On the Trajectory of Ubiquitin Using Molecular Dynamics

Atsushi Haruta

School of Knowledge Science,
Japan Advanced Institute of Science and Technology
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1 Introduction

Owing to today's Genome Project revealing the genome sequences of the various kinds of living things, a most of DNA and protein sequences have come to stored at genome databases. However, while the project completed sequence reading only, the functions of genes and proteins are not founded out. Now, the approaches clarifying the functions of the each gene become the public attention. Life activity is realized by complex interactions of proteins. Therefore it is very important for clarifying the function of a life to understand dynamics of the proteins. For that purpose, it is required to reveal the protein structure and its folding process. In latest researches, it is said that several kinds of diseases(e.g. cancers, and brain diseases) are caused by the abnormalities of protein decomposition system called Ubiquitin-Proteasome System. In this decomposition system, Ubiquitin binds to a lysine residue of the target protein, called Ubiquitination, with iso-peptide bond by several enzymes, and this reaction produces poly-Ubiquitin, The poly-Ubiquitin becomes thee signal of decomposition. Ubl(Ubiquitin like protein) play important role to control the protein decomposition. Ubl is homologus to Ubiquitin and also binds to various kinds of proteins. But the dynamics of this ubiqutination(how to recognized the target protein) is not clear. Molecular Dynamics(MD) Simulation is one of the leading approach to solve the problem, which can analyze a thermodynamic action of atom.
Molecular dynamics allow us to find trajectory at atom-order based on free-energy.

Considering the above, we have been focusing on the following things; (1)understanding how Ubiquitin recognize its target proteins, because it is one of the important factors of the protein decomposition,(2)understanding protein foldings using molecular dynamics.

The purpose of this study is to consider the function of Ubiquitin regarding its structual changes in a cell. So, we aim at clarifying the structural change based on free-energy minimization by molecular dynamics simulation.

In this study, we challenged following things; (1)consideration about the stable structure of Ubiquitin and Ubls by MD simulation. Besides, MD simulation have huge amounts of calculation. So we challenged (2) parallelization of molecular dynamics and evaluattion of its efficiency.

2 MD Simulation of Ubiquitin and Ubl(SUMO-1,NEDD8)

Ubiquitin is a small protein consists of 8,600 molecules. When this Ubiquitin binds to its target protein at 76 residue, it orders disassembly of the target protein. The each Ubiquitin binds and forms Ubiquitin conjugating complex (Ubiquitination) at 48 residue lysine. In this research, our main target is Ub and Ubl(SUMO-1,NEDD8- human Ubl). We focused on poly-peptide back born structure (30 to 40 molecules) which contains the region of ubiqutination and binding site to target proteins. We have the computational experiment to know the stable structure, whole topology, and location of binding sites, using the temperature controled MD simulation considering the trajectory based on free energy of atoms. Each of our predicted structure is not similar to each other, though they have similar topology at first. We think that it is because of energy unstability of the initial structure. here, we have a interesting result; 2 out of 3 proteins have the structure which is similar with secondary structure such as α-Helix and β-sheet. Some binding sites are inside of the secondary structure. The reason would be; we did not consider the other atom exclude carbon, and we did not have boundary condition with water solvent. So we could not represent hydrophilicity and hydrophobicity. we found the fact that our simulation model, i.e. the force(potential) field to deal with protein only back born of poly-peptide, is too simple.

3 Parallelization of Molecular Dynamics

To calculate the force and potential for each atom in molecular dynamics, there should be huge amounts of calculation, and an expensive high performance computer has been needed to deal with large scale simulation such as MDs. Research for parallel molecular dynamics

using parallel processing technology has been developed. In this research, we parallelized our MD program with MPI library so that it can be run on PC cluster. Generally, in large scale MD simulation for protein foldings, a domain dividing method which is one of the method of parallelization of molecular dynamics is used, but we choose a particle dividing method (uniformly distribute each atom's load to each processor), because we deal with less scale simulation about 100 atoms, and it is not probably distributed uniformly in simulation space. And we run some benchmarks on PC cluster. We considered performance evaluation and prediction of the improvement in performance. Consequently, in the load distribution by particle division, we obtained the 70% parallelization efficiency. Our evaluation shows that we can calculate 3 times faster than single processor system in MD simulation.

4 Conclusion

In this research, the molecular dynamics program was developed and the computational experiment conducted the following things.

1. Though Ubiquitin and Ubl have homologeneous and similar topology, they did not become similar structure by MD only using poly-peptide back born. It is because of the energy unstablity of first structure.
2. Using particle division method of parallel MD. We obtained the 70% parallelization efficiency. And improvement of processing speed up to 3.08 times with 16 processors is estimated.

Moreover, the following things are mentioned for out future work, (1) since consideration of other kinds of atoms and modeling which consider hydrogen and solvent of water and boundary conditions is indispensable in order to raise the accuracy of the simulation of a protein molecules.(2)Investigate whether the parallelized efficiency on PC cluster is more effective method of particle division or the domain dividing. It should be required to consider dynamic load balancing.