Large Scale MD Simulations of Proteins on the Earth Simulator: MD simulations of hemoglobin in water

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The purpose of our subgroup is to computationally demonstrate large structural changes of hemoglobin using COSMOS90 which was accelerated on the Earth Simulator by vectorization and parallelization for all subroutines. COSMOS90 can efficiently simulate proteins in the realistic conditions i.e., in water with all degrees of freedom and long-range Coulomb interactions. We carried out molecular dynamics simulations of hemoglobin in water using COSMOS90 on the Earth Simulator for 45 nsec. We found the following features for the dynamics of the subunits. The dimer $\alpha_1\beta_1$ shifted its relative position against to $\alpha_2\beta_2$ like a rigid protein. The α_1 and α_2 subunits were strongly combined with another subunits β_1 and β_2, respectively. In contrast, the α_1 and α_2 subunits flexibly interacted with other subunits except for β_1 and β_2, respectively. These dynamical features of the subunits were consistent with the experimental hypothesis, i.e., the subunit $\alpha_1\beta_1$ relatively moves against to the $\alpha_2\beta_2$ subunit like two stacks of dumbbells.

Keywords: Molecular dynamics simulation, Allosteric effect, RMSD, Hemoglobin, Structural change

1. Introduction

High-speed computers become a necessary tool to simulate proteins and reveal their dynamical features. Proteins are large molecules consisting of thousands of atoms and have complicated structures. Furthermore, they largely fluctuate and easily change the whole structure even at the room temperature. Our purpose is to demonstrate large conformational changes of hemoglobin by performing realistic simulations. To perform the realistic simulations of proteins, we must include all atoms of proteins in water and their all interactions from chemical bonds to long-range Coulomb interactions.

The purpose of our project at this stage was to computationally demonstrate large structural changes of proteins on the Earth Simulator using COSMOS90 tuned up in this study. As a target protein, we chose a hemoglobin molecule (Fig. 1). A hemoglobin molecule can efficiently transfer four oxygen molecules from the lungs to the muscles. The binding of an oxygen molecule enhances additional oxygen bindings on other sites. Various experimental studies revealed that this cooperative binding is associated with large structural change. However, the X-ray crystal studies could not reveal the dynamical process of the structural changes, although they observed the structural difference between the initial and final states (Fig. 1). The purpose of our group is to computationally demonstrate large conformational changes of hemoglobin by performing long-time simulations.

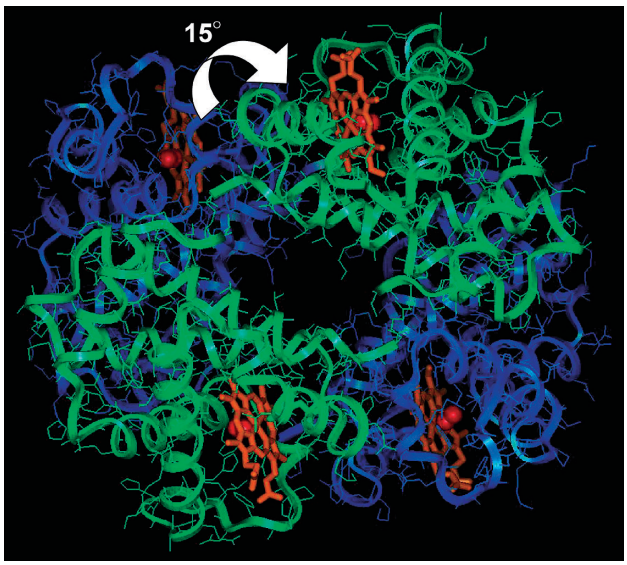

Fig. 1 X-ray structure of hemoglobin. The green color denotes two β subunits and blue denotes two α subunits. The structural difference between the oxy and deoxy hemoglobin suggests that the $\alpha_1\beta_1$ dimmer rotates against to another dimmer $\alpha_2\beta_2$ according to the oxygen binding to heme.

COSMOS90 was developed by one of the authors (M.S.) in 1990 and made it possible to simulate a protein in water with all degrees of freedom and with long-range Coulomb

interactions using the Particle-Particle and Particle-Cell (PPPC) method[1]. The PPPC method was proposed also by the author to efficiently calculate long-range Coulomb interactions between atomic charges in the order NlogN instead of N^2 by dividing a system into hierarchical cubic cells based on the Barnes & Hut tree code. In 2004, one of the authors (M.S.) tuned up COSMOS90 on the Earth Simulator by vectorizing and parallelizing its all subprocesses including the Barnes-Hut tree construction[2].

2. MD simulations of hemoglobin

Hemoglobin consists of four small proteins (subunits α_1, α_2, β_1, and β_2) which associate with each other and locate at four tops of a tetrahedron (Fig. 1). The α_1 and β_1 subunits are identical with α_2 and β_2 subunits and the α and β subunits consist of 141 and 146 amino acids, respectively. Each subunit contains a common heme molecule (iron-porphyrin). Hemoglobin was immersed in a water sphere of 66 Å radius and consisted of about 120000 atoms (number of protein atoms is about 9000 and number of water molecules is about 37000.) (Fig. 2). Hemoglobin was surrounded by about 200 crystal waters and about additional 36800 waters. Ordinary super computers such as VPP5000 at Research Center for Computational Science (RCCS) in Okazaki do not have enough performance speed to simulate the hemoglobin system. Molecular dynamics simulations of hemoglobin in water were carried out using COSMOS90 on the Earth Simulator for 45 nsec. MD simulations were performed for the entire system for all degrees of freedom and with long-range Coulomb interactions. The temperature of the system was slowly increased and kept at 300°K during 45 nsec.

2. Simulation results

To investigate structural changes of hemoglobin, the root mean square deviation (RMSD) of main-chain atoms (C_α, C, and N) was plotted for the entire hemoglobin and four subunits, as shown in Fig. 3, where the RMSD of a subunit was calculated by independently fitting only the subunit to the respective subunit of the initial X-ray structure. The four subunits had RMSD values (about 1.5 Å) which were closed to those of other proteins[4], although the β_2 subunit had a slightly larger RMSD value than the other subunits. In contrast, the RMSD values of the entire hemoglobin was clearly larger than those of the four subunits.

In order to clarify the reason, we evaluated the RMSD for various combinations of subunits (i.e., dimers $\alpha_1\beta_1$, $\alpha_2\beta_2$, $\alpha_1\alpha_2$, and $\beta_1\beta_2$), as shown in Fig. 4 and 5, where the RMSD of dimers were calculated by independently fitting a dimer ($\alpha_1\beta_1$, $\alpha_2\beta_2$, $\alpha_1\alpha_2$, and $\beta_1\beta_2$) to the respective dimer of the initial X-ray structure. In Fig. 4, the dimers fitted to the initial X-ray structure had almost the same RMSD values (red lines in Fig. 4) as those of the monomer subunit (α_1, α_2, β_1, and β_2) of Fig. 3. In contrast, the dimers without fitting had significantly large RMSD values compared with the fitted dimers, as shown by the blue lines of Fig. 4. The RMSD was also evaluated for the other dimers $\alpha_1\alpha_2$, and $\beta_1\beta_2$ (different combinations of the subunits), as shown in Fig. 5. The RMSD values of the dimers were almost the same values independent of whether the dimers were fitted to the respective X-ray dimers or not.

We found the following features for the interactions of the subunits. The dimer $\alpha_1\beta_1$ shifted its relative position against to $\alpha_2\beta_2$ like a rigid protein. The α_1 and α_2 subunits were strongly combined with another subunits β_1 and β_2, respectively. In contrast, the α_1 and α_2 subunits flexibly interact with other subunits except for β_1 and β_2, respectively. These dynamical features of the subunits were consistent with the experimental hypothesis, i.e., the subunit $\alpha_1\beta_1$ relatively rotates against to the $\alpha_2\beta_2$ subunit like two stacks of dumbbells according to with the oxygen binding to the heme iron atom (Fig. 1). This hypothesis was derived from the structural comparison between the hemoglobins with and without the oxygen molecules. The experimentally observed struc-

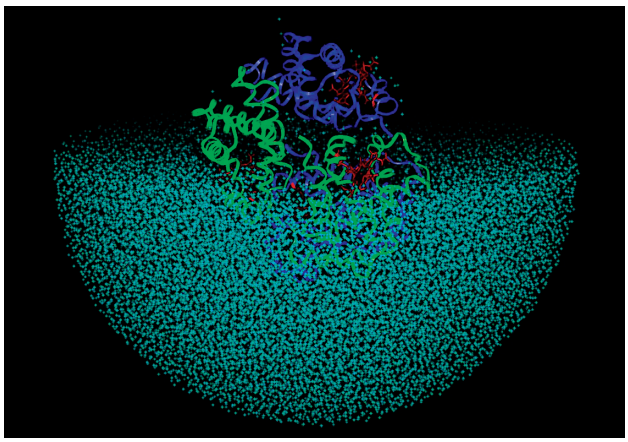

Fig. 2 Hemoglobin in water (about 120000 atoms). Radius of water sphere is 66 Å.
Reference 2.

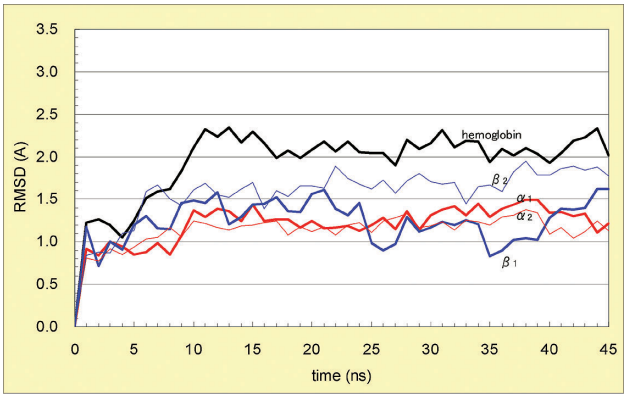

Fig. 3 Root-mean-square deviations (RMSDs) of hemoglobin and four subunits as a function of time.

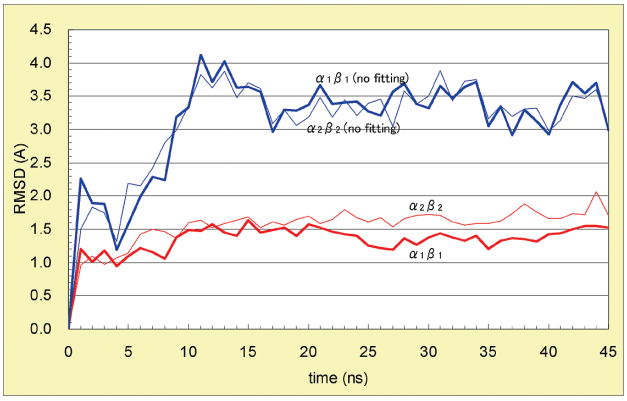

Fig. 4 Root-mean-square deviations (RMSDs) of the dimers as a function of time. One of the two dimers was independently fitted to the initial X-ray structure. The red and blue lines denote the RMSDs of the dimers with and without fitting, respectively.

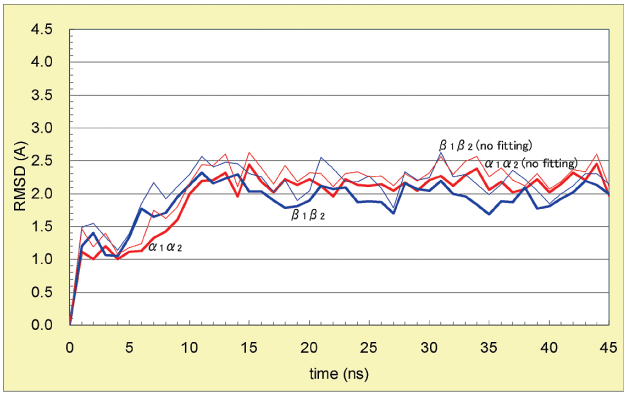

Fig. 5 Root-mean-square deviations (RMSDs) of the dimers as a function of time. One of the two dimers was independently fitted to the initial X-ray structure. The blue and red lines denote the RMSDs of the dimers with and without fitting, respectively.

tural difference (about 15° relative rotations) corresponds to about 6 Å RMSD for the dimer $\alpha_1\beta_1$ or $\alpha_2\beta_2$ that was not superimposed to the initial X-ray structure and still larger than those of the present MD simulations (3.5 Å as shown in Fig. 4).

3. Next stage

We are analyzing whether the relative shift of $\alpha_1\beta_1$ against to $\alpha_2\beta_2$, was explained as a simple motion like the experimental hypothesis. Furthermore, we will analyze the present MD trajectories for a few months to clarify the fluctuations as well as structural changes at the atomic level. After that, we hope to continue MD simulations of hemoglobin to demonstrate larger structural changes expected from the X-ray structural comparison.

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地球シミュレータによる蛋白質の大規模シミュレーション：水中のヘモグロビンの分子動力学シミュレーション

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我々のグループの目的は、ヘモグロビンの大きな立体構造変化を、独自に開発したソフトウエアCOSMOS90と地球シミュレータを用いて、分子動力学シミュレーションによって追跡することである。COSMOS90は、そのすべてのサブルーチンを、地球シミュレータ上でベクトル化と並列化を行って高速化している。COSMOS90を用いることによって、蛋白質を水中に置き、すべての自由度と長距離クーロン相互作用を含めたすべての相互作用を考慮することによって、リアルな条件下でシミュレーションすることができる。従来のヘモグロビンのシミュレーションは、あまりに大きいために水の無い真空中か一部の水を置いて位置を束縛した条件下で行われていた。そのために、ヘモグロビンの立体構造変化を実験と同じリアルな条件下でシミュレーションし追跡することができなかった。我々は、水中のヘモグロビンを45nsecにわたってシミュレーションした。その結果、我々は以下のように、ヘモグロビンを構成するサブユニット間の構造変化を観察することに成功した。二つのサブユニットα_1とβ_1（同様にα_2とβ_2）は、互いに強く会合しており大きな構造変化は示さないが、α_1とβ_1の複合体は、もうひとつの複合体$\alpha_2\beta_2$に対して相対的な位置を大きく変えた。

キーワード：分子動力学シミュレーション, アロステリック効果, RMSD, ヘモグロビン, 構造変化