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Theoretical Studies on the Stability and Dynamics of Protein Complexes by Coarse-grained Simulations

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[Introduction]

In recent times, computational studies have become powerful tools to observe the properties of protein at the atomic or residue level. The development on computational study of protein has been greatly advanced by various approaches. For instance, coarse-grained simulation has gained much attention to replace the all-atom molecular dynamics simulation since it allows us to simulate larger systems and longer time scale. However, coarse-grained models involving protein–protein interaction are still limited. Meanwhile proteins actually are often found to form a complex to undergo their function.

Our previous works on coarse-grained for protein complex suggested that Gō-like model has good accuracy to represent the intermolecular interaction but lacks transferability since it can be applied only to the known structure [1]. Nevertheless, we cannot easily simplify the intermolecular interaction [2]. To overcome this gap, we need to develop more accurate and transferable coarse-grained model which represents the interactions of protein complex system.

In present work, we develop a coarse-grained potential model by introducing a parameter representing the strength of attractive interaction to simulate azurin complex [3]. This parameter is determined from the intermolecular distances at the native state and is simplified to be applicable for every dimer of azurin but is unique for each inter-particle. We will test our model to reproduce a native tetramer of azurin and extend the implementation of our model to simulate larger azurin complex. This study will offer a new coarse-grained model with better accuracy, transferability, and applicable for unknown or larger structure.

[Material and Method]

We simulated azurin tetramer taken from the X-ray crystal structure (PDB ID: 4AZU) [3] at the residue level. We employed Gō-like [4] model as the intramolecular potential to treat the monomer chain as rigid as possible. Meanwhile, we modified the widely used 6-12 Lennard-Jones potential as the intermolecular interactions as follows:

$$E(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - a_{ij}^{\alpha\beta}\left(\frac{\sigma}{r}\right)^{6}\right], \quad \text{where} \quad a_{ij}^{\alpha\beta} = \left(\frac{2^{1/6}\sigma}{r_{ij\ crys}^{\alpha\beta}}\right)^{6}$$

Here, we introduce new potential parameter, $a_{ij}^{\alpha\beta} > 0$, where the superscripts "α" and "β" represent different chains: chain α and chain β, and the subscripts "i" and "j" represent $i-$th and $j-$th particles of chain α and chain β respectively. The term $r_{ij\ crys}^{\alpha\beta}$ on this parameter is the inter-particle distance obtained from the

crystal structure. From six dimers on the tetramer azurin, we simplify this parameter to be more transferable. If we let α, β, and γ be three different chains, our parameter should satisfy the condition where $a_{ij}^{\alpha\beta} = a_{ij}^{\alpha\gamma} = a_{ij}^{\beta\gamma}$. Meanwhile other variables: r, σ, and ε represent the inter-particle distance, the finite distance where the potential is zero, and the potential strength, respectively. In this work, parameter σ will be set as the average of van der Waals radii of azurin, and ε will be adapted from the statistical contact potentials [5,6]. Our simulations were performed using Langevin dynamics under a constant temperature of 300 K. For the analyses, we monitored some physical properties calculated from the simulated trajectories such as root mean square displacement (RMSD), surface area, and intermolecular contacts.

[Results]

We measured the displacement of the system from the simulated trajectories through the RMSD calculation. Fig. 1 shows that the RMSD values are not so large (averagely below 5 Å). The RMSD of each chain also indicates that there is no significant deformation of each monomer as shown in Fig. 2. Moreover, we also compared our result to an all-atom molecular dynamics simulation of tetramer azurin with explicit water solvent. We measured the residue fluctuation for each individual chain and found that RMSF in our coarse-grained simulation is higher than RMSF in all-atom simulation but the plots of RMSF in both simulations have quite similar pattern (data are not shown here).

However we found that the final conformation is less packed than the native conformation. It is also confirmed that the surface area gradually increases during simulation time (data are not shown). In present calculation, the RMSD and number of contacts imply that our system becomes relatively stable, but the increase of surface area indicates that our system is starting to separate. Longer simulation time is needed to investigate more deeply the stability of azurin complex. Detailed results and the implementation on larger systems will be shown in the presentation.

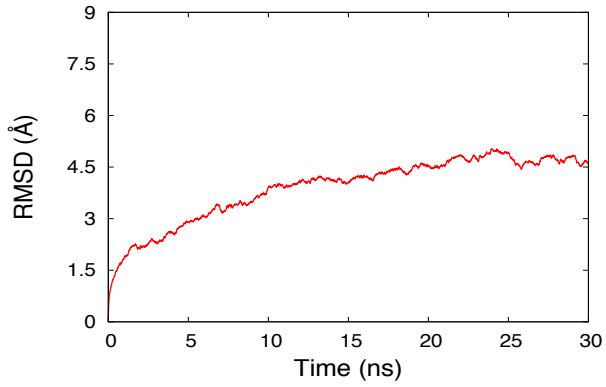

Fig 1. RMSD profile of tetramer azurin.

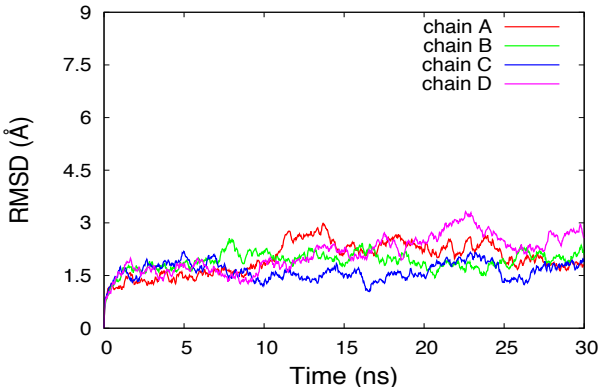

Fig 2. RMSD profile for each chain.

References:

[1] Rusmerryani, M., et. al. *Recent Development on Computational Science* **4**, 2013.
[2] Rusmerryani, M., et. al. *JPS Conf. Proc.*, **1**: 012054, 2014.
[3] Nar, H. Messerschmidt A., Huber R. *J. Mol. Biol.* 221: 765, 1991.
[4] Clementi, C., Nymeyer, H., Onuchic, J. N. *J. Mol. Biol.* **298**: 937–953, 2000.
[5] Kim, Y. C. and Hummer, G. *J. Mol. Biol.* **375**(5),1416-1433, 2008.
[6] Miyazawa, S. and Jernigan, R. L. *J. Mol. Biol.* **256**:623-644, 1996.