Usage Report for Fiscal Year 2022

Project Title: Molecular dynamics simulations and structure modeling of biological macromolecules

Name:

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1. Background and purpose of the project, relationship of the project with other projects

Atomic structures of biological molecules are mainly determined by X-ray crystallography. Obtained structural models provide essential information for elucidating the mechanisms of their functions. Furthermore, observation of protein motions is becoming possible with the recent development of time-resolved X-ray crystallography. However, crystal environments could severely affect the motions, and the observed motions may not correctly represent the functionally relevant motions in the solution environment.

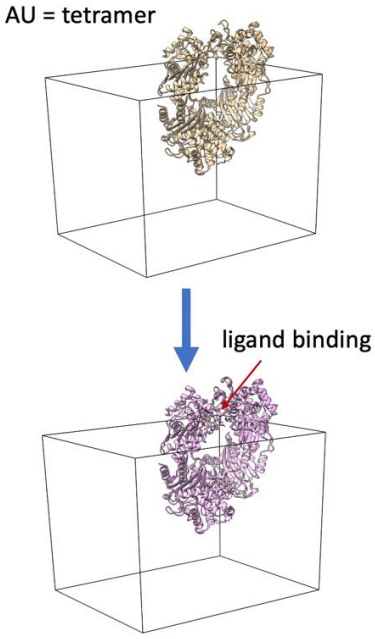

Fig 1: Unit cell dimensions of BlaC protein crystal change upon ligand binding.

In this project, we aim to examine the effect of crystal environment on protein motions using molecular dynamics (MD) simulations. As a first step toward this goal, we developed a procedure to perform the simulation of protein crystals. To test, we run the simulations of the microcrystal of a protein BlaC. A recent experiment showed that the ligand binding to BlaC alters the crystal unit cell dimensions (Fig 1). We compared our simulation to this experimental data to evaluate the effectiveness of such a simulation approach.

2. Specific usage status of the system and calculation method

To explicitly simulate the protein crystal environment, we assembled unit cells and performed MD simulations (Fig 2). Considering the size of the system, we used a coarse-grained (all-atom Go) model without water molecules. The parameter files are prepared using SMOG2 software. https://smog-server.org/smog2/.

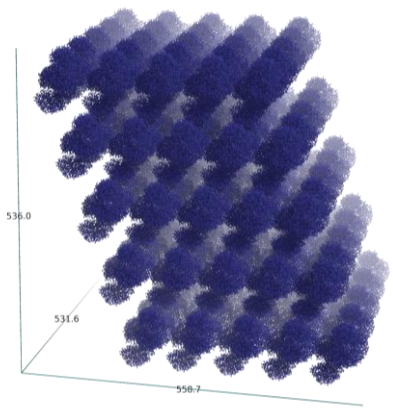

Fig 2: An example of constructed protein microcrystal.

In the all-atom Go model, the energy functions of

proteins are defined using the provided structure. Thus, we first prepared the parameter set for ligand-free protein structure. The interactions between protein molecules were also defined using the crystal information of the ligand-free state. Then, we also prepared the parameters for the ligand-bound structure, and the effect of ligand binding was simulated by switching these two parameter sets. Here, the interactions between the molecules are not altered. Thus the effect of the ligand-binding is included in the simulation only as the parameters of protein structures. MD simulations were performed using Gromacs.

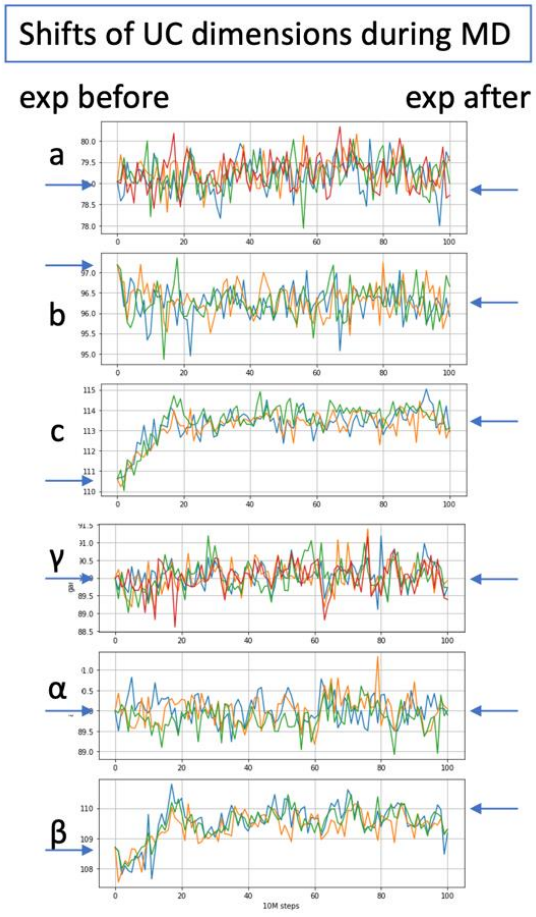

Fig 3: Unit cell dimensions, lengths, a, b, c, and angles, α, β, γ, as the function of MD steps. Arrows indicate the experimental data before and after ligand binding.

3. Result

5 million steps of MD simulations were performed after the parameter sets were switched to the ligand-bound state. The dimensions of the unit cell were measured during the simulations.

During the course of MD simulations, the unit cells were deformed. The shifts observed in the MD simulation are in good agreement with the experimental data. In particular, the unit cell edge length c expanded during MD simulations, which agrees with the experimental data. The angle β also changed during MD simulations, showing consistency with the experimental data.

4. Conclusion

We established a protocol to perform MD simulations of protein crystals using a coarse-grained (all-atom Go) model. We developed tools to construct the structure files of the protein crystal by assembling the protein monomer structures. The parameter files for MD simulations were prepared using SMOG2 software, and MDs were performed using Gromacs. Test simulations performed for the crystal of protein BlaC produced the unit cell dimension changes consistent with experimental data.

5. Schedule and prospect for the future

The established protocol can be used to perform MD simulations of other protein crystals. We plan to perform simulations for bacterial rhodopsin to examine how the crystal environment affects the conformational transitions observed in time-resolved crystallographic studies.

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