Chapter 10

Computational Biophysics Research Team

10.1 Members

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10.2 Research Activities

Our team has developed highly parallelized MD software using the hybrid (MPI+OpenMP) parallelization technique, which is suitable to massively parallel supercomputers, like K or post-K computers. Since 2015, we have released our MD software, GENESIS (Generalized-ensemble simulation system), as freeware under the GPLv2 license and have continued the development for improving performance and reliability in MD simulations. One of the key features for GENESIS is that the efficient parallelization allows us to simulate very large biological systems using supercomputers. GENESIS also includes various enhanced conformational sampling methods for investigating slow conformational dynamics of biomolecules. By developing new functions in GENESIS, we would like to achieve more reliable predictions of biomolecular structure, molecular interaction, and biological function, and contribute to basic life science as well as drug discovery and medical science.

In this fiscal year, we updated GENESIS with better performance and with advanced algorithms, which is released as GENESIS 1.3. For more accurate MD simulations under the isothermal-isobaric (NPT) conditions, we developed a more accurate temperature evaluation. Data-driven MD simulations approaches are also developed.

10.2.1 Release of GENESIS 1.3

In the last fiscal year, we released GENESIS 1.3 including new functions and advanced algorithms. The main features of GENESIS 1.3 are (1) generalized replica exchange with solute tempering (gREST), (2) improvement of nonbonded interaction with GPU, (3) options of pressure\textunderscore virial/pressure\textunderscore rmsd, which includes virial terms from position/rmsd restraints in pressure evaluations, (4) fixing setup of AMBER force field when constraint is not set, and (5) fixing principal component (PC) restraints for computational performance.

10.2.2 Development of new integration algorithm in MD simulations

In MD simulations, not only the performance but also the reproducible computation result is essential. Recently, we found that accurate evaluation of temperature is important for controlling temperature as well as pressure in the isothermal-isobaric conditions (the NPT ensemble). Based on the Tolman’s equipartition theorem, all the particle motions should share a single temperature. However, conventional temperature estimation from kinetic energy does not include Hessian terms properly. As a result, the equipartition theorem is not accurately satisfied in MD simulations with a large time step.

By combining two kinetic energies, which are evaluated at full- and half-time steps in the velocity Verlet integrator, we could estimate instantaneous temperature up to the third order of the time step. The new definition of temperature, which we call “Optimal temperature”, is tested for a one-dimensional harmonic oscillator, a pure water system, a Bovine pancreatic trypsin inhibitor (BPTI) in water, and a hydrated DPPC lipid bilayer. In all cases, the optimal temperature estimator fulfills the equipartition theorem better than the existing methods. The MD simulation using Optimal temperature could reproduce physical properties, such as Area per lipid (APL) distribution in the hydrated DPPC lipid bilayer, even for longer time steps (4 fs or 5 fs) (Figure 10.1). In contrast, APLs in the MD simulations with the conventional temperature are deviated for longer time steps, suggesting the higher reliability of the MD simulation with Optimal temperature.

10.2.3 Conformational changes of Ca$^{2+}$-ATPase

Sarco(endo)plasmic reticulum Ca$^{2+}$-ATPase is a representative protein of P-type ATPases, which transports Ca$^{2+}$ across membrane against $10^4$ times concentration gradient by utilizing ATP hydrolysis. It is, however, difficult to investigate the conformational changes due to its slow time-scale. We introduced a rare event sampling method, string method, into MD simulation package, GENESIS and applied the method to the reaction step dissociating ADP and Ca$^{2+}$. We show that large scale motion of the cytoplasmic domains causes rearrangements of transmembrane helices, and the rearrangements result in large opening of the lumen gate. We further investigate structures of Ca$^{2+}$-binding site and the lumen gate. We performed MD simulations for
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Figure 10.1: Area per lipid (APL) distributions obtained by the MD simulations using the conventional (left and middle) or the optimal temperature (right). Using the optimal temperature, MD simulations with a longer time step can generate the same APL for the simulation with a shorter time step.

the protein with different protonation states in Ca^{2+}-binding site. From the simulation, the lumen gate has a wider open structure when one acidic residue (E908) is protonated, while it is not widely opened when three acidic residues (E309, E771, E908) are protonated. The results suggest that the conformation change of the lumen gate is triggered by the proton transfer to Ca^{2+}-binding site after dissociation of Ca^{2+} (Figure 10.2).

10.2.4 Free energy analysis for the conformational changes of a heme importer

Heme importer BhuUV-T is a member of the type-II ATP-binding cassette (ABC) transporters which transport heme across the biomembrane of a Gram-negative bacterium. Recently, crystal structures of BhuUV-T in the nucleotide-free inward-facing (IF) form have been solved. Based on the structures and biochemical experiments, a molecular mechanism for the heme transport cycle was proposed. According to the proposal, the transport cycle would initiate from the IF form. Binding of two ATPs to the nucleotide-binding domains of the IF state is thought to be essential to induce conformational changes toward the occluded (Occ) intermediate (10.3(a)). However, no structural information on the Occ state is available. In this study, a computational modeling approach is adopted to predict the Occ intermediate with bound nucleotides. The predicted model is further validated by the free energy analysis based on the string method. The computational results support the proposed transport cycle of BhuUV-T (10.3(b,c)).

10.2.5 Simulating large-amplitude transitions in proteins with a coarse-grained Gō model

Biochemical reactions are often coupled with large-amplitude structural transitions. A very common case is a protein transitioning from an open to closed state upon substrate binding. For these types of motions, coarse-grained (CG) models will be the method of choice, since they reduce the computational time by several orders of magnitude, allowing access to millisecond timescales which are unreachable by conventional all-atom MD simulations. In this work, we designed a scheme to effectively simulate such transitions and implemented it in GENESIS.

As a starting model we use the structure-based off-lattice Gō model. In this model, the representation of the protein is reduced to its Cα atoms, which are connected via virtual bonds with potentials acting between its bonds, angles and dihedrals. The heart of the model lies in the stabilization of the native structure of the protein, achieved by applying an attractive potential between the native contacts. In order to describe transitions between two stable minima, we adjust the original off-lattice Gō model, which assumes a single basin. We employ a mixing scheme which combines two potentials, one for each state, and apply varying weights depending on the coordinates of the system at each step of the simulation. Being a structure-based model, the off-lattice Gō model is very sensitive to the choice of initial parameters. Here, we use the Multistate Bennett Acceptance Ratio (MBAR) method for an efficient determination of the parameters. Using the method, we can predict the free energy of an unsampled data in any desired condition, by weighing sampled data obtained from simulations at various other conditions.

We applied the scheme to several well-studied systems and show that our mixing model was successful in describing structural transition for proteins undergoing large-amplitude transitions between distant states.
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Figure 10.2: Structure of Ca$^{2+}$-ATPase with different protonation states. Upper: E908 is protonated. Lower: E309, E771, and E908 are protonated.

Figure 10.3: Free energy analysis of BhuUV-T. (a) Schematic picture for the proposed IF-to-Occ conformational change of BhuUV-T. (b,c) The predicted free energy along the IF-to-OCC conformational pathway. The result is shown for the system (b) with bound ATP and (c) without ATP.
10.3  PUBLICATIONS

10.3.1  Articles


10.3.2  Invited Talks

[4] Yuji Sugita “Optimization and Parallelization of GENESIS on GPU platforms” International Workshop on GPU accelerated Molecular Dynamics Simulations, HKUST, Hong Kong, December 12, 2018

[5] Yuji Sugita and Yasuhiro Matsunaga “Data-driven molecular simulations for integrative dynamic structural biology” The 2nd workshop on Advances in Theory and Computation of Complex Systems - Biological Systems, Nanjing University, Nanjing, China, December 3, 2018


[8] Chigusa Iwahashi, “Development of simulation methods for conformational changes in membrane transport proteins”, The 5th project report meeting of the HPCI system including K computer, Tokyo, November 2, 2018

[9] Yuji Sugita, “Protein-Drug Interaction in Dilute Solution and In Cellular Environments”, XIVth ICISE Workshop on Computational Biophysics at the Molecular and Meso Scales, Quy Nhon, Vietnam, October 30, 2018


[12] Yuji Sugita, “Conformational changes between E1P to E2P states of SERCA by MD simulations based on string method and free-energy calculations”, the 256th ACS National Meeting in Boston on “Membrane Protein Simulations & Free Energy Approaches”, Westin Boston Waterfront, Boston, MA, USA, August 19, 2018


[15] Yuji Sugita, “Molecular simulations of protein dynamics in crowded environments”, WS on “Protein Aggregation and anti-aggregation” n the 18th Annual Meeting of the Protein Science Society of Japan, Toki Messe, Niigata, June 28, 2018

10.3.3  Oral and Poster presentations


10.3.4 Software