

## STOCHASTIC BOUNDARY CONDITIONS FOR MOLECULAR DYNAMICS SIMULATIONS OF ST2 WATER

Axel BRÜNGER, Charles L. BROOKS III and Martin KARPLUS

*Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA*

Received 26 November 1983

The deformable stochastic boundary method developed previously for treating simple liquids without periodic boundary conditions, is extended to the ST2 model of water. The method is illustrated by a molecular dynamics simulation of a sphere containing 98 water molecules. Comparison with the results of the periodic boundary simulation by Stillinger and Rahman shows very good agreement for structural and dynamic properties.

### 1. Introduction

Molecular dynamics simulations have provided important insights into the details of condensed phase chemical dynamics [1]. More recently, the application of molecular dynamics to proteins has opened the way for understanding the relation between structure, dynamics and function in these molecules [2–4]. Although considerable progress has been made, the study of reactive processes in solution [5–7] and in biomolecules [8] by the methods of molecular dynamics still remains a challenging problem.

A feature of many reactive processes in dense media (liquids, solids, and proteins) is their spatial localization, e.g., butane isomerization in water requires consideration only of the region around the butane molecule and an enzyme catalysed reaction takes place in an active site. For such localized processes, relatively few atoms participate directly and it is desirable to eliminate from the calculation the need to determine the detailed dynamics of atoms distant from the reaction site. This clearly implies that the use of standard molecular dynamics with periodic boundary conditions is inefficient, if not inappropriate. The simplest approach to the problem is to treat a region around the reactive site by molecular or activated dynamics and to surround it by a fixed set of atoms whose potentials act on the particles in the reaction region. This has been done in a simulation of aromatic ring flips in

a protein [8]. Although of considerable interest, such a simple treatment involving hard boundaries and allowing no energy transfer can introduce artifacts into the results. An alternative, more realistic approach surrounds the active region by a stochastic heat bath. This heat bath should be constructed to preserve the equilibrium structure and structural fluctuations in the region near the reaction site. It can also provide an appropriate sink and source for the local energy fluctuations which are produced by the reaction.

Two closely related approaches to the problem of constructing such a localized simulation system have been proposed recently [9,10]. In these approaches the effects of distant solvent atoms are included by introducing two types of contributions. First, there is a static force field that mimics the detailed atom–atom interactions and second, there is an intermediate region of Langevin particles which account for the many-body dissipative and random force interactions. To construct such a reaction system, the many-body solvent is decomposed into two major regions, a boundary or reservoir region and a reaction zone. The reaction zone is further divided into a reaction region and a buffer region. Atoms in the reaction region are treated by molecular dynamics in accord with Newton's equations. The buffer region atoms evolve in time according to Langevin dynamics and therefore provide the stochastic heat bath. The boundary or reservoir region surrounds the reaction zone and provides a static

force field that maintains the equilibrium properties of the atoms in the reaction zone. Neglect of these static forces is known from earlier work to lead to spurious density effects within the simulation region [10, 11].

The major difference between the two proposed methods is in the representation of the static force field. Berkowitz and McCammon [9] introduce the reservoir region forces by explicitly including a shell of fixed atoms. In the method proposed by Brooks and Karplus [10], the static forces are computed from an analytic mean field approach, this avoids any dependence of the results on the chosen reservoir structure and eliminates the necessity of explicitly including many additional force centers from the reservoir region in the computation [9]. Both approaches yield radial distribution and velocity autocorrelation functions for liquid argon in satisfactory agreement with full computer simulations

The purpose of this paper is to explore the extension of these boundary methods to more complicated fluids. The specific system we examine is the ST2 model for liquid water [12]\*. The ST2 model was chosen for our initial investigation because of its importance as a water model and because its properties are well established from conventional simulations [12,13]; application of the approach to the other water models now in use would be straightforward [14]. As we show below, a combination of the ideas introduced in the two boundary simulations for simple fluids provides a model for a localized simulation of ST2 water with properties that justify its application to specific problems of reactions in solution and its extension to biomolecules.

## 2. Method

A representative configuration of water molecules was chosen to fill a sphere of 15.7 Å radius. This configuration was constructed by periodically repeating an equilibrated cubic box of 125 water molecules obtained from a previous Monte Carlo simulation of MCY water [15] and "cutting away" all molecules with centers outside the 15.7 Å sphere. The resulting 15.7 Å sphere of 534 molecules represents the simulation sys-

tem. It was partitioned into a preliminary reaction zone consisting of the molecules within a radius of 10.7 Å from the origin (168 molecules) and the reservoir region comprised of the remainder of the system between 10.7 and 15.7 Å (365 molecules); the final reaction zone used in the simulations was a reduced sphere with a 9 Å radius. All the water molecules were adjusted to the correct ST2 geometry with the SHAKE algorithm and the lone pair positions were built using the computer program CHARMM [16]. This procedure produced a starting configuration of ST2 molecules with a mean density near 0.0334 molecules/Å<sup>3</sup> (0.9982 g/cm<sup>3</sup>) appropriate for water at 283 K and 1 atm.

The most direct approach to utilizing this spherical system is to follow the method of Berkowitz and McCammon [9], i.e. to perform a dynamics simulation for the molecules within the reaction zone in the field of the fixed molecular force centers in the reservoir region. A short simulation was performed for such a system with the reaction zone consisting of a molecular dynamics reaction region extending from the origin to 6.0 Å and a Langevin buffer region between radii 6.0 and 9.0 Å. The reservoir region in this simulation consisted of fixed molecules between radii 9.0 and 14.7 Å. The 9.0 Å reaction zone was chosen to be consistent with the average boundary force simulation (see below).

As an alternative to the fixed molecule reservoir region, boundary forces on the molecules in the reaction zone were determined by an adaptation of the mean field approach of Brooks and Karplus [10]. To obtain a radial force acting on each site (oxygen, hydrogens, lone pairs) of the ST2 molecules, an average over positions within the reaction zone was performed. It consisted of placing an ST2 site at a position ( $r, \theta, \phi$ ) within the cavity defined by the reservoir region and computing the force on this site due to interactions with the static reservoir molecules. The radial component of this force was projected out and accumulated on a radial grid of 0.08 Å for angular grids ( $\Delta\theta$  and  $\Delta\phi$ ) of 10°. The radial forces were then averaged over spherical surfaces for each  $r$  by use of a bicubic spline integration scheme to yield an average ST2 site boundary force. From the tabulated forces a potential was computed by a trapezoidal integration and fitted to a cubic spline on the grid of points. The resulting spline coefficients served to define a boundary poten-

\* For a comparison of different water molecules, see ref. [13].

tial with a consistent set of first and second derivative functions for the numerical studies.

Decomposition of the forces on an ST2 molecule into individual site contributions involves an approximation due to the electrostatic switching function centered on the oxygen in the model [12]. To circumvent this problem it was assumed that the test ST2 site and the test ST2 oxygen atom were coincident in the calculation of the boundary forces. This maintains the site decomposibility and the radial nature of the boundary forces, but essentially eliminates the electrostatic contributions from the boundary force

Given the boundary forces and the reaction zone, the positions of the water molecules were relaxed to relieve close contacts between water molecules and the boundary by performing 200 steps of constrained energy minimization with a conjugate gradient method [17]. The molecules within the reaction region were then propagated according to molecular dynamics with a combination of SHAKE and the Verlet algorithm [16]. The stochastic dynamics algorithm employed for motion in the buffer region is a variant of the Verlet algorithm and is based on the simple Langevin equation in the limit that  $\beta\Delta t \ll 1$ , with  $\Delta t$  the time step in the integration. The algorithm, written here for a generic atomic coordinate  $x$ , is

$$x(t + \Delta t) = (1 + \frac{1}{2}\beta\Delta t)^{-1} \{2x(t) - x(t - \Delta t) + [F(t) + f(t)] \Delta t^2/m + \frac{1}{2}x(t - \Delta t)\beta\Delta t\}, \quad (1)$$

where  $\beta$  is the friction constant and  $f(t)$  is a gaussian random force with statistical properties

$$\langle f(t) \rangle = 0, \quad \langle f(t)f(0) \rangle = 2k_B T\beta m \delta(t). \quad (2)$$

The force  $F(t)$  is the sum of terms from direct interactions involving molecules in the reaction zone and the contribution from the reservoir region. In the first approach this is calculated by summing over all interactions; in the second approach, the force due to the reservoir region can be written as

$$F_B^i(r^i) = (r^i/|r^i|)F_W^i(|r^i|), \quad (3)$$

where force  $F_W^i$  is the boundary force on site  $i$  obtained by the averaging and fitting procedure described above.

The Langevin forces were applied to the oxygen atoms for ST2 molecules within the buffer region. Assignment of friction only to the oxygen atom centers is consistent with the spirit of a simplified heat bath

model and our use of rigid molecules. The friction coefficient for the oxygens,  $51.3 \text{ ps}^{-1}$ , was chosen to be consistent with the center of mass translational diffusion coefficient near 283 K.

### 3. Results and discussion

In this section we describe briefly the simulation and results obtained with the explicit fixed molecule model for the reservoir region and then concentrate on the average boundary force model.

#### 3.1. Fixed molecular boundary force

A trial simulation was carried out for 2.7 ps, 1.5 ps of thermalization and equilibration plus 1.2 ps of dynamics for analysis. At the end of this short simulation period, it was clear that the fluid was too structured with the density of molecules increasing towards the boundary region. Specifically, the oxygen atom velocity autocorrelation function was highly oscillatory and the site-site radial distribution functions were of poor quality. Apparently, the explicit molecule static reservoir region was "freezing" water molecules on its surface. This is not surprising in view of the strong directional forces present due to hydrogen bonding (electrostatic) interactions.

#### 3.2. Averaged boundary force

Fig. 1 shows the average boundary potentials obtained for the sites of ST2 water. We see that the potentials acting on the hydrogens and lone pairs are essentially constant over the region of interest, while that for the oxygen approximates a simple van der Waals potential with a strong repulsion as the atom approaches the boundary. This results from the fact that the model employed here averages out most of the electrostatic contributions; this would be expected from a uniform shell boundary. Such a structureless potential is a good first approximation that avoids the freezing effects noted in the simulation with the fixed molecule boundary force. However, a more detailed representation of the electrostatic interactions at the boundary may be important for the study of inhomogeneous systems, such as solvated biomolecules. Use of the analytic deformable boundary treatment [10]

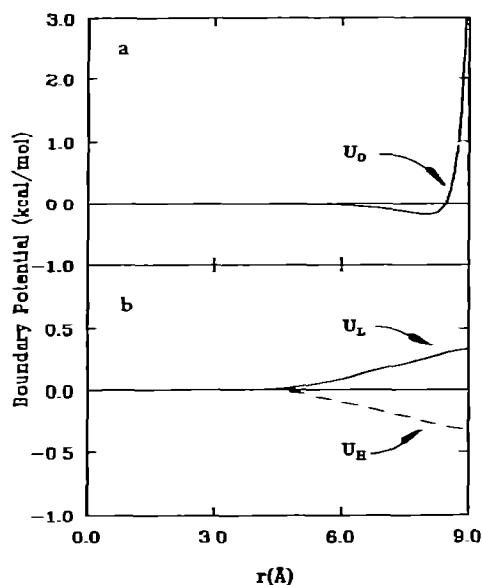


Fig. 1 Site boundary potentials for ST2 water. The boundary potential in kcal/mol is plotted versus separation of the site from the origin  $r$  in Å: (a) the ST2 oxygen site; (b) the ST2 hydrogen site and the ST2 lone pair site.

for a site decomposable model (e.g., TIPS water [12–14]) introduces more structure than appears here.

A molecular dynamics simulation was performed with the boundary potential just described and 98 ST2 molecules in a sphere of 9.0 Å radius, comprising the reaction zone. This reduced radius results from the spherical averaging of the boundary force over the non-uniform 10.7 Å cavity in the reservoir region. For the oxygens, most of the contribution to the boundary force comes from Lennard-Jones interactions with static reservoir ST2 molecules near the boundary. The average position of these ST2 molecules is roughly  $\langle R \rangle = 10.7 \text{ Å} + \frac{1}{2} R_{OO}$ , where  $R_{OO}$  is the separation at which  $g_{OO}(r)$ , the oxygen–oxygen distribution function, has its first maximum (see e.g. fig. 3a). The repulsive “wall” from this averaged Lennard-Jones interaction occurs at approximately  $\langle R \rangle - \sigma$ ; with  $R_{OO} \approx 2.84 \text{ Å}$  and  $\sigma = 3.1 \text{ Å}$ , this is equal to  $\approx 9.0 \text{ Å}$ , the effective radius of the reaction zone. The dynamics simulation was carried out for 20 ps (with a time step of 0.001 ps); the resulting average temperature and density within a 9.0 Å sphere were 286 K and 0.0321 molecules/Å<sup>3</sup>, respectively; four additional ST2 mole-

cules in the reaction zone would have raised the density to 0.0334 molecules/Å<sup>3</sup>. In this simulation, molecules within an 8.2 Å radius sphere centered at the origin were labeled as reaction region molecules and moved with the molecular dynamics algorithm. The remaining molecules between 8.2 and 9.0 Å were labeled as buffer region molecules and propagated according to the stochastic molecular dynamics algorithm. Since molecules go from one region to another during the course of the simulation, the labeling was updated every five dynamics steps.

From the 20 ps simulation, basic properties describing the equilibrium structure and dynamics of the system were computed; the entire simulation period was used for analysis since no differences were observed in separate analyses of 5 ps subperiods. The properties computed include the oxygen atom velocity autocorrelation function and its spectral density for the oxygen atoms within a 6.0 Å radius analysis region centered at the origin (fig. 2), the site–site radial distribution functions around molecules within a 4.0 Å analysis sphere (fig. 3), and the density profile of molecules within the 9.0 Å radius reaction zone (fig. 4).

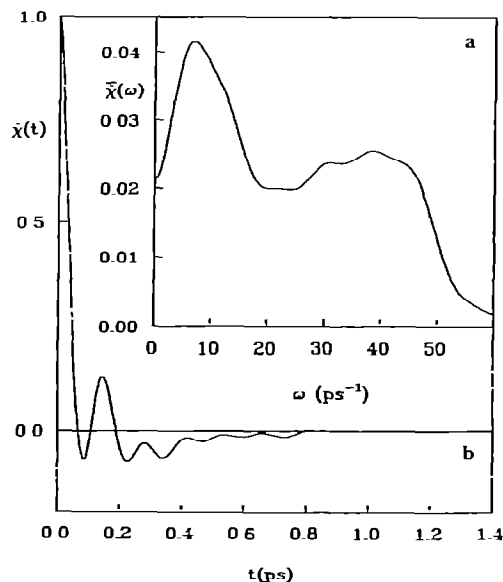


Fig. 2. Velocity autocorrelation function and spectral density function for the ST2 oxygen atom: (a) The normalized velocity autocorrelation function versus time  $t$ , in ps; (b) the spectral density in ps versus frequency  $\omega$ , in ps<sup>-1</sup>.

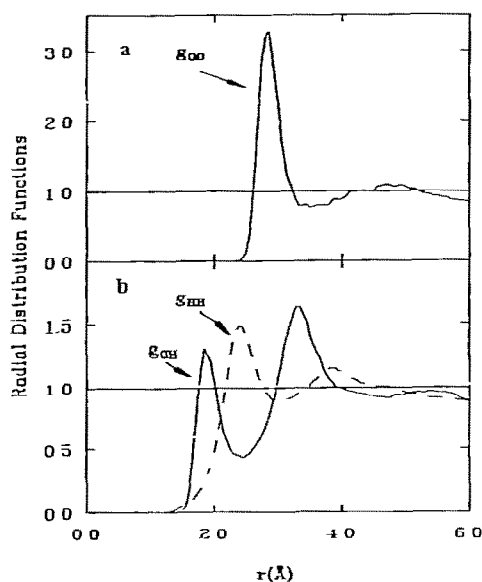


Fig. 3. Radial distribution functions versus site-site separation  $r$  in Å: (a) Oxygen-oxygen distribution function; (b) oxygen-hydrogen distribution function and hydrogen-hydrogen distribution function.

The velocity autocorrelation function and its spectral density are in good agreement with the standard periodic boundary molecular dynamics ST2 simulation results by Stillinger and Rahman [12]. The self-diffusion coefficient for the oxygen atom (which is essentially the ST2 center of mass) is  $D = 2.3 \times 10^{-5} \text{ cm}^2/\text{s}$ , in reasonable agreement with earlier work ( $D = 1.9 \times 10^{-5} \text{ cm}^2/\text{s}$  at 283 K). The site-site radial distribution functions also show good agreement with the results of Stillinger and Rahman out to a distance including the second peak, i.e. the positions of the maxima and minima and their amplitudes are accurate out to  $\approx 5 \text{ Å}$ . Beyond the second peak,  $g_{OO}$  drops off too much due to the lack of "periodic image" molecules outside the  $9.0 \text{ Å}$  radius sphere, which is not corrected for in the present analysis; corresponding behavior is observed in  $g_{OH}$  and  $g_{HH}$ . The partitioning of molecular density (see fig. 4) within successive equal volume shells inside the  $9.0 \text{ Å}$  radius sphere is reasonably uniform except near the boundary where it falls off. We emphasize that this uniformity is an important feature which must be reproduced in finite simulation regions. It indicates the absence of spurious edge or boundary effects [10,11].

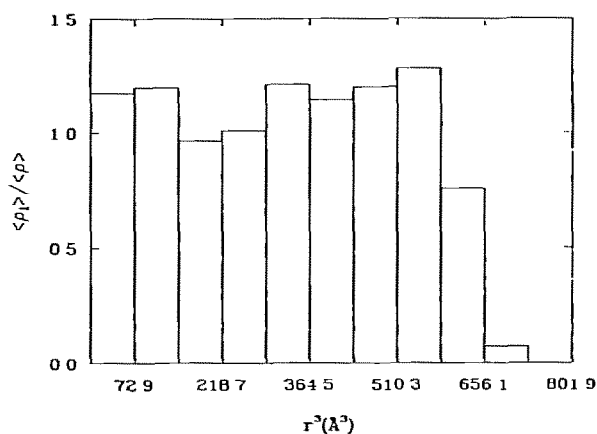


Fig. 4. Normalized local density profile: the local molecular density within each of 10 equal volume shells inside a  $9.0 \text{ Å}$  radius sphere is plotted versus shell number; the average number density ( $\langle \rho \rangle = 0.3209/\text{Å}^3$ ) is taken as the reference value.

The results obtained for the simulation of ST2 water in a  $9.0 \text{ Å}$  sphere without periodic boundary conditions are very encouraging. Extension of the earlier work for liquid argon to a realistic representation of a molecular solvent is an important step in the study of the dynamics of localized chemical processes. Such models and analytic extensions of them [14] will allow one to study processes occurring in solution over time scales that would be prohibitive if a much larger number of solvent particles had to be included [18]. Moreover, difficulties arising from periodic boundary conditions in exothermic or endothermic processes are avoided [9,10]. When the present methodology is combined with analogous approaches for eliminating distant non-participating atoms in biomolecules, a powerful approach for studying biological activity in localized sites emerges [19].

#### Acknowledgement

We would like to thank Dr. B. Montgomery Pettitt for many helpful discussions. We are grateful to Professor David Weaver and the Tufts University Computing Center for providing assistance with the computations. AB would like to acknowledge the support of a NATO postdoctoral fellowship. We would also like to thank

Dr. S. Swaminathan for providing the initial configuration of MCY water.

#### References

- [1] W.W. Wood and J.J. Erpenbeck, *Ann. Rev. Phys. Chem.* 27 (1976) 319;  
J.P. Hansen and I.R. McDonald, *Theory of simple liquids* (Academic Press, New York, 1976).
- [2] J.A. McCammon and M. Karplus, *Ann. Rev. Phys. Chem.* 31 (1980) 29.
- [3] M. Levitt, *Ann. Rev. Biophys. Bioeng.* 11 (1982) 251.
- [4] M. Karplus and J.A. McCammon, *Ann. Rev. Biochem.* 53 (1983) 263.
- [5] D.W. Robertus, D. Chandler and B.J. Berne, *J. Chem. Phys.* 70 (1979) 3395.
- [6] P. Bado, P. Berens, J. Bergsma, M. Coladonto, C. Dupuy, P. Edelsten, J. Kahn, K. Wilson and D. Fredkin, in *Proceedings of the International Conference on Photochemistry and Photobiology*, ed. A. Zewail (Harwood, New York, 1983).
- [7] S.A. Adelman and C.L. Brooks III, *J. Phys. Chem.* 86 (1982) 1511.
- [8] J.A. McCammon and M. Karplus, *Proc. Natl. Acad. Sci. US* 76 (1979) 3585;
- [9] S.H. Northrup, M.R. Pear, C.Y. Lee, J.A. McCammon and M. Karplus, *Proc. Natl. Acad. Sci. US* 79 (1982) 4035.
- [10] M. Berkowitz and J.A. McCammon, *Chem. Phys. Letters* 90 (1982) 215.
- [11] C.L. Brooks III and M. Karplus, *J. Chem. Phys.*, to be published
- [12] G. Ciccotti and A. Tenenbaum, *J. Stat. Phys.* 23 (1980) 767;  
A. Tenenbaum, G. Ciccotti and R. Gallico, *Phys. Rev. A* 25 (1982) 2778.
- [13] F.H. Stillinger and A. Rahman, *J. Chem. Phys.* 60 (1974) 1545.
- [14] M. Morse and S. Rice, *J. Chem. Phys.* 76 (1982) 65;  
W. Jorgensen, J. Chandrasekhar, J. Madura, R. Impey and M. Klein, *J. Chem. Phys.* 79 (1983) 926.
- [15] C.L. Brooks III and M. Karplus, in progress.
- [16] O. Matsuoka, E. Clementi and M. Yoshimine, *J. Chem. Phys.* 64 (1976) 1351.
- [17] B.R. Brooks, R.E. Brucoleri, B.O. Olafson, D.J. States, S. Swaminathan and M. Karplus, *J. Comp. Chem.* 4 (1983) 187.
- [18] A. Brunger, unpublished.
- [19] W.F. van Gunsteren and M. Karplus, *Nature* 293 (1981) 677.
- [20] C.L. Brooks III, A. Brunger and M. Karplus, to be published.