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Comparison of Additive and Polarizable Models with Explicit Treatment of Long-Range Lennard-Jones Interactions using Alkane Simulations

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Abstract

Long-range Lennard-Jones (LJ) interactions have a significant impact on the structural and thermodynamic properties of nonpolar systems. While several methods have been introduced for the treatment of long-range LJ interactions in molecular dynamics (MD) simulations, increased accuracy and extended applicability is required for anisotropic systems such as lipid bilayers. The recently refined Lennard-Jones particle-mesh Ewald (LJ-PME) method extends the particle-mesh Ewald (PME) method to long-range LJ interactions, and is suitable for use with anisotropic systems. Implementation of LJ-PME with the CHARMM36 (C36) additive and CHARMM Drude polarizable force fields improves agreement with experiment for density, isothermal compressibility, surface tension, viscosity, translational diffusion, and ^{13}C T_1 relaxation times of pure alkanes. Trends in the temperature dependence of the density and isothermal compressibility of hexadecane are also improved. While the C36 additive force field with LJ-PME remains a useful model for liquid alkanes, the Drude polarizable force field with LJ-PME is more accurate for nearly all quantities considered. LJ-PME is also preferable to the isotropic long-range correction for hexadecane because the molecular order extends to nearly 20 Å, well beyond the usual 10–12 Å cutoffs used in most simulations.

Graphical Abstract

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SUPPORTING INFORMATION

The supporting information contains two sections. The first section evaluates the energy conservation of the LJ-PME method via simulations of pure water and pure hexadecane. The second section provides simulation results for systems of pure octane. This information is available free of charge via the internet at <http://pubs.acs.org>.

Keywords

Lennard-Jones; particle-mesh Ewald; CHARMM; Drude; polarizable force field; hexadecane; temperature dependence

1. INTRODUCTION

The CHARMM36 (C36)¹ additive force field (FF) for lipids has been widely used for molecular dynamics (MD) simulations of pure and complex lipid bilayers since its publication in 2010. It has been extended from the original set of six lipids (five phosphatidylcholines and one phosphatidylethanolamine) to sphingolipids,² polyunsaturated lipids,³ glycolipids,⁴ and lipopolysaccharides.⁵ While the initial validation of the FF was primarily based on bilayer surface areas and densities (from X-ray and neutron diffraction data), and chain order and dynamics (from deuterium and ¹³C NMR data), subsequent comparisons with experiment for head group order parameters,^{6, 7} bending constants, and spontaneous curvatures^{8, 9} have been very positive. The FF has also been tested with lipid mixtures containing cholesterol with glycerophospholipids and/or sphingolipids, and agrees with X-ray form factors and NMR order parameters.^{10–13} This has allowed for accurate interpretations of liquid ordered/disordered phases of lipid mixtures¹⁴ and lipid composition effects on hydrogen bonding and lipid clustering.^{12, 13} Although simulations with the C36 lipid FF have been successful, the FF does have inherent flaws. It was appreciated at the time of publication that the surface tensions for bilayers and monolayers are inconsistent with experiment, and that the dipole potential is too large.¹ More recently, after taking periodic boundary conditions into account,¹⁵ it has been demonstrated that diffusion constants are overestimated by a factor of 3 for at least two lipids.¹⁶

The C36 lipid FF (and other additive lipid FFs^{17, 18}) has two attested shortcomings: it was parameterized without accounting for long-range Lennard-Jones (LJ) interactions for most parameters,¹⁹ and it is not polarizable. Polarizability is known to affect dipole potentials²⁰ and dielectric constants (ϵ).²¹ For example, ϵ of decane in CHARMM27r²² (C27r; the precursor to C36) is 1.02, approximately half the experimental value of 1.97.²¹ This underestimate of ϵ increases the interaction of charges on opposite sides of the bilayer. It is not unreasonable to speculate that the balance of forces leading to good agreement with experimental bilayer surface areas for C36 is partly due to cancellation of errors. The natural solution here is to use a polarizable FF.

The CHARMM Drude FF accounts for atomic polarizability by implementing the classical Drude oscillator model.²³ The value of ϵ for decane is 2.06, in near-perfect agreement with

experiment. Because free energy of solvation scales with $(1 - 1/\epsilon)$, improvement of this quantity should give better energetics of transfer between polar and nonpolar media. However, like C36, most of the Drude lipid FF was originally parameterized without inclusion of long-range LJ interactions.^{1, 20} The lack of long-range LJ interactions is clearly related to the difficulties of reproducing monolayer surface tensions, given the importance of these terms for alkane/air interfaces.²⁴

This paper sets the groundwork for a reparametrization of the C36 and Drude lipid FFs with explicit inclusion of long-range LJ interactions. Following the strategy used for the development of C36, alkanes, the principal component of saturated lipid chains, are considered first.²² The main focus is on including the long-range LJ terms in a computationally efficient manner that is applicable anisotropic systems. This has proven to be difficult because most methods for including long-range LJ terms are only applicable to isotropic systems.^{25, 26} Fortunately, recent work has refined the particle-mesh Ewald (PME) method for Lennard-Jones interactions.²⁷ Lennard-Jones PME (LJ-PME) can be used with bilayers, monolayers, and other anisotropic systems in both constant pressure and constant volume ensembles. The implementation of LJ-PME utilized here involves the calculation of LJ interaction coefficients using geometric combining rules. It can be used in tandem with electrostatic PME, lowering the direct-space cutoff (r_{cut}) necessary for accurate calculations and computational efficiency. This paper introduces the implementation of LJ-PME in CHARMM, and explores its effects on equilibrium and transport properties of alkanes in the condensed phase.

By way of outline, Section 2 provides simulation specifications and describes the implementation of LJ-PME in CHARMM. Section 3 presents simulation results. Section 4 discusses the effects of LJ-PME, evaluates trends in the temperature dependence of thermodynamic properties, and summarizes the study.

2. METHODS

2.1. Common Simulation Specifications and Torsional Parameters.

To investigate the effects of LJ-PME, simulations were run using four distinct force fields: C36 without a correction for long-range LJ interactions, C36 with LJ-PME (denoted C36/LJ-PME), Drude without a correction, and Drude with LJ-PME (Drude/LJ-PME).

All simulations were performed in CHARMM.²⁸ Initial coordinates of systems containing 256 molecules of pure normal forms of hexadecane ($\text{C}_{16}\text{H}_{34}$), pentadecane ($\text{C}_{15}\text{H}_{32}$), and heptane (C_7H_{16}) were built using packmol.²⁹ Resulting mean cubic box sizes of between 50 and 51 Å for hexadecane (the longest chain tested) were sufficiently larger than the average radius of gyration (5.07 ± 0.02 Å) and root-mean-square end-to-end distance (14.7 ± 0.1 Å) to avoid finite-size effects. The Nosé-Hoover thermostat³⁰ was used to maintain system temperature, and a modified Andersen-Hoover barostat to maintain constant pressure.^{31, 32} For the C36 simulations, a thermostat coupling constant of 2000 kcal/mole-ps² was used for all simulations, and a piston mass of 1200 amu for NPT simulations. Drude simulations specified the relaxation time of the thermostat to be 0.1 ps, applied to real atoms, and the relaxation time of the barostat to be 0.1 ps in NPT simulations. All simulations were

performed using periodic boundary conditions and SHAKE algorithm to constrain covalent bonds involving hydrogens.³³

Long-range electrostatic interactions were evaluated using PME³⁴ with $r_{cut} = 12 \text{ \AA}$ when LJ-PME was not used and $r_{cut} = 10 \text{ \AA}$ with use of LJ-PME. Sec. 2.6 provides the details on the real-space cutoff scheme for the LJ portion of the FF. The standard errors (se) were estimated as the standard deviation (σ_B) in block averages divided by the square root of the number of blocks (n_B):

$$se = (1/\sqrt{n_B})\sigma_B \quad (1)$$

Quantities calculated from simulations were: density (ρ), isothermal compressibility (β_T), viscosity (η), surface tension (γ), translational diffusion constant (D), Nuclear Magnetic Resonance (NMR) C^{13} spin-lattice relaxation time (T_1), coefficient of thermal expansion (α_V), and radial distribution function ($g(r)$). Simulations were performed using each FF for each set of simulation specifications in Table 1 using a 1-fs timestep. A separate set of simulations were used to examine the dependence of ρ and γ on r_{cut} (Sec. 3.2). In these simulations, 64 molecules of $C_{16}H_{34}$ were simulated at 298.15 K for 10 ns using a 2-fs timestep in the NPT ensemble to calculate ρ , and in the NVT ensemble to calculate γ .

For simulations used to calculate η , γ , and D , initial coordinates were obtained from the equilibrated NPT simulations used to determine ρ . A coordinate set representing the average ρ of each simulation was used to start a simulation in the NVT ensemble. Systems for the surface tension simulations consisted of an alkane slab surrounded by vacuum layers, as described previously,²⁴ with the x and y dimensions matching the equilibrated boxsize from the NPT simulations used to calculate ρ and the z dimension (normal to the surface) elongated. For example, for hexadecane at 303.15 K in the Drude FF, the dimensions of the box were $50.1197 \text{ \AA} \times 50.1197 \text{ \AA} \times 100 \text{ \AA}$.

This paper uses standard alkane parameters in C36¹ and Drude.²¹ There have been several adjustments to the alkane torsional parameters since publication of C27r.¹ Table 2 lists the parameters used here to avoid confusion. The form of the CHARMM torsion potential, where φ is the dihedral angle, is

$$U_\varphi = \sum_i K_{\varphi,i} (1 + \cos(n_i \varphi - \delta_i)) \quad (2)$$

2.2. Density and Isothermal Compressibility.

Density was determined by averaging the volume of the simulation box after equilibration. Isothermal compressibility β_T was evaluated from

$$\beta_T = \frac{\langle \delta V^2 \rangle}{\langle V \rangle k_B T}, \quad (3)$$

where k_B is Boltzmann's constant, $\langle V \rangle$ is the average volume, $\langle \delta V^2 \rangle$ is the fluctuation in volume, and T is the temperature.²⁵

2.3. Viscosity, Translational Diffusion Constant, and Surface Tension.

Shear viscosity was evaluated using the Green-Kubo formula:²⁵

$$\eta = \frac{V}{k_B T} \int_0^\infty \langle P_{\alpha\beta}(t) P_{\alpha\beta}(0) \rangle dt, \quad (4)$$

where $P_{\alpha\beta}$ are the off-diagonal elements of the pressure tensor, and V is the volume of the simulation box. The pressure tensor was assumed to be symmetric ($P_{\alpha\beta} = P_{\beta\alpha}$).

CHARMM²⁸ was used to compute the correlation function of the three unique off-diagonal elements, average them, and sum the integral.

The surface tensions of the alkane-vacuum interfaces were evaluated from:

$$\gamma = 0.5 \left\langle L_z [P_{zz} - 0.5(P_{xx} + P_{yy})] \right\rangle, \quad (5)$$

where L_z is the size of the simulation box normal to the interface,³⁵ P_{zz} is the normal component of the internal pressure tensor, and P_{xx} and P_{yy} are the tangential components. A prefactor of 0.5 accounts for the fact that the systems contained two interfaces.

Translational diffusion constants were obtained from the Einstein relation $\langle r^2 \rangle = 6Dt$, where r is the displacement of a molecule at time t . The Yeh and Hummer³⁶ correction was used to account for periodic boundary conditions:

$$D^\infty = D^{PBC} + \frac{k_B T \xi}{6\pi\eta L}, \quad (6)$$

where D^{PBC} is the diffusion constant measured from simulation, L is the box length, $\xi = 2.837297$, η is the viscosity of the fluid, and D^∞ is the infinite system result.

2.4. NMR Spin-Lattice Relaxation Times.

T_1 were calculated using the standard formula for dipolar relaxation from the reorientational correlation function of the CH vectors in the motional narrowing limit:³⁷

$$\frac{1}{NT_1} = (1.855 \times 10^{10} s^{-2}) \int_0^\infty \langle P_2(\hat{\mu}(0))(\hat{\mu}(t)) \rangle dt, \quad (7)$$

where N is the number of protons bonded to the carbon, $\hat{\mu}$ is the CH vector, and the constant preceding the integral contains an effective CH bond length of 1.117 Å.³⁸

2.5. Analysis of Temperature Dependence.

The volumetric coefficient of thermal expansion (α_V) describes the dependence of volume, and therefore also of density, on temperature at constant pressure:

$$\alpha_V = \frac{1}{V} \left(\frac{\partial V}{\partial T} \right)_p. \quad (8)$$

The same trajectories used to determine ρ were used to calculate α_V at 313.15 K and to compare with the experimental value of molar volume (V_{mol}) at that temperature. A linear dependence of V_{mol} on temperature was assumed.

To find the functional form of the temperature dependence of β_T , chi-squared statistical values were calculated for regressions of the form $a + bT^c$, with values of 1/3, 1/2, 1, 2, 3, 4, and 5 for c . The χ^2 statistic is given by:

$$\chi^2 = \sum_{i=1}^N \frac{1}{E_i} (O_i - E_i)^2, \quad (9)$$

where N is the number of data points in the sample, O_i is the value of the i^{th} sample, and E_i is the value predicted by the distribution. Values of χ^2/N were minimized to determine c .

2.6. Implementation of LJ-PME in CHARMM.

The contributions of long-range dispersion to the energy and pressure that are neglected by cutoff methods were historically accounted for by various correction terms. A popular correction, the isotropic long-range correction (LRC),²⁵ is derived by assuming that the radial distribution function $g(r)$ is unity beyond r_{cut} . The isotropic LRC is usually satisfactory for bulk fluids of small molecules, but fails when anisotropy is significant, as is the case for lipid bilayers and other interfacial systems. The pressure-based LRC,²⁶ where LJ interactions outside r_{cut} are approximated with the application of an additional pressure which is periodically calculated from the difference of the instantaneous pressures at the selected r_{cut} and a very long r_{cut} , is applicable to larger molecules, but not to interfaces. CHARMM also supports the IPS (Isotropic Periodic Sum) method³⁹ to approximate long-range LJ interactions. This method defines a local region for each particle, and sums the

remaining region (including images) as an integral of virtual images of the local region statistically distributed in an isotropic and periodic manner. The version denoted 3D-IPS is not applicable to interfacial systems. 2D-IPS and the more computationally efficient 3D-IPS/DFFT⁴⁰ do accurately model interfaces.^{24, 41} The IPS methods have not been widely implemented because of assumptions of homogeneity.

The preceding methods are all available in CHARMM. Others^{42–44} have proposed a slab-based correction to specifically address inhomogeneity at interfaces. This method approximates long-range LJ forces with an additive force contribution in the direction perpendicular to the interface. The added force is a function of the density of an isotropic slice within the simulation box. Janecek⁴³ shows accurate treatment of surface tensions for Lennard-Jones fluids with an adaptation of this slab-based method. It is possible to explicitly include long-range effects in slab-like systems using the two-dimensional Ewald formulation of Hautman and Klein.⁴⁵ Although formally correct, this 2D Ewald method requires a factor of 20 more computational effort to evaluate than regular 3D Ewald methods. It has been shown⁴⁶ that conventional 3D Ewald methods, including the LJ-PME approach, deliver equivalent properties to the 2D method when modified to include empty space between layers, without incurring the extra computational overhead.

As is well known, long-range electrostatic forces can be evaluated explicitly and with high computational efficiency, thereby eliminating the need to truncate interactions using a cutoff. The use of cutoffs leads to substantial artifacts for electrostatics,⁴⁷ and the PME⁴⁸ method is widely used for this reason. The PME approach for dispersion has its origins in the 1957 work of Nijboer and de Wette,⁴⁹ who generalized the Coulomb operator partitioning to faster decaying interactions. Williams used this generalized partitioning in 1971 to develop an Ewald-like treatment of dispersion interactions,⁵⁰ which was later expanded by Karasawa and Goddard to include energy derivatives.⁵¹ Though in 1995 Pedersen and coworkers demonstrated a modification of Ewald dispersion to use the highly efficient PME methodology,³⁴ the use of a cutoff on the Lennard-Jones attractive (r^{-6}) term has persisted. Recently, a number of workers^{52–55} have increased the computational efficiency of the PME method for r^{-6} potentials, and the method is being incorporated into popular simulation programs.²⁷ The repulsive potential term decays much more quickly and is therefore neglected at long range by simply truncating the interaction past r_{cut} . Hence, the name of the method, “LJ-PME,” should not be understood to correct the entire LJ potential.

For the r^{-6} kernel, the Ewald partitioning of the summation over unit cells n can be expressed as:

$$E_6 = -4 \sum_{\mathbf{n}, i, j} \sqrt{\epsilon_i \epsilon_j} \frac{\sigma_i^3 \sigma_j^3}{r_{ij}^6} = -4 \sum_{\mathbf{n}, i, j} \sqrt{\epsilon_i \epsilon_j} \frac{\sigma_i^3 \sigma_j^3 f(\kappa r_{ij})}{r_{ij}^6} - 4 \sum_{\mathbf{n}, i, j} \sqrt{\epsilon_i \epsilon_j} \frac{\sigma_i^3 \sigma_j^3 [1 - f(\kappa r_{ij})]}{r_{ij}^6}, \quad (10)$$

where we assume geometric mean combination rules:

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}, \sigma_{ij} = \sqrt{\sigma_i \sigma_j} \quad (11)$$

and introduce the shorthand notation $r_{ij} = |r_{ij} + \mathbf{n}|$ in addition to the screening function $f(x) = e^{-x^2} (1 + x^2 + x^4/2)$, which depends on the attenuation parameter κ (we avoid the often-used β for this quantity to disambiguate it from the isothermal compressibility). The decomposition of the lattice sum yields two terms. The first is short-ranged and rapidly convergent in a standard pairwise summation, while the second long-range, nonsingular term converges rapidly in reciprocal space and can be treated using Fast Fourier Transforms (FFTs). The attenuation parameter determines the relative computational efforts in real and reciprocal space. For suitably chosen r_{cut} and FFT grids, the answer is independent of κ , which is chosen to minimize computational cost with the pairwise r_{cut} adjusted accordingly.

The multiplicatively separable form assumed above is important for the PME treatment of the long-range term, which proceeds by first discretizing the density due to all particles on a grid, transforming the density to a potential via FFTs, and then probing the potential grid at each atomic center to yield the energy and forces. However, the CHARMM FFs use the Lorentz-Berthelot (LB) combination rule, which defines off-diagonal hard sphere radii in a form incongruous with the multiplicatively separable form described above:

$$\sigma_{ij} = \frac{\sigma_i + \sigma_j}{2}. \quad (12)$$

One potential remedy for this situation is to express the interaction coefficient using a binomial expansion:

$$(\sigma_i + \sigma_j)^6 = \sum_{n=0}^6 \binom{6}{n} \sigma_i^n \sigma_j^{6-n}. \quad (13)$$

This expansion transforms E_6 in Eq. 10 to a sum of seven terms, possessing the requisite separable form of which only four are unique by symmetry. The need for multiple FFTs is avoided using the strategy developed by Wennberg *et al.*²⁷ Briefly, their approach proceeds by a subtle change to the partitioning introduced above:

$$E_6 = -4 \sum_{\mathbf{n}, i, j} \sqrt{\epsilon_i \epsilon_j} \frac{(\sigma_i + \sigma_j)^6}{64 r_{ij}^6} = -4 \sum_{\mathbf{n}, i, j} \sqrt{\epsilon_i \epsilon_j} \left[\frac{(\sigma_i + \sigma_j)^6}{64 r_{ij}^6} - \frac{\sigma_i^6 \sigma_j^6 [1 - f(\kappa r_{ij})]}{r_{ij}^6} \right] - 4 \sum_{\mathbf{n}, i, j} \sqrt{\epsilon_i \epsilon_j} \frac{\sigma_i^6 \sigma_j^6 [1 - f(\kappa r_{ij})]}{r_{ij}^6}. \quad (14)$$

Again, the first term on the righthand side is treated in real space and the second term in Fourier space. The net effect is that a multiplicatively separable form is used to determine the long-range correction in Fourier space. This approach is also compatible with pair-specific LJ parameters (NBFIX terms) that are often used in FFs, with $\sigma_i + \sigma_j$ in Eq. 14 replaced by the corresponding NBFIX parameters.

In real space, the exact functional form of the potential is used up to r_{cut} , and another term is present to partially account for spurious short-range multiplicatively separable terms introduced in reciprocal space. This scheme is no longer rigorously insensitive to the choice of r_{cut} , but the difference between the two sets of combination rules is small enough at long range that this is a very good approximation. A discontinuity in the potential energy is averted at r_{cut} by applying a shift to account for the difference between the treatments at short and long range:

$$E_{\text{shift}} = -4 \sum_{\mathbf{n}, i, j} \sqrt{\epsilon_i \epsilon_j} \left(\frac{\left(\frac{\sigma_i + \sigma_j}{2} \right)^{12}}{r_{\text{cut}}^{12}} + \frac{\sigma_i^3 \sigma_j^3 [1 - f(\kappa r_{\text{cut}})] - \left(\frac{\sigma_i + \sigma_j}{2} \right)^6}{r_{\text{cut}}^6} \right). \quad (15)$$

In Eq. 15, the first term cancels the repulsive part of the LJ potential at r_{cut} , while the second term ensures a smooth transition from the real-space treatment to the multiplicatively separable regime. Although this correction guarantees a smooth potential, there may still be discontinuities in the forces. Differentiation of equation (15) yields

$$F_{\text{shift}} = 4 \sum_{\mathbf{n}, i, j} \sqrt{\epsilon_i \epsilon_j} \left(12 \frac{\left(\frac{\sigma_i + \sigma_j}{2} \right)^{12}}{r_{\text{cut}}^{13}} + 6 \frac{\sigma_i^3 \sigma_j^3 [1 - f'(\kappa r_{\text{cut}})] - \left(\frac{\sigma_i + \sigma_j}{2} \right)^6}{r_{\text{cut}}^7} \right), \quad (16)$$

where $f'(x) = e^{-x^2} (1 + x^2 + x^4/2 + x^6/6)$. Eq. 16 quantifies the force discontinuity due to the truncation of the repulsive term and the handoff between the two combination rules; the logarithm of the absolute value of this quantity is displayed in Fig. 1, for selected pairs of atom types, as a function of κ and r_{cut} . As expected, the lowest discontinuity error occurs where κ is large, *i.e.*, there are long-range terms present to account for the truncation of the attractive LJ term, and also where r_{cut} is large. Assuming a typical force on each atom to be ~ 10 kcal/mol/Å, the white contour lines in Fig. 1 represent an error in the contribution to the forces of about 1 part per million, which will be incurred every time a pairwise interaction crosses r_{cut} . To further quantify the consequences of the force discontinuities, NVE simulations were carried out on n-hexadecane and neat water, demonstrating that the energy drift is within 0.2 kcal/mol/ns, even with r_{cut} as low as 7 Å; the supporting information

contains full details of these tests. Because the microcanonical ensemble is maintained so well, a correction for the force discontinuity is not included in the current CHARMM implementation; there is an option to use potential switching⁵⁶ for ensuring continuous energies and gradients in free energy calculations.

Finally, the instantaneous virial stress tensor is required to generate constant pressure ensembles. The real-space contribution is exactly analogous to the standard outer-product form, involving forces and positions, that is used to evaluate the LJ virial. The reciprocal-space tensor is obtained by summation over reciprocal space lattice vectors m , with norm m ,

$$\Pi_{\alpha\beta} = \frac{\pi^{3/2}}{6V} \sum_m e^{-\frac{\pi^2 m^2}{\kappa^2}} \begin{pmatrix} 3\pi^2 \left(\pi^{3/2} m e^{-\frac{\pi^2 m^2}{\kappa^2}} \operatorname{Erfc}\left(\frac{\pi m}{\kappa}\right) - \kappa \right) m_\alpha m_\beta + \\ \delta_{\alpha\beta} \left(2\pi^{7/2} m^3 e^{-\frac{\pi^2 m^2}{\kappa^2}} \operatorname{Erfc}\left(\frac{\pi m}{\kappa}\right) + \kappa^3 - 2\pi^2 \kappa m^2 \right) \end{pmatrix} \quad (17)$$

and including the $m = 0$ term, in contrast to the Coulombic case.

3. RESULTS

3.1. Alkanes in C36 and Drude.

Results for ρ , β_T , η , γ , and D of hexadecane at biologically relevant temperatures are listed in Table 3. The final column of each table lists the deviation from experiment, averaged over the temperatures. Table 3 also includes results for ρ , β_T , and η for systems simulated using the isotropic LRC with the Drude FF.

The effects of long-range Lennard-Jones interactions are statistically significant for all cases. LJ-PME increases ρ by 2% for C36 and 1% for Drude. As consistent with an increase in density, β_T decrease (20% for C36, 10% for Drude), η increase (17% for C36, 12% Drude), and D decrease (23% for C36, 11% for Drude).

Results using the isotopic LRC for ρ and β_T are 0.3% higher and 4% lower than for LJ-PME, respectively. These are close, but not statistically equivalent. (Statistical errors in η are large, so it is not possible to assign statistical significance to the differences.) Recall that the isotropic LRC assumes that $g(r) = 1$ for $r > r_{\text{cut}}$. As is evident from the $g(r)$ for hexadecane plotted in Fig. 2, $g(r)$ only becomes constant at approximately 18 Å, well beyond the standard $r_{\text{cut}} = 12$ Å.

C36 without long-range LJ shows the largest differences from experiment for all quantities reported in Table 3. This is expected because the alkanes in C36 were originally parameterized with a pressure-based correction.²² Both polarizability and the use of LJ-PME

improve agreement with experiment in all cases, and in nearly all cases, Drude/LJ-PME achieves results closest to experiment. The agreement with experimental surface tensions is also best for Drude/LJ-PME (an average error of 1.6%).

Fig. 3 plots T_1 for heptane and pentadecane at 312.15 K. Agreement with experiment for carbons near the center of pentadecane is excellent for all but C36. The terminal carbon (C1) is not as well described as the others in the Drude FF, indicating that a slight adjustment of the C1 torsional parameters should be considered. Differences with experiment are uniformly larger for heptane (approximately 25% lower for Drude/LJ-PME, and 40–65% higher for the others). The reduction in T_1 , when long-range LJ terms are included, is consistent with the increase in η . This is because rotational diffusion of the long molecular axis, commonly referred to as tumbling, makes a significant contribution to the reorientational correlation functions of alkanes,⁵⁹ and the rotational correlation time τ (the integral of the correlation function) is proportional to viscosity. Hence, from Eq. 7, an increase in τ reduces T_1 . The effect of tumbling on hexadecane T_1 is somewhat smaller than for heptane, because the contribution of isomerization is larger. Heptane T_1 times are more influenced by rotational diffusion about the long axis (spinning) than those of hexadecane. Spinning of symmetric molecules is relatively insensitive to viscosity but is highly sensitive molecular shape and packing.⁶⁰ The large difference between Drude and Drude/LJ-PME results suggests a modulation of the relaxation associated with spinning.

3.2. Dependence on r_{cut} for Non-Bonded Interactions.

To investigate the dependence of ρ and γ on r_{cut} , simulations of bulk hexadecane and the hexadecane/vacuum interface were carried out at 298.15 K using C36 and C36/LJ-PME for a range of values for r_{cut} . As Fig. 4 indicates, LJ-PME is relatively insensitive to r_{cut} , and a value as low as 9 Å may be used for systems of pure alkanes. Without LJ-PME, ρ does not converge until approximately 24 Å, and γ is still increasing at this value of r_{cut} . The snapshots in Fig. 5 illustrate the effect of cutoff for C36. The system simulated with LJ-PME has a smooth interface consistent with a surface tension of 25 dyn/cm (left). The surface is borderline unstable for $r_{\text{cut}} = 8$ Å, and a molecule can be seen evaporating (right).

3.3. Temperature Dependence of Density and Isothermal Compressibility.

At 313.15 K, the volumetric coefficient of thermal expansion (α_V) for hexadecane is $9.07 \times 10^{-4} \text{ K}^{-1}$.⁶¹ This value is compared with simulation by fitting V_{mol} at three or four temperatures using a linear regression (Fig. 6). While the trends are qualitatively correct, α_V from simulation overestimate experiment by 20–40% (Table 4). This indicates that the error in V_{mol} , and therefore density, will increase if simulations are run at higher temperatures. Slopes of the lines of best fit for Drude and Drude/LJ-PME are nearer to the slope of the experimental line of best fit; however, over the range of temperatures shown, V_{mol} for C36/LJ-PME most closely match the experimental data.

Table 5 lists ρ and β_T at 393.15 K for an evaluation of the FFs at an elevated temperature. Deviations from experiment are generally 2–3 times larger than at biological temperatures (Table 3). The best agreement is obtained for Drude/LJ-PME.

Experimental β_T for hexadecane at temperatures from 298.15–433.15 K, calculated from measurements of the velocity of sound, can be fit with a polynomial regression.⁶¹ As evident from Fig. 7, $a + bT^4$ provides a good fit to the data (Table 6 lists b for each fit), and Drude/LJ-PME again is the best model.

4. DISCUSSION AND CONCLUSIONS

Long-range LJ dispersion interactions have a significant impact on numerous properties of alkanes. While they are especially important at the alkane-vacuum interface, they increase ρ and thereby decrease β_T and increase η . This effect is less pronounced in systems of polar molecules (where long-range electrostatic interactions tend to dominate and are accounted for by PME). For example, increasing r_{cut} from 8 Å to 25 Å has a substantially smaller effect on the calculated surface tension (γ) of pure water than of pure hexadecane.²⁴ Specifically, water surface tension at 323.15 K for the C27r FF is 41.5 ± 0.5 dyn/cm for $r_{\text{cut}} = 8$ Å and 51.3 ± 0.4 dyn/cm for $r_{\text{cut}} = 25$ Å; an increase of nearly 25 %. For hexadecane, $\gamma = 5.9 \pm 0.2$ and 22.7 ± 0.4 dyn/cm at 8 and 25 Å respectively; an increase of nearly 400 %. Nevertheless, increasing r_{cut} to include more long-range LJ interactions brings γ closer experiment in both cases.

The simplest way to include long-range LJ interactions is to use the isotropic correction.²⁵ This correction assumes the system is isotropic in pressure, which precludes its use for anisotropic systems. A key assumption in the isotropic LRC is that the $g(r)$ is 1 at distances larger than r_{cut} . The present study shows that fluids of larger molecules like hexadecane have significant structure beyond the usual 10–12 Å cutoffs (Fig. 2), indicating that the isotropic LRC is less generally applicable than previously assumed. The pressure-based LRC²⁶ is also not applicable to anisotropic systems, while assumptions of homogeneity limit the appeal of the IPS methods.^{24, 39}

The LJ-PME formalism solves a long-standing problem in the simulation field: the rigorous and computationally efficient treatment of long-range LJ interactions. Its recent reformulation permits the use of arbitrary LJ combination rules, making it ideally suited to macromolecular FFs. While the modified LJ-PME method suffers from small discontinuities in the forces at r_{cut} , microcanonical simulations of n-hexadecane and water boxes reveal that these force discontinuities have a negligible impact on simulations, even for r_{cut} as low as 7 Å. Our implementation defaults to potential shifting, with an option to use switching to remove force discontinuities. Properties evaluated for alkane systems are consistent for values of r_{cut} as low as 9 Å (Fig. 4), and adjustments for different styles of combining rules are straightforward (see Sec. 2.6).

The present study focuses on alkanes, a natural starting point for parametrization of lipid force fields. In Drude and C27r, which was later slightly modified to become C36, alkanes were originally parameterized using a pressure-based correction to account for long-range LJ interactions.^{21, 22} This correction was needed, among other reasons, to bring the densities of alkanes into satisfactory agreement with experiment. The C36 lipid FF did not include long-range LJ interactions (explicitly or with a correction) for reasons of consistency with other CHARMM FFs.

The results here (Table 3) indicate that use of the new LJ-PME approach to evaluate density and surface tension has an effect similar to earlier methods for estimating the long-range LJ interactions. That is, the densities of both the C36 and the Drude systems increased slightly at all temperatures tested, while the surface tensions increased more significantly, bringing all measurements of these quantities closer to experimental target values. In some cases, the isotropic LRC yielded results nearer to experiment than LJ-PME. For example, Drude densities with the isotropic LRC are nearer to experiment than with LJ-PME. This result is expected because the Drude FF was originally parameterized using a spatially isotropic, pressure-based correction.²¹ However, a distinction must be drawn between similarity with experimental results and accurate treatment of the long-range forces in simulation. Fig. 2 shows that use of the isotropic LRC for C₁₆H₃₄ is not valid with the standard value of $r_{\text{cut}} = 12 \text{ \AA}$ because $g(r) \neq 1$. Fig. 4 shows that increasing r_{cut} causes ρ to converge to the value obtained using LJ-PME, indicating that LJ-PME treats the long-range dispersion forces accurately.

In a recent study, Fischer *et al.*⁶² evaluated the effect of LJ-PME on properties of 146 organic liquids as parametrized in three different force fields. While a quantitative comparison with this work is difficult (alkanes were not included, different programs were used, and LJ cutoff is lower), most of the trends are similar. In particular, surface tensions increased when LJ-PME was implemented. The increase was not uniform because the contributions of long-range electrostatics differed among the molecules. Many, but not all, of the surface tensions generated with LJ-PME overestimated experiment. This implies that the attractive term in the LJ interaction (C_6/r^6) is too large for these molecules, even though two of the three FFs were developed with an analytic correction for long-range LJ interactions. The effect of LJ-PME on bulk properties was typically smaller. These results are similar to those obtained here for alkanes, although the surface tension of hexadecane underestimates experiment by approximately 20% even with LJ-PME (Table 3). The present study shows that the effect of long-range LJ forces on surface tension is treated accurately with LJ-PME (see convergence in Fig. 4), indicating the fault lies in parameterization. Therefore, to ensure proper tuning of the C_6 coefficient, future parameterization efforts should include surface tension as a target and accurately sum LJ forces.

Like surface tension, isothermal compressibility (β_T) is significantly affected by long-range Lennard-Jones interactions. The Drude FF consistently over-estimates β_T , indicating the systems are not sufficiently compact because the long-range attractive LJ interactions are absent. In contrast, use of the isotropic LRC results in consistent under-estimation. With LJ-

PME, there is less error in the compressibility measurements and no clear trend of over- or under-estimation in the range of temperatures applicable to biological phenomena.

LJ-PME brings the dynamical properties viscosity and self-diffusion closer to experiment, as consistent with an increase in density. Without LJ-PME, both C36 and Drude underestimate viscosity and overestimate diffusion.

NMR spin lattice relaxation times (T_1) for carbons of pentadecane are reasonably described for C36/LJ-PME and the Drude models (Fig. 3, bottom), and improvements are likely to be found by modifying the torsion angles. The relatively worse results found for heptane (Fig. 3, top) highlight the difficulties of accurately capturing the nuances of molecule shape on rotational diffusion. It would be of interest to simulate rotational relaxation of highly symmetric molecules such as benzene to refine force field to this level of detail. However, because the primary application of the CHARMM FFs is to biopolymers and membranes, pentadecane is the more important target.

While many MD simulations are run at temperatures near standard or body temperature, simulations at elevated temperatures also yield valuable information for biomolecular systems. Simulations of pure bilayers with higher-than-biological melting temperatures can be compared with experimental data to check for force field accuracy.^{63, 64} Furthermore, simulations of large systems, such as membrane-bound proteins, are routinely run at high temperatures to populate the energy landscape using the replica exchange method.⁶⁵

Modeling atomic polarizability provides MD methods with additional degrees of freedom, which should increase the transferability of parameters, allowing polarizable FFs to achieve better temperature dependence trends. Fig. 6 and Table 4 show that Drude/LJ-PME obtains the closest agreement with the experimental thermal expansion coefficient of hexadecane. The slope of the linear regression for V_{mol} vs. T is also nearest to the experimental slope for Drude/LJ-PME; however, the y intercept of the line of best fit is too high, causing V_{mol} to be slightly higher than experimental values across the temperatures tested. Although C36/LJ-PME has smaller errors from experiment in V_{mol} over the temperatures represented in the figure, the effective thermal expansion coefficient is not as close to the experimental value. Thus, Drude/LJ-PME obtains densities closer to experiment 393.15 K (Table 5).

Because the dependence on temperature of β_T is quartic, errors in temperature dependence are exacerbated at elevated temperatures (Fig. 7). The b parameter of C36 without LJ-PME is almost three times larger than experiment (Table 6), causing a greater than 100% overestimation of β_T at 400 K. With LJ-PME, this is dramatically improved, but C36/LJ-PME still overestimates β_T at 400 K by about 25 %. In contrast, Drude/LJ-PME overestimates b by only 13%. At 393.15 K, Drude/LJ-PME overestimates β_T by only 6 % and under-estimates density by only 2 % (Table 5). This improvement in temperature dependence could simply be attributed to the specific parameterization. A more general explanation is that polarizable models, with their additional degrees of freedom and enhanced electrostatic response capabilities, enable modeling of the larger range of

configurations available as temperature increases. Polarization effects are incorporated in the additive, fixed-charge force fields in a mean-field way through parametrization, which is typically performed at the room temperature and might lead to larger errors at elevated temperatures.

Consistent with the second explanation, polarizable force fields have previously been shown to perform better at elevated temperatures in systems of pure water,⁶⁶ water/salt solutions,⁶⁷ and polypeptides.⁶⁸ Jiang *et al.*⁶⁷ found that, for various concentrations of aqueous NaCl, the Drude polarizable FF developed by Kiss and Baranyai, AH/BK3,^{69, 70} yields ρ and η nearer to experimental values at 373.15 and 473.15 K than the additive SPC/E+SD models.^{71, 72} The induced-dipole AMOEBA force field shows close agreement with experimental temperature dependence for ρ of pure water up to 363 K, whereas the additive, five-site TIP5P model underestimates density above 320 K.⁶⁶ Polarizability also improves the temperature dependence of spontaneous folding: A study on cooperative helix formation in the (AAQAA)₃ peptide indicates that, in events driven by hydrogen bonding, the temperature dependence of secondary structure is more accurately represented by Drude than by C36.⁶⁸

In summary, LJ-PME is a rigorous method for including long-range LJ interactions in simulations. It allows the use of a shorter real-space cutoff for LJ and electrostatic interactions, thereby increasing computational efficiency. The use of LJ-PME improves agreement with experiment for density, isothermal compressibility, viscosity, diffusion constant, and surface tension at all temperatures simulated for both the C36 additive and Drude polarizable FFs. Additionally, LJ-PME improves agreement with experimental trends in temperature dependence for calculations of V_{mol} and β_T , though results at biological temperatures (303 to 323 K) are better than at 393.15 K. It is now practical and advisable to include long-range LJ interactions in subsequent FF development. While the C36 additive force field with LJ-PME remains a useful model for liquid alkanes, overall, the Drude force field with LJ-PME shows the closest agreement with the experiments considered here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The logarithm of the magnitude of the force discontinuities present when only potential shifting is used to smooth the potential, as a function of κ and r_{cut} . Parameters for various atom types are taken from the C36 lipid FF.

Figure 2. Radial distribution functions for hexadecane at 323.15 K using the Drude FF without long-range LJ interactions. “C1-C” is between C1 and all other carbons; “C8-C” is between C8 and all other carbons. The first two peaks arising from nearest and next-nearest neighbors are not shown

Figure 3. Comparison of NMR spin-lattice relaxation times (T_1) from simulation and experiment for heptane (top) and pentadecane (bottom).

Figure 4. Density (top) and surface tension (bottom) of hexadecane vs. r_{cut} for C36 and C36 LJ-PME compared with experiment. Standard errors are comparable to symbol for density.

Figure 5. Hexadecane fluid/vacuum interface for $r_{\text{cut}} = 8 \text{ \AA}$ for C36 with long-range Lennard-Jones interactions (left) and without (right). The boundaries of the unit cell are depicted with brass rods.

Figure 6. Temperature dependence of V_{mol} of hexadecane. Solid lines show the fit used to calculate values for α_V in Table 4.

Figure 7. Temperature dependence of β_T for hexadecane. Curves show fits to the simulation and experimental data with a regression of the form $a + bT^4$. The exponent of T was chosen using χ^2 analysis of the experimental data.

Table 1.

Simulations. Species, temperatures (T), number and length of runs (t_{run}), ensembles used, and quantities evaluated. For each set of specifications, simulations of 256 molecules were performed using C36 and Drude, with and without LJ-PME.

Species	T (K)	t_{run} (ns)	Ensemble	Use
$\text{C}_{16}\text{H}_{34}$	303.15, 310.15, 323.15, 393.15	1×30	NPT	$\rho, \beta_T, \alpha_V, g(r)$
$\text{C}_{16}\text{H}_{34}$	303.15, 310.15, 323.15; 323.15	3×100 (C36) 2×100 (Drude)	NVT	η ; D
$\text{C}_{16}\text{H}_{34}$	303.15, 310.15, 323.15	1×50	NVT	γ
$\text{C}_{15}\text{H}_{32}$	312.15	2×30	NPT	T_1
C_7H_{16}	312.15	2×30	NPT	T_1

Table 2.

Torsional Parameters for Alkanes

Term	Drude			C36 Lipid FF ¹		
	K_{φ}	N		K_{φ}	N	δ
CH ₃ -CH ₂ -CH ₂ -CH ₃	0.150	1	0	0.060	2	0
	0.170	2	0	0.035	5	0
	0.114	3	0			
	0.094	4	0			
	0.070	5	0			
CH ₃ -CH ₂ -CH ₂ -CH ₂	0.093	1	0	0.162	2	0
	0.143	2	0	0.047	3	180
	0.055	4	0	0.105	4	0
	0.102	5	0	0.177	5	0
CH ₂ -CH ₂ -CH ₂ -CH ₂	0.073	1	0	0.101	2	0
	0.043	2	0	0.142	3	180
	0.119	3	180	0.074	4	0
	0.098	4	0	0.097	5	0
	0.046	5	0			

Table 3.

Hexadecane Simulation Averages and Standard Errors for Density (ρ), Isothermal Compressibility (β_T), Shear Viscosity (η), Surface Tension (γ), and Translational Diffusion (D) at Various Biological Temperatures

		Temperature (K)			Average deviation from Exp.
		303.15	310.15	323.15	
ρ [g/mL]	C36	0.7483 ± 0.0001	0.7416 ± 0.0001	0.7289 ± 0.0001	-2.7 %
	C36, LJ-PME	0.7654 ± 0.0003	0.7593 ± 0.0001	0.7481 ± 0.0001	-0.40 %
	Drude	0.7544 ± 0.0002	0.7483 ± 0.0003	0.7375 ± 0.0001	-1.8 %
	Drude, LJ-PME	0.7620 ± 0.0002	0.7564 ± 0.0001	0.7460 ± 0.0002	-0.70 %
	Drude, LRC	0.7649 ± 0.0002	0.7591 ± 0.0001	0.7490 ± 0.0002	-0.40 %
	Exp. ⁵⁷	0.7665	0.7617 *	0.7528	
β_T [$10^{-10} \text{ m}^2/\text{N}$]	C36	12.48 ± 0.12	13.16 ± 0.11	14.40 ± 0.09	41 %
	C36, LJ-PME	10.04 ± 0.16	10.48 ± 0.22	11.35 ± 0.20	13 %
	Drude	9.99 ± 0.35	9.99 ± 0.31	11.94 ± 0.46	12 %
	Drude, LJ-PME	8.78 ± 0.14	9.49 ± 0.15	10.22 ± 0.16	0.60 %
	Drude, LRC	8.51 ± 0.17	9.11 ± 0.23	9.68 ± 0.25	-3.7 %
	Exp. ⁵⁷	8.896	9.307 *	10.059	
η [cP]	C36	2.16 ± 0.06	1.89 ± 0.14	1.47 ± 0.03	-22 %
	C36, LJ-PME	2.55 ± 0.13	2.05 ± 0.12	1.81 ± 0.07	-8.4 %
	Drude	2.37 ± 0.08	2.22 ± 0.11	1.80 ± 0.13	-8.4 %
	Drude, LJ-PME	2.70 ± 0.20	2.52 ± 0.10	1.95 ± 0.20	2.6 %
	Drude, LRC	3.07 ± 0.32	2.34 ± 0.30	2.08 ± 0.26	6.8 %
	Exp. ⁵⁷	2.766	2.388 *	1.866	
γ [dyn/cm]	C36	18.03 ± 0.49	16.86 ± 0.68	16.74 ± 0.67	-34.6 %
	C36, LJ-PME	24.79 ± 0.80	22.77 ± 0.72	19.73 ± 0.60	-18.6 %
	Drude	21.97 ± 0.41	21.89 ± 0.33	20.58 ± 0.26	-17.2 %
	Drude, LJ-PME	27.74 ± 0.56	26.26 ± 0.57	25.06 ± 0.42	1.60 %
	Exp. ⁵⁷	26.7	26.1 *	25.0	
D [$10^{-6} \text{ cm}^2/\text{s}$]	C36	5.48 ± 0.03	6.41 ± 0.04	8.47 ± 0.08	34 %
	C36, LJ-PME	4.16 ± 0.04	4.95 ± 0.05	6.53 ± 0.08	3.0 %
	Drude	4.81 ± 0.03	5.77 ± 0.07	7.45 ± 0.06	1.8 %
	Drude, LJ-PME	4.30 ± 0.01	5.02 ± 0.05	6.63 ± 0.10	5.0 %
	Exp. ⁵⁸			6.32	

* Values at 310.15 K interpolated with a polynomial fit.

In agreement with previous work,^{24, 41} the influence of long-range LJ terms on surface tensions of alkanes is large. For the cutoffs used here, γ is increased 18–37% for C36 and 20–26% for Drude, depending on the temperature.

Table 4.

Thermal expansion coefficients α_V calculated for each FF over the range of biological temperatures tested, found using a linear fit

Force Field	$\alpha_V(\text{K}^{-1} \times 10^{-3})$
C36	1.30
C36 LJ-PME	1.16
Drude	1.11
Drude LJ-PME	1.07
Exp.	0.907

Table 5.Hexadecane Simulation Averages and Standard Errors for ρ and β_T at 393.15 K

		Temperature (K)	Avg. Error from Exp.
		393.15	
ρ [g/mL]	C36	0.6570 ± 0.0002	-6.6 %
	C36, LJ-PME	0.6775 ± 0.0002	-3.7 %
	Drude	0.6897 ± 0.0002	-2.0 %
	Drude, LJ-PME	0.6896 ± 0.0002	-2.0 %
	Exp.	0.7036	
β_T [$10^{-10} \text{ m}^2/\text{N}$]	C36	32.98 ± 0.80	103 %
	C36, LJ-PME	20.44 ± 0.14	26 %
	Drude	21.20 ± 0.23	30 %
	Drude, LJ-PME	17.26 ± 0.23	6.0 %
	Exp.	16.24	

Table 6.

Parameter b describing temperature dependence of β_T for hexadecane.

Force Field	$b \text{ (K}^{-4} \text{ m}^2/\text{N} \times 10^{-10})$
C36	13.6
C36 LJ-PME	6.81
Drude	7.38
Drude LJ-PME	5.41
Exp.	4.77