Hybrid Particle-Field Molecular Dynamics Under Constant Pressure

Sigbjørn Løland Bore,1, a) Hima Bindu Kolli,1, b) Antonio De Nicola,2 Maksym Byshkin,3 Toshihiro Kawakatsu,4 Giuseppe Milano,2 and Michele Cascella1, c)

1) Department of Chemistry, and Hylleraas Centre for Quantum Molecular Sciences, University of Oslo, PO Box 1033 Blindern, 0315 Oslo, Norway
2) Department of Organic Materials Science, Yamagata University, 4-3-16 Jonan Yonezawa, Yamagata-ken 992-8510, Japan
3) Institute of Computational Science, Università della Svizzera italiana, 6900 Lugano, Switzerland
4) Department of Physics, Tohoku University, Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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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.

a) email: s.l.bore@kjemi.uio.no
b) Present address: Department of Physics and Astronomy, The University of Sheffield, United Kingdom
c) email: michele.cascella@kjemi.uio.no
I. INTRODUCTION

Hybrid particle-field simulations (hPF) are a group of computationally efficient approaches for studying mesoscale soft matter systems with molecular resolution.\textsuperscript{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 efficiency\textsuperscript{5}. 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 particles\textsuperscript{6}.

Coupling hPF to molecular dynamics algorithms has widened the range of applicability of hPF systems, from more conventional soft polymer mixtures to biological systems\textsuperscript{7–10}. Examples from the literature include nanocomposites, nanoparticles, percolation phenomena in carbon nanotubes\textsuperscript{11–14}, lamellar and nonlamellar phases of phospholipids\textsuperscript{15–17}, and more recently polypeptides\textsuperscript{18}, and polyelectrolytes\textsuperscript{19–22}.

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 Morse\textsuperscript{23} 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 hPF\textsuperscript{24} by a virtual displacement approach\textsuperscript{25}, obtaining a good correspondence of the equation of state for polymer chains compared to that derived from particle-based simulations. In a very recent publication\textsuperscript{26}, 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 \textit{local pressure profiles} in density field based methods.\textsuperscript{26} Finally, Sgouros et al.\textsuperscript{27} derived the pressure for hPF using the thermodynamic definition of the pressure tensor\textsuperscript{28}.

Despite the capability of deriving and computing the pressure in \textit{NVT} conditions, two important issues hinder hPF simulations under constant pressure. First, the interaction energy functionals commonly used in hPF simulations\textsuperscript{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.\textsuperscript{24,26} and is emphasized in ref.\textsuperscript{27}, pure density terms \textit{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 \textit{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 systems\textsuperscript{29} and by Cahn and Hilliard on two-component systems\textsuperscript{30}. Particularly relevant for the hPF method is its recent implementation in \textit{hPF-Brownian dynamics} to model polymer-air interfaces\textsuperscript{27}. 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.

\section*{II. \textit{NPT} Ensemble Hybrid Particle-Field}

\subsection*{A. hPF Hamiltonian}

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

\[
H = \sum_{m=1}^{N} H_0(\{\mathbf{r}, \mathbf{\dot{r}}\}_m) + W[\{\phi(\mathbf{r}), \nabla \phi\}].
\] (1)
$H_0$ is the single-particle Hamiltonian for the $m$-th molecule:

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

(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:

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

(3)

a. $W_0$: Flory-Huggins mixing entropy and compressibility

The original formulation for hPF under $NVT$ conditions employed the following interaction energy functional $3,24$:

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

(4)

where $\phi_0$ is the average total number density, $\tilde{\chi}_{k\ell}$ is the Flory-Huggins coupling parameter between species $k$ and $\ell$, and $\kappa$ controls the fluctuations of the local density. To generalize this formulation to $NPT$ conditions, we propose the following modified interaction energy:

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

(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:

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

(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.
b. \textit{W}$_1$: Square gradient interactions  To model interfaces we introduce a square gradient term to the interaction energy\cite{27,31} dependent on multiple species:
\[
W_1[\nabla \phi] = \frac{1}{2\rho_0} \sum_{k,\ell} \int \text{d}r \ K_{k\ell} \nabla \phi_k(r) \cdot \nabla \phi_\ell(r),
\]
(7)
where $K_{k\ell}$ is a coupling constant between the gradients of species $k$ and $\ell$. The corresponding external potential is given by (see Appendix 1 a):
\[
V_{1,k}(r) = -\sum_{\ell=1} K_{k\ell} \rho_0 \nabla^2 \phi_\ell(r).
\]
(8)

B. Calculation of the pressure in hPF

We calculate the pressure using a derivation similar to the one used by Hünenberger for the reciprocal space part of Ewald summation\cite{32}. The pressure inside a simulation box with side lengths $L_\mu$ and volume $V$ is given by:
\[
P_\mu = \frac{2T_\mu - \text{Vir}_\mu(\{r,L\})}{V}
\]
(9)
where $T_\mu$ denotes a Cartesian component of kinetic energy and $\text{Vir}_\mu = L_\mu \frac{\partial U_{\text{tot}}}{\partial L_\mu}$ is obtained directly from the potential energy of the system $U_{\text{tot}}$, defined as:
\[
U_{\text{tot}} = \sum_{m=1}^N U_0(\{r\}_m) + W_0[\{\phi\}] + W_1[\{\nabla \phi\}].
\]
(11)
The bonded interactions ($U_0(\{r\}_m)$) contribute to the virial term as in ordinary molecular dynamics. The interaction energy contributions to the pressure are computed as:
\[
P_{0,\mu} = -\frac{L_\mu}{V} \frac{\partial W_0[\{\phi\}]}{\partial L_\mu}, \quad P_{1,\mu} = -\frac{L_\mu}{V} \frac{\partial W_1[\{\nabla \phi\}]}{\partial L_\mu},
\]
(12)
corresponding to (see Appendix 1 b for their derivation):
\[
P_{0,\mu} = \frac{1}{V} \int \text{d}r \ \frac{1}{\rho_0} \left( \frac{1}{2} \sum_{k,\ell} K_{k\ell} \phi_k(r) \phi_\ell(r) + \frac{1}{2\kappa} \left( \sum_\ell \phi_\ell(r) \right)^2 - a^2 \right), \]
(13a)
\[
P_{1,\mu} = \frac{1}{V} \int \text{d}r \sum_{k,\ell} \frac{K_{k\ell}}{\rho_0} \left( \frac{1}{2} \nabla \phi_k(r) \cdot \nabla \phi_\ell(r) + \nabla_\mu \phi_k(r) \nabla_\mu \phi_\ell(r) \right).
\]
(13b)
The total pressure in a direction $\mu$ is thus given by:

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

Here we note the following: (i) Although $a$ gives no contributions to the force, it gives rise to a nonzero pressure. This gives added flexibility to control the isotropic pressure, similarly to the constant term in the stiffened gas equation of state$^{33}$. (ii) The contribution of $W_0$ to the pressure is isotropic, while the contribution of $W_1$ is not. (iii) The local pressure density (the integrand in (13b)) does not contain a Laplace term as reported in refs.$^{27,31}$. However, as shown in Appendix 1 b, the expressions are equivalent.

### III. COMPUTATIONAL DETAILS

#### A. hPF-MD simulations

The model described in the previous section was implemented into hPF-molecular dynamics software OCCAM$^5$. This enables the possibility of sample configurations of the molecular system governed by our new hPF Hamiltonian (1) following directly the evolution of the corresponding equations of motion. The forces on the $i$-th particle of type $k$ due to $W_0$ and $W_1$ are computed from the gradients of the external potentials $V_{0,k}(r)$ and $V_{1,k}(r)$:

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

by a particle mesh approach$^{17}$. First, particles are distributed onto a different Cartesian grid for each species $k$ by linear interpolation to the nearest vertices (cloud-in-cell). Derivatives are computed on a staggered grid by finite differences. Finally, the derivatives are interpolated back onto the particles giving the forces. As shown in ref.$^{17}$, the external potentials are slow variables, and can be updated with good approximation at intervals of up to $\sim 100$ steps$^{17}$, yielding efficient parallelization$^5$.

#### B. Computation of square gradient forces

The computation of the external potential due to the square gradient term $W_1$ involves computing the Laplacian of the densities. To obtain a rotational invariant estimate without the appearance of spurious oscillations, we employ a spectral approach$^{34}$ filtering out fast oscillations of the
derivatives in Fourier space. The filtering is done by convolution:

\[ \tilde{\phi}_k(r) = \int du \, \phi_k(r - u)H(u). \]  

(16)

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

\[ V_{1,k}(r) = -\sum_{\ell=1}^{M} \frac{K_{k\ell}}{\rho_0} \int dy \, H(r - y) \nabla^2 \tilde{\phi}_\ell(y). \]  

(17)

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

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

(18)

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

C. Barostat

We employ the Berendsen barostat\(^35\) with isotropic coupling for isotropic systems, and semi-isotropic coupling for lipid bilayers. The efficiency of the hPF-MD approach is dependent on having \( i) \) little communication among processors and \( ii) \) avoiding heavy calculation (typically involving the grid) between density updates. Similarly to the multi-time-step approach used in the GPU version of Tinker-OpenMM\(^36\), we average contributions from bonded terms and keep volume and field contributions constant between density update steps. This is done by scaling the components of the box lengths and the coordinates every \( n \) time steps \( \Delta t \) using Berendsen scaling factor \( \alpha_\mu \):

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

(19)

where \( \kappa_T, \tau_p \) and \( P_0 \) are the isothermal compressibility, the time constant and the pressure of the barostat respectively.

D. Simulation details

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

A. Homogeneous system: Water

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

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

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

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


(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 \(\kappa = 0.03, 0.05, 0.10\) kJ\(^{-1}\)mol, \(a = 9.10, 9.47, 10.40\) 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 \(\rho\) 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 \(\kappa\) the density equilibrates to the correct density. In the next systems, if not otherwise stated, we adopt \(\kappa = 0.05\) kJ\(^{-1}\)mol and \(a = 9.47\) nm\(^{-3}\).

**B. Binary mixture**

![Graph](image)

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

**a. Phase separation** We consider a toy binary mixture between two ideal fluids. The two components differ only by \(\tilde{\chi}\) 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 \(\tilde{\chi}\) 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 \(\tilde{\chi}\), mixing of the two fluids is favourable, and the density increases. For positive values of \(\tilde{\chi}\) 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 theory 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 kJ mol$^{-1}$ 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 $\Psi$ is defined by the equation:

$$\Psi = \frac{\pi^{1/3} (6V)^{2/3}}{A}, \quad (21)$$
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 vesicles\(^{39}\). 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 \( V_k(r) \) in Fourier space using FFT.

C. Effect of square gradient term on lipid bilayers

Modeling of surface tension

\[
W_1 \simeq \frac{1}{\rho_0} \int dr \ K_{CW} \nabla \phi_W(r) \cdot \nabla \phi_C(r)
\]

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 literature\(^{17}\), as summarized in Fig. 4. Here, we add to the preexisting model the
Square gradient interaction limited to only one $K_{m\ell}$ term between the hydrophobic lipid tail (C) and the water (W) beads ($K_{CW}$), disregarding all other terms.

![Square Gradient Interaction](image)

**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 $K_{CW}$.

### flat lipid bilayers – Surface area

*NVT* simulations of lipid bilayers in periodic boundary conditions impose an arbitrary effective area per lipid $A$, defined as:

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

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 $\gamma$ of the membrane, Fig. 5B, which can be calculated from:

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

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 $\gamma$ 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.

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We thus simulated a 20nm × 100nm × 100nm 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 field$^{45}$, 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 profile (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 model\textsuperscript{17}. (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.\textsuperscript{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 Edholm\textsuperscript{44}. 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.\textsuperscript{46} Fig. 6C,D report the local difference
between normal and lateral pressure computed with hPF-MD and all-atom by Lindahl, and the contributions by the different terms of the Hamiltonian. While the magnitude of the all-atom pressure is about four times that of hPF-MD, we nevertheless identify the appearance of three key qualitative features: the presence of a negative peak between water and the lipid heads, a positive peak in between heads and tails, and a rather flat region in the tail part. Unlike all-atom simulations, the hPF profile has a positive sign to the pressure difference at the carbon tails, indicating compressed carbon tails in the normal direction. We note that this may be part an artifact of the coarseness of the mesh, which can cause a spill out of pressure into the middle part of the membrane, as well as by the absence of a square gradient terms between water and glycerol or polar head beads. The local pressure contributions from $P_0$ and $P_1$ were computed at the vertices of the mesh. This is at one hand rigorous as it avoids subtleties related to local pressure assignment, however higher resolution would be advantageous for computing properties from the local pressure profiles. A natural route for achieving higher resolution assignment of pressure would be to follow the procedure proposed in ref. by Harasima assignment.

Our simulations present a very flat bilayer without the detection of significant undulations on the tensionless surface of the bilayer. The stiffness of the bilayer can be quantified by computing the area compressibility as in ref. For the DPPC lipid bilayer, in our case, we obtain $K_A = 22\,000\,\text{mNm}^{-1}$. This is about two orders of magnitude larger than what has been reported in the literature confirming that the present setup produces an excessively rigid system. Although it is well known that the Berendsen barostat is not suited for studying fluctuations of the membrane, we stress here, in these preliminary test implementation, that we have only considered carbon water interactions for the square gradient term. Moreover, this term was naively added to $\tilde{\chi}$ parameters that were preoptimized to reproduce accurate density profiles in the absence of an explicit surface tension term, with consequent possible double counting of the repulsion between the water and the hydrophobic tails. Overall, the discrepancy on the fluctuation of the DPPC bilayer together with the qualitative but not quantitative agreement on the lateral pressure profiles indicate that $NPT$ simulation of realistic systems require a global parameterization of both the $\tilde{\chi}$ and $K_{ml}$ matrices, while a simple addition of the second term to the first may not be sufficient to obtain quantitatively accurate data.
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 $K_m$ 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 $\tilde{\phi}$. 
a. **External potential** $V_{1,k}$

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

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

(24)

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

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

(25)

Inserting (1 a) into (24) yields:

$$
V_{1,k}(r) = \int dxdy \sum_{\ell=1}^{M} \frac{K_{k\ell}}{\rho_0} \nabla \tilde{\phi}_\ell(x) \nabla \delta(x-y) H(r-y)
$$

$$
= \int dy H(r-y) \int dx \sum_{\ell=1}^{M} \frac{K_{k\ell}}{\rho_0} \nabla \tilde{\phi}_\ell(x) \nabla \delta(x-y)
$$

$$
= - \int dy H(r-y) \int dx \sum_{\ell=1}^{M} \frac{K_{k\ell}}{\rho_0} \nabla^2 \tilde{\phi}_\ell(x) \delta(x-y)
$$

$$
= - \sum_{\ell=1}^{M} \frac{K_{k\ell}}{\rho_0} \int dy H(r-y) \nabla^2 \tilde{\phi}_\ell(y).
$$

(26)

Without filter ($H(r-y) = \delta(r-y)$) we obtain:

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

b. **Virial terms from interaction energies**

The pressure is given by the Viral:

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

(27)

where

$$
\text{Vir}_{\mu} = L_{\mu} \frac{\partial U}{\partial L_{\mu}}.
$$

(28)

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

$$
\frac{\partial W_0}{\partial L_{\mu}} = \int \left( \frac{\partial dr}{\partial L_{\mu}} w_0(\phi(r)) + dr \frac{\partial w_0(\phi(r))}{\partial L_{\mu}} \right)
$$

$$
= \int \left( \frac{dr}{L_{\mu}} w_0(\phi(r)) - dr \frac{\partial w_0(\phi(r))}{\partial \phi} \frac{\phi(r)}{L_{\mu}} \right)
$$

(29)

(30)
giving:

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

Inserting the energy density:

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

We compute interface virial of \( W_1 \) by:

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

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

The last partial derivative is given by:

\[
\frac{\partial}{\partial L_{\mu}} (\nabla_{\nu} \tilde{\phi}(\mathbf{r})) = \left( \frac{\partial}{\partial L_{\mu}} \nabla_{\nu} \right) \tilde{\phi}(\mathbf{r}) + \nabla_{\nu} \frac{\partial \tilde{\phi}(\mathbf{r})}{\partial L_{\mu}}
\]  (35)

\[
= -\delta_{\mu \nu} \nabla_{\nu} \tilde{\phi}(\mathbf{r}) + \nabla_{\nu} \frac{\partial \tilde{\phi}(\mathbf{r})}{\partial L_{\mu}}.
\]  (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:

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

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

The contributions from the three first terms are given by:

\[
\frac{\partial \text{d} \mathbf{q}}{\partial L_{\mu}} = -\frac{\text{d} \mathbf{q}}{L_{\mu}}, \quad \frac{\partial \tilde{\phi}(\mathbf{q})}{\partial L_{\mu}} = 0, \quad \frac{\partial e^{-i\mathbf{q} \cdot \mathbf{r}}}{\partial L_{\mu}} = 0.
\]  (40)

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

\[
H(\mathbf{q}) \equiv H(\mathbf{q} \cdot \mathbf{l}),
\]  (41)

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

\[
\frac{\partial \hat{H}(\mathbf{q})}{\partial L_{\mu}} = 0.
\]  (42)
Therefore we have
\[
\frac{\partial \tilde{\phi}(\mathbf{r})}{\partial L_\mu} = -\frac{\tilde{\phi}(\mathbf{r})}{L_\mu}
\]  
which results in the following expression:
\[
\text{Vir}_{1,\mu} = \int \mathbf{d} \mathbf{r} \left( w_1(\{\nabla \tilde{\phi}(\mathbf{r})\}) - \sum_{\ell=1}^M \left( \frac{\partial \tilde{\phi}_\ell(\mathbf{r})}{\partial L_\mu} + \nabla \tilde{\phi}_\ell(\mathbf{r}) \right) \frac{\partial w_1(\{\tilde{\phi}(\mathbf{r})\})}{\partial \tilde{\phi}_\ell(\mathbf{r})} \right). 
\]  
For the square gradient term, the virial term is given by:
\[
\text{Vir}_{1,\mu} = -\int \mathbf{d} \mathbf{r} \sum_{k\ell} \frac{K_{k\ell}}{\rho_0} \left( -\frac{1}{2} \nabla \tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r}) \right) - \frac{1}{2} \nabla \tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r}) + \nabla \mu \tilde{\phi}_k(\mathbf{r}) \nabla \mu \tilde{\phi}_\ell(\mathbf{r}) \right). 
\]  
We rewrite (46) as:
\[
\text{Vir}_{1,\mu} = -\int \mathbf{d} \mathbf{r} \sum_{k\ell} \frac{K_{k\ell}}{\rho_0} \left( -\nabla (\tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r})) + \frac{1}{2} \nabla \tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r}) + \nabla \mu \tilde{\phi}_k(\mathbf{r}) \nabla \mu \tilde{\phi}_\ell(\mathbf{r}) \right). 
\]  
Finally, for periodic boxes, the integral of the gradient sums to zero giving:
\[
\text{Vir}_{1,\mu} = -\int \mathbf{d} \mathbf{r} \sum_{k\ell} \frac{K_{k\ell}}{\rho_0} \left( \nabla (\tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r})) + \frac{1}{2} \nabla \tilde{\phi}_k(\mathbf{r}) \nabla \tilde{\phi}_\ell(\mathbf{r}) + \nabla \mu \tilde{\phi}_k(\mathbf{r}) \nabla \mu \tilde{\phi}_\ell(\mathbf{r}) \right), 
\]  
which is the same as (45).

2. Computational details

a. Computation of Laplace term

The forces from the gradient term involves a gradient of the Laplace operator. As hPF-MD uses a coarse grid with distribution of particles to only neighbouring grid points, special numerical techniques are required to avoid amplification of unphysical high frequency modes for higher order derivatives. We introduce the following regularized density variable:
\[
\tilde{\phi}_k(\mathbf{r}) = \int \mathbf{d} \mathbf{u} \phi_k(\mathbf{r} - \mathbf{u}) H(\mathbf{u}),
\]
where $H(u)$ 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:

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

(51)

where $\tilde{\cdot}$ 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:

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

(52)

### 3. Simulation details

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

#### a. Simulation procedures and parameters

Constant temperature simulations are achieved by the *Andersen thermostat*\textsuperscript{51} with a collision frequency of 7 ps\textsuperscript{-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 $4.5 \times 10^{-5}$ bar with a coupling time of 12 ps. Equations of motion are integrated using the *velocity Verlet algorithm*\textsuperscript{52} with time step 0.03 ps. The densities used for computing the particle-field forces are updated every 3 ps. For all simulations $\rho_0 = 8.33$ nm\textsuperscript{-3}. The number of cells used is chosen such that their lengths are $\sim 0.67$ 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 nm × 15 nm × 15 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.
b. Binary mixtures  The binary mixture results presented in Fig. 2, a box of 25 nm × 25 nm × 25 nm containing 130156 beads with a 50%/50% mixture of type A and B. The system was first equilibrated for 15 ns and the data was then gathered for 15 ns gathering pressure at every 0.15 ns. For the compressibility term a κ = 0.05 kJ⁻¹ mol was used. For snapshots of the droplets presented in Fig. 3 are obtained with the same box only starting from 10%/90% mixture with \( \tilde{\chi}_{AB} = 20 \text{kJ mol}^{-1} \).

c. Lipid bilayers

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

NPT  The starting configuration was prepared by the insane-code⁵³, with an initial box of 100 nm × 100 nm × 20 nm containing 33282 lipids and 1238345 water beads (corresponding to 4953380 water molecules). A coupling time of 12 ps was used for the barostat. The system was first equilibrated for 15 ns, then the cells for the density grids are updated to fit the new box and a second simulation lasting 150 ns is performed. The profiles presented in Fig. 6 were obtained for a system of 528 DPPC lipids solvated with 24000 water beads (960000 water molecules) with an initial equilibration of 15 ns followed by a simulation of 90 ns of data gathering every 75 ps.

4. Parameterization of temperature dependence of \( a \) for water

![Graph](image.png)

**FIG. 7.** Required \( a \) to reach 1 bar for \( \kappa = 0.03 \text{kJ}^{-1} \text{mol} \) and 0.05 kJ⁻¹ mol for different temperatures.
The parameterization of $a$ is obtained by considering a box of water beads with density 995 kg m$^{-3}$ under $NVT$ conditions. Keeping $a = 0$, a pressure $P$ as a function of the parameters is found. Using (20), the required $a$ to get the correct density at 1 bar is obtained. Fig. 7 shows for two commonly used compressibility values the required $a$ as function of temperature.

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