The tension of a curved surface from simulation

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This paper demonstrates a method for calculating the tension of a system with a curved interface from a molecular dynamics simulation. To do so, the pressure of a subset of the system is determined by applying a local (virtual) mechanical deformation, fitting the response to that of a bulk fluid, and then using the Young-Laplace equation to infer the tension of the interface. The accuracy of the method is tested by calculating the local pressure of a series of water simulations at various external pressures. The tension of a simulated curved octane-water interface is computed with the method and compares well with the planar tension (≈ 46.7 dyn/cm). Finally, an ambiguity is resolved between the Harasima and Irving-Kirkwood methods of calculating the local pressure as a means for computing the tension. [<http://dx.doi.org/10.1063/1.4769880>]

I. INTRODUCTION

Evaluating the surface tension of curved interfaces from simulation presents theoretical and practical problems not encountered for planar systems.¹ For planar systems with periodic boundary conditions, the tension can be computed by examining the external force on the simulation cell necessary to keep the system at constant area, see, e.g., Refs. 2 and 3. For a spherical drop, no simple ensemble exists to keep the area constant; i.e., an ensemble that would be constrained by a measurable external force. The problem is compounded by the fact that the area of a curved molecular surface is rarely well defined, unlike the projected area of a planar interfacial system. Quantification of the energy of deformation of a curved surface then depends on how that surface is defined. This paper develops a practical solution to the problem of the tension of curved interfaces by examining the local pressure at the center of an enclosed surface (a quantity that can be measured experimentally) using virtual mechanical deformations. The method presented herein relies on the connection between pressure differences and tensions described by the Young-Laplace equation (YL), so that quantifying the tension of a curved surface is reduced to calculating the pressure at the interior of that curved surface.

The question of how to model curved surfaces is important in a biophysical context largely due to the interest in how the properties of the cell membrane affect and are affected by biological machinery. For example, the spontaneous curvature of a lipid leaflet in a bilayer may influence transmembrane protein conformation, spacing, and aggregation, as well as the energy of tubes or intermediates in endo- and exocytosis.^{4–7} Given a practical theory of the tension of curved systems applicable to detailed biophysical models, simulations could provide a description of bending free energies of the various biological constituents under controlled conditions.

To further motivate the need for an unambiguous theory for calculating the local pressure, in Sec. II the bending free

energy of a curved surface of finite thickness is examined and the model is reviewed for the case of a curved lipid leaflet in the inverse hexagonal phase of lipids. Section III presents a method for applying mechanical deformations to a region of a fluid, the response of which is modeled as having an internal pressure and effective surface tension. Equivalence between the local pressure and the thermodynamic pressure is established in the limit of large regions for which surface term can be neglected. Section IV describes the simulation protocol and some implementation details. Section V tests the mechanical deformation methodology on two molecular systems, a homogeneous fluid and a curved octane/water interface. Section VII proceeds with a summary and a brief commentary on the application of the method to biological systems. The Appendix discusses alternative methods of calculating surface tensions, and resolves an apparent ambiguity between the Irving-Kirkwood (IK)⁸ and Harasima-like⁹ (H-like) pressure profiles: specifically, for a uniform fluid the H-like pressure is non-uniform near the origin, in polar-coordinates. The Appendix demonstrates that the IK pressure has the same abnormality at the origin. Additionally, the use of the IK or H-like local pressure is shown to be irrelevant to the calculation of the tension of a curved surface in the absence of external constraints (as is commonly the case for curved systems).

II. REVIEW OF THEORY AND CONNECTION TO THE INVERSE HEXAGONAL PHASE OF LIPIDS

In biophysical analysis of the behavior of cells or membrane proteins, the lipid bilayer is often described by a flat surface with the ability to bend. The most common model of the surface free energy is the Helfrich Hamiltonian,^{10,11} where the free energy, F_H of surface S is parameterized in terms of the bending modulus, K_b , the radius of curvature $R(t, u)$ at a point, and the preferred, or spontaneous, curvature R_0^{-1}

$$F_H = \int_S dt du \frac{K_b}{2} [R(t, u)^{-1} - R_0^{-1}]^2, \quad (1)$$

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where t and u determine a point on the surface. The bending modulus K_b has units of energy; multiplied by $(R^{-1} - R_0^{-1})^2$, it is the energy per unit area for a surface deformed by curvature $R^{-1} - R_0^{-1}$ (so the per area units cancel the curvature units). This model takes into account the area change of a bent surface to second order. Although it is a model of an infinitely thin surface, Eq. (1) implicitly refers to the mechanical properties of real surfaces of finite thickness, like lipid bilayers or other thin films.

According to the YL equation, for a system with a curved interface that encloses an interior space (with radius R_s), the interior matter may be under different pressure than the total system pressure

$$\Delta p = \frac{2\gamma}{R_s} \quad (\text{sphere}), \quad (2)$$

$$\Delta p = \frac{\gamma}{R_s} \quad (\text{cylinder}). \quad (3)$$

Here, $\Delta p = p_{\text{int}} - p_{\text{ext}}$ is the difference of a measurable external pressure and the interior of, for example, a bubble or tube. Figure 1 shows a schematic of an interface between two fluids that is entirely enclosed by a surface region (labeled R2) responsible for the external/internal pressure difference (p_{ext} and p_{int} in the figure).

For a flat surface simulated with an ensemble of constant area, the tension of the projected surface area is unambiguously evaluated as

$$\gamma = \int_{-\infty}^{\infty} dz [p_N(z) - p_T(z)], \quad (4)$$

where the surface normal is along z , $p_N(R)$ is the normal pressure, and $p_T(R)$ is the tangential pressure.¹²

For a cylinder aligned along z with xy center at the origin, Schofield and Henderson state (in Eq. (5.3) of Ref. 13) that

the tension can be computed as (adapted from a sphere to a cylinder)

$$\gamma(R_s) = R_s \int_0^\infty dr \frac{1}{r} [p_N(r) - p_T(r)], \quad (5)$$

where now γ depends on where the curvature of the surface is chosen, R_s (i.e., the area of the surface is measured at R_s). Both Eqs. (4) and (5) measure free energy changes against external constraints that maintain the surface area. In the planar case, the constraint is naturally applied with fixed periodic boundary conditions. For use in simulation, Eq. (5) would require an external constraint on a curved surface. Such a constraint would likely prove to be impractical. The principal idea of this paper is that the tension of a curved surface can be calculated without applying external constraints. As described in detail in Sec. III, a particular region is assumed to be homogeneous (i.e., R1 of Fig. 1) and then the external system is treated as a constraining container whose applied pressure can be estimated by using free energy perturbations.

Due to surface thickness, γ is minimized at a particular value of the curvature; this variation of the tension with curvature was described by Tolman.¹⁴ Briefly, it is a consequence of the variation of the surface area of the distinct regions of a thick surface with curvature; when a surface curves, regions with unique chemical elements compress or expand proportionately (the r^{-1} term in Eq. (5)). An example is a leaflet of the lipid membrane with a lateral distribution of chemical polarity (alkyl tails, glycerol moieties, and charged head groups). The variation of tension with curvature is critical for a description of complex surfaces like the lipid membrane, and is a prime motivation for this study of curved surfaces.

Returning to Eq. (1), the mechanical parameterization of a surface, x-ray diffraction experiments^{15–18} of the inverse hexagonal phase of lipids, depicted in Fig. 2, measure the spontaneous curvature and bending modulus simultaneously. The experiment determines the pressure at the interior of the cylindrical lipid surface at different radii, where the radius is determined by the diffraction of x-rays that depends on the

FIG. 1. A diagram of a system consisting of two fluids with a surface (at R_s) enclosing interior pressure p_{int} and surrounded by exterior pressure p_{ext} . Three regions, inner (R1), the surface region (R2), and outer (R3), are delimited by dashed lines. The pressures in R1 (p_{int}) and R2 (p_{ext}) are considered to be approximately constant; the pressure becomes closer to uniform the further from the surface. A pressure description near the surface is poorly defined.

FIG. 2. A cartoon of the inverse hexagonal phase of a two-tailed phospholipid, where circles indicate zwitterionic head groups. The interiors of the cylinders are filled with water subject to pressure from the curvature frustration of the lipid surface. Liquid alkane molecules may be added that fill the interstitial voids.²⁰

lattice spacing. The pressure is measured relative to a polyethylene glycol regulated water bath of controlled osmotic pressure. According to Eq. (3), the interior pressure will depend on the surface tension and radius. The bending modulus is determined by the variation of γ with curvature, and the spontaneous curvature is determined by the minimum of pressure. These parameters apply to a specific point along the normal of the thick surface as described in Ref. 19. Frequently, the pivotal (or neutral) plane is chosen, where area compression and bending are decoupled. This plane is discussed in detail in the experimental work, for example, Ref. 16.

The task is then to determine the pressure at a particular region of a simulated condensed system. The above experiment uses an osmotic pressure difference with the assumption that the interior fluid is behaving like the homogeneous fluid that the pressure measurement was calibrated against. For a flat surface, the infinite volume above the surface is eventually bulk, so at one limit the approximation is clearly valid. For the curved system, where the interior fluid is not homogeneous it would have to be considered a part of the surface, and the quadratic expansion of the surface would diverge (the curvature of the interior surface would diverge and then no longer exist); i.e., the interior enclosed by the surface must be approximately homogeneous for the Young-Laplace model to be valid. This point is illustrated in Fig. 1; i.e., there must be a region of isotropic pressure at the interior, subject to the tension of the surface, for which the YL equation predicts the pressure. For the purposes of analyzing surfaces experimentally characterized in the above way, the question is then: How does one determine the pressure at a particular point in an inhomogeneous fluid, given that it is behaving like a region of an homogeneous fluid? This is the subject of Sec. III.

III. LOCAL MECHANICAL DEFORMATIONS

A. The external pressure from a mechanical deformation

A molecular dynamics simulation performed at constant volume experiences an effective external pressure, p_{ext} , maintaining the system volume. For a NVT ensemble (constant particle number, volume, and temperature), it can be calculated by summing over the forces and particle kinetic energies of the ensemble, using the virial formula

$$p_{\text{ext}} = -\frac{\partial F}{\partial V} = \left\langle \sum_{i,j} \frac{\mathbf{r}_{ij} \cdot \mathbf{f}_{ij}}{3V} \right\rangle + \rho k_B T, \quad (6)$$

where F is the free energy, V is the volume, $\mathbf{r}_{ij}$ is the Cartesian vector separating sites i and j exerting force $\mathbf{f}_{ij}$, ρ is the density, k_B is Boltzmann's constant, and T is the temperature. Bold symbols denote vector quantities ($\mathbf{r}_i$ is the position of particle i , whereas r is the distance from the origin). This expression can be obtained by calculating the derivative of the partition function with respect to a homogeneous expansion of the coordinates.

In this work, the same idea is used to calculate the pressure of a local, homogeneous region of a system. Instead of a simple $p_{\text{ext}}V$ term maintaining the system volume, the vol-

ume of the homogeneous region is maintained by the surrounding, inhomogeneous material. The method in this paper is to calculate the free energy change of expanding the local region, which increases proportionally to the volume of the region, and relate this to the local pressure. However, the free energy change is complicated by an additional tension-like term that increases with the surface area of the locally deformed region. By examining the size-dependence of the change in the free energy, these two terms can be fit and separated, as demonstrated in Secs. V and VI. First, the free energy change of expanding a local region by a general deformation must be described.

The free energy derivative with respect to an arbitrary deformation is available in Schofield and Henderson's work on spatially resolved pressure in Ref. 13, so it will only be summarized here. An infinitesimal mechanical deformation of the ensemble is represented by a coordinate transformation from $\mathbf{r}$ to $\mathbf{r}'$

$$\mathbf{r}' = \mathbf{r} + \lambda \mathbf{u}(\mathbf{r}), \quad (7)$$

where $\mathbf{u}(\mathbf{r})$ is a vector field and λ is a scaling parameter whose limit will be taken to zero. The partition function is calculated using the new coordinates, and the free energy change expanded in λ . Adapted from Ref. 13 for the case where the total potential is a sum of pair potentials and in the presence of an external force, $\mathbf{f}_{\text{ext}}(\mathbf{r})$

$$\Delta F(\lambda) = -\lambda \left\langle \sum_{i,j < i} [\mathbf{u}(\mathbf{r}_i) - \mathbf{u}(\mathbf{r}_j)] \cdot \mathbf{f}_{ij} + \sum_i \mathbf{u}(\mathbf{r}_i) \cdot \mathbf{f}_{\text{ext}}(\mathbf{r}_i) + \sum_i k_B T u_\alpha^\alpha(r_i) \right\rangle + O[\lambda^2]. \quad (8)$$

Here, $u_\alpha^\alpha(r)$ is the trace of the matrix formed by the derivative of the α component of $\mathbf{u}(\mathbf{r})$ with respect to the α Cartesian coordinate. This term is the Jacobian for the coordinate transformation and represents the local volume expansion. The first and second terms represent how the deformation acts against the forces of the system, i.e., the free energy goes down when the deformation $\mathbf{u}$ acts in the direction of the force. As demonstrated in Ref. 13, Eq. (8) can be generalized to arbitrary (not just pairwise) potentials.

In the case that $\mathbf{u}$ is an isotropic expansion, u_α^α is three (for three dimensions) and $\mathbf{u}(\mathbf{r})$ is $\mathbf{r}$. The first term reduces to $\sum_{i,j > i} \mathbf{r}_{ij} \cdot \mathbf{f}_{ij}$, and the third term reduces to $-3Nk_B T$. The transformation deforms the total volume through $\frac{dV}{d\lambda} = 3V$. Finally, with $\partial F / \partial V = \frac{\partial F}{\partial \lambda} / \frac{dV}{d\lambda}$, Eq. (6) is recovered (with $\mathbf{f}_{\text{ext}} = 0$).

The transformation $\mathbf{u}(\mathbf{r})$ can also be applied to a local homogeneous region of the system to obtain free energy derivatives of deforming the subsystem with the external system fixed. Equation (8) is still operative, but now the undeformed material acts on the homogeneous region through $\mathbf{f}_{\text{ext}}$. At equilibrium the free energy change from any perturbation included in the simulated ensemble is zero, implying that $\Delta F(\lambda)$ is zero for the planned local deformation of the homogeneous region when the contribution from the external force is included ($(\mathbf{f}_{\text{ext}}(\mathbf{r}) \cdot \mathbf{u}(\mathbf{r}))$). Just as for the total pressure in the NVT ensemble when $p_{\text{ext}}V$ is deduced from the internal virial,

$\langle \mathbf{f}_{\text{ext}}(\mathbf{r}) \cdot \mathbf{u}(\mathbf{r}) \rangle$ will be deduced from an effective local internal virial.

B. Deformations of a confined ideal gas

It may be helpful at this point to consider the simplest confined homogeneous fluid: an ideal gas in a cylindrical container with radius R_c that, upon collision, reflects the particle's incident momentum over a timescale of t_r . With no internal forces, from Eq. (8), the change of free energy (labeled with i.g. for the ideal gas) due to an isotropic radial expansion of the system (such that $\mathbf{u}(\mathbf{r}) = \{r_x, r_y, 0\}$ and $\mathbf{u}_\alpha^\alpha(\mathbf{r}) = 2$) is

$$\Delta F_{\text{i.g.}}(\lambda) = -\lambda \left[2Nk_B T + \sum_i \langle \mathbf{f}_{\text{ext}}(\mathbf{r}_i) \cdot \mathbf{r}_i \rangle \right] + O[\lambda^2], \quad (9)$$

which is expected to be zero because this equilibrium system should be stable with respect to local deformations.

The wall imparts, over a time period of t_r , a change in momentum of $2m\mathbf{v}$ where m is the particle mass and $\mathbf{v}$ is the velocity. The corresponding force over this time period is approximately $\frac{2m\mathbf{v}}{t_r}$ (the limit will be taken where t_r goes to zero). The thickness of the wall will be approximated as the distance a particle travels normal to the wall during this impulsive force, $|\mathbf{v} \cdot \hat{\mathbf{r}}|t_r$. The gas is present at the surface of the wall at density ρ . Integrating over the thickness of the wall gives (after integrating over the cylinder height and the polar angle)

$$\begin{aligned} \sum_i \langle \mathbf{f}_{\text{ext}}(\mathbf{r}_i) \cdot \mathbf{r}_i \rangle &= -2\pi h \int_{R_c - \frac{1}{2}|\mathbf{v} \cdot \hat{\mathbf{r}}|t_r}^{R_c + \frac{1}{2}|\mathbf{v} \cdot \hat{\mathbf{r}}|t_r} dr \frac{2mr^2|\mathbf{v} \cdot \hat{\mathbf{r}}|}{t_r} \rho \\ &= -4\pi h m \rho \langle |\mathbf{v} \cdot \hat{\mathbf{r}}|^2 \rangle R_c^2 + O[t_r^2]. \end{aligned} \quad (10)$$

The quantity is negative because the external force acts in the opposite direction of the deformation. Integration over the polar angle and simulation cell height introduced the factor of $2\pi h$.

Integrating over the Boltzmann distribution of velocities incident with the wall (chosen to be along the x axis without loss of generality) yields

$$\begin{aligned} Q_v &= \int_{-\infty}^{\infty} dv_x \int_{-\infty}^{\infty} dv_y \int_{-\infty}^{\infty} dv_z e^{-\frac{m}{2k_B T} (v_x^2 + v_y^2 + v_z^2)}, \\ \langle |\mathbf{v} \cdot \hat{\mathbf{r}}|^2 \rangle &= Q_v^{-1} \int_0^{\infty} dv_x \int_{-\infty}^{\infty} dv_y \int_{-\infty}^{\infty} dv_z v_x^2 e^{-\frac{m}{2k_B T} (v_x^2 + v_y^2 + v_z^2)} \\ &= \frac{k_B T}{2m}. \end{aligned} \quad (11)$$

Here, the integration over v_x only includes the half of the velocities that would cause collisions with the wall. Inserting the last line of Eq. (11) into Eq. (10) gives, in the limit of small reflection time t_r (or equivalently, wall thickness)

$$\sum_i \langle \mathbf{f}_{\text{ext}}(\mathbf{r}_i) \cdot \mathbf{r}_i \rangle = -2\pi h R_c^2 \rho k_B T = -2Nk_B T. \quad (12)$$

When Eq. (12) is inserted into Eq. (9), $\Delta F(\lambda)$ is zero to first order in λ as expected. Computing how the deformation impacts the internal virial alone implies that the total external

pressure is $\rho k_B T$

$$\Delta F_{\text{i.g.}}^*(\lambda) = -\lambda 2\pi h R_c^2 \rho k_B T + O[\lambda^2],$$

$$\Delta V(\lambda) = \lambda 2\pi h R_c^2 \rho k_B T + O[\lambda^2], \quad (13)$$

$$-\lim_{\lambda \rightarrow 0} \frac{\Delta F_{\text{i.g.}}^*(\lambda)}{\Delta V(\lambda)} = \rho k_B T.$$

Here, the asterisk on ΔF^* indicates this is the deformation free energy from Eq. (8) without the containing field term. Although here the steps are done analytically, in practice $\Delta F^*(\lambda)$ could be computed by recording $\langle u_\alpha^\alpha(\mathbf{r}) \rangle$ from a simulation of an ideal gas, and the quadratic term of ΔF^* (scaling like ΔV) would be fit well by an internal pressure. This is the strategy for estimating the pressure of a locally homogeneous region of fluid embedded in a complex heterogeneous environment, described in detail in Subsection III C.

C. The method

As with the case of the ideal gas in Subsection III B, it is necessary to separate the free energy of deforming a local homogeneous region of a large simulation into internal (virial) and external (containing field) contributions. An F^* with asterisk will refer to the free energy change of the internal region with the influence of the external matter treated as an unknown “container”-like term, modeled as

$$\begin{aligned} \Delta F^*(\lambda, R) &= -\lambda \left(\sum_{i, |\mathbf{r}_i| < R} \sum_{j < i, |\mathbf{r}_j| < R} [\mathbf{u}(\mathbf{r}_i) - \mathbf{u}(\mathbf{r}_j)] \cdot \mathbf{f}_{ij} \right. \\ &\quad \left. + \sum_{i, |\mathbf{r}_i| < R} k_B T u_\alpha^\alpha(\mathbf{r}_i) \right) + O[\lambda^2], \end{aligned} \quad (14)$$

$$= \lambda \sum_{i, |\mathbf{r}_i| < R} \langle \mathbf{f}_{\text{ext}}(\mathbf{r}_i) \cdot \mathbf{u}(\mathbf{r}_i; \lambda) \rangle + O[\lambda^2], \quad (15)$$

$$\approx -p_{\text{ext}} \Delta V(\lambda, R) - \gamma \Delta A_s(\lambda, R) + O[\lambda^2], \quad (16)$$

where A_s is the surface area of the region.

The parameters p_{ext} and γ can be extracted from multiple measurements of $\Delta F^*(\lambda)$ by selecting smaller or larger locally deformed regions (with radius R), because ΔV and ΔA_s will vary differently with R . R will refer exclusively to the size of the deformed region. Sections V and VI contain plots of $\partial F^*(\lambda, R)/\partial \lambda$ (to first order in λ and scaled by $(2\pi h)^{-1}$) vs. R from which p_{ext} is extracted. These examples demonstrate the accuracy of this model with detailed molecular force fields common in biophysical simulations.

Two mechanical perturbations will be used to calculate the local pressure of an approximately homogeneous region of a fluid. First, the isotropic expansion

$$r'^\alpha(\mathbf{r}) = r^\alpha + \lambda u^\alpha(\mathbf{r}) = r^\alpha + \lambda r^\alpha \quad (17)$$

will be applied to a cylindrical region with extent R , where α indicates a Cartesian component of the vector. The transformation u^α affects only the x and y coordinates, leaving z unchanged. It expands the volume to first order in λ by

$$\Delta V'(\lambda, R) = \pi h [(R + \lambda R)^2 - R^2] = 2\pi h \lambda R^2 + O[\lambda^2], \quad (18)$$

and changes the surface area at R by

$$\Delta A'_s(\lambda, R) = 2\pi h[(R + \lambda R) - R] = 2\pi h\lambda R, \quad (19)$$

where h is the height of the simulation cell in the axial direction. Second, the density preserving transformation

$$r'^\alpha(\mathbf{r}) = r^\alpha + \lambda u^\alpha(\mathbf{r}) = r^\alpha + \frac{\lambda r_0^2}{r_{xy}^2} r^\alpha, \quad (20)$$

will also be applied to a cylindrical region with extent R . Here, α refers only to the x and y components of $\mathbf{r}$; it leaves z (aligned along the cylindrical axis) unmodified. The transformation expands the volume to first order in λ by

$$\Delta V(\lambda, R) = \pi h \left[\left(R + \lambda \frac{R_0^2}{R} \right)^2 - R^2 \right] = 2\pi h\lambda R_0^2 + O[\lambda^2] \quad (21)$$

in the vicinity of the origin, and changes the surface area by

$$\Delta A_s(\lambda, R) = 2\pi h \left[\left(R + \lambda \frac{R_0^2}{R} \right) - R \right] = \frac{2\pi h\lambda R_0^2}{R}, \quad (22)$$

where the arbitrary factor R_0 is included so that λ is unitless. This second transformation has zero divergence everywhere except at the origin and so preserves the density everywhere except at the origin. Equation (21) indicates that for any size cylinder the transformation has the same volume change, so the volume change must be at the origin. This transformation is examined in additional detail in Sec. VI, where its use illuminates the YL equation for surfaces of finite thickness, and in the Appendix, where the behavior of the IK contour is counter-intuitive and has been a source of confusion in the literature.

The divergence at the origin makes calculation of the local internal virial impractical using the density preserving deformation. In this case, it is computationally less problematic to restrict the deformation to the material outside of the cylinder, and then calculate $\langle \mathbf{f}_{\text{ext}}(\mathbf{r}) \cdot \mathbf{u}(\mathbf{r}) \rangle$, where $\mathbf{f}_{\text{ext}}(\mathbf{r})$ is the force on the outer matter due to the local homogeneous region. An ideal gas container term is also included, as restricting the measurement of the partition function to when the particles are inside the local region is equivalent to applying a hard cylindrical container.

In practice, a simulation is executed using standard protocols, but with $\Delta F^*(\lambda, R)$ of the homogeneous region (from Eq. (14)) sampled periodically. The free energy of the mechanical deformation is then compared to what would be expected for a bulk fluid, using the model in Eq. (16). For R sufficiently large, ΔA_s would be negligible so that the free energy change would be attributable to an external pressure, p_{ext} . For finite sized regions, the R dependence will be used to determine p_{ext} and γ . The tension γ depends on the transformation used to compute ΔF^* , for example, $\mathbf{u}(\mathbf{r})$ in Eq. (20) expands the surface at constant density. It does not necessarily represent a physically observable tension like this work tries to calculate, instead it is simply a term in the fit of the free energy of deformation that depends on the deformed surface. As described in Sec. IV, the many R values required to construct the model can be sampled efficiently, with little overhead.

This method is only applicable in the case that the target region (e.g., R1 of Fig. 1) can be accurately described by an isotropic pressure. If this is not the case, for example, if the deformed region intersects part of the surface, $\Delta F(\lambda, R)$ will no longer scale as R^2 (in the case of the isotropic deformation). Instead it will depend on the complex nature of the surface, likely indescribable by any simple mechanical property like a tension or pressure.

An alternative to modeling the local pressure of a region is to measure the local chemical potential at points enclosed by a surface. The surface tension will be related to the change in chemical potential at the center of the surface with surface shape and size, for example, see Ref. 21. This method has the additional benefit of being well-defined even when the fluid at the center is inhomogeneous. However, fluctuating particle number simulations tend to be prohibitively expensive for complex force fields.

D. Equivalence with the total internal virial for large deformation regions

In the limit that the cylinder volume is much larger than its surface area, and for a simulation with periodic boundary conditions, the formula reduces to the virial expression for the pressure. The change in free energy is computed as

$$\Delta F^*(\lambda) = \lambda \sum_{i,j \in R} -\langle (\mathbf{r}_i^{x,y} - \mathbf{r}_j^{x,y}) \cdot \mathbf{f}_{ij}^{x,y} \rangle - \lambda k_B T (2\pi R^2 h) \rho. \quad (23)$$

Written in terms of the lattice vector R_c for each simulation cell

$$\Delta F^*(\lambda) = \lambda \sum_{c \in R} \sum_{i \in c, j \in R} -\langle (\mathbf{R}_c + \mathbf{r}_i^{x,y} - \mathbf{r}_j^{x,y}) \cdot \mathbf{f}_{ij}^{x,y} \rangle - \lambda k_B T (2\pi R^2 h) \rho. \quad (24)$$

Reduction to the virial expression requires making an assumption about the decay of interactions between a surface simulation cell and an interior cell. At the limit of large mechanical displacement, R , the number of surface simulation cells interacting with the interior, per unit height, will be $2\pi R$. The total interaction, $v_{\text{surface,central cell}}$, of a surface cell with the central cell (which individually go as n) will asymptote to some power of R^{-1}

$$v_{\text{surface,central cell}} \propto \int_{-\infty}^{\infty} dz 2\pi R \frac{1}{(z^2 + R^2)^{n/2}} \propto \frac{1}{R^{n-2}}. \quad (25)$$

If n is, for example, three, like the interaction between two dipole moments, the surface-interior interactions grow like R^{-1} . The mechanical deformation of the surface area goes like R (Eq. (19)) while the number of interior cells is proportional to R^2 (the total volume is $\pi R^2 h$). The contribution to the free energy will go as R^2 , and will appear to contribute to the total pressure in Eq. (16). This is a well-known complication of the use of Coulomb interactions for periodic boundary conditions when the unit cell has a dipole moment;²² the energy depends on the order of summation of the charges and is a boundary effect. This work assumes that the isotropic fluid does not have a dipole moment, a reasonable assumption for simple fluids

for which the constitutive molecules are rotationally averaged. For large R , the interior contributions, of which there are $\propto R^2$, dominate the surface interactions, of which there are only $\propto R$, and so

$$\frac{\partial F}{\partial V} = \lim_{\lambda \rightarrow 0} \frac{\Delta F^*(\lambda)}{\Delta V(\lambda)} = \sum_{i \in 0,j} - \left\langle \frac{\mathbf{r}_{ij}^{x,y} \cdot \mathbf{f}_{ij}^{x,y}}{2V_{\text{cell}}} \right\rangle - \rho k_B T, \quad (26)$$

the negative of which is the virial expression for the external xy pressure.

Before the limit of large R is reached to yield Eq. (26), the free energy change will include surface and volume terms. In this work, the dependence of the free energy change on the range of the deformation, R , is used to fit terms that are assigned as pressure and tension values, depending on how they scale with the deformation, according to Eq. (16).

Surface terms are the complicating factor behind local calculation of the pressure (if no forces cross the boundary of a region, the pressure is trivial). Indeed surface effects give rise to pressure variations (or what one interprets as pressure variations), so modifications to where surface effects are assigned (e.g., using the IK or H-like contours to define local pressures as discussed in the Appendix) changes the value of the pressure. The theory only yields observables through Eq. (8), where the mechanical deformation extends over the whole system volume and all surface effects between neighboring regions are canceled. Interpreting the value of a local pressure given by a particular choice of contour is thus not guaranteed to be meaningful. The Appendix explores a particular (but arguably representative) case of this phenomenon in the context of calculating surface tensions. This work avoids this problem by focusing on regions with (approximately) isotropic character, likely the only instance in which local pressure is meaningful, and by fitting and eliminating unambiguous surface terms that arise from treating the exterior, inhomogeneous system as exerting the external force.

IV. SIMULATION METHODS

Water/alkane and bulk water simulations were performed using standard simulation protocols, using the velocity-Verlet integration method²³ with a 1 fs time step. Bonds involving hydrogens were constrained using the SHAKE algorithm.²⁴ Long range electrostatics were incorporated using the particle mesh Ewald method.²⁵ Lennard-Jones type nonbonded interactions were switched to zero between 10 and 12 Å using the force switching algorithm of CHARMM.²⁶

Two octane/water systems were assembled, with 1323 and 923 TIP3P^{27,28} water molecules, respectively, and each with 649 octane molecules. The octane model is parameterized by the C27r alkane force field.²⁹ The initial water coordinates were taken from a bulk simulation, with water molecules removed outside of the target radius. The octane molecules were similarly extracted from a bulk simulation with those molecules overlapping significantly with the water cylinder removed. The configuration was minimized to relieve strong repulsions and equilibrated prior to extracting the free energies of deformation. The production segment of the trajectory was performed with the xy area fixed and the

z direction allowed to fluctuate at 1 atm pressure. Additional simulations at fixed xy tension were executed using the 923 water molecule system, otherwise using the same simulation protocols.

Dynamics trajectories were generated by the molecular dynamics software package NAMD³⁰ and pressure calculations were made using a developmental version of the CHARMM software package.

The quantity $\Delta F^*(R)$ in Eq. (14) is fit according to Eq. (16) to give the internal pressure of the region within R of the origin. The first term can be calculated efficiently by binning all particles or force centers within some maximum cutoff, e.g., 10 Å. For all particle pairs within the upper cutoff, the virtual deformation is accounted for by adding $-\mathbf{u}(\mathbf{r}_i) \cdot \mathbf{f}_i + \mathbf{u}(\mathbf{r}_j) \cdot \mathbf{f}_j$ to an array at the position of the highest bin. Finally, $\Delta F^*(R)$ can then be resolved for each bin (i.e., many R) by summing over interior bins. The second term of Eq. (14) can be calculated simply by averaging the density over the region, or by looping over the particles and applying the transformation $\mathbf{u}(\mathbf{r})$

$$\Delta F^*(R) \leftarrow \sum_{r_i < R} -m_i v_i^\alpha v_i^\beta \nabla^\beta u^\alpha(\mathbf{r}_i), \quad (27)$$

where v_i^α is the α component of the velocity of particle i , and $\nabla^\beta u^\alpha(\mathbf{r}_i)$ is the β component of the gradient of $\mathbf{u}(\mathbf{r})$ with respect to $\mathbf{r}$. For cylinders in periodic boundary conditions in the z direction (orthogonal to $\mathbf{R}$), it may be necessary to extend the sum over many neighboring unit cells. In the case of the density conserving transformation $\mathbf{u}(\mathbf{r})$ defined in Eq. (20), it is necessary to use Eq. (15) because the transformation diverges at the origin, and force contributions between pairs extend between the interior region and far-away force centers. The fast multipole method³¹ was used in this case, as charges can be scaled by $\mathbf{u}(\mathbf{r}_i)$ and the interactions summed over vast distances efficiently, although this requires separate calculations for each Cartesian component.

V. A COMPUTATION OF THE LOCAL PRESSURE

The applicability of the deformation energy method for calculating the pressure will depend on the details of the water model and the desired accuracy of the pressure. Figure 3 shows the results of using Eq. (14) to calculate the deformation free energy of bulk TIP3P water under various normal pressures, from 25 atm up to 600 atm (0.0004–0.0088 kcal/Å³). The values of ΔF^* , to first order in λ , are scaled by $(2\pi h)^{-1}$ so that the pressure dependence corresponds to the fit of the R^2 term. The computed local pressure matches the applied pressure within precision. Figure 4 (top) shows the scaled free energy of mechanical deformation as a function of the range of the deformation; the quadratic term is used to fit the pressure. In Fig. 4 (bottom), the deformation energy of water at 1 atm normal pressure has been subtracted (removing the substantial surface effect) to best show the quadratic dependence of the pressure on the free energy of deformation. The change in volume/area of the simulation is somewhat ambiguous in that the volume of a selected subsystem is ambiguous. This gives rise to, for example, the flat behavior of the free energy at small deformations. The

FIG. 3. Calculated pressure from a local region of an isotropic fluid (TIP3P water).

area uncertainty is fit by including in $\Delta V(\lambda)$ a displacement Δr such that, e.g., for Eq. (18), $\Delta V(r) = \lambda \pi h(r + \Delta r)^2$; this introduces a constant term in the fit to $\Delta F(R)$. The pressure is fit using the region only between 3.0 Å and 10.0 Å. The lower section is discarded because of the relatively large ambiguity of the volume of the deformation. The upper section is discarded to establish the accuracy of the procedure for small internal cavities; in Sec. VI, an octane/water interface is simulated with a small internal pressure region (ca. 10 Å). The method predicts the applied pressure within the certainty provided by the simulation, demonstrating that the pressure of a local region of a fluid can be calculated using a fit to Eq. (14) or Eq. (15). The supplementary material contains the results of applying the density-conserving transformation to compute the pressure, as well as fit information for the individual

FIG. 4. Free energy of deformation vs. the range of deformation for TIP3P water. At bottom the deformation free energy is subtracted from a 1 atm pressure calibration simulation.

isotropic pressure deformation simulations.³² The pressure is extracted with similar accuracy; interestingly, the effective tension present in the response to the transformation (50.5 dyn/cm) is close to the TIP3P water/vapor surface tension (53.2 dyn/cm) simulated with a planar interface.³³ This does not indicate, necessarily, how to short-cut the YL equation to compute a liquid/vapor tension (a segment of the isotropic fluid surface does not necessarily closely match the vapor/fluid surface) but it does nicely illustrate how effective Eq. (16) is as a model.

VI. COMPUTATION OF THE TENSION OF A CURVED SURFACE WITH FINITE THICKNESS

A tube of water in octane (Fig. 5) provides a simple model of the lipid hexagonal phase (Fig. 2). The correspondence is not complete because the octane-water surface area can adjust the amount of polar/apolar exposure by deforming the boundary conditions, whereas for the lipid system the area is largely fixed by the number of lipids. However, the principle of measuring a pressure drop to infer the tension using the YL equation can be tested thoroughly.

According to the YL equation, the tension is implied by measurement of the response of the fluid at the interior of the surface; large tension over a small surface area leads to a compressed fluid. It is helpful to reconsider the mechanical deformation in Eq. (20) applied to a cylindrical equilibrium system that has three regions, shown in Fig. 1: R1 consists of a homogeneous fluid at constant pressure p_{int} . R2 completely encloses a surface of ambiguous area whose tension is to be calculated. R3 consists of a homogeneous fluid at constant pressure p_{ext} . The pressure is constant across the region boundaries so that there are no surface tension terms between regions. Upon deformation by $\mathbf{u}(\mathbf{r})$ in Eq. (20), the entire system undergoes volume change $2\pi h R_0^2 \lambda$ and so the total free energy changes by $-2p_{\text{ext}}\pi h R_0^2 \lambda$. Volume changes of R2 and R3 are zero because they do not include the origin. R3 undergoes no free energy change because the volume change is zero, and there are no surface tensions between it and R2. R1 undergoes the same volume change, $\pi h R_0^2 \lambda$ but with pressure

FIG. 5. An image of the simulation cell of an octane-water cylinder generated with VMD (Visual Molecular Dynamics).³⁴

FIG. 6. The free energy of mechanical deformation for the water/octane system. The fit of the free energy of deformation indicates that the water interior is under substantial normal pressure due to the surface tension of the interface.

p_{int} . The remaining free energy change, $(p_{\text{int}} - p_{\text{ext}})2\pi h R_0^2$, is attributable to the change in R_2 . Suppose R_2 is modeled as having a surface with tension γ_s located at R_s . Under the deformation the area of the surface changes by $2\pi h \lambda R_0^2 / R_s$ so that

$$\gamma_s = \Delta p R_s. \quad (28)$$

A continuum of γ_s, R_s pairs satisfy this equation. The “correct” value of R_s is only defined through the model; i.e., does choosing R_s to be at a particular surface (e.g., the Gibbs dividing surface) produce the predicted Δp when the surface geometry is changed? At least two simulations appear to be necessary to model a consistent surface of tension,¹ e.g., if the tensions of two simulations are equated, the ratio of the two radii can be deduced and matched to a model.

Figure 6 shows the free energy of deformation of two octane/water cylindrical systems (with different radii) as a function of the range of the deformation. The values correspond to $\Delta F^*(R)$ from Eq. (14), scaled by $(2\pi h)^{-1}$ so that the R^2 term is fit directly as the pressure. The fit to the deformation energy yields the local pressure relative to the bulk calibration. For this system, the fit was truncated at 7.5 Å, past which the smaller radius simulation exhibits the effects of the surface interactions with octane (i.e., the fit pressure began to depend on the upper cutoff beyond 8 Å, while below this it was approximately uniform). The quadratic term of the fit indicates that the water at the interior of the system is at a pressure of 0.00520 kcal/Å² (ca. 355 ± 11 atm) for the system with surface at approximately 15 Å, and 0.00629 kcal/Å² (ca. 430 ± 7 atm) for the system with surface at approximately 13 Å. These are internal pressures (p_{int}) measured against an external pressure of 1 atm (p_{ext}). The ratio $\frac{R_1}{R_2} = \frac{\Delta p_2}{\Delta p_1} = 1.21$ agrees well with the water density plotted in Fig. 7, that is, the larger radius is approximately 20% greater than the smaller.

A γ and R_s pair consistent with the YL equation can be extracted with reference to a particular surface. The variation of the mechanical constants depending on the position of the surface is discussed in depth in Ref. 19.

A Gibbs-like dividing surface should produce a “scale-invariant” value for the surface radius, one that does not depend on the size of the droplet. In this example, the planar value of the surface tension is compared to the curved value;

FIG. 7. The densities plotted as a function of the distance from the origin for two simulations with different radii. The water at the center of the smaller radius is under greater pressure, as predicted by the YL equation ($p_{\text{int}} = \gamma / R_s$). The inset shows that the density at the interior of the water cylinder is larger for the system under greater pressure.

if the area per surface water molecule is inconsistent between the finite (curved) and infinite (planar) system, γ will be inconsistent. The following example illustrates how the tension is independent of intensive choices of the radius.

The surface could be chosen with respect to the fluid density, for example, where the interior fluid falls to 50% of its isotropic value. This can be made less arbitrary by optimizing the surface so that it satisfies the YL equation, which implies that $R_1 \Delta p_1 = R_2 \Delta p_2$. Offset the radius of the surface by the parameter δ and solve

$$\frac{R_1 + \delta}{R_2 + \delta} = \frac{\Delta p_2}{\Delta p_1}. \quad (29)$$

This gives γ_s, R_s pairs consistent with the YL equation. The water densities of the two octane-water simulations are plotted in Fig. 7. The point at which the density reaches 50% of its isotropic interior value is 15.8 for the larger drop and 13.55 for the smaller drop. Applying this procedure to the radii at 50% and 5% density yields approximately the same γ equal to 46.7 dyn/cm and an offset of −2.8 Å for the 50% pair (45.8 dyn/cm and −0.4 Å for 5%). The error bars on this value of γ are quite large for this procedure, in part because of the freedom of δ . The 66% confidence interval is 42–50 dyn/cm. Compared with the planar value of 45.1 dyn/cm for the interfacial tension of TIP3P water and c27r octane,³³ a value between 42 and 50 dyn/cm is in excellent agreement.

Similar to how the internal tension of a planar surface can be calculated by holding the system at a fixed area or external tension via periodic boundary conditions, the water/octane surface can be fixed by applying an external surface tension γ_x on the xy dimension of the simulation box; when the internal surface (here, the water surface) is at a non-optimal height/radius ratio, it applies an internal force on the simulation cell to deform. Allowing the cell dimensions to fluctuate independently provides an equilibrium condition for the cell height, h ,

$$\frac{dF}{dh} = \frac{dF_A}{dh} + \frac{dF_w}{dh} = 0, \quad (30)$$

where F_A is the free energy of the projected xy area of the cell, and F_w is the free energy for the water surface. Assuming the system volume V and water volume V_w are constants, F_A and

TABLE I. Measurement of the surface tension, γ_w , by allowing the radius of a water/octane cylindrical interface to relax under applied tension, γ_x . The quantity h_{eq} is the equilibrium value of the simulation cell height. The average of γ_w across the five simulations is 47.6 dyn/cm.

γ_x (dyn/cm)	h_{eq} (Å)	γ_w (dyn/cm)
8	24.2	48.1
10	29.1	45.7
12	31.7	48.1
14	35.8	46.7
16	37.8	49.4

F_w can each be written down in terms of h

$$F_A = \gamma_x \frac{V}{h},$$

$$F_w = \gamma_w A_w = \gamma_w 2\sqrt{\pi V_w h},$$
(31)

yielding the equilibrium condition

$$\frac{dF}{dh} = -\gamma_x \frac{V}{h^2} + \gamma_w \sqrt{\frac{\pi V_w}{h}} = 0,$$

$$\gamma_w = h_{eq}^{-3/2} \frac{\gamma_x V}{\sqrt{\pi V_w}}.$$
(32)

Under these assumptions the height of the simulation cell (h_{eq}) implies the ratio of water surface tension to external surface tension, with γ_w applicable at the surface defined by R_s equal to $\sqrt{V_w/(\pi h_{eq})}$. To demonstrate this relation and provide another estimate of the tension, five octane/water simulations at various external tensions γ_x were generated: 8, 10, 12, 14, and 16 dyn/cm. The starting configuration was taken from the smaller simulation performed above; the cell height h relaxes in approximately 5 ns. Averaging over the final 20 ns of the trajectory to find the simulation cell heights, h_{eq} , and using V_w equal to N_w/ρ_{bulk} , gives, through Eq. (32), an average γ_w equal to 47.6 ± 0.5 dyn/cm. Results for individual tension simulations are shown in Table I. The R_s at $\sqrt{V_w/(\pi h_{eq})}$ is ca. 5% larger than the 50% density point, so to compare with the above calculation, γ should be scaled to 45.3 dyn/cm. The planar calculation, combined with the two methods of calculating the tension of the curved surface, demonstrate three consistent values of the octane/water interfacial tension, and indicate that any tension variation with curvature is at most very small.

VII. CONCLUSIONS

This work presents a method for calculating the pressure of local region of a fluid, with the objective of using the method for calculating the surface tensions of curved interfacial systems. The first example showed that the pressure of an isotropic fluid could be computed by only examining a local region of the fluid. The second example applied the method to calculate the surface tension of a curved water-octane interface, with good agreement with the theoretically simpler case of a planar interface. Additionally, the Appendix shows that a commonly employed method for calculating local pressure is

intrinsically flawed, and resolves an apparent contradiction in the simulation of surface tensions.

With this method of estimating local pressures, the tension of a curved lipid leaflet or other thin film can be determined using a single simulation. The variation of the tension with curvature can then be used to infer the mechanical properties of the surface, including surfaces doped with biologically active molecules.

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APPENDIX: BEHAVIOR OF THE IK PRESSURE AT THE CENTER OF A DROP

The calculation of surface tensions relies intrinsically on a calculation of free energy derivatives, specifically with respect to the surface area of the system. Free energy perturbation methods³⁵ are commonly used to compute free energy differences of generalized coordinates and particle numbers (i.e., a calculation of the chemical potential). Given a system with the same fluid inside and outside of a surface (i.e., a drop surrounded by vapor), the local chemical potential implicitly provides a description of the surface area; i.e., $\gamma \Delta A (\Delta N)$ is now balanced by $\mu_{inside/outside} \Delta N$ instead of $P \Delta V$. Computing the local chemical potential as a function of drop size has successfully been applied to Lennard-Jones fluids and other simple systems.^{21,36,37} In many cases, some properties of surfaces are also obtainable from the fluctuation spectra of large simulations.^{38–40}

How to quantify the local pressure or local tension of a curved system has been examined with various strategies that appear to work well for simple systems, but are likely unfit for complicated potentials due to the reliance on short-range interactions of these systems, as well as unjustified assumptions on the properties of local pressures. The local deformation method presented in this paper is similar to that of another line of research on tension calculations^{41–44} that have been applied to simple systems. The method in these papers uses similar mechanical deformations as are used in Sec. III, but does not appear to separate internal (the sought-after pressure) and surface contributions (i.e., the penalty to mechanical deformation that might stabilize a drop even if no external surface were present). These two contributions are both significant in the case of realistic force fields for biophysics, as is shown for two examples in Sec. V.

The method for calculating the pressure of a local region of space presented here differs from that in previous work, commonly: Select a contour to determine $p^{\alpha\beta}(\mathbf{r})$, and equate that function with the pressure.^{45–49} The IK straight line contour between particles experiencing pairwise forces has been singled out as the contour of choice due to a number of appealing properties such as symmetry and translational invariance.

A study of the local pressure in a hard-sphere fluid⁵⁰ revealed an apparent breakdown in the Young-Laplace equation when a H-like contour⁹ was employed, contradicting Schofield and Henderson's assertion that the pressure drop across a surface can be calculated with

$$\Delta p = \frac{-1}{4\pi} \int d^3\mathbf{r} \frac{(\delta^{\alpha\beta} - 3\hat{r}^\alpha \hat{r}^\beta)}{r^3} p^{\alpha\beta}(\mathbf{r}) \quad (\text{A1})$$

independently of the contour used to evaluate $p^{\alpha\beta}(\mathbf{r})$. Specifically, it was shown that with a H-like contour the pressure of the homogeneous hard-sphere fluid dropped to $\rho k_B T$ at the origin, an unphysical result for a system with no surface across which the pressure would drop. This breakdown can be explained by an analysis of the expected free energy change of deformation compared with the actual values of $p^{\alpha\beta}(\mathbf{r})$, and illustrates the incorrectness of interpreting even the IK contour as a local pressure without further justification.

The configurational component of a local pressure tensor at time t is defined as

$$p_c^{\alpha\beta}(\mathbf{r}, t) = \sum_{i,j>i} v^\alpha(|\mathbf{r}_i - \mathbf{r}_j|) \oint_{C_{ij}} dl^\beta \delta(r_x - l_x) \delta(r_y - l_y) \times \delta(r_z - l_z). \quad (\text{A2})$$

Superscripts α and β refer to Cartesian components. Normal and tangential components may be calculated using the decomposition

$$p_c^{\alpha\beta}(\mathbf{r}, t) = \hat{r}^\alpha \hat{r}^\beta p_N(r) + (\delta^{\alpha\beta} - \hat{r}^\alpha \hat{r}^\beta) p_T(r). \quad (\text{A3})$$

The configurational contribution to the total pressure is one third the trace of $p_c^{\alpha\beta}(\mathbf{r})$, averaged over the system volume.

Equilibrium properties of a homogeneous one-component system with central pair forces may be calculated in terms of the pair potential $v(r)$ and pair correlation function $g(r)$. For example, the system pressure is

$$p_c = \frac{\rho^2}{6} \int dr r v'(r) g(r) 4\pi r^2 dr. \quad (\text{A4})$$

The pair functions may also be used to calculate the local pressure tensor

$$p_c^{\alpha\beta}(\mathbf{r}) = \rho^2 \int d^3\mathbf{r}_1 \int d^3\mathbf{r}_2 g(|\mathbf{r}_1 - \mathbf{r}_2|) v^\alpha(|\mathbf{r}_1 - \mathbf{r}_2|) \times \oint_{C_{ij}} dl^\beta \delta(r_x - l_x) \delta(r_y - l_y) \delta(r_z - l_z). \quad (\text{A5})$$

This formalism will be used to analyze the behavior of the IK local pressure in spherical coordinates in the vicinity of $r = 0$. In this limit matters are simplified as only contours completely crossing the sphere need to be considered, so that

$$p_0^{IK} = \lim_{R \rightarrow 0} \rho^2 \int_R^\infty dr_1 4\pi r_1^2 \int_0^{\Theta(r_1)} d\theta \frac{f_p^c(r_1, \theta, R)}{(4/3)\pi R^3} \times \int_R^\infty dr_2 l(r_1, r_2, R) v'(l(r_1, r_2, R)) g(l(r_1, r_2, R)). \quad (\text{A6})$$

The function $f^c(r_1, \theta, R)$ is a placeholder for the contribution to a desired quantity (in this case the pressure) due to the set of contours crossing a sphere with radius R starting from r_1

away and continuing to a point at $r_2 > R$, crossing at an angle θ . The θ limit of integration Θ is $\arctan(R/r_1)$; this will be set to R/r_1 in the limit of small R . Other functions f will be used to calculate the normal and tangential pressures as well as the expected local pressure drop.

The pressure due to a single straight line contour is proportional to the path length (for central forces) contained in the volume V

$$v^\alpha(l) \int_V d^3\mathbf{R} \int_0^1 dt [\delta(\mathbf{R}) - \mathbf{l}(t)] \left| \frac{d\mathbf{l}^\alpha}{dt} \right| = v'(l) \int_0^1 \left| \frac{d\mathbf{l}}{dt} \right|, \quad (\text{A7})$$

where the contour is parameterized such that the integration limits specify the intersection of the contour with V . A parameterization of the IK contour inside the sphere defined by R with parameter t is

$$\begin{aligned} \mathbf{r}^{IK}(t) &= \{x_0 + t\Delta x, y_0 + t\Delta y\} \\ \hat{\mathbf{r}}^{IK}(t) &= (x_0^2 + y_0^2 + t(2\Delta x x_0 + 2\Delta y y_0) \\ &\quad + t^2(\Delta x^2 + \Delta y^2))^{-1/2} \{x_0 + t\Delta x, y_0 + t\Delta y\} \\ \left| \frac{d\mathbf{r}^{IK}(t)}{dt} \right| &= \sqrt{\Delta x^2 + \Delta y^2}, \end{aligned} \quad (\text{A8})$$

where $x_0, y_0, \Delta x$, and Δy depend on θ and r_1 . Integration over the azimuthal angle gives a factor of $2\pi y(t)$ into the integrand. The contour is illustrated in Fig. 8.

In terms of the rotationally invariant variables r_1, R , and θ , we have

$$\begin{aligned} y_0 &= \sin(\theta)[r_1 \cos(\theta) - \sqrt{R^2 - r_1^2 \sin^2(\theta)}], \\ x_0 &= -\sqrt{R^2 - y_0^2}, \\ \Delta y &= 2 \sin(\theta) \sqrt{R^2 - r_1^2 \sin^2(\theta)}, \\ \Delta x &= \sqrt{R^2 - (\Delta y + y_0)^2} + \sqrt{R^2 - y_0^2}. \end{aligned} \quad (\text{A9})$$

Integration over the sphere with radius R is now expressed by integration over t . The total pressure in the region is found by integrating over the path, which is parallel to the force. Isolating the contribution due to the parameterized contour,

FIG. 8. The Irving-Kirkwood parameterization of the contour used in evaluating local pressure quantities in the vicinity of the origin. The dark dashed line intersecting the sphere is the contour contributing to the integrand. Rotating around the x axis (integrating over the azimuthal angle) introduces a factor of $2\pi(y_0 + t\Delta y)$ into the integral over the contour. This paper does not use the Irving-Kirkwood or similar local pressures to compute tensions.

including the Jacobian factor $y(t)$ gives f_p^c

$$f_p^c(r_1, \theta, R) = \int_0^1 dt y(t) \sqrt{\Delta x^2 + \Delta y^2}, \quad (\text{A10})$$

so that

$$\begin{aligned} \int_0^\pi d\phi \int_0^{R/r_1} d\theta \frac{f_p^c}{4\pi R^3} \\ = (4\pi R^3)^{-1} \int_0^{R/r_1} d\theta \int_0^1 dt 2\pi y(t) \sqrt{\Delta x^2 + \Delta y^2} \\ = \frac{1}{3r_1} + O[R]. \end{aligned} \quad (\text{A11})$$

The total pressure is one third the trace over the pressure tensor. The normal component will depend on the angle between the contour and $\mathbf{r}(t)$, following Eq. (A3)

$$\begin{aligned} \int_0^{R/r_1} d\theta 2\pi \frac{f_N^c}{4\pi R^3} &= (4\pi R^3)^{-1} \int_0^{R/r_1} d\theta \int_0^1 dt 2\pi y(t) \\ &\times \frac{|\hat{\mathbf{r}}(t) \cdot \{\Delta x, \Delta y\}|^2}{\sqrt{\Delta x^2 + \Delta y^2}} = \frac{1}{9r_1} + O[R], \end{aligned} \quad (\text{A12})$$

with the tangential contribution to the total pressure being the difference, $\frac{2}{9r_1}$. Normal and tangential components of the pressure may be used to calculate the pressure drop across the region by

$$\begin{aligned} \Delta p_c &= 2 \int_0^R dr \frac{1}{r} [p_N(r) - p_T(r)] \\ &= (4\pi)^{-1} \int_V d^3\mathbf{r} \frac{\delta^{\alpha\beta} - 3\hat{r}^\alpha \hat{r}^\beta}{r^3} p^{\alpha\beta}(\mathbf{r}). \end{aligned} \quad (\text{A13})$$

The contribution of the set of contours to the pressure drop is

$$\begin{aligned} \int_0^{R/r_1} d\theta 2\pi \frac{f_\Delta^c}{4\pi} &= \int_0^{R/r_1} d\theta \int_0^1 dt \frac{y(t)}{2} \\ &\times \frac{(\Delta x^2 + \Delta y^2) - 3|\hat{\mathbf{r}}(t) \cdot \{\Delta x, \Delta y\}|^2}{\sqrt{\Delta x^2 + \Delta y^2} |\mathbf{r}(t)|^3} \\ &= \frac{1}{3r_1} + O[R]. \end{aligned} \quad (\text{A14})$$

Applying the result of Eq. (A11) to Eq. (A6) yields

$$\begin{aligned} p_0^{\text{IK}} &= \lim_{R \rightarrow 0} \frac{\rho^2}{3} \int_R^\infty dr_1 4\pi r_1 \\ &\times \int_R^\infty dr_2 (r_1 + r_2) v'(r_1 + r_2) g(r_1 + r_2) + O[R], \end{aligned} \quad (\text{A15})$$

with $l(r_1, r_2, R)$ equal to $r_1 + r_2$ to lowest order in R . The series expansions and integrals were performed using the software program MATHEMATICA.⁵¹ The MATHEMATICA notebook file is available as part of the supplementary material.³²

Performing the variable substitution $r = r_1 + r_2$ and integrating by parts gives

$$p_0^{\text{IK}} = \frac{\rho^2}{6} \int_0^\infty dr r 4\pi r^2 v'(r) g(r) = p_c = \Delta p_{\text{IK}}(0) \quad (\text{A16})$$

when compared with Eq. (A4). Equations (A11) and (A14) give the same result, which is surprising: even for the IK contour the configurational contribution to the pressure drops to zero at the origin. This pressure drop is not seen if $p_N(r)$ and $p_T(r)$ are calculated independently. The H-like and IK contours give the same value for what is interpreted as $p_{\text{int}} - p_{\text{ext}}$ from Eq. (A1), zero, even though they have dramatically different values of p near the origin. This result was confirmed for particles with repulsive r^{-12} interactions confined in a quadratic potential, where Eq. (A1) was sampled directly instead of post-processing $p_N(r) - p_T(r)$.

According to Schofield and Henderson's derivation, the predicted configurational contribution to the free energy change due to $\mathbf{u}(\mathbf{r})$ in Eq. (20) should be zero if the simulation is at equilibrium and without external constraints, even if the system has a well-defined surface. Given a particular model it may be the case that the IK contour could be used to calculate the true pressure drop, but when the theory refers back to the rigorous calculation of the tension due to the free energy change, the change will be zero if no external constraints are at play. There is the special case that when the range of interactions are short enough, the IK pressure will be the proper local pressure (as shown here). Models of fluids commonly used in biophysical force fields do not fulfill this requirement, in that they contain long-ranged Coulomb interactions. If the surface is surrounded on both sides by an ideal gas, Eq. (A1) is trivially correct, in that the pressure drop can be implied by the density of the gas inside and outside the surface. This test system is of little use because the surface tensions between the ideal gases and the non-ideal surface will contribute to the pressure change, rather than that γ would be an intrinsic property of the surface.

Equation (A16) calls into question the results of calculating tensions of curved interfaces from the normal and tangential components of pressure profiles,^{52,53} and could explain the unexpected behavior near the origin in the pressure profiles of droplets.⁵³ In summary, with no acting external constraint (i.e., a constraint on the surface area) the free energy against any useful area-changing displacement is zero, in contrast to the case of a planar interface where the surface area is constrained by periodic boundary conditions.

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