1 Hybrid Particle-Field Molecular Dynamics Under Constant Pressure

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Hybrid particle-field methods are computationally efficient approaches for modelling soft matter systems. So far applications of these methodologies have been limited to constant volume conditions. Here, we reformulate particle-field interactions to represent systems coupled to constant external pressure. First, we show that the commonly used particle-field energy functional can be modified to model and parameterize the isotropic contributions to the pressure tensor without interfering with the microscopic forces on the particles. Second, we employ a square gradient particle-field interaction term to model non-isotropic contributions to the pressure tensor, such as in surface tension phenomena. This formulation is implemented within the hybrid particle-field molecular dynamics approach and is tested on a series of model systems. Simulations of a homogeneous water box demonstrate that it is possible to parameterize the equation of state to reproduce any target density for a given external pressure. Moreover, the same parameterization is transferable to systems of similar coarse-grained mapping resolution. Finally, we evaluate the feasibility of the proposed approach on coarse-grained models of phospholipids, finding that the term between water and the lipid hydrocarbon tails is alone sufficient to reproduce the experimental area per lipid in constant-pressure simulations, and to produce a qualitatively correct lateral pressure profile.

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I. INTRODUCTION

Hybrid particle-field simulations (hPF) are a group of computationally efficient approaches for studying mesoscale soft matter systems with molecular resolution.¹⁻⁴ In hPF models, computationally expensive, intermolecular pair interaction potentials are replaced by an inhomogeneous external potential that is functionally dependent on the densities of the particles composing the system. As a consequence, the motion of the moieties composing the system decouples, yielding a substantial simplification for the sampling of the phase space. From an algorithmic point of view, the hPF methods are efficiently represented by particle-mesh approaches, giving excellent parallelization efficiency⁵. Very recently, a GPU-based implementation of the Monte Carlo based hPF (*single chain in mean field*) set a new milestone with simulations of polymer melts with 10 billion particles⁶.

Coupling hPF to molecular dynamics algorithms has widened the range of applicability of hPF systems, from more conventional soft polymer mixtures to biological systems⁷⁻¹⁰. Examples from the literature include nanocomposites, nanoparticles, percolation phenomena in carbon nanotubes¹¹⁻¹⁴, lamellar and nonlamellar phases of phospholipids¹⁵⁻¹⁷, and more recently polypeptides¹⁸, and polyelectrolytes¹⁹⁻²².

Despite the growing level of maturity reached by hPF simulations, to the best of the authors knowledge, all works that have appeared in the literature so far have been restricted to canonical, constant volume (NVT) thermodynamic conditions. In fact, the study of many important phenomena requires targeting constant pressure conditions (NPT). For example, structural and dynamic properties of lipid membranes are typically defined at fixed tension (prominently, at zero tension), which are best represented within the NPT ensemble. Furthermore, the average density of heterogeneous or multiphase systems often cannot straightforwardly be determined from the bulk values of its constituents, making it difficult to establish physically sound NVT conditions in the absence of a preliminary equilibration at NPT , or of additional information from other experimental or computational sources.

The main issue related to the calculation of the pressure in hPF resides in determining the contribution by the particle-field interaction energy. In particular, contrary to ordinary pair potentials, such term cannot be computed from the virial of the intermolecular forces. In 2003, Tyler and Morse²³ proposed a derivation of the pressure in a *continuum self-consistent field theory* formalism by computing the change in free energy upon a change in the volume. More recently, some of

us proposed a first formulation for pressure in hPF²⁴ by a virtual displacement approach²⁵, obtaining a good correspondence of the equation of state for polymer chains compared to that derived from particle-based simulations. In a very recent publication²⁶, Ting and Müller also considered local pressure profiles in multiphase systems within self-consistent field theory, putting particular emphasis on bilayer structures. With the added novelty of using Kirkwood-Irving assignment of pressure contributions from bonded terms, they obtained excellent agreement between interface properties computed from local pressure profiles and thermodynamic considerations, demonstrating also the usefulness of *local pressure profiles* in density field based methods.²⁶ Finally, Sgouros et al.²⁷ derived the pressure for hPF using the thermodynamic definition of the pressure tensor²⁸.

Despite the capability of deriving and computing the pressure in *NVT* conditions, two important issues hinder hPF simulations under constant pressure. First, the interaction energy functionals commonly used in hPF simulations^{1,3} are not designed to give a realistic representation of the equation of state. Second, as can be seen from inspection of density field contributions in refs.^{24,26} and is emphasized in ref.²⁷, pure density terms *contribute only isotropically* to the pressure. This is particularly detrimental for interfacial phenomena, where the appearance of any surface tension is only limited to the eventual non-isotropic orientation of the bonded terms for spatially organized molecules.

In density field approaches, the *square gradient term* is one of the simplest ways to model the surface tension explicitly. Such terms have been used all the way back to pioneering works of van der Waals on one-component systems²⁹ and by Cahn and Hilliard on two-component systems³⁰. Particularly relevant for the hPF method is its recent implementation in *hPF-Brownian dynamics* to model polymer-air interfaces²⁷. Here, we reformulate the interaction energy for hPF simulations, also including anisotropic square gradient terms, to allow for an appropriate representation of the equation of state, making it possible to simulate constant pressure conditions.

II. *NPT* ENSEMBLE HYBRID PARTICLE-FIELD

A. hPF Hamiltonian

We consider a system formed by N molecules subject to the following Hamiltonian:

$$H = \sum_{m=1}^N H_0(\{\mathbf{r}, \dot{\mathbf{r}}\}_m) + W[\{\phi(\mathbf{r}), \nabla\phi\}]. \quad (1)$$

H_0 is the single-particle Hamiltonian for the m -th molecule:

$$H_0 = T(\{\dot{\mathbf{r}}\}_m) + U_0(\{\mathbf{r}\}_m), \quad (2)$$

where T and U_0 are its kinetic and intramolecular potential energies. In hPF models, intermolecular interactions are typically taken into account by the interaction energy functional W , which is implicitly dependent on the position of the particles through the set of number densities $\{\phi_k\}$, where the index k indicates a particle type. Here we introduce a new formulation of the energy functional, making it also dependent on density gradients $\{\nabla\phi_k\}$. We separate the interaction energy into two terms:

$$W[\{\phi_k(\mathbf{r}), \nabla\phi_k\}] = W_0[\{\phi_k\}] + W_1[\{\nabla\phi_k\}]. \quad (3)$$

a. W_0 : Flory-Huggins mixing entropy and compressibility The original formulation for hPF under NVT conditions employed the following interaction energy functional^{3,24}:

$$W_0[\{\phi_k(\mathbf{r})\}] = \frac{1}{2\phi_0} \int d\mathbf{r} \left(\sum_{k\ell} \tilde{\chi}_{k\ell} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_{\ell} \phi_\ell(\mathbf{r}) - \phi_0 \right)^2 \right), \quad (4)$$

where ϕ_0 is the average total number density, $\tilde{\chi}_{k\ell}$ is the Flory-Huggins coupling parameter between species k and ℓ , and κ controls the fluctuations of the local density. To generalize this formulation to NPT conditions, we propose the following modified interaction energy:

$$W_0[\{\phi_k(\mathbf{r})\}] = \frac{1}{2\rho_0} \int d\mathbf{r} \left(\sum_{k\ell} \tilde{\chi}_{k\ell} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_{\ell} \phi_\ell(\mathbf{r}) - a \right)^2 \right). \quad (5)$$

Here $\rho_0 = 1/v_0$ is a constant related to the scale of coarse graining, where v_0 is the molecular volume of the coarse grained particles. a is an independent parameter of the equation of state with the dimension of a number density. The corresponding external potential is given by:

$$V_{0,k}(\mathbf{r}) = \frac{\delta W_0[\phi_k(\mathbf{r})]}{\delta \phi_k(\mathbf{r})} = \frac{1}{\rho_0} \left(\sum_{\ell} \tilde{\chi}_{k\ell} \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_{\ell} \phi_\ell(\mathbf{r}) - a \right) \right). \quad (6)$$

We emphasize that because the parameter a gives a constant contribution the potential $V_{0,k}$, it does not affect the forces acting on the particles. We also note that in the case of $\rho_0 = \phi_0 = a$, this new potential becomes strictly the same as the one used in the NVT formulation.

89 *b. W_1 : Square gradient interactions* To model interfaces we introduce a square gradient
 90 term to the interaction energy^{27,31} dependent on multiple species:

$$W_1[\nabla\phi] = \frac{1}{2\rho_0} \sum_{k,\ell} \int d\mathbf{r} K_{k\ell} \nabla\phi_k(\mathbf{r}) \cdot \nabla\phi_\ell(\mathbf{r}), \quad (7)$$

where $K_{k\ell}$ is a coupling constant between the gradients of species k and ℓ . The corresponding external potential is given by (see Appendix 1 a):

$$V_{1,k}(\mathbf{r}) = - \sum_{\ell=1} \frac{K_{k\ell}}{\rho_0} \nabla^2 \phi_\ell(\mathbf{r}). \quad (8)$$

91 **B. Calculation of the pressure in hPF**

92 We calculate the pressure using a derivation similar to the one used by Hünenberger for the
 93 reciprocal space part of Ewald summation³². The pressure inside a simulation box with side
 94 lengths L_μ and volume V is given by:

$$P_\mu = \frac{2T_\mu - \text{Vir}_\mu(\{\mathbf{r}, \mathbf{L}\})}{V} \quad (9)$$

95 where T_μ denotes a Cartesian component of kinetic energy and

$$\text{Vir}_\mu = L_\mu \frac{\partial U_{\text{tot}}}{\partial L_\mu} \quad (10)$$

96 is obtained directly from the potential energy of the system U_{tot} , defined as:

$$U_{\text{tot}} = \sum_{m=1}^N U_0(\{\mathbf{r}\}_m) + W_0[\{\phi\}] + W_1[\{\nabla\phi\}]. \quad (11)$$

97 The bonded interactions ($U_0(\{\mathbf{r}\}_m)$) contribute to the virial term as in ordinary molecular dynam-
 98 ics. The interaction energy contributions to the pressure are computed as:

$$P_{0,\mu} = -\frac{L_\mu}{V} \frac{\partial W_0[\{\phi\}]}{\partial L_\mu}, \quad P_{1,\mu} = -\frac{L_\mu}{V} \frac{\partial W_1[\{\nabla\phi\}]}{\partial L_\mu}, \quad (12)$$

corresponding to (see Appendix 1 b for their derivation):

$$P_{0,\mu} = \frac{1}{V} \int d\mathbf{r} \frac{1}{\rho_0} \left(\frac{1}{2} \sum_{k\ell} \tilde{\chi}_{k\ell} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{2\kappa} \left(\left(\sum_\ell \phi_\ell(\mathbf{r}) \right)^2 - a^2 \right) \right), \quad (13a)$$

$$P_{1,\mu} = \frac{1}{V} \int d\mathbf{r} \sum_{k\ell} \frac{K_{k\ell}}{\rho_0} \left(\frac{1}{2} \nabla\phi_k(\mathbf{r}) \cdot \nabla\phi_\ell(\mathbf{r}) + \nabla_\mu \phi_k(\mathbf{r}) \nabla_\mu \phi_\ell(\mathbf{r}) \right). \quad (13b)$$

99 The total pressure in a direction μ is thus given by:

$$P_\mu = \frac{2T_\mu}{V} + \frac{1}{V} \sum_i \left[-\frac{\partial U_0(\mathbf{r}_i)}{\partial r_{i,\mu}} \cdot r_{i,\mu} \right] + P_{0,\mu} + P_{1,\mu} \quad (14)$$

100 Here we note the following: (i) Although a gives no contributions to the force, it gives rise to a
 101 nonzero pressure. This gives added flexibility to control the isotropic pressure, similarly to the
 102 constant term in the stiffened gas equation of state³³. (ii) The contribution of W_0 to the pressure
 103 is isotropic, while the contribution of W_1 is not. (iii) The local pressure density (the integrand
 104 in (13b)) does not contain a Laplace term as reported in refs.^{27,31}. However, as shown in Ap-
 105 pendix 1 b, the expressions are equivalent.

106 III. COMPUTATIONAL DETAILS

107 A. hPF-MD simulations

108 The model described in the previous section was implemented into hPF-molecular dynamics
 109 software OCCAM⁵. This enables the possibility of sample configurations of the molecular system
 110 governed by our new hPF Hamiltonian (1) following directly the evolution of the corresponding
 111 equations of motion. The forces on the i -th particle of type k due to W_0 and W_1 are computed from
 112 the gradients of the external potentials $V_{0,k}(\mathbf{r})$ and $V_{1,k}(\mathbf{r})$:

$$\mathbf{F}_{0,i} = -\nabla V_{0,k}(\mathbf{r}_i), \quad \mathbf{F}_{1,i} = -\nabla V_{1,k}(\mathbf{r}_i). \quad (15)$$

113 by a particle mesh approach¹⁷. First, particles are distributed onto a different Cartesian grid for
 114 each species k by linear interpolation to the nearest vertices (cloud-in-cell). Derivatives are com-
 115 puted on a staggered grid by finite differences. Finally, the derivatives are interpolated back onto
 116 the particles giving the forces. As shown in ref.¹⁷, the external potentials are slow variables, and
 117 can be updated with good approximation at intervals of up to ~ 100 steps¹⁷, yielding efficient
 118 parallelization⁵.

119 B. Computation of square gradient forces

120 The computation of the external potential due to the square gradient term W_1 involves comput-
 121 ing the Laplacian of the densities. To obtain a rotational invariant estimate without the appear-
 122 ance of spurious oscillations, we employ a spectral approach³⁴ filtering out fast oscillations of the

123 derivatives in Fourier space. The filtering is done by convolution:

$$\tilde{\phi}_k(\mathbf{r}) = \int d\mathbf{u} \phi_k(\mathbf{r} - \mathbf{u})H(\mathbf{u}). \quad (16)$$

The tilde symbol denotes filtered densities by the applied filter H . The corresponding external potential is given by:

$$V_{1,k}(\mathbf{r}) = - \sum_{\ell=1}^M \frac{K_{k\ell}}{\rho_0} \int d\mathbf{y} H(\mathbf{r} - \mathbf{y}) \nabla^2 \tilde{\phi}_\ell(\mathbf{y}). \quad (17)$$

124 which takes the following simple expression in Fourier space (see Appendix 1 a for its derivation):

$$\hat{V}_{1,k}(\mathbf{q}) = \sum_{\ell=1}^M \frac{K_{k\ell}}{\rho_0} q^2 H^2(\mathbf{q}) \hat{\phi}_\ell(\mathbf{q}). \quad (18)$$

125 Real space values are computed by backwards Fast Fourier Transform routines (FFT). For consis-
126 tency, the gradients in P_1 are also filtered with the same filter H . Details on the filtering algorithm
127 are provided in Appendix 2 a.

128 C. Barostat

129 We employ the Berendsen barostat³⁵ with isotropic coupling for isotropic systems, and semi-
130 isotropic coupling for lipid bilayers. The efficiency of the hPF-MD approach is dependent on
131 having *i*) little communication among processors and *ii*) avoiding heavy calculation (typically in-
132 volving the grid) between density updates. Similarly to the multi-time-step approach used in the
133 GPU version of *Tinker-OpenMM*³⁶, we average contributions from bonded terms and keep vol-
134 ume and field contributions constant between density update steps. This is done by scaling the
135 components of the box lengths and the coordinates every n time steps Δt using Berendsen scaling
136 factor α_μ :

$$\alpha_\mu = \left(1 - \frac{\kappa_T n \Delta t}{\tau_p} (P_a - P_0) \right)^{\frac{1}{3}}, \quad (19)$$

137 where κ_T , τ_p and P_0 are the isothermal compressibility, the time constant and the pressure
138 of the barostat respectively.

139 D. Simulation details

140 We tested our model on a set of homogeneous and inhomogeneous systems. Details on the
141 composition of each individual system, as well as information about other simulation parameters
142 are given in Appendix 3.

143 IV. RESULTS AND DISCUSSION

144 A. Homogeneous system: Water

FIG. 1. Parameterization of water for NPT simulation. (A) Simulation box of water. (B) Pressure as function of κ for $a = 0$. (C) Calibration of a to obtain an internal pressure of 1 bar as function of κ . The least square fit line is $a(\kappa) = 8.54 + 18.61\kappa$. (D) Equilibration of a overly dense liquid by NPT simulation.

145 Within the hPF model, the representation of a homogeneous phase requires the consideration of
 146 the interaction energy W_0 only. Furthermore, considering a single-component system, the forces
 147 are only dependent on its compressibility term. In Fig. 1 we report the parameterization of pure
 148 liquid water employing the commonly used explicit bead model in hPF-MD where four water
 149 molecules are mapped into a single body¹⁷ (Fig. 1A). Such a mapping implies a molecular volume
 150 per bead $v_0 = 0.120 \text{ nm}^3$, thereby $\rho_0 = 1/v_0 = 8.33 \text{ nm}^{-3}$. In Fig. 1B, the pressure under NVT
 151 conditions is plotted as function of κ for a system with a density of 995 kg m^{-3} and temperature
 152 of 300 K, using $a = 0 \text{ nm}^{-3}$. The combination of the two positive definite kinetic energy and
 153 compressibility terms produce an average internal pressure $\langle P \rangle \gg 1 \text{ bar}$. From (14) and (13), it is
 154 possible to predict the value of a :

$$a = \sqrt{(\langle P \rangle_{a=0} - P_0) / (2\kappa\rho_0)}, \quad (20)$$

155 that would yield an equilibrium value $\langle P \rangle_a = P_0$, where P_0 is any target pressure of choice. In-
 156 serting $P_0 = 1 \text{ bar}$ and values of $\langle P \rangle_{a=0}$ into (20), we find a parameterization of a as function of κ

(Fig. 1C) which yields a pressure of 1 bar for a density of 995 kg m^{-3} at 300 K. The parameterization of $a(\kappa)$ is fitted well by a linear regression line. Using this regression line we find, for three commonly used values of $\kappa = 0.03, 0.05, 0.10 \text{ kJ}^{-1} \text{ mol}$, $a = 9.10, 9.47, 10.40 \text{ nm}^{-3}$ respectively. Having parameterized a , we can now simulate the water model under NPT conditions. Fig. 1D reports the time evolution of total mass density ρ under NPT conditions with barostat pressure of 1 bar and temperature of 300 K for a water system with an initial density of 1100 kg m^{-3} . For the three values of κ the density equilibrates to the correct density. In the next systems, if not otherwise stated, we adopt $\kappa = 0.05 \text{ kJ}^{-1} \text{ mol}$ and $a = 9.47 \text{ nm}^{-3}$.

B. Binary mixture

FIG. 2. (A) Density of a binary mixture of two ideal fluids A, B of equal density as function of $\tilde{\chi}_{AB}$. (B) Representative snapshots from hPF-MD after equilibration, highlighting the phase behavior for different $\tilde{\chi}_{AB}$ (values of $\tilde{\chi}_{AB}$ are in kJ mol^{-1}).

a. Phase separation We consider a toy binary mixture between two ideal fluids. The two components differ only by $\tilde{\chi}_{AB}$ in the potential energy term W_0 . In Fig. 2 we survey the state of this mixture by plotting its total density as a function of $\tilde{\chi}_{AB}$ at 1 bar. The total density of the mixture exhibits a strong excess volume effect, where the density of the mixture is different from its components. For negative values of $\tilde{\chi}_{AB}$, mixing of the two fluids is favourable, and the density increases. For positive values of $\tilde{\chi}_{AB}$ the density is lower and stabilizes to a constant value for high

values of $\tilde{\chi}_{AB}$. The stabilization can be interpreted from the snapshot at $\tilde{\chi}_{AB} = 30 \text{ kJ mol}^{-1}$ as the formation of a sharp interface between the two phases. The abrupt change in the first derivative of the total density at about $\tilde{\chi}_{AB} = 5 \text{ kJ mol}^{-1}$ signals a phase transition. This is further evidenced by the snapshots showing a transition from miscible to phase-separated fluids before and after $\tilde{\chi}_{AB} = 5 \text{ kJ mol}^{-1}$. We note that the critical value found here matches perfectly the critical value from Ginzburg-Landau theory³⁷ of $\chi = 2$ or $\tilde{\chi} = k_B T \chi = 4.96 \text{ kJ mol}^{-1}$.

FIG. 3. hPF-MD simulations of a droplet of an immiscible liquid A in liquid B ($\tilde{\chi}_{AB} = 20 \text{ kJ mol}^{-1}$), using different values of K_{AB} . (A) Sphericity of the droplet as function of K_{AB} . (B) Snapshots of the droplet after equilibrated by hPF-MD, liquid B enveloping the droplet is represented by a transparent red surface. Values of K_{AB} are in $\text{kJ mol}^{-1} \text{ nm}^2$.

b. Ideal water/oil droplet While the $\tilde{\chi}_{AB}$ term in W_0 controls the partitioning and the level of phase separation between the two liquids, the interaction energy W_1 is necessary for modelling interfacial properties, and in particular surface tension. In the case of a binary system, W_1 requires the definition of only one parameter K_{AB} to control the surface interaction between the two phases. We survey how K_{AB} affects interfaces by simulating an ideal oil droplet (particle type A) in water (particle type B, constituting 90% of the particles in the simulation) and by computing its sphericity for different values of K_{AB} (Fig. 3A). The sphericity Ψ is defined by the equation³⁸:

$$\Psi \equiv \frac{\pi^{1/3} (6V)^{2/3}}{A}, \quad (21)$$

where A and V are the surface area and the volume of the droplet. For very negative values of K_{AB} , we find a sphericity close to 1, corresponding to almost a perfect sphere (snapshot in Fig. 3B). This is consistent with a sphere having the lowest possible surface for a given volume. By increasing K_{AB} , we lower the interfacial energy. This allows for larger surface areas of the droplet, and thus the appearance of other shapes than a sphere. In our simulations, for $K_{AB} = 0 \text{ kJ mol}^{-1} \text{ nm}^2$, we found a configuration in between sphere and cube and for $K_{AB} = 5 \text{ kJ mol}^{-1} \text{ nm}^2$ we observed a configuration very close to a cube (snapshots in Fig. 3B). We note that the formation of a cube is likely affected by the orientation of the grid used to calculate particle-field forces, which has been reported to produce cube shaped vesicles³⁹. In ref.³⁹ it was shown that this problem can be remedied by using a rotational invariant finite difference stencil for the estimate of the derivative of the external potential. Another possible solution is to estimate the derivatives of $V_k(\mathbf{r})$ in Fourier space using FFT.

C. Effect of square gradient term on lipid bilayers

FIG. 4. *Left*: CG model used for hPF-MD simulations of DPPC lipid bilayers in water. *Right*: functional form of the intra-molecular potential for DPPC, and particle-field interaction terms used in the simulations.

To test the feasibility of the proposed approach to models with specific molecular features, we investigate a realistic model of a dipalmitoylphosphatidylcholine (DPPC) lipid bilayer in water, employing a molecular CG representation, and the corresponding $\tilde{\chi}$ interaction energy matrix present in the literature¹⁷, as summarized in Fig. 4. Here, we add to the preexisting model the

square gradient interaction limited to only one K_{ml} term between the hydrophobic lipid tail (C) and the water (W) beads (K_{CW}), disregarding all other terms.

FIG. 5. *NVT* simulations of DPPC lipid bilayer. (A) Snapshots of equilibrated membranes using different K_{CW} values. (B) Surface tension of DPPC lipid bilayer as a function of K_{CW} .

a. flat lipid bilayers – Surface area *NVT* simulations of lipid bilayers in periodic boundary conditions impose an arbitrary effective area per lipid A , defined as:

$$A = \frac{2L_x L_y}{N}, \quad (22)$$

where L_x, L_y are the edges of the simulation box in the x, y directions spanning lipid bilayer, and N is the number of assembled lipids. In this case, *NVT* simulations allow for a controlled study of the effects of K_{CW} on the morphology of the system. Fig. 5A reports equilibrated conformations for different values of K_{CW} . As we start from preoptimized $\tilde{\chi}$ values to reproduce flat bilayers at $K_{CW} = 0 \text{ kJ mol}^{-1} \text{ nm}^2$, a negative value of $K_{CW} = -6 \text{ kJ mol}^{-1} \text{ nm}^2$ does not produce strong structural modifications. On the contrary, $K_{CW} = 2 \text{ kJ mol}^{-1} \text{ nm}^2$ induces an abrupt change in the bilayer with the formation of visible bump within the first 190 ns of simulations. This deformation is consistent with the fact that positive values of K_{CW} promote the expansion of the interface area.

This trend can be quantified by computing the surface tension γ of the membrane, Fig. 5B, which can be calculated from:

$$\gamma = \frac{1}{2} \int dz (P_N(z) - P_L(z)). \quad (23)$$

Here, $P_N(z)$ and $P_L(z)$ are the values of the pressure in the normal and lateral directions of the membrane plane, respectively. The $1/2$ factor takes into account the presence of two interfaces. A negative value of γ in the absence of the square gradient interaction energy indicates that the area per lipid is not at equilibrium, and the system would tend to expand laterally if let free to relax.

$K_{CW} \sim -6 \text{ kJ mol}^{-1} \text{ nm}^2$ balances the two pressures, and should predict an equilibrium area per lipid at NPT conditions equal to the initial target value.

TABLE I. Predicted area per lipid compared against literature data from experiment and simulations.

Source	DMPC		DPPC		DSPC		DOPC	
	A/nm^2	T/K	A/nm^2	T/K	A/nm^2	T/K	A/nm^2	T/K
Nagle ⁴⁰	0.596	323	0.630	323	-	-	0.725	303
Waheed ⁴¹ sim	0.625	303	0.644	323	-	-	-	-
Waheed ⁴¹ exp	0.606	303	0.630	323	-	-	-	-
Levine ⁴²	-	-	0.629	323	-	-	0.689	298
Petrache ⁴³	0.600	303	0.633	323	0.66	338	-	-
	0.654	323	0.671	338	-	-	-	-
hPF-MD	0.61	323	0.64	325	0.66	338	0.70	303

We thus simulated a $20 \text{ nm} \times 100 \text{ nm} \times 100 \text{ nm}$ large DPPC/water system at NPT condition employing the same $a = 9.59 \text{ nm}^{-3}$ determined for pure water at 325 K (see Appendix 4) and using $K_{CW} = -6 \text{ kJ mol}^{-1} \text{ nm}^2$. After an initial relaxation, the DPPC bilayer reaches an equilibrium configuration characterized by a well defined area per lipid of 0.64 nm^2 (Table I). This value is in excellent agreement with what has been previously reported in the literature^{40,41,43}.

The transferability of K_{CW} was tested on three other lipids, namely: dimyristoylphosphatidylcholine (DMPC), distearoylphosphatidylcholine (DSPC) and dioleoylphosphatidylcholine (DOPC), which differ from DPPC only for the length of the carbon tail while retaining the same chemical structure of the polar head. As for DPPC, we used the W_0 parameters from ref.¹⁷; hPF-MD NPT simulations ran using the same $a = 9.59 \text{ nm}^{-3}$, $K_{CW} = -6 \text{ kJ mol}^{-1}$. Remarkably, these parameter produce in all cases excellent agreement with literature data, as presented in Table I, indicating indeed a high level of transferability among chemically similar moieties.

b. Flat lipid bilayers – membrane structure We survey the effect of K_{CW} on the equilibrium structure of the bilayer by computing the electron density profiles along the membrane normal axis for a small DPPC lipid bilayer (See Appendix 3 b for a detailed system description). Fig. 6A reports a comparison between the density profiles from experiment, a CG simulation using the MARTINI force field⁴⁵, reference hPF simulations under NVT without the square gradient term, and hPF in NPT with $K_{CW} = -6 \text{ kJ mol}^{-1} \text{ nm}^2$. All the profiles exhibit the peaks at the head and low

FIG. 6. Density and pressure profiles for DPPC. (A) Comparison between the experimental electron density profilea (black line), hPF-MD using $K_{CW}=0 \text{ kJ mol}^{-1} \text{ nm}^2$ (red line), $K_{CW} = -6 \text{ kJ mol}^{-1} \text{ nm}^2$ (blue line) and reference CG MARTINI model¹⁷. (B) Density profiles for the different bead types. Continuous lines are for hPF-MD data using $K_{CW} = -6 \text{ kJ mol}^{-1} \text{ nm}^2$, dashed lines are by De Nicola et al.¹⁷ at NVT conditions without a square gradient term. (C) Difference between normal and lateral components of the pressure for tensionless hPF-MD simulations compared against all-atom pressure profiles by Lindahl and Edholm⁴⁴. Two different scales are used for the y-axis for the two models. (D) Contributions to the pressure difference shown in (C) from density field, bonded, and angular interactions.

electron density in the middle of the bilayer. The profile obtained with $K_{CW} = -6 \text{ kJ mol}^{-1} \text{ nm}^2$ has better agreement with experiment and MARTINI in the middle of the bilayer, showing instead some excessive elongation in the position of the polar head beads. This trend is corroborated by drawing the individual bead contributions to the density profile, as shown in Fig. 6B. Such opposite trends are not entirely surprising, keeping in mind that the square gradient term has been applied to the carbon tails only, while the polar head have not been corrected by any surface tension contribution. The current results suggest that by an appropriate calibration of the whole $K_{\ell m}$ matrix, the square gradient term can improve significantly the agreement between hPF and its underlying CG model. Interestingly, the peaks of the individual beads appear sharper, indicating a more regular bilayer compared to hPF NVT simulations.

We also computed local pressure profile, using the values of P_0 and P_1 at the vertices of the mesh, and Kirkwood-Irving assignment of bonded virials.⁴⁶ Fig. 6C,D report the local difference

252 between normal and lateral pressure computed with hPF-MD and all-atom by Lindahl,⁴⁴ and the
 253 contributions by the different terms of the Hamiltonian. While the magnitude of the all-atom
 254 pressure is about four times that of hPF-MD, we nevertheless identify the appearance of three
 255 key qualitative features: the presence of a negative peak between water and the lipid heads, a
 256 positive peak in between heads and tails, and a rather flat region in the tail part. Unlike all-atom
 257 simulations, the hPF profile has an positive sign to the pressure difference at the carbon tails,
 258 indicating compressed carbon tails in the normal direction. We note that this may be part an
 259 artifact of the coarseness of the mesh, which can cause a spill out of pressure into the middle
 260 part of the membrane, as well as by the absence of a square gradient terms between water and
 261 glycerol or polar head beads. The local pressure contributions from P_0 and P_1 were computed at
 262 the vertices of the mesh. This is at one hand rigorous as it avoids subtleties related to local pressure
 263 assignment, however higher resolution would be advantageous for computing properties from the
 264 local pressure profiles. A natural route for achieving higher resolution assignment of pressure
 265 would be to follow the procedure proposed in ref.^{46,47} by Harasima assignment.⁴⁸

266 Our simulations present a very flat bilayer without the detection of significant undulations on
 267 the tensionless surface of the bilayer. The stiffness of the bilayer can be quantified by computing
 268 the *area compressibility* as in ref.⁴⁹.

269 For the DPPC lipid bilayer, in our case, we obtain $K_A = 22\,000\text{ mN m}^{-1}$. This is about two
 270 orders of magnitude larger than what has been reported in the literature⁴² ($\sim 200\text{ mN m}^{-1}$) con-
 271 firming that the present setup produces an excessively rigid system. Although it is well known that
 272 the Berendsen barostat is not suited for studying fluctuations of the membrane⁵⁰, we stress here, in
 273 these preliminary test implementation, that we have only considered carbon water interactions for
 274 the square gradient term. Moreover, this term was naively added to $\tilde{\chi}$ parameters that were preop-
 275 timized to reproduce accurate density profiles in the absence of an explicit surface tension term,
 276 with consequent possible double counting of the repulsion between the water and the hydrophobic
 277 tails. Overall, the discrepancy on the fluctuation of the DPPC bilayer together with the qualitative
 278 but not quantitative agreement on the lateral pressure profiles indicate that *NPT* simulation of re-
 279 alistic systems require a global parameterization of both the $\tilde{\chi}$ and $K_{m\ell}$ matrices, while a simple
 280 addition of the second term to the first may not be sufficient to obtain quantitatively accurate data.

V. CONCLUSION AND OUTLOOK

We presented a reformulation of the hPF interaction energy suitable for constant pressure simulations using both isotropic and anisotropic coupling. First, we modified the commonly used interaction energy by introducing an equation of state parameter a . By design, this adjustment conserves the dynamics of the old formulation. Second, we introduced a square gradient term to the interaction energy to model interfacial phenomena. Particle-field contributions to the pressure were derived by considering change in free energy upon change in simulation box lengths. The equation of state parameter a enters as an added constant to the pressure. The square gradient contributes to nonisotropic pressure, thereby allowing for direct modeling of surface tension. Our approach was implemented into the OCCAM code, where the dynamics of system governed by the hPF Hamiltonian was sampled by MD and pressure was coupled to the Berendsen barostat.

Testing on simple single particle fluids demonstrated how by tuning a we can reproduce the densities at ambient conditions, also showing how the $\tilde{\chi}$ -term can be used to modulate variations in the partial molar volume in liquid mixtures. We also verified that the square gradient term can be tuned to control the shape of liquid droplets.

Finally, we tested the effect of the new hPF Hamiltonian on a realistic model of a phospholipid bilayer previously proposed in the literature. Interestingly, the square gradient term is not only important, but mandatory for achieving an area per lipid within the experimental range under NPT conditions, as well as a qualitatively reasonable lateral pressure profile. Interestingly, we also found that the same parameterization of a and K_{CW} is transferable to other lipids of similar chemical composition.

Remarkably, the application of only one square gradient contribution between the carbon tails and water was sufficient to obtain a qualitatively correct physical behaviour of the lipids as well as some impressive improvement of some of their key structural features like average area per lipid, or lateral pressure profiles. Nonetheless, we found that such correction produced inconsistent variations in the lateral density profiles, and a too stiff bilayer, indicating that a consistent recalibration of the $\tilde{\chi}$ parameters as well as the use of the full $K_{m\ell}$ matrix is necessary for quantitative agreement between hPF and other higher resolution models as well as the experiment.

Accessing constant pressure conditions significantly expands the applicability of hPF simulations. For example, it is now possible predict density changes in bulk systems, or to represent surface phenomena. The future challenge is in the calibration of appropriate square gradient force

constant matrices, possibly through combined global parameterizations with the bulk energy terms, aiming for quantitatively accurate description of interfaces.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

APPENDIX

In this appendix we provide the details on *derivations*, *computational procedures*, *simulation setups* and *parameterizations*, that are needed for reproducing the results obtained in this manuscript.

1. Derivations

All derivations involving square gradient term are performed with filtered densities $\tilde{\phi}$.

333 **a. External potential $V_{1,k}$**

334 We compute the external potential by using the functional derivative chain rule twice:

$$V_{1,k}(\mathbf{r}) = \frac{\delta W_1[\nabla \tilde{\phi}]}{\delta \phi_k(\mathbf{r})} = \int d\mathbf{x} d\mathbf{y} \frac{\delta W_1}{\delta \nabla \tilde{\phi}_k(\mathbf{x})} \frac{\delta \nabla \tilde{\phi}_k(\mathbf{x})}{\delta \tilde{\phi}_k(\mathbf{y})} \frac{\delta \tilde{\phi}_k(\mathbf{y})}{\delta \phi_k(\mathbf{r})}. \quad (24)$$

335 The terms in the integrand of (24) are given by:

$$\frac{\delta W_1}{\delta \nabla \tilde{\phi}_k(\mathbf{x})} = \sum_{\ell=1}^M \frac{K_{k\ell}}{\rho_0} \nabla \tilde{\phi}_\ell(\mathbf{x}), \quad \frac{\delta \nabla \tilde{\phi}_k(\mathbf{x})}{\delta \tilde{\phi}_k(\mathbf{y})} = \nabla_{\mathbf{x}} \delta(\mathbf{x} - \mathbf{y}), \quad \frac{\delta \tilde{\phi}_k(\mathbf{y})}{\delta \phi_k(\mathbf{r})} = H(\mathbf{r} - \mathbf{y}). \quad (25)$$

Inserting (1 a) into (24) yields:

$$\begin{aligned} V_{1,k}(\mathbf{r}) &= \int d\mathbf{x} d\mathbf{y} \sum_{\ell=1}^M \frac{K_{k\ell}}{\rho_0} \nabla \tilde{\phi}_\ell(\mathbf{x}) \nabla_{\mathbf{x}} \delta(\mathbf{x} - \mathbf{y}) H(\mathbf{r} - \mathbf{y}) \\ &= \int d\mathbf{y} H(\mathbf{r} - \mathbf{y}) \int d\mathbf{x} \sum_{\ell=1}^M \frac{K_{k\ell}}{\rho_0} \nabla \tilde{\phi}_\ell(\mathbf{x}) \nabla_{\mathbf{x}} \delta(\mathbf{x} - \mathbf{y}) \\ &= - \int d\mathbf{y} H(\mathbf{r} - \mathbf{y}) \int d\mathbf{x} \sum_{\ell=1}^M \frac{K_{k\ell}}{\rho_0} \nabla^2 \tilde{\phi}_\ell(\mathbf{x}) \delta(\mathbf{x} - \mathbf{y}) \\ &= - \sum_{\ell=1}^M \frac{K_{k\ell}}{\rho_0} \int d\mathbf{y} H(\mathbf{r} - \mathbf{y}) \nabla^2 \tilde{\phi}_\ell(\mathbf{y}). \end{aligned}$$

336 Without filter ($H(\mathbf{r} - \mathbf{y}) = \delta(\mathbf{r} - \mathbf{y})$) we obtain:

$$V_{1,k}(\mathbf{r}) = - \sum_{\ell=1}^M \frac{K_{k\ell}}{\rho_0} \nabla^2 \phi_\ell(\mathbf{r}) \quad (26)$$

337 **b. Virial terms from interaction energies**

338 The pressure is given by the Virial³²:

$$P_\mu = \frac{2K_\mu - \text{Vir}_\mu(\{\mathbf{r}, \mathbf{L}\})}{V} \quad (27)$$

339 where

$$\text{Vir}_\mu = L_\mu \frac{\partial U}{\partial L_\mu}. \quad (28)$$

Focusing on nonbonded terms and starting with W_0 , we denote the integrand by interaction energy density $w(\{\phi(\mathbf{r})\})$, we compute derivative with respect to box size:

$$\frac{\partial W_0}{\partial L_\mu} = \int \left(\frac{\partial d\mathbf{r}}{\partial L_\mu} w_0(\phi(\mathbf{r})) + d\mathbf{r} \frac{\partial w_0(\phi(\mathbf{r}))}{\partial L_\mu} \right) \quad (29)$$

$$= \int \left(\frac{d\mathbf{r}}{L_\mu} w_0(\phi(\mathbf{r})) - d\mathbf{r} \frac{\partial w_0(\phi(\mathbf{r}))}{\partial \phi} \frac{\phi(\mathbf{r})}{L_\mu} \right) \quad (30)$$

340 giving:

$$\text{Vir}_{0,\mu} = \int d\mathbf{r} \left(w_0(\{\phi(\mathbf{r})\}) - \sum_{\ell=1}^M \frac{\partial w_0(\{\phi(\mathbf{r})\})}{\partial \phi_\ell(\mathbf{r})} \phi_\ell(\mathbf{r}) \right). \quad (31)$$

341 Inserting the energy density:

$$\text{Vir}_{0,\mu} = - \int d\mathbf{r} \frac{1}{\rho_0} \left(\frac{1}{2} \sum_{k\ell} \tilde{\chi}_{k\ell} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{2\kappa} (\phi(\mathbf{r})^2 - a^2) \right) \quad (32)$$

We compute interface virial of W_1 by:

$$\frac{\partial W_1}{\partial L_\mu} = \int \left(\frac{\partial d\mathbf{r}}{\partial L_\mu} w([\nabla \tilde{\phi}(\mathbf{r})]) + d\mathbf{r} \frac{\partial w([\nabla \tilde{\phi}(\mathbf{r})])}{\partial L_\mu} \right) \quad (33)$$

$$= \int \left(\frac{d\mathbf{r}}{L_\mu} w([\nabla \tilde{\phi}(\mathbf{r})]) + d\mathbf{r} \frac{\partial w([\nabla \tilde{\phi}(\mathbf{r})])}{\partial \nabla_v \tilde{\phi}(\mathbf{r})} \frac{\partial \nabla_v \tilde{\phi}(\mathbf{r})}{\partial L_\mu} \right). \quad (34)$$

The last partial derivative is given by:

$$\frac{\partial}{\partial L_\mu} (\nabla_v \tilde{\phi}(\mathbf{r})) = \left(\frac{\partial}{\partial L_\mu} \nabla_v \right) \tilde{\phi}(\mathbf{r}) + \nabla_v \frac{\partial \tilde{\phi}(\mathbf{r})}{\partial L_\mu} \quad (35)$$

$$= -\frac{\delta_{\mu v}}{L_\mu} \nabla_v \tilde{\phi}(\mathbf{r}) + \nabla_v \frac{\partial \tilde{\phi}(\mathbf{r})}{\partial L_\mu}. \quad (36)$$

The partial derivative filtered density with respect to box lengths depends on the filter. This dependence is easily understood by using the Fourier transform:

$$\frac{\partial \tilde{\phi}(\mathbf{r})}{\partial L_\mu} = \frac{\partial}{\partial L_\mu} \int d\mathbf{q} \tilde{\phi}(\mathbf{q}) e^{-i\mathbf{q}\mathbf{r}} = \frac{\partial}{\partial L_\mu} \int d\mathbf{q} \hat{\phi}(\mathbf{q}) \hat{H}(\mathbf{k}) e^{-i\mathbf{q}\mathbf{r}} \quad (37)$$

$$= \int \left(\frac{\partial d\mathbf{q}}{\partial L_\mu} \hat{\phi}(\mathbf{q}) \hat{H}(\mathbf{k}) e^{-i\mathbf{q}\mathbf{r}} + d\mathbf{q} \frac{\partial \hat{\phi}(\mathbf{q})}{\partial L_\mu} \hat{H}(\mathbf{k}) e^{-i\mathbf{q}\mathbf{r}} + \right. \quad (38)$$

$$\left. d\mathbf{q} \hat{\phi}(\mathbf{q}) \hat{H}(\mathbf{k}) \frac{\partial e^{-i\mathbf{q}\mathbf{r}}}{\partial L_\mu} + d\mathbf{q} \hat{\phi}(\mathbf{q}) \frac{\partial \hat{H}(\mathbf{k})}{\partial L_\mu} e^{-i\mathbf{q}\mathbf{r}} \right). \quad (39)$$

342 The contributions from the three first terms are given by:

$$\frac{\partial d\mathbf{q}}{\partial L_\mu} = -\frac{d\mathbf{q}}{L_\mu}, \quad \frac{\partial \hat{\phi}(\mathbf{q})}{\partial L_\mu} = 0, \quad \frac{\partial e^{-i\mathbf{q}\mathbf{r}}}{\partial L_\mu} = 0. \quad (40)$$

343 Whether the last term contributes, depends on the specifics of the filter. The filter we employ is of
344 the form:

$$H(\mathbf{q}) \equiv H(\mathbf{q} \cdot \mathbf{l}), \quad (41)$$

345 where $\mathbf{l}$ is the cell size, which means the filter is independent of box size, and thus:

$$\frac{\partial \hat{H}(\mathbf{q})}{\partial L_\mu} = 0. \quad (42)$$

346 Therefore we have

$$\frac{\partial \tilde{\phi}(\mathbf{r})}{\partial L_\mu} = -\frac{\tilde{\phi}(\mathbf{r})}{L_\mu} \quad (43)$$

347 which results in the following expression:

$$\text{Vir}_{1,\mu} = \int d\mathbf{r} \left(w_1(\{\nabla \tilde{\phi}(\mathbf{r})\}) - \sum_{\ell=1}^M \left(\frac{\partial \tilde{\phi}_\ell(\mathbf{r})}{\partial L_\mu} + \nabla \tilde{\phi}_\ell(\mathbf{r}) \right) \frac{\partial w_1([\nabla \tilde{\phi}(\mathbf{r})])}{\partial \nabla \tilde{\phi}_\ell(\mathbf{r})} \right). \quad (44)$$

348 For the square gradient term, the virial term is given by:

$$\text{Vir}_{1,\mu} = - \int d\mathbf{r} \sum_{k\ell} \frac{K_{k\ell}}{\rho_0} \left(\frac{1}{2} \nabla \tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r}) + \nabla_\mu \tilde{\phi}_k(\mathbf{r}) \nabla_\mu \tilde{\phi}_\ell(\mathbf{r}) \right). \quad (45)$$

349 *a. Consistency with literature* The pressure computed in^{27,31} corresponds to a virial of the
350 form:

$$\text{Vir}_{1,\mu} = - \int d\mathbf{r} \sum_{k\ell} \frac{K_{k\ell}}{\rho_0} \left(-\frac{1}{2} \tilde{\phi}_k(\mathbf{r}) \nabla^2 \tilde{\phi}_\ell(\mathbf{r}) - \frac{1}{2} \nabla \tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r}) + \nabla_\mu \tilde{\phi}_k(\mathbf{r}) \nabla_\mu \tilde{\phi}_\ell(\mathbf{r}) \right). \quad (46)$$

351 We rewrite (46) as:

$$\text{Vir}_{1,\mu} = - \int d\mathbf{r} \sum_{k\ell} \frac{K_{k\ell}}{\rho_0} \left(-\nabla (\tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r})) + \frac{1}{2} \nabla \tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r}) + \nabla_\mu \tilde{\phi}_k(\mathbf{r}) \nabla_\mu \tilde{\phi}_\ell(\mathbf{r}) \right). \quad (47)$$

352 where we have used:

$$\phi \nabla^2 \phi = \nabla(\phi \nabla \phi) - \nabla \phi \nabla \phi. \quad (48)$$

353 Finally, for periodic boxes, the integral of the gradient sums to zero giving:

$$\text{Vir}_{1,\mu} = - \int d\mathbf{r} \sum_{k\ell} \frac{K_{k\ell}}{\rho_0} \left(\frac{1}{2} \nabla \tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r}) + \nabla_\mu \tilde{\phi}_k(\mathbf{r}) \nabla_\mu \tilde{\phi}_\ell(\mathbf{r}) \right), \quad (49)$$

354 which is the same as (45).

355 2. Computational details

356 a. Computation of Laplace term

357 The forces from the gradient term involves a gradient of the Laplace operator. As hPF-MD
358 uses a coarse grid with distribution of particles to only neighbouring grid points, special numerical
359 techniques are required to avoid amplification of unphysical high frequency modes for higher order
360 derivatives. We introduce the following regularized density variable:

$$\tilde{\phi}_k(\mathbf{r}) = \int d\mathbf{u} \phi_k(\mathbf{r} - \mathbf{u}) H(\mathbf{u}), \quad (50)$$

where $H(\mathbf{u})$ is a normalized distribution often referred to as a kernel, window function or transfer function. Using the spectral method the derivative is obtained to arbitrary order through:

$$\nabla^n \tilde{\phi}_k(\mathbf{r}) = \text{FFT}^{-1} \left[(i\mathbf{q})^n \hat{\phi}_k(\mathbf{q}) \hat{H}(\mathbf{q}) e^{i\mathbf{q} \cdot \mathbf{r}} \right], \quad (51)$$

where $\hat{\cdot}$ denotes variable in Fourier space. In the literature many transfer functions are reported, some more commonly used are raised cosine and Gaussian filter. Our main interest lies in computation of second order derivative, therefore we use the following specialized second-order filter:

$$\hat{H}(\mathbf{q}, \mathbf{l}) = \frac{1}{\sqrt{1 + (|\mathbf{q} \cdot \mathbf{l}|)^4}}. \quad (52)$$

3. Simulation details

Here we provide details on all the systems simulated. Unless otherwise specified for a specific system, parameters in Appendix 3 a are employed.

a. Simulation procedures and parameters

Constant temperature simulations are achieved by the *Andersen thermostat*⁵¹ with a collision frequency of 7 ps^{-1} and a coupling time of 0.1 ps. For *NPT* simulations, pressure is kept constant by the Berendsen barostat with a compressibility parameter set to $4.5 \times 10^{-5} \text{ bar}$ with a coupling time of 12 ps. Equations of motion are integrated using the *velocity Verlet algorithm*⁵² with time step 0.03 ps. The densities used for computing the particle-field forces are updated every 3 ps. For all simulations $\rho_0 = 8.33 \text{ nm}^{-3}$. The number of cells used is chosen such that their lengths are $\sim 0.67 \text{ nm}$.

b. System setups

a. Water simulations The pressure graph in presented in Fig. 1, is obtained by simulating a cubic box of size $15 \text{ nm} \times 15 \text{ nm} \times 15 \text{ nm}$ containing 28113 beads under *NVT* conditions at 300 K. The system was first equilibrated for 15 ns and data was then gathered for 15 ns gathering pressure every 0.15 ns. Next the *NPT* equilibration of density was performed on the same box size, but with 30915 beads. In this specific simulation, a coupling time constant for the barostat of 12 ps was used.

384 *b. Binary mixtures* The binary mixture results presented in Fig. 2, a box of $25\text{ nm} \times 25\text{ nm} \times$
 385 25 nm containing 130156 beads with a 50%/50% mixture of type A and B. The system was
 386 first equilibrated for 15 ns and the data was then gathered for 15 ns gathering pressure at every
 387 0.15 ns. For the compressibility term a $\kappa = 0.05\text{ kJ}^{-1}\text{ mol}$ was used. For snapshots of the droplets
 388 presented in Fig. 3 are obtained with the same box only starting from 10%/90% mixture with
 389 $\tilde{\chi}_{AB} = 20\text{ kJ mol}^{-1}$.

390 *c. Lipid bilayers*

391 *NVT* As starting configuration for the Fig. 5, a highly undulating membrane solvated in water
 392 in a box of $40\text{ nm} \times 40\text{ nm} \times 20\text{ nm}$ was used. The membrane is composed out of 5000 lipids
 393 with 12 beads each and 206400 water beads (corresponding with this mapping to 825600 water
 394 molecules). This specific membrane is kept at 325 K. The membrane was simulated for a total
 395 time of 190 ns, and data was gather from 30 ns every 0.3 ns.

396 *NPT* The starting configuration was prepared by the *insane-code*⁵³, with an initial box of
 397 $100\text{ nm} \times 100\text{ nm} \times 20\text{ nm}$ containing 33282 lipids and 1238345 water beads (corresponding to
 398 4953380 water molecules). A coupling time of 12 ps was used for the barostat. The system was
 399 first equilibrated for 15 ns, then the cells for the density grids are updated to fit the new box and a
 400 second simulation lasting 150 ns is performed. The profiles presented in Fig. 6 were obtained for
 401 a system of 528 DPPC lipids solvated with 24000 water beads (960000 water molecules) with an
 402 initial equilibration of 15 ns followed by a simulation of 90 ns of data gathering every 75 ps.

403 4. Parameterization of temperature dependence of a for water

FIG. 7. Required a to reach 1 bar for $\kappa = 0.03\text{ kJ}^{-1}\text{ mol}$ and $0.05\text{ kJ}^{-1}\text{ mol}$ for different temperatures.

404 The parameterization of a is obtained by considering a box of water beads with density
 405 995 kg m^{-3} under NVT conditions. Keeping $a = 0$, a pressure P as a function of the parame-
 406 ters is found. Using (20), the required a to get the correct density at 1 bar is obtained. Fig. 7 shows
 407 for two commonly used compressibility values the required a as function of temperature.

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