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The Effects of Truncating Long-Range Forces on Protein Dynamics

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ABSTRACT **This paper considers the effects of truncating long-range forces on protein dynamics. Six methods of truncation that we investigate as a function of cutoff criterion of the long-range potentials are (1) a shifted potential; (2) a switching function; (3) simple atom–atom truncation based on distance; (4) simple atom–atom truncation based on a list which is updated periodically (every 25 steps); (5) simple group–group truncation based on distance; and (6) simple group–group truncation based on a list which is updated periodically (every 25 steps). Based on 70 calculations of carboxymyoglobin we show that the method and distance of long range cutoff have a dramatic effect on overall protein behavior. Evaluation of the different methods is based on comparison of a simulation's rms fluctuation about the average coordinates, the rms deviation from the average coordinates of a no cutoff simulation and from the X-ray structure of the protein. The simulations in which long-range forces are truncated by a shifted potential shows large rms deviations for cutoff criteria less than 14 Å, and reasonable deviations and fluctuations at this cutoff distance or larger. Simulations using a switching function are investigated by varying the range over which electrostatic interactions are switched off. Results using a short switching function that switches off the potential over a short range of distances are poor for all cutoff distances. A switching function over a 5–9 Å range gives reasonable results for a distance-dependent dielectric, but not using a constant dielectric. Both the atom–atom and group–group truncation methods based on distance shows large rms deviation and fluctuation for short cutoff distances, while for cutoff distances of 11 Å or greater, reasonable results are achieved. Although comparison of these to distance-based truncation methods show surprisingly larger rms deviations for the group–group truncation, contrary to simulation studies of aqueous ionic solutions. The results of atom–atom or group–group list-based simulations generally appear to be less stable than the distance-based simulations, and require more frequent velocity scaling or stronger coupling to a heat bath.**

Key words: long range truncation, molecular dynamics, myoglobin, truncation effects, protein electrostatics

INTRODUCTION

Throughout the field of molecular simulations there are many methods[1–3] in which the truncation of long-range forces, particularly electrostatic forces, is achieved. Several papers detailing the effects of long-range truncation for pure water,[1,4,5] fluids, [1–3] solutions of ions,[6] and aqueous ionic solutions[7–9] using analytic and statistical methods have been reported. To our knowledge no papers have been reported that specifically deal with the effects of truncating long-range forces on protein dynamics; although there has been one study involving the truncation of nonbond interactions in protein minimization.[10] There have been examples of cases where problems found in the analysis of protein simulations have resulted in a better treatment of the effects of the long-range potential,[11] but most of these are imbedded in papers not dealing specifically with long-range truncation. In other instances there has been a tendency to diminish some adverse affects such as discontinuities in the force, by coupling the entire system to a heat bath,[12] instead of removing the discontinuities. In all of these cases, there are tradeoffs between efficiency, accuracy, ease of programming, vectorizability, and justifiability. Due to the complexity of protein–protein interactions, it is not feasible to accurately determine the effects of different long-range truncation schemes other than by direct simulation.

We extend here a series of molecular dynamics simulations which explore the effects of long-range truncation on protein dynamics.[13] Two main questions are addressed in this paper. (1) What is the best functional form for truncating long-range forces? (2) What is the best distance to effect trun-

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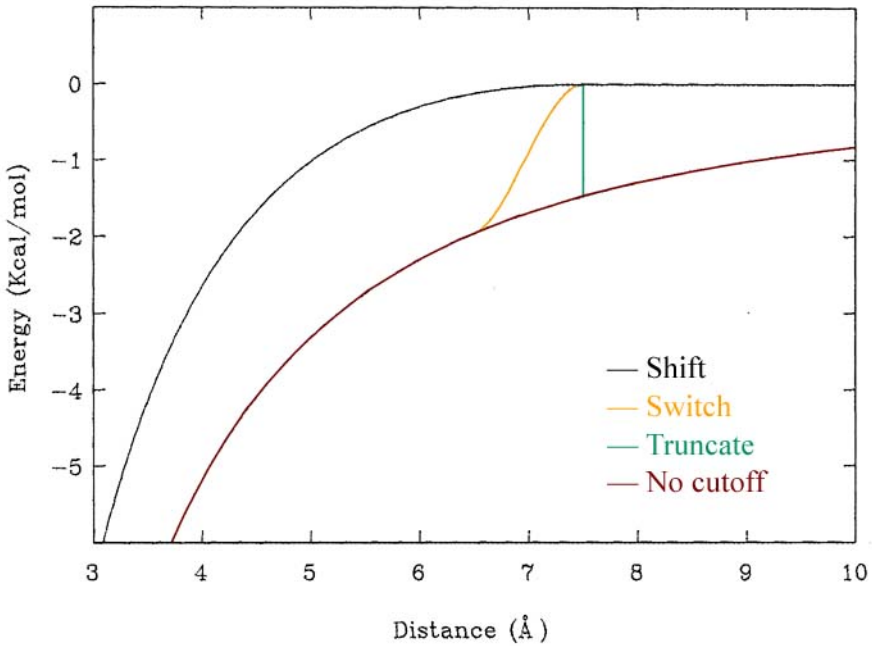


Fig. 1. The electrostatic potential energy for atoms with half charge of opposite signs for the different methods of long range truncation.

cation? Several additional points are also addressed. (3) What is the effect of switching off the potential over a short range of distances? (4) What is the relationship between a constant dielectric and a distance-dependent dielectric for pseudo-vacuum simulations? (5) What is the effect of increasing the dielectric constant?

The six approximation schemes to truncate long range forces that we investigate in this paper are (1) a shifted potential; (2) a switching function; (3) simple atom–atom truncation based on distance; (4) simple atom–atom truncation based on a list which is updated periodically (every 25 steps); (5) simple group–group truncation based on distance; and (6) simple group–group truncation based on a list which is updated periodically (every 25 steps). In the first four methods the nonbond pair interactions are computed on an atom–atom pair basis. In the latter two methods the nonbond pair interactions are achieved on a group–group basis. The functional forms studied are discussed below and are depicted in Figure 1. This study also compares the different methods by an energy time series and considers an error analysis of the values for comparing simulations results.

MATERIALS AND METHODS

Methods and Theory

The form of the equation to calculate nonbond pair interactions in CHARMM[14] is as follows:

$$E_{ij} = \sum F(r) \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{4\pi\epsilon r} \right] \qquad (1)$$

where the three terms of the summation correspond to core repulsion, dispersion, and Coulombic interactions between a pair of atoms separated by a distance r. The first two terms comprise the van der Waals interactions where A and C are constants. The parameters q_i, q_j of the electrostatic term are the electric charges of atoms i and j. The parameter ϵ is equal to $\epsilon_0\,\epsilon_r$, which are the permittivity of vacuum and the dielectric constant (or relative permittivity), respectively. In calculating electrostatics interactions with a constant dielectric (cdie) the dielectric constant, ϵ_r, is equal to 1.0. For a distance dependent dielectric (rdie), the dielectric constant is set equal to the value of r. The latter approach has been routinely used to approximate solvation effects in protein dynamics.[15] Calculation of all nonbond pair interactions requires the computer time for the sum of $[N \times (N - 1)]/2$ pairs, in our model system 1.17 million pairs. To save an enormous amount of simulation time the total number of nonbond pair interactions is often reduced by modification with a truncation potential function $F(r)$.

Shifted potential

The shifted potential[14] used here has the following form:

$$F(r) = \left[1 - 2\left(\frac{r}{r_{cut}}\right)^2 + \left(\frac{r}{r_{cut}}\right)^4 \right] \quad r < r_{cut} \qquad (2)$$

$$= 0 \qquad r > r_{cut}$$

The functional form of this method is continuous

and there are no large forces at long range; however there is damage done to the short-range potential (i.e., large forces) which should probably be reparameterized to compensate for this. Other forms of the shifting function have been studied elsewhere.[1]

Switching function

The atom–atom switching function[14] switches the electrostatic interaction off over the range $r_{on} \leq r \leq r_{off}$. The mathematical form of the switching function is shown in equation 3.

$$F(r) = \begin{cases} 1 & r \leq r_{on} \\ \left[\dfrac{(r_{off}^2 - r^2)(r_{off}^2 + 2r^2 - 3r_{on}^2)}{(r_{off}^2 - r_{on}^2)^3}\right] & r_{on} < r \leq r_{off} \\ 0 & r_{on} > r_{off} \end{cases} \quad (3)$$

In this method the potential energy is modified to approach zero smoothly beyond the cutoff separation. The functional form has no discontinuities in the potential, but there can be large derivatives and changes in the potential at long distances if the switching region is short (i.e., $r_{off} - r_{on} < 2$ Å). For a larger switching range (i.e., $r_{off} - r_{on} = 4$ Å) the effects are not as extreme.

Simple atom–atom truncation based on distance and simple atom–atom truncation based on a list

Simple atom–atom truncation method is used widely in molecular simulation studies and has the following form.

$$F(r) = \begin{cases} 1 & r < r_{cut} \\ 0 & r \geq r_{cut} \end{cases} \quad (4)$$

The simple atom–atom truncation is a spherical truncation method of all interactions beyond a selected cutoff distance. In particular, the interatomic potential and forces are set equal to zero beyond the cutoff distance. There are discontinuities in the potential energy and first derivatives (forces) at the cutoff separation. This makes this method inappropriate for minimizations, and causes problems for dynamics, particularly if solvent is included because of the mobility of the water molecules. For this truncation method two procedures are compared. In the first procedure a nonbond list is updated per step giving rise to a distance-based truncation scheme, and in the second procedure a fixed nonbond list is kept between a periodic update (per 25 steps) to afford a list-based truncation scheme. The list-based functional form is easiest to program and to vectorize.

Simple group–group truncation based on distance and simple group–group truncation based on a list

Equation (4) shows the form of simple group–group truncation.

$$F(r) = \begin{cases} 1 & |\langle \mathbf{r}_I \rangle - \langle \mathbf{r}_J \rangle| < r_{cut} \\ 0 & > r_{cut} \end{cases} \quad (5)$$

This method is similar to the simple atom–atom truncation except that dipolar groups are not split by the cutoff criterion. There is still the problem of discontinuities in the potential energy and first derivatives, but these are less extreme than in the case of the simple atom–atom truncation method. In cases where water is explicitly included, this approach exhibits the curious phenomenon of hot water and cold protein if the entire system is coupled to a heat bath. That is, the more mobile water atoms are subject to more discontinuities making them hotter than the less mobile protein atoms.[11] It should be noted that this is one of the most commonly used methods of truncation for simulations where CHARMM[14] is not routinely used. Two procedures are studied for the group–group-based truncation method. The first procedure is distance based, which is equivalent to a procedure in which the nonbond list is updated per step, and the second procedure is list based in which a fixed list is kept between a periodic update of the list per 25 steps.

Model and Procedure

The model system for these calculations is carboxy-myoglobin starting from the X-ray coordinates.[16] The polar hydrogen parameter set PARAM19[17] is used for all calculations. It is not expected that the results of this study would change substantially if a different protein or if a different parameter set were used. In the carboxy-myoglobin representation there are 1532 atoms. The architecture of the molecule is that of eight connected α helices that essentially form a box around the heme group. Figure 2 shows the atoms of peptide backbone using a continuous space curve model[18] drawn with the LIGHT program from NIH. The protein is of size that would fit in a box 46 × 43 Å. Figure 2a illustrates how severely the truncation of long-range forces is on protein dynamics, the 7.5 and 13.5 Å cutoff distances from the α carbon (white) of residue Lys-50 are shown in yellow and red, respectively. The use of the larger truncation criterion dramatically indicates that nonbond pair interactions of this α carbon (in the CD region) would not be possible with the heme group or the A, E, F, G, and H helices. Figure 2b illustrates the spherical nature of using the 7.5 and 13.5 Å cutoff criteria in yellow and red, respectively, from the Heme Fe (white). Using the 7.5 and 13.5 Å cutoff criteria for this representation of carboxy-myoglobin merely results in on average 5 and 22%, respectively, of all possible nonbond pair interactions over all atoms.

Each simulation is carried out as follows: (1) 1000 steps of steepest descents minimization to remove large forces, (2) 30 psec of heating to 300 K using identical random numbers for all truncation meth-

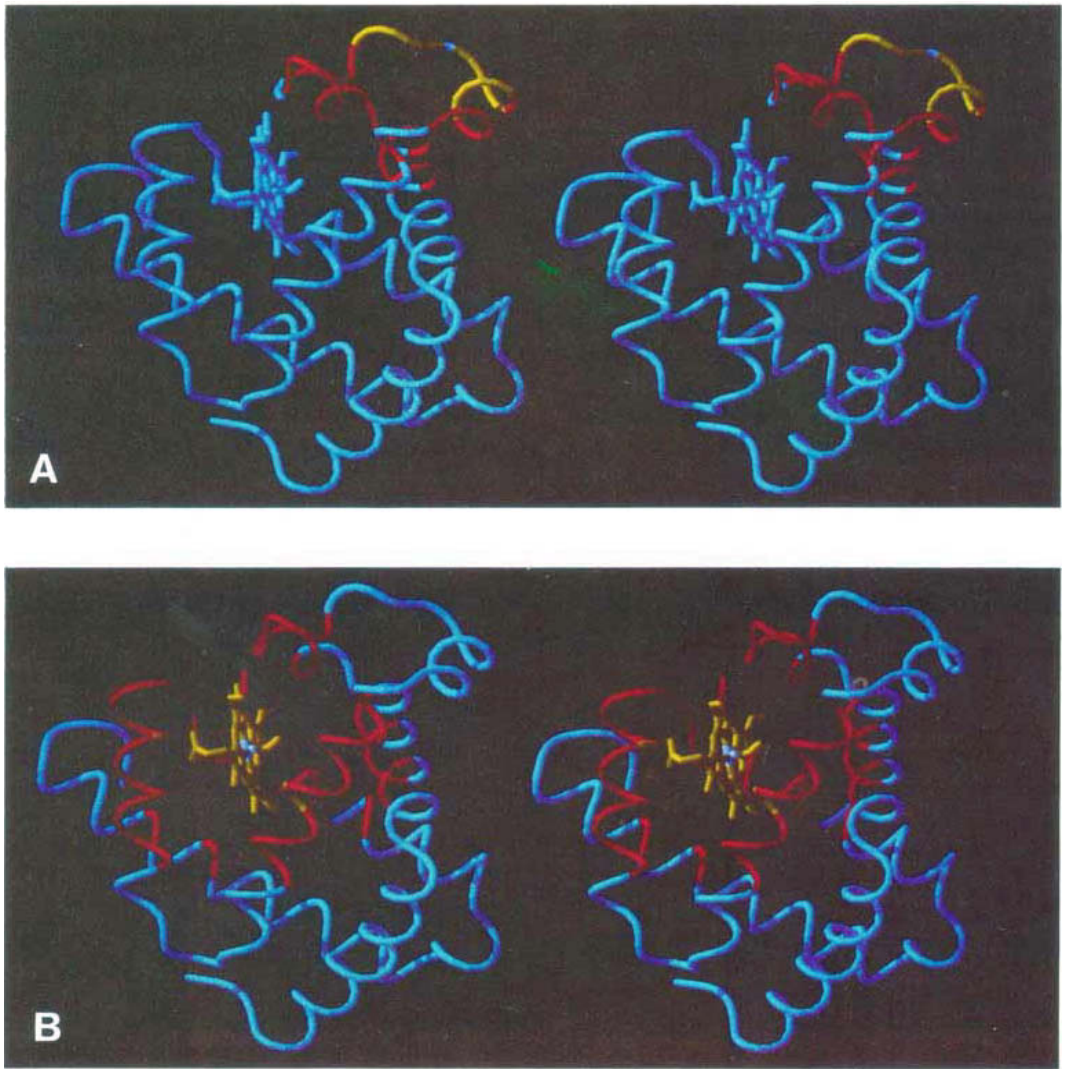


Fig. **2A.** A continuous space curve model of the backbone atoms of the carboxy-myoglobin protein (shown in cyan). The α carbon of residue Lys-50 is shown in white. The 7.5 and 13.5 Å cutoff criteria from this atom are shown in yellow and red, respectively. Figure **2B.** A continuous space curve model of the backbone atoms of the carboxy-myoglobin protein (shown in cyan). The Heme-Fe is shown in white. The 7.5 and 13.5 Å cutoff criteria from this atom are shown in yellow and red, respectively.

ods, (3) 20 psec of equilibration at 300 K, and (4) 100 psec of analysis at 300 K. The integration timestep is 0.001 psec for all integration. All simulations are performed on the Star Technologies ST-50 and ST-100 array processors (the latter is comparable to the CRAY X-MP for molecular simulation performance). Data transfer to the array processors is accomplished with Apollo DSP-160 and DSP-80 host computers.

Seventy simulations of 150 psec in length were carried out on the carboxy-myoglobin protein. The study explores simulations of a shifted potential at cutoff criteria of 4.5, 5.5, 6.5, 7.5, 8.5, 10.5, 13.5 Å, and no cutoff using the distance-dependent dielectric, and at 7.5, 13.5 Å, and no cutoff using a constant dielectric. The shifted potential was also studied using a scale factor of 2.0 for the electrostatic term at the 7.5 cutoff criterion using a constant dielectric and a distance-dependent dielectric, and without cutoff using a distance-dependent dielectric. A switching function was investigated using a 1 Å switching region at 4.5, 5.5, 6.5, 7.5, 8.5, 10.5, and 13.5 Å with a distance-dependent dielectric and at 8.5 and 13.5 Å using a constant dielectric. The switching function was also investigated with switching regions of 5.0–9.0, 6.0–8.0, 6.5–7.5, 6.75–7.25, 6.875–7.125, and 11.0–15.0 Å using a distance-dependent dielectric, and with switching regions of 6.5–7.5, 12.5–13.5, 5.0–9.0, and 11.0–15.0 using a constant dielectric. Each of the latter four methods of this paper were studied with cutoff criteria of 4.5, 5.5, 6.5, 7.5, 8.5, 10.5, 13.5 Å, and no

cutoff using a distance-dependent dielectric and at 7.5, 13.5 Å, and no cutoff using a constant dielectric.

RESULTS AND DISCUSSION

The results for the 100 psec analysis section of all of the simulations where nonbond interactions are computed on an atom–atom and on a group–group basis are summarized in Table I. For each simulation, several types of analysis are performed, but the values which may best reflect the behavior of a simulation are the root mean square (rms) atomic fluctuation about the average coordinates, the rms deviation from the X-ray coordinate values, and from the average coordinates of a no cutoff simulation (in parentheses). A scaling factor to correct for thermal drift is also presented in Table I. At every 10 psec of the analysis stage of dynamics the temperature of the system was checked to see if the value was within the temperature window (±10 K) of the desired temperature. If the temperature was not inside the window the velocities were scaled to give the desired temperature, otherwise a scale factor of 1.0 was employed. In the simulations using short cutoff distances, velocity scaling (in some cases by a factor of zero) may have occurred every 10 psec of the analysis phase, whereas in simulations of the long cutoff distances the velocity scaling usually occurred only once. In order to weight this difference, the number presented in the table is the geometric mean scaling of the energies. The number represents an equal partition of energy into kinetic and potential energy by a geometric mean of one-half times the quantity of velocity scale factor plus one. Thus the smallest possible energy scale factor is 0.5.

The ideal result of each method of truncation is deemed to be the simulation without cutoffs. This is not to say that the simulations without long-range cutoffs will always be better than those that employ a cutoff. In fact for a simulation that uses a constant dielectric, the truncation may be an essential (though perhaps unintentional) part of the dielectric screening. However, for some of these calculations we employ a distance-dependent dielectric which incorporates its own screening. Although the distance-dependent dielectric has no physical basis, it is used routinely for pseudo-vacuum simulation since better results are achieved than with simulations which use a constant dielectric.[15] Nevertheless, if it were not for the question of efficiency, few researchers would carry out simulations with truncations.

TABLE I. RMS Fluctuations and Deviations for the Last 100 psec of Each Simulation (in Angstroms)*

Method	Energy term cutoff distance	rms fluctuations		rms deviations†		Scaling factor
		All atoms	Main chain	All atoms	Main chain	
Atom rdie shifted	4.5	2.23	1.96	5.70 (5.78)	5.27 (5.42)	0.99370
	5.5	1.34	1.10	4.59 (4.54)	3.72 (3.85)	0.99582
	6.5	0.97	0.81	2.81 (3.18)	2.27 (2.78)	0.99696
	7.5	0.74	0.59	2.87 (2.79)	2.34 (2.31)	0.99590
	8.5	0.90	0.77	2.35 (2.29)	1.91 (1.89)	0.99724
	10.5	0.70	0.59	3.05 (2.74)	2.44 (2.18)	0.99831
	13.5	0.65	0.53	2.36 (2.00)	1.96 (1.72)	0.99505
	None	0.63	0.50	2.20 (0.00)	1.68 (0.00)	0.99567
Atom cdie shifted	7.5	0.71	0.59	3.23 (3.53)	2.57 (2.93)	0.99610
	13.5	0.66	0.53	2.66 (2.43)	2.20 (2.08)	0.99528
	None	0.65	0.53	2.79 (0.00)	2.24 (0.00)	0.99568
Atom cdie shifted eps2	7.5	0.98	0.77	3.87 (3.31)	3.23 (2.62)	0.99384
Atom rdie shifted eps2	7.5	0.99	0.81	2.67 (3.02)	2.25 (2.67)	0.99623
	None	0.78	0.62	2.26 (0.00)	1.81 (0.00)	0.99596
Atom rdie switched	3.5–4.5	0.58	0.46	2.89 (3.24)	2.54 (2.84)	0.98852
	4.5–5.5	0.53	0.43	2.35 (2.58)	1.82 (2.17)	0.99283
	5.5–6.5	0.63	0.49	1.97 (2.29)	1.63 (1.92)	0.99143
	6.5–7.5	0.58	0.44	1.84 (2.25)	1.43 (1.87)	0.99366
	7.5–8.5	0.60	0.47	2.68 (2.61)	2.26 (2.29)	0.99302
	9.5–10.5	0.62	0.48	1.88 (2.24)	1.39 (1.92)	0.99404
	12.5–13.5	0.51	0.38	2.17 (2.17)	1.69 (1.89)	0.99505
	None	0.63	0.50	2.20 (0.00)	1.68 (0.00)	0.99567
Atom rdie switched	5.0–9.0	0.77	0.63	2.20 (1.01)	1.75 (0.65)	0.99672
	6.0–8.0	0.73	0.59	2.34 (2.30)	1.86 (1.94)	0.99547
	6.5–7.5	0.58	0.44	1.84 (2.25)	1.43 (1.87)	0.99366
	6.75–7.25	0.50	0.40	1.68 (2.13)	1.27 (1.72)	0.98865
	6.875–7.125	0.42	0.29	1.56 (2.20)	1.16 (1.76)	0.98041
	11.0–15.0	0.64	0.52	2.43 (1.56)	1.94 (1.07)	0.99536
Atom cdie switched	7.5–8.5	0.28	0.17	1.58 (2.78)	1.22 (2.10)	0.98774
	12.5–13.5	0.25	0.11	1.38 (3.12)	1.04 (2.67)	0.99391
	5.0–9.0	0.55	0.43	2.59 (3.14)	2.07 (2.55)	0.99247
	11.0–15.0	0.51	0.36	2.23 (2.55)	1.80 (1.98)	0.99564
	None	0.65	0.53	2.79 (0.00)	2.24 (0.00)	0.99568

(continued)

TABLE I. RMS Fluctuations and Deviations for the Last 100 psec of Each Simulation (in Angstroms)* (continued)

Method	Energy term cutoff distance	rms fluctuations		rms deviations†		Scaling factor
		All atoms	Main chain	All atoms	Main chain	
Atom rdie truncated	4.5	1.40	1.14	5.92 (5.87)	4.74 (4.93)	0.99141
	5.5	1.44	1.21	4.49 (4.84)	4.04 (4.49)	0.99185
	6.5	1.07	0.87	2.91 (2.58)	2.49 (2.19)	0.99360
	7.5	0.81	0.66	2.23 (2.22)	1.78 (1.90)	0.99532
	8.5	0.79	0.61	2.63 (1.97)	2.16 (1.54)	0.99320
	10.5	0.77	0.64	2.26 (1.34)	1.70 (0.90)	0.99571
	13.5	0.77	0.65	2.45 (2.05)	1.96 (1.67)	0.99551
	None	0.63	0.50	2.20 (0.00)	1.68 (0.00)	0.99567
Atom cdie truncated	7.5	0.76	0.59	2.72 (2.72)	2.17 (2.33)	0.99397
	13.5	0.60	0.47	2.66 (2.84)	2.15 (2.44)	0.99578
	None	0.65	0.53	2.79 (0.00)	2.24 (0.00)	0.99568
Atom rdie list	4.5	6.27	5.75	12.81 (12.79)	11.85 (11.92)	0.50000
	5.5	2.29	1.90	5.89 (5.93)	5.14 (5.28)	0.73473
	6.5	0.88	0.73	2.56 (2.57)	2.20 (2.24)	0.98597
	7.5	0.73	0.58	2.89 (2.78)	2.42 (2.34)	0.95254
	8.5	0.86	0.76	2.28 (1.62)	1.78 (1.24)	0.97007
	10.5	0.72	0.58	2.43 (1.69)	2.06 (1.33)	0.98013
	13.5	0.61	0.48	2.36 (1.87)	1.90 (1.42)	0.99476
	None	0.63	0.50	2.20 (0.00)	1.68 (0.00)	0.99567
Atom cdie list	7.5	5.81	5.31	8.19 (8.48)	7.10 (7.56)	0.50000
	13.5	1.31	1.09	3.67 (3.04)	3.14 (2.51)	0.73642
	None	0.65	0.53	2.79 (0.00)	2.24 (0.00)	0.99568
Group rdie truncated	4.5‡	—	—	—	—	—
	5.5	2.13	1.84	5.59 (5.59)	4.88 (4.92)	0.95434
	6.5	1.07	0.92	3.27 (3.27)	2.79 (2.75)	0.98500
	7.5	1.05	0.88	2.16 (2.07)	1.69 (1.69)	0.98913
	8.5	0.86	0.71	2.14 (1.16)	1.66 (0.75)	0.99291
	10.5	0.65	0.53	2.44 (1.73)	2.04 (1.33)	0.99638
	13.5	0.76	0.63	2.44 (2.23)	2.09 (1.91)	0.99554
	None	0.63	0.50	2.20 (0.00)	1.68 (0.00)	0.99567
Group cdie truncated	7.5	1.30	1.07	5.58 (5.17)	5.01 (4.50)	0.92629
	13.5	0.72	0.57	3.19 (3.00)	2.85 (2.75)	0.98354
	None	0.65	0.53	2.79 (0.00)	2.24 (0.00)	0.99568
Group rdie list	4.5‡	—	—	—	—	—
	5.5	1.56	1.34	5.55 (5.54)	4.96 (5.01)	0.95434
	6.5	1.14	0.95	2.67 (2.82)	2.22 (2.32)	1.01842
	7.5	0.66	0.55	2.76 (2.05)	2.27 (1.68)	1.01209
	8.5	0.74	0.56	2.29 (1.28)	1.86 (0.78)	0.99860
	10.5	0.63	0.51	2.28 (1.57)	1.91 (1.23)	0.99540
	13.5	0.61	0.48	2.50 (1.58)	2.09 (1.15)	0.99603
	None	0.63	0.50	2.20 (0.00)	1.68 (0.00)	0.99567
Group cdie list	7.5	1.33	1.09	4.04 (3.81)	3.53 (3.34)	0.87425
	13.5	0.86	0.70	3.39 (2.93)	2.96 (2.51)	0.94307
	None	0.65	0.53	2.79 (0.00)	2.24 (0.00)	0.99568

*The term "rdie" indicates that a distant-dependent dielectric is used, "cdie" indicates that a constant dielectric is used, and "eps2" indicates that the electrostatic forces are scaled by 0.5.
†The values presented are the rms deviations from X-ray coordinates and the values in parentheses are the rms deviations from the average coordinates of a no cutoff simulation.
‡The simulations were not completed since the rms deviation was greater than 12 Å in 10 psec.

These calculations are performed without explicit solvent, thus all electrostatic interactions are insufficiently screened. However, since solvent screening reduces the strength of an interaction by introducing opposing forces, through indirect interactions, and not by modifying the direct interaction, we do not anticipate that artifacts from truncation effects will be reduced by adding solvent.

The shifted potential

As seen in Table I the results for the rdie shifted potential tend to exhibit comparatively larger rms deviations than the other methods of truncating long-range forces. In proceeding along the series from a 4.5 Å to the 13.5 Å cutoff distance the rms deviation from X-ray and from the no cutoff simulation decreases with the exception of the 10.5 Å cutoff. With the 10.5 Å cutoff separation the potential is apparently less restrictive than the shorter cutoff distances and results in a larger deviation. The rms deviation of all atoms as a function of time for some of the shifted potential simulations are shown in Figure 3. The figure shows clearly that the longer cutoff distance of 14 Å results in a smaller rms de-

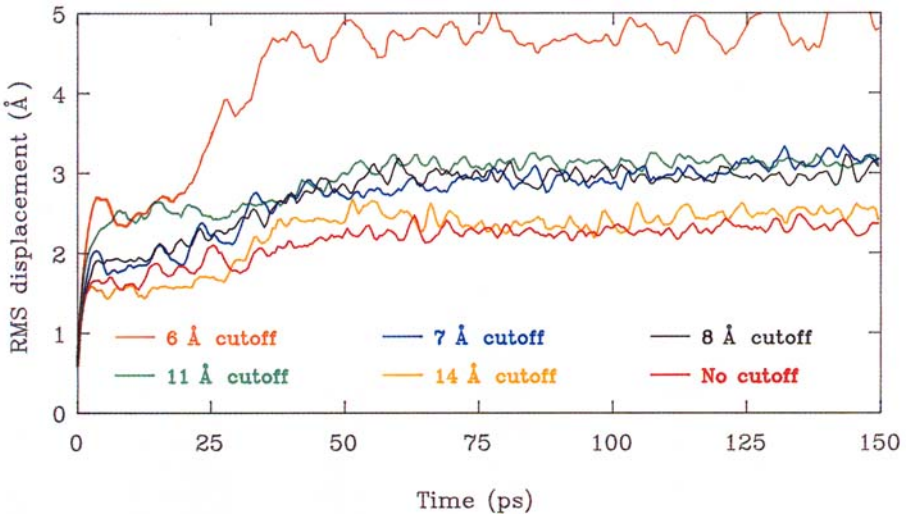


Fig. 3. The rms deviation for all atoms from the X-ray structure as a function of time for the simulations using the shift potential at different cutoff distances.

viation from X-ray coordinates and a more stable oscillatory behavior. The rms fluctuations using the shifted potential also tend to be comparatively larger than with the other truncation methods at the short cutoff distances, but are much better at the larger cutoff distances. In simulations of the shifted potential the scale factor is close to unity, which is typical of truncation methods that do not have discontinuities in the force. A scale factor which is close to unity is a necessary criterion, but not a sufficient criterion, for a good simulation.

The simulation results using the shifted potential with a constant dielectric at 7.5 Å, 13.5 Å, and no cutoff distance of the energy term is also presented in Table I. The results using the cdie shifted potential for all cutoff distances show 0.3–0.5 Å larger rms deviations than the results with the rdie shifted potential. However, the rms fluctuations for the three cases using the cdie shifted potential almost reproduce the corresponding rdie results.

With this method of truncation the effect of increasing the dielectric constant is also presented in Table I. The effect of doubling the dielectric constant in the 7.5 Å cdie shifted potential shows about a 0.6 Å increase in the rms deviation from X-ray coordinates and a 0.2 Å increase in the rms fluctuation. By contrast, increasing the dielectric constant using the rdie shifted potential for the 7.5 Å cutoff distance and for the no cutoff distance show only a 0.1–0.2 Å increase in the rms deviations from X-ray coordinates and fluctuations.

The switching function

The method of truncation using the switching function is investigated using a 1 Å switching range for several cutoff distances, and with a switching function of various ranges centered at a 7.5 Å cutoff distance. The results of simulations with a 1 Å switching range seem to reproduce rms deviations from X-ray reasonably well and also reduce the overall fluctuation of the system. In the cases of the shorter cutoff distances, namely, 5.5–6.5 and 6.5–7.5 Å, the rms deviations from X-ray are considerably less than in the case of no cutoff. The rms fluctuations for these two cases only differ slightly from that of the no cutoff example. By contrast, the simulation with the longer cutoff distance of 12.5–13.5 Å exhibits about the same rms deviation from X-ray and considerably less rms fluctuation than with no cutoff imposed. It must be emphasized that in comparison to the ideal simulation the fluctuations are too restrictive in all cases using the 1 Å switching region, even at the 13.5 Å cutoff distance. It is clear there are balancing effects which occur in this series of simulations. The damage done to the potential by removing atom–atom interactions tends to make the structures deviate more, and the large forces which are imposed at long range tend to restrict motion. Whereas for the shifted potential there are no nonphysical forces to restrict the motion, and both deviations from X-ray and fluctuations are larger.

The rms deviations from the average coordinates of the no cutoff simulation seem to decrease smoothly in proceeding along the series of cutoff distances, with the exception of the 7.5–8.5 Å cutoff distance. Furthermore, it is quite clear that the rms deviations from the average coordinates of the no cutoff simulation are routinely larger than the rms deviations from X-ray coordinates.

In order to investigate the best range to use for the switching function, the effects of using a 4.0, 2.0, 1.0, 0.5, and 0.25 Å switching region centered at 7.5 Å were considered. The rms deviations from the X-ray structure as a function of time for these simulations

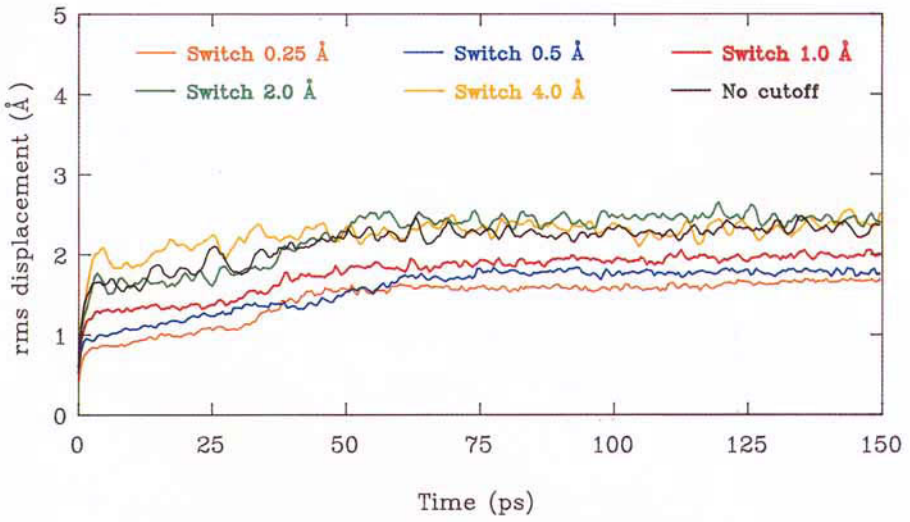


Fig. 4. The rms deviation for all atoms from the X-ray structure as a function of time for the simulations using various ranges in the switching function.

are shown in Figure 4. The longer switching regions of 2.0 and 4.0 Å appear reasonably good as compared to the no cutoff case. It appears that the longer switching regions alleviate the restrictions imposed by the 1 Å switching region. The nature of the restrictions using a short switching region become more evident when the results of the 0.5 and 0.25 Å switching function simulations are considered. In the extreme case both the fluctuations and the deviations from X-ray are dramatically less than in all other cases as a result of the severely restricted potential. Furthermore, the rms deviations from the no cutoff simulation for all simulations where the potential is switched off over a range of distances less than or equal to 2 Å are intrinsically about the same magnitude. To summarize, a short switching region for any cutoff distance gives poor results.

Analysis of the latter group of simulations suggested that we also perform a simulation with a 4 Å switching range centered around 13 Å. The results of this case can be compared directly to the 1 Å switching region at 13.5 Å. Both the deviations from X-ray and fluctuations are larger in the former case. The restrictions imposed with a 1 Å switching region are relaxed with the longer switching region of 11–15 Å.

It is also interesting to compare the results of a 4 Å switching region centered at 13 Å with that centered at 7 Å. The rms deviations are larger in the former case. However, the better criterion to compare these two cases is the rms fluctuation. The 4 Å switching function for the longer cutoff distance shows smaller fluctuations. It is also noteworthy that the fluctuations of this example compare well with the ideal simulation. Although both simulations using a long switching region give reasonable results, the choice of using the switching function for the larger cutoff distance (11–15 Å) versus the shorter distance (5–9 Å) should take into consideration that the former requires three times the computational time.

The constant dielectric is employed for several cases using the switching potential. In the cases with the 1 Å switching range, both the rms deviations from X-ray and fluctuations are unreasonably restrictive. In the cdie switched simulations with the 5–9 and 11–15 Å switching regions the deviations are more reliable, however, the fluctuations are still too restrictive. In all cases the rms deviations relative to the average coordinates of the no cutoff simulation are very large. When using a constant dielectric the truncation of long-range forces with an atom-based switching function should not be employed.

A recent harmonic analysis[19] of bovine pancreatic trypsin inhibitor (BPTI), a 58 residue globular protein, supports differences in the shifted potential and a 1 Å switching region in the harmonic limit. Harmonic analysis was carried out in the cartesian basis (1740 degrees of freedom). Structures were prepared by exhaustively minimizing, to a minimum energy conformation, the average coordinates of the last 1000 psec of a 2000 psec simulation. The results using a shifted potential with a 7.5 Å cutoff show the lowest five normal mode frequencies for BPTI are 5.79, 7.45, 9.28, 10.30, and 11.89 cm^{-1}. Reminimizing using a switching function over a range of 6.5–7.5 Å shows the lowest frequencies are 14.37, 15.26, 16.65, 18.83, and 20.43 cm^{-1}. The shifted frequencies better agree with previously calculated no cutoff harmonic analysis results,[20] where the lowest three normal modes are 3.1, 4.4, and 4.8 cm^{-1}. However, the results[19] using a switching function have considerably higher frequencies; indi-

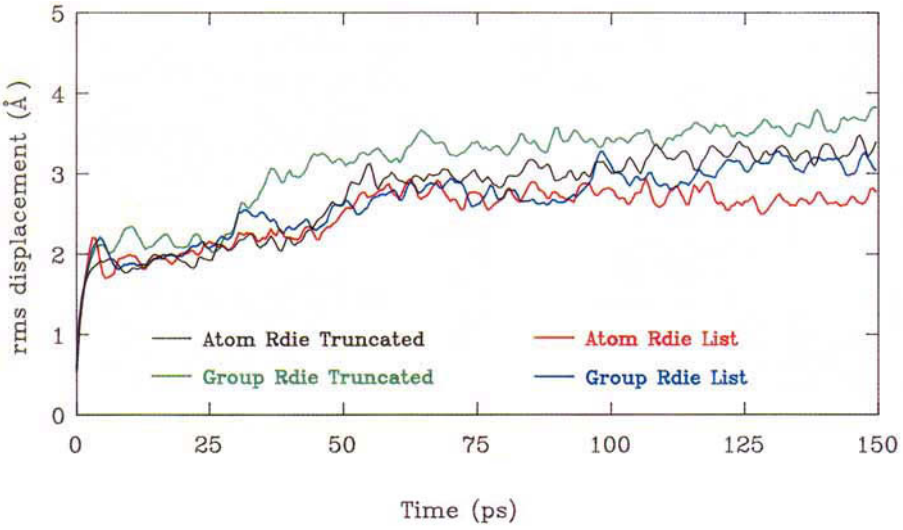


Fig. 5. The rms deviation for all atoms from the X-ray structure as a function of time for the atom–atom and group–group truncations methods at the 6.5 Å cutoff distance. Results for both the distance-based and list-based truncation schemes are shown.

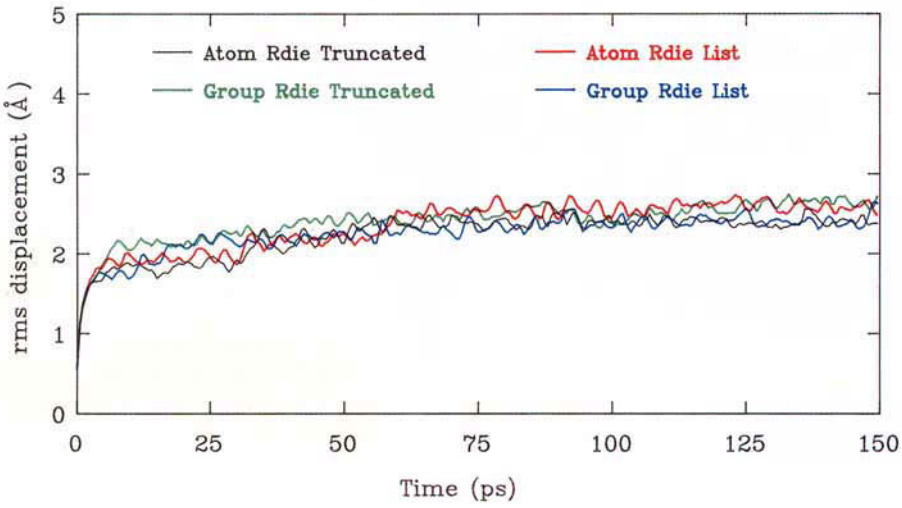


Fig. 6. The rms deviation for all atoms from the X-ray structure as a function of time for the atom–atom and group–group truncations methods at the 10.5 Å cutoff distance. Results for both the distance-based and list-based truncation schemes are shown.

cating that the potential has substantially changed. This also agrees with the reduced fluctuations in the current simulations of carboxy-myoglobin that employ a 1 Å switching region.

Simple atom–atom truncation based on distance

The results of the simple atom–atom truncation simulations based on distance show large rms deviations and fluctuations at the shorter cutoff distances. The results in proceeding along the series of cutoff distances appear better at 11 Å or greater cutoff separation. The results of the truncated potential are generally about the same as the shifted potential, but are less restrictive than truncating with the switching function. Noticeably, the rms deviations from X-ray and the fluctuations of the atom–atom truncation simulation for the 14 Å cutoff distance are about the same as that of the simulation using the 5–9 Å switching function. However, a drawback of the 14 Å atom truncation simulation is that the computational time is more than two times the computational time of truncating long range forces using the 5–9 Å switching function. The trends of the rms deviations from the average coordinates of the no cutoff simulation do not decrease monotonically along the series of cutoff distances. Although the results do indicate that atom rdie truncated simula-

tions deviate less from the average coordinates of the no cutoff simulation than from the X-ray coordinates. In the cases using the constant dielectric the deviations are slightly higher and the fluctuations are slightly lower than the corresponding atom rdie truncated simulations.

Simple atom–atom truncation based on a list

By contrast to the distance-dependent atom truncation results, the atom–atom truncated simulations where the nonbond list is updated every 25 steps of the trajectory appear less stable with a short-range cutoff. In particular, the atom–atom truncation at the 4.5 Å cutoff distance shows a rms deviation from X-ray of greater than 12 Å. The trajectories using the 4.5 and 5.5 Å cutoffs are influenced considerably by scaling to compensate for thermal drift. The rms fluctuations and rms deviations from X-ray of the distance-based and list-based atom truncation methods approach one another for larger cutoff separations ($\geq$ 10.5 Å). The scale factor also becomes closer to unity at cutoff distances of $\geq$ 10 Å.

In comparison to the rdie list-based simulations the cdie list-based simulations show considerable deviations and fluctuations. The scaling in the cases using the constant dielectric occurs every 10 psec, which contributes to the poor results even at large cutoff distances.

Simple group–group truncation based on distance

The molecular simulation results using the simple group–group truncation method based on distance generally show larger rms fluctuations and rms deviations from X-ray at short cutoff separations as compared to the simple atom-atom truncation method. For example, this point is illustrated from comparison of the results using the 5.5 and 6.5 Å cutoffs for the two methods. This is also demonstrated in Figure 5. As the cutoff distance becomes 11 Å or larger the results of the atom–atom truncation and the group–group truncation start to converge. The fluctuations are almost identical for the two distance based methods at 10.5 and 13.5 Å cutoffs. However, with the group–group truncation based on distance the rms deviations from X-ray and from the average coordinates of the no cutoff simulation are 0.1–0.4 Å larger than the results of the corresponding atom truncated simulations. The rms deviations from X-ray for all atoms as a function of time for the 11 Å case are shown in Figure 6. The results here are unexpected; truncation with neutral groups is expected to show a less severe truncation effect than that observed for the atom–atom truncation. This phenomena in protein dynamics simulations is in contrast to that found in aqueous ionic solutions.[8] As with the atom rdie truncated simulation results, the trends of the rms deviations from the average coordinates of the no cutoff simulation do not decrease monotonically along the series of cutoff separations, but do appear to deviate less than the value from the X-ray coordinates.

TABLE II. RMS Fluctuations and Deviations for the Last 100 psec of the 6.5–7.5 Å rdie Switched Simulation (in Angstroms)

	rms fluctuations		rms deviations*	
Simulation	All atoms	Main chain	All atoms	Main chain
1	0.58	0.44	1.84 (2.25)	1.43 (1.87)
2	0.58	0.46	1.89 (2.00)	1.33 (1.50)
3	0.74	0.61	1.94 (1.91)	1.42 (1.55)
4	0.68	0.53	2.04 (2.20)	1.59 (1.78)
5	0.56	0.42	1.99 (2.46)	1.55 (1.94)
6	0.72	0.57	2.08 (2.05)	1.64 (1.53)
$\bar{m}$	0.64	0.51	1.96 (2.15)	1.49 (1.70)
σ	0.08	0.08	0.09 (0.20)	0.12 (0.19)
q	0.05	0.05	0.06 (0.13)	0.08 (0.13)

*The values presented are the rms deviations from X-ray coordinates and the values in parentheses are the rms deviations from the average coordinates of a no cutoff simulation.

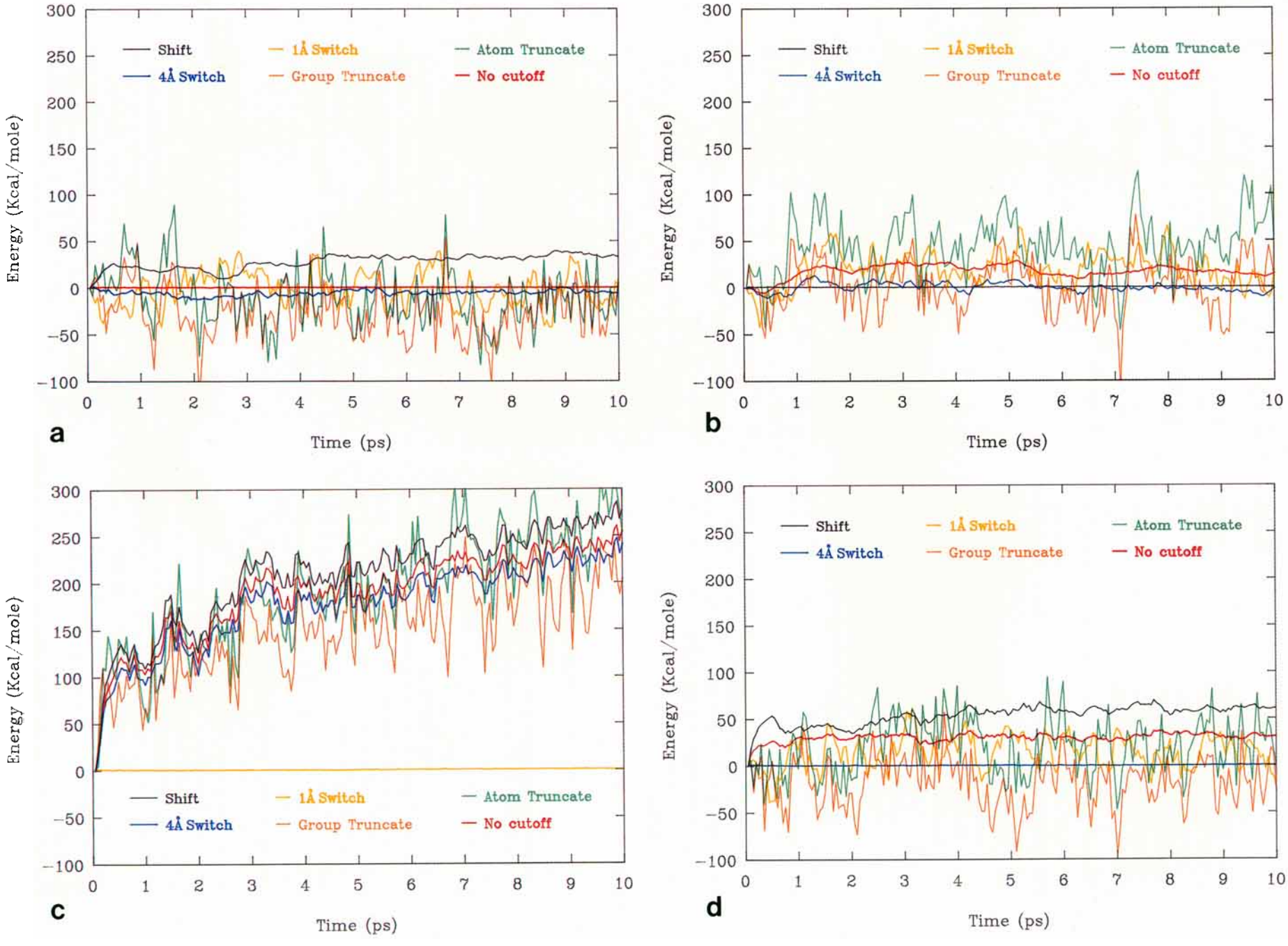
Simple group–group truncations based on a list

In general, the results of the simulations using a list-based group truncation method are less stable than the results of simulations using the distance-based method. These results also seem to show a slightly larger rms deviation from X-ray than the results of the simple atom–atom truncation method based on a list. The fluctuations tend to be about the same in the atom–atom and group–group truncation methods at long cutoff distances. As expected, the group cdie truncated simulations show larger rms fluctuations and deviations from X-ray than the group rdie truncated simulations.

For the group rdie list-based simulations with cutoff distances of 10.5 Å or larger the results are comparable to that of the group rdie truncated simulations. Again, the simulations using the constant dielectric show larger deviations and fluctuations than the simulations using the distance-dependent dielectric constant.

Error Analysis

Here we estimate the statistical errors in the rms deviations and fluctuations in Table I; by carrying out five additional simulations of one of the entries, the atom rdie switched method with a cutoff distance of 6.5–7.5 Å. Table II presents the results of six different simulations; each differs by varying the seed for the random number generator. The random number generator is used to set the initial velocities of the atoms, and hence only influences the initial direction of the trajectories. The arithmetic mean, $\bar{m}$, standard deviation, σ, and probable error, q, are


Shift
1Å Switch
Atom Truncate
4Å Switch
Group Truncate
No cutoff
Energy (Kcal/mole)
Time (ps)
a
b
c
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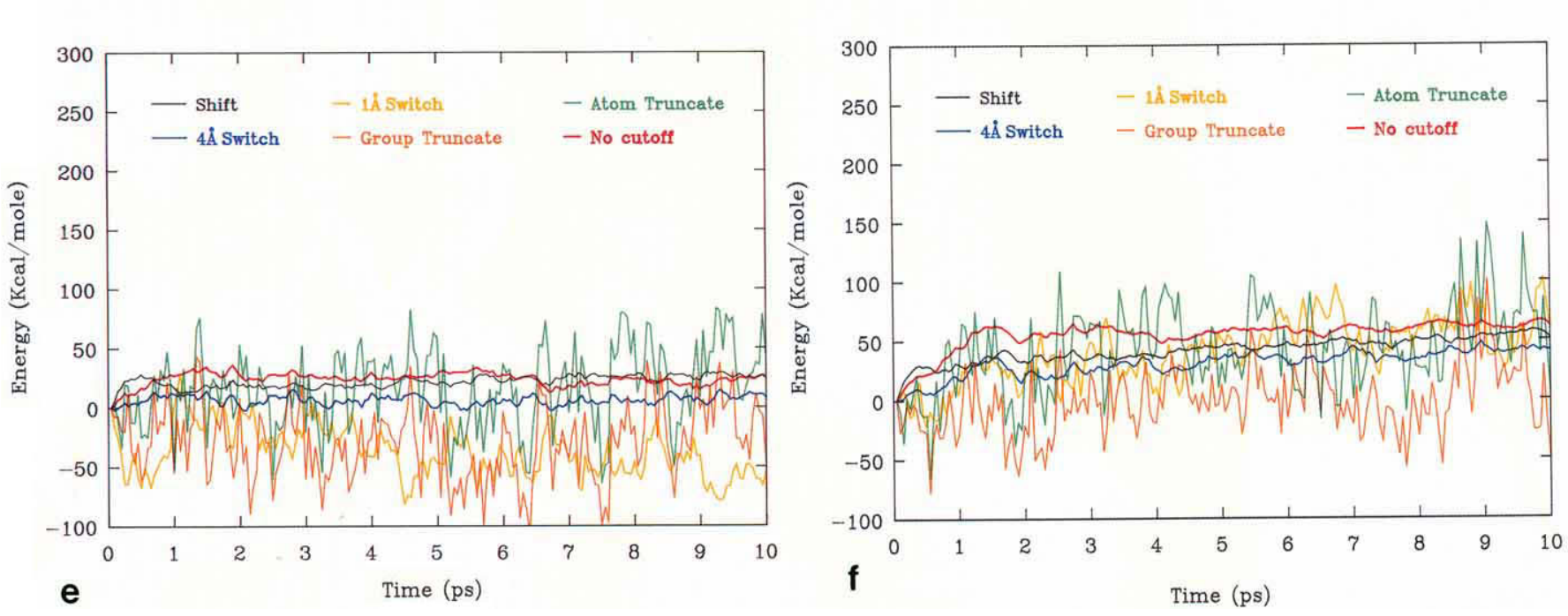

Fig. 7. Potential energy of the 7.5 Å cutoff potentials (atom–atom and group–group truncation based on distance, shift potential, 1 Å and 4 Å switching function) and the no cutoff potential on heating portion of the trajectories of **(a)** the no cutoff simulation, **(b)** the 7.5 Å shift simulation,**(c)** the 6.5–7.5 Å switching function simulation, **(d)** the 5.0–9.0 Å switching function simulation, **(e)** the 7.5 Å simple atom truncation simulation, and **(f)** the 7.5 Å simple group truncation simulation.

also shown in the table. The standard deviation is 0.08 in the rms fluctuations, 0.09 in the rms deviations of the main chain atoms from X-ray, and 0.20 in the rms deviations of the main chain atoms from the average coordinates of the no cutoff simulation. This corresponds to errors of 12.5, 4.0, and 9.3% in the fluctuations and deviations from X-ray and the no cutoff simulation, respectively. We expect that the percent error of the remaining entries of Table I is comparable. The general trends in the results of all the simulations should be meaningful since the probable errors are 0.05, 0.06, and 0.13 Å for the fluctuations, deviations from X-ray, and deviations from the no cutoff simulation.

Energy Time Series

To explore the relationship of several methods of truncating long range forces, an energy time series is employed for the shifted potential, the 1 Å and 4 Å switching regions, the atom–atom distance-based truncation, the group–group distance-based truncation, and the simulation with no cutoff. Except in the no cutoff example, a truncation distance of 7.5 Å is used for analysis. For each of these six truncation schemes an energy time series is computed for the simulation of each other method for the first 10 psec of the heating phase of dynamics. This means that one of the six truncation schemes is chosen to drive the trajectory, and then that energy surface is subsequently evaluated at each step of dynamics for each of the other five truncation methods. The results of these simulations are shown in Figure 7. In each plot the energies are all shifted so that the initial energies at the beginning of the simulations are all zero. At first glance of the six plots it is clear that Figure 7c is quite different from the other plots. In this figure, that of the 1 Å switching region energy surface, the energies of the other five methods increase by roughly 300 kcal/mol in 10 psec. By contrast, in all other plots the energies of six methods look fairly stable, more similar to the energy evaluation using the no cutoff truncation scheme. The drastic difference in the potential energy surface of the 1 Å switching region is caused by a realignment of groups of atoms, separated by a distance close to the cutoff distance, in a way which induces repulsive electrostatic interactions to be turned off while still maintaining attractive terms. For example, when the separation distance of a favorably oriented carbonyl (C=O) and a amide (H–N) group is increased through the cutoff distance, the electrostatic attraction of the carbon with the nitrogen is turned off first, followed by the two repulsive interactions of the carbon with the hydrogen and the oxygen with the nitrogen, finally followed by the other attractive interaction of the oxygen with the hydrogen going to zero. The distance at which only one attractive term remains can be a deep well in terms of the energetics, which forces the molecule into nonphysical behavior. There is no physical basis for this rearrangement that occurs with a small switching region (i.e., $r_{off} - r_{on} < 1$Å), but is similar to the Coulomb truncation problem that causes distortions in the distribution functions of ion–water interactions.[8] However, the nonphysical distortions in the energies of simulations with a 1 Å switching function surface are not found in simulations with a 4 Å switching region.

CONCLUSIONS

The nature and character of a simulation depend very heavily on the choice of method and distance used to truncate the long range forces. This manifests itself in severely affecting every observable we have examined. Molecular simulations using the shifted potential to truncate long-range forces give large deviations for cutoff distances less than 11 Å. Deviations and fluctuations are good in simulations where a cutoff distance beyond 11 Å is used, both for constant and distance-dependent dielectric screening. This method should be avoided unless the short-range potential is reparameterized or cutoff values of 11 Å or larger are used. For simulations using the 1 Å switching region, the rms deviation from X-ray as well as the fluctuations are consistently too small, even if switching off at distances of 14 Å. Furthermore, the energy time series plots indicate that when a short switching region is used, the resultant trajectory is energetically unfavorable using all other truncation methods. Simulations with longer switching function regions (e.g., from 5 to 9 Å using rdie) give acceptable fluctuations and deviations. This is because there is no short-range damage, as is found with the shifted potential, and that there are no large forces due to the derivatives of the switching function when switching over a long range (i.e., $r_{off} - r_{on} = 4$ Å). For simulations using a constant dielectric, even switching from 11–15 Å gave unacceptable results, thus an atom-based switching function should not be used for simulations employing a constant dielectric. *As a rule, truncation methods that introduce artificially large forces for long cutoff distances give poor results.* For these calculations, truncating long-range forces with a switching function based on neutral groups and over a very long range is probably best. For simple distance-dependent atom–atom truncation the deviations are reasonably good, but the fluctuations are consistently too large. Surprisingly this did not improve when neutral groups are employed. In the simple group–group distance-based truncation method fluctuations and deviations at short-range cutoffs exceed those in simulations using the atom–atom truncation method. At longer cutoff distances the atom–atom and group–group truncation methods yield similar results; although the latter method shows slightly large rms deviations. Both the atom–atom and group–group truncation

schemes based on list give less stable results than the corresponding distance based method for short distance cutoffs. *Moreoever, when truncating forces with any of these four methods the use of a large cutoff distance is important.*

A final point to remember: the rdie simulation with the smallest deviation from the X-ray structure (0.25 Å switching region) is probably the least realistic of the entire set of simulations that were truncated near 7.5 Å. *Consequently a simulation should not be judged by deviation from X-ray coordinates alone.* We hope that the results of these simulations provide assistance in choosing a method of truncating long range potentials in protein dynamics.

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