Can Brownian Dynamics be a Useful Tool for Structure-Based Drug Design?

Akifumi Oda
oda@tohoku-pharm.ac.jp

Hisao Matsuzaki
matuzaki@tohoku-pharm.ac.jp

Noriyuki Yamaotsu
yamaotsun@pharm.kitasato-u.ac.jp

Shuichi Hirono
hironos@pharm.kitasato-u.ac.jp

1 Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 981-8558, Japan
2 School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

Keywords: Brownian dynamics, implicit solvent, drug design, protein folding, statistical physics

1 Introduction

Molecular simulations play important roles in computer-aided drug design (CADD). Especially, these calculations are useful for the analyses of 3D structures of biopolymers, such as proteins, nucleic acids or sugar chains, in structure-based drug design (SBDD) trials. The molecular dynamics (MD) simulation is most widely used for the molecular simulations of biopolymers, and it plays significant roles not only in CADD but also fundamental biological researches. On the other hand, because calculations of solvent effects caused by water molecules surrounding biopolymers are indispensable to MD simulations of biopolymers, high computational costs are often required for MD.

Brownian dynamics (BD) simulation is one of the molecular simulation methods. In BD simulations, solvent effects are represented by random power and viscosity of the solvent without using explicit water molecules. Because of the implicit solvent model, BD calculations require much less computational resources than MD with explicit solvent molecules.

Recently, we developed BD program, named as “brownian”. The operationality of this program is very similar to AMBER, which is one of the most widely used MD program especially for biopolymers. For example, parameter variables which have same names between brownian and AMBER have same meanings in both programs. The command options and input file formats of these two programs are also similar to each other. The similarity of operationality is advantage of brownian, because BD simulations can be easily carried out even if users are not skillful for BD. In addition, because brownian can read AMBER topology and coordinate files without any additive operation, it can use all types of AMBER force fields, which is one of the most reliable force field for biological systems. Although we have already tested the brownian for simulating induced fit caused by protein-ligand docking, more detailed tests are required for investigating whether brownian can be used for CADD or not. In this study, the structural stabilities of the wild type and mutant proteins were calculated, and the ability of brownian for biopolymer simulations were evaluated by comparing these results.

2 Method

The movements of particles which follow Brownian motion are described by Langevin equation. Because the differential equation is required to be approximated by the difference equation in BD calculations same as MD, following equations (1) derived by Ermak and Buckholz[1] were implemented in brownian program in order to calculate the velocities and locations of particles.

\[
    r(t + h) = r(t) + \frac{1}{\zeta} v(t)(1 - e^{-\zeta h}) + \frac{1}{m\zeta} F(t) \left[ h - \frac{1}{\zeta}(1 - e^{-\zeta h}) \right] + r^d(t + h)
\]
\[ v(t + h) = v(t)e^{-\zeta h} + \frac{1}{m\zeta} F(t)(1 - e^{-\zeta h}) + \frac{1}{m\zeta h} \left( F(t + h) - F(t) \right) \left( h - \frac{1}{\zeta} \left( 1 - e^{-\zeta h} \right) \right) \]  

(1)

where, \( r \) and \( v \) are the location and velocity of the particle, respectively, \( h \) is the time step, \( \zeta \) is the friction coefficient, \( m \) is the mass, \( F \) is the interaction force, \( v^B \) is random difference of location, and \( v^B \) is random difference of velocity.

In this study, BD simulations of Bovine Pancreatic Trypsin Inhibitor (BPTI) were carried out. Both wild type and a mutant of BPTI are calculated, and structural changes were observed. In the mutant of BPTI, three disulfide bonds, which play important roles in 3D-structure formation of BPTI [2], were removed. In this study, initial structure of simulations was experimentally observed structure of BPTI obtained from RSCB protein databank (PDB ID: 6PTI). The proteins using this study are shown in Table 1. In addition to BD, MD simulations were also carried out for comparison study. For BD and MD calculations, brownian 1.1 and AMBER9 were used, respectively, and ff03 force field in AMBER9 was adopted. Simulation times of both calculations were 2 ns and time step was 1 fs. Temperature was set to 300 K. For MD simulations, implicit solvent were adopted by using generalized Born model. In this study, cyclic boundary condition was not used, and infinite dilution model was adopted both for MD and BD simulations.

Table 1: Wild type and a mutant of BPTI used in this study

<table>
<thead>
<tr>
<th>mutation</th>
<th>BPTI activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 wild type</td>
<td>Active</td>
</tr>
<tr>
<td>2 C5A, C14A, C30A, C38A, C51A, C55A</td>
<td>Inactive</td>
</tr>
</tbody>
</table>

### 3 Results and Discussion

RMSD of the structures of wild type and mutant BPTI were illustrated in Figure 1. The references of RMSD calculations were the initial structures of the simulations. As shown in the figure, although RMSD of wild type 1 were only around 2.0 Å both for MD and BD simulations, 3D-structures of protein 2 were more transformed after simulations. These results are consistent with experimental activities of wild type and mutant of BPTI (shown in Table 1), and they indicate that mutant 2 seems to be inactive because of different 3D-structure from wild type. Because the results of BD simulations were similar to those of MD simulations both for 1 and 2, BD is expected to be used for protein simulations instead of MD. Furthermore, computational time of BD simulation was much less than that of MD (Both for 1 and 2, the former were less than one-third of latter). These results indicate that BD simulations by brownian program are very useful for the simulations of biopolymers.

![Figure 1: RMSDs of both calculations](image)

### References
