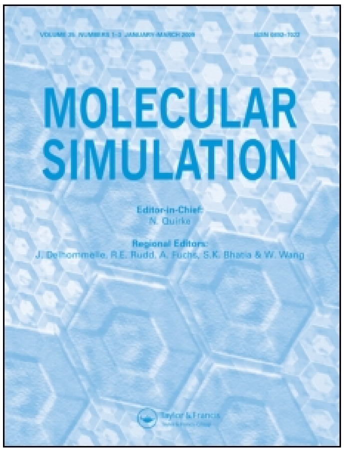

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# The Application of the Reaction-Field Method to the Calculation of Dielectric Constants

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# THE APPLICATION OF THE REACTION-FIELD METHOD TO THE CALCULATION OF DIELECTRIC CONSTANTS

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The behaviour of the popular TIP3P water model has been investigated using both molecular dynamics and Monte Carlo simulation procedures. Long-range electrostatic interactions were included through a reaction-field treatment, and the nonbonded interactions were either truncated at the cutoff distance, or smoothly scaled to zero using a switching function. The thermodynamic observables, and in particular the dipole-dipole correlation functions, are found to differ between the two simulation techniques if a rigid nonbonded cutoff is applied. However, use of a switching function gives exact agreement between the simulation methodologies. This difference is ascribed to the effect of energy pumping in the molecular dynamics simulations, and suggests that dielectric constants calculated using this simulation method with the fluctuation procedure in conjunction with a reaction field should be reappraised. Thus the Monte Carlo simulation procedure offers a number of intrinsic advantages over molecular dynamics for the calculation of dielectric constants with a reaction field. The most precise value for the dielectric constant of TIP3P is calculated to be $102 \pm 3$ at 298 K.

*Keywords:* Monte Carlo; molecular dynamics; reaction field; dielectric constant; TIP3P water; nonbonded cutoff

## INTRODUCTION

The evaluation of macroscopic properties using computer simulations of small systems is generally achieved through the application of periodic boundary conditions. To improve simulation efficiency, nonbonded interactions are usually truncated at some distance smaller than $L/2$ where $L$ is the length of each side of the simulation cell. While such a truncation is generally regarded as acceptable for the short-ranged components of the intermolecular potential, such as the repulsion-dispersion terms, the long-ranged nature of the Coulombic interactions makes this approximation less satisfactory. It has long been recognised that a consequence of this abrupt truncation at distances of the order of 10 Å is that energy is not conserved in the course of a molecular-dynamics simulation. The continual crossing at the cutoff boundary by molecules leads to steady heating of the system, and hence a non-Newtonian trajectory is followed [1]. For solvated protein systems this effect leads to faster heating of the solvent than the protein, and thus if some form of uniform temperature scaling is selected the solvent is often hotter than the solute [2]. Furthermore, it has been shown that the use of a cutoff leads to a non-uniform temperature distribution in the protein [3]. These effects do not arise in a Monte Carlo simulation since the temperature is a parameter in the acceptance criterion. A number of procedures have been suggested to eliminate this effect, including the use of switching functions [1,2,4–7], shifting functions [2,4–6], and a jump-correction [8]. These approaches have, however, been criticised on the grounds that they perturb the dynamic behaviour of the system [9–11], and may also lead to artificially large atomic-fluctuations in the simulation of proteins [4,12]. A second problem arising from the use of a cutoff that is applicable to both the molecular dynamics and Monte Carlo approaches is that the long-ranged electrostatic interactions are discarded. While it has been demonstrated for dipolar fluids that this has a small effect on the simple thermodynamic and structural properties of the system (for example the intermolecular energy [13–16], free-energy of hydration [17], and radial distribution functions [13–16, 18–20]) the system properties that are dependent on intermolecular angular correlations (such as the static dielectric constant) are very sensitive to these excluded interactions [15, 16, 21–23]. For simulations involving species with a finite electrical charge, the exclusion of long-ranged electrostatic interactions has a marked effect on even the simple thermodynamic and structural properties [24–27]. Furthermore, their exclusion has been shown to affect profoundly the stability of protein simulations [28–30]. Two general procedures exist to evaluate long-range electrostatic interactions. In the Ewald summation approach [21,22,31], the electrostatic interactions are evaluated through an infinite lattice sum over all periodic images, thereby imposing pseudocrystalline order on the liquid. In the reaction-field approach [21, 23, 32, 33], electrostatic interactions beyond the spherical cutoff $r_C$, are approximated by treating the system in excess of $r_C$ as a polarisable continuum of dielectric constant $\varepsilon_{rf}$. Each molecule of the liquid experiences an electric field arising from the polarisation of the continuum by the net dipole moment within the cutoff sphere centred on that molecule. There is some controversy as to whether the two procedures yield identical dielectric constants; such an equivalence has been demonstrated for SPC water, but through markedly different orientational behaviour [34]. However, it has also been noted that the reaction field procedure yields values systematically smaller than the Ewald approach [35], and that the dielectric constants calculated using a reaction field are profoundly more sensitive to cutoff than those derived using the Ewald method [36]. The reaction field approach has proved particularly popular for the calculation of dielectric constants because of its conceptual simplicity and computational efficiency. However, while a correctly implemented Ewald summation procedure should not suffer the energy pumping effects described above [37], a reaction-field molecular dynamics calculation will suffer this fate. Indeed, use of the reaction field over a conventional truncation of the nonbonded interactions has been reported to exacerbate the effect [1]. It is possible to combine a reaction field with a switching function in a consistent manner, although concern has been expressed that this may serve to artificially enhance the calculated dielectric constant [14].

In this paper, the influence of the reaction field procedure on the thermodynamic and structural properties of the TIP3P water model is examined with great care using molecular dynamics and Monte Carlo calculations, both with and without a switching function. The majority of the molecular-dynamics simulations performed with a reaction field that have been reported in the literature did not used a switching function, but the consequences of this choice on the orientational correlated-properties, especially with regard to the heating effect, have not been addressed. The static dielectric constant of TIP3P is also calculated, and to the author's knowledge this is the first published report of a converged value of this important property for this model.

## METHODOLOGY

The molecular-dynamics simulations were performed using AMBER 4.0 [38], and the Monte Carlo simulations using BOSS 3.4 [39]. The programs were modified to include a reaction-field treatment of long-range electrostatic interactions by the addition of a single term to the Coulombic potential for the interaction between site $i$ and all sites $j$ in other molecules within the cutoff $r_C$ [40].

$$V(rf)_i = \sum_j \frac{(q_i q_j / r_{ij})(\varepsilon_{rf} - 1)}{(2\varepsilon_{rf} + 1)} \left( \frac{r_{ij}}{\alpha r_C} \right)^3 \tag{1}$$

$q_i$ and $q_j$ represent the charges on atomic sites $i$ and $j$, respectively, $r_{ij}$ is the distance between the atomic sites, and $\alpha$ is a parameter that takes account of the effect of a switching function; $\alpha$ is unity in the absence of a switching function. This expression is valid provided that the molecules of the liquid are electrically neutral and that the nonbonded cutoff is applied with respect to the molecule as a whole. It is apparent from equation (1) that a value of $\varepsilon_{rf}$, the dielectric constant of the polarisable continuum outside $r_C$, has to be selected. Ideally, $\varepsilon_{rf}$ should be identical to the dielectric constant of the liquid within $r_C$, $\varepsilon_r$, if discontinuities at the cutoff boundary are to be avoided. In practice, however, any choice of $\varepsilon_{rf}$ such that $\varepsilon_r \leqslant \varepsilon_{rf} \leqslant \infty$ has been demonstrated to yield consistent values of $\varepsilon_r$ from moderate to highly polar liquids [40, 41]. Since $\varepsilon_r$ is not known reliably for the TIP3P water model $\varepsilon_{rf}$ was set equal to $\infty$. A switching function, $S(r_{oo})$, of the form given in equation (2) was added to both programs to scale the nonbonded interactions smoothly to zero at the nonbonded cutoff [14].

$$\begin{aligned} S(r_{oo}) &= 1, \quad r_{oo} \leqslant r_L \\ S(r_{oo}) &= C_0 + C_1\delta^3 + C_2\delta^4 + C_3\delta^5, \quad r_L \leqslant r_{oo} \leqslant r_C \\ S(r_{oo}) &= 0, \quad r_{oo} \geqslant r_C \end{aligned} \tag{2}$$

where

$$\delta = r_{oo}^2 - r_L^2$$

$r_{oo}$ is the interatomic distance between the oxygen atoms of the water molecules, $r_L$ is the distance at which the switching function is turned on, and $r_C$ is the nonbonded cutoff radius. The coefficients $C_0, C_1, C_2$ and $C_3$ are chosen to make the smoothing function and its first two derivatives continuous at $r_L$ and $r_C$.

$$\begin{aligned} C_0 &= 1 \\ C_1 &= \frac{-10}{(r_C^2 - r_L^2)^3} \\ C_2 &= \frac{15}{(r_C^2 - r_L^2)^4} \\ C_3 &= \frac{-6}{(r_C^2 - r_L^2)^5} \end{aligned} \tag{3}$$

The effect of the switching function on the reaction-field term was correctly incorporated in the manner described in reference [42]. Switching functions are a solution to the problem of energy pumping in molecular dynamics simulations since potential energy and the associated forces are then continuous at the nonbonded cutoff.

The dielectric constant of TIP3P water was evaluated by two procedures. First, the average of the square of the total dipole moment of the system, $\langle \mathbf{M}^2 \rangle$, was evaluated. The finite system $g$ factor, $G_k$, is defined in equation (4).

$$G_k = \frac{\langle \mathbf{M}^2 \rangle}{N\mu^2} \tag{4}$$

$N$ is the number of molecules in the simulation system, and $\mu$ is the dipole moment of a single TIP3P molecule. For reaction field boundary conditions, equation (5) is then applied to give $\varepsilon_r$.

$$\left(\frac{\varepsilon_r - 1}{3}\right)\left(\frac{2\varepsilon_{rf} + 1}{2\varepsilon_{rf} + \varepsilon_r}\right) = \frac{4\pi\rho\mu^2}{9k_bT} G_k \tag{5}$$

$\rho$ is the density of the simulation system, $k_b$ is the Boltzmann constant, and $T$ the temperature. It has been shown that markedly different values of $G_k$ arise from different choices of $\varepsilon_{rf}$ but that identical values of $\varepsilon_r$ are obtained through the consistent application of equation (5) [40, 42, 43]. In practice, however, the choice of $\varepsilon_{rf} \approx \varepsilon_r$ yields the most rapid convergence of $G_k$ [43, 44]. This method will be subsequently referred to as the fluctuation approach. Second, the polarisation of the system as a function of an applied electric field, $\mathbf{E}_0$, was measured to confirm the realiability of the results obtained using equation (5) [18]. If the average system dipole moment along the direction of the applied field, per unit volume, is $\langle \mathbf{P} \rangle$, the $\varepsilon_r$ can be calculated using equation (6) for reaction field geometry [42].

$$(4\pi/3)\langle \mathbf{P} \rangle/\mathbf{E}_0 = \frac{((\varepsilon_r - 1)/3)(2\varepsilon_{rf} + 1)}{(2\varepsilon_{rf} + \varepsilon_r)} \tag{6}$$

This approach is between 2 and 4 times more efficient than the fluctuation method for SPC water [14]. It does, however, require the perturbation of the liquid structure through the application of an applied electric field. In practice, therefore, care must be taken to ensure that the observed polarisation,

$\langle \mathbf{P} \rangle$, is linear in the applied field strength, $\mathbf{E}_0$; *i.e.* dielectric saturation is avoided [14, 45]. This method will be subsequently referred to as the polarisation approach. Other methods exist for the calculation of dielectric constants through computer simulations. They include the use of ion-ion potentials of mean force [46] and an umbrella sampling approach whereby the complete probability distribution of the net dipole moment, P(**M**), is calculated [47]; a related approach involves computing P($\mathbf{M}^2$) [36]. However, this study is intended to address primarily the influence of simulation methodology on correlated behaviour and the fluctuation method (equation (5)) was therefore adopted.

Cubic simulation systems of 216 TIP3P water molecules [48] with edge dimensions of 18.7014 Å were constructed, corresponding to a system density of 1.0 g cm$^{-3}$. Nonbonded cutoffs of 8.0 Å were applied based on the separation of the water oxygen-atoms, and in the situations where the switching function was used, $r_L$ was set to 7.5 Å. With the switching function, the value of $\alpha$ used in the expression for the reaction field energy, equation (1), was calculated to be 0.9107712. All simulations were performed under constant NVT conditions. For the Monte Carlo simulations, Metropolis sampling was used [21], and the magnitudes of the attempted translational and rotational moves were selected to yield an acceptance probability of approximately 40 %. In the molecular dynamics simulations, a constant temperature of 298.15 K was applied through the Berendsen algorithm with the recommended coupling constant of 0.2 ps [49]. A simulation was also performed using a coupling constant of 0.02 ps to increase the strength of the temperature scaling. All bonds were constrained using the SHAKE algorithm [50] in conjunction with a timestep of 0.002 ps. The reliability of the dielectric constants calculated using equation (5) was confirmed through the use of equation (6) in conjunction with an applied field of $1.0 \times 10^8$ Vm$^{-1}$; only Monte Carlo simulations were performed. To examine the size consistency of the results, the simulations were repeated using a cubic simulation system of 267 TIP3P water molecules with edge dimensions of 20.0000 Å. Nonbonded cutoffs of 10.0 Å were applied based on the separation of the water oxygen atoms, and in the situations where the switching function was used, $r_L$ was set to 9.5 Å. With the switching function, a value of 0.9279041 was calculated for $\alpha$. To examine the size consistency of the results the simulation of 512 molecules would be desirable. This is, however, impracticable owing to limitations in computational resources.

In the Monte Carlo simulations, the system was equilibrated for a total of 10 million (10 M) configurations, followed by, for the 216 molecule system, 10 successive batches of data collection each of 50 M configurations. Thus a total of 500 M configurations were obtained for analysis. It has been shown that the precise calculation of correlated properties such as dielectric constants requires simulations of this length. For the 267 molecule system, 15 successive batches of data collection were performed, each of 50 M configurations, giving a total of 750 M configurations for data analysis. In the molecular dynamics simulations of the 216 molecule system, an equilibration period of 100 ps was followed by 10 successive batches of 200 ps, giving a total simulation of 2 ns for data collection. For the 267 molecule system, 15 successive batches of data collection, each of 200 ps, was performed, giving a total simulation of 3 ns. Structural properties were obtained by analysing coordinate sets every 200 Monte Carlo configurations, and every 0.1 ps. Where an applied field was used to calculate the dielectric constant, the system was equilibrated for 10 M configurations, followed by 5 successive batches of data collection each of 50 M configurations.

## RESULTS AND DISCUSSION

The thermodynamic properties computed for the smaller TIP3P simulation system using the molecular dynamics and Monte Carlo procedures are given in Table I. The data are averaged over the 10 batches defined above, and the quoted errors correspond to the standard errors on those averages. The intermolecular interaction energies include the self-interaction term arising from the interaction of a dipole with its own reaction field, given in

TABLE I Thermodynamic properties of the 216 TIP3P water-molecule system

| *Simulation method*[a] | *Switch*[b] | *Temp*[c]*/K* | $E^d$*/kcalmol*$^{-1}$ | $G_k$ | $\varepsilon_r$*(298.15 K)* | $\varepsilon_r$*(311 K)* |
|---|---|---|---|---|---|---|
| MC | no | 298.15 | −9.61 ± 0.00 | 5.75 ± 0.33 | 107 ± 6 | – |
| MC | yes | 298.15 | −9.56 ± 0.00 | 6.92 ± 0.59 | 129 ± 11 | – |
| MC | no | 311.00 | −9.46 ± 0.00 | 6.17 ± 0.35 | – | 110 ± 6 |
| MD | no | 311 | −9.32 ± 0.00 | 4.53 ± 0.16 | – | 81 ± 3 |
| MD | yes | 298 | −9.56 ± 0.00 | 7.27 ± 0.32 | 136 ± 6 | – |
| MD, tight[e] | no | 299 | −9.45 ± 0.00 | 4.81 ± 0.17 | 90 ± 3 | – |

[a]MC denotes a Monte Carlo simulation, MD denotes a molecular dynamics simulation. [b]"yes" or "no" indicates whether or not the switching function, equation (3), is implemented. [c]For the Monte Carlo simulations, the specified simulation temperature is given; for the molecular dynamics simulation, the average simulation temperature is given. [d]Includes the self-interaction energy of an individual dipole in its own reaction field. [e]Simulation conducted using a temperature coupling constant of 0.02 ps. All other molecular dynamics simulations used a constant of 0.2 ps.

equation (7) [51].

$$E = -\left(\frac{\mu^2}{\alpha r_C^3}\right)\frac{\varepsilon_{rf} - 1}{2\varepsilon_{rf} + 1} \tag{7}$$

This energy is a constant which amounts to $-0.077$ kcal mol$^{-1}$ or $-0.085$ kcal mol$^{-1}$ for TIP3P water ($\mu = 2.35$ D) with a cutoff of 8.0 Å, excluding or including the switching function, respectively. For the simulations performed with a 10.0 Å cutoff, the values are $-0.040$ kcal mol$^{-1}$ or $-0.043$ kcal mol$^{-1}$, excluding or including the switching function, respectively. The error bars on the potential energies reported in this paper are uniformly $\pm 0.00$ since this observable is well converged in these simulations.

For the simulations performed without a switching function, the molecular dynamics calculations consistently ran with a higher temperature than specified by the temperature scaling algorithm; use of the recommended coupling constant of 0.2 ps gave an average simulation temperature of 311 K, and decreasing the coupling constant to 0.02 ps, thereby increasing the effect of the temperature coupling algorithm, still resulted in an average simulation temperature of 299 K. This effect has been reported before and is a consequence of the abrupt nonbonded cutoff [1]. The average potential energies per molecule are clearly dependent on the simulation method. Furthermore, a Monte Carlo calculation performed at 311 K yielded a different potential energy to that of the molecular dynamics simulation, suggesting that the configurations sampled in the molecular dynamics calculation are inconsistent with the system being in equilibrium at that temperature. It should again be noted that the Monte Carlo method generates configurations representative of the appropriate temperature, and that identical average properties should be derived from the molecular dynamics simulations if they are in equilibrium at the same state point. For the simulations performed with a switching function, the molecular dynamics and Monte Carlo calculations gave identical potential energies, and moreover the temperature of molecular dynamics simulation was 298 K, as specified by the temperature coupling algorithm. Thus despite the objections raised concerning the use of switching functions, a molecular dynamics simulation performed with this method is in thermal equilibrium.

The radial distribution functions (RDFs) for the Monte Carlo and molecular-dynamics simulations (data not presented) are almost indistinguishable, suggesting that the structure of the fluid as monitored by the RDFs is insensitive to the choice of simulation procedure.

In Figure 1, the dipole-dipole correlation functions, defined in equation (8), for the molecular dynamics and Monte Carlo simulations performed without a switching function are presented.

$$\langle \cos\theta(r)\rangle = \boldsymbol{\mu}_i\cdot\boldsymbol{\mu}_j/|\boldsymbol{\mu}_i||\boldsymbol{\mu}_j| \tag{8}$$

$\boldsymbol{\mu}_i$ and $\boldsymbol{\mu}_j$ are the dipole moments of molecules $i$ and $j$ separated by a distance $r$, and $\langle\cos\theta(r)\rangle$ is the mean value of $\cos\theta(r)$, where $\theta(r)$ is the angle between the dipole moment vectors of molecules $i$ and $j$. The distance $r$ is calculated on the same basis as the nonbonded cutoff. The data were accumulated in histograms bins of width 0.1 Å. The correlation functions obtained from the Monte Carlo simulations show discontinuities at the value of the nonbonded cutoff, consistent with simulation results reported for other systems [13, 52, 53]. The correlation functions for the molecular

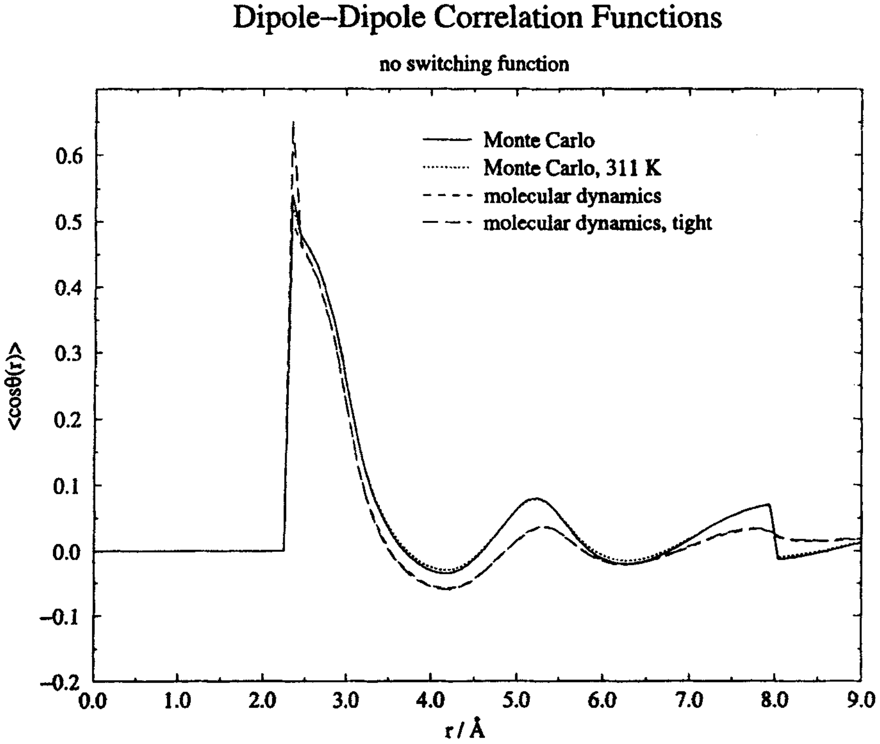

FIGURE 1 Dipole-dipole correlation functions for 216 TIP3P water molecules. Simulations performed without a switching function.

dynamics simulations show a subtle step at the value of the nonbonded cutoff, again consistent with literature results on other systems [14,43], but clearly different from the Monte Carlo results, irrespective of simulation temperature. Thus on the basis of both thermodynamic and structural behaviour, the molecular dynamics and Monte Carlo simulation procedures do not yield identical results with an abrupt nonbonded cutoff; the orientational correlation functions are particularly sensitive. In Figure 2 the dipole-dipole correlation functions obtained for the simulations using the switching function are presented; the results are virtually identical, showing a smooth step in the function at the cutoff distance; this is again consistent with other literature results [14]. The largest difference is at the shortest contact distance and is a consequence of poor convergence; the number of intermolecular contacts observed at this distance is very small and the statistical uncertainty is consequently high. Moreover, the correlation functions for

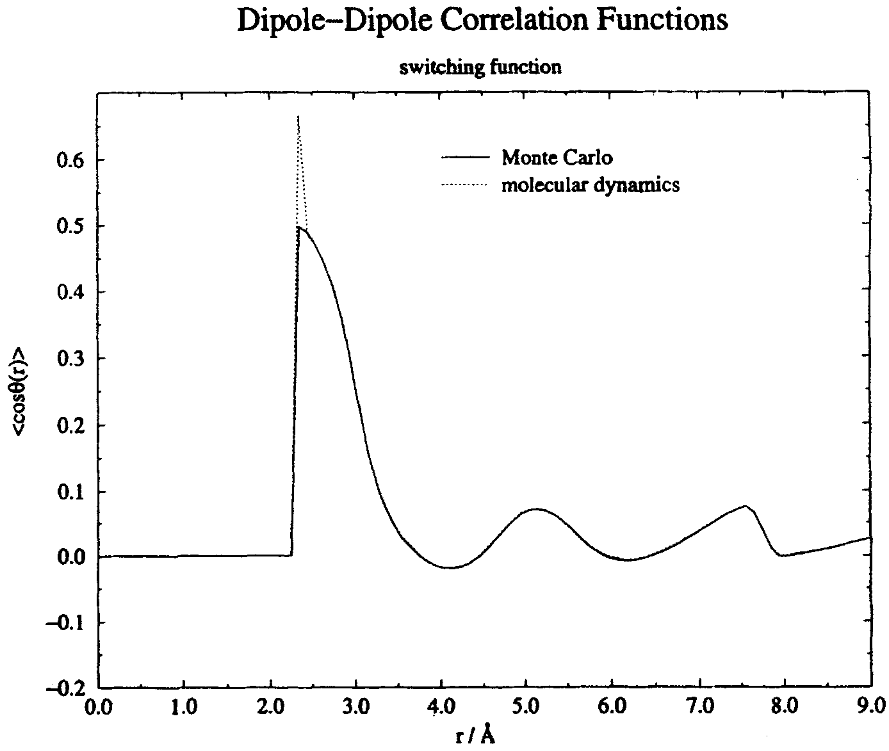

FIGURE 2 Dipole-dipole correlation functions for 216 TIP3P water molecules. Simulations performed with a switching function.

the Monte Carlo simulations are better converged than those of the molecular dynamics calculations because coordinate sets were analysed more frequently in the former.

In Table I, the values of $G_k$ obtained from the simulations are presented. The quoted statistical uncertainties correspond to standard errors on the batch averages of either 50 M Monte Carlo configurations, or 200 ps of molecular dynamics. Also presented are the dielectric constants calculated from these values using equation (5). The Monte Carlo and molecular dynamics simulations performed using the switching functions gave dielectric constants that are identical to within simulation error. Combining these two results gives a value of $133 \pm 4$. The simulations performed without a switching function gave values for $\varepsilon_r$ that are consistently lower than this value. The standard errors suggest that these differences are statistically significant, and inspection of data in other work confirms this observation [14]. The results also suggest that the simulations using molecular dynamics without a switching function give dielectric constants that are smaller than the equivalent result obtained using the Monte Carlo procedure. In Table II, the dielectric constants calculated using the polarisation method are presented; Monte Carlo simulations conducted with and without the switching function give values for $\varepsilon_r$ that are identical to within error. Furthermore, these data agree with the Monte Carlo result obtained using the fluctuation formula with abrupt truncation, to within error, but not the molecular dynamics result. Combining these three results gives a value for the static dielectric constant of the TIP3P water model of $102 \pm 3$. These data suggest firstly, that molecular dynamics and Monte Carlo simulations with abrupt truncation of nonbonded interactions do not yield identical values of $\varepsilon_r$, and that this is a consequence of the discontinuity at the cutoff boundary. Secondly, although molecular dynamics and Monte Carlo simulations yield identical results when a switching function is used, the calculated value of $\varepsilon_r$ obtained using the fluctuation formula is significantly higher than that observed using the polarisation

TABLE II Observed polarisation, $\langle \mathbf{P} \rangle$, and calculated static dielectric constant, $\varepsilon_r$, for 216 TIP3P water molecules

| *Switch*[a] | *Temp/K* | $\langle \mathbf{P} \rangle \times 10^{-8}/Vm^{-1}$ | $\varepsilon_r$ |
|---|---|---|---|
| no | 298.15 | $7.72 \pm 0.16$ | $98.0 \pm 2.0$ |
| yes | 298.15 | $7.94 \pm 0.28$ | $100.8 \pm 3.6$ |

[a] "yes" or "no" indicates whether or not the switching function, equation 3, is implemented.

method, or the fluctuation method with abrupt truncation. This effect has been alluded to elsewhere [14].

In Figure 3, the radial decomposition of $G_k$, as defined in equation (9), is presented for a single representative batch of the simulations performed without the switching function.

$$G_k(r) = \frac{\sum_{r_{ij} \leq r_c} \langle \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j \rangle}{N\mu^2} \tag{9}$$

The Monte Carlo simulations show peaks in $G_k(r)$ at the value of the nonbonded cutoff that are absent from the molecular dynamics calculations. In Figure 4, the equivalent data are presented for one batch of the simulations using the switching function; the general shape of the curve is independent of the simulation procedure, and shows a small peak at the

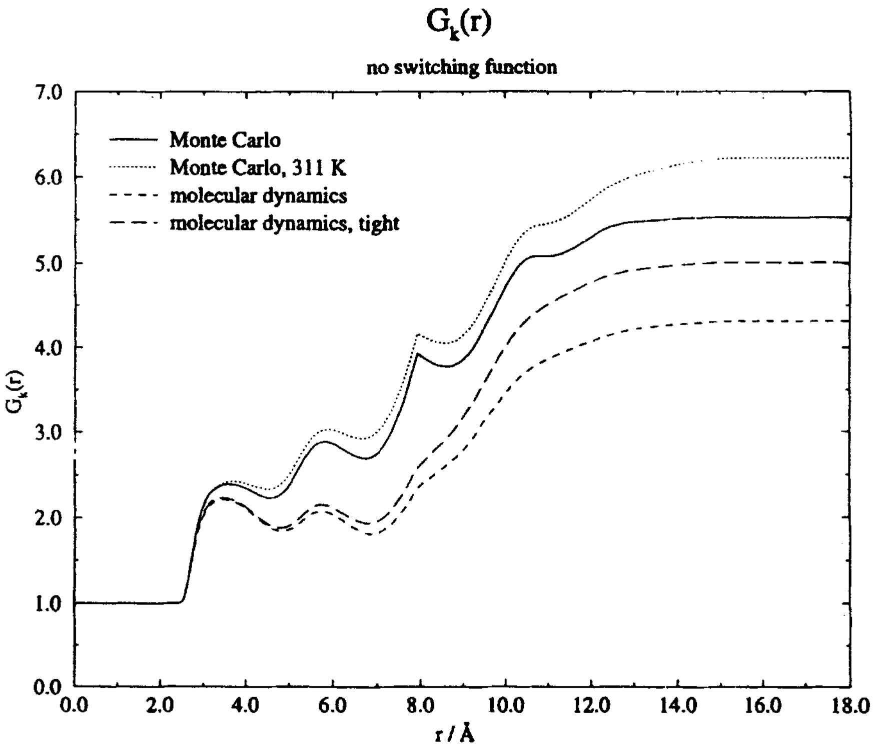

FIGURE 3 $G_k(r)$ for 216 TIP3P water molecules. Simulations performed without a switching function.

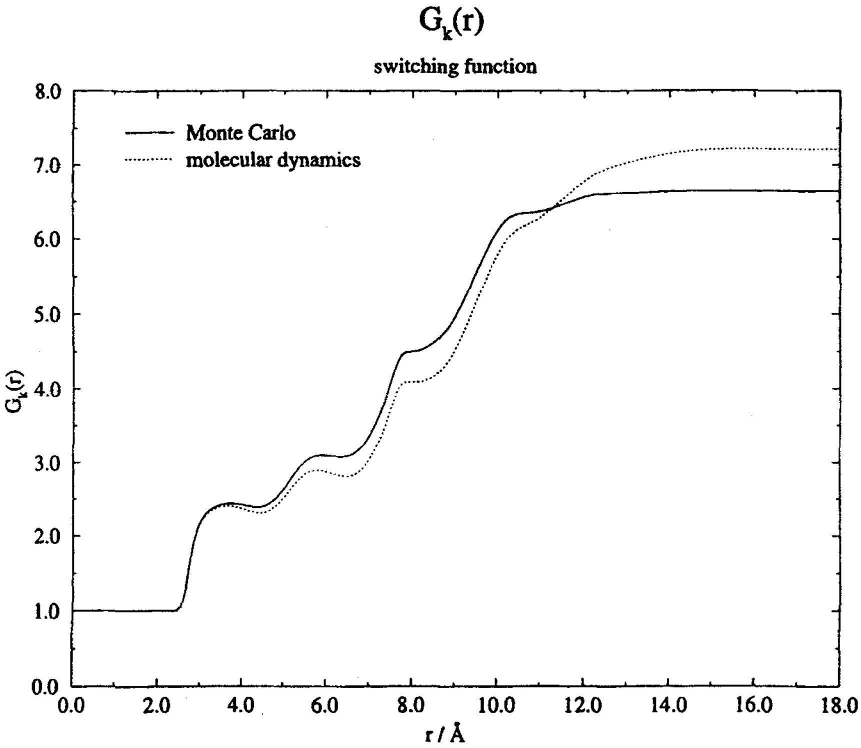

FIGURE 4 $G_k(r)$ for 216 TIP3P water molecules. Simulations performed with a switching function.

nonbonded cutoff. These curves are plotted to distances larger than half the box length, but the minimum image convention is never violated *i.e.* each intermolecular pair is only counted once.

These results suggest that the application of a conventional truncation of the nonbonded interactions, in conjunction with a reaction field treatment of the long-range electrostatic interactions, results in a molecular dynamics trajectory that is not in thermal equilibrium. This has a subtle effect on the system energetics, but a profound influence on orientational correlations and the dielectric constant. Use of a switching function results in identical thermodynamic and structural averages between molecular dynamics and Monte Carlo simulations, but the use of the fluctuation procedure results in values of $\varepsilon_r$ that are significantly higher than that obtained with either the polarisation method, or the fluctuation method with abrupt truncation. To calculate $\varepsilon_r$ using a reaction field treatment of long-ranged electrostatics, these results suggest that Monte Carlo simulations can be used with abrupt truncation and either the fluctuation or polarisation methods, or with a switching function and the polarisation method. For molecular dynamics, however, a switching function should be used otherwise the system is not in thermal equilibrium, and then only with the polarisation procedure.

In Table III, the thermodynamic data obtained from the simulations using 267 TIP3P water molecules with a 10.0 Å nonbonded cutoff are presented. The molecular dynamics simulation performed without the switching function ran with a temperature of 303 K. This is higher than that specified by the temperature scaling algorithm, but lower than the value obtained for the smaller simulation system. This is as expected given the decrease in the surface area to volume ratio of the cutoff sphere on increasing the cutoff radius. The behaviour of the average potential energies per molecule are identical to that observed for the 216 water molecule system; simulations conducted with the switching function are virtually identical, whereas those performed using the abrupt cutoff are not. In Figure 5, the dipole-dipole correlation functions as defined in equation (8) are presented. As observed for the 216 molecule system, the Monte Carlo simulations performed without the switching function show a discontinuity at the nonbonded cutoff; the equivalent molecular dynamics results show a subtle step at this distance. The results obtained from the simulations using the switching function are virtually identical; the large difference at the shortest contact distance is again due to poor convergence. In Table III, the values of $G_k$ obtained from the simulations are presented, together with the dielectric constants calculated using equation (5). The quoted statistical uncertainties are standard errors on batch averages of either 50 M Monte Carlo configurations, or 200 ps of molecular dynamics. The results obtained from the

TABLE III Thermodynamic properties of the 267 TIP3P water-molecule system

| *Simulation method*[a] | *Switch*[b] | *Temp*[c]*/K* | $E^d/kcal mol^{-1}$ | $G_k$ | $\varepsilon_r(298.15\ K)$ | $\varepsilon_r(303\ K)$ |
|---|---|---|---|---|---|---|
| MC | no | 298.15 | $-9.61 \pm 0.00$ | $5.89 \pm 0.31$ | $110 \pm 6$ | – |
| MC | yes | 298.15 | $-9.59 \pm 0.00$ | $5.57 \pm 0.21$ | $104 \pm 4$ | – |
| MD | no | 303 | $-9.51 \pm 0.00$ | $5.11 \pm 0.15$ | – | $94 \pm 3$ |
| MD | yes | 298 | $-9.60 \pm 0.00$ | $5.94 \pm 0.23$ | $111 \pm 4$ | – |

[a] MC denotes a Monte Carlo simulation, MD denotes a molecular dynamics simulation. [b] "yes" or "no" indicates whether or not the switching function, equation (3), is implemented. [c] For the Monte Carlo simulations, the specified simulation temperature is given; for the molecular dynamics simulation, the average simulation temperature is given. [d] Includes the self-interaction energy of an individual dipole in its own reaction field.

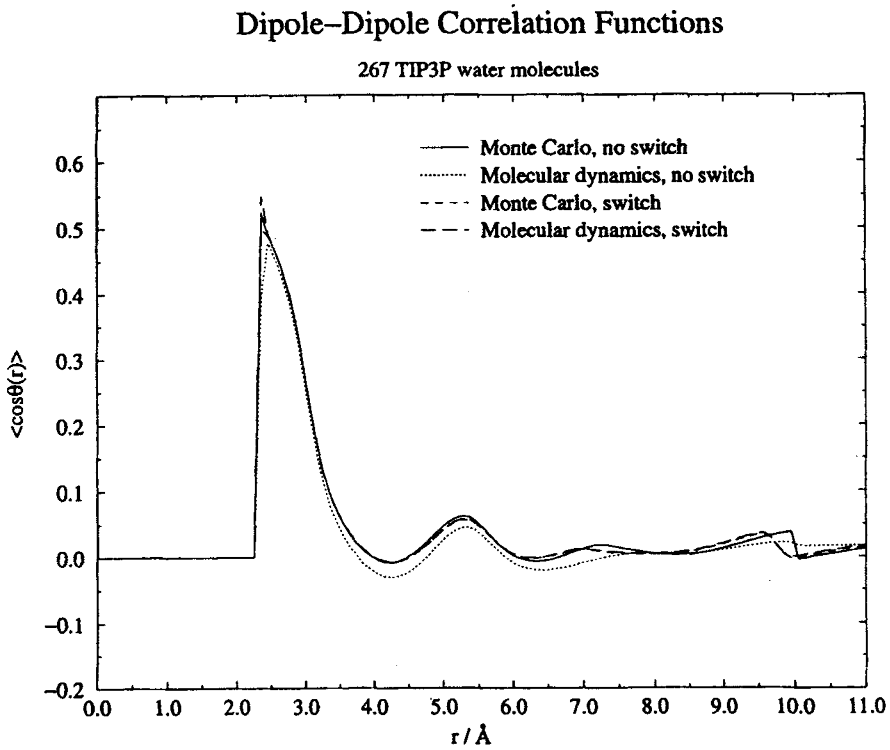

FIGURE 5 Dipole-dipole correlation functions for 267 TIP3P water molecules.

Monte Carlo and molecular dynamics simulations using the switching function agree to within error, and give an average dielectric constant of 108 ± 3. It is noticeable that this is significantly smaller than the value determined for the 216 molecule system under identical conditions, namely 133 ± 4. These results suggests that increasing the system size reduces the influence of the switching function on the calculated dielectric constant. The dielectric constant calculated from the molecular dynamics simulation performed without a switching function is again smaller than the equivalent Monte Carlo result, but larger than that obtained from the simulation conducted using 216 molecules. This is expected since the perturbing influence of the abrupt truncation of nonbonded interactions will decrease as the cutoff increases. Finally, the dielectric constant derived from the Monte Carlo simulation performed without a switching function agrees with the equivalent result obtained from the 216 molecule system to within error.

## CONCLUSION

The behaviour of the popular TIP3P water model has been investigated using both the molecular dynamics and Monte Carlo simulation procedures to determine the reliability of the reaction field treatment of long-range electrostatic interactions as applied to the calculation of dielectric constants. Nonbonded interactions were either truncated at the cutoff distance, or smoothly scaled to zero using a switching function. The results reported in this paper suggest the following:

1. Molecular dynamics calculations performed without a switching function do not give a simulation trajectory consistent with the simulation temperature. Energy-pumping effects distort the dipole-dipole correlation function, and decrease the magnitude of the calculated dielectric constant. In light of this conclusion, dielectric constants calculated using this protocol should be reappraised. The effect of abrupt truncation of the nonbonded interactions on $\varepsilon_r$ decreases with increasing cutoff, so that use of a large simulation system is a solution to this problem, albeit an unsatisfactory one from a computational viewpoint.
2. Use of a switching function yields identical thermodynamic averages between the Monte Carlo and molecular dynamics simulation methods, but dielectric constants calculated using the fluctuation procedure are larger than those obtained by other methods. The effect of the switching function decreases with increasing cutoff, so that use of a large simulation system is again a solution.
3. In light of these results, dielectric constants calculated using the fluctuation method are best obtained from Monte Carlo simulations without a switching function. The calculated dielectric constants are much less sensitive to system size, and are consistent with the results obtained using the polarisation method.
4. It has been reported in the literature that dielectric constants calculated using the reaction field treatment of long-range electrostatic interactions are more sensitive to the choice of nonbonded cutoff than those obtained using the Ewald method [36]. The simulations upon which this conclusion are based were molecular dynamics calculations performed without a switching function, and it is therefore possible that this observed sensitivity arises from the energy pumping effects described above. Indeed, it is notable that the dielectric constants calculated from the Monte Carlo simulations presented here are not sensitive to

the nonbonded cutoff if abrupt truncation of the nonbonded interactions is used.

5. It has also been reported in the literature that the reaction field procedure yields dielectric constants that are significantly smaller than those obtained using an Ewald approach [35]. This conclusion was derived from molecular dynamics simulations with an abrupt nonbonded cutoff, and this observation may therefore be due to energy pumping effects in the molecular dynamics simulations, rather than to any intrinsic problem with the reaction field approach.
6. The simulations reported here have allowed the dielectric constant of the popular TIP3P water model to be estimated. The most reliable value obtained at 298 K is 102 ± 3. The result reported here is unexpected in that the dielectric constants of other water models of this generation are generally smaller than the experimental value of roughly 80 [52]. To the author's knowledge, only three other values for this property have been reported in the literature. Chipot *et al.* [17] report a dielectric constant of 96, although they do not consider their result to be reliably converged. The second value of 69 was also obtained form a short simulation [41]. The third reported value is derived from simulations on a water droplet, giving a value of 82 ± 5 [54]. However, the boundary conditions used were not identical to those applied here, *i.e.* periodic boundary conditions were not used, and furthermore the Charmm implementation of TIP3P was used in which Lennard-Jones parameters are added to the water hydrogen-atoms [55]. The TIP3P water model was therefore not implemented in its original form. Given these differences, the lack of agreement between the value given here and that reported in reference 54 is not surprising.

In this paper, it has been demonstrated that the Monte Carlo simulation procedure offers a number of intrinsic advantages over molecular dynamics for the calculation of dielectric constants with a reaction field treatment. Furthermore, in the course of this work it has proved possible to suggest explanations for a number of statements made in the literature concerning the reliability of the reaction field procedure in the calculation of dielectric constants. In particular, the previously noted sensitivity of dielectric constants to the nonbonded cutoff when calculated using a reaction field [36,41] may be ascribed to energy pumping in the molecular dynamics simulations, rather than to any intrinsic problem with the reaction field itself. In light of the results presented here, it appears that the reaction field method can be used in conjunction with the Monte Carlo simulation method with some confidence.

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