries. The color bar is for \log_{10} .

4.2.4 Fluctuating hydrodynamics

Once algorithms that address quadrature, adaptive time stepping, and contact are implemented, we will embark on incorporating fluctuating hydrodynamics that are especially important at scales of amphiphilic particles. Bao et al. [8, 9] developed two-dimensional BIE formulations for Brownian rigid bodies. To satisfy the covariance of the rigid body velocities, they use an ill-conditioned, first-kind integral equation method. The proposed work will consider a layer potential formulation that has much better conditioning properties. This strategy was attempted in [9], but they claim that a necessary regularization of the covariance matrix leads to a drastic loss of accuracy in numerical fluctuation-dissipation balance. However, only one regularization strategy was considered, and as PI BQ has shown in previous work, the regularization choice significantly affects the resulting physics [156]. Therefore, different regularization strategies will be investigated with the goal of finding well-conditioned BIE formulations that control the accuracy of the fluctuation-dissipation balance.

4.3 Specific Aim 3: Dynamics of self-assembly by HAP under an external flow/field

4.3.1 Vesicles in background flows

Numerically solving the Stokes and screened Laplace system (2) and (7) is nontrivial, and we will develop efficient, robust, high-order-in-time and -space algorithms suited to the problem. There are a few challenges. **(i)** The equations express a two-way coupling since the flow changes the position of the suspended particles, and in return, the geometry-dependent hydrophobic stresses impart a force on the flow. **(ii)** The inputs to the Stokes equations are particle configurations, forces, and torques. The outputs are the rigid body translation and angular velocities used to update the particle positions (see Figure 7). Although the underlying equations are linear, the overall problem is highly nonlinear because the domain is constantly changing. **(iii)** Self-assembly causes the particles to come into close contact. As a result, an exceptional spatial accuracy is required to resolve the fields between adjacent particles. Furthermore, physically relevant elastic properties of bilayers become apparent at large length scales and for large particle-numbers, which increases the computational complexity of our simulations.

We include a background flow by replacing the third equation in (7) with the condition $\mathbf{u}(\mathbf{x}) \rightarrow \mathbf{u}_\infty(\mathbf{x})$ as $|\mathbf{x}| \rightarrow \infty$. To incorporate the far-field flow, we use the representation

$$\mathbf{u} = \mathbf{u}_\infty + \mathcal{K}\boldsymbol{\eta} + \sum_{i=1}^N (S(\cdot, \mathbf{a}_i)\mathbf{F}_i + R(\cdot, \mathbf{a}_i)\mathbf{G}_i), \quad (11)$$

where S and R are stokeslets and rotlets supported at the respective particle centers [116] and $\mathcal{K}\boldsymbol{\eta}$ is a layer potential for the unknown density function $\boldsymbol{\eta}$. With the exception of the rigid body conditions, the representation (11) automatically satisfies all the hydrodynamic equations including the far-field condition. The rigid body conditions follow by requiring the viscous stresses to vanish across the particle boundaries. We will compare the behavior of our particle-based vesicles in Stokes flow to well-established models that enforce area incompressibility and volume conservation in vesicle membrane dynamics [125, 134, 201, 203]. §5 contains our preliminary results.

4.3.2 Electromechanical effects on the dynamic assembly of amphiphiles

In recent experiments [56], membrane bending rigidity was determined as a function of lipid composition from 0 to 100 mol % of charged lipids using flicker spectroscopy of the shape fluctuations

of a giant unilamellar vesicle (GUV). Membrane bending rigidity increases with increasing lipid surface charge, which decreases with increasing salt concentration in the bulk solution due to the screening of the lipid surface charge. This agrees with several theoretical models [112, 126, 140] that also assume the quadratic form of the elastic energy density in the presence of surface charge and bulk charge [50, 212]. As the electrostatic interaction is non-local in nature, we expect that the controversy of the HK elastic energy form (see §4.1) would worsen in the presence of electrostatic interactions and electrokinetics. The PIs will extend the approaches in §4.1 to charged lipids to calculate the bending moduli and compare against the experimental results in [56]. We propose to incorporate an explicit surface charge on each particle boundary P_i and compute the electrostatic potential as a functional of particle configuration. Adding the electrostatic force to the hydrophobic attraction force between particles, we will assess the dependence of elastic moduli on electric charges using the methods described in §4.1. Results from these proposed calculations will provide further comparisons and validations of the HAP model against the continuum mechanics.

Once the effects of lipid charges on the moduli are verified, the PIs propose to examine how to use an external electric field to control the amphiphilic self-assembly in solvent. PI YNY has a track record of working on electrohydrodynamics of an elastic, inextensible membrane using both asymptotic analysis [151, 219, 220] and numerical simulations [153] and will work with both PIs RR and BQ to extend the HAP model to study the electromechanical effects on the assembly of amphiphile. Results from this research will yield a quantitative understanding of how to utilize an electric field to achieve optimal control of assembly of amphiphiles in solvent.

5 Preliminary work

PIs RR and YNY started work on HAP modeling with Szu-Pei Fu (then PI YNY's student and now PI RR's postdoc) and collaborators in 2017. The results are summarized in [67], where small particle-number simulations successfully demonstrated gradient-driven self-assembly of amphiphilic particles into two-dimensional micelles and bilayer membranes with realistic values of the model parameters: decay length $\rho = 2.5$ nm (based on measurements of hydrophobic attraction between surfactant-coated surfaces [54, 95, 124, 160]), particle diameter $\delta = 2.0$ nm (the physical monolayer thickness [16]), and interfacial tension $\gamma = 4$ pN nm⁻¹ (based on measurements for single-component bilayer lipid membranes [70, 97, 115, 162]).

n	(rel. err.) _F	(rel. err.) _G
32	$4.07 \times 10^{+0}$	$1.56 \times 10^{+0}$
64	2.47×10^{-1}	3.48×10^{-2}
128	6.30×10^{-4}	6.00×10^{-5}

Table 2. Relative numerical errors $(\text{rel. err.})_F = \max_i \|\mathbf{F}_i - \mathbf{F}_i^{\text{exact}}\| / \|\mathbf{F}_i^{\text{exact}}\|$ and $(\text{rel. err.})_G = \max_i \|\mathbf{G}_i - \mathbf{G}_i^{\text{exact}}\| / \|\mathbf{G}_i^{\text{exact}}\|$ for force and torque, respectively, as a function of number of grid points n per particle. The data is for $N = 5$ particles; two of the particles are nearly touching at a distance of 1% of the particle diameter.

that the two main HAP parameters, γ and ρ , were assigned physical values from the outset rather

	HAP	experiment	ref.
k_B	11 ± 2.5 k _B T	10 k _B T	[96, 149, 150, 209]
k_A	34 k _B T nm ⁻²	$30\text{--}40$ k _B T nm ⁻²	[147, 148]
k_θ	12 k _B T nm ⁻²	10 k _B T nm ⁻²	[108, 115]

Table 1. Comparison of values of elastic moduli from the experimental literature and derived by HAP simulation.

The paper [67] considered three types of simulations. The first measured bending by loading a partially clamped planar bilayer. The second used a harmonic bond to dilate a circular bilayer. The third measured tilt using a decay equation from [115]. These simulations isolated three of the five deformations of (8), enabling us to read off elastic moduli from simulation data. The results agreed remarkably well with the values reported in the experimental literature (Table 1). The agreement is underscored by the fact

than being tuned to fit data.

PIs RR, BQ, and YNY initiated a collaboration in summer 2020 to develop the hydrodynamic model of §4.3. To date, we have written solvers for the two-dimensional boundary integral formulations of (2) and (7) that achieve third-order accuracy up to the boundary of the particles. The specialized reciprocal identity (10) gives spectral accuracy for force and torque (Table 2).

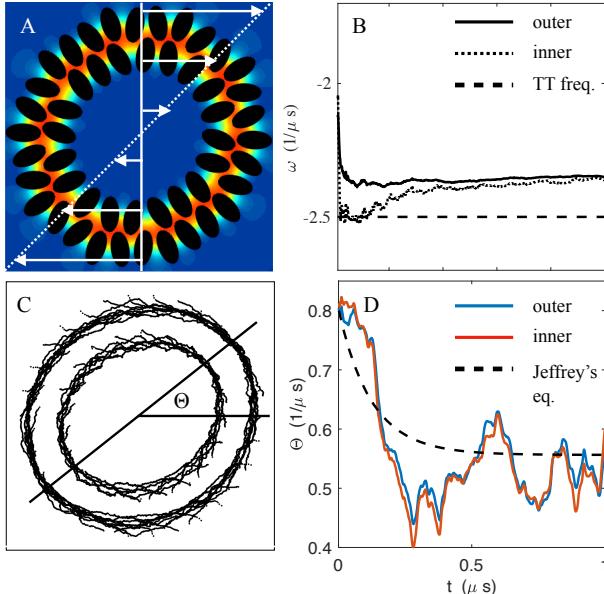


Figure 10. Panel A: A two-dimensional, particle-based vesicle in a shear flow (arrows); $\mu = 1 \text{ mPa s}$ and $\dot{\gamma} = 0.5 \mu\text{s}^{-1}$ (compare with [55]). Panel B: Angular velocities for the outer and the inner leaflets. Panel C: The trajectory of the particle centers forms two ellipses with well-defined inclination angle Θ . Panel D: The evolution of the inclination angle. Panels B and D share the same time axis.

an initial increase and then plateau in vesicle circumference, the particle collection permits a small amount of stretching. The theoretical calculations give an increase of length by 3.6%, in agreement with our measured length increase. The simulations also suggest that the particle system behaves as a semipermeable vesicle [27, 215].

The above considerations further justify using the particle-based model to study material properties as outlined in §4.1. Furthermore, the particle system allows for intermonolayer slip [191, 192]. In Figure 10B, the inner angular velocity is slightly less than the outer angular velocity. Intermonolayer slip enters zero-thickness membrane models as a velocity jump boundary condition [186], for example, but in the present model, it is a consequence of monolayer independence. For large shear rates, viscous forces exceed the hydrophobic attraction leading to vesicle rupture [158], at which point the flow carries away segmented membrane patches (Figure 11).

In conclusion, the HAP model accurately mimics the behavior of continuous membranes while at the same time capturing the reconnection during the topological change of lipid molecules on the scales of membrane thickness, overcoming one of the long-standing

We have simulated two-dimensional vesicles in shear flow $\mathbf{u}_\infty = \dot{\gamma}x_2\mathbf{i}_1$ with shear rate $\dot{\gamma}$, and the particle-based system mimics the behavior observed in continuous vesicles [125, 134, 201, 203]. The basic pattern is that of a vesicle bilayer approaching a steady, tank-treading ellipse (Figure 10C). We analyzed the simulation data in the context of theoretical work on tank-treading [60, 208]. Jeffrey’s equation predicts a tank-treading frequency $-\dot{\gamma}/2$ (dashed line in Figure 10B). In the particle simulation, we measured a tank-treading frequency as the mean of the particle angular velocities. The measured steady-state frequencies were within 7% of the predicted frequency (dotted and solid curves in Figure 10B). The inclination angle of the particle-based simulation also follows the inclination angle $\Theta(t)$ predicted by Jeffrey’s equation (Figure 10D), albeit with higher frequency oscillation coming from particle reorganization.

Analyzing for any underlying constitutive laws, the particles reorganize so that there is an initial increase and then plateau in vesicle circumference. As is the case with real lipid bilayer membranes, the particle collection permits a small amount of stretching. The theoretical calculations give an increase of length by 3.6%, in agreement with our measured length increase. The simulations also suggest that the particle system behaves as a semipermeable vesicle [27, 215].

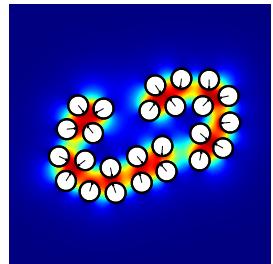


Figure 11. Rupture of a two-dimensional vesicle at large shear rates.

challenges of continuum modeling.

6 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 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 [65, 151–153, 157, 219, 220]. 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.

Bryan Quaife: *NSF DMS-2012560, Erosion, Transport, and Dispersion in Granular and Porous Media*, \$249,636, 08/01/2020–07/31/2023, PI. *Intellectual Merit:* The goal of this research is to develop high-order numerical methods to simulate hydrological processes including erosion.

Broader impacts: A second-year PhD student (Jake Cherry) has been assigned to this project. Since the funding just began, results have not yet been published or presented.

7 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. Quaife has been working on integral equation methods, fast algorithms, and their applications to fluid dynamics for many years. Their recent collaborative work on the HAP model in two dimensions has provided a solid foundation for the proposed research.

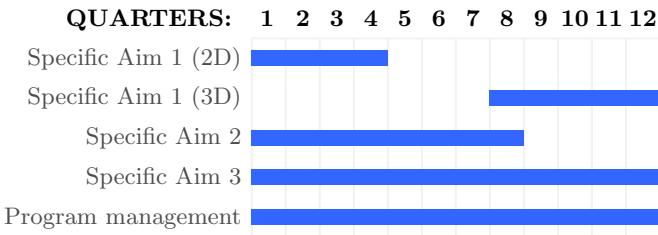


Figure 12. Schedule for the proposed work, measured in quarters from the beginning of the project.

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 §4. The PIs, the postdocs, and students will meet frequently on Zoom and in person when possible. During the pandemic, weekly Zoom meetings between the three PIs will be held. Once the pandemic is under control, PI RR and PI YNY will conduct biweekly meetings in person, with PI BQ Zoom in from Florida. 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 Figure 12. Specific Aim 1 is split over two periods to allow time for 3D code to be developed.

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