First-principle hydrodynamics and kinetics for solvent-free coarse-grained membrane models

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The great challenge with simulating bilayer membranes is the wide range of scales involved, from nanometer/picosecond pertaining to individual lipids, to the micrometer/millisecond scale of biological membranes. While solvent-free coarse-grained membrane models are convenient for large-scale simulations, and promising to provide insight into slow cellular processes involving membranes, the fact remains that these models cannot be trusted to reproduce the kinetics of lipid bilayer motion, even at their scales of interest. This is due to the fact that the dynamics of the solvent cannot be ignored at any scale, while a secondary, composition-dependent time-scale due to the in-plane diffusion of the lipids is also present. Thus, developing an implicit method that incorporates both dynamics into a unified approach remains a challenge. Here, we lay out a framework for implementing anisotropic stochastic dynamics based on semi-analytical solutions to Stokes hydrodynamic equations. We show how this approach offers realistic kinetics for membranes at both time-scales, while still offering very large timesteps. Using this framework, we study dispersion relations of planar membrane patches and show it to coincide very well with continuum-based predictions. We also demonstrate how the in-plane viscosity and diffusion can be tuned independently to empirical range of values.

I. INTRODUCTION

Due to their significant role in biological systems, lipid bilayers have been extensively studied from a biophysical point of view during the past four decades\textsuperscript{198}. Numerous computational models have also been proposed for membrane simulations at different scales,\textsuperscript{7–9} ranging from all-atom\textsuperscript{10–11} to coarse-grained\textsuperscript{12–16} and mesoscopic models\textsuperscript{17–20}. Still, providing integral models incorporating large-scale dynamic biomembranes, with robustly tunable parameter-spaces that reflect composition as well as local mechanics, and can interact with and be sculpted by proteins in the course of a biological process such as exo/endocytosis\textsuperscript{21}, remains a sizable challenge\textsuperscript{22}.

Considering length- and time-scales involved in biological processes, using highly granulated models is a necessity for comprehensive simulations\textsuperscript{23}. The so-called interacting particle reaction-dynamics (iPRD) models are good examples\textsuperscript{24,33}. Especially, considering the possibility to encode thermodynamic and kinetic information from the atomistic scale into the interactions and reactions driving these models\textsuperscript{24}. We have recently proposed a parametric membrane model that seamlessly integrates into iPRD simulations, while accurately reproducing bending rigidity, area compressibility, in-plane fluidity, and budding of biomembranes\textsuperscript{25}. While this, and similar approaches to coarse-graining membranes mostly focus on reproducing membrane properties in thermodynamic equilibrium, capturing membrane kinetics has attracted much less attention. All biological functions happen far from thermodynamic equilibrium\textsuperscript{35–36}, and the evolutions that these systems undergo, when they relax to metastable states or transition between them, directly depends on the kinetics. This fact necessitates the implementation of realistic kinetics as an essential part of membrane modeling, especially when dealing with the so-called solvent-free models, in which interactions are adjusted such that stable membranes are formed without requiring explicit solvents and hydrophobic effects\textsuperscript{31,34,35}. There has been different approaches to introducing solvent effects back into a solvent-free model. Examples are coarse-grained explicit solvents\textsuperscript{36–39}, time-mapping\textsuperscript{40–42}, and using the lattice Boltzmann method\textsuperscript{43–45}. In this paper, we aim to introduce a method more naturally integrable into the stochastic dynamics often used with coarse-grained models. The key is to use the well-established framework of hydrodynamic interactions.

Modeling hydrodynamic interactions has historically been of interest in the context of polymer physics\textsuperscript{46–47}. On the membrane front, the traditional approach has been to study hydrodynamic effects in the relaxation dynamics of membrane's undulatory modes\textsuperscript{48–50} in the context of continuum membrane models based on the Helfrich functional\textsuperscript{51–55}. This spectral approach allows for analytical solutions of Stokes equations in Fourier space, and closed-form dispersion relations\textsuperscript{49,51,55,57}. Although successful in describing macroscopic experimental observations\textsuperscript{52–59}, as previously observed by other researchers\textsuperscript{60}, these approaches are not readily applicable to particle-based simulations. There has been a recent interest in studying the hydrodynamics of the membrane and the solvent, when it affects in-plane diffusion of lipids\textsuperscript{51–55}, but out-of-plane dynamics of membranes and the corresponding hydrodynamic are still missing. This is understandable considering the sig-
ificant gap in the time-scales between in-plane and out-of-plane kinetics. In most investigations, small patches of membrane are considered and trajectories are not long enough for the membrane undulations and their kinetics to have a detectable effect. But if we are to look at system in which both time scales are present, e.g. membranes being remodeled by clustering proteins, hydrodynamics of the solvent can no longer be ignored.

Towards tackling this challenge, we propose an anisotropic stochastic dynamics to be used in conjunction with the hydrodynamics obtained from first principles. We introduce analytical or semi-analytical solutions to Stokes equations, in the form of the fluid domain response to localized displacements or forces. The resulting pressure and velocity fields are used to obtain friction and diffusion tensors, readily applicable to particle-based simulations. To showcase the validity of this approach, we derive dispersion relations of flat membrane patches, using membrane rigidity and anisotropic stochastic dynamics to be used in conjunction with the hydrodynamics obtained from first principles, we derive dispersion relations of the fluid response to point forces at particle positions. The outcome is referred to as the Oseen tensor, which uses the Stokes-Einstein relation for a particle, and adds

\[ D_{ij} = \frac{kT}{8\pi n_{ij}} (\mathbf{I} + \frac{n_{ij}}{r_{ij}}) \]  

with \( i \neq j \) for hydrodynamic interactions between particle pairs. Further improvements to this model are also available in the form of Rotne-Prager and Rotne-Prager-Yamakawa tensors.

The major reason that such solutions are not readily applicable to a coarse-grained membrane model, is the fact that the densely-packed assembly of particles forming a membrane, divides the solvent region into two half-spaces, breaking the symmetry assumed for the fluid domain in these solutions. Thus, a new description for the hydrodynamics compliant with this geometry is required. Even when hydrodynamic interactions are neglected, as will be shown, the out-of-plane mobility of membrane particles are poorly described by the Stokes-Einstein formula.

We consider a membrane model as schematically shown in Fig. 1A. With a local orthonormal basis at the outer surface of one of the leaflets, and the displacement of each particle decomposed as the sum of in-plane and out-of-plane contributions, it is trivial to see the two dissipative mechanisms acting in-plane and out-of-plane. The in-plane coordinates (projected on the \( b \)-axes) evolve in a stochastic motion governed by the viscosity of the bilayer membrane, whereas the out-of-plane coordinates (along the \( n \)-axis) are coupled to the fluid domain. To encapsulate both these regimes into one description, we propose the following general form for the diffusion tensor of membrane particles,

\[ D_{ii} = D_i^\parallel \mathbf{I} + (D_i^\parallel - D_i^\perp)n_i n_i \]

\[ D_{ij} = D_{ij}^\parallel n_i n_j , \ i \neq j \]  

where \( D_i^\parallel \) and \( D_i^\perp \) respectively representing the in-plane and the out-of-plane diffusion coefficients and \( n_i \) is the unit vector normal to the membrane surface at the position of the \( i \)-th particle. It is worth mentioning that a similar description holds for friction tensors with the \( \zeta^\parallel \) and \( \zeta^\perp \) components. In proposing these expressions, we have assumed that the most important contribution to hydrodynamic forces exerted by the solvent only occurs along the membrane normal. Considering the much larger in-plane viscosity of the membrane, shearing contributions of the solvent are overshadowed by the in-plane forces. Also, as we will explain further in Sec. III we have neglected in-plane hydrodynamic interactions.

\[ \Delta r_i = \Delta t \sum_j \mathbf{v}_j \cdot \mathbf{D}_{ij} + \frac{\Delta t}{kT} \sum_j \mathbf{D}_{ij} \cdot \mathbf{f}_j (t) + \mathbf{\chi}_i (t) \]

\[ \langle \mathbf{\chi}_i (t) \rangle = 0 \]

\[ \langle \mathbf{\chi}_i (t) \mathbf{\chi}_j (t') \rangle = 2\delta (t - t') \mathbf{D}_{ij} \Delta t \]  

For the case of spherical particles, several approximations of the \( D_{ij} \) tensor are available. The simplest, and most widely used approach, which completely neglects hydrodynamic interactions, is the Stokes-Einstein formula,

\[ D_{ij} = \frac{kT}{6\pi \eta R} \delta_{ij} \]  

with \( k \) being the Boltzmann constant, \( T \) the temperature, \( \eta \) the viscosity of the solvent, and \( R \) the particle radius. The primary approach in finding hydrodynamic interactions is to find the so-called Stokeslet, which is a Green’s function solution of Stokes hydrodynamic equations (Eq. (9)). This corresponds to the fluid response to point forces at particle positions.

\[ D_{ij} = \frac{kT}{8\pi n_{ij}} (\mathbf{I} + \frac{n_{ij}}{r_{ij}}) \mathbf{I} \]

\[ D_{ij} = D_{ij}^\parallel n_i n_j , \ i \neq j \]  

where \( D_{ij} \) is the diffusion tensor for the pair of particles \( i \) and \( j \), and the noise term, \( \mathbf{\chi}_i (t) \), is the outcome of a Gaussian process described by the moments,

\[ \langle \chi_i (t) \rangle = 0 \]

\[ \langle \chi_i (t) \chi_j (t') \rangle = 2\delta (t - t') \mathbf{D}_{ij} \Delta t \]  

with \( D_{ij} \) and \( D_{ij}^\perp \) respectively representing the in-plane and the out-of-plane diffusion coefficients and \( n_i \) is the unit vector normal to the membrane surface at the position of the \( i \)-th particle. It is worth mentioning that a similar description holds for friction tensors with the \( \zeta^\parallel \) and \( \zeta^\perp \) components. In proposing these expressions, we have assumed that the most important contribution to hydrodynamic forces exerted by the solvent only occurs along the membrane normal. Considering the much larger in-plane viscosity of the membrane, shearing contributions of the solvent are overshadowed by the in-plane forces. Also, as we will explain further in Sec. II we have neglected in-plane hydrodynamic interactions.
Figure 1: Schematic of first-principle hydrodynamics introduced into the mesoscopic membrane model. (a) the particle-based membrane model composed of a close-packed lattice of representative particle-dimers. For a membrane suspended in solvent, distinct membrane and solvent domains are shown. The local coordinate system describing the in-plane and out-of-plane directions, as well as a schematic of the Gaussian function used to represent velocity or stress boundary conditions per particle, are also shown for a selected particle. (b) three distinct membrane geometries used in the derivation of friction and diffusion tensors: (i) single planar membrane, (ii) parallel planar membranes, (iii) spherical vesicle.

Having the general form of the diffusion tensors, we can also inspect the divergence terms, \( \nabla \cdot D_{ij} \) in Eq. (2). Unlike the Oseen or Rotne-Prager tensors, these terms do not vanish identically, and are instead given by,

\[
\nabla \cdot D_{ii} = (D_{ii}^{\perp} - D_{ii}^{\parallel}) (\nabla \cdot n_i) n_i
\]

\[
\nabla \cdot D_{ij} = (n_i \cdot \nabla D_{ij}^{\perp}) n_j + D_{ij}^{\perp} n_i \cdot \nabla j n_j , \quad i \neq j
\]

The numerical values of the divergence terms in general depend on the way the normal vectors are defined. But considering the particles to define a smooth surface, we can conveniently replace \( \nabla \cdot n_i = -2H_i \), where \( H_i \) is the mean curvature at the position of the \( i \)-th particle. Also, noting that \( n_i \cdot \nabla j \) is the directional derivative along the \( n_i \), both terms would be negligible for low-curvature membranes.

In order to find expressions for \( D^{\parallel} \) and \( D^{\perp} \) (or equivalently, \( \zeta^{\parallel} \) and \( \zeta^{\perp} \)), in what follows, we look at the hydrodynamics of coarse-grained particles in the in-plane and out-of-plane directions.

### III. IN-PLANE DYNAMICS OF MEMBRANE PARTICLES

Although the in-plane hydrodynamics of bilayer membranes can also be studied rigorously\(^{(2)}\), it is not worth the effort to do so in a highly coarse-grained model that represents a collection of lipid molecules with just one particle. Also, it has been shown that for the in-plane diffusion in a membrane crowded with proteins, the hydrodynamics might reduce to a collision-based dynamics, resulting in a Stokes-Einstein-like diffusion\(^{(72)}\). That is the reason for resorting to a local mobility description in Eq. (4) for the in-plane hydrodynamics.

Now, if we consider our recently developed membrane model\(^{(20)}\), which shares some aspects of triangulated membrane models\(^{(73-75)}\), it can be argued that the in-plane dynamics of membrane particles in such a model is indeed affected by two cumulative dissipative mechanisms. The first dissipation is due to the stochastic dynamics used to update in-plane positions. To use a physically sound model for the in-plane mobility of particles, either the Stokes-Einstein model,

\[
D_i^{\parallel} = \frac{kT}{6\pi \mu_m R_i}
\]

or the more sophisticated Saffman-Delbrück model of the diffusion of cylindrical inclusions in fluid sheets\(^{(76,77)}\),

\[
D_i^{\parallel} = \frac{kT}{4\pi \mu_m d_m} \left[ \ln \left( \frac{\mu_m d_m}{\eta R_i} \right) - \gamma \right]
\]

can be used. In the former approach, particles are considered spherical with the radius \( R_i \), while in the latter they are cylindrical inclusion in the membrane domain, with the radius \( R_i \), which we consider to be half the lattice parameter of the model. \( \mu_m \) and \( d_m \) are the viscosity and thickness of the membrane domain, \( \eta \) is the viscosity of the surrounding medium, and \( \gamma \approx 0.577 \) is the Euler–Mascheroni constant. It is to be noted that we reserve \( \eta_m \) to represent the surface viscosity of the membrane when it is considered a two-dimensional surface, whereas \( \mu_m \) is arbitrarily attributed to a “fluid” filling the membrane domain.

The second dissipative mechanism is due to the bond-flipping Monte Carlo moves, in which the shared bond
between two neighboring triangles is flipped into the 
 opposing diagonal in a stochastic manner to simulate in-
 plane fluidity. As we previously showed[20], even with
 a deterministic integrator, in which the first dissipative
 mechanism is absent, the effective surface viscosity of
 the membrane, \( \eta_{m} \), can vary in a wide range of values,
 by changing the frequency of proposing bond-flipping
 moves. Here, the prescribed viscosity of the membrane
 domain, \( \mu_{m} \), offers another controlling mechanism. In
 Sec. [VIA] we show how we can measure and tune the
 accumulative outcome of these two mechanisms.

IV. HYDRODYNAMICS OF THE FLUID DOMAIN IN
THE VICINITY OF MEMBRANES

In contrast to the rather simple approach we took for
 in-plane dynamics, we are interested to include a real-
 istic model of the hydrodynamics of the solvent for the
 out-of-plane components, \( D_{ij}^{\perp} \) and \( D_{ij}^{\parallel} \). We derive these
 expressions in the following, through offering rigorous
 solutions to the hydrodynamics of the solvent domain
 described by Stokes equations.

For this purpose, we consider the response of the fluid
 domain to prescribed velocity and stress boundary con-
 ditions on the membrane surface. On the scales of inter-
 est, the viscous forces are much larger than the inertial
 effects of the fluid. For such a flow regime, the inertia-
 less Stokes equations hold:

\[
\eta \nabla^2 \mathbf{v} = \nabla p \quad \text{(8a)}
\]

\[
\nabla \cdot \mathbf{v} = 0 \quad \text{(8b)}
\]

where \( \eta \) is the viscosity, and \( \mathbf{v}(\mathbf{r}) \) and \( p(\mathbf{r}) \) are the respon-
sive velocity and pressure fields of the fluid. Considering
the solvent to be an incompressible Newtonian
 fluid, the stress tensor is given by:

\[
\sigma = \eta \left[ (\nabla \mathbf{v}) + (\nabla \mathbf{v})^T \right] - p \mathbf{I} \quad \text{(9)}
\]

We have considered the three geometries shown in Fig.
[1b] subject to velocity or stress Gaussian functions of the
following form,

\[
v^\pm(\mathbf{r}) = \frac{W}{4\pi \alpha^2} \exp \left( -\frac{r^2}{4\alpha^2} \right) \quad \text{(10a)}
\]

\[
\sigma^\pm(\mathbf{r}) = \frac{F}{4\pi \alpha^2} \exp \left( -\frac{r^2}{4\alpha^2} \right) \quad \text{(10b)}
\]

centered at the position of each particle (see Fig. [1a],
with the length-scale parameter \( \alpha \) giving the “size” of
particles from the perspective of the fluid domain. This
approach basically substitutes the usual Green’s func-
tion solution or Stokeslets with a more relaxed Gaussian
boundary condition.

We now consider the three geometries depicted in
Fig. [1b] in infinite solvent domains, and obtain analyti-
cal, or semi-analytical solutions to Eqs. (8), subjected to
boundary conditions generally described by Eqs. (10),
and specifically fashioned to each geometry.

A. Single planar membrane

Considering an infinite planar membrane suspended
in fluid, and assuming that the height fluctuations of the
membrane are negligible compared to the size of the
fluid domain, we are looking for solutions in the \( \mathbb{R}^3_{+} \) half-
space for prescribed velocities or stresses at the \( z = 0 \)
boundary (see Fig. [1b] (i)). Consider the Fourier trans-
form of the velocity field only in the \( x \) and \( y \) directions,

\[
\mathbf{v}(x, y, z) = \frac{1}{(2\pi)^2} \int d^2 q \tilde{\mathbf{v}}(q_1, q_2, z) \exp(\mathbf{iq} \cdot \mathbf{r}) \quad \text{(11)}
\]

where \( q = (q_1, q_2, 0) \) and \( d^2 q \) is a shorthand for \( dq_1 dq_2 \).
A similar Fourier transform is used for the pressure
field, \( p(x, y, z) \), and the stress field, \( \sigma_{ij}(x, y, z) \), respec-
tively denoted by \( \tilde{p}(q_1, q_2, z) \) and \( \tilde{\sigma}(q_1, q_2, z) \). Following
Kramers[28], we use the orthonormal basis \( \hat{z}, \hat{q}, \) and \( \hat{z} \times \hat{q} \)
in the Fourier space, with the respective components of
the \( \mathbf{v} \) vector field given by \( \tilde{v}_\parallel = (\hat{z} \times \hat{q}) \cdot \mathbf{v}, \tilde{v}_\perp = \hat{q} \cdot \mathbf{v}, \) and
\( \tilde{v}_z = \hat{z} \cdot \mathbf{v} \). Thus transforming both sides of the continuity
equation (Eq. (8b)) yields,

\[
\mathbf{iq} \tilde{v}_\parallel + \frac{\partial \tilde{v}_z}{\partial z} = 0 \quad \text{(12)}
\]

Similarly, for the momentum diffusion equation (Eq.
8a):

\[
\eta \left( -q^2 + \frac{\partial^2}{\partial z^2} \right) \tilde{v}_\perp = \left( \mathbf{iq} \times \hat{z} \frac{\partial}{\partial z} \right) \tilde{p} \quad \text{(13)}
\]

which component-wise breaks down to

\[
\eta \left( -q^2 + \frac{\partial^2}{\partial z^2} \right) \tilde{v}_\perp = 0 \quad \text{(14a)}
\]

\[
\eta \left( -q^2 + \frac{\partial^2}{\partial z^2} \right) \tilde{v}_\parallel = i\mathbf{q} \tilde{p} \quad \text{(14b)}
\]

\[
\eta \left( -q^2 + \frac{\partial^2}{\partial z^2} \right) \tilde{v}_z = \frac{\partial \tilde{p}}{\partial z} \quad \text{(14c)}
\]

Combining Eqs. (12), (14b), and (14c) leads to

\[
\frac{\partial^2 \tilde{p}}{\partial z^2} = q^2 \tilde{p}, \quad \text{which has the general solution of}
\]

\[
\tilde{p} = A_1(q) \exp(-qz) + A_2(q) \exp(qz) \quad \text{(15)}
\]

Similarly, from Eq. (14a) we have \( \tilde{v}_\perp = B_1(q) \exp(-qz) + B_2(q) \exp(qz) \). Finally, for \( \tilde{v}_z \),
the general solution that satisfies both Eqs. (14c) and
(15) is[29]

\[
\tilde{v}_z = \left[ \frac{A_1(q)}{2\eta} z + C_1(q) \right] \exp(-qz) + \left[ \frac{A_2(q)}{2\eta} \left( -\frac{1}{2q} + z \right) + C_2(q) \right] \exp(qz) \quad \text{(16)}
\]

Using Eq. (12) we have,

\[
\tilde{v}_\parallel = i \left[ \frac{A_1(q)}{2\eta} \left( \frac{1}{q} - z \right) - C_1(q) \right] \exp(-qz) + i \left[ \frac{A_2(q)}{2\eta} \left( \frac{1}{2q} + z \right) + C_2(q) \right] \exp(qz) \quad \text{(17)}
\]
For comparison, results from (a) and (b) are reproduced in other plots (black dashed lines).
Using Eq. (9), the normal stress in the \( z \) direction is
\[
\sigma_{zz} = 2\eta \frac{\partial \tilde{v}_z}{\partial z} - \tilde{p} = -\left[ A_1 (q) z + 2\eta C_1 (q) \right] q \exp(-qz) + \left[ A_2 (q) \left( -\frac{1}{2q} + z \right) + 2\eta C_2 (q) \right] q \exp(qz)
\] (18)

For a planar membrane in contact with a half-space of fluid, the velocity and the pressure fields should remain bounded as \( z \to \infty \). Thus, the \( \exp(qz) \) terms in Eqs. (15), (16), (17), and (18) are non-physical, leading to \( A_2 (q) = B_2 (q) = C_2 (q) = 0 \). On the \( z = 0 \) boundary, the solution reduces to:
\[
\tilde{v}_z (z = 0) = C_1 (q) \quad \text{(19a)}
\]
\[
\tilde{v}_\parallel (z = 0) = i \left[ \frac{A_1 (q)}{2\eta q} - C_1 (q) \right] \quad \text{(19b)}
\]
\[
\sigma_{zz} (z = 0) = -2\eta C_1 (q) q \quad \text{(19c)}
\]

We can now apply either a velocity or a stress boundary condition to obtain \( A_1 (q), B_1 (q), \) and \( C_1 (q) \). The boundary at \( z = 0 \) is formed by the particle-based membrane. If the no-slip condition is assumed on the membrane surface, the fluid velocity field and the surface velocity distribution, \( w(x, y) \), which is dictated by the motion of membrane particles, should coincide. Assuming the membrane also to follow the continuity condition of an incompressible fluid, we have \( iq\tilde{w}_\parallel (q) = 0 \). Thus, at the boundary, \( \tilde{v}_\parallel (q, z = 0) = \tilde{w}_\parallel (q) = 0 \) and
\[
A_1 (q) = 2\eta q C_1 (q)
\] (20)

The only remaining boundary condition corresponds to distributions of either \( v_z \) or \( \sigma_{zz} \) at \( z = 0 \). Considering one membrane particle, we can safely assume the prescribed boundary conditions (see Eqs. (10)) to be rotationally symmetric in the \( xy \) or the \( q \) plane. If the velocity distribution on the boundary is given by \( v_z^* (r) \) with \( r = \sqrt{x^2 + y^2} \), and the origin considered on a specific particle, the coefficient \( C_1 (q) \) is simply given by the Fourier transform of \( v_z^* (r) \) (Eq. (19a)), which due to its rotational symmetry is related to the Hankel transform of order zero as \( \tilde{v}_z^* (q) = 2\pi \mathcal{H}_0 [v_z^* (r)] \), with the transform pair \[79,80\]
\[
F (q) = \mathcal{H}_0 [f (r)] = \int_0^{\infty} f (r) J_0 (qr) r \, dr
\]
\[
f (r) = \mathcal{H}_0^{-1} [F (q)] = \int_0^{\infty} F (q) J_0 (qr) q \, dq
\] (21)

where \( J_0 \) is the zeroth order Bessel function of the first kind. The resulting stress distribution on the boundary is obtained using the Eq. (19c). Making use of the connection between Fourier and Hankel transforms, we have:
\[
\sigma_{zz} (r, z = 0) = -2\eta \mathcal{H}_0^{-1} [q \mathcal{H}_0 [v_z^* (r)]]
\] (22)

Similarly, if the stress is prescribed on the boundary by the function \( \sigma_{zz}^* (r) \), the resulting velocity on the boundary is
\[
v_z (r, z = 0) = -\frac{1}{2\eta} \mathcal{H}_0^{-1} \left[ \frac{1}{q} \mathcal{H}_0 [\sigma_{zz}^* (r)] \right]
\] (23)

Armed with Eqs. (22) and (23), and through assuming specific distributions for boundary velocity or normal stress, we can obtain corresponding velocity and stress fields.

**Gaussian velocity distribution:** We first consider the velocity boundary condition given by Eq. (10a), which in the current setup translates to \( v_z^* (r) = v_z^0 (r) \). We can consider \( W \) as an effective flux, to be thought of as \( W = A_p v_p \), with \( A_p \) being the area per particle and \( v_p \), an effective particle velocity. It is trivial to show that if the surface density of the membrane is given by \( \rho = m/A_p \), the upward linear momentum resulting from this velocity distribution would be the same as one particle with mass \( m \) and velocity \( v_p \). Using this boundary condition, and performing the Hankel transform, we get,
\[
\sigma_{zz} (r, z = 0) = -\frac{\eta W}{4\sqrt{\pi} \alpha^3} \times 1 \mathcal{H}_1 \left[ \frac{3}{2}; 1; \frac{r^2}{4\alpha^2} \right]
\] (24)

where \( 1 \mathcal{H}_1 \left[ a; b; z \right] \) is the confluent hypergeometric function of the first kind. For this special case of inputs, the hypergeometric function has a closed form expression in terms of Bessel functions,
\[
\sigma_{zz} (r, z = 0) = -\frac{\eta W}{4\sqrt{\pi} \alpha^3} \times e^{-\xi} \left[ (1 - 2\xi) I_0 (\xi) + 2\xi I_1 (\xi) \right]
\] (25)

where \( \xi = \frac{r^2}{4\alpha^2} \) and \( I_0 \) and \( I_1 \) are the modified Bessel functions of the first kind.

**Gaussian stress distribution:** Moving to the next case and applying the stress boundary condition given by Eq. (10b) to Eq. (23), we have,
\[
v_z (r, z = 0) = \frac{F}{8\sqrt{\pi} \alpha^3} \times e^{-\xi} I_0 (\xi)
\] (26)

where \( F \) now represents the total force existing between the membrane and the fluid.

Numerical results for the two cases are plotted in Figs. 2a and 2b, respectively. The applied Gaussian boundary conditions are also superimposed on the figures for range comparison. It can be observed that the fluid response to Gaussian velocity or stress boundary conditions is rather localized; though it decays more slowly when the stress boundary conditions are applied. Also, through integrating the resultant stress on the boundary in the former case, it can be shown that the total force exerted on the membrane by the solvent is identically zero. Obviously, no such property exists for the latter case, as we have forced a non-vanishing value of force to exist between the two through Eq. (10b). One last point to
mention is that having access to the solution for a general Gaussian boundary condition, and considering the fact the Stokes equations are linear PDE’s, superposition of such solutions can also be used to model more exotic velocity or stress distributions corresponding to different physical scenarios.

B. Parallel planar membranes

Now we consider a pair of parallel planar membranes separated by a distance \( h \), such that one lies on the \( z = 0 \) and the opposing one on \( z = h \) planes (Fig. 1b(ii)). The general results of Sec. IV A given in Eqs. (16), (17), and (18) are also valid for this case. We only need to apply a different set of boundary conditions,

\[
\tilde{v}_z (q, z = 0) = \tilde{v}_z (q, z = h) = 0
\]

\[
\tilde{\sigma}_{zz} (q, z = 0) = \tilde{\sigma}_{zz} (q, z = h) = 0
\]

For each of the two cases (application of the velocity or stress boundary conditions) four corresponding relations given in Eq. (27) are enough to yield values of \( A_1 (q) \), \( A_2 (q) \), \( C_1 (q) \), and \( C_2 (q) \). Without explicitly giving the expressions for these coefficients, we reproduce the final results. In the case of the prescribed velocity boundary conditions of Eq. (10a) applied on the membrane at \( z = 0 \), we have,

\[
\tilde{\sigma}_{zz} (q, z = 0) = -2\eta q \left[ \frac{1 + 2b e^{-b} - e^{-2b}}{1 - (b^2 + 2) e^{-b} + e^{-2b}} \right] \tilde{v}_z (q)
\]

\[
\tilde{\sigma}_{zz} (q, z = h) = -2\eta q \left[ \frac{e^{-b} \left[ 2 + b + (b - 2) e^{-b} \right]}{1 - (b^2 + 2) e^{-b} + e^{-2b}} \right] \tilde{v}_z (q)
\]

where \( b = 2qh \). It can be seen that if \( q > 0 \), with \( h \to \infty \), the solution given in Eq. (28a) converges to the one given for a single planar membrane in Eq. (19). The \( q = 0 \) case is a special exception arising from the fact that in this pure Dirichlet problem, the pressure and consequently, stress, are undetermined up to a constant. So, the fact that the solutions given in Eqs. (28a) and (28b) are singular at \( q = 0 \) in Fourier space amounts to the addition of an indeterminate constant in real space.

For the second case, where the stress boundary conditions of Eq. (10b) are applied on the membrane at \( z = 0 \), we have,

\[
\tilde{v}_z (q, z = 0) = -\frac{1}{2\eta q} \left[ \frac{1 + 2b e^{-b} - e^{-2b}}{1 - 2e^{-b} + e^{-2b}} \right] \tilde{\sigma}_{zz} (q)
\]

\[
\tilde{v}_z (q, z = h) = -\frac{1}{2\eta q} \left[ \frac{e^{-b} \left( 2 + b + (b - 2) e^{-b} \right)}{1 - 2e^{-b} + e^{-2b}} \right] \tilde{\sigma}_{zz} (q)
\]

It is to be noted that the velocity and stress boundary conditions used in Eqs. (28a), (28b), (29a), and (29b) and the resulting velocity and stress fields apply with mirror symmetry to both membranes. Given the complexity of these expressions, it is only possible to calculate the Hankel transforms numerically. To do so, we have used a piece-wise Gauss quadrature. To also remove the effect of the indeterminate constant pressure field in case of velocity boundary conditions, we set the far-field values of stress and pressure to zero.

Figs. 2c to 2f show the semi-analytically obtained stress and velocity distributions on the two membranes, in response to velocity or stress boundary conditions applied on one. These results are valid for hydrodynamic interaction between two parallel planar membranes as well as between a single membrane and a rigid wall in its vicinity, similar to what has been extensively investigated for continuum membrane model.54 Results are given for different values of the inter-planar separation, \( h \). In each graph, the corresponding values form the single planar membrane are also reproduced as black dashed lines. As expected, the solution for parallel membranes converges to that of the single membrane as \( h \to \infty \). Although, for values of \( h \) as large as 20\( \alpha \), there still exists a non-negligible deviation from a single membrane case, especially when the stress boundary conditions are considered.

C. Spherical vesicle

Finally, we consider the hydrodynamics predicted by the Stokes equations around a spherical vesicle (see Fig. 1b(iii)). This is an interesting case, especially to investigate the effect of membrane curvature on the hydrodynamics. Solutions of Stokes equations in rotationally symmetric spherical coordinates are best achieved through the introduction of the divergence-free stream function, \( \psi (r, \theta) \), defined such that

\[
v_r (r, \theta) = -\frac{1}{r^2 \sin (\theta)} \frac{\partial \psi}{\partial \theta} \tag{30a}
\]

\[
v_\theta (r, \theta) = \frac{1}{r \sin (\theta)} \frac{\partial \psi}{\partial r} \tag{30b}
\]

In this case, the general solution to the Stokes equations is given as

\[
\psi = \sum_{m=0}^{\infty} f_m (r) [A_m P_m^\prime (\cos \theta)] \tag{31}
\]
in which $P_m$ denotes the Legendre polynomial of order $m$ and $f_m(r) = \sum k_i r_i^k$ with $k_i$'s being the roots of the polynomial $k \frac{(k-3)}{(k-1)(k-2)-2m(m+1)} = -m(m+1)(m-2)(m+3)$. Using this stream function, we obtain the velocity and stress fields as

$$v_r(r, \theta) = \sum_{m=0}^{\infty} \frac{-A_m P_m(\cos \theta)}{r^2} \left[ m(m+1) f_m(r) \right]$$  \hspace{1cm} (32a)$$

$$v_\theta(r, \theta) = \sum_{m=0}^{\infty} \frac{A_m P'_m(\cos \theta)}{r} \left[ f_m(r) \sin(\theta) \right]$$  \hspace{1cm} (32b)$$

$$\sigma_{rr}(r, \theta) = \eta \sum_{m=0}^{\infty} A_m P_m(\cos \theta) \left[ r^3 f'''(r) \right]$$
$$- 3m(m+1)rf''(r) + 6m(m+1)f_m(r)$$  \hspace{1cm} (32c)$$

Assuming the following boundary conditions,

\begin{align*}
  v_\theta(r = R, \theta) &= 0 \\
  v_r(r = R, \theta) &= \sum_{m=0}^{\infty} v_m P_m(\cos \theta) \quad \text{or} \quad \sum_{m=0}^{\infty} s_m P_m(\cos \theta) \\
  \sigma_{rr}(r = R, \theta) &= \sum_{m=0}^{\infty} s_m P_m(\cos \theta)
\end{align*}  \hspace{1cm} (33)$$

and given the sequence of values of either the $v_m$ or $s_m$, we can find the values of $A_m$ coefficients and determine the velocity and stress fields uniquely. If we want to use a similar Gaussian distributed velocity or stress boundary condition here as well, due to the need for it to be rotationally symmetric, we need to consider it at the zenith ($\theta = 0$). The Gaussian function then needs to be expanded in terms of a finite number of Legendre polynomials to obtain values of $v_m$ or $s_m$. To achieve accurate results, we performed numerical expansion up to 87 terms in both cases.

The resulting stress and velocity distributions, in response to the two boundary conditions of Eqs. (10), are shown in Figs. 2a and 2b respectively. The distance between particles, $r_{ij}$, is measured along a great circle passing the two. Again, the results from a single planar membrane are reproduced for comparison. As expected, with increasing vesicle radius, the results approach those of a single planar membrane. Yet, they are in surprising agreement, even for small radii. This points to the fact that the curvature in general has little effect on the hydrodynamic interactions across the membrane. Based on this, we can confidently prescribe the use of the results obtained for a single planar membrane to more realistic cases where thermal undulations induce curvature distributions across the membrane.

\section{V. OUT-OF-PLANE COMPONENTS OF FRICTION AND DIFFUSION TENSORS}

Having a description of the hydrodynamics of the solvent in the vicinity of the membrane given in Sec. IV, we are now in a position to calculate the numerical values of the out-of-plane components of friction and diffusion tensors, $\z_{ii}$ and $D_{ii}^\perp$. The underlying approach is to interpret the boundary conditions of Eq. (10) as a test input, and numerically integrate the resulting fields over selected patches on the surface of the membrane, to obtain the response. We consider the boundary conditions to be applied at the position of the particle $j$, and we take the portion of the membrane surface attributed to the particle $i$ to be defined by the domain $\Omega_i$ with area $A_p$. This way we have,

$$\z_{ij}^\perp = \frac{F_{ij}^\perp}{v_{ij}^\perp} = -\frac{\int_{\Omega_i} \sigma_n \cdot dS}{W/A_p}$$  \hspace{1cm} (34a)$$

$$D_{ij}^\perp = kT \frac{v_{ij}^\perp}{F_{ij}} = \frac{kT/A_p \int_{\Omega_i} v \cdot dS}{F}$$  \hspace{1cm} (34b)$$

Considering circular disks as integration domains, for the case of a single planar membrane, the out-of-plane friction and diffusion components, $\z_{ii}^\perp$ and $D_{ii}^\perp$, can be analytically obtained,

$$\z_{ii}^\perp = 16\pi^{3/2} \eta \alpha c \frac{\zeta_c e^{-\zeta_c}}{[I_0(\zeta_c) - I_1(\zeta_c)]} \hspace{1cm} (35a)$$

$$D_{ii}^\perp = \frac{kT}{8\sqrt{\pi} \eta \alpha} \frac{\zeta_c e^{-\zeta_c}}{[I_0(\zeta_c) + I_1(\zeta_c)]} \hspace{1cm} (35b)$$

where $\zeta_c = \frac{r_i^2}{8\pi \eta c} = \frac{A_p}{8\pi \eta c}$. Having these results as functions of the length scale $\alpha$, it is possible to also consider the limiting case where $\alpha \to 0$. As the Gaussians given in Eqs. (10) would approach to delta functions, this would be equivalent to switching to an Stokeslet for the fluid response. Taking the limit in Eqs. (35a) and (35b), we have,

$$\lim_{\alpha \to 0} \z_{ii}^\perp = 2\pi \eta v_c$$  \hspace{1cm} (36a)$$

$$\lim_{\alpha \to 0} D_{ii}^\perp = \frac{kT}{2\pi \eta v_c}$$  \hspace{1cm} (36b)$$

Eq. (35b) and its limiting case, Eq. (36b), provide expressions, most similar in nature to the Stokes-Einstein formula $D = kT/6\pi \eta r$. Interestingly, the limiting case shows that membrane particles experience a threefold decrease in friction compared to free-floating spherical particles in a fluid. This is the result of the symmetry breaking in the fluid domain due to the presence of the membrane. Also, the solvent cannot permeate the membrane, and does not engulf the particles, but only affects them from one side. Using the approximation that for particles far apart, the expression under the integral in Eq. (34b) only weakly depends on radial separation, we can also find an approximation for the $D_{ij}^\perp$, 

$$\lim_{r_{ij} \to \infty} D_{ij}^\perp \approx \frac{kT}{4\pi \eta r_{ij}}$$  \hspace{1cm} (37)$$
Compared to the Oseen tensor (see Sec. III), this result shows half the magnitude of hydrodynamic interactions between membrane particles of a single planar membrane.

Apart from the given cases, it is not in general possible to find closed-form expressions for friction and diffusion tensors. However, we can find numerical results by considering the approach laid out in Eqs. (34a) and (34b). As we are interested in application of the introduced method in our particle-based membrane model, we have carried out the calculations for a hexagonal lattice of points with the constant lattice parameter of $a$. We have used disks with the area of $A_p$ around each particle as integration domains. The area per particle is
calculated based on the surface density of model particles forming each leaflet. Numerical integrations on the disks are performed using the Gauss quadrature with integration points and weights given by Kim and Song.

As was mentioned in Sec. [IV] the value of the parameter \( \alpha \) gives a length scale to the derived solutions of the Stokes equations. Thus, the ratio \( \alpha/a \) would serve as an effective scaling factor. To demonstrate, we have chosen \( \alpha/a = 0.1 \) and \( \alpha/a = 0.5 \), and we have calculated \( \zeta^{eq}_{ij} \) and \( D^{eq}_{ij} \) values for (i) a single planar membrane, (ii) two systems of parallel planar membranes, respectively distanced 5.0a and 10.0a apart, and (iii) two spherical vesicles with the respective radii of 6.7a and 13.3a. Numerical results for all the cases are compiled in Figs. 3a - 3d, as the values of \( \zeta^{eq}_{ij} \) and \( D^{eq}_{ij} \), versus the inter-particle distance, \( r_{ij} \). For the sake of comparison, the diffusion coefficient given by the Stokes-Einstein formula for a sphere whose cross-section area is the same as \( A_p \), as well as the hydrodynamic interactions predicted by the Oseen tensor are included in Figs. 3b and 3d.

Comparing the results of different configurations, it is pertinent to observe, as we also implied in Sec. [IV] membrane curvature has little effect on the out-of-plane components of the diffusion tensor (compare, for example, the results corresponding to single planar membrane, and the two spherical vesicles in Fig. 3b). Also, for the case of parallel membranes, the generally larger diffusion coefficients between particles lying on the same membrane can be considered as the cause for fluctuation-magnification observed for membranes near walls.

VI. RESULTS AND DISCUSSION

In order to investigate the in-plane and out-of-plane kinetics described by the methods laid out so far, we perform simulations using our recently developed membrane model. The bilayer is modeled as formed by particle-dimers in a close-packed arrangement, with a large lattice parameter of \( \sim 10 \) nm. The potential model governing bonded interaction is as follows:

\[
U_s(r_{ij}) = D_s \left[ 1 - \exp(-\alpha (r_{ij} - r_{eq})) \right]^2 \tag{38a}
\]

\[
U_{\theta_{ij}}(\theta_{ij}) = K_{\theta} (\theta_{ij} - \theta_{eq})^2 \tag{38b}
\]

\[
U_d(d_{ij}) = K_d (d_{ij} - d_{eq})^2 \tag{38c}
\]

Particles belonging to each leaflet are connected to their nearest-neighbor counterparts via Morse-type bonds (Eq. (38a)). Also, harmonic angle-bending potentials given by Eq. (38b) act against the out-of-plane rotations of these bonds (the primed index designates the opposing particle in a dimer). Finally, particles in a dimer are connected via harmonic bonds of the form described by Eq. (38c), which keeps the two leaflets together. Potential parameters for \( U_s \) and \( U_{\theta} \) are obtained using the parameter-space optimization technique described in. The physical properties of the membrane used as input for this procedure are as listed in Tab. [I] whereas the values of the potential parameters, obtained or chosen for simulations, are summarized in Tab. [I].

Particle trajectories are obtained by updating the positions of particles according to Eq. (2). The diffusion tensor is updated in each integration step based on instantaneous normal vectors. Normal vectors are calculated for triangles formed between in-plane bonds and averaged for each particle based on its neighboring triangles. All the simulations are performed at \( T = 298 \) K and we have chosen water with the viscosity of \( 0.890 \) mPa s as the surrounding fluid.

To sample from microstates describing a tensionless membrane, the in-plane degrees of freedom are coupled to the Langevin piston barostat.

Table I: Properties of the membrane used for the parameterization of the membrane model used with simulations in Secs. VI A and VI B. Values of the bending rigidity, \( \kappa \), and Gaussian curvature modulus, \( \bar{\kappa} \), are based on data given in, while for area compressibility modulus, \( K_{area} \), data from have been considered.

| \( d_{eq} \) (nm) | \( \kappa (kT) \) | \( \bar{\kappa} (kT) \) | \( K_{area} (Nm^{-1}) \) |
|-----------------|----------------|----------------|-------------------|
| 4.0             | 18.73          | -14.98         | 0.270             |

Table II: Parameters for the potential model given in Eq. (38), used for the membrane model. The first row corresponds to simulations in Secs. VI B and VI A while the second and third row are the reference values used for interpolation of parameters in Sec. ??.

| \( r_{eq} \) (nm) | \( \theta_{eq} \) (rad) | \( d_{eq} \) (nm) |
|-----------------|----------------|----------------|
| 10.0            | \( \pi/2 \)     | 4.0            |

| \( D_b \) (kJ/mol) | \( \alpha \) (1/\( \mu \)) | \( K_b \) (kJ/mol) | \( K_d \) (kJ/mol nm^2) |
|--------------------|----------------|----------------|-----------------|
| 9.91               | 0.12           | 20.74          | 6.19            |

A. Effective surface viscosity

In order to determine the effective in-plane kinetics arising from the dissipative mechanisms described in Sec. [III] we measure the surface viscosity of square-shaped membrane patches of \( 0.5 \) \( \mu \)m side length. We use 10 ms trajectories to ensure reliable statistics. In order to focus only on the in-plane kinetics, the out-of-plane direction of motion is constrained with a harmonic penalty. During the simulation, particle trajectories as well as the Virial stress tensor are sampled. We take two different approaches to measuring the effective surface viscosity. The first approach is to use the corre-
Thus, when the mobility increases, and in change the viscosity for more than one order of magnitude. The bond-flipping moves show a strong effect that can produce comparable results. For the in-plane diffusion coefficients, the value $D^\parallel = 0.5 \, \mu \text{m}^2 \text{s}^{-1}$ is comparable to the lateral diffusion coefficients of proteins bound to the surface of bilayer membranes. This is an ideal outcome, where the coarse-grained beads of the model can be used to represent positions of membrane-bound proteins.

**B. Dispersion relation for a planar membrane patch with hydrodynamic interactions**

In order to investigate the out-of-plane kinetics of membranes subject to the hydrodynamics described here, we have used the numerical values obtained in Secs. III and IV to fully construct diffusion tensors of Eq. (4). It is well-known that hydrodynamic interactions are in general long-range and there are methods similar to tackling their long-range contributions similar to electrostatic interactions, but it is worth noting that in contrast to systems of free particles, the hydrodynamic interactions among membrane particles have to compete with large forces resulting from the bending rigidity of the membrane. Based on this, and to reduce the complexity of the model, we have used a finite cut-off for hydrodynamic interactions, which at most coincides with half the lateral patch size. In order to construct the correlated random displacements given by Eq. (3), it is possible to use Cholesky decomposition of the assembled diffusion matrix, but this $O(N^3)$ operation in each step is very expensive. Instead, we use the approximation developed by Geyer and Winter to fully consider the long-range contributions similar to electrostatic interactions.

We investigate the relaxation dynamics of a planar membrane patch to extract its dispersion relation. Considering $h_q(t)$ to denote the amplitude of the undulatory mode with the wave vector $q$, for a square membrane patch of side $L$, in the absence of in-plane tension, we have:

$$\frac{1}{L^2} \langle h_q(t) h_q^\ast(0) \rangle = A_1 e^{-\omega_1(t) t} + A_2 e^{-\omega_2(t) t}$$

where $\kappa$ is the bending modulus of the membrane. Seifert et al. have provided theoretical values for the relaxation frequencies $\omega_{1,2}(q)$, based on a continuum elastic membrane with fluctuating leaflet densities. These values, denoted here as $\tilde{\omega}_{1,2}(q)$, are the eigenvalues of the time evolution operator.
Figure 5: Dispersion relation for a planar membrane patch suspended in water, modeled with the particle-based membrane model with the lattice parameter of 10 nm. Results are shown for (a) different cut-off radii used in the treatment of hydrodynamic interactions and (b) different choices of the scaling factor $\alpha/a$. Predictions of the continuum-based model ($\bar{\omega}_1$ and $\bar{\omega}_2$ functions) are included for comparison. The gray region shows the range of frequencies available depending on the sampling rate and the length of the trajectory.

Figure 6: Power spectrum of thermal undulations of membrane patches, for which the dispersion relations are given in Fig. 5. Dashed lines are fits of the function $C(qL)^n$ to the data, whereas the solid black line is the prediction of the continuum model as given by Eq. (40a).

Figure 7: Relaxation of the energy of the largest undulation mode, from a state far from equilibrium to the equilibrium value. Results are given for different choices of the cut-off radii considered in hydrodynamic interactions. Dashed lines are fitted exponential functions.
\[ \Gamma(h_q) = -\Gamma \left( \frac{\partial}{\partial t} \right) \bar{\rho}_q \]

\[ \bar{\rho}_q = -\Gamma(h_q) \]

\[ \Gamma(q) = \left( \begin{array}{cc} \frac{1}{4q^2} & 0 \\ 0 & \frac{1}{2(4b+2q^2+\kappa a_q q^2)} \end{array} \right) \]

\[ E(q) = \left( \begin{array}{c} -\frac{kq^2}{2} K_{\text{area}} q^2 - \frac{\eta q}{2 K_{\text{area}}} \\ -\frac{\eta q}{2 K_{\text{area}}} \end{array} \right) \]

with \( K_{\text{area}} \) being the area compressibility modulus of one leaflet, \( \kappa = \kappa_0 + \frac{1}{4} \kappa_0^2 K_{\text{area}} \), the effective bending modulus and \( b \) a phenomenological inter-leaflet friction coefficient. The smaller eigenvalue (slower dynamics) corresponds to in-plane density fluctuations, as well as the friction between the two leaflets, while the larger value (faster dynamics) corresponds to the viscous loss in the fluid. To use these expressions, the viscosity of the solvent, thickness, viscosity, bending rigidity, and area compressibility modulus of the membrane, are all a priori values used in the parametrization of the model and calculation of the diffusion tensors. The only remaining parameter is the inter-leaflet friction, \( b \). Experimental values of \( b \) are in the range \( 10^9 \) to \( 10^{10} \text{ N m}^{-2} \), while coarse-grained membrane simulations predict much smaller values of \( 1.4 \times 10^6 \text{ N m}^{-2} \). It is to be expected that the inter-leaflet friction coefficient be highly sensitive to the resolution with which the lipids are modeled Here, we have assumed \( b = 10^9 \text{ N m}^{-2} \) quite arbitrarily. Inter-leaflet friction mostly affects the slow mode \( \omega_1 \) and has little effect on the larger eigenvalue, which is the focus of our investigation.

We have used two different values of the scaling factor \( \alpha \) equal to 0.01 and 0.1 to obtain diffusion tensors. Also, for the case of \( \alpha = 0.1 \), we have performed simulations with cut-off radii of 50 nm, 100 nm, 150 nm and the maximum possible cut-off of \( L/2 \). We have performed simulations for a total time of 1.0 ms. For each frame, the height function, \( h(x,y,t) \), is obtained by mapping the vertical position of particles to a regular grid. Fast Fourier transform is used to obtain values of \( h_q(t) \), which are used to calculate the ensemble averages and the auto-correlation functions in Eqs. (40a) and (40b). The resulting dispersion relations, obtained by fitting bi-exponential functions to the autocorrelations, are given in Figs. 5a and 5b. The former plots show the effect of cut-off used for hydrodynamic interactions, while the latter gives results for two choices of the scaling parameter \( \alpha \). The power spectra of thermal undulations for all cases are given in Fig. 6.

Looking at the power spectra of thermal undulations, expected to follow Eq. (40a) (black solid lines in Fig. 3), demonstrates that the correct equilibrium distribution is achieved in all cases.

Figs. 5a and 5b show that in all cases, very good approximations of the desired dispersion relations, especially, the fast mode, \( \omega_2 \), are achieved. The cut-off radius, as well as the choice of the hydrodynamic scale parameter, \( \alpha \), at least in the range of inspection, are of little consequence to the general dynamical behavior. This outcome demonstrated that the proposed first-principle approach to hydrodynamics has yielded a valuable tool, that robustly reproduces correct large-scale membrane kinetics, when used with a highly coarse-grained membrane model. Instead of tampering with the inherent time-scales of the model itself, the out-of-plane dynamics is controllable by the \( a \) priori choice of solvent properties.

We now shift our attention from fluctuations around equilibrium configurations, which are what is modeled by Eqs. (40a) and (40b), towards the equilibration of the membrane from the initial flat configuration, which is inherently non-equilibrium. We observe that the cut-off radius of hydrodynamic interactions has a significant effect on the rate of this process. To quantify this, we have considered the time evolution of the thermal undulatory mode with the longest wavelength, and have considered the energy of this mode as a function of time. Fig. 7 shows the results for the four choices of the cut-off radius. Dashed lines in the plot are fits of the equation,

\[ \frac{kT}{\kappa (qL)^2} (1 - \exp(-t/\tau)) \]

to the initial segment of these time series. Note that unlike Eq. (40b), this is not a rigorous expression. The reason is that we are no longer considering fluctuations around an equilibrium state, but the dynamics of the system far from equilibrium, for which, arguably, no reliable statistical theory exists. The parameter \( \tau \) in such a model serves as an indicator for the time it takes for each case to equilibrate. The values of \( \tau \) as a function of the cut-off radius of the hydrodynamic interactions are plotted in the in-set pane in Fig. 7. The trend shows faster equilibration with the increase in the hydrodynamic interaction range. As we lack a complete understanding of the expected kinetics in this case, it is difficult to vouch for the betterment of the result. That being said, comparing the time-scales with their near-equilibrium counterparts from Fig. 5 suggests that larger cut-off values produce more consistent results across the equilibrium and non-equilibrium regimes.

VII. CONCLUSION

We have introduced a novel approach to anisotropic stochastic dynamics applied to coarse-grained membrane models. Using exact solutions of Stokes hydrodynamic equations in idealized geometries, we derived friction and diffusion tensors that fully describe in-plane and out-of-plane dynamics of model particles, while accounting for hydrodynamic interactions. This approach offers a simple, robust, and computationally viable means for tackling the two-scale dynamics of membrane particles in solvent-free models.
Apart from describing hydrodynamic interactions across the membrane itself, the resultant velocity and stress fields can in general be used as a background in which other entities such as proteins and nanoparticles, reside. This would result in a first approximation for the hydrodynamics experienced by these particles as well, and can lead to a more realistic dynamics for these particles in the vicinity of a fluctuating membrane.

We have looked at the two different kinetics present in the system, namely the in-plane diffusion and out-of-plane undulations of the membrane, as predicted by the current approach. We demonstrated that the in-plane kinetics of the model particles can be adjusted to match experimental observations in terms of the effective surface viscosity or lateral diffusion of model particles. The anisotropic scheme presented here allows for such manipulation without disturbing the out-of-plane dynamics of the membrane. This makes the model very reliable in simulating complex systems involving membrane-bound proteins, where in-plane diffusion affects their collective behavior. For investigating the much slower out-of-plane dynamics, we looked at dispersion relation for planar membrane patches. We showed how our first-principles approach to hydrodynamics facilitates the kinetics expected from a suspended membrane, when a priori values for membrane and solvent properties are used for parameterization of the particle-based model and calculation of diffusion tensors. We further investigated the effect of the range at which hydrodynamic interactions are included, and showed how this parameter affects the kinetics of membrane relaxing toward the equilibrium state. This is a very important result, when the model is considered at states far from equilibrium.

The approach described here is applicable to a wide range of coarse-grained membrane model with little adjustments. This dynamical picture, containing realistic kinetics for all the constituents of the system, opens the door to large-scale high-performance dynamical simulations. We believe this to be the only viable means to reliably investigate complex, membrane-related biological processes at their native time-scales.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare for this study.

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