

Development of an Atomistic Brownian Dynamics Algorithm with Implicit Solvent Model for Long Time Simulation

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We report the implementation of an atomistic Brownian dynamics simulation of proteins. A protein was described by united-atom model with AMBER91 force field. The solvent was treated by distance-dependent dielectric/surface area model. The computation time of the Brownian dynamics and the calculated results on structure and dynamics of 28-mer $\beta\beta\alpha$ fold peptide with the implicit solvent model were compared with those of molecular dynamics simulation with explicit solvent. The Brownian dynamics simulation was 53 times faster than molecular dynamics simulation with explicit solvent. The simulation was stable and the artifacts often observed in simulations at vacuum condition were reduced. The results indicate that the Brownian dynamics with the implicit solvent model can be widely used in studies of protein dynamics by long time simulation in future.

Keywords: Brownian dynamics, implicit solvent model, distance-dependent dielectric, surface area

1 Introduction

Recent progress of genomic analysis necessitates the development of prediction methods of protein structure and function [1]. Methods of protein structure prediction are classified into three main categories: homology modeling, fold recognition and *ab initio* folding. The first two methods use structures already solved as templates. The third method does not require such information and is based on physical chemistry in principle. In this respect, the *ab initio* method is useful not only to predict protein structures but also to design novel functional proteins or drugs, thus should be developed.

Molecular dynamics (MD) and Monte Carlo (MC) simulations are mainly used for the *ab initio* method at present. For protein structure prediction by these methods, it is necessary to develop an accurate energy function for the protein-solvent system and an efficient conformational search algorithm [2–5]. By the MD method, actual smooth motion of atoms is reproduced. However, since the folding of even small proteins takes more than a few milliseconds [6], it is difficult to simulate the complete folding process with explicit solvent molecules with present computer power, because the limit of time step in MD is 2 fsec. By the MC method, it is possible to obtain

thermodynamic parameters without long time simulation, if efficient sampling is applied. However, the sampling efficiency is not satisfactory when this method is applied to a condensed polymer system like a protein, since random displacements of atoms in a polymer cause frequent collisions with other atoms. In this respect, new sampling methods, such as multicanonical, simulated tempering, replica exchange and so on have been developed for MD or MC simulations [7].

Stochastic dynamics simulation is another solution for conformational search efficiency; it enables long time simulation because mild instabilities of certain long-time steps are masked [8, 9]. In Langevin dynamics simulation [8], one can treat the effects of solvent as a dissipative random force. Since the motion of polypeptide in aqueous solvent is slow, the solvent damping is large and the inertial memory is lost in a very short time. The relevant approximate equation is called the Brownian equation [9]. So far, each residue in a polypeptide has been mainly represented by one or two spheres connected by virtual bonds in Brownian dynamics of proteins [10, 11]. In order to obtain detailed information on the folding process, it is necessary to use more realistic models. So far, only a few attempts have been made using the atomistic model for 20-mer polyalanine [12] and 4-mer peptide [13]. In

this report, we present an atomistic Brownian dynamics (BD) algorithm with implicit solvent model for protein folding simulation. We test the effectiveness of this algorithm using 28-mer $\beta\beta\alpha$ peptide as a model. This is the first report of the stable simulation of an actual protein using an atomistic BD algorithm with implicit solvent model.

2 Methods

2.1 Brownian Dynamics Algorithm

By treating the effects of solvent as a dissipative random force, the Langevin equation can be expressed as

$$m_i \frac{d^2 \mathbf{r}_i}{dt^2} = -\zeta_i \frac{d\mathbf{r}_i}{dt} + \mathbf{F}_i + \mathbf{R}_i. \quad (1)$$

Here, \mathbf{r}_i and m_i represent the mass and position of atom i , respectively. ζ_i is a frictional coefficient and is determined by the Stokes' law, that is, $\zeta_i = 6\pi a_i^{\text{Stokes}} \eta$ in which a_i^{Stokes} is a Stokes radius of atom i and η is the viscosity of water ($= 0.205 \text{ kcal/mol}/\text{\AA}^3 \cdot \text{psec}$ at 280 K). \mathbf{F}_i is the systematic force on atom i . \mathbf{R}_i is a random force on atom i having a zero mean $\langle \mathbf{R}_i(t) \rangle = 0$ and a variance $\langle \mathbf{R}_i(t) \mathbf{R}_j(t) \rangle = 2\zeta_i k_B T \delta_{ij} \delta(t) \mathbf{I}$, where \mathbf{I} is 3×3 unit tensor; this derives from the effects of solvent.

For the overdamped limit (the solvent damping is large and the inertial memory is lost in a very short time), we set the left side of Eq. 1 to zero,

$$\zeta_i \frac{d\mathbf{r}_i}{dt} = \mathbf{F}_i + \mathbf{R}_i. \quad (2)$$

The integrated equation of Eq. 2 is called Brownian dynamics [9];

$$\mathbf{r}_i(t+h) = \mathbf{r}_i(t) + \frac{\mathbf{F}_i(t)}{\zeta_i} h + \sqrt{\frac{2k_B T}{\zeta_i}} h \mathbf{z}_i, \quad (3)$$

where h is a time step and \mathbf{z}_i is a random noise vector obtained from Gaussian distribution.

2.2 United-Atom Model and Force Field

The AMBER91 united-atom force field [14] was used; non-polar hydrogens are included in the carbon atoms they attach, while polar hydrogens are explicitly treated. The Stokes radius of each atom is its van der Waals radius plus 1.4 \AA .

In this simulation, the effective energy of the system $W(\mathbf{r}^N)$ for a protein containing N atoms with Cartesian coordinates $\mathbf{r}^N = (\mathbf{r}^1, \mathbf{r}^2, \mathbf{r}^3, \dots)$ consists of two parts, intramolecular energy $V_{\text{intra}}(\mathbf{r}^N)$ given by AMBER91 force field and mean solvation energy term $G_{\text{solv}}(\mathbf{r}^N)$,

$$W(\mathbf{r}^N) = V_{\text{intra}}(\mathbf{r}^N) + G_{\text{solv}}(\mathbf{r}^N). \quad (4)$$

Intramolecular energy $V_{\text{intra}}(\mathbf{r}^N)$ is composed of bonds, angles, dihedrals (including improper), van der Waals, hydrogen bonding and electrostatic contributions. In the original AMBER91 force field, the hydrogen-bond term was just a function of distance. However, since there have been many successful reports for protein designing by using distance-dependent and angle-dependent functions for the hydrogen-bond term [15–19], we used an angle-dependent, 12-10 hydrogen-bond potential:

$$V_{hb} = \sum_{i,j} \left(\frac{C_{i,j}}{r_{i,j}^{12}} - \frac{D_{i,j}}{r_{i,j}^{10}} \right) F(\theta_{A-H-D}, \theta_{AA-A-H}). \quad (5)$$

The angle-dependent term, $F(\theta_{A-H-D}, \theta_{AA-A-H})$, varies depending on the type of hybridized orbital of the acceptor atom:

For sp^2 acceptor,

$$F(\theta_{A-H-D}, \theta_{AA-A-H}) = \cos^4(\theta_{A-H-D}) \cos^2(\theta_{AA-A-H})$$

$$(\theta_{A-H-D} > 90^\circ, \theta_{AA-A-H} > 90^\circ), \quad (6)$$

and for sp^3 acceptor,

$$F(\theta_{A-H-D}, \theta_{AA-A-H}) = \cos^4(\theta_{A-H-D}) \cos^2(\theta_{AA-A-H} - 109.5^\circ)$$

$$(\theta_{A-H-D} > 90^\circ, \theta_{AA-A-H} - 109.5^\circ > 90^\circ),$$

where θ_{A-H-D} is the acceptor-hydrogen-donor angle and θ_{AA-A-H} is the base-acceptor-hydrogen angle (where the base is the atom that attaches to the acceptor).

2.3 Solvation Energy

It has been reported that no continuum solvent model can completely account for the effect of explicit inclusion of solvent [20, 21]. But explicit solvent simulation expands the time cost enormously in order to appropriately sample the solvent configurations. Therefore, various implicit solvent models for protein simulation have been developed to represent the effect of explicit solvent; distance-dependent dielectric models [22], surface area models [23–26], Gaussian solvent exclusion model [27], generalized Born/surface area (GB/SA) models [28–31], generalized Born/analytical continuum electrostatic (GB/ACE) model [32], reference interaction site model (RISM) theory [33] and so on. In this study, we used an implicit solvent model combining two models; Distance-dependent Dielectric (DD) model and Surface Area (SA) model. DD model assumes the dielectric constant $\epsilon = Cr_{ij}$ where C is a constant value and r_{ij} is the distance between atom i

and j . This model is approximating the long-range electrostatic screening effects [22]. In the SA model, the solvation energy is given by:

$$G_{solv}(\mathbf{r}^N) = \sum_{i=1}^N \sigma_i \cdot SA_i(\mathbf{r}^N). \quad (7)$$

where $SA_i(\mathbf{r}^N)$ is the solvent accessible surface area of atom i and σ_i is a solvation parameter depending on the atom type. In this study, we used $\epsilon = 2r_{ij}$ and $\sigma_{N,O} = -60$ cal/mol/Å², $\sigma_C = 12$ cal/mol/Å² and $\sigma_{H,S} = 0$ cal/mol/Å² for DD/SA model [25]. $SA_i(\mathbf{r}^N)$ was calculated using the approximate analytical expression of Hasel et al. [34]. The solvation term was calculated at every time step of dynamics simulation.

2.4 Bond Length Constraints and Adaptive Time Step

BD algorithm makes it possible to use longer time steps in the simulations. The LINCS algorithm [35] was used to constrain bond lengths. The time step used was 10 fsec. However, angle energy divergence occurred sometimes (especially in PRO residue) when the long time step was used. To avoid this problem, we used the adaptive time step method [13] in the simulation: A normal time step Δt was used mostly and the time step was split into n giving smaller time step $\Delta t/n$ when the angle energy became larger than a predetermined threshold. In our simulations, the normal time step was 10 fsec, the threshold was 20 kcal/mol and $n = 5$. Small time steps were used less than 1% of the simulation time. 9 Å non-bonded cut-off was used and the non-bonded pair list was updated every 10 steps.

2.5 BD Simulation

The effectiveness of the BD algorithm with the implicit solvent model was tested for a 5 nsec simulation of designed $\beta\beta\alpha$ fold 28-mer peptide pda8d (PDB code 1psv) [15]. The sequence is KPYTARIKGRFSNEKELRD-FLETFTGR with 304 atoms [15]. We used the reported

structure as the starting structure (Figure 1). Simulation temperature was 280 K. Coordinates and energies were recorded every 10 psec during the simulation. BD simulation without solvation energy calculation (i.e. $G_{solv}(\mathbf{r}^N) = 0$ kcal/mol and $\epsilon = 1$) was also performed for comparison of computation time.

The BD simulation program was written in Fortran. All calculations were performed on an 800 MHz Duron processor.

2.6 MD Simulation

We also performed MD simulation in explicit water molecules and *in vacuo* ($\epsilon = 1$) to compare with the results of BD simulation with implicit solvent model. Both simulations were performed using the MD program AMBER 4.1 [36] with united-atom force field, which was the same as that used in BD simulation. The starting structures were the same as used for BD simulation. The explicit water simulation was performed in the constant NPT ensemble using the peptide (initial structure model determined by NMR) that was solvated with TIP3P water in a box extending at least 10 Å in all directions, producing the system of 2,459 water molecules and total 7,681 atoms. The periodic boundary condition was used for explicit water model simulation. The system was energy minimized with standard procedure. The temperature of the system containing water molecules was maintained by coupling solute and solvent (only for explicit water model simulation), separately, to an external heat bath fixed at the reference temperature [37]. The temperature coupling constant was 0.2 psec. The pressure of the system containing water molecules was maintained by coupling the system to an external pressure bath at 1 atm with a coupling constant of 0.2 psec [37]. All covalent bonds were constrained with SHAKE algorithm [38]. The time step was 2 fsec. The 9 Å non-bonded cut-off was used and the non-bonded pair list was updated every 10 steps. Simulation temperature and sampling were the same as used for BD simulation.

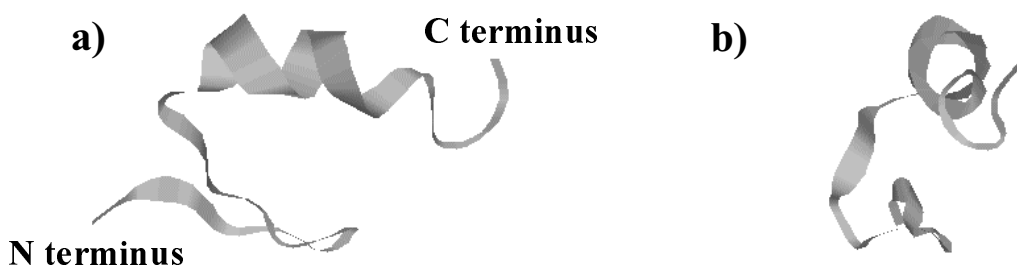


Figure 1. Ribbon representations of the pda8d NMR structure [15]. (a) A view from one side, with N and C termini labeled. (b) A view of the peptide rotated by 90° with respect to (a) around the vertical axis. The figures are generated with RasMol [43].

3 Results

3.1 Computational Cost

Table 1 lists the time required to run 1 nsec simulation of pda8d with various solvent models on an 800 MHz Duron processor in a personal computer. It also lists the relative times compared to *in vacuo* ($\epsilon = 1$) MD simulation. *in vacuo* MD simulation required 1.6 (85.1/52.5) times more simulation time than the BD simulation without solvation energy. Therefore, the increase of time step from 2 fsec (MD) to 10 fsec (BD) was not so effective for time-saving. On the contrary, BD simulation with DD/SA sol-

vent model required 53 (4,230/80.0) times less time than the MD simulation with explicit water molecules with the same cut-off radius (9 Å).

3.2 Dynamics

As described above, the BD simulation with DD/SA model was proved useful for long time simulation. Next we asked whether the BD simulation gave satisfactory simulation trajectories concerning the structure and dynamics. We compared the simulation results on structure and dynamics obtained by the various simulation procedures.

Table 1. Computation Time for 1 nsec Dynamics of 28-mer $\beta\beta\alpha$ Peptide

Solvent model	Cut-off radius(Å)	Time(min)	Relative time
Vacuum MD ^a	9	85.1	1.0
BD without solvation energy ^b	9	52.5	0.6
DD/SA BD ^b	9	80.0	0.9
Explicit water MD ^c	9	4,230	49.7

^aThe simulation was performed using the MD program AMBER with united-atom force field. Dielectric constant was 1. All covalent bonds were constrained with SHAKE algorithm. The time step was 2 fsec. Number of atoms was 304.

^bThe simulations were performed using the BD program developed here. All covalent bonds were constrained with LINCS algorithm. The time step was 10 fsec. Number of atoms was 304.

^cThe simulation was performed using the MD program AMBER with united-atom force field. The peptide was solvated using a box extending at least 10 Å in all directions. All covalent bonds were constrained with SHAKE algorithm. The time step was 2 fsec. Number of atoms was 7,681.

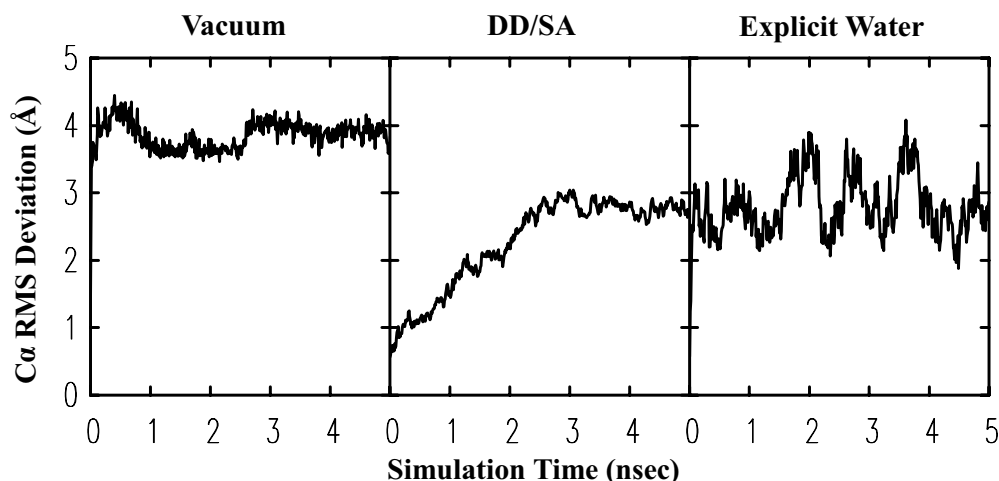


Figure 2. The C α RMS deviations from NMR structure as a function of simulation time. From left to right: vacuum, DD/SA model, explicit water model.

Figure 2 shows C α RMS deviations of the peptide from the NMR structure as a function of time. Snapshots of each trajectory at various periods are shown in Figure 3. The DD/SA model and explicit water model simulations appeared to give relatively stable trajectories, as judged by the smaller RMS deviations compared to that of *in vacuo* MD simulation. By *in vacuo* MD simulation the structure was almost collapsed quickly and the collapsed structure was stable until 5 nsec. On the other hand, the simulations using the DD/SA solvent model and explicit solvent model gave stable trajectories of the secondary and tertiary structures of the native peptide over the 5 nsec simulation.

Figure 4 shows the radius of gyration (R_g) of the peptide as a function of time. The DD/SA solvent model gave

stable R_g s at 9.5 Å during 5 nsec simulation. The R_g s by DD/SA simulation were almost similar to those obtained by the explicit solvent simulation. *in vacuo* simulation gave much smaller R_g s.

We examined the C α positional RMS fluctuations of the peptide during simulation using various solvent models (Figure 5). The RMS fluctuations observed in the simulation using DD/SA model were only a little smaller throughout the peptide than those observed in the simulation using the explicit solvent model, in which the fluctuations around the C terminus region of the peptide and the hairpin turn (residues 7 and 8) were specifically much larger. On the other hand, the fluctuations observed in the *in vacuo* simulation were very small throughout the peptide.

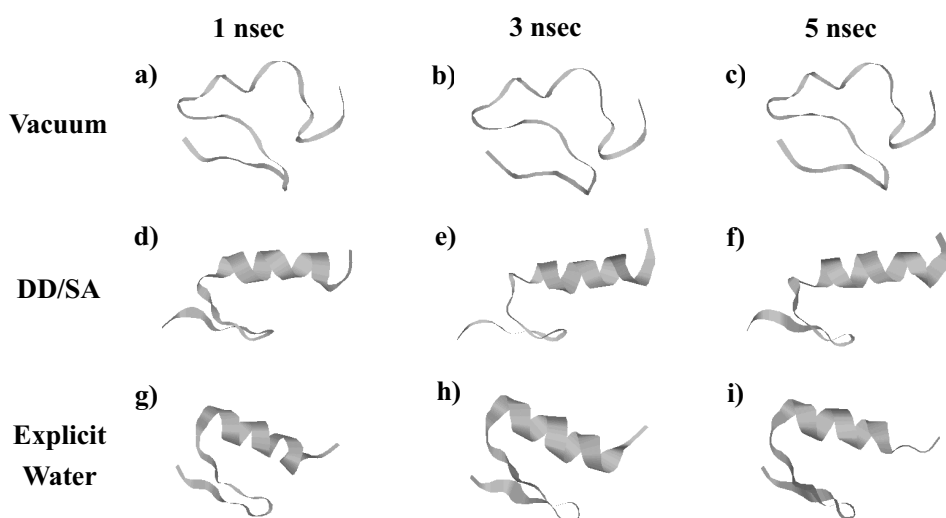


Figure 3. Ribbon representations of the snapshots at 1 nsec (a, d, g), at 3 nsec (b, e, h), and at 5 nsec (c, f, i) in various solvent model simulations. First row is from vacuum simulation (a, b, c), second row is for DD/SA model (d, e, f) and third row is for explicit water model (g, e, f). The figures are generated with RasMol [43].

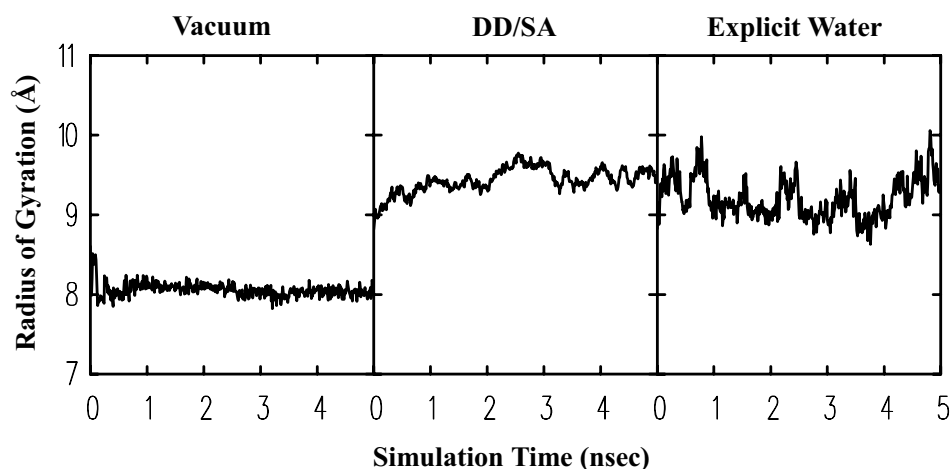


Figure 4. The radii of gyration as a function of simulation time. From left to right: vacuum, DD/SA model, explicit water model.

4 Discussion

The BD simulation using the implicit solvent model was effective for stable simulation in two senses. 1) BD simulation enables us to use longer time step, which saves much computer time for longer simulation (i.e. efficient conformational search). In this study we used the time step of 10 fsec for 1 step in BD simulation which should be 5 times more time-saving than MD with 2 fsec for 1 step, but actually BD simulation was only 1.6 fold time-saving (Table 1). This is partly due to the intrinsic difference of dynamics algorithm and partly due to the immature optimization of our BD program, which can be improved by further refinement. 2) BD simulation with the implicit solvent model provides stable simulation similar to the MD with explicit solvent molecules (Figures 2, 4). In BD simulation, the number of atoms was 304 for pda8d (Table 1, legend), while in MD simulation with explicit water, the number was 7,681. The implicit solvent model was effective for saving computation time by decreasing the number of atoms considered and the effect is estimated as $53/1.6 \approx 33$ times.

Especially the smaller radii of gyration often observed by *in vacuo* simulations [39], which were claimed as main artifacts, considerably improved to similar R_g values to those obtained with explicit solvent molecules. A little bit smaller atomic fluctuations observed in the BD simulation were different from those with the explicit solvent model (Figure 5). This difference may be attributed to the energy function using the mean solvation energy. In addition, the solvation parameters for DD/SA solvent model in this study have been originally parameterized for GROMOS87 force field (ionized side chains were neutralized) with $\epsilon = 1$ by Fraternali and Gunsteren

[26]. Then, those parameters have been applied in GROMOS96 force field with $\epsilon = r_{ij}$ [31] and almost the same ones have been used for CHARMM19 force field with $\epsilon = 2r_{ij}$ [40–42]. The difference in solvation parameters between GROMOS96 and CHARMM19 force fields is only for σ_S , the former has 0 cal/mol/\AA^2 and the latter 12 cal/mol/\AA^2 . However, there has been no study that used such solvation parameters for AMBER91 force field. Therefore, the original solvation parameters for SA model may not be suitable for direct usage with AMBER91 force field, which might have resulted in smaller atomic fluctuations. The parameterization of those parameters for AMBER91 force field is necessary to solve this issue.

We used LINCS algorithm [35] to constrain bond lengths instead of SHAKE algorithms [38] in our BD simulations. Both algorithm saved simulation time similarly, thus were useful. However, when we used SHAKE algorithm in BD simulation, the simulation was sometimes suspended since SHAKE did not converge for large atomic displacements, especially at high temperatures. Therefore, we implemented the more stable constraint algorithm, LINCS, in this study.

Although a simple surface area model was used for solvation energy calculation in this initial development of the atomistic Brownian dynamics method, the Generalized Born [30] or Poisson-Boltzmann solvation model can be utilized to improve accuracy of solvation energy calculation. Furthermore, the replica exchange method [7] can be combined to increase sampling efficiency in future development. The results shown in this paper indicate that BD simulation with the implicit solvent model is a promising approach that replaces MD simulation with explicit water molecules.

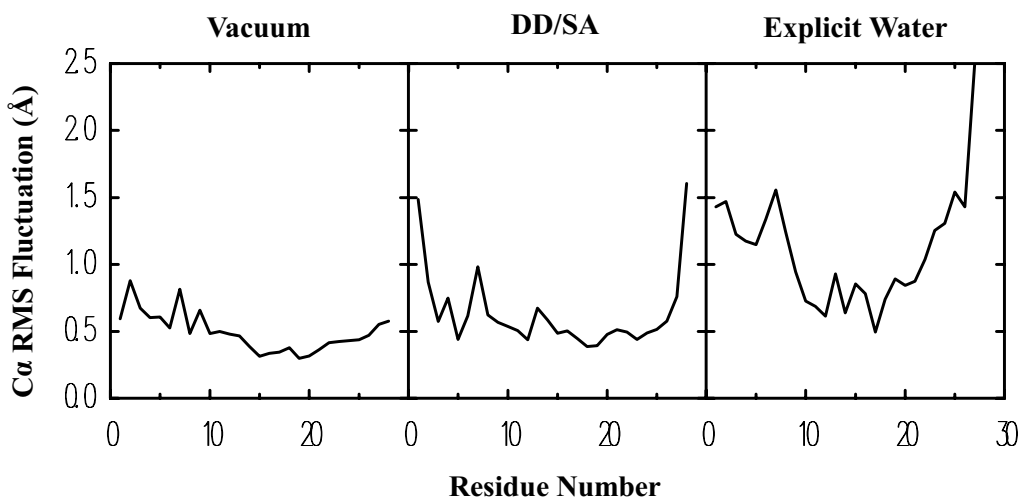


Figure 5. The RMS fluctuations of $C\alpha$ atom positions obtained from simulations using different solvent models. The RMS fluctuation values were calculated from the average values over 2.5 nsec to 5 nsec period. From left to right: vacuum, DD/SA model, explicit water model.

5 Conclusions

In this work we have developed an atomistic Brownian dynamics simulation with implicit solvent model for long time simulation. We tested it by simulating 28-mer peptide. The atomistic Brownian dynamics algorithm with implicit solvent model was applied for the first time to an actual protein having its own structure $\beta\beta\alpha$. The BD simulation using DD/SA solvent model was 53 times faster than the corresponding MD simulation using the explicit solvent model. The main artifacts typically encountered in *in vacuo* simulations, namely smaller radii of gyration and atomic fluctuations, were considerably reduced when applying the DD/SA solvent model to BD simulation. Therefore, the BD simulation with the implicit solvent model is potentially useful for studying thermodynamics and kinetics of protein folding.

6 Agreement for using the program

This atomistic Brownian dynamics program is freeware. Please contact us by e-mail when you want to use the program.

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長時間シミュレーションのための水和モデルを用いた Brownian dynamics アルゴリズムの開発

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タンパク質の Brownian dynamics シミュレーションアルゴリズムを開発した。タンパク質は AMBER91 の力場を持つ、ユナイテッド・アトムモデルを用いた。溶媒の効果は距離依存型誘電率 / 露出表面積モデルで表し計算に組み込んだ。構造を保持する 28 残基のペプチドをモデルとし (Figure 1)、Brownian dynamics の計算効率およびペプチドの構造変化とダイナミックスの結果を、水分子を顕わに扱った分子動力学法による結果と比較した。Brownian dynamics シミュレーションは分子動力学計算に比べ 53 倍と、非常に高速な計算が可能であった (Table 1)。また、5 ナノ秒のシミュレーションの間、ペプチドの立体構造は安定に保持されており (Figures 2, 3)、真空中におけるシミュレーションで頻繁に見られるアーチファクトは軽減されていた (Figure 4)。これらの結果は、本 Brownian dynamics アルゴリズムは長時間の計算を必要とするタンパク質折り畳みの研究に広く利用可能であることを示すものである。

キーワード: Brownian dynamics, 非分子論的水和モデル, 距離依存型誘電率, 露出表面積