A simple test for evaluating the truncation effects in simulations of systems involving charged groups

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Abstract

We report the results from a molecular dynamics (MD) simulation on a 1.0 M aqueous NaCl solution using the classical SPC water model and a treatment of long-range electrostatic forces involving a 9–16 Å twin-range cut-off. This study was undertaken to explore the importance of truncation effects in simulations involving charged species which employ cut-offs at longer range than typically used in MD. Artefacts were discerned in the ion–ion radial distribution functions at \( \approx 16 \) Å, indicating that increasing the length scale of the truncation scheme does not necessarily lead to reliable trajectories. Our results indicate that ‘charge group–charge group’ radial distribution functions are a sensitive test for the detection of artefacts due to truncation and it is suggested that they should be used as a routine screening device in the analysis of MD systems involving charged groups.

The treatment of long-range forces in molecular dynamics simulations is a subject of considerable interest. One widely used technique is the use of ‘cut-offs’, i.e. truncation of the Coulomb forces beyond a certain threshold, with or without additional shifting or switching functions [1,2], since avoiding the computation of numerous, supposedly inconsequential, interactions should result in an obvious cost-saving strategy in a computationally intensive undertaking. Artefacts generated by the utilization of these truncation methods at short range (7.5–9.5 Å) have recently been documented [3–7] and have suggested the use of longer-range cut-offs [8,9], or alternative strategies such as Ewald sums [1,2]. The problems associated with truncation of the potential affect especially interactions involving charged groups, and will manifest themselves particularly in ionic systems. We report herein the analysis of a molecular dynamics simulation on a 1.0 M aqueous NaCl solution using truncations of a longer range than previously reported.

Molecular dynamics simulations were carried out on a system of 29 Na\(^+\) cations, 29 Cl\(^-\) anions and 1531 water molecules in a 36 Å side cubic cell treated under periodic boundary conditions using the program GROMOS87 [10]. The force field utilizes the SPC model for water [11] and van der Waals parameters given by Åqvist [12] for Na\(^+\) and Rao and Singh [13] for Cl\(^-\). The truncation scheme employed here is a 9–16 Å twin-range cut-off [2]. In this method, short-range interactions are calculated at each step of the simulation, whereas interactions at longer distance are only calculated at each update of the non-bonded pair list and kept constant up to the
next update. The justification for this time saving method is that interactions at long-range change in magnitude and gradient more slowly than interactions at short-range. Avbelj et al. [14] have tested this method, and found it to be reliable. In this simulation, long-range electrostatic forces between 9 and 16 Å were updated every 10 steps (20 fs), hence, the use of a twin-range cut-off produced a gain of approximately 70% in CPU time when compared to the utilization of a classical 16 Å cut-off. Ion–solvent and solvent–solvent truncations were applied in a manner that avoided the splitting of the water dipoles [15]. The system was equilibrated for 100 ps at constant temperature (300 K) and pressure (1 atm) with a time step of 2 fs, and data were collected over the next 100 ps of simulation.

The calculated ion–ion radial distribution functions (RDF) are shown in Fig. 1. The peaks describing the short-range structure of the NaCl aqueous solution are qualitatively in accord with those found in previously reported theoretical studies [16–20]. The Na\textsuperscript{+} ··· Cl\textsuperscript{−} RDF shows a first peak at ≈ 2.8 Å corresponding to contact ion pairs, and a second peak at ≈ 5.0 Å corresponding to solvent-separated ion pairs. Both Na\textsuperscript{+} ··· Na\textsuperscript{+} and Cl\textsuperscript{−} ··· Cl\textsuperscript{−} RDF show peaks occurring at respectively 3.8 and 5.0 Å corresponding to solvent-bridged ion pairs, as well as peaks occurring at respectively 5.0 and 7.5 Å corresponding to solvent-separated ion pairs.

Examining the RDF at long-range, two sharp peaks are seen in the Na\textsuperscript{+} ··· Na\textsuperscript{+} and Cl\textsuperscript{−} ··· Cl\textsuperscript{−} distribution at ≈ 16 Å, and a corresponding minimum appears for the Na\textsuperscript{+} ··· Cl\textsuperscript{−} distribution. These peaks reflect cut-off artefacts which are present in the simulation even when long-range truncation schemes are employed. These effects alter significantly the structural properties of the system at long-range, but also at medium-range, between 8 and 14 Å where there appears an accumulation of Na\textsuperscript{+} ··· Cl\textsuperscript{−} ion pairs. The short-range structure, under 8 Å is probably perturbed as well, but to a not yet known extent given the lack of accurate experimental data on related systems. No perturbations of the ion–ion RDF (Fig. 1) are apparent at 9 Å, the limit chosen for the twin-range cut-off. Also no discontinuities appear in the ion–water RDF at this limit as well as the 16 Å boundary.

In related studies, similar problems at the cut-off limit were reported by Madura and Pettitt [3] in MD simulations on ionic systems. They showed that the shape of the radial distribution function of a Cl\textsuperscript{−} ion in water is dependent on the cut-off distance chosen and that a buildup of solvent molecules occurs around that limit. Smith and Pettitt [4], from a simulation of a cyclic peptide in a 1.0 M NaCl aqueous solution, observed that the use of a switching function over the 7.5–8.5 Å range resulted in reduced flexibility of the peptide. The calculated self-diffusion coefficients for the Na\textsuperscript{+} and Cl\textsuperscript{−} ions were in good agreement with experiment when they used Ewald summation but dropped to zero when they used switching functions, demonstrating that short truncations affect not only structural but also dynamical properties of the system. Schreiber and Steinhauser [5–7], from a study of a small α-helix in water, showed that protein–water and water–water orientational correlation functions were strongly perturbed by the use of truncations. Similar artefacts associated with the use of small cut-offs in simulations of nucleic acids have been recently revealed [21].

Kitson et al. [8] have also used radial distribution functions for pairs of like-charged and oppositely charged protein residues in a simulation of the large streptomyces griseus protease A protein in a crystalline ionic environment. They showed that using a 15 Å twin-range cut-off with a long switching function led to a depletion and an aggregation in the cut-off region of the RDF for, respectively, the same and oppositely charged pairs, not apparent in another simulation using a 25 Å twin-range cut-off with no
switching function. They interpreted this observation as a consequence of the introduction of artefactual forces due to the switching functions. This effect is opposite to that observed here, indicating that distinct truncation schemes can induce different but detectable artefacts in a simulation. These authors, however, studied only the RDF for charged protein residues and not for the surrounding ions in solution and did not analyze the RDF at the 25 Å cut-off limit.

This study demonstrates that the perturbation generated by even a 16 Å twin-range cut-off introduces strong artefacts into the simulation of systems containing monovalent ions. These perturbations are large at the cut-off limit, but are also detectable at medium-range and probably present at short-range. It is assumed that increasing further the cut-off size will not completely eliminate these artefacts, as 1/r electrostatic potentials decrease slowly with distance, while more severe problems will certainly appear with systems containing multivalent ions. Additional tests will have to be undertaken to clarify these points. Twin-range techniques, which are presently the only way to use truncation distances of the size used here, may also have introduced perturbations in the system even if they were not detectable in the calculated radial distribution function. Thus, alternative methods such as Ewald summation [1,2], used in a simulation of a rigid DNA triplex in a 1.0 M NaCl solution [22], are worthy of further attention in applications of MD to problems of chemical and biochemical interest. We note, in conclusion, that it is a simple matter to screen for cut-off artefacts by monitoring the radial distribution of charged groups. Based on the results described herein and by Kitson et al. [8], the general use of such screening tests is recommended.

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