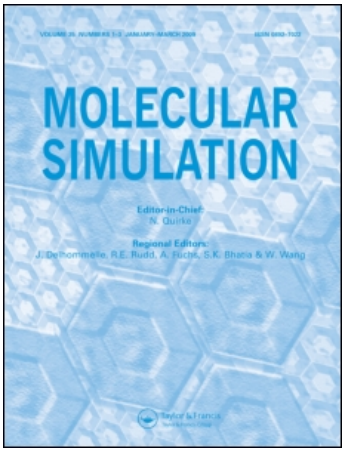

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Multiple Time Steps: Limits on the Speedup of Molecular Dynamics Simulations of Aqueous Systems

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MULTIPLE TIME STEPS: LIMITS ON THE SPEEDUP OF MOLECULAR DYNAMICS SIMULATIONS OF AQUEOUS SYSTEMS

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We have empirically tested limits of the magnitude of multiple time steps in molecular dynamics simulations of aqueous systems, and the extent to which these offer a means to shorten computation time. Three different steps were employed, $\delta_0 t$ for calculation of "bonded" forces, $\delta_1 t$ for calculations of short-range (<6 Å) non-bonded forces, and $\delta_2 t$ for long-range (<10 Å) non-bonded forces. Each longer step was a multiple of the shortest one. The leap-frog integration algorithm was used with SHAKE for restraint of all bond lengths and water molecules. For a system of SPC water molecules, calculation of short-range non-bonded forces could be done with a time step $\delta_1 t = 10$ fs, without appreciable change of the average temperature and energy, radial distribution function or diffusion coefficient. These properties were found to be insensitive to the inclusion of long-range non-bonded forces. A multiple-step protocol with $\delta_0 t = 2$, $\delta_1 t = 4$ and $\delta_2 t = 16$ fs has been compared with a single-step procedure with $\delta t = 2$ fs for small polypeptides in water. The exploration of conformation space, with crossing of low energy barriers, was tested with the glycine dipeptide and was found to proceed at similar rates. Mean, hysteresis and statistical error of the free energy for changing alanine to α-amino butyric acid in the dipeptide, calculated by the slow-growth method, proved independent of the cutoff distance or exact protocol, within 1 kJ/mol. In conclusion, we recommend, instead of use of a single time step of 2 fs at a 10 Å cutoff, use of a time step $\delta_t = 4$ fs for short-range nonbonded forces and a time step $\delta_2 t = 16$ fs for long-range nonbonded forces for a 60% reduction of computation time.

KEY WORDS: Multiple time steps, molecular dynamics, free energy calculations, conformational explorations, SPC water, peptides, precision

INTRODUCTION

Computer simulations of molecular dynamics of biological macromolecular systems require a gargantuan use of computer time. Even small improvements in the ratio of cpu time to simulated time are important. A good example is the introduction of SHAKE [1] which allows use of a larger integration time step and hence a significant savings in computer time at the cost of a non-physical constraint of all bond lengths to fixed values. Multiple time steps offer an additional or alternate opportunity to use less cpu time; the advantage is obtained by less frequently calculating forces that change slowly with time. The forces for bond stretching change the most rapidly and require an integration time step of 0.2 fs if all bonds, including bonds to H are unconstrained, but, as said, these forces are not calculated if SHAKE is used. Other deformations of the geometry (bond angle bend and out-of-plane twist) produce the next most rapidly changing class of forces, and require a

2 fs integration time step. Nonbonded forces vary more slowly especially forces for atom pairs not in immediate contact.

One possible way of establishing how frequently a particular force needs calculating, is to observe and analyze its time dependence [2]. We have instead followed an empirical procedure for testing the usable upper limits of time steps for short-range and long-range non-bonded forces, and arrive with new recommendations for a multiple time step protocol in molecular dynamics for aqueous systems. Multiple time-step schemes were first demonstrated by Streett *et al.* [3, 4] for fluids and by Swindoll [5] for chain molecules. Other schemes have been described for biomolecular systems by Telemann *et al.* [2] and by Grubmüller *et al.* [6]. Multiple time-step schemes for biomolecular systems have been used also by Berendsen *et al.* [7] and have been implemented in the AMBER program [8] by Darden (personal communication), but the methods used there have not been described in the literature.

METHODS

Multiple Time Steps With The Leap-Frog Algorithm

The leap-frog integration method is particularly suited for molecular dynamics with implementation of the SHAKE algorithm [1]. We have adapted the leap-frog integration method to a scheme with multiple time steps, as follows.

In the leap-frog method successive positions and successive velocities are half a time step apart: the force at the n-th time step, i.e. at time $n\cdot\delta t$, $\boldsymbol{F}_{i,n}$ is used to update the velocity of each particle, i from the value at time $n\cdot\delta t-\delta t/2$, $\boldsymbol{V}_{i,n-1}$ to that at $n\cdot\delta t+\delta t/2$, $\boldsymbol{V}_{i,n}$ according to

$$\boldsymbol{V}_{i,n}=\boldsymbol{V}_{i,n-1}+\delta t\ \boldsymbol{F}_{i,n}/m_i \tag{1}$$

(with m_i the atomic mass) and the velocity $\boldsymbol{V}_{i,n}$ is used to update the atomic position from the value at time $n\cdot\delta t$, $\boldsymbol{R}_{i,n}$ to that at $n\cdot\delta t+\delta t$, $\boldsymbol{R}_{i,n+1}$ according to

$$\boldsymbol{R}_{i,n+1}=\boldsymbol{R}_{i,n}+\delta t\ \boldsymbol{V}_{i,n} \tag{2}$$

The leap-frog scheme is a variant of Verlet's integration method [9, 10]; Verlet's method is characterized by the fact that it properly takes into account the linear part of any variation of the force and the velocity over the time step δt.

We have examined the implementation of multiple time-steps with the leap-frog scheme. We consider a leap-frog method in which a part of the force, $\boldsymbol{F}^{[1]}$ is calculated at every time step, but another part, $\boldsymbol{F}^{[k]}$ is calculated only once every k time steps, i.e., at times 0, kδt, $2k\delta t$, etc., i.e., the force $\boldsymbol{F}^{[k]}$ is applied unchanged at each time step that is not an integer multiple of k.

This method requires one to take into account $\boldsymbol{F}^{[k]}$'s linear change at the times at which it is not calculated, i.e., at times δt, $2\delta t$, . . . $(k-1)\,\delta t$, and again $(k+1)\,\delta t$, $(k+2)\,\delta t$, . . . $(2k-1)\,\delta t$, etc. The required change of $\boldsymbol{F}^{[k]}$ at these times is not known until the next evaluation of $\boldsymbol{F}^{[k]}$, i.e., at times $k\delta t$, $2k\delta t$, etc.

Corrections are applied that are equal to the cumulative difference in the velocities and positions for applying not a constant force, but a force that is linearly changing between successive values of $\boldsymbol{F}^{[k]}$. For the step at time $(nk+j)\ \delta t$, the

difference between the two forces is given by

$$\delta \boldsymbol{F}^{[k]}_j = (j/k)\{\boldsymbol{F}^{[k]}_{t=(nk+k)\delta t} - \boldsymbol{F}^{[k]}_{t=nk\delta t}\} = (j/k)\ \delta \boldsymbol{F}^{[k]} \tag{3}$$

and with equations 1 and 2 this gives

$$\delta \boldsymbol{V}_{i,j} = \delta \boldsymbol{F}^{[k]}_{i,j}\ \delta t/m_i \tag{4}$$

$$\delta \boldsymbol{R}_{i,m} = \sum_{l=1}^{m} \delta \boldsymbol{V}_{i,l}\ \delta t \tag{5}$$

Summation of all $k-1$ corrections over the interval works out to give

$$\delta \boldsymbol{V}_i = \sum_{j=1}^{k-1} \delta \boldsymbol{V}_{i,j} = \delta \boldsymbol{F}^{[k]}_i\ \delta t\,(k-1)/(2\,m_i) \tag{6}$$

$$\delta \boldsymbol{R}_i = \sum_{m=1}^{k-1} \delta \boldsymbol{R}_{i,m} = \delta \boldsymbol{F}^{[k]}_i\ (\delta t)^2\ (k^2-1)/(6\ m_i) \tag{7}$$

These corrections are added after calculation of new forces $\boldsymbol{F}^{[k]}$ at step nk, then the SHAKE algorithm is applied to the corrected positions, and after this the integration step continues normally. It is clearly essential for the longer time steps to be integer multiples of the shortest. Also, the time steps for non-bonded force calculations, the intervals for generation of a new pairlist and for extension of the trajectory output file, and the total simulated time are required to be successive multiples.

The application of this method requires additional storage for two copies of (each set of) the forces $\boldsymbol{F}^{[k]}$: one copy to use at the intervals when $\boldsymbol{F}^{[k]}$ is not recalculated, and another copy to contain the previous values as required by equations 3 through 7. The implementation by Grubmüller *et al.* [6] similarly requires two additional force arrays for each different multiple of the shortest time step.

Simulations

Simulations were performed with the Cedar program, running on a Convex C240, a Cray YMP or an IBM RS/6000 workstation. All simulations were done using all-atom representations [11].

Simulations of *liquid water* were performed on 266 rigid SPC water molecules [12] in a cubic periodic system slightly over 20 Å on each edge. The SHAKE procedure was applied at intervals of 2 fs in order to preserve the rigid molecular geometry of the model [1]. The system was coupled to a bath of constant temperature (300 K) and pressure (1 bar) with time constants of 50 fs and 200 fs for temperature and pressure coupling, respectively [13]. The non-bonded pairlist was updated every 100 fs (*c.q.*, every 96 fs in a scheme with a 16 fs time step).

The *glycine dipeptide* was studied with free dynamics in a periodic box with 256 water molecules (box edge slightly over 20 Å).

Free energies for *molecular replacement* were calculated with a system containing a molecule of the alanine dipeptide, N-acetyl alanine N′-methylamide in which one of the hydrogen atoms attached to C_β could be replaced with a methyl group, in

order to produce the dipeptide of α-amino butyric acid (Abu). This was studied in a periodic box with 499 water molecules (edge = 27.7 Å). Slow-growth molecular replacements calculations were carried out as described in recent reports from this laboratory [14, 15, 16]. In this method, the potential energy, U is made dependent on a coupling constant, λ, in such a way that for $\lambda = 0$ the potential energy describes the system with Ala, and for $1 - \lambda$ the potential energy corresponds to the system with Abu, the value of λ is changed after every dynamics step (starting at $\lambda = 0$ and ending at $\lambda = 1$, or *vice versa*) and the free energy change is estimated with

$$\Delta G^\circ_a = \Sigma \partial U/\partial\lambda \; \delta\lambda \tag{8}$$

Torsional bonds were used to select the most stable conformations of the dipeptides (β conformation for the backbone; side chain dihedral angle of Abu near 300°).

(Dis)similarity of time averages. The similarity or dissimilarity of computed system properties has been established, if possible using properties, y that can be computed by averaging of a time series. In such cases, a relaxation time, τ was computed from the autocorrelation function of the time series; it was then possible to compute an estimate of the variance of the *mean value* $\langle y \rangle$ over a simulation time θ, with the expression

$$\text{var}(\langle y \rangle_\theta) = (2\tau/\theta) \; \text{var}(y). \tag{9}$$

where $\tau \ll \theta$ and the mean-square deviation of y could be used as an estimate of var (y) [17]. Thus, it could be established if a different protocol produced the same or different value of a particular time average *and of its associated precision*, within tolerances that could be controlled by varying the length of the simulation.

This procedure was applied to the diffusion coefficient, D calculated from the correlation of the molecular positions and velocities with

$$3D = \langle \boldsymbol{R} \cdot \boldsymbol{V} \rangle_{N,\theta} \tag{10}$$

from a time series of $\langle \boldsymbol{R} \cdot \boldsymbol{V} \rangle_N$ (averaged over the N molecules in the system). It was also applied in order to estimate the precision of the free energy calculated for the transformation of Ala to Abu.

As in recently published work from this laboratory [15, 18] a time series of $\partial U/\partial\lambda$, calculated at *constant* λ, was used to estimate the variance of the mean, and this was used to indicate the magnitude of the variance of ΔG°_a (which is the mean of a time series $\partial U/\partial\lambda$ calculated while λ *varies*). While this method provides only an estimate of the variance of ΔG°_a, in this case, it provides a precise way of comparing the magnitude of the statistical error in ΔG°_a obtained with different time step schemes.

RESULTS

Overall Observations

Simulations with long time steps were frequently found to be unstable, in that sooner or later an atomic velocity would become very large and produce a

subsequent molecular conformation that was unsuited for the SHAKE procedure. In simulations with *slightly* shorter time steps the energy was not conserved: a considerable amount of energy was continually produced and removed by coupling to a heat bath. [However in the simulations with short time step and long, 10 Å cutoff the heat flow from the system to the bath was negligible.] In the simulations with a short time step and short, 6 Å cutoff, a small amount of energy was continually produced and removed, apparently because of systematic changes in the non-bonded pairlist: unfavorable interactions drive some atom pairs apart to separations greater than the cutoff, the next pairlist does not contain these pairs, which then can drift together to again be included in a pairlist. The excess energy produced by this mechanism is known to be greater if a small cutoff distance is used [19]. Since any flow of energy between the system and the heat bath requires a temperature difference, the system is at a slightly different temperature than the heat bath.

We have accordingly proceeded as follows. For any given system, we have first determined time step protocols that would allow stable dynamics simulations in which excess heat production due to the length of the time step was insignificant. We have then asked if use of the longer of these time steps produced identical system properties (within statistical error). By following this procedure we have been able to arrive at a recommended time saving protocol.

LIQUID WATER

Limits of the time step for nonbonded forces. Several key properties of the SPC water model were found to be conserved when a larger time step, $\delta_1 t$, was used for the short-range (6 Å) non-bonded forces. The translational diffusion coefficient of the SPC water model with a 10 fs time step was comparable to that found with a 2 fs time step while the diffusion constant found with a time step of 14 fs (6 Å cutoff) is significantly lower. The oxygen–oxygen radial distribution functions from simulations for increasing time steps up through 14 fs for non-bonded forces were not significantly different (data not shown) and densities were very similar (Table 1 and 2).

Table 1 Results from 2 ps simulations of SPC water with different cutoffs and different time step schemes.

Time step (fs)		⟨*Temp*⟩	⟨*Pot. Energy*⟩	*Relative*	*Heat loss*[a]	Density
<6 Å	*6–10 Å*	*(K)*	*(kJ mol^{-1})*	*cpu time*	*(kJ mol^{-1} ps^{-1})*	*(g ml^{-1})*
2	—	305	−41.8	0.28	1.9	1.00
4	—	303	−41.9	0.22	0.9	0.99
8	—	298	−41.8	0.20	−1.5	1.00
10	—	298	−41.9	0.19	−2.8	0.99
12	—	308	−41.7	0.17	3.2	0.99
14	—	443	−38.2	0.16	69.	1.02
2	2	301	−41.6	[1.00]	.03	0.99
2	16	304	−41.3	0.70	1.5	0.98
2	20	398	−38.4	0.60	47.	1.00
4	16	302	−42.0	0.40	0.3	0.98

[a] Energy passed from the system to the heat bath.

Table 2 Comparison of diffusion coefficients obtained by two different methods from 30-ps simulations.

Time step		D^a	D^b
0–6 Å	*6–10 Å*	*(10^{-5} cm^2 s^{-1})*	*(10^{-5} cm^2 s^{-1})*
2	—	3.8 (0.6)	3.5
10	—	3.9 (0.6)	4.0
14	—	1.8 (0.4)	1.7
2	2	3.5 (0.6)	3.7
4	16	3.3 (0.7)	3.4

[a] From the correlation of molecular position and velocity (Eq. 10). Root-mean-square deviations in parentheses (cf. Equation (9)).
[b] Values from the mean-square displacement (cf. Figure 1).

The results clearly show elevated mean temperatures for several cases with long time steps for nonbonded forces. There appears at first a systematic small *decrease* of the mean temperature as the time step for the non-bonded forces is increased, before the eventual steep rise. One may exploit this feature by selecting a multiple time step scheme with long time step(s) for non-bonded forces, in which the inherent tendency towards more elevated temperatures associated with long time steps just balances the tendency of the integration algorithm to produce a slightly lower temperature.

Limits on the time step for long-range nonbonded forces. Longer-range non-bonded forces (>6 Å) have less of an influence on system properties, such as the radial distribution function and diffusion coefficient; these forces vary less rapidly with distance, and therefore also with time. Thus, it should not be necessary to compute these as frequently as the shorter-range non-bonded forces. The non-bonded interactions from 6 to 10 Å were found to contribute about 10% of the total energy, while the longer range non-bonded interactions from 10 to 13 Å contribute only 1%. The energy calculated for the former was found to be sensitive to the history of the sample: after these interactions had contributed to the interatomic forces for some time, their energy was negative, whereas when these interactions were not made to contribute to the interatomic forces, their energy was positive. Thus, the sign and magnitude of the energy contributed by the long-range non-bonded interactions are (rare) indicators of whether these interactions are being treated properly with use of a longer time step. This energy term was found to have the same magnitude for all tested protocols in which long-range interactions were included.

As has been indicated, the energy for the long-range forces changes from a positive to a negative value at the beginning of a simulation in which these forces are included, if this immediately follows a period of simulations in which these forces have not been included. The change has an approximate half-time of *circa* 1 ps (data not shown).

A dual time step with short-range nonbonded forces calculated every 2 fs and long-range nonbonded forces at different time steps up to time steps of 16 fs gave comparable results to the single step method with a cutoff of 10 Å. With a time step of 20 fs for the long-range forces, mean temperature, energy and heat loss to the water bath were significantly different, as was the diffusion coefficient ($2.1 \cdot 10^{-5}$ cm^2 s^{-1}).

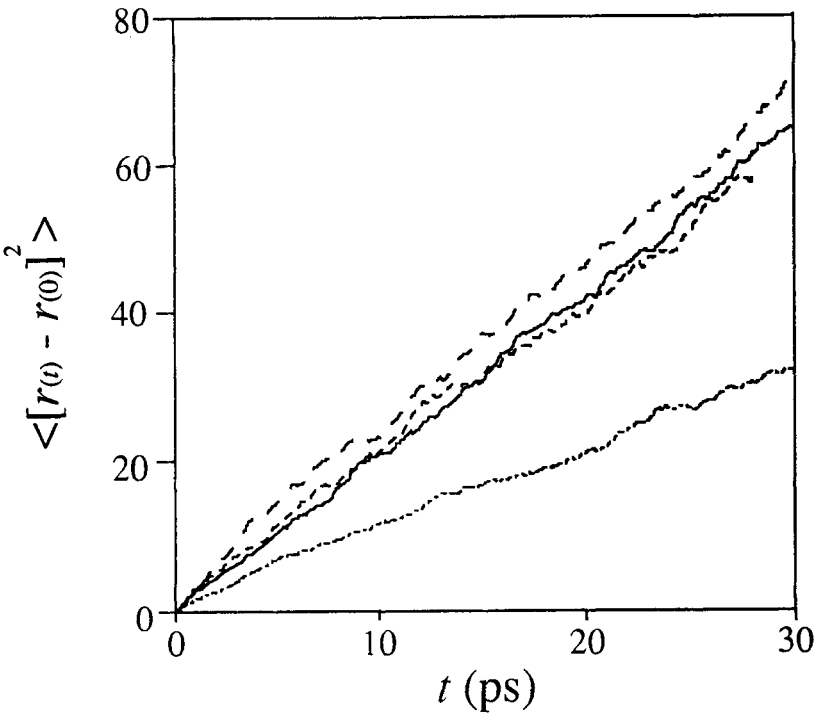

Figure 1 Mean-square displacement of SPC water molecules *versus* time. Solid line: single time step (2 fs, 6 Å cutoff). Short dashes: dual time step ($\delta_0 t = 2$ fs, $\delta_1 t = 14$ fs; non-bonded cutoff = 6 Å). Long dashes: single time step (2 fs, 10 Å cutoff). Medium dashes: triple time step ($\delta_0 t = 2$ fs, $\delta_1 t = 4$ fs, $\delta_2 t = 16$ fs).

The diffusion coefficient was determined from the mean square displacement away from the starting position (Figure 1) and, for some simulations, also from the correlation of velocity and position (equation 10). The two methods gave very similar results (Table 2). The estimated root-mean-square deviation of the mean diffusion coefficients was found to vary between 0.4 and 0.7 10^{-5} cm^2 s^{-1}.

It was, however, noted that with the addition of protein or polypeptides to the SPC water, the systems' mean temperature and energy were consistently well behaved with somewhat shorter time steps. Therefore, a protocol with time steps of $\delta_0 t = 2$ fs, $\delta_1 t = 4$ fs, $\delta_2 t = 16$ fs was tested in these and in subsequent experiments.

Conformational Explorations

Free simulations of the glycine dipeptide with explicit solvation have been reported from this laboratory [20, 21]; in these the dipeptide readily explored all low energy conformations. The low energy barriers separating the four almost iso-energetic minima were crossed on the average once every 10 ps. This system was used here in order to determine if the multiple time step scheme ($\delta_0 t = 2$ fs, $\delta_1 t = 4$ fs, and $\delta_2 t = 16$ fs) explores conformation space at a similar rate. Results from 300-ps simulations performed with single and multiple time steps were compared. The rate of conformation change was estimated from the time correlation of the backbone

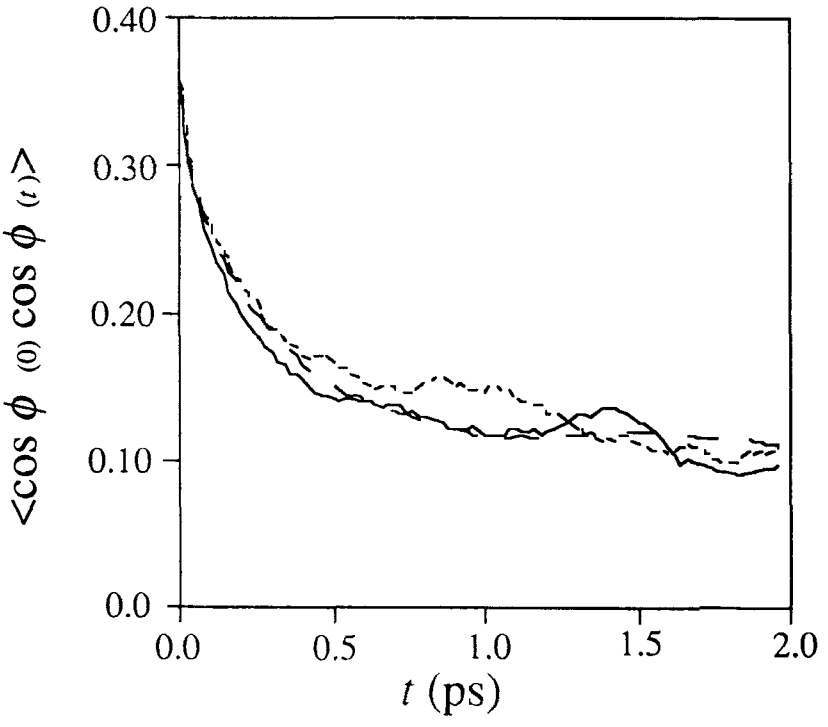

Figure 2 Autocorrelation function of $\cos\phi$ for the glycine dipeptide in free dynamics simulations. Long dashes: single time step, $\delta t = 2$ fs, cutoffs of 6 Å, over 1 ns; Solid curve: single time step, $\delta t = 2$ fs, cutoff of 10 Å, over 300 ps; short dashes: multiple time steps ($\delta_0 t = 2$ fs, $\delta_1 t = 4$ fs, $\delta_2 t = 16$ fs), over 300 ps.

dihedral angles, ϕ and ψ, of the dipeptide. As shown in Figure 2, single and multiple time step schemes produced equally rapid relaxation of the backbone conformation.

Free Energy Calculations

Different protocols were applied to free energy calculations where Ala was mutated to Abu in a dipeptide. As in earlier work [22], the free energy changes were computed from several runs with alternatingly increasing and decreasing coupling parameter λ, separated by short equilibrations at constant λ. Mean value and mean-square deviation of the free energy change were calculated for each direction of the change of λ. The sum of the means for the two directions gave the hysteresis, and half the difference was taken as the best estimate of the sought free energy difference. Results are given in Table 3.

According to these results, the value and the statistical error of the computed free energy difference are insensitive to the change in the cutoff distance and to the variation of the time-step protocol within 1 kJ/mol. The variance of the mean $\partial U/\partial\lambda$ calculated from a time series at constant $\lambda = 1$ was identical for all protocols within a much narrower limit (cf. equation 8; data not shown).

Table 3 Free energies calculated for changing Ala to Abu and the reverse in the dipeptide.

Time step (fs)		*Mean* ΔG°_{a}	*Simulation time*
0–6 Å	*6–10 Å*	*(kJ/mol)*[a]	*(ps)*
2	—	−5.9 (0.9)	60
4	—	−5.9 (0.9)	60
2	2	−5.6 (0.5)	60
4	16	−6.1 (1.2)	32

[a] Averages of 8 values, each obtained in the indicated simulation time, alternatingly with increasing and decreasing λ, with 12 ps equilibrations in between. (Root-mean-square deviations in parentheses).

Other results.

For the sake of completeness we report here also that some tests were done using this multiple time step scheme for simulations of a small protein in water. These results were inconclusive, as the simulated time was too short because insufficient computer time was available to us in order to exhaustively study this much larger system. Small differences between the results with and without long-range interactions and with different time step schemes can as easily be attributed to differences in time evolution of similarly behaved systems, as to differences in physical behavior. Much longer simulations are required in order to determine if such small differences are significant, as was done, for example, in a study by Brooks [23] of the effects of various truncation schemes for the non-bonded forces.

DISCUSSION

The extent to which, in a system of SPC water molecules, the time step for non-bonded forces could be increased without a change in structure, energy or dynamics came as an agreeable surprise. The results obtained here with use of multiple time steps suggest that routine molecular dynamics simulations of biological macromolecules in aqueous systems can be speeded up by a factor of more than 2 relative to calculations with a single time step of 2 fs and a non-bonded cutoff of 10 Å, and by a correspondingly larger factor relative to calculations with a single time step of 1 fs. A speedup of this magnitude is significant because of the extent to which molecular dynamics simulations are currently being applied to problems of structure and function of biological macromolecules.

The simulation techniques that are most commonly employed in studies of biological macromolecules are far from perfect. The lack of energy conservation due to use of a non-bonded pairlist and an energy function that has not decayed to zero at any cutoff distance are commonly accepted. Any use at all of a non–bonded cutoff introduces inaccuracies in the way the model is implemented in the simulation. In addition, the molecular mechanics model can never be more than an imperfect representation of the intermolecular forces. In deciding whether to adopt the longer time step, one must weigh the disadvantage of a certain mathematical error in the integration method, which may affect physical properties of interest, against the advantages of increased sampling of the Boltzmann distribution by the use of an increased simulated time interval.

The ability to perform longer simulations is especially important in macromolecular systems because of their long relaxation times and because the particles in these systems are not equivalent, and the statistics are correspondingly poor. The longer time steps whose use is here advocated presumably do affect the precision of the model, although we have failed to establish to what extent. The use of longer time steps is justified as long as the precision attainable with use of longer time steps exceeds the precision demanded of the model, for example by the precision attainable in parallel experimental studies. This does not nullify the need to use short integration time steps for precise determination of properties of systems such as liquids, for which relaxation times are usually shorter and sampling is better because many equivalent particles are simulated simultaneously.

As with any change of protocol, the validity of this altered scheme will have to be further tested by application in different systems, with a variety of tasks, such as, structure refinement, free energy simulations and studies of dynamics.

This study did not test the appropriateness of using longer time steps for interactions over distances larger than 10 Å. The reason for this was that the system properties that were investigated proved themselves rather insensitive to increases of the cutoff distance. This question should presumably be studied with one or more systems containing ions. *A priori*, one expects that the forces between a set of positive and negative ions in a solvent would change more slowly with time due to diffusive motion of the ions, the greater the separation of the ions. Of course, the energy is determined not only by the interaction of the ions but also by the interactions of the ions with the solvent water molecules and the interactions of the water molecules with each other. It is to be expected that the water molecules adapt much more quickly to changes in the field of the other particles as a result of rotational diffusion, than do the ions themselves as a result of translational diffusion. The upper limit of the time step for very-long-range electrostatic forces will be determined by the requirement to maintain the water molecules properly oriented as a dielectric. The magnitude of this upper limit remains to be determined.

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