Conformational Sampling Methods for Macromolecules and Recent Advances

Yuichi Togashi

2016/10/28

Abstract:

Conformational changes of macromolecules such as proteins are generally slow, sometimes taking longer than milliseconds. In many cases, we cannot obtain satisfactory conformational ensembles (distributions) at a realistic time and cost by simply running molecular dynamics (MD) simulations in equilibrium, and hence a variety of enhanced sampling methods have been proposed. Ref. [1] is a recent review article on this field.

Among them, replica-exchange molecular dynamics (REMD) has been widely used. In REMD, MD simulation for replicas of the system are run in parallel, and the conditions (e.g. temperatures) are swapped between the replicas with such criteria that the correct canonical ensembles are reproduced. Generally, frequent swaps are desirable for good sampling however computationally expensive. An interesting variant, so-called infinite-swap REMD, was suggested, in which we assume infinitely frequent swaps of replica and derive limiting equations (i.e., an effective force-field mixed over all the replicas with different parameters), which could mediate the problem [2]. However, with many replicas, the implementation was almost impossible as we need to consider all the possible permutations (N!) of the replicas. Recently, a possible workaround for this problem was suggested, using multiscale modeling and Gillespie's stochastic simulation algorithm [3]. In this seminar, I would like to overview methods in the field and then introduce this particular paper.

Although these methods are originally intended for single biomolecules such as proteins, they are theoretically valid for other kinds of molecules or complexes as long as a force-field is given. I would like to discuss also possible applications of such methods to more macroscopic chromatin structures, e.g., ensemble-based structural optimization depending on Hi-C data.

References:

1. T. Maximova, et al., Principles and overview of sampling methods for modeling macromolecular structure and dynamics, PLoS Comput. Biol. 12, e1004619 (2016). doi:10.1371/journal.pcbi.1004619

2. N. Plattner, et al., An infinite swapping approach to the rare-event sampling problem, J. Chem. Phys. 135, 134111 (2011). doi:10.1063/1.3643325

3. T.-Q. Yu, et al., Multiscale implementation of infinite-swap replica exchange molecular dynamics, Proc. Natl. Acad. Sci. USA 113, 11744-11749 (2016). doi:10.1073/pnas.1605089113