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Efficient Ewald electrostatic calculations for large systems

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Abstract

A method is described which improves the efficiency of Ewald simulations of large condensed phase systems. This is achieved by partitioning the real space sum into a short and long range component. The long range component is calculated every time the pair list is generated and included in subsequent steps using a multiple time step algorithm. The corresponding increase in the effective cutoff distance results in an algorithm which is only slightly more expensive than a traditional cutoff simulation, but with fewer artifacts than obtained using a cutoff. The method is tested on a 1.0 M solution of sodium chloride.

Keywords: Cutoffs; Saline solutions; Long range forces; Molecular dynamics; Computer simulations

1. Introduction

The Ewald Summation method is a well-established technique for the evaluation of electrostatic interactions required for many computer simulations [1]. While the Ewald technique does much to improve the reliability of many simulation results [2], the method is often dismissed as impractical, especially in the area of large scale biomolecular simulations. Although many studies have shown that the use of a cutoff or switching function for the truncation of electrostatic interactions produces artifacts in both radial distribution functions and dipole–dipole correlations within the system [2,3], the Ewald technique removes or substantially decreases such unwanted artifacts [4]. However, even though biomolecular systems often contain many isolated charged residues/groups, which could make the simulation results sensitive to the method of truncation, the application of the Ewald technique to biomolecules has been limited to fewer studies [5,6].

There are at least three basic objections to the Ewald

technique. The first is complexity. The Coulomb potential is transformed into a series of terms which are not as physically transparent as the classical electrostatic potential. The choice of a convergence parameter and the number of lattice vectors to be included in the sum are system dependent, and therefore have to be determined separately for each new system [7].

The second objection concerns the lattice nature of the Ewald summation. As a consequence of determining the electrostatic potential corresponding to a series of replicated central cells several problems may arise. Large permanent or fixed multipoles present in the system will generate large fields within the simulation cell. Unfortunately, due to the presence of the surrounding images, these fields may not be representative of those typical for an infinite medium (the usual goal for liquid state simulations) [8]. Hence, one can experience artifacts due to the “enhanced” periodicity of the system. For simple fluids with no permanent multipole moments this is not a problem, but for biomolecular systems where a peptide or protein

may possess a significant unscreened charge, dipole moment, etc., this may be a cause for concern. Alternatively, one could argue that the “enhanced” periodicity is a direct consequence of invoking periodic boundary conditions, and not due to the Ewald technique per se, and is therefore simply a finite system effect. The determining factor is the effective screening length of the medium. If the central cell is large in comparison with the screening length of the medium, “enhanced” periodicity effects should be small.

Last, and often most damaging, is the extra computational expense involved in using the Ewald summation technique. Typically, the Ewald technique scales as $N^{3/2}$ (N , number of sites) rather than N and is roughly twice as expensive as a traditional cutoff simulation for a few hundred particles. For small systems, e.g. a few hundred atom simple fluid, the additional expense is not too severe. However, for biomolecular systems, where the number of atoms may be in the tens of thousands, the Ewald technique turns an already expensive simulation into a nearly infeasible one. Hence the reluctance to use Ewald methods. Here we describe a simple method which helps to significantly reduce the computational expense involved in simulating larger systems. The method has features of the twin range technique of van Gunsteren and Berendsen [9], and the multiple time scale method of Tuckerman et al. [10]. The method was tested on a 1.0 M sodium chloride salt solution system.

2. Theory

The Ewald electrostatic potential energy of a periodic system of N charges ($\{q\}$) with a total charge of Q in a cubic box of length L surrounded by a dielectric continuum of relative permittivity ∞ is given by [11,12]

$$V = \frac{1}{4\pi\epsilon_0} \left[\sum_{i<j}^N \frac{q_i q_j}{|r_{ij}|} \operatorname{erfc}(\alpha|r_{ij}|) + \frac{1}{2\pi L} \sum_{|n| \neq 0} \frac{e^{-\pi^2|n|^2/(\alpha^2 L^2)}}{|n|^2} \left| \sum_{j=1}^N q_j e^{-2\pi i n \cdot r_j / L} \right|^2 \right]$$

$$+ \frac{2\alpha}{\sqrt{\pi}} \sum_{i<j}^N q_i q_j - \frac{\alpha Q^2}{\sqrt{\pi}} - \frac{\pi Q^2}{2\alpha^2 L^3} \Bigg], \quad (1)$$

where erfc is the complementary error function,

$$\operatorname{erfc}(x) = 1 - \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2} dt, \quad (2)$$

with $r_{ij} = r_j - r_i$, and r_i is the position of atom i . Here we have assumed that the value of the convergence parameter α has been chosen such that the first term on the r.h.s. of Eq. (1) is negligible beyond a certain cutoff radius R_C , which is less than $L/2$. The summation over $n = (n_x, n_y, n_z)$ represents a sum over images of the central cell in three dimensions (n_α , $\alpha = x, y$ or z are integers with $|n_\alpha| \leq n_{\max}$).

From experience we have found that the optimal value of α is one which ensures that the cost of performing the real space (first term of Eq. (1)) and reciprocal space (second term of Eq. (1)) sums are equally balanced. This is feasible for relatively small systems ($L < 2.5$ nm). For larger systems, e.g. a fully solvated protein, the equal balance condition can only be maintained by increasing R_C . In order to do this one requires the use of very large pair lists which result in heavy memory demands. Hence, the value of R_C is limited to values of 1.0–1.2 nm or so, depending on the density of the system. As the system size is increased, αL also increases, and more images are required for the reciprocal space sum to converge. Unfortunately, the number of reciprocal lattice vectors to be included increases rapidly ($\propto |n|^3$), and the sum quickly becomes too expensive.

To solve this problem we introduce a second “effective” cutoff, R_E , which is always larger than R_C and typically equal to $L/2$. The forces arising from atoms situated between R_C and R_E are calculated every time the pair list is updated. This is the twin range method of van Gunsteren and Berendsen [9], and assumes that the long range contribution from these distant atoms varies slowly with time and therefore does not need to be evaluated at every time step. To include the long range contribution during the simulation we have used the multiple time step algorithm of Tuckerman et al. [10]. Hence, the real space sum can be effectively extended to $L/2$, requiring a smaller α , which in turn requires the inclusion of fewer lattice vectors in the

reciprocal space sum. The only problem with this approach is that the system has somewhat worse energy conservation properties and coupling to a temperature bath may be desirable for long runs.

3. Method

Simulations of an aqueous sodium chloride solution were performed using the CHARMM force field for sodium and chloride ions and the TIP3P water model [13]. The system was prepared as follows. Using a pre-equilibrated box of length 2.477 nm containing 512 TIP3P waters, 18 water molecules were replaced at random with 9 sodium and 9 chloride ions. The system was then relaxed with 50 steps of steepest descent minimization. This system was then equilibrated at 300 K for 100 ps in the NVE ensemble using values of $\alpha = 2.5 \text{ nm}^{-1}$, $R_C = 1.2 \text{ nm}$, $R_E = 1.2 \text{ nm}$ and $n_{\text{max}} = 6$. During this time velocities were reassigned to 300 K every 0.1 ps. The final configuration was then replicated once in each direction. The resulting system contained a total of 12000 atoms from 3952 waters, 72 sodiums and 72 chlorides in a cubic box of length $L = 4.9554 \text{ nm}$. This system was then equilibrated for 10 ps using values of $\alpha = 3.0 \text{ nm}^{-1}$, $R_C = 1.0 \text{ nm}$, $R_E = 1.0 \text{ nm}$ and $n_{\text{max}} = 17$.

Six different simulations were then performed. The six simulations differed only in the manner in which the electrostatic interactions were evaluated. The exact parameters used are given in Table 1. Simulations with $\alpha = 0.0$ correspond to the traditional Coulomb potential. For the twin range simulations the distinction between short and long range interactions was determined on a group basis [14], i.e. if a water oxygen atom was found within R_C the corresponding water hydrogens were also included in the short range interaction, irrespective of whether they lay beyond R_C or not. Each simulation consisted of a further 10 ps of equilibration, using the respective parameters, during which velocities were reassigned at 300 K every 0.1 ps. Production runs of 10 ps were then performed in the NVT ensemble with temperature regulation achieved using the extended system method of Nosé [15] and a “mass” of 100 kJ/mol ps^2 for the temperature variable. All simulations used a time step of 2 fs and the SHAKE algorithm [16] to constrain all bonds and angles. The nonbond update frequency was 20 fs. Con-

figurations were saved every 20 fs for analysis. All averages, radial distribution functions, diffusion constants and dipole correlations were calculated from the last 10 ps of simulation.

The reciprocal space sum evaluated during the Ewald calculations requires many sine and cosine function calls. These are traditionally expensive function calls. Hence, we have replaced these calls with sine and cosine tables which result in a significant computational advantage. By Taylor expansion one obtains the following interpolation formulas:

$$\begin{aligned}\cos(x + dx) &= (1 - 1/2dx^2) \cos x - dx \sin x \\ &\quad + O(dx^3), \\ \sin(x + dx) &= (1 - 1/2dx^2) \sin x + dx \cos x \\ &\quad + O(dx^3),\end{aligned}\quad (3)$$

which, for a grid spacing of 5×10^{-4} radians, gives an accuracy of greater than 10^{-10} .

4. Results

In order to determine the accuracy of the new method we have compared results obtained for both the twin range Ewald and twin range Coulomb simulations with those obtained from a full Ewald simulation. This, of course, assumes that the Ewald simulation gives the “correct” picture of the structure and dynamics for the system of interest. As there is evidence which suggests that simulations using a Coulomb potential truncated at R_C tend, for most properties of interest here, to converge to the corresponding Ewald results as R_C increases, we believe this is the most objective comparison. Hence, all results are compared with simulation 1 (see Table 1).

Table 1 contains the simulation results obtained for the sodium chloride solution. Unfortunately, direct comparison of the interaction energies is complicated by the reciprocal space energy which does not distinguish between interaction pairs (in the form given in Eq. (1)). One can see that the introduction of a sine/cosine table lookup procedure (simulation 2) gave identical results compared with a simulation using the respective intrinsic functions as expected, but with a significant decrease in execution time. The large diffusion constant observed for water is also ob-

Table 1
Molecular dynamics results^a

	1	2	3	4	5	6
Electrostatics	Ewald	Ewald	Ewald	Coulomb	Ewald	Coulomb
α (nm ⁻¹)	3.0	3.0	1.2	0.0	1.2	0.0
R_C (nm)	1.0	1.0	1.0	1.0	1.2	1.2
R_E (nm)	1.0	1.0	L/2	L/2	L/2	L/2
n_{\max}	17	17	6	0	6	0
lookup tables ^b	N	Y	Y	N	Y	N
H	-194879	-194805	-195162	-190290	-195464	-187943
V_{vv}	-139562	-139704	-128232	-120915	-128178	-122616
V_{vi}	-49324	-48980	-72072	-75433	-73539	-74719
V_{ii}	-37186	-38317	-25014	-24049	-23896	-20711
V_k	1092	1095	54	0	51	0
P (atm)	-681	-639	-893	-861	-931	-596
$D_{H_2O} \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$	5.0	4.9	4.0	2.9	5.0	3.4
$D_{Na} \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$	2.2	2.3	1.6	1.1	2.1	1.3
$D_{Cl} \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$	2.0	2.3	1.6	1.3	2.3	1.7
relative speed ^c	1.64	1.00	0.40	0.33	0.45	0.36

^a Energies in kJ/mol. H = total energy, V_{vv} = solvent potential energy, V_{vi} = solvent-ion potential energy, V_{ii} = ion-ion potential energy and V_k = reciprocal space potential energy. D is the diffusion constant.

^b Sine/cosine functions evaluated using lookup tables.

^c Determined for a Cray C90. Execution time for simulation 2 is 13.3 s per step.

served for pure water simulations using Ewald electrostatics (data not shown) and is probably a feature of the truncation method. The low pressures observed for this system are a reflection of the electrostriction effects of the ions.

The short cutoff twin range methods using $R_C = 1.0$ nm and $R_E = L/2$ result in substantial computational savings (simulations 3, Ewald, and 4, Coulomb, in Table 1). However, the results are not satisfactory. In particular, the diffusion constants were reduced, especially for the Coulomb potential (simulation 4). On increasing R_C to 1.2 nm, the twin range Ewald technique (simulation 5) was in excellent agreement with the target simulation, however, the Coulomb technique (simulation 6) still displayed significantly reduced diffusion rates. It is unlikely that the diffusion rates for the Coulomb technique would converge with increasing R_C before memory demand became excessive.

Radial distribution functions are not presented here as the ion-ion distributions are not statistically meaningful, while the ion-solvent and solvent-solvent distributions did not display statistically significant differences as expected. However, differences were ob-

served for the orientation of water dipoles within the system. We define two spatial dipole correlation functions, the first representing the orientation between a water dipole and the ion-water intermolecular vector,

$$C_{r\mu}(r) = \left\langle \frac{(\mathbf{r}_{Na} - \mathbf{r}_O) \cdot \boldsymbol{\mu}}{|\mathbf{r}_{Na} - \mathbf{r}_O| |\boldsymbol{\mu}|} \right\rangle_r, \quad (4)$$

and the second representing the orientation between water dipoles as function of their separation,

$$C_{\mu\mu}(r) = \left\langle \frac{\boldsymbol{\mu} \cdot \boldsymbol{\mu}}{|\boldsymbol{\mu}|^2} \right\rangle_r. \quad (5)$$

Here, $\boldsymbol{\mu}$ represents the orientation of the water dipole and the angular brackets denote an ensemble average for a particular value of r . For our purposes it is more convenient to monitor differences from simulation 1. Hence, we define $\Delta C_{r\mu}(r)$ and $\Delta C_{\mu\mu}(r)$ as the differences between the corresponding function obtained for a particular simulation, and that obtained for simulation 1.

Figs. 1–3 shows the sodium-water, chloride-water and water-water dipole orientations, respectively. All three figures display the same trends between the

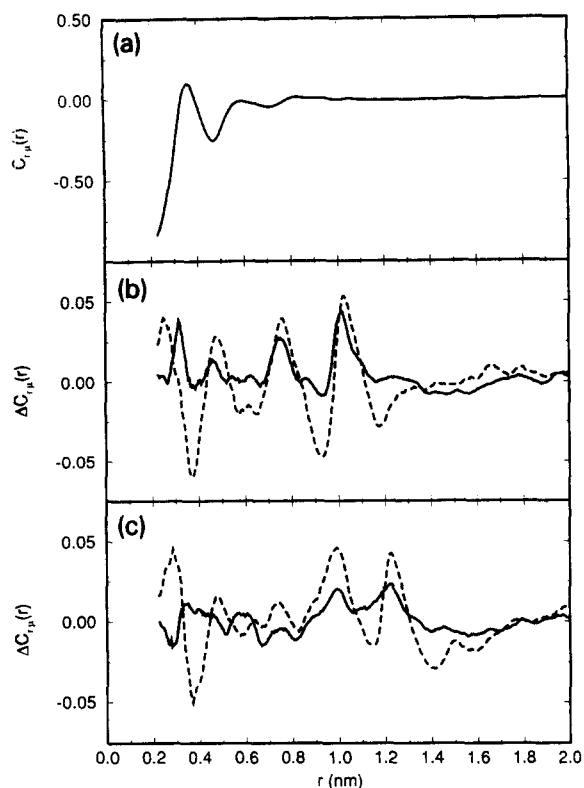


Fig. 1. (a) $C_{r\mu}(r)$ for water dipoles as a function of distance from a Na^+ ion obtained from simulation 1. (b) $\Delta C_{r\mu}(r)$ for the modified Ewald procedure (solid line, simulation 3) and the Coulomb potential (dashed line, simulation 4) using a value of $R_C = 1.0$ nm. (c) $\Delta C_{r\mu}(r)$ for the modified Ewald procedure (solid line, simulation 5) and the Coulomb potential (dashed line, simulation 6) using a value of $R_C = 1.2$ nm.

different simulation procedures. The difference plots show that for values of $R_C = 1.0$ nm and $R_E = L/2$, both the twin range Ewald and Coulomb techniques displayed artifacts associated with the discontinuity in the force at R_C . Especially apparent are the nodes which appear at, or around, R_C [2,17]. The Coulomb technique also exhibited more oscillatory behaviour which persisted at long distances. This is more significant due to the increasing number of waters present at larger distances. For the simulations with $R_C = 1.2$ nm and $R_E = L/2$, the twin-range Ewald technique displayed only small artifacts while the Coulomb technique improved only marginally, in accordance with the trends observed for the diffusion constant results.

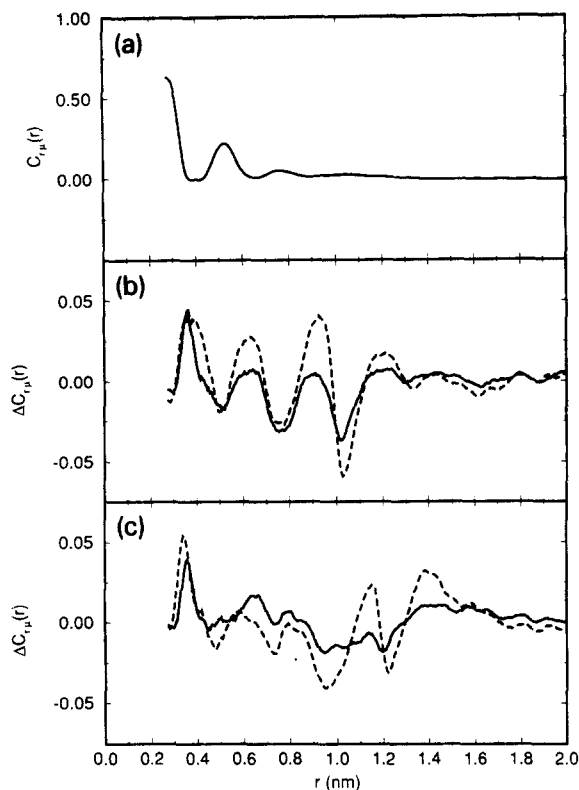


Fig. 2. (a) $C_{r\mu}(r)$ for water dipoles as a function of distance from a Cl^- ion obtained from simulation 1. (b) $\Delta C_{r\mu}(r)$ for the modified Ewald procedure (solid line, simulation 3) and the Coulomb potential (dashed line, simulation 4) using a value of $R_C = 1.0$ nm. (c) $\Delta C_{r\mu}(r)$ for the modified Ewald procedure (solid line, simulation 5) and the Coulomb potential (dashed line, simulation 6) using a value of $R_C = 1.2$ nm.

5. Conclusions

The cost of performing traditionally expensive simulations of large liquid state systems can be substantially reduced by separating the real space summation into a short range and long range component and using a multiple time step algorithm. The increased effective cutoff decreases the number of lattice vectors which need to be evaluated making the twin range Ewald technique only a third more expensive than a traditional Coulomb simulation. It appears that for values of $R_C \geq 1.2$ nm that the artifacts associated with the discontinuity at R_C are eliminated, as illustrated by the corresponding diffusion rates and dipole-dipole correlations. This is not true for Coulomb simulations with a value of $R_C = 1.2$ nm.

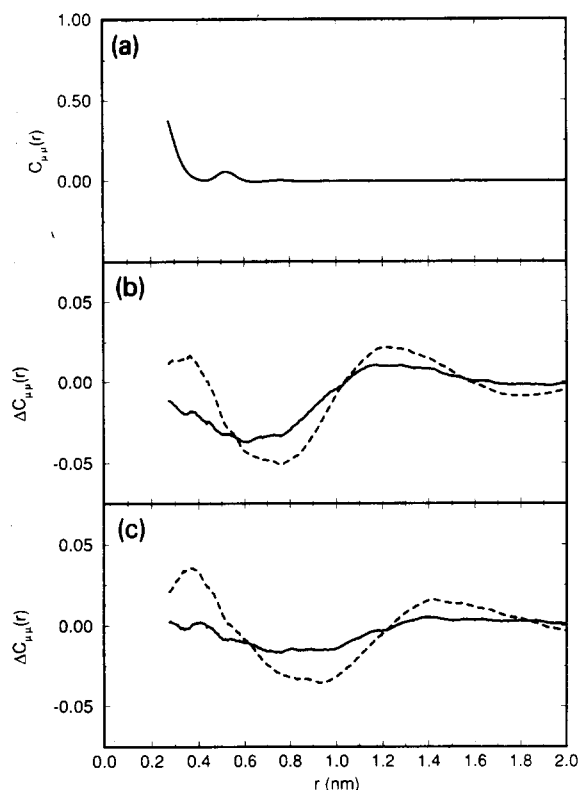


Fig. 3. (a) $C_{\mu\mu}(r)$ for water dipoles as a function of the separation of water molecules obtained from simulation 1. (b) $\Delta C_{\mu\mu}(r)$ for the modified Ewald procedure (solid line, simulation 3) and the Coulomb potential (dashed line, simulation 4) using a value of $R_C = 1.0$ nm. (c) $\Delta C_{\mu\mu}(r)$ for the modified Ewald procedure (solid line, simulation 5) and the Coulomb potential (dashed line, simulation 6) using a value of $R_C = 1.2$ nm.

The ability to simulate large systems with the increased accuracy that the Ewald technique provides, and with a negligible increase in expense compared with a traditional simulation, will enhance the usefulness of the technique. Correspondingly, this will enable the study of larger systems which will help to eliminate potential “enhanced periodicity” effects.

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Note added in proof

While in press the following article appeared which has a similar algorithm: T. Forester and W. Smith, *Mol. Simul.* 13 (1994) 195–204.

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