Incorporating Hydration Force Determined by Boundary Element Method into Stochastic Dynamics

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This paper describes a new method for incorporating the extra mean force terms of solvent including the Coulombic interactions with the induced surface charge and surface pressure of solvent into stochastic dynamics simulation. The boundary element method based on the classical continuum approximation has been used to evaluate those mean force terms. Calculations with our method have been performed on a cyclic undecapeptide cyclosporin A that has been investigated by stochastic dynamics and molecular dynamics in the previous simulations. The detailed analysis has been accomplished in terms of internal hydrogen-bonding forms, conformational fluctuations, and atomic positional correlation function. Compared with the data obtained from previous simulations, our results indicate that the new simulation method presented in this work provides an obvious improvement over the conventional stochastic dynamics simulation technique. This suggests that the average solvent effects should produce a significant influence on the simulated structure and dynamics behavior of biomolecules in aqueous solution.

Introduction

Molecular dynamics (MD) simulation has become a widely used technique for analyzing the structure and function of chemical and biological systems.1–4 The interactions of all degrees of freedom in the system are explicitly taken into account in MD simulation. For a system of a protein in water, most of the computational time is used to calculate the interactions between solvent atoms and solute atoms as well as among the solvent atoms. In many cases one is not interested in the details of the solvent itself but only in its effects on the macromolecule. Therefore, one can eliminate the explicit treatments of solvent molecules in the simulation to save large amounts of computational time on simulating water molecules. The conventional stochastic dynamics (SD) simulation yields an approximation with missing solvent to the dynamics of macromolecule in solution. Shi and co-workers suggested that for nonpolar solvents conventional SD simulation without using an extra mean force term seems to be a good approximation. However, for polar solvents the omission of the mean force of solvent effects is not justified.5

Recently, there has been a great deal of interest in the incorporation of solvent effect into molecular mechanics or MD simulations using the Poisson–Boltzmann equation (PBE).6–9 Davis and McCammon have pointed out that there should exist the solvent boundary pressure acting on the surface solute atoms besides the electrostatic force on a solute atom resulting from the interaction of the atomic charge with the local electrical field.10 Thus, any method for incorporating the PBE into MD or SD simulations must account for this additional pressure force term. Zauhar has reported on the feasibility of incorporating continuum electrostatic forces including surface pressure in SD simulations. Zauhar has reported on the feasibility of incorporating the PBE into MD simulations using the Poisson–Boltzmann equation (PBE).6 Since this method includes an explicit dielectric boundary surface, it is possible to calculate directly boundary pressure using the Maxwell stress tensor. Sharp has presented a way of combining solvent and ion screening with conventional SD using the finite difference method for solving the PBE.7 More recently, Gilson and co-workers have described an efficient method for incorporating the effects of solvent into MD simulations using rather coarse finite difference grids to solve the PBE.9 Up to now, it is found that no one has reported any approach to combine the solvent effects determined by the BEM into SD simulation of biomolecules.

In this article, we have applied the BEM to evaluate the solvent effects that is regarded as the mean force of solvent and combined with SD simulation for cyclosporin A (CPA). We have selected the CPA as our simulated system because the conventional SD and full MD simulations for CPA have been studied in the previous simulations9,11 with which our methods and results can be examined. The real goal of the present work is to study the methodology of SD with a potential of mean force determined by the BEM and to test the reliability of the method through comparing our analysis results with the previous simulation data.

Theory

The normal form of SD for a system of N atoms is given by the ordinary Langevin equation:

\[ m_i \ddot{x}_i = F_i(x_i) - m_i \gamma_i \dot{x}_i + R_i(t) \]  

(1)

where \( x_i \) is the coordinate component of all atoms, \( \gamma_i \) is the atomic friction coefficient, and \( R_i \) denotes the random force. The system force \( F_i \) is derived from the system potential of mean force \( V_{\text{mean}}(x_i) \) and has a form

\[ F_i(t) = -\partial V_{\text{mean}}(x_i)/\partial x_i \]  

(2)

where \( V_{\text{mean}} \) can be written as

\[ V_{\text{mean}}(x_i) = V_{\text{int}}(x_i) + V_{\text{sol}}(x_i) \]  

(3)

The interactions of all atoms are included in the potential of mean force \( V_{\text{mean}}(x_i) \). Therefore, it is possible to evaluate the influence of the solvent on the structure and dynamics behavior of biomolecules in aqueous solution.
where \( V_{\text{mol}}(x_i) \) presents the internal potential of solute atom in the system, and \( V_{\text{sol}} \) is the potential of mean force from the environment solvent. Obviously, eq 2 can be rewritten as

\[
F_i = \varphi_i - \frac{\partial V_{\text{mol}}(x_i)}{\partial x_i} - \frac{\partial V_{\text{sol}}(x_i)}{\partial x_i}
\]

\[
= F_i^{\text{int}} + F_i^{\text{sol}}
\]

where the internal force \( F_i^{\text{int}} \) is due to the explicitly simulated atoms and the external force \( F_i^{\text{sol}} \) is called hydration force originating from the environment.

In the present study, the hydration force \( F_i^{\text{sol}} \) is calculated by using the classical continuum models of electrostatic interactions and considered as the sum of the Coulombic interaction with the induced surface charge and a purely mechanical pressure of the polarized solvent.\(^{6,8}\) The electrostatic component of the hydration force acting on charge \( q_i \) is calculated with the expression

\[
F_i^{\text{pol}}(R) = \int_S \varphi_i(r)(R - r) \frac{d^2r}{|R - r|^3}
\]

where the integration is carried out over the entire molecular surface \( S \) and \( \varphi_i(r) \) is the density of the induced polarization charge at an arbitrary point \( r \) on the molecular surface \( S \). The relation between the \( \varphi_i(r) \) and the exterior field \( E_e(r) \) is given by\(^{12}\)

\[
\varphi_i(r) = \frac{1}{4\pi} \left( \frac{D_i - D_s}{D_i} \right) \cdot E_e(r) \cdot n(r)
\]

where \( D_i \) and \( D_s \) are the dielectric constants of the solvent and the molecular interior, respectively. The exterior electric field \( E_e(r) \) can be evaluated on the solvent side of the molecular surface, and \( n \) is the outward unit normal to the surface.

The purely mechanical boundary pressure can be calculated based on the expression developed by Gilson and co-workers\(^8\) as

\[
P(r) = \frac{1}{8\pi} (D_e - D_i) E_e \cdot E_i
\]

\[
P(r) = \frac{1}{8\pi} (D_e - D_i) \left( E_e \cdot n \right) \left( \frac{D_e - D_i}{D_i} \right) + |E_0|^2
\]

Thus, the force of a solvent pressure on the \( i \)th atoms is given by

\[
F_i^{\text{press}} = \int_S -nP(r) \, d^2r
\]

where the integration is performed only over the portion of the solvent accessible surface associated with the \( i \)th atom. Therefore, both the charged atom and the uncharged atom on the molecular surface will be subject to a force exerted by the boundary pressure of the solvent.

In this work, the BEM is used to calculate the electrostatic potential inside and around the molecule. Since the detailed discussions of the BEM can be found in a number of other works,\(^{12-19}\) here we only give an outline of the method and main equations used in this work.

The interior potential \( \phi^i \) and the exterior potential \( \phi^e \) are governed by the Poisson equation and the linearized PBE, respectively:\(^{15}\)

\[
\nabla^2 \phi^i = -\frac{1}{D_i} \sum q_i \delta(r_p - r_i)
\]

\[
\nabla^2 \phi^e = \kappa^2 \phi^e(r_p)
\]

where \( r_p \) is a point inside or outside the molecule, and \( \delta(r_p - r_i) \) in eq 10 is the delta function at \( r_p \) at which the \( k \)th charge \( q_i \) is placed, and \( \kappa \) in eq 11 is the Debye inverse screening length. The potential \( \phi^i \) and \( \phi^e \) should satisfy the following boundary conditions:

\[
\phi^i = \phi^e
\]

\[
D_i \frac{\partial \phi^i}{\partial n} = D_e \frac{\partial \phi^e}{\partial n}
\]

The fundamental solutions of eqs 10 and 11 can be expressed as

\[
G_{pq} = \frac{1}{4\pi r_{pq}}
\]

\[
\mu_{pq} = \exp(-\kappa r_{pq}/4\pi r_{pq})
\]

where \( r_{pq} \) is the distance between points \( p \) and \( q \), and \( \kappa \) is the Debye inverse screening length. \( G_{pq} \) and \( \mu_{pq} \) are the fundamental solutions to the eqs 10 and 11, respectively. Using Green’s second theorem on eqs 10 and 11, we obtain the following two boundary integral equations for the interior and exterior potentials:

\[
\phi^i_p = \frac{1}{s} \int G_{pq} \frac{\partial \phi^i_q}{\partial n} \frac{\partial G_{pq}}{\partial n} \, dA_k + \frac{1}{D_i} \sum q_k G_{pk}
\]

\[
\phi^e_p = \frac{1}{s} \int -\mu_{pk} \frac{\partial \phi^e_q}{\partial n} + \phi^e_q \frac{\partial \mu_{pk}}{\partial n} \, dA_k
\]

where the integration is taken over the entire molecule surface \( S \), \( k \) is a point on the surface \( S \), and \( p \) is a point inside or outside the molecule. If the jump discontinuity of the double-layer potential at the boundary \( S \) is taken into account,\(^{14} \) eqs 16 and 17 can be written as

\[
\frac{1}{s} \int \phi^i_p = \frac{1}{s} \int G_{pq} \frac{\partial \phi^i_q}{\partial n} \frac{\partial G_{pq}}{\partial n} \, dA_k + \frac{1}{D_i} \sum q_k G_{pk}
\]

\[
\frac{1}{s} \int \phi^e_p = \frac{1}{s} \int -\mu_{pk} \frac{\partial \phi^e_q}{\partial n} + \phi^e_q \frac{\partial \mu_{pk}}{\partial n} \, dA_k
\]

The surface potential and their normal derivatives can be evaluated from eqs 18 and 19 plus boundary conditions eqs 12 and 13 with the BEM. Then, the internal electric field \( E_i \) and the exterior field \( E_e \) are obtained with following expressions:

\[
E_i = -\nabla \phi^i
\]

\[
E_e = -\nabla \phi^e
\]
In order to incorporate the total hydration force defined by eqs 5 and 9 into SD simulation, we first linked our BEM programs (MACBEM)\textsuperscript{18} with the GROMOS package.\textsuperscript{20} It is well-known that the most difficult part in BEM is to generate a proper triangulation. In the present work, we followed the triangulation method developed by Juffer and co-workers.\textsuperscript{15} The triangulation procedure contained three steps: (1) A high-density dot surface of the molecule was generated using the Connolly program.\textsuperscript{21} (2) After the triangulated grids on a sphere surface were defined from a regular polyhedron, the center of the sphere was translated and coincided with the center of mass of the molecule. (3) The triangulation vertices on the molecular surface were assigned by selecting the surface point with the shortest distance to the vectors between the center of mass and the vertices on the sphere, in which each vector of the vertices must intersect the molecular surface only once. Figure 1 shows a triangulation of the solvent accessible surface for X-ray structure of CPA. The probe radius is 0.14 nm. The surface is defined at the center of probe rolling around the molecule. The number of total triangles is 760.

If the coordinates and the charges of the system are given, the potentials in the interior or exterior region can be determined by integrating over all surface triangle elements with eq 18 or eq 19, respectively. The distribution of induced polarization charge on the molecular surface and the corresponding hydration force on charge were evaluated from eqs 6 and 5. The solvent boundary pressure acting on the surface atoms was computed with eqs 8 and 9, in which the pressure was distributed over all surface atoms associated with the solvent accessible surface elements. The direction of the pressure is toward the inside of the molecule and perpendicular to the molecular surface.

The subroutine programs for calculating the hydration force on charge and the solvent pressure based on the BEM were written with FORTRAN 77 and jointed with the subroutine program FORCE in GROMOS package. The relevant input and output and the corresponding subroutine programs in GROMOS were modified to set up the SDBEM program package with which the following simulation was carried out.

The initial structure of CPA molecule was used from the X-ray structure.\textsuperscript{22} The schematic structure of the cyclic undecapeptide CPA can be found in Figure 1b. The GROMOS force field was used for all simulations. Nonpolar hydrogen atoms were included in the carbon atoms (unit atom approach) while polar hydrogen atoms were treated explicitly. The system contained 90 atoms in total. In the beginning, 100 steps of energy minimization with the steepest descent method were performed. Then 10 ps conventional SD simulation without the extra mean force terms was carried out for system equilibrium. After that time, 50 ps SDBEM simulation was performed, and the configurations of the trajectories were saved every 25 time steps for further analysis. The time step, 2 fs, was taken for integrating the equations of motion. No cutoff radius was applied to the nonbonded interactions. All bond lengths were kept rigid using the SHAKE algorithm with a relative tolerance of 10\textsuperscript{-4}.\textsuperscript{23} Coupling to a temperature bath and a pressure bath was applied to keep the system at 300 K and 1 atm.\textsuperscript{24} All simulations and analysis were carried out on an IRIS 4D/50GT workstation and a Micro VAX 3500 computer.

Figure 1. (a) A complete triangulation of the solvent accessible surface for X-ray structure of CPA. The number of total triangles is 760. (b) The X-ray structure of CPA and its solvent accessible surface that were plotted with points. The probe radius is 0.14 nm.

Therefore, the density of the induced polarization charge can be calculated with eq 6, and the hydration force on charge and the boundary pressure can be obtained from eqs 5 and 9, respectively.

Methods

In order to incorporate the total hydration force defined by eqs 5 and 9 into SD simulation, we first linked our BEM programs (MACBEM)\textsuperscript{18} with the GROMOS package.\textsuperscript{20} It is well-known that the most difficult part in BEM is to generate a proper triangulation. In the present work, we followed the triangulation method developed by Juffer and co-workers.\textsuperscript{15} The triangulation procedure contained three steps: (1) A high-density dot surface of the molecule was generated using the Connolly program.\textsuperscript{21} (2) After the triangulated grids on a sphere surface were defined from a regular polyhedron, the center of the sphere was translated and coincided with the center of mass of the molecule. (3) The triangulation vertices on the molecular surface were assigned by selecting the surface point with the shortest distance to the vectors between the center of mass and the vertices on the sphere, in which each vector of the vertices must intersect the molecular surface only once. Figure 1 shows a triangulation of the solvent accessible surface for X-ray structure of CPA. The probe radius is 0.14 nm. The surface is defined at the center of probe rolling around the molecule. The number of total triangles is 760.

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Results and Discussion

Convergence Behavior of the Simulation. To verify the convergence behavior of the SDBEM simulation, we analyzed the root mean square (rms) deviation of atomic positions versus the simulation time relative to two reference structures, i.e., the starting structure (t = 0) after 10 ps SD equilibration (Figure 2a) and the X-ray crystal structure (Figure 2b). As shown in Figure 2a, the RMS shift in position reaches a stable value of 0.08–0.12 nm for all atoms and 0.04–0.08 nm for C\textsubscript{alpha} atoms around 10–50 ps. The magnitudes of the RMS values relative to the X-ray structure (Figure 2b) also have a stable values of 0.08–0.17 nm for all atoms and 0.04–0.12 nm for C\textsubscript{alpha} atoms from 10 to 50 ps of the simulation. It is clear from Figure 2 that our SDBEM simulation appears to reach an equilibrium state after 10 ps SDBEM simulation. After this initial period, the trajectories obtained from final 40 ps simulation are used for the following conformation and dynamics analyses.

Hydrogen-Bonding Analysis. Table 1 lists the results of hydrogen-bond (H bond) analysis in CPA for SDBEM trajectories data of the last 40 ps. In order to compare our results obtained from the SDBEM simulation with previous simulations using different approaches, we have also reported the results obtained from MD\textsuperscript{11} and conventional SD\textsuperscript{5} simulations in Tables 1–4.

The criteria used to determine an H bond are purely geometric: for each coordinate set, every potential donor–acceptor is tested and considered to form an H bond if the hydrogen to acceptor distance is less than 0.25 nm and the donor–acceptor angle is larger than 90\textdegree. The frequencies of H bonds are determined from the occurrences registered on the simulation trajectory frames.

As seen in Table 1, the occupancies of H bonds among 2Abu–11Meval, 5Val–2Abu, and 5Val–3Sar obtained from
with that from SD simulation. This means that our SDBEM simulation except three H-bonding patterns among 1MeBmt have added the hydration force on charge and solvent surface pressure into the mean force of solvent in our simulation.

Conformation and Structure Analysis. Table 2 shows the averaged backbone dihedrals (φ, ψ, ω) and their fluctuations in parentheses for three various simulations. Since the influence of solvent effects on the conformation of backbone is not so much, most of backbone dihedrals for both SD and SDBEM simulated structure are quite similar within their RMS fluctuations. However, the values of several backbone dihedral angles obtained from the SDBEM simulation, such as dihedrals 2Abu φ, ω, 3Sar ω; 4MeLeu φ; and 5Val ω, are much closer to that from MD simulation compared with the data in SD simulation (see Table 2).

The averaged side-chain dihedrals and their rms fluctuations are reported in Table 3 for the MD, SD and SDBEM simulations, respectively. It is found that the obvious conformational change for three various simulations occurs in the 1MeBmt side chain. For instance, the dihedral χ2 in 1MeBmt is 72° for MD simulation but −132° for SD simulation. This means that the side-chain dihedral χ2 in 1MeBmt yields a big rotation between MD and SD simulations. However, a very consistent value of dihedral χ2 in 1MeBmt side-chain between MD and SD simulations. Although the value of χ2 in 1MeBmt in our SDBEM simulation has a near 20° difference from MD simulation, our result for χ2 is much better than that from SD simulation (see Table 3). For the side-chain dihedrals that have big deviation between MD and SD simulation, such as dihedrals 1MeBmt χ1, 2, χ3, 2Abu χ1; 4MeLeu χ2; and 10MeLeu χ2, our SDBEM results have a distinct modification compared with SD results. On the other hand, for the remaining

### TABLE 2: Averaged Backbone Dihedral Angles (in deg) and Their Rms Fluctuations (in Parentheses) in CPA

<table>
<thead>
<tr>
<th>Donor</th>
<th>Acceptor</th>
<th>MD°</th>
<th>SD°</th>
<th>SDBEM°</th>
</tr>
</thead>
<tbody>
<tr>
<td>1MeBmt O-H</td>
<td>1MeBmt O</td>
<td>110 (8)</td>
<td>128 (8)</td>
<td>110 (10)</td>
</tr>
<tr>
<td>2Abu N-H</td>
<td>10MeLeu O</td>
<td>94 (15)</td>
<td>102 (9)</td>
<td>92 (13)</td>
</tr>
<tr>
<td>5Val N-H</td>
<td>11MeVal O</td>
<td>121 (11)</td>
<td>118 (10)</td>
<td>116 (9)</td>
</tr>
<tr>
<td>3Sar N-H</td>
<td>4MeLeu O</td>
<td>109 (14)</td>
<td>112 (10)</td>
<td>111 (11)</td>
</tr>
<tr>
<td>6MeLeu N-H</td>
<td>5Val O</td>
<td>71 (9)</td>
<td>75 (10)</td>
<td>129 (8)</td>
</tr>
<tr>
<td>7Ala N-H</td>
<td>11MeVal O</td>
<td>115 (9)</td>
<td>113 (7)</td>
<td>115 (9)</td>
</tr>
<tr>
<td>8Ala N-H</td>
<td>12MoLeu O</td>
<td>87 (12)</td>
<td>71 (15)</td>
<td>71 (15)</td>
</tr>
</tbody>
</table>

*Values from ref 11. *Values from ref 5. This hydrogen bond has the unrealistic value for the donor–hydrogen–acceptor angle θ < 100°; all other θ values are larger than 127°.

### TABLE 1: Frequencies of Intramolecular Hydrogen Bonds Obtained from Different Simulation Data in CPA (in %)

<table>
<thead>
<tr>
<th>Donor</th>
<th>Acceptor</th>
<th>MD in water</th>
<th>SD</th>
<th>SDBEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1MeBmt O-H</td>
<td>1MeBmt O</td>
<td>11 (0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2Abu N-H</td>
<td>5Val O</td>
<td>18 (8)</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>5Val N-H</td>
<td>11MeVal O</td>
<td>18 (10)</td>
<td>72</td>
<td>57</td>
</tr>
<tr>
<td>7Ala N-H</td>
<td>5Val O</td>
<td>12 (0)</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>8Ala N-H</td>
<td>6MeLeu O</td>
<td>22 (0)</td>
<td>29</td>
<td>73</td>
</tr>
</tbody>
</table>

*Values from ref 11. *Values from ref 5.
TABLE 3: Averaged Side-Chain Dihedral Angles (in deg) and Their Rms Fluctuations (in Parentheses) in CPA

<table>
<thead>
<tr>
<th>atom type</th>
<th>MD(^a)</th>
<th>SD(^b)</th>
<th>SDBEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1MeBmt</td>
<td>(\chi_1) -167 (8) -148 (38) -175 (8) (\chi_2) 72 (10) -132 (42) 68 (12) (\chi_3) -173 (12) -77 (27) -169 (12) (\chi_4) -153 (27) -139 (57) -165 (45) (\chi_5) 179 (8) -179 (8) 178 (8) (\chi_6) -114 (46) -131 (57) -114 (50) (\chi_7) -80 (15) -76 (11) -73 (12) (\chi_8) -103 (43) -74 (12) -90 (33) (\chi_9) -61 (12) -62 (12) -61 (14) (\chi_{10}) -170 (9) -166 (10) -166 (10) (\chi_{11}) -141 (31) -105 (20) -107 (27) (\chi_{12}) -70 (13) -75 (14) -75 (14) (\chi_{13}) -77 (18) -88 (26) -88 (28) (\chi_{14}) -169 (10) -164 (9) -166 (10) (\chi_{15}) -164 (13) -130 (40) -145 (33) (\chi_{16}) -61 (15) -59 (10) -59 (10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Values from ref 11. \(^b\) Values from ref 5.

TABLE 4: Rms Atomic Positional Fluctuations\(^a\) and the Mean Anisotropy for Atomic Motion in CPA

<table>
<thead>
<tr>
<th>atom type</th>
<th>MD(^b)</th>
<th>SD(^b)</th>
<th>SDBEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>all atoms</td>
<td>0.052</td>
<td>0.072</td>
<td>0.059</td>
</tr>
<tr>
<td>Ca atoms</td>
<td>0.036</td>
<td>0.033</td>
<td>0.036</td>
</tr>
<tr>
<td>MeLeu C(_R)</td>
<td>0.052</td>
<td>0.046</td>
<td>0.053</td>
</tr>
<tr>
<td>MeLeu C(_Z)</td>
<td>0.065</td>
<td>0.059</td>
<td>0.072</td>
</tr>
<tr>
<td>MeLeu C(_\delta)</td>
<td>0.096</td>
<td>0.089</td>
<td>0.099</td>
</tr>
<tr>
<td>anisotropy(^d)</td>
<td>0.44</td>
<td>0.42</td>
<td>0.41</td>
</tr>
<tr>
<td>all atoms</td>
<td>0.53</td>
<td>0.49</td>
<td>0.42</td>
</tr>
<tr>
<td>Ca atoms</td>
<td>0.44</td>
<td>0.42</td>
<td>0.41</td>
</tr>
</tbody>
</table>

\(^a\) Fluctuations are in nm. \(^b\) Values from ref 11. \(^c\) Values from ref 5. \(^d\) Ratio of the shortest to the longest axis of the anisotropic fluctuation ellipsoids.

side-chain dihedrals in which there exist small deviations between MD and SD simulations, our SDBEM simulation data are consistent with the SD results. As mentioned above, we suggest that the side-chain conformation is obviously affected by the hydration force on charge and solvent pressure that are taken into account in our SDBEM simulation.

Table 4 represents the rms atomic positional fluctuations and the mean anisotropy for atomic motion for the MD, SD and SDBEM simulations. As seen in Table 4, the rms atomic positional fluctuation of our SDBEM simulation is 0.059 nm for all atoms, which is smaller than that of SD simulation (0.072 nm) and comparable to that obtained in MD simulation (0.052 nm). For the averages over Ca atom and other side-chain carbon atoms, the rms fluctuations of atomic positions for our SDBEM simulation are agreement with the values of the MD simulation. In addition, the mean anisotropy in the atomic motion is provided by evaluating the ratio of the smallest to the longest principal axis of the anisotropic fluctuation ellipsoids. The values for anisotropy are comparable for all three simulations (see Table 4).

Dynamics Behavior. The solvent environment of a biomolecule not only influences its equilibrium conformation but also affects its dynamics behavior. Therefore, the time evolution of the atomic positional fluctuation has been examined using autocorrelation function that is defined as

\[
C_r(t) = \frac{\langle \Delta r(t) \Delta r(t+r) \rangle - \langle \Delta r(t) \rangle^2}{\langle \Delta r^2 \rangle} \tag{22}
\]

where the brackets \(\langle \rangle\) indicate an average over the simulation time, \(\Delta r(t) = r(t) - \langle r \rangle\), and \(\langle \Delta r^2 \rangle = \langle (r - \langle r \rangle)^2 \rangle\).

In the present study, we have selected two backbone atoms and two side-chain atoms of CPA for analyzing their positional fluctuations. The mean anisotropy for atomic motion is provided by evaluating the ratio of the smallest to the longest principal axis of the anisotropic fluctuation ellipsoids. The values for anisotropy are comparable for all three simulations (see Table 4).

Dynamics Behavior. The solvent environment of a biomolecule not only influences its equilibrium conformation but also affects its dynamics behavior. Therefore, the time evolution of the atomic positional fluctuation has been examined using autocorrelation function that is defined as

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C_r(t) = \frac{\langle \Delta r(t) \Delta r(t+r) \rangle - \langle \Delta r(t) \rangle^2}{\langle \Delta r^2 \rangle} \tag{22}
\]

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correlation function and compared with that obtained from the previous SD and MD simulations. Figure 3a–d shows the correlation functions for those four atoms of CPA, in which backbone atom 5-Val-Cα and the side-chain atom 4-Me-Leu-Cβ are in the β-sheet and, the backbone atom 9-Me-Leu-Cα and the side-chain atom 9-Me-Leu-Cβ are in the loop region. The correlation functions for 5-Val-Cα atom (Figure 3a) in SDBEM and SD simulations have a similar behavior. They show a rapid initial decay followed by slow oscillations with a low amplitude. For this case, both SDBEM and SD simulations are comparable with MD simulation. For 9-Me-Leu-Cα atom in the loop region (Figure 3b), all the correlation functions show a slower decay than that in Figure 3a. This indicates that the 5-Val-Cα atom is much more fixed in its position in the β-sheet than the 9-Me-Leu-Cα atom in the loop region. For the side-chain atom 4-Me-Leu-Cβ in the β-sheet (Figure 3c), the correlation functions show the much slower decay followed by a linear decrease, in which our SDBEM simulation is much closer to the MD simulation compared with SD simulation. However, the correlation functions for side-chain atom 9-Me-Leu-Cβ in loop region (Figure 3d) display different features, in which the results for both SDBEM and SD simulations are very similar and a shorter relaxation time can be found compared with Figure 3c. This means that the sidechain of 4-Me-Leu has much more flexibility than the sidechain of 9-Me-Leu. Through the above analysis, we suggest that in general both SDBEM and SD simulation generate a similar correlation function. But for the side chain in the β-sheet of CPA, the SDBEM simulated data are better than the SD data compared with MD simulation.

Conclusions

In this work, a methodology of combining BEM with SD simulation technique offers a possible tool to study the structure and dynamic properties of biomolecules. The two extra mean force terms of hydration force on charge and surface pressure of solvent determined by the BEM have been added into SD simulation to represent the average solvent effect on the solute atoms. To examine the reliability of the new approach, we have selected the CPA molecule as our study target to carry out 50 ps SDBEM simulation. The analysis results for H-bonding network, molecular conformation, and dynamic behavior have been compared with the previous SD and MD simulation. Our results show that the SDBEM simulation approach has an obvious improvement relative to the conventional SD simulation technique without use of the extra mean force of solvent.

The further study of this method will focus on the increasing calculation speed and precision of algorithms for solving the Poisson–Boltzmann equation using the BEM. For the CPA molecule, 0.3 h CPU time for each picosecond was taken for the conventional SD simulation, but 0.7 h CPU time was taken for each picosecond for our SDBEM simulation on an IRIS 4D/50GT workstation computer. Although this method requires more computation time than the conventional SD simulation technique, we believe that with further development of algorithms, it should be possible to use this method for studying larger biomolecular systems without use of the cutoff radius in electrostatic interaction calculation.

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References and Notes