Theoretical Molecular Science Laboratory (2019)
Chief Scientist: Yuji Sugita (D.Sci.)

(0) Research field

CPR Subcommittee: Chemistry

Keywords: Molecular dynamics simulation, *ab initio* quantum chemistry, multi-scale simulation, crowded cellular environment, integrative dynamic structural biology

(1) Long-term goal of laboratory and research background

Our long-term goal is to understand molecular mechanisms for various dynamical processes in chemical and biological systems using computational chemistry. Multi-scale simulation methods, which include hybrid quantum mechanics/molecular mechanics (QM/MM), all-atom molecular dynamics (AAMD), and coarse-grained MD (CGMD) methods, are necessary to study the structure-dynamics-function relationships in molecular systems. We develop and implement the multi-scale methods in our MD software, GENESIS (GENeralized-Ensemble SImulation System). The next step is to connect the results of QM/MM, AAMD, and CGMD using data science, such as machine learning and data assimilation. Using this approach, we investigate protein dynamics and function in crowded cellular environments and examine the roles of weak and non-specific molecular interactions on biomolecular functions in living cells. AAMD and CGMD are useful to explore large conformational changes in biomolecules, while QM/MM is required to compute enzymatic reactions based on the electronic structures. Using supercomputers efficiently, we carry out large-scale biomolecular simulations of various biological processes. Such simulation results are integrated with single-molecule experiments and cryo-electron microscopy for our better understanding of molecular and cellular functions.

(2) Current research activities (FY2019) and plan (until Mar. 2025)

(A) Development of multi-scale simulation methods for chemical and biological systems

GENESIS has been developed to utilize K or Fugaku supercomputers. This software has two unique features. GENESIS contains several computational techniques to enable high-performance computing in massively parallel supercomputers. In FY2019, we collaborated with Dr. Karissa Y. Sanbonmatsu in Los Alamos National Laboratory, USA, to simulate a chromatin system that contains more than one billion atoms in atomistic MD simulations [1]. This is one of the largest biomolecular simulations in computational biophysics. We also optimized GENESIS to Fugaku supercomputer in collaboration with Fugaku system and hardware developers. By the 'co-design' strategy, we could accelerate MD simulations using GENESIS on Fugaku more than a hundred times faster than that on K computer.

Several enhanced conformational sampling methods, like replica-exchange MD, have been available in GENESIS. These methods are useful to compute free-energy changes upon the conformational changes in biomolecules. They could be applied to binding free-energy calculations, which are often used in *in-silico* drug discovery. In FY2019, we computed binding free energies of several ligand molecules for T4 Lysozyme, using the gREST (generalized Replica Exchange with Solute Tempering) method. This simulations successfully distinguished binder ligands from non-binder ones for T4 Lysozyme without using any experimental information. The predicted binding poses are very close to the crystal structures of T4 Lysozyme/ligand complexes.

To extend the limitations of current MD simulations, we further develop CGMD and QM/MM simulations in GENESIS until March 2025. The developments of QM/MM modules in GENESIS showed significant progress in FY2019. Enzymatic reaction analysis based on QM/MM and AAMD would be available near future. We also developed a new implicit solvent model for micelle systems to simulate membrane proteins in the membrane environments [3].

(B) Biomolecular structure, dynamics, and function in crowded cellular environments

Fibroblast growth factor receptor 3 (FGFR3) is a member of receptor tyrosine kinases, which is involved in skeletal cell growth, differentiation, and migration. FGFR3 transduces biochemical signals from the extracellular ligand-binding domain to the intracellular kinase domain through the conformational changes of the transmembrane (TM) helix dimer. In FY2019, we applied gREST to wild type (WT) and G380R mutant (G380R) of FGFR3 in biological membranes [4]. The simulation results are in good agreement with the solid-state nuclear magnetic resonance (NMR) spectroscopy. TM helices in G380R, whose interfaces are different from WT, are extended more than WT, and thereby, G375 in G380R contacts near the N-termini of the TM helix dimer. Considering that both G380R and G375C show the

constitutive activation, the formation of the N-terminal contacts of the TM helices can be generally important for the activation mechanism.

Reverse osmosis (RO) membranes based on aromatic polyamide (ar-PA) are widely used in desalination of seawater. However, the microscopic mechanism for fast water diffusion through a polyamide layer remains elusive. Here, we study the structure and dynamics of ar-PA chains and water molecules in comparison to nylon 6 (one of aliphatic polyamides) under various water contents (0.0–15.9 wt%). The infrared (IR) difference spectrum between dry and moist ar-PA shows little changes in amide A bands, in contrast to that of nylon 6, which yields a prominent dip. Theoretical analyses using molecular dynamics simulations and quantum electronic and vibrational calculations reveal that the dip in nylon 6 is caused by breaking of hydrogen bonds (HBs) among amide groups [5]. The incoming water molecules that break amide-amide HBs are bound to polyamide chains nearby and diffuse slowly. On the other hand, the amide-amide HBs in ar-PA are kept upon hydration. Such polymer structure facilitates growth of large water clusters with more than 100 water molecules and rapid diffusion of water molecules. The amide A band serves as a fingerprint to characterize the water permeability of polyamide materials. In this way, our multi-scale simulation is shown to be useful in biological as well as other chemical systems.

Until March 2025, we will use Fugaku or other supercomputers to investigate structure-dynamics-function relationships of biomolecules or others in complex chemical and biological environments.

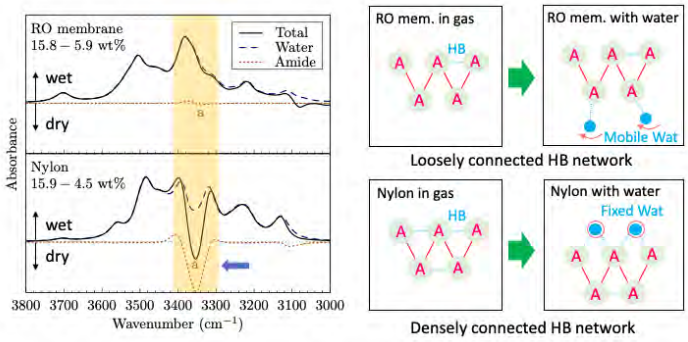

Fig. 1. Infrared (IR) difference spectrum of ar-PA and nylon 6 (left).
Schematic drawings of water diffusion and amide-water interactions (right).

(3) Members

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(4) Representative research achievements

1. “Scaling molecular dynamics beyond 100,000 processor cores for large-scale biophysical simulations”, J. Jung, W. Nishima, M. Daniels, G. Bascom, C. Kobayashi, A. Adedoyin, M. Wall, A. Lappala, D. Phillips, W. Fischer, C.-S. Tung, T. Schlick, Y. Sugita, K. Y. Sanbonmatsu, *J. Comput. Chem.* 40 (2019) 1919-1930.
2. “De Novo Prediction of Binders and Nonbinders for T4 Lysozyme by gREST Simulations”, Ai Niitsu, Suyong Re, Hiraku Oshima, Motoshi Kamiya, Yuji Sugita, *J. Chem. Inf. Model*. 59 (2019) 3879-3888.
3. “Implicit Micelle Model for Membrane Proteins Using Superellipsoid Approximation”, Takaharu Mori and Yuji Sugita, *J. Chem. Theory Comput.* 16 (2020) 711-724.
4. “Role of the N-Terminal Transmembrane Helix Contacts in the Activation of FGFR3”, Daisuke Matsuoka, Motoshi Kamiya, Takeshi Sato, Yuji Sugita, *J. Comp. Chem.* 41 (2020) 561-572.
5. “Amide A band is a fingerprint for water dynamics in reverse osmosis polyamide membranes”, Donatas Surblys, Taro Yamada, Bo Thomsen, Tomonori Kawakami, Isamu Shigemoto, Jun Okabe, Takefumi Ogawa, Masahiro Kimura, Yuji Sugita, Kiyoshi Yagi, *J. Membrane. Sci.* 596 (2020) 117705.

Supplementary

Group Photo

Laboratory Homepage

https://www.riken.jp/en/research/labs/chief/theor_mol_sci/index.html

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