

MASS AND STEP LENGTH OPTIMIZATION FOR THE CALCULATION OF EQUILIBRIUM PROPERTIES BY MOLECULAR DYNAMICS SIMULATION

Régis POMÈS and J. Andrew McCAMMON

Department of Chemistry, University of Houston, Houston, TX 77204-5641, USA

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The effectiveness of combining an assumed hydrogen mass of 10 amu with large step lengths of up to 10 fs in molecular dynamics calculations of equilibrium properties of pure water is investigated. Results are evaluated with respect to simulations featuring an H mass of 1 amu and time step of 2 fs. Although the increased mass reduces the rate of sampling of configurations somewhat, this method allows a significant reduction in the computer time needed to calculate structural and thermodynamic properties.

1. Introduction

Statistical thermodynamic calculations based on molecular dynamics (MD) simulations have become a method of choice in the study of condensed phases. These techniques have been used in studies of solvation phenomena [1], and in studies of molecular recognition and binding [2], as described in a number of recent reviews [3–8]. To limit the cost of such simulations, it may be useful to apply some unphysical scaling to the masses of the atoms in the system. In liquid water, for example, rapid librational motions occur that limit the step length of MD simulations even if rigid models are used for the individual molecules. In order to slow these fastest motions, one can increase the mass of the light atoms. This procedure will allow the use of longer time steps in the simulations, without affecting the recovery of classical thermodynamic or structural properties (which are independent of the particle masses) as time averages over configurations generated during the MD run. Assuming that the increased mass has a smaller effect on the rate that the system explores the configuration space, the use of increased masses could allow more efficient sampling of that space. Thus, thermodynamic averages could be calculated using fewer but larger time steps.

The idea of scaling particle masses to improve the efficiency of calculation of equilibrium properties is not new. Bennett introduced an anisotropic mass

tensor in order to improve the efficiency of configuration sampling in MD simulations [9]. Wood reported equilibrium results from MD simulations of water in which hydrogen masses were scaled by a factor of ten [10]. However, no systematic study has been done to assess the effectiveness of combining heavy assumed hydrogen masses with long time steps. In the present work, we investigate the effects of step length and hydrogen mass variation in MD simulations of liquid water. The total internal energy, radial distribution functions, and free energy changes were computed from a series of simulations, for water models with hydrogen masses of 1 and 10 amu, respectively. The relative accuracy of these calculations is compared and discussed.

2. Methodology

The system studied consists of 215 water molecules in a cubic box of 1.877 nm edge, i.e. with a density of 0.97 g/cm³. Periodic boundary conditions were applied so as to simulate an infinite liquid structure. The TIP3P water model [11] was used for both the geometry of the molecules and their non-bonded interaction parameters. MD calculations were carried out using the Amber package [12], in which the equations of motion are integrated using the leap-frog algorithm. The SHAKE algorithm [13] was used to constrain molecular geometry. The ST2

switching function [14] was implemented so as to minimize artifacts due to the neglect of potential energy and force terms beyond 0.75 nm. Thermalization of a lattice system was achieved by a 1 ps *NVE* run with velocity rescaling at 300 K every 0.2 ps. The system was then equilibrated during a 10 ps *NVE* run with a time step of 1 fs. The resulting configuration was stored to be used as a common starting point for the following simulations.

A series of *NVE* simulations over 0.6 ps was first performed with time steps varying from 1 to 10 fs. The average value and rms fluctuations of the total internal energy were computed. The simulations were then repeated with an H mass of 10 amu. For consistency, in these and the following runs as well, the non-bonded pair list was updated every 10 fs or the closest possible interval, whatever the step length.

Three 30 ps *NVT* simulations were then performed with the following parameters: respectively, a hydrogen mass of 1 amu with a time step of 2 fs; 10 amu with 6 fs; and 10 amu with 10 fs. The temperature was constrained at 300 K by coupling to an external bath; the Berendsen algorithm for rescaling the velocities [15] was used with a relaxation time of 0.4 ps. The position coordinates of oxygen atoms were stored every 10 or 12 fs and used to compute the oxygen–oxygen radial distribution function. The rms displacements of oxygen atoms were also calculated and averaged over three consecutive periods of 10 ps.

Finally, the free energy change for removing partial charges on a solvated water molecule was computed for two systems combining respectively a hydrogen mass of 1 amu with a time step of 2 fs, and 10 amu with 10 fs. *NVT* simulations over 150 ps with a changing Hamiltonian were performed in both forward and reverse directions. Helmholtz free energy differences were computed by the thermodynamic integration method [16]. The integration parameter, λ , was varied between 0.0 (the fully charged case) and 0.5 over 100 ps, and between 0.5 and 1.0 over 50 ps, so as to take into account the larger changes in ΔA when λ is small.

3. Results and discussion

The influence of hydrogen mass and step length on

the stability of simulations of water at equilibrium is illustrated in fig. 1. The expected quadratic dependence of the rms fluctuations in total energy upon step length [17] is well exhibited for both systems. Heavy hydrogen masses diminish the destabilizing influence of long time steps. In the low mass case, using a time step larger than 8 fs caused the interruption of the run, because the SHAKE algorithm became unstable and was unable to constrain the bond lengths. Using hydrogen masses of 10 amu, it seems that one can afford a time step of 5 to 6 fs before recovering the same magnitude of relative rms fluctuations as exhibited by the combination most frequently used, namely a hydrogen mass of 1 amu and a time step of 2 fs. This is likely due to the reduction of the highest frequencies of motion in this system, namely, those corresponding to the librations of the water molecules.

The plots of the oxygen–oxygen radial distribution functions calculated for both standard and heavy water (fig. 2) with respective step lengths of 2 and 6 fs show no deviation other than statistical. Similarly, no change appears when the time step is increased to 10 fs with a hydrogen mass of 10 amu.

Fig. 3 shows that the rate of displacement of the oxygen atoms does depend somewhat on the mass of the attached hydrogens, even at fairly long times (10 ps). Although this rate is not physically meaningful for the system with the large hydrogen masses, these

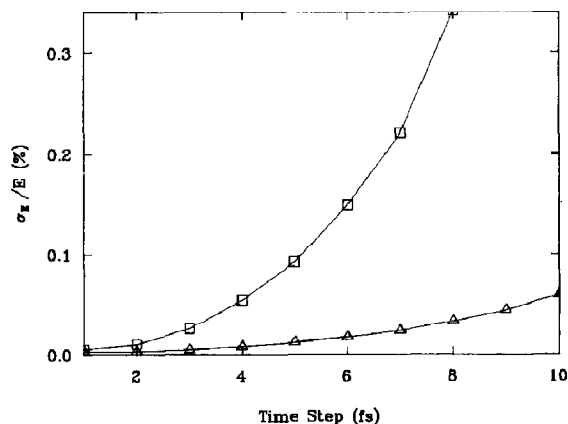


Fig. 1. Relative rms fluctuations in total internal energy as a function of the time step. Squares and triangles are for hydrogen masses of 1 amu and 10 amu, respectively.

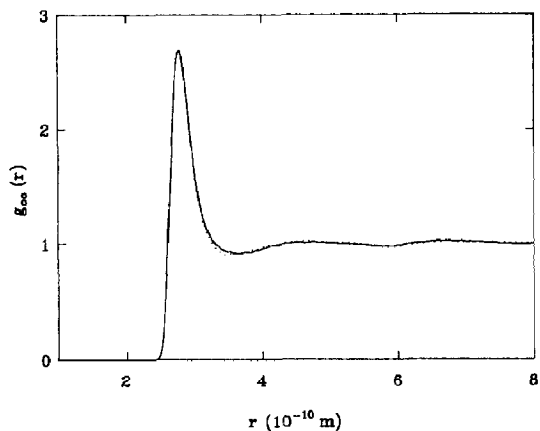


Fig. 2. Oxygen-oxygen radial distribution functions. Solid and dotted lines are for hydrogen masses of 1 amu and 10 amu, respectively.

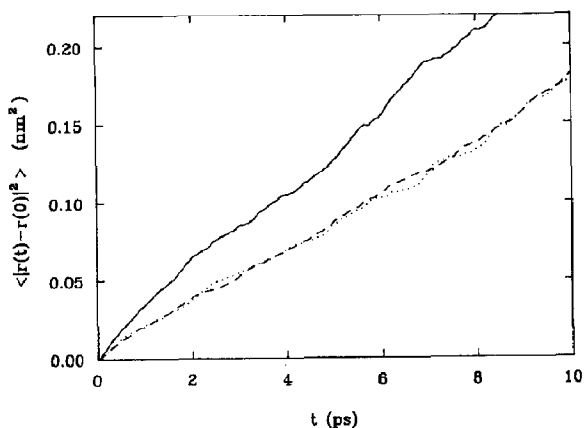


Fig. 3. Rms displacements of oxygen atoms as a function of time. Solid line is for hydrogen mass of 1 amu and time step of 2 fs. Dashed and dotted lines are for hydrogen mass of 10 amu and time steps of 6 and 10 fs, respectively.

results are a measure of the rate of exploration of configuration space and are therefore relevant to the rate of convergence in calculations of equilibrium quantities. From these data the apparent self-diffusion coefficient of water, D , was calculated using Einstein's equation

$$D = (1/6t) \langle |r(t) - r(0)|^2 \rangle,$$

which is valid at long times. Results are $(4.2 \pm 0.4) \times 10^{-5} \text{ cm}^2/\text{s}$ for a hydrogen mass of 1

amu and $(3.0 \pm 0.3) \times 10^{-5} \text{ cm}^2/\text{s}$ for a hydrogen mass of 10 amu. Thus, there is a 28% loss of diffusional mobility of the molecules upon increasing the mass of the hydrogen atoms from 1 to 10 amu. Because the long-time displacements of the water molecules are diffusional in character, and the diffusion constant depends only on the particle size and the viscosity of the surrounding medium, the above results can be interpreted as arising from an increase in the apparent viscosity of the liquid associated with the increased mass.

Helmholtz free energy changes for switching off and on the charges of a solvated water molecule are plotted in fig. 4. The values of the free energy differences averaged over forward and reverse integrations are 8.2 ± 0.1 and 8.5 ± 0.2 kcal/mol respectively, for the standard and heavy water systems. The hysteresis is respectively 0.09 and 0.43 kcal/mol. The relative error exhibited by the heavy hydrogen system with respect to the standard water system amounts to only 4%. Previous studies of the dependence of the hysteresis in such calculations upon the simulation time showed that the hysteresis was larger for shorter simulations [18]. The slight increase in hysteresis for the heavy water system compared to the standard water system therefore simply reflects the somewhat reduced rate of configurational sampling in the former system.

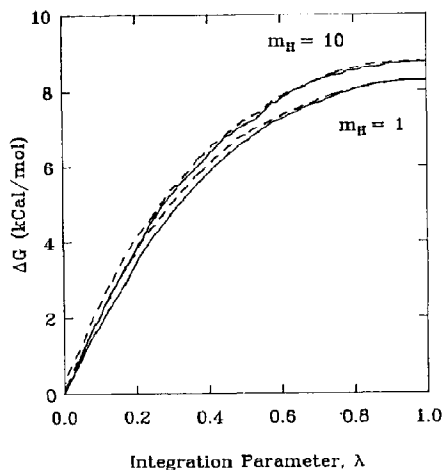


Fig. 4. Free energy changes for removing (forward) and adding (reverse) partial charges on a water molecule in solution. Forward runs are solid lines, reverse runs are dashed.

4. Conclusions

We have seen that from strict stability arguments, it is possible to increase the step length of MD simulations of water from 2 to 6 fs by assuming a hydrogen mass of 10 amu. Furthermore, the recovery of the radial distribution function, an equilibrium property, is not affected when the step length is further increased to 10 fs for the system with increased masses. On the other hand, the computed value of the self-diffusion coefficient, a dynamical property, was reduced by 28% upon hydrogen mass scaling, but not further affected by the use of a 10 fs time step. Finally, the free energy difference between an uncharged and normally charged water molecule, calculated with a 10 fs time step and the heavy hydrogen mass, did not differ significantly from its 2 fs time step, standard mass analog.

From a practical point of view, these results suggest that one can carry out more efficient simulation calculations of equilibrium properties by using an H mass of 10 amu along with a step length of 10 fs. Simulation times longer by about 30% may be needed to recover the same extent of configuration sampling (as monitored by the rms displacements of individual molecules), compared to calculations using a time step of 2 fs. Such simulations should yield classical free energy changes of similar accuracy. In terms of computer time, the gain associated with the longer time step is then somewhat offset, both by the need to run simulations for a longer time so as to get equivalent sampling and by the possible need to update the non-bonded list after a smaller number of time steps. In the calculations reported here, the frequent updating used in these simulations reduced gains in computer time by 40%. Ultimately, however, there was a threefold reduction in the cost of our calculations of free energy changes, so that the use of heavy masses for hydrogen atoms can be recommended as a simple and reasonably effective means of increasing the computational efficiency of such studies.

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