

A polarizable model of water for molecular dynamics simulations of biomolecules

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Abstract

The SWM4-DP polarizable water model [G. Lamoureux, A.D. MacKerell, Jr., B. Roux, *J. Chem. Phys.* 119 (2003) 5185], based on classical Drude oscillators, is re-optimized for negatively charged Drude particles. The new model, called SWM4-NDP, will be incorporated into a polarizable biomolecular force field currently in development. It is calibrated to reproduce important properties of the neat liquid at room temperature and pressure: vaporization enthalpy, density, static dielectric constant and self-diffusion constant. In this Letter, we also show that it yields the correct liquid shear viscosity and free energy of hydration.

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1. Introduction

Computer simulations of atomic models based on empirical force fields have an ever increasing impact on our understanding of biological molecules. Central to the success of the approach is the quality of the force field representing the biomolecules, as well as the proper treatment of their aqueous environment. For this purpose, a molecular mechanical model of water should reproduce properties pertaining to the structure, dynamics and energetics of water (e.g., radial distribution function, dielectric screening, viscous drag, excess chemical potential, etc.) as accurately as possible, yet remain computationally tractable. For the model to be transferable, the dipole of each water molecule should vary (increase) with the polarity of its

environment: 1.85 D in the gas phase, between 2.5 and 3.0 D in a hydrogen-bonding environment [1], and perhaps even higher in the vicinity of a small ion such as sodium or potassium.

A polarizable water model fulfilling some of these goals was introduced recently [2]. It includes explicit polarization implemented with a classical Drude oscillator model [3], and correctly reproduces many important properties of the liquid: vaporization enthalpy, density, static dielectric constant and self-diffusion constant. Before it is incorporated into the extended ‘Drude oscillator’ biomolecular force field currently being developed [4,5], some additional properties, the shear viscosity and the hydration free energy, should be tested.

In the original model, SWM4-DP, the Drude particle was assigned a positive charge [2]. Because the charge is shifting over a finite distance (away from a counter-charge) and does not rigorously represent a point-dipole, the choice of the sign has some physical consequences. Intuitively, it seems better justified to assign a *negative* charge to the auxiliary moving particle, as they are meant to represent the electronic degrees of freedom of the system (e.g., a model

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with negatively charged Drude particles might capture higher order polarization effects more correctly). This motivated the development and evaluation of a modified version of the SWM4 polarizable water model with a negative charge on the Drude particle, that will be referred to as SWM4-NDP.

2. Model and methods

2.1. Functional form of the model

The functional form of the model is almost exactly that of the original SWM4-DP model [2]. It has a fixed HOH geometry with $\ell_{\text{OH}} = 0.9572 \text{ \AA}$ and $\theta_{\text{HOH}} = 104.52^\circ$, and an additional, massless site ‘M’ along the axis of symmetry of the molecule, at a fixed distance from the oxygen site. Similarly to the TIP4P model [6], the permanent molecular dipole is created by positive charges on the hydrogen atoms (q_{H}) and a negative charge on the M site ($q_{\text{M}} \equiv -2q_{\text{H}}$). The polarizability is represented by a Drude particle of negative charge $-q_{\text{D}}$ attached to the oxygen site with a force constant $k_{\text{D}} = 1000 \text{ kcal/mol/\AA}^2$. The oxygen site itself has a positive $+q_{\text{D}}$ charge.

The Lennard-Jones (LJ) parameters for the oxygen site (ϵ_{O} and σ_{O}), the charge on the Drude particle ($-q_{\text{D}}$, hence the polarizability $\alpha = q_{\text{D}}^2/k_{\text{D}}$), and the OM distance (ℓ_{OM}) are treated as parameters and are adjusted empirically to reproduce the experimental properties of the neat liquid. The charges q_{M} and q_{H} are set so that the permanent, zero-field dipole μ_0 is 1.85 D. Since the HOH geometry is fixed, they depend exclusively on ℓ_{OM} .

2.2. Simulation protocol

To compute the thermodynamic properties of the liquid, 250 water molecules are simulated with molecular dynamics (MD) in a cubic box with periodic boundary conditions (PBCs). Electrostatic interactions are calculated using particle-mesh Ewald summation [7], with $\kappa = 0.33$ for the charge screening, mesh points approximately every Ångström, and fourth-order splines for the mesh interpolations. The real-space portion of the Ewald sum is cut-off at 15 Å. LJ interactions are cut-off at 15 Å as well, with long-range contribution corrected for by an average, density-dependent term [8,9].

The polarizable model is simulated in the *NPT* ensemble, using an extended Lagrangian scheme [3]. Atoms are kept at room temperature (298.15 K) and pressure (1 atm), while the induced dipoles are maintained near the self-consistent induction regime by keeping the motion of the Drude particles relative to that of the nuclei at a low temperature (1 K). The rigid molecular geometry is enforced by the SHAKE/Roll and RATTLE/Roll procedures [10]. The trajectory of the extended system (particles, two thermostats and barostat) is integrated with a 1-fs time step, using a multistep integration scheme ($n_{\text{c}} = 20$) for the thermostat variables [3].

2.3. Method of optimization

Again, the model has four free parameters: α , ℓ_{OM} , ϵ_{O} and σ_{O} . These parameters are adjusted to reproduce the experimental values of four essential properties of liquid water: the change in internal energy upon liquefaction, $\Delta u = -9.92 \text{ kcal/mol}$ (corresponding to a vaporization enthalpy $\Delta h = 10.52 \text{ kcal/mol}$ [11]); the average molecular volume, $\langle v \rangle = 29.94 \text{ \AA}^3$ (corresponding to a density of 0.997 g/cm^3); the self-diffusion constant, $D = 2.30 \times 10^{-5} \text{ cm}^2/\text{s}$ [12]; and the static dielectric constant, $\epsilon = 78.4$ [13]. The optimal set of parameters is found by a four-dimensional rectangular grid search in the $(\alpha, \ell_{\text{OM}}, U_{\text{dimer}}, d_{\text{OO}})$ space [2]. (U_{dimer} and d_{OO} are the binding energy and oxygen–oxygen distance of the water dimer at zero temperature.) Each $(U_{\text{dimer}}, d_{\text{OO}})$ pair corresponds to a unique $(\epsilon_{\text{O}}, \sigma_{\text{O}})$ pair, so no region of the parameter space is lost in the mapping. Simulations are performed for all combinations of the following values: $\alpha = (0.95, 1.00, 1.05, 1.10) \text{ \AA}^3$, $\ell_{\text{OM}} = (0.23, 0.24, 0.25) \text{ \AA}$, $U_{\text{dimer}} = (-5.20, -5.15, -5.10, -5.05) \text{ kcal/mol}$ and $d_{\text{OO}} = (2.81, 2.82, 2.83) \text{ \AA}$ (144 simulations in all).

The model corresponding to each grid point is simulated for 150 ps. The last 100 ps of the simulation provide reasonably well-converged values for Δu and $\langle v \rangle$. The height of the first peak of the oxygen–oxygen radial distribution function, $g_{\text{OO}}^{(1)}$, and the average molecular dipole, $\langle \mu \rangle$, are calculated as well. A second-order polynomial interpolation formula, **P**, is fitted for these four properties [2]. The polynomial **P** does not predict the diffusion constant and dielectric constant – which cannot be estimated from only 100 ps of sampling – but because $g_{\text{OO}}^{(1)}$ and $\langle \mu \rangle$ are strongly correlated to D and ϵ [2], it greatly accelerates the iterative search for the optimal model.

P is inverted to estimate the parameters that produce the desired values for Δu and $\langle v \rangle$, and some chosen values for $g_{\text{OO}}^{(1)}$ and $\langle \mu \rangle$. For each trial pair $(g_{\text{OO}}^{(1)}, \langle \mu \rangle)$, D and ϵ are calculated as in [2], from the last 100 ps of 20 replicas of 150 ps simulations. Hence, 20 simulations are performed for each attempt at finding the pair $(g_{\text{OO}}^{(1)}, \langle \mu \rangle)$ that corresponds to correct D and ϵ . Assuming that the interpolation formula **P** is a reliable estimator of Δu and $\langle v \rangle$, each of these attempts should automatically yield the correct vaporization enthalpy and density. Seven iterations were needed to optimize the diffusion constant and dielectric constant of the model. The properties of the optimal model are further converged using 20 additional replicas (i.e., using a total of 4 ns of sampling).

3. Results

3.1. Optimal model

The parameters of the optimal model (SWM4-NDP) are displayed in Table 1, along with the corresponding values for the original SWM4-DP model [2]. If the Drude oscillator dipole was truly point-like, the original SWM4-DP

Table 1
Parameters of the SWM4-NDP, SWM4-DP and non-polarizable TIP3P water models

	TIP3P ^a	SWM4-DP ^b	SWM4-NDP ^c
ℓ_{OH} (Å)	0.9572	0.9572	0.9572
θ_{HOH} (°)	104.52	104.52	104.52
ℓ_{OM} (Å)		0.23808	0.24034
q_{O} (e)	−0.834	−1.77185	1.71636
q_{M} (e)		−1.10740	−1.11466
q_{H} (e)	0.417	0.55370	0.55733
q_{D} (e)		1.77185	−1.71636
k_{D} (kcal/mol/Å ²)		1000	1000
ϵ_{O} (kcal/mol)	0.1521	0.20568	0.21094
σ_{O} (Å)	3.1506	3.18030	3.18395

^a Ref. [6].

^b Ref. [2].

^c This work.

parametrization would yield the correct liquid properties independently of the sign of the Drude particle charge. However, a test simulation shows that simply inverting the sign of the fictitious charge q_{D} in the SWM4-DP gives incorrect basic liquid properties: $\Delta u = -10.56$ kcal/mol (instead of -9.92 kcal/mol) and $\langle v \rangle = 29.1$ Å³ (instead of 29.94 Å³). Since the Drude particles are meant to represent

the electronic degrees of freedom of the system, it seems intuitively reasonable that a model with negatively charged particles should be preferable. These observations motivated the optimization of the SWM4-NDP model. SWM4-NDP reproduces accurately the four targeted liquid properties: Δu , $\langle v \rangle$, D and ϵ (see Table 2). Apart from the signs of the charges q_{O} and q_{D} , the new parameters are similar to those of the SWM4-DP model, but distinct nonetheless because the O–D pair is not quite a point-dipole. The molecular polarizability α that yields the correct dielectric constant is 6% smaller than that of the SWM4-DP model (see Table 2), but the average molecular dipole it produces in the condensed phase, $\langle \mu \rangle$, is almost the same. For reference, the usual radial distribution functions are presented in Fig. 1. They are very close to those of the SWM4-DP model.

3.2. Additional dynamic properties

To characterize the dynamic properties of SWM4-NDP independent of artificial perturbations from the extended Lagrangian degrees of freedom, averages are calculated from forty 100 ps simulations in the microcanonical ensemble. The *NVE* simulations are started from state points

Table 2
Properties of the SWM4-NDP model compared to those of the original SWM4-DP model and the non-polarizable TIP3P model

	Expt. ^a	TIP3P ^b	SWM4-DP ^c	SWM4-NDP ^d
<i>Monomer</i>				
μ_0 (D)	1.85	2.347	1.85	1.85
α (Å ³)	1.44		1.04252	0.97825
Q_{xx} (D Å)	−0.134	−0.080	−0.2421	−0.2479
Q_{yy} (D Å)	2.626	1.762	2.4068	2.4247
Q_{zz} (D Å)	−2.493	−1.681	−2.1647	−2.1768
<i>Dimer (0 K)</i>				
U_{dimer} (kcal/mol)	−5.4	−6.50	−5.18	−5.15
d_{OO} (Å)	2.98	2.74	2.82	2.83
θ_{A} (°)	58	20	70	71
μ_{dimer} (D)	2.643	3.866	2.087	2.062
<i>Bulk liquid (298.15 K)</i>				
Δu (kcal/mol)	−9.92	−9.82	−9.927	−9.923
$\langle v \rangle$ (Å ³)	29.94	29.9	29.93	29.91
$\langle \mu \rangle$ (D)		2.347	2.456	2.461
D (10 ^{−5} cm ² /s)	2.3	5.1	2.30 ± 0.04	2.33 ± 0.02
ϵ	78.4	92 ± 5	79 ± 5	79 ± 3
η (cp)	0.89			0.70 ± 0.05
τ_{D} (ps)	8.27, 8.32, 8.40		11.1 ± 1.5 ^e	11 ± 2
τ_{NMR} (ps)	2.1			1.87 ± 0.03
ΔG_{hydr} (kcal/mol)	−6.32, −4.4, −5.74, −6.33	−6.10	−6.0 ± 0.1 ^f	−5.9 ± 0.1 ^g , −6.0 ^h
<i>Air/water interface (298.15 K)</i>				
γ (dyn/cm)	72.0	52.7	66.9 ± 0.9	67 ± 4
$\Delta \phi$ (mV)		−500	−540	−545

^a Shear viscosity η from [14], τ_{D} from [15–17], τ_{NMR} from [18], ΔG_{hydr} values from [19–22] ([20] at 27 °C). For other properties, see [2] and references therein.

^b Ref. [6] for the model, γ and $\Delta \phi$ from [23], ΔG_{hydr} from [24].

^c Ref. [2], except for ΔG_{hydr} .

^d This work.

^e Correct value, obtained from trajectories of [2].

^f From TI calculation in bulk water, using 100 ps per window instead of 300.

^g From TI calculation in bulk water.

^h From PMF calculation in the slab system.

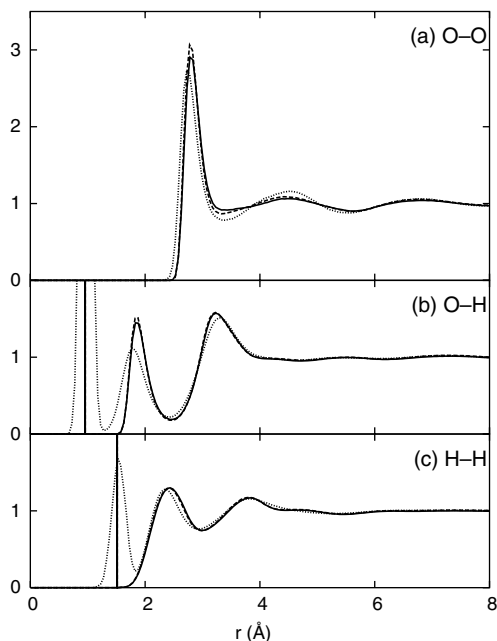


Fig. 1. (a) Oxygen–oxygen, (b) oxygen–hydrogen and (c) hydrogen–hydrogen radial distribution functions for the SWM4-NDP model (solid lines, this work), compared to the SWM4-DP distributions (dashed lines, [2]) and to neutron diffraction data (dotted lines, [25]).

sampled from a MD trajectory in the NVT ensemble at a volume corresponding to the density of SWM4-NDP and $T = 298.15$ K [3]. No thermostat is applied to the motion of the Drude particles, because it is very weakly coupled to the atomic motions. After 100 ps of simulation, the average temperature of the atom–Drude vibrations is still lower than 1 K. We note that the calculated diffusion coefficient does not change significantly from the value calculated in the NPT simulation.

The shear viscosity, η , is calculated from the correlations of off-diagonal components of the pressure tensor [9]:

$$\eta = \frac{1}{3} \sum_{\alpha\beta=xy,yz,zx} \frac{V}{k_B \langle \mathcal{T} \rangle} \int_0^\infty dt \langle \mathcal{P}_{\alpha\beta}(t) \mathcal{P}_{\alpha\beta}(0) \rangle, \quad (1)$$

where \mathcal{T} and \mathcal{P} are the instantaneous temperature and instantaneous pressure tensor, respectively. The viscosity value reported in Table 2 (0.70 ± 0.05 cp) is in relatively good agreement with the experimental value, 0.89 cp [14].

The Debye relaxation time, τ_D , is evaluated from an exponential fit to the autocorrelation function of the total dipole of the system (see [2]), for times greater than 2 ps. The SWM4-NDP model yields $\tau_D = 11 \pm 2$ ps, a value somewhat larger than the experimental results, ~ 8.3 ps [15–17]. To investigate the rotational dynamics of the model, we compute

$$C(t) = \langle P_2[\mathbf{e}(t) \cdot \mathbf{e}(0)] \rangle, \quad (2)$$

where \mathbf{e} is the unit vector along the axis connecting the hydrogen atoms within a water molecule and the function $P_2(x)$ is the second-order Legendre polynomial. The long time decay ($t > 2$ ps) of $C(t)$ is fitted to a function of the

form $Ae^{-t/\tau}$ [26]. To a good approximation, the NMR relaxation time is given by $A\tau$. The resulting $A\tau$ value, 1.87 ± 0.03 ps, is somewhat smaller than the experimental value, 2.1 ps [18].

3.3. Air/water interface

To obtain the air/water interface properties, the SWM4-NDP model is simulated in a ‘slab’ geometry. A system of 250 molecules contained in a $19.56 \text{ \AA} \times 19.56 \text{ \AA} \times 19.56 \text{ \AA}$ cube is equilibrated in a rectangular cell of dimensions $19.56 \text{ \AA} \times 19.56 \text{ \AA} \times 58.68 \text{ \AA}$ with PBCs. In this larger volume, the liquid sustains two well-separated vacuum/water interfaces, whose properties are calculated from a 5 ns simulation in the NVT ensemble.

The surface tension, γ , is calculated following [9]. The value for the new model, 67 ± 4 dyn/cm, is practically unchanged from that for the SWM4-DP model (see Table 2).

The electrostatic potential profile across the air/water/air system, $\phi(z)$, is obtained from the charge density $\rho(z)$, as a solution of the Poisson equation $\partial^2 \phi(z)/\partial z^2 = -4\pi\rho(z)$:

$$\phi(z) = -2\pi \int_{-\infty}^z dz' \left[\int_{-\infty}^{z'} dz'' \rho(z'') - \int_{z'}^{\infty} dz'' \rho(z'') \right]. \quad (3)$$

The air-to-bulk potential drop is 545 mV, consistent with the 540 mV drop for the SWM4-DP model [2].

3.4. Hydration free energy

The hydration free energy, ΔG , is calculated from the thermodynamic integration (TI) of: (1) transforming the full potential of one SWM4-NDP molecule into a LJ sphere (ϵ_O, σ_O) by scaling to zero all charges of the model in 10 steps and (2) annihilating the LJ sphere through 10 steps of ‘shifted scaling’ of the LJ potential [27]. This transformation is realized in the NPT ensemble, from a cubic box of 125 water molecules. Each step of the complete annihilation is simulated for 300 ps. Transformation (1) contributes to -2.0 ± 0.1 kcal/mol ($-\Delta G_{LJ}$), and transformation (2) to 7.9 ± 0.1 kcal/mol ($-\Delta G_{elec}$). The total, which represents $-\Delta G$, is 5.9 ± 0.1 kcal/mol (see Table 2).

This calculation of ΔG is validated using two alternate methods. First, the TI calculation of $-\Delta G_{LJ}$ is reproduced using a water box of 250 molecules and the staged protocol of Deng and Roux [28], and yields a value of -2.0 ± 0.1 kcal/mol. Second, ΔG is obtained from the potential of mean force (PMF) on a water molecule moving out of a water slab into vacuum. This process is represented by multiple umbrella simulations of a slab system of 250 water molecules (prepared as in Section 3.3). In each simulation, one water molecule is forced by a harmonic potential centered at a position z . To get the gas phase portion of the PMF to converge, the water molecules are coupled to a Langevin thermostat [29] instead of the Nosé thermostat used in Section 3.2. This insures that the water molecule

pulled out of the liquid has a canonical z -distribution even when it is not strongly coupled to the rest of the system. The PMF is obtained via a weighted histogram analysis method (WHAM) [30,31] from forty 800 ps simulations with biasing potentials equally spaced from $z = -20$ Å (gas phase) to 0 Å (in solution). Results yield $\Delta G = -6.0$ kcal/mol, and an additional PMF calculation of just the LJ sphere yields $\Delta G_{\text{LJ}} = 2.0$ kcal/mol. Both free energies are in excellent agreement with the TI results.

4. Summary

The functional form of the new model SWM4-NDP is different from the original SWM4-DP only by the sign of the charge on the Drude particle (and on the oxygen site). For the original model in the liquid phase, the average-induced dipole corresponds to the Drude particle shifted toward the M site by approximately 0.07 Å [2]. For the new model, however, the Drude particle is shifting *away* from the M site. This difference in the effective molecular electrostatics is corrected for in the new parametrization. One can guess that a SWM4-like model using a true point-dipole would require some parametrization intermediate to SWM4-DP and SWM4-NDP.

The overall quality of the new model is comparable to that of the original. It has a correct vaporization enthalpy, density, static dielectric constant and self-diffusion constant. The present work shows that it has a satisfactory viscosity (η) and a hydration free energy (ΔG) within the range of experimental estimates. Accordingly, both SWM4 models should be suitable for polarizable simulations of molecules that require explicit treatment of the aqueous environment. The value of ΔG , which was not adjusted, suggests that the SWM4-NDP model will provide realistic hydration energies for a wide range of molecules. The viscosity of the SWM4-NDP model is better than that of common non-polarizable models like TIP3P [23] and SPC/E[32]. This may help in reproducing the timescales of dynamical processes such as the assembly of large biomolecules and the diffusion through pores.

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References

- [1] J.K. Gregory, D.C. Clary, K. Liu, M.G. Brown, R.J. Saykally, *Science* 275 (1997) 814.
- [2] G. Lamoureux, A.D. MacKerell Jr., B. Roux, *J. Chem. Phys.* 119 (2003) 5185.
- [3] G. Lamoureux, B. Roux, *J. Chem. Phys.* 119 (2003) 3025.
- [4] V.M. Anisimov, G. Lamoureux, I.V. Vorobyov, N. Huang, B. Roux, A.D. MacKerell Jr., *J. Chem. Theory Comput.* 1 (2005) 153.
- [5] I.V. Vorobyov, V.M. Anisimov, A.D. MacKerell Jr., *J. Phys. Chem. B* 109 (2005) 18988.
- [6] W.L. Jorgensen, J. Chandrasekhar, J.D. Madura, R.W. Impey, M.L. Klein, *J. Chem. Phys.* 79 (1983) 926.
- [7] T. Darden, D. York, L. Pedersen, *J. Chem. Phys.* 98 (1993) 10089.
- [8] P. Lagüe, R.W. Pastor, B.R. Brooks, *J. Phys. Chem. B* 108 (2004) 363.
- [9] M.P. Allen, D.J. Tildesley, *Computer Simulation of Liquids*, Clarendon Press, Oxford, 1987.
- [10] G.J. Martyna, M.E. Tuckerman, D.J. Tobias, M.L. Klein, *Mol. Phys.* 87 (1996) 1117.
- [11] G. Jancsó, W.A. van Hook, *Chem. Rev.* 74 (1974) 689.
- [12] K. Krynicki, C.D. Green, D.W. Sawyer, *Discuss. Faraday Soc.* 66 (1978) 199.
- [13] D.P. Fernandez, Y. Mulev, A.R.H. Goodwin, J.M.H.L. Sengers, *J. Phys. Chem. Ref. Data* 24 (1995) 33.
- [14] D.R. Lide (Ed.), *CRC Handbook of Chemistry and Physics*, 66th ed., CRC Press, Boca Raton, FL, 1985.
- [15] U. Kaatz, *J. Chem. Eng. Data* 34 (1989) 371.
- [16] J. Barthel, K. Bachhuber, R. Buchner, H. Hetzenauer, *Chem. Phys. Lett.* 165 (1990) 369.
- [17] J.T. Kindt, C.A. Schmittenmaer, *J. Phys. Chem.* 100 (1996) 10373.
- [18] J. Jonas, T. DeFries, D.J. Wilbur, *J. Chem. Phys.* 65 (1976) 582.
- [19] A. Ben-Naim, Y. Marcus, *J. Chem. Phys.* 81 (1984) 2016.
- [20] R.G. Pearson, *J. Am. Chem. Assoc.* 108 (1986) 6019.
- [21] J. Hermans, A. Pathiaseril, A. Anderson, *J. Am. Chem. Assoc.* 110 (1988) 5982.
- [22] M.H. Abraham, G.S. Whiting, R. Fuchs, E.J. Chambers, *J. Chem. Soc., Perkins Trans. 2* 2 (1990) 291.
- [23] S.E. Feller, R.W. Pastor, A. Rojnuckarin, S. Bogusz, B.R. Brooks, *J. Phys. Chem.* 100 (1996) 17011.
- [24] M.R. Shirts, V.S. Pande, *J. Chem. Phys.* 122 (2005) 134508.
- [25] A.K. Soper, *Chem. Phys.* 258 (2000) 121.
- [26] S.W. Rick, S.J. Stuart, B.J. Berne, *J. Chem. Phys.* 101 (1994) 6141.
- [27] M. Zacharias, T.P. Straatsma, J.A. McCammon, *J. Chem. Phys.* 100 (1994) 9025.
- [28] Y. Deng, B. Roux, *J. Phys. Chem. B* 108 (2004) 16567.
- [29] M.E. Tuckerman, B.J. Berne, *J. Chem. Phys.* 95 (1991) 4389.
- [30] A.M. Ferrenberg, R.H. Swendsen, *Phys. Rev. Lett.* 63 (1989) 1195.
- [31] M. Souaille, B. Roux, *Comp. Phys. Commun.* 135 (2001) 40.
- [32] S. Balasubramanian, C.J. Mundy, M.L. Klein, *J. Chem. Phys.* 105 (1996) 11190.