Compatibility of advanced water models with a united atom model of lipid in lipid bilayer simulation

Cite as: J. Chem. Phys. **151**, 065104 (2019); https://doi.org/10.1063/1.5108830 Submitted: 02 May 2019 . Accepted: 18 July 2019 . Published Online: 13 August 2019

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J. Chem. Phys. **151**, 065104 (2019); https://doi.org/10.1063/1.5108830 © 2019 Author(s).

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Cite as: J. Chem. Phys. 151, 065104 (2019); doi: 10.1063/1.5108830 Submitted: 2 May 2019 • Accepted: 18 July 2019 • Published Online: 13 August 2019



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ABSTRACT

Molecular dynamics simulation of lipid bilayers generally uses all-atom, united-atom, and coarse-grained models of lipid molecules. The GROMOS united-atom model of lipid constructs a balance between accuracy and computational cost. The above-mentioned model satisfactorily reproduces many of the structural and dynamical properties of different lipid bilayers. However, the GROMOS force field is parameterized only with the SPC model of water. Unfortunately, SPC is not an excellent model of water for predicting the structure and dynamics of the interfacial water near the lipid bilayer. More advanced water models, such as TIP3P-FB and TIP4P-FB, outperform the SPC model in predicting different thermodynamic and microscopic properties of bulk water. This motivates us to check the compatibility of five different water models, including SPC, with the GROMOS96 53A6_L united atom model of two different lipid bilayers, DPPC and POPC. A systematic comparison of the bilayer structure and dynamics, resulting from the simulations with different water models, is done. We find general agreement of the results for different water models with the experiment. In fact, the more advanced water models provide better agreement with the experiment. This study, therefore, helps in widening the range of choice of water models in simulating the lipid bilayer using the GROMOS united-atom model of the lipid molecules.

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I. INTRODUCTION

Molecular dynamics (MD) simulation studies have immensely contributed to understanding the structural and dynamical properties of lipid bilayers. This has been made possible by the continuous development of more and more accurate force fields of various lipid molecules. Three major classes of force fields are used in the MD simulation of the lipid bilayers. They are all-atom, united atom, and coarse-grained models. CHARMM,^{1–5} AMBER,^{6–11} OPLS-AA,^{12–14} and SLIPIDS^{15,16} are three major all-atom force fields of lipid, among which the CHARMM force field has been extensively used in many MD simulations. Being all-atom, these models accurately describe the structure of a lipid molecule. However, the agreement of different simulated parameters with experimental quantities is not always seen.¹⁷ The coarse-grained model of the lipid molecule, such as MARTINI force field,^{18,19} considers mainly four-to-one mapping, where four heavy atoms are represented by only one coarse-grained site. This allows choosing a longer simulation time (microsecond) and a much bigger system size (millions of lipid molecules) than those in all-atom models. The coarse-grained model can be used to study much more complex phenomena, such as undulations of membrane surfaces, formation of aggregates, phase transformation, behavior of membrane proteins, and lipid-protein interaction.²⁰ However, the use of this model is associated with several limitations, such as freezing of the coarse-grained lipid model at normal temperature.^{18,19}

Apart from the all-atom and the coarse-grained model, there is also the united-atom model of lipid, which constructs a balance between the complexity of the lipid molecules and the computational overhead. GROMOS^{21,22} is a computationally efficient united-atom force field, which considers nonpolar CH, CH₂, and CH₃ as single carbon atoms. There are mainly two classes of force field parameters: one with original GROMOS parameters^{21–23} and the other with Berger modifications.²⁴ Major versions of the GROMOS

force field are GROMOS87²⁵ and GROMOS96.²⁶ The GROMOS force field reproduces the properties of the system almost accurately. The latest version of GROMOS96 includes 53A5 and 53A6.²⁷ GROMOS96 53A6_L,²⁸ a modified version of 53A6, attempts to maintain the fluidity of the membrane, which was lacking in the 53A6 version.

The structural and dynamical properties of the lipid bilayer are sensitive to the interaction between the hydrophilic head group of lipids with water. Use of an arbitrary water model in a lipid bilayer simulation is generally not recommended. In principle, one should use that particular water model, with which the lipid model is parameterized. For example, the CHARMM force field of lipid was initially been parameterized with the TIP3P model²⁹ of water and later reparameterized with a flexible SPC³⁰ model of water.³¹ However, recently,^{32,33} it has been found that the CHARMM36 force field of lipid is also compatible with the TIP4P/2005, TIP3P-FB, and TIP4P-FB water models³⁴ as the above combinations of force field do not lead to severe flaws in the structure and dynamics of the lipid bilayer. Unfortunately, the GROMOS96 53A6_L model of lipid has been parameterized only with the SPC model of water.²⁸ Even though the above combination of force fields reproduces the experimentally observed properties with reasonable accuracy, it is still essential to work with more advanced water models-such as TIP4P/2005³⁵ and TIP4P-FB—mainly when a study focuses on the structure and dynamics of water at the lipid bilayer interface. Compatibility of water models, such as TIP4P/2005 and TIP4P-FB, would also allow one to simulate the lipid bilayer at low temperatures where the SPC model does not reproduce the experimental properties of liquid water as well as the former models. Note that the MD simulation study of lipid membrane at low temperatures is significant as it may shed some light on the mechanism of cold adaptation of psychrophiles, which is a class of extremophilic organisms capable of growth and reproduction at low-temperature conditions (-20 °C to +10 °C).

Widely used three site water models, TIP3P and SPC, reproduce many properties of bulk water under normal conditions.³⁷ However, the self-diffusion coefficient and static dielectric constant are poorly described.³⁸ In addition, the solvation entropies are not well reproduced by these water models.³⁹ The freezing temperatures of these models are less than 200 K.⁴⁰ The density maximum arises at a much lower temperature for these two models.⁴¹ Four-point water models perform better than the three- and five-point models in reproducing many of the thermodynamic properties of water at a broader range of temperatures. TIP4P/2005 accurately reproduces the density of water at a wide range of temperatures (240 K-370 K).³¹ However, it deviates from the observed values for some other properties, such as dielectric constant³⁴. The relatively recently developed water models, TIP3P-FB and TIP4P-FB, are parameterized to well reproduce the enthalpy of vaporization, density, dielectric constant, isothermal compressibility, heat capacity, and the thermal expansion coefficient of liquid water.³⁴ They are found to describe many of the key physical properties of water, such as the dielectric constant and the viscosity, with very good accuracy.³⁴ Some of these parameters are listed in Table S1 of the supplementary material for different water models.

The above discussion may motivate one to reparameterize the existing model of the lipid membrane, which can be compatible with more advanced models of water. However, it is far easier to check the compatibility between the GROMO96 53A6_L and different water models in the first place. Here, our goal is to check the reproducibility of a large number of experimentally observed quantities using the GROMO96 53A6L²⁸ force field for two lipids POPC and DPPC, in combination with five different models of water: SPC, TIP3P, TIP4P/2005, TIP3P-FB, and TIP4P-FB. Note, POPC contains a saturated sn1 chain and an unsaturated sn2 chain, and it is observed in most naturally occurring lipid membranes (see Fig. 1 for the labeling of the chains). It is mostly present in the outer leaflet where it functions as part of the permeability barrier. DPPC contains two saturated chains and is a welldocumented lipid. This study may guide the best possible water model(s) to consider with the GROMOS G53A6L force field. In addition, the present study may indicate the requirement of reparameterization of the lipid force field to combine with a particular water model.

The following is the outline for the remainder of this paper. The molecular models and simulation details are detailed in Sec. II. Section III details the simulation results and discussions. Concluding remarks are offered in Sec. IV.



FIG. 1. Scheme for the two lipid molecules with the relevant atoms and the two chains labeled.

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II. SIMULATION DETAILS

Each of the two bilayers, POPC and DPPC, is simulated with five different water models: SPC, TIP4P/2005, TIP3P, TIP3P-FB, and TIP4P-FB. These aggregate a total of ten different simulation systems. The lipid molecules are modeled as a united-atom model with GROMOS96 G53A6_L²⁸ force field parameters.

Initial configurations of the lipid bilayers are built using the PACKMOL software.⁴² Each system includes 200 lipids with 7000 water molecules in a simulation box of dimension 8 nm × 8 nm \times 8.5 nm. The above composition ensures a well-hydrated lipid bilayer structure with the hydration number of 35. The above area of the xy plane (64 nm^2) at the initial stage is set close to the experimentally observed area per lipid 0.643 nm² for the POPC⁴³ and 0.631 nm² for the DPPC lipid bilayer.⁴⁴ The MD simulation for these systems is done using the GROMACS software package.⁴⁵ First, we use the steepest-descent algorithm for energy minimization of these systems. The bonds are constrained with the LINCS algorithm⁴⁶ for both lipid and water. The systems are then equilibrated using the NPT ensemble for 50 ns. The temperature is maintained at 300 K for POPC and 323 K for the DPPC lipid layer-which is above their respective melting temperatures (for POPC $T_m = 270.5 \text{ K}^{47}$ and for DPPC $T_m = 314 \text{ K}^{48}$)—using the Nose-Hoover thermostat^{49,50} (coupling constant 0.1 ps). The pressure is fixed at 1 bar in the lateral and normal directions (semi-isotropically) using the Parrinello-Rahman barostat.⁵¹ The semi-isotropic pressure bath has an isothermal compressibility of 4.6×10^{-5} bars⁻¹ and a coupling constant of 1 ps. These simulation parameters were also used elsewhere.²⁸ The equations of motion are always solved using the Verlet leapfrog algorithm every after 2 fs. The Lennard-Jones interactions are scaled to zero after a distance of 14 Å for SPC and 20 Å for all other water models. The cutoff distance for short-range force is taken as 8 Å for SPC and 21 Å for other models. Long-range electrostatic interactions are handled by the Particle Mesh Ewald (PME) summation method. The interactions are updated every 5 simulations steps. The equilibration of each system up to 50 ns time is followed by the final production run by the NPT ensemble for another 150 ns, during which we save the configurations every after 250 fs for the analyses.

III. RESULTS AND DISCUSSION

A. Structural properties

1. Average area per lipid

The average area per lipid ($\langle A_L \rangle$) is calculated by dividing the time-averaged lateral dimension of the simulation box by the number of lipid molecules present in each leaflet n_l ,

$$\langle A_L \rangle = \langle A_{xy} \rangle / n_l. \tag{1}$$

Some studies also probe the curved area per lipid, which takes into account the curved lipid membrane surface. However, a recent simulation study¹⁷ has indicated that for PC lipids, such as DPPC and POPC, the standard area per lipid shows closer agreement with the experimental value than the curved area. Therefore, we avoid the calculation of the curved area per lipid. Note that the reliability of the experimental $\langle A_L \rangle$ values is always questionable. The $\langle A_L \rangle$ value of a lipid bilayer cannot be measured directly from the experiment. In addition, the thermal fluctuations of the fluid phase of the lipid bilayer do not allow an accurate determination of the $\langle A_L \rangle$ values from the experimental studies.^{52,53} Due to the above fact, a wide range of $\langle A_L \rangle$ values for a particular lipid bilayer is reported in the literature.⁵⁴ Although a direct comparison with experimental results is not very much reliable, it is always important for a simulation study to predict the $\langle A_L \rangle$ value in agreement with the experimental range.

The simulated $\langle A_{\rm L} \rangle$ values are reported in Table I for different models of water and compared with the experimental^{43,55-57} and some previously reported simulated data.24,58,59 The time dependencies of $\langle A_{xy} \rangle$ for all ten systems are shown in Fig. S1 of the supplementary material, where we see the convergence of the lateral dimension of the box after 50 ns simulation time. General agreement between the simulated $\langle A_L \rangle$ values for different water models and the experimental values is evident in Table I. While the TIP4P/2005 water model gives relatively lower values of $\langle A_L \rangle$, a closer agreement is observed for the other water models, TIP3P, TIP3P-FB, and TIP4P-FB, between the simulated and experimental $\langle A_L \rangle$ values⁵⁵ for both the lipid membranes. The value of $\langle A_L \rangle$ is lowest in the case of TIP4P/2005 water model probably because of the lowest dielectric constant (~60) of the latter water model compared to those of all other models. The dielectric constant values for different water models are listed in Table S1 of the supplementary material.

2. Isothermal area compressibility modulus

The isothermal area compressibility modulus K_A is calculated from the fluctuation of average area per lipid in an equilibrium simulation by the following equation:

$$K_A = \frac{k_B T \langle A_L \rangle}{n_L \langle \delta A_L^2 \rangle}.$$
 (2)

Here, k_B is the Boltzmann constant, T is the average temperature, $\langle A_L \rangle$ is the average area per lipid, and δA_L^2 is the variance associated with A_L . The simulated average area compressibility moduli are

TABLE I. The simulated $\langle A_L \rangle$ values of the two lipid bilayers—each of which is simulated with different water models—and their comparison with earlier simulated and experimental data. The values in the parentheses are the standard error calculated by block averaging.

Lipid	Water model	$\langle A_{\rm L} \rangle ({\rm nm}^2)$	Literature (nm ²)
	SPC	0.61(0.003)	
POPC	TIP3P	0.66(0.003)	
	TIP3P-FB	0.67(0.002)	Expt.: ^{43,55} 0.630–0.683
	TIP4P/2005	0.60(0.002)	Simulation: ⁵⁸ 0.655
	TIP4P-FB	0.68(0.002)	
	SPC	0.60(0.002)	
	TIP3P	0.65(0.001)	
	TIP3P-FB	0.67(0.003)	Expt.: ^{56,57} 0.57–0.717
DrrC	TIP4P/2005	0.57(0.002)	Simulation: ^{24,59} 0.61–0.637
	TIP4P-FB	0.67(0.002)	

given in Table II. The simulated values are consistent with the experimental values for both the POPC and DPPC except when SPC water model is used. This is because $\langle A_L \rangle$ is also not correctly predicted by the SPC water model. The higher values of K_A , predicted by the SPC water, were also reported in a previous study.¹⁷ Therefore, the agreement between the experimental^{60,61} and simulated^{17,62,63} K_A values is significantly improved by the use of more advanced water models. However, it is also true that the accuracy of the experimental K_A values is limited by the accuracy of the measurement of $\langle A_L \rangle$ value in the experiment.

3. Average volume per lipid

The volume occupied by lipid molecules is one of the essential parameters characterizing the lipid bilayer structure. In the simulation, the following equation calculates the volume per lipid molecule V_L :

$$V_L = (V - n_W V_W)/n_L. \tag{3}$$

Here, n_L and n_w are the numbers of lipids and water molecules, respectively. V_w is the volume per water molecule, which has been determined from a 15 ns long independent simulation of pure bulk water. V_L can be measured by different experimental techniques, such as neutral buoyancy,^{64–66} dilatometry,^{67,68} pyknometry,⁶⁹ and vibrating tube densitometry.^{70,71} Unfortunately, any of these techniques do not provide very accurate V_L values.⁷² Therefore, MD simulations⁷³ better predict the molecular volume and overcome the error bars associated with the experimental estimation of V_L . Simulated V_L for ten different systems are reported in Table III. In the case of POPC, water models do not significantly influence the simulated values, which are in good agreement with the experimental values.^{43,61,74} However, we see some deviation from the experimental values for the DPPC lipid bilayer.

4. Bilayer electron density and scattering form factors

Detailed structural information of the lipid bilayer is obtained from electron density profiles (EDPs) along the bilayer normal. However, the experiment cannot measure EDPs directly. Therefore, we Fourier transform the simulated electron and neutron

TABLE II. The simulated K_A values of the two lipid bilayers—each of which is simulated with different water models—and their comparison with earlier simulated and experimental data. The values in the parentheses are the standard error calculated by block averaging.

Lipid	Water model	K_A (N/m)	Literature (N/m)
POPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$\begin{array}{c} 0.54(0.08)\\ 0.23(0.01)\\ 0.35(0.03)\\ 0.34(0.07)\\ 0.31(0.04) \end{array}$	Expt.: ⁶⁰ 0.18–0.33 Simulation: ^{62,63} 0.2–0.6
DPPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$\begin{array}{c} 0.48(0.05)\\ 0.28(0.01)\\ 0.27(0.03)\\ 0.23(0.07)\\ 0.28(0.03) \end{array}$	Expt.: ⁶¹ 0.231 Simulation: ^{62,63} 0.2–0.6

TABLE III. Average volume per lipid molecule V_L for DPPC and POPC lipid bilayers
simulated with different water models and the comparison between the present results
with earlier simulated and experimental data. The values in the parentheses are the
standard error calculated by block averaging.

System	Water model	$V_L (\mathrm{nm}^3)$	Literature (nm ³)
POPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$\begin{array}{c} 1.23(0.0003)\\ 1.20(0.0002)\\ 1.20(0.0005)\\ 1.26(0.0003)\\ 1.20(0.0001)\\ \end{array}$	Expt.: ^{43,74} 1.223–1.256 Simulation: ²⁸ 1.232
DPPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$\begin{array}{c} 1.20(0.0003)\\ 1.17(0.0002)\\ 1.18(0.0003)\\ 1.20(0.0004)\\ 1.18(0.0002)\end{array}$	Expt.: ^{43,61} 1.229–1.232 Simulation: ²⁸ 1.226

density profile to obtain the simulated X-ray and neutron scattering form factors, which are directly compared with those from the experiment.

Figures 2(a) and 2(b) present the total EDPs for DPPC and POPC bilayers, each with five different water models. The EDPs for water are also exhibited in the same figures. The EDPs for individual groups are shown in Fig. S2 of the supplementary material. Comparison of the EDP for the total system with those of the individual groups reveals the origin of different peaks and dips of the total EDPs for the overall system. The nearly symmetrical profiles for all the systems indicate proper equilibration of the lipid bilayers. The two most pronounced peaks of the EDPs correspond to the phosphate group in the head group region of lipid. Water molecules penetrate the bilayers up to the CO groups, but the terminal methyl groups in the acyl chains stay dehydrated. This is in agreement with the experiment.⁴³ A dip is observed in the middle of the EDPs, which indicates a reduction in the interaction between the lipid layers at the center. The EDPs for different water models are overall consistent with each other. However, we see that the dip of the bilayer center is slightly more intense in the case of SPC and TIP4P/2005 water models than the remaining three.

The lipid bilayer thickness is an important quantity to identify the flexibility and packing of the lipid bilayer. There are multiple interpretations for the bilayer thickness. One of them is the distance between the two phosphate peaks $D_{\rm HH}$ in EDPs. Experimental scattering form factors can provide the $D_{\rm HH}$ value⁶¹ only indirectly. This is because the scattering form factors only probe the transverse lipid organization of the bilayer. Therefore, the Fourier transformed electron density profiles do not accurately give the head group-head group distance for the calculation of bilayer distance D_{HH} .⁶¹ However, being motivated by many simulation works,^{77–81} we have compared the obtained thickness with the experimentally reported values. The simulated $D_{\rm HH}$ values of the two lipid bilayers, simulated with different water models, are presented in Table IV. All water models result in the bilayer thickness almost consistent with the experimental values.^{43,61,75}

Now, we compare the simulated structures of the lipid membranes with those from the experiment.⁴³ The X-ray and neutron



FIG. 2. Electron densities [(a) and (b)], X-ray [(c) and (d)], and neutron [inset of (c) and (d)] scattering form factors for POPC [(a) and (c)] and DPPC [(b) and (d)] bilayers. Total electron densities are shown in solid lines, while the electron densities for water are shown in broken lines. The results for different water models are shown in color-coded lines (SPC: red; TIP3P: blue; TIP4P/2005: pink; TIP3P-FB: dark red; and TIP4P-FB: dark gray). The experimental X-ray and neutron scattering form factor (for different D₂O concentration) data⁴³ are presented in open circles.

scattering experiments probe the lipid bilayer structure by scattering form factors, which determine the scattering length density along the bilayer normal. The form factor is connected to the atom number density through the following equation:

$$F(q) = \left(\int_{-D/2}^{D/2} \sum_{\alpha} f_{\alpha}(q_z) n_{\alpha}(z) - \rho_s\right) \exp(izq_z) dz.$$
(4)

Here, $n_{\alpha}(z)$ is the number density of the α th atom as a function of the distance from the bilayer center across the bilayer normal. $f_{\alpha}(q_z)$ is

TABLE IV. The average thickness of the DPPC and POPC lipid bilayers simulated with different water models and the comparison between the present results with earlier simulated and experimental data. The values in the parentheses are the standard error calculated by block averaging.

Lipid	Water model	D_{HH} (nm)	Literature (nm)
POPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$\begin{array}{c} 3.42(0.04)\\ 3.46(0.04)\\ 3.41(0.02)\\ 3.47(0.01)\\ 3.35(0.02) \end{array}$	Expt.: ⁴³ 3.70 Simulation: ²⁸ 3.46
DPPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$\begin{array}{c} 3.59(0.02)\\ 3.43(0.04)\\ 3.34(0.01)\\ 3.52(0.03)\\ 3.44(0.05)\end{array}$	Expt.: ^{61,75} 3.42–3.83 Simulation: ²⁸ 3.57

J. Chem. Phys. **151**, 065104 (2019); doi: 10.1063/1.5108830 Published under license by AIP Publishing the scattering length density, ρ_S is the solvent scattering length density, and *D* is the bilayer thickness. For a symmetric bilayer, Eq. (4) reduces to the following form:

$$F(q) = \int_{-D/2}^{D/2} \Delta \rho_e(z) \cos(zq_z) dz.$$
 (5)

Here, $\Delta \rho_e(z)$ is the scattering length density difference between the solvent and the bilayer. We calculate the atom number density profile from the simulations and determine the form factor using the SIMtoEXP software.⁷⁶ X-ray scattering form factors for the lipid bilayer systems are studied in water, while the neutron scattering form factors are studied in three different concentrations of D₂O (100%, 70%, and 50%) for POPC and two different D₂O (100% and 50%) concentrations for the DPPC lipid bilayer. The simulated and experimental form factors for different systems are shown in Figs. 2(c) and 2(d). Usually, qualitative comparisons are made with the experimentally obtained scattering profiles. Some quantitative ^{0,81} the minima and maxcomparisons, such as the peak heights,¹ ima positions,⁷⁸ and the root mean square deviation (RMSD) or a reduced χ^2 value,⁷⁶ are also made between the simulated and measured scattering profiles.

Overall, we see a good agreement with the experiment for both the DPPC and POPC lipid bilayers simulated with all five water models. A closer comparison reveals that the TIP3P, TIP3P-FB, and TIP4P-FB water models reproduce the positions and the heights of all three experimental lobes much better than the SPC and TIP4P/2005 water models. Importantly, in the case of SPC, the simulation does predict well the experimental peak heights and the peak positions. A better agreement is observed at lower q values for all the water models. Note that the first lobe of the X-ray scattering profile represents the structural properties of the bilayer and therefore better agreement of the first simulated lobe with the experimental one indicates the better mimicking of the lipid bilayer structure.

Neutron scattering length density (NSLD) profiles of proton and deuterium are sharply different. Thus, we calculate the NSLD for the lipid bilayer relative to the deuterons of heavy water and the reciprocal space neutron scattering curves give the neutron scattering form factors. As expected, the neutron form factor increases with increasing concentration of deuterium. The simulated form factors match well with the experimental values for q < 0.2. We see better agreement with experimental form factors for TIP3P, TIP3P-FB, and TIP4P-FB water models. SPC and TIP4P/2005 water models slightly overestimate the NSLD value at q = 0.

5. Deuterium order parameter of the acyl chain and the head group

The ordering of the acyl chains is determined using the deuterium order parameter S_{CD} , which can be calculated using the following equation:

$$S_{CD} = \frac{1}{2} \langle 3\cos^2\theta - 1 \rangle. \tag{6}$$

Here, θ is the angle between a C–D bond of the methylene group of the hydrophobic tail and the bilayer normal. The angular bracket indicates the ensemble average. Since no hydrogen/deuterium atom is present in the united-atom model of the lipid molecule, one needs to construct the positions of the methylene bound hydrogen/deuterium using the neighboring carbon atoms' positions and assuming a tetrahedral geometry around the carbon.^{28,83}

There is another way to obtain S_{CD} , which we have adopted in our calculation. We have used the "gmx_order" analysis tool (as incorporated in Gromacs 2019), which calculates S_{CD} using the following equation:

$$S_{CD} = \frac{2}{3}S_{xx} + \frac{1}{3}S_{yy},$$
(7)

where $S_{xx} = \frac{1}{2} (3\cos^2 \theta_x - 1)$ and θ_x is the angle between the *x* axis and the bilayer normal *z* axis. For this, the order of atoms should be correctly provided. Note that Eq. (7) assumes the same S_{CD} values for the two hydrogen atoms of the methylene carbon atoms. To rectify this issue, the equations are modified as follows:

$$S_{CD1} = \frac{2}{3}S_{xx} + \frac{1}{3}S_{yy} - \frac{2\sqrt{2}}{3}S_{xy},$$
 (8)

$$S_{CD2} = \frac{2}{3}S_{xx} + \frac{1}{3}S_{yy} + \frac{2\sqrt{2}}{3}S_{xy}.$$
 (9)

Equations (8) and (9) work well for saturated carbons, but for the unsaturated site, they are slightly modified as follows:

$$S_n = \frac{1}{4}S_{zz} + \frac{3}{4}S_{yy} - \frac{\sqrt{3}}{2}S_{yz},$$
 (10)

$$S_{n+1} = \frac{1}{4}S_{zz} + \frac{3}{4}S_{yy} + \frac{\sqrt{3}}{2}S_{yz}.$$
 (11)

These equations assume an angle of 120° around the double bond, which has been taken care of in the fixed version of the "gmx_order" program ("fixed-gmx_order") provided by Van Lehn *et al.*⁸⁴ However, this modified tool still produces wrong results for the second carbon of the double bond. Further modification has been done by Piggot *et al.*⁸⁵ The S_{CD} values of the unsaturated methylene positions of POPC are recalculated using the "fixed-gmx_order" tool.

The simulated S_{CD} values for the 9th and the 10th methylene carbon are in better agreement with the experimental values. (The tool provides the S_{CD} values same for the two hydrogen atoms.)



FIG. 3. Deuterium order parameters for the sn1 and sn2 chains of the POPC [(a) and (b)] and DPPC [(c) and (d)], simulated with different water models: SPC (red), TIP3P (blue), TIP4P/2005 (pink), TIP3P-FB (dark red), and TIP4P-FB (dark gray). Black filled squares present the experimental values. Error bars of simulated data are the standard error, calculated from block averaging. See Fig. 1 for the labels of the two chains.

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0.08

TABLE \	 Order 	parameter	S _{CD}	for	the	head	group	carbon	atom	ns of	POPC	and
DPPC lip	oid bilaye	ers simulate	ed in	diffe	erent	wate	r mode	els and	their	com	parison	with
experime	ntal data	a.										

Lipid	Water model	α	β	<i>γ1</i>	<i>γ2</i>	ү3
	SPC	0.08	0.02	0.05	0.09	0.15
	TIP3P	0.09	0.03	0.10	0.13	0.21
POPC	TIP3P-FB	0.09	0.03	0.13	0.15	0.23
	TIP4P/2005	0.09	0.01	0.07	0.11	0.17
	TIP4P-FB	0.10	0.02	0.12	0.15	0.23
Literature	Expt.	0.04	0.05	0.13	0.2	0.21
	SPC	0.09	0.004	0.04	0.10	0.17
	TIP3P	0.11	0.03	0.09	0.16	0.22
DPPC	TIP3P-FB	0.10	0.02	0.11	0.16	0.23
	TIP4P/2005	0.11	0.01	0.03	0.12	0.18
	TIP4P-FB	0.09	0.02	0.09	0.16	0.23
Literature	Expt.	0.05	0.02	0.07	0.21	0.22

(a) (b) DPPC POPC SPC TIP3P (Ndン)*d* TIP3P-FB TIP4P-FB 0.00 -⁸⁰ ζ_{PN}(°) $^{80}\zeta_{PN}{}^{(\circ)}{}^{120}$ 40 40 160 0 120 160 (c)(d) POPC DPPC 0.08 *b*(سا) 0.04 0.00 $^{80}\omega_1(^{\circ})^{120}$ $^{80}\omega_1(^{\circ})^{120}$ 0 40 160 0 40 160 $DPPC \downarrow (f)$ POPC (e) 0.08 (C³)d 0.00 80 $\omega_2(^\circ)^{120}$ 80 40 160 40 120 160 $\omega_2(^{\circ})$

However, for the saturated chains of both DPPC and POPC, the results are found to be invariant for the original "gmx_order" and the fixed version. Thus, we have provided the results for the sn1 chain of POPC and for both the sn1 and sn2 chains of DPPC as obtained from the original "gmx_order" tool in Fig. 3. It is worth mentioning that the original "gmx_order" tool can still provide S_{CD} values of the unsaturated position, which are in semiquantitative agreement with the experimental values. The method of getting semiquantitative results using the original "gmx_order" tool and the performance analysis of both the original and the fixed "gmx_order" tools have been detailed in Sec. S3 of the supplementary material.

 $S_{\rm CD}$ gives an insight into the overall ordering of the bilayer. For example, a higher value indicates an increase in the overall ordered arrangement. A lower $S_{\rm CD}$ value is generally observed for unsaturated lipids, such as POPC.⁸⁶ The presence of the double bond introduces kinks in the lipid molecule and makes the system less ordered. Figure 3 presents $S_{\rm CD}$ for both the sn1 and sn2 chains of DPPC and POPC in different water models. These simulated values are compared with the experimental values, obtained from NMR based measurements.^{87–89} For both the DPPC and POPC bilayers, the SPC

FIG. 4. Probability distribution of the angles between the bilayer normal and different residues: the head group vector P-N [(a) and (b)], the C=O vector of the sn1 chain [(c) and (d)], and the C=O vector of the sn2 chain [(e) and (f)] for the DPPC and POPC lipid bilayers in different water models. The distributions are color-coded for different water models SPC: red; TIP3P: blue; TIP4P/2005: pink; TIP3P-FB: dark red; and TIP4P-FB: dark gray. The experimental tilt value⁹⁰ for vectors P-N and the simulated values are shown in Table VI.

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DPPC lipid bilayers in different water models.

and TIP4P/2005 water models overestimate the experimental values. TIP3P, TIP3P-FB, and TIP4P-FB reproduce the experimental order parameter more accurately for both the sn1 and sn2 chains of DPPC and POPC bilayers. Consistent with the experimental values for the first few carbons in DPPC, the order parameter remains almost the same. The sharp drop for the double bond of oleoyl chain (sn2) of POPC is more accurately reproduced by TIP3P, TIP3P-FB, and TIP4P-FB water models.

The ordering of the head group carbon atoms of choline and glycerol groups are calculated in different water models. The methylene carbons in the choline head group are termed α and β . Two methylene carbons and one methanetriyl carbon in the glycerol group are termed y_1 , y_3 , and y_2 , respectively. The different groups are labeled in Fig. 1. The S_{CD} values in different water model show characteristic differences in their ordering. The results are compared with experimental values for assessing the obtained structures in different water models. The S_{CD} values are listed in Table V. Similar to the previous simulation, we observed that the S_{CD} for α carbon is always higher than the β carbon for both the DPPC and POPC bilayers in all the water models. For α carbons, the simulated values are not in good agreement with the experimental values for both the lipid bilayer. Better agreement is obtained for β carbon atoms with values in the range of 0.02-0.03, which is less than that of the α carbon. For y1, y3, and y2 carbons, TIP3P, TIP3P-FB, and TIP4P-FB water models better predict the values. The groups are less ordered in SPC and TIP4P/2005 water models. We will see in the next paragraph that the S_{CD} values for the head group carbons closely follow the angular distribution of the head groups to the lipid bilayer normal.

6. The orientation of the head groups and the carbonyls

The fluctuation of the head group of a lipid provides a qualitative insight into the flexibility of the lipid bilayer. This is analyzed by the angular distribution of characteristic vector(s) in the head group region to the bilayer normal. Here, we consider the P-N and C=O

Water model	$\langle \zeta_{\rm PN} \rangle$ (deg)	$\langle \omega_1 \rangle$ (deg)	$\langle \omega_2 \rangle$ (deg)
SPC	77	110	135
TIP3P	75	111	130
TIP3P-FB	71	110	129
TIP4P/2005	78	113	132
TIP4P-FB	72	110	130
Expt.	70° – 80°		
SPC	79	110	131
TIP3P	77	109	125
TIP3P-FB	72	109	126
TIP4P/2005	80	112	129
TIP4P-FB	73	109	127
Expt.	70° – 80°		
	Water model SPC TIP3P-FB TIP4P/2005 TIP4P-FB Expt. SPC TIP3P-FB TIP3P-FB TIP4P/2005 TIP4P-FB Expt.	Water model ζζ _{PN} (deg) SPC 77 TIP3P 75 TIP3P-FB 71 TIP4P/2005 78 TIP4P-FB 72 Expt. 70°-80° SPC 79 TIP3P-FB 72 TIP3P-FB 72 TIP3P-FB 72 TIP3P-FB 72 TIP4P/2005 80 TIP4P-FB 73	Water model $\langle \zeta_{PN} \rangle$ (deg) $\langle \omega_1 \rangle$ (deg) SPC 77 110 TIP3P 75 111 TIP3P-FB 71 100 TIP4P/2005 78 113 TIP4P-FB 72 110 Expt. 70° -80°

TABLE VI. Most probable values of ζ for the head group atom vector P-N. ω_1 for

the C=O vector of sn1 chain, and ω_2 for the C=O vector of sn2 chain of POPC and

bond vectors of the sn1 and sn2 chains of the two lipids, DPPC and POPC. See Fig. 1 for the atom labels. Figure 4 presents the following distributions: (i) probability distribution $p(\zeta)$ of angle ζ between the P-N vector and the bilayer normal, (ii) $p(\omega_1)$ of angle ω_1 between the C=O vector of the sn1 chain and the bilayer normal, and (iii) $p(\omega_2)$ of angle ω_2 between the C=O vector of the sn2 chain and the bilayer normal.

For SPC, TIP3P-FB, and TIP4P-FB water models, $p(\zeta)$ is centered around 70°–80° for both the lipid bilayers. This is in agreement with the experimental value.⁹⁰ Therefore, on average, the lipid head groups lie parallel with the bilayer surface for both the lipids. The most probable values are given in Table VI. Characteristic differences in the shape of the distribution in different water



FIG. 5. The radial distribution function g(r) between the oxygen atom of the carbonyl group (O_C) with water oxygen (O_W) [(a) and (b)], and between the phosphorus atom of the PO4³⁻group (P) and the water oxygen (O_W) [(c) and (d)] for the DPPC and the POPC bilayers, simulated with different water models: SPC (red), TIP3P (blue), TIP4P/2005 (pink), TIP3P-FB (dark red), and TIP4P-FB (dark gray). See Fig. 1 for the atom labels.

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		(CN	FSW	(nm)
System	Water model	P-O _W	$O_C - O_W$	P-O _W	$O_C - O_W$
POPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$\begin{array}{c} 4.36(0.02)\\ 5.86(0.01)\\ 5.48(0.01)\\ 4.35(0.03)\\ 5.65(0.02)\end{array}$	$\begin{array}{c} 1.18(0.008)\\ 1.44(0.005)\\ 1.43(0.01)\\ 1.12(0.009)\\ 1.42(0.02)\end{array}$	$\begin{array}{c} 0.46(0.0002)\\ 0.44(0.006)\\ 0.43(0)\\ 0.45(0.0007)\\ 0.43(0) \end{array}$	$\begin{array}{c} 0.34(0.0005)\\ 0.33(0.0004)\\ 0.32(0.0005)\\ 0.33(0.0005)\\ 0.32(0.0004)\end{array}$
DPPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$\begin{array}{c} 4.41(0.03)\\ 5.95(0.02)\\ 5.50(0.01)\\ 4.39(0.01)\\ 5.62(0.02)\end{array}$	$\begin{array}{c} 1.10(0.009)\\ 1.37(0.004)\\ 1.40(0.003)\\ 1.05(0.004)\\ 1.42(0.003)\end{array}$	$\begin{array}{c} 0.47(0.0008)\\ 0.44(0.0004)\\ 0.43(0.0006)\\ 0.46(0)\\ 0.43(0.0004)\end{array}$	$\begin{array}{c} 0.34(0.0004)\\ 0.33(0.0004)\\ 0.33(0.0005)\\ 0.33(0.0008)\\ 0.33(0.0004) \end{array}$

TABLE VII. Characteristics of the lipid hydration calculated as a water coordination number to a phosphorus (P) and carbonyl oxygen (O_C) atom in its first solvation shell along with the solvation shell width (FSW) in different water models for POPC and DPPC lipid bilayers. The values in the parentheses are the standard error calculated by block averaging.

models are observed. For TIP3P, TIP3P-FB, and TIP4P-FB, sharp peaks are obtained for the Gaussian type distributions. For SPC and TIP4P/2005, the distributions are broader with the indistinct peak position. In particular, for SPC, the distribution is unsymmetrical with a hump at ~110°, which is 20° below the bilayer plane. For TIP4P/2005 water model, the distribution is bimodal with equal populations at $\sim 70^{\circ}$ (20° above the bilayer plane) and $\sim 110^{\circ}$ (20° underneath the bilayer plane). Although the bimodal distributions may emanate from a fluid lamellar phase,⁹¹ a previous study⁹² has observed that molecules with preferential head group orientations of $\pm 20^{\circ}$ to the membrane plane are quite stable. The occurrence of the additional shoulder/peak at 110° may be linked to the dielectric constant of the water model. Both SPC and TIP4P/2005 water models have the dielectric constant less than 65 (see Table S1 of the supplementary material), while the dielectric constant for other water models is more than 77. The connection between the dielectric constant of the water solvent and the head group orientation can be understood in terms of the different ion-dipole or dipole-dipole interaction between the head group and water.

The above results suggest that the head group atoms of both the lipids are more ordered in the presence of any of the three water models TIP3P, TIP3P-FB, and TIP4P-FB. We note that the S_{CD}



Both the distributions, $p(\omega_1)$ and $p(\omega_2)$, are found to be almost insensitive to the water model. This is expected since the C=O groups are more buried inside the bilayer than the head group. While the angular distribution $p(\omega_1)$ is centered at $\omega_1 = 110^\circ$, the distribution $p(\omega_2)$ shows the peak at $\omega_1 = 135^\circ$ for all the water models in both the DPPC and POPC lipid membrane.

7. Radial distribution function

In order to understand the hydration structure of the lipid head group, we calculate the radial distribution functions g(r) between the lipid head-group atoms and water. Figure 5 presents g(r) between the P/O_C atom of the lipid (see Fig. 1 for the atom labels) and water O_W for different models of water. Interestingly, the hydration structures of POPC and DPPC lipid head groups are very similar to each other, suggesting a negligible influence of slight modifications in the hydrophobic chain(s) of the lipid molecule on the hydration of the lipid head group. We see that the force field of water influences both the position of the first peak and the first solvation shell width [FSW, the position of the first minima of g(r)]. For TIP3P,



FIG. 6. Lateral mean square displacement (MSD) of the DPPC (a) and POPC (b) molecules along the *xy* plane (perpendicular to the lipid bilayer normal) in different water models SPC (red), TIP3P (blue), TIP3P-FB (dark red), TIP4P/2005 (pink), and TIP4P-FB(dark gray).

J. Chem. Phys. **151**, 065104 (2019); doi: 10.1063/1.5108830 Published under license by AIP Publishing TIP3P-FB, and TIP4P-FB water models, the intensities of the first peaks of g(r) between O_C-O_W and P- O_W for both the lipids are higher than those for SPC and TIP4P/2005 water models. The larger first hydration shell width for both the SPC and the TIP4P/2005 water models suggest significantly low penetration of these water models in lipid bilayers. The mass density distributions of the phosphate group and water, plotted in Fig. S5 of the supplementary material, clearly show that the SPC and TIP4P/2005 water models penetrate the lipid bilayer much less than the remaining three water models. This is probably the reason behind the poorer hydration of the lipid head group by the SPC and TIP4P/2005 water models.

Now, we calculate the first-hydration-shell coordination number around the phosphate group by integrating the g(r) up to the distance where g(r) has a minimum. The hydration numbers of the phosphate group and the O_C atom, and their first-hydration-shell widths are listed in Table VII. The first hydration shell coordination numbers of the phosphate group are less for SPC and TIP4P/2005 water models than those for the remaining three water models by approximately 1-1.5 water molecules. On the other hand, the first hydration shell coordination numbers of the O_C atom are less for SPC and TIP4P/2005 water than those for the remaining three water models by approximately 0.2-0.3 water molecule. Therefore, we see comparatively weak penetration of the SPC and TIP4P/2005 water in the lipid bilayers. This is consistent with the earlier study,¹⁷ where similar low hydration of the phosphate group was observed for the GROMOS united atom model of lipid simulated with the SPC force field of water. The relatively higher first solvation shell coordination **TABLE VIII.** The simulated D_{xy} values of the two lipid bilayers—each of which is simulated with different water models—and their comparison with earlier simulated and experimental data. The values in the parentheses are the standard error calculated by block averaging.

System	Water model	$D_{xy}/10^{-8}$ (cm ² /s)	Literature value (cm ² /s)
POPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$13.07(0.4) \\ 14.1(0.9) \\ 9.39(0.5) \\ 4.77(0.4) \\ 9.81(0.5)$	Expt.: ^{95,96} 13.5×10^{-8} Simulation: ⁸⁶ 9 ± 3 × 10 ⁻⁸
DPPC	SPC TIP3P TIP3P-FB TIP4P/2005 TIP4P-FB	$17.21(0.8) \\ 22.97(1.0) \\ 15.24(0.6) \\ 8.34(1.6) \\ 16.86(0.9)$	Expt.: ^{95,96} 14 × 10 ⁻⁸ Simulation: ⁸⁶ 12 \pm 3 × 10 ⁻⁸

number (~5.5–6.0)¹⁷ around the phosphate groups in all-atom models of the lipid molecule is well reproduced by the GROMOS united atom model of lipid molecules when more advanced water models (TIP3P or TIP3P-FB or TIP4P-FB) are used. Therefore, the current results suggested that these water models describe the hydration of the lipid head group better than the SPC or TIP4P/2005 water model do.



FIG. 7. First-order reorientation autocorrelation functions for the head groups (P-N) [(a) and (b)], sn1 chain [(c) and (d)], and sn2 chain [(e) and (f)] of the two lipids, POPC and DPPC, respectively, simulated with different water models: SPC (red), TIP3P (blue), TIP3P-FB (dark red), TIP4P/2005 (pink), and TIP4P-FB (dark gray). See Fig. 1 for the atom labels and the label of two chains.

J. Chem. Phys. **151**, 065104 (2019); doi: 10.1063/1.5108830 Published under license by AIP Publishing In addition, the first-hydration-shell widths (FSWs) around the phosphate group for SPC and TIP4P/2005 water models are slightly higher than for the rest of the water models. The predictions of FSW with the remaining three water models are closer to those for all-atom models of lipids.¹⁷ Therefore, while the SPC and TIP4P/2005 water models result in the reasonable structure of lipid membrane, the TIP3P or TIP3P-FB or TIP4P-FB water models increase the accuracy of the lipid bilayer structure, which is even comparable to the results obtained from an all-atom model of lipid.

B. Dynamical properties

1. Lateral diffusion coefficient

DPPC and POPC have a distinct structure in their hydrophobic region and thus have different packing and fluidity. It is known that the introduction of unsaturation produces characteristic kinks and thereby makes less ordered packing. To have an understanding of the fluidity of the lipids, we determine the lateral diffusion coefficient of lipids in the membrane. The lateral diffusion coefficient of lipids in the *xy* direction D_{xy} is obtained by fitting the mean square displacement (MSD) using the following equation:

$$\lim_{t \to \infty} \left\langle |\boldsymbol{r}(t) - \boldsymbol{r}(0)|^2 \right\rangle = 4D_{xy}t. \tag{12}$$

Here, D_{xy} is the lateral self-diffusion coefficient, r(t) and r(0) are the center of mass positions of the lipid molecules at time t and t = 0, respectively. The single brackets indicate the ensemble average which is an average over all lipid molecules and many time origins (t = 0). Figure 6 plots the MSD profiles of the POPC and DPPC lipid molecules in different water models as functions of time. We

TABLE IX. The fitting parameters and the average	e rotational time for	r the head group,	sn1 and sn2	regions of the	POPC and
DPPC lipid bilayers in different water models.					

Lipid	Water model	Region	a_1	$ au_1$ (ps)	a_2	τ_2 (ns)	<i>a</i> ₃	τ_3 (ns)	$\langle \tau \rangle$ (ns)
		Head	0.37	90.12	0.39	3.27	0.24	35.1	9.73
	SPC	sn1	0.08	63.87	0.12	4.06	0.8	258	207
		sn2	0.06	40.69	0.06	2.99	0.88	430	379
		Head	0.36	45.30	0.28	0.54	0.36	7.20	2.76
	TIP3P	sn1	0.11	101.8	0.23	3.91	0.66	180	120
		sn2	0.08	76.32	0.12	3.95	0.8	242	194
POPC		Head	0.32	66.26	0.31	0.77	0.37	10.8	4.26
	TIP3P-FB	sn1	0.09	100.51	0.21	4.95	0.7	198	140
		sn2	0.06	74.25	0.11	4.75	0.83	304	253
		Head	0.33	113.18	0.46	3.46	0.21	40.7	10.2
	TIP4P/2005	sn1	0.07	60.35	0.11	4.50	0.82	283	233
		sn2	0.05	38.60	0.06	3.74	0.89	538	479
		Head	0.31	58.92	0.31	0.63	0.38	8.04	3.27
	TIP4P-FB	sn1	0.09	107.87	0.22	5.04	0.69	178	124
		sn2	0.07	75.77	0.11	4.61	0.82	288	237
		Head	0.63	42.91	0.28	0.41	0.09	36.22	3.40
	SPC	sn1	0.10	72.24	0.19	4.30	0.71	275	196
		sn2	0.07	45.34	0.09	3.99	0.84	248	209
		Head	0.43	18.22	0.49	0.11	0.08	3.07	0.31
	TIP3P	sn1	0.17	120.49	0.34	3.74	0.49	201	100
		sn2	0.12	114.07	0.23	5.64	0.65	144	94.9
DPPC		Head	0.44	25.73	0.49	0.15	0.07	5.04	0.44
	TIP3P-FB	sn1	0.13	114.19	0.32	4.11	0.55	167	93.2
		sn2	0.09	92.26	0.18	4.96	0.73	154	113
		Head	0.61	46.44	0.30	0.42	0.09	47.9	4.47
	TIP4P/2005	sn1	0.09	68.84	0.17	4.66	0.74	307	228
		sn2	0.07	43.80	0.08	4.51	0.85	362	308
		Head	0.42	23.44	0.51	0.13	0.07	3.89	0.35
	TIP4P-FB	sn1	0.14	119.96	0.31	3.96	0.55	169	94.2
		sn2	0.09	97.92	0.19	5.13	0.72	160	116

see three distinct regions in the MSD profiles. In between, the ballistic regime at the short time and the diffusive regime at the long time, there exists a subdiffusive regime. This reminds of the MSD profiles obtained for the diffusion of supercooled water.^{93,94} The D_{xy} values are obtained by fitting Eq. (12) only in the diffusive regime (>1 ns). As the lipid molecules encounter large friction while diffusing, the uncertainty in the MSD analysis is expected to be very high. Therefore, we may obtain less accurate D_{xy} values. To encounter this problem, we analyze two independent trajectories (each of 200 ns duration) for calculating the diffusion coefficients. Table VIII presents the D_{xy} values (averaged over two independent trajectories) for the lipid molecules in different water models. The values are in reasonable agreement with experimental^{95,96} and the earlier simulation data.⁸⁶ Very similar diffusivities are observed for the lipids in TIP3P or SPC water models. In addition, the diffusion coefficients of the lipids in these water models are higher than those in the rest models. TIP4P-FB, TIP3P-FB, and TIP4P/2005 water models give almost similar diffusivities of the lipids. Therefore, we can arrange the water models according to the decreasing order of diffusion coefficients of the lipids as follows: TIP3P ~ SPC > TIP4P-FB ~ TIP3P-FB ~ TIP4P/2005. Interestingly, the above trend closely follows the following viscosity trend of the water models at the bulk regime. $\eta_{\text{TIP3P}} \sim \eta_{\text{SPC}} < \eta_{\text{TIP4P-FB}} \sim \eta_{\text{TIP3P-FB}} \sim \eta_{\text{TIP4P/2005}}$ (see Table S1 of the supplementary material).

It is worthwhile mentioning that there is a large range in experimental and MD simulation predictions of D_{xy} values of the lipid. D_{xy} of a lipid molecule can be estimated experimentally using a number of methods, including fluorescence techniques, electron paramagnetic resonance (EPR) spectroscopy, quasielastic neutron scattering (QENS), and NMR spectroscopy. A list of values of D_{xy} for DPPC lipid, obtained from different experiment and MD simulations, is available elsewhere,⁵⁴ where it is seen that the D_{xy} values span over three orders of magnitude. This large range of the experimental D_{xy} values makes it hard to judge a force field of a lipid in predicting the lateral diffusion coefficient.

2. Reorientation autocorrelation function

Reorientation time autocorrelation function C(t) is calculated for estimating the rotational time of a molecule. C(t)s of lipid molecules in the bilayer give insight into the fluidity of the lipid bilayer. Here, we calculate C(t) of 1st order for the head group and the two chains (sn1 and sn2) of the lipid. For studying the rotation of the head group, we consider the N-CN1 vector. The vectors C1A-C1B and C2A-C2B are considered for the rotation of the sn1 and the sn2 chains, respectively (see Fig. 1 for the atom labels).

Figure 7 presents the above three C(t)s as functions of time for different systems. Evidently, the correlation functions (particularly for the lipid tails) do not decay to zero over an available range of time. This makes it challenging to obtain an average rotational time by a simple integration of the correlation functions. Thus, we fit the curves by multiexponential equations. The correlation decays are nicely fit with tri-exponential functions (biexponential fitting is not proper),

$$C(t) = a_1 e^{(-t/\tau_1)} + a_2 e^{(-t/\tau_2)} + a_3 e^{(-t/\tau_3)}; a_1 + a_2 + a_3 = 1.$$
(13)

Here, a_1 , a_2 , and a_3 are the coefficients and τ_1 , τ_2 , and τ_3 are the relaxation times. Therefore, the average rotational time is given by

$\langle \tau \rangle = a_1 \tau_1 + a_2 \tau_2 + a_3 \tau_3.$

The fitting parameters and the average rotational times for different systems are listed in Table IX.

The average rotational time for the head group is the lowest. The sn1 chains rotate a bit faster than the sn2 chain (particularly for POPC). Other observations are summarized as follows: (i) The rotational time for the head group and the sn2 chain is much faster for DPPC compared to those for POPC. (ii) The sn1 chain rotates at comparable time scale for both the lipid in the same water model. Of course, the values are not the same, but the difference is the lowest for the sn1 chain. (iii) The average rotational times for all regions follow the following trend for different water models: TIP3P < TIP4P-FB ~ TIP4P-FB < SPC < TIP4P/2005.

IV. CONCLUDING REMARKS

In this work, we have checked the compatibility of five different water models with the GROMOS96 53A6L united atom model of two different lipids, DPPC and POPC. A systematic comparison of the structure and dynamics of the lipid bilayers, simulated with different water models, has been done. We have calculated properties, such as area per lipid, isothermal compressibility modulus, average volume per lipid, electron density profile, X-ray and neutron scattering form factors, and bilayer thickness, and deuterium order parameters of the hydrocarbon chains and the head groups, angular distribution, and radial distribution function for understanding the structure of the lipid bilayer. Lateral diffusion and reorientation correlation function of the lipid molecules are calculated for elucidating the dynamics of the lipid bilayer. The broad comparison of these parameters for different water models reveals that the simulations better predict the structure and dynamics of the lipid bilayers when either TIP3P-FB or TIP4P-FB water model is used.

Simulations with SPC and TIP4P/2005 water models predict more densely packed structures as understood from the lower area per lipid and slower rotation of the lipid molecules. Importantly, the simulated deuterium order parameters and the scattering form factors of the lipids are in quantitative agreement with the experimentally measured values when any of the three water models, TIP3P, TIP3P-FB, and TIP4P-FB, is considered in the simulation. The worst agreements are found for the SPC and TIP4P/2005 water models. This is a crucial observation since the above two quantities are measured directly from experiments. The rotational time of the lipid molecules in different water models closely follows the area per lipid for the two bilayers in different water models. For example, the lipid bilayers, simulated with SPC or TIP4P/2005 water, are of minimum area, and therefore, the rotation of the lipids is slower in these water models. The lateral diffusion coefficient of the lipid molecules, on the other hand, strongly follows the simulated viscosities of different models of water. Since both the SPC and TIP3P water models have a lower viscosity coefficient ($\eta \le 0.4$) than the other models, the lateral diffusion coefficients of both the lipid molecules are higher. These results indicate that the bulk properties of different models of water may strongly influence the structure and dynamics of the lipid bilayer. Therefore, it is essential to work with a better model of water (such as TIP3P-FB and TIP4P-FB), which better predicts various experimentally measured quantities.

Finally, we can conclude that water models, such as TIP3P-FB, TIP4P-FB, and TIP3P, are also very much compatible with the GROMOS96 53A6_L united-atom model of lipid for the simulation of lipid bilayers. More importantly, these water models (particularly TIP3P-FB and TIP4P-FB) overall improve the agreement of the simulated quantities with the experimental ones. However, the performance of the TIP4P/2005 water model for quantitative predictions of lipid bilayer properties is not satisfactory, particularly for properties like deuterium order parameter. These results, therefore, actively support using TIP3P-FB and TIP4P-FB water models (in combination with the GROMOS96 53A6_L united-atom model of lipid) for quantitative studies of the structure and dynamics of the lipid bilayer and interfacial water. In addition, our study does not particularly recommend the use of TIP4P/2005 model of water in combination with the GROMOS96 $53A6_L$ force field of lipid for the simulation of the lipid bilayer in water.

SUPPLEMENTARY MATERIAL

The supplementary material contains a table listing the physical properties of different water models, the time dependences of the average area per lipid of the two lipid bilayers simulated with five different water models, decomposed electron density profiles for the different groups of the lipid DPPC and POPC, performance comparison of "gmx_order" and "fixed-gmx_order" for the prediction of the S_{CD} values, and the mass density profiles for the head group of the lipid and water.

ACKNOWLEDGMENTS

We acknowledge IIT Patna for the computational facility. We acknowledge Professor Norbert Kučerka for providing the experimental X-ray and neutron scattering form factor data for the two lipid bilayers. Shakkira acknowledges DST Inspire Fellowship (INSPIRE No. IF180090) for the research fellowships.

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