

10. Computational Biophysics Research Team

10.1. Team members

Yuji Sugita (Team Leader)

Jaewoon Jung (Research Scientist)

Osamu Miyashita (Research Scientist)

Ryuhei Harada (Postdoctoral Researcher)

Raimondas Gavelius (Postdoctoral Researcher)

Yasuhiro Matsunaga (RIKEN Special Postdoctoral Researcher)

Naoyuki Miyashita (Research Scientist (Concurrent))*

Yasuhito Karino (Postdoctoral Researcher (Concurrent))*

Takaharu Mori (RIKEN Special Postdoctoral Researcher (Concurrent))*

Takao Yoda (Visiting Scientist) **

Mitsunori Ikeguchi (Visiting Scientist)***

Hiromi Kano (Assistant (Concurrent))*

* The main affiliation of these people is Laboratory for Biomolecular Function Simulation, Computational Biology Research Core, RIKEN Quantitative Biology Center.

** The main affiliation is Nagahama Bio Institute

*** The main affiliation is Yokohama City University

10.2. Research Activities

Recent advances in structural biology, atomic structures of macromolecules have been determined by X-ray crystallography and nuclear magnetic resonance (NMR). These coordinates stored in protein data bank (PDB) are utilized for academic researches or industrial usages like drug design. The 'static' atomic structures are quite useful to understand molecular mechanisms underlying protein stability, large-scale conformational changes, ligand-receptor bindings, and enzymatic reactions. However, due to the complexity and flexibility of biomolecules, dynamical information, like conformational fluctuations or transitions between different physiological states is necessary for deeper understanding of the biological phenomena.

Computer simulations based on molecular dynamics (MD) method using the macromolecular structures now become important research tools also in life sciences. Conventional MD software allows us to carry out simulations of proteins or nucleic acids for several hundred nsec or longer. We aim to develop new MD software (GENESIS), which is highly parallelized for the usage of K computer. GENESIS also contains enhanced conformational sampling methods and multi-scale and multi-resolution simulation methods. Using GENESIS, we would like to start cellular-scale simulations based on the molecular representation of proteins and other biomolecules.

10.3. Research Results and Achievements

10.3.1. Parallelization of molecular dynamics simulation codes

GENESIS consists of two molecular dynamics simulation programs, named as ATDYN and SPDYN. In ATDYN, force decomposition is implemented as a parallel scheme, whereas SPDYN employs spatial decomposition scheme for obtaining a good scalability in massively parallel supercomputers. By last year, we have almost finished the development and parallelization of ATDYN and in this year, we focused on the development of SPYN. In SPDYN, we use a modified midpoint method originally developed by D.E.Shaw and his colleagues. In the original midpoint method, two particles interact on a particular box if and only if the midpoint of the segment connecting them falls within the region of space associated with that box. This method reduces the amount of communications between different processors during the nonbonded interaction calculations. We employ smooth particle mesh ewald method for long-range electrostatic interactions. In the reciprocal part of electrostatic calculations, we use three-dimensional decomposition of fast Fourier transform (FFT). Due to these schemes, we could get a good scalability in MD simulations.

10.3.2. Enhanced conformational sampling techniques

Free-energy landscapes of proteins or other biomolecules have usually rugged free-energy landscapes with huge number of local energy minima. Due to the complexity, the conventional MD has limitation in surveying all of the possible conformations. One of the possible ways to overcome this is to pre-define collective variables and bias the dynamics by adding the history-dependent potential (meta-dynamics). Recently, we have introduced well-tempered meta-dynamics scheme in ATDYN where new Gaussian is added at fixed time interval as a history-dependent bias potential. In addition to this scheme, three addition meta-dynamics schemes are being developed in ATDYN: multiply-walker, parallel-tempered, and bias-exchange meta-dynamics.

10.3.3. Protein stability under cellular environments

The effect of cellular crowding environments on protein structure and stability is a key issue in molecular and cellular biology. The classical view of crowding emphasizes the volume exclusion effect that generally favors compact, native states. Here, results from molecular dynamics simulations and NMR experiments show that protein crowders may destabilize native states via protein-protein interactions. In the model system considered here, mixtures of villin head piece and protein G at high concentrations, villin structures become increasingly destabilized upon increasing crowder concentrations. The denatured states observed in the simulation involve partial unfolding as well as more subtle conformational shifts. The unfolded states remain overall compact and only partially overlap with unfolded ensembles at high temperature and in the presence of urea. NMR

measurements on the same systems confirm structural changes upon crowding based on changes of chemical shifts relative to dilute conditions. An analysis of protein-protein interactions and energetic aspects suggests the importance of enthalpic and solvation contributions to the crowding free energies that challenge an entropic-centered view of crowding effects.

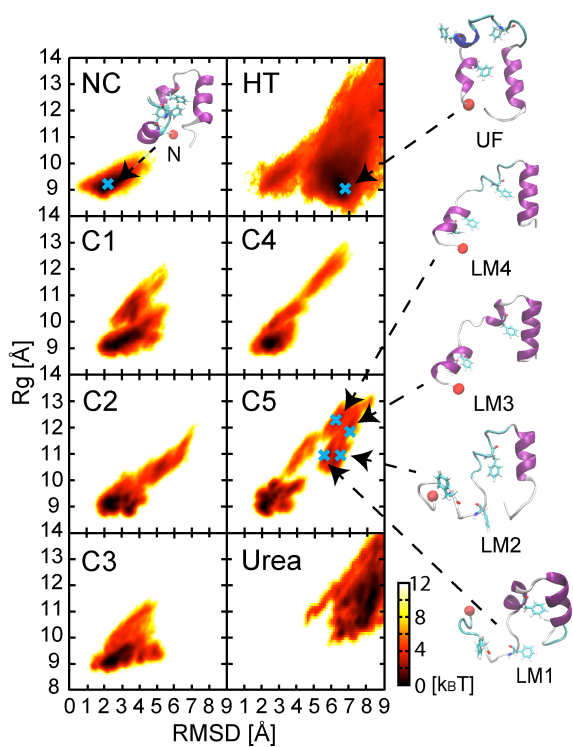


Figure 1. Potential of mean force (PMF) as a function of RMSD and Rg of villin at different protein concentrations (C1 (12%vol), C2 (17%vol), C3 (25%vol), C4 (37%vol), C5 (43%vol)) in units of $k_B T$.

10.3.4. Data assimilation algorithm for analyzing protein conformational motions

Protein functions, such as enzymatic catalysis and signal transduction, are mediated by the conformational transitions on the complex energy landscape in high-dimensional conformational space. The recent advances in computational power enable us to sample such conformation transitions of small proteins with all-atom molecular dynamics simulations. For moderate-sized proteins typical in living cells, however, it is still challenging to observe functionally relevant motions or conformational changes *in silico*. In order to simulate functionally relevant conformational transitions in moderate-sized proteins, we are developing a methodology to sample hidden conformation states or variables from low-dimensional experimental data, such as

single-molecule FRET photon trajectories. In this methodology, called the data assimilation, a bunch of (coarse-grained) protein models are concurrently simulated and also filtered (resampled) during the simulation in a bootstrapping manner according to the likelihoods with the experimental data. In this fiscal year, we have implemented the basic algorithm (particle filter) and an advanced version (merging particle filter) in GENESIS, and studied the performance of the algorithms by using a coarse-grained model (mixed elastic network model) and emulated single-molecule FRET trajectories. In the future, we are planning to apply the code to real single-molecule FRET trajectories.

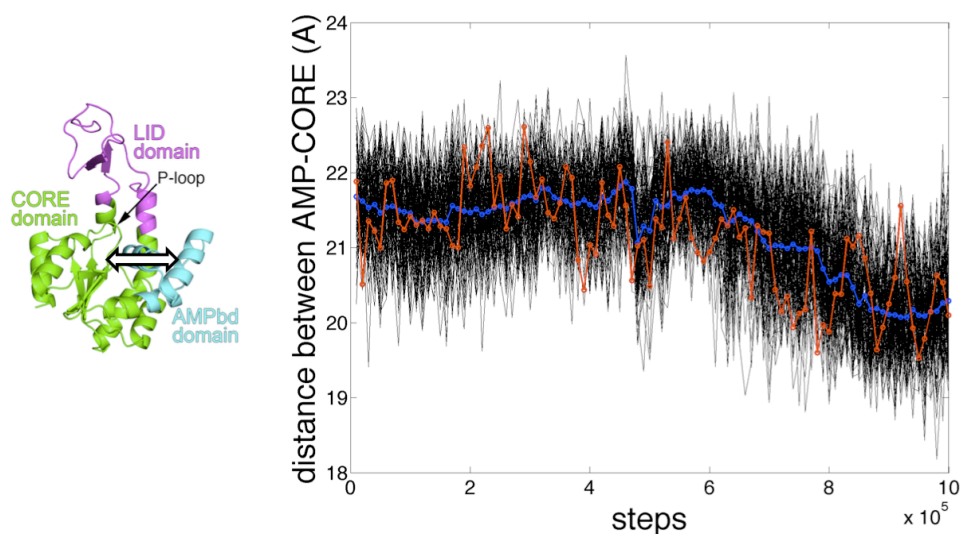


Figure 2. Estimation of a hidden variable from emulated single-molecule FRET data by using the data assimilation. The FRET data was emulated by a simulation of a coarse-grained model of Adenylate kinase. From the distance trajectory between the dyes attached to the CORE and LID domains (colored by green and magenta in the left panel, respectively), the FRET data was created. Here, we considered the distance between the CORE and AMPbd domains (colored by cyan) as the hidden variable and estimated that from the FRET data using the particle filter simulation. In the right panel, the “true” answer is indicated by the red line, and the estimation is the blue line. The distances of all particles are superimposed by the black lines.

10.4. Schedule and Future Plan

By the end of FY2013, we will open the source code of GENESIS version 1.0 for academic researchers as well as industrial users under GPL license. We need to finish the development of classical MD simulations and REMD simulations in GENESIS in FY2013. After that, we try to improve the parallel performance of GENESIS, by introducing new ideas and schemes. We also introduce new conformational sampling algorithms and coarse-grained models of biomolecules in GENESIS. We are also planning to develop QM/MM molecular dynamics module in our code in

collaboration with Dr. Nakajima's team at RIKEN AICS. By combining with parallelized QM code developed by Dr. Nakajima's group, we can perform highly parallelized QM/MM molecular dynamics simulations or QM/MM free-energy calculations of biomolecules or other molecular systems.

10.5. Publication, Presentation and Deliverables

(1) Journal Papers

1. Ryuhei Harada, Naoya Tochio, Takanori Kigawa, Yuji Sugita, and Michael Feig: "Reduced Native State Stability in Crowded Cellular Environment Due to Protein-Protein Interactions", *J. Am. Chem. Soc.* **135** (2013) 3696-3701.
2. Jaewoon Jung, Suyong Re, Yuji Sugita, and Seiichiro Ten-no: "Improved constrained optimization method for reaction-path determination in the generalized hybrid orbital quantum mechanical/molecular mechanical calculations", *J. Chem. Phys.* **138** (2013) 044106.
3. Yasuhiro Matsunaga, Ryutaro Koike, Motonori Ota, J.H. Tame, and Akinori Kidera "Influence of Structural Symmetry on Protein Dynamics", *PLoS ONE* **7**, (2012) e50011.

(2) Conference Papers

-None

(3) Invited Talks

1. Ryuhei Harada, ○Yuji Sugita and Michael Feig: "Protein Crowding Affects Hydration Structure and Dynamics", 2012 Telluride Workshop on Protein and Peptide Interactions in Cellular Environments, Colorado, USA, June 26, 2012.
2. ○Yuji Sugita, Ryuhei Harada, and Michael Feig: "Hydration structure and dynamics under protein crowding environments", ACS meeting, Philadelphia, USA, August 21, 2012.
3. ○Yasuhiro Matsunaga "Exploring the minimum free energy path of conformation transition in Adenylate Kinase by using the finite-temperature string method", Symposium "New Frontier of Chemical Reaction Path Search 2012", Tokyo, September 21-22, 2012.
4. ○Yuji Sugita: "How macromolecular crowding affects protein stability and dynamics?", 4th Biosupercomputing Symposium, December 3, 2012.

(4) Posters and presentations

1. Jaewoon Jung, Takaharu Mori, and Yuji Sugita, "Hybrid (MPI+OPENMP) parallelization of molecular dynamics with cell-pair Verlet list", The 26h Annual Meeting of the Molecular Simulation Society of Japan, Fukuoka, November 26-28, 2012

2. Yasuhiro Matsunaga, Takaharu Mori, and Yuji Sugita, “Data Assimilation in Molecular Dynamics Simulation”, The 26th Annual Meeting of the Molecular Simulation Society of Japan, Fukuoka, November 26-28, 2012.
3. Jaewoon Jung, Suyong Re, Yuji Sugita, and Seiichiro Ten-no, “Improved constrained optimization method for reaction-path determination in quantum mechanical/molecular mechanical calculations”, Biophysical Society 57th Annual Meeting, Philadelphia, USA, February 2-6, 2013
4. Ryuhei Harada, Yuji Sugita, and Michael Feig, “Stability of proteins in cellular environments”, Biophysical Society 57th Annual Meeting, Philadelphia, USA, February 2-6, 2013
5. Jaewoon Jung, Takaharu Mori, and Yuji Sugita, “Hybrid parallelization of Molecular dynamics with cell-pair Verlet list”, The third AICS International Symposium, Kobe, February 28-March 1, 2013
6. Takaharu Mori, Jaewoon Jung, and Yuji Sugita, “Development of a New Replica-Exchange Molecular Dynamics Method for Bio-Membrane Systems”, The third AICS International Symposium, Kobe, February 28-March 1, 2013
7. Yasuhiro Matsunaga, Takaharu Mori, Jaewoon Jung, and Yuji Sugita, “Tracking Protein Dynamics from Single-Molecule FRET via sequential Monte Carlo filtering”, The third AICS International Symposium, Kobe, February 28-March 1, 2013

(5) Patents and Deliverables

-None.