【Grant-in-Aid for Scientific Research (S)】

Broad Section G

Title of Project： Multi-scale molecular dynamics simulation on biomolecular dynamics in crowded cellular environments

SUGITA, Yuji
(RIKEN, Cluster for Pioneering Research, Chief Scientist)

Research Project Number：19H05645　Researcher Number：80311190
Keyword：Multi-scale simulation, crowded cellular environment, liquid-liquid phase separation, protein conformational flexibility, enzyme reaction

【Purpose and Background of the Research】

Proteins or other biomacromolecules are crowded at high concentration in a living cell. Recently, the role of non-specific molecular interaction in the environments is found to be essential for various cellular functions.

In this research, we study both specific and non-specific molecular interactions and biomolecular dynamics in crowded cellular environments. For this purpose, we develop multi-scale molecular dynamics simulation methods combining coarse-grained models, atomistic models, and hybrid quantum mechanics/molecular mechanics (QM/MM) models. Simulations using different molecular models are connected by informatics approach.

【Research Methods】

The multi-scale simulation methods are developed and implemented into GENESIS molecular dynamics software. This software has been developed in RIKEN for large-scale atomistic simulations on K computer or post-K (Fugaku) computer.

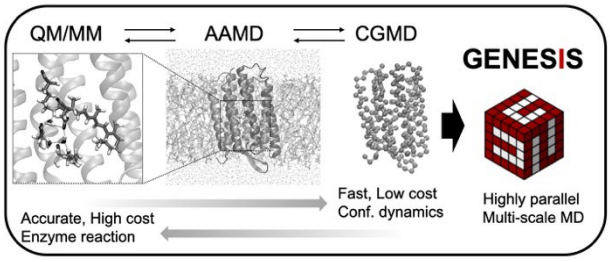

Figure 1　Multi-scale simulation method

In this research, we mainly develop coarse-grained simulations as well as QM/MM calculations. We also develop new methods to connect simulations with different molecular models by using informatics approaches, such as machine learning or Bayesian theory.

The developed methods are applied to two biological phenomena. One is liquid-liquid phase separation caused by proteins in signal transduction pathways. We examine the role of protein conformational flexibility and stability on the formation of liquid-liquid phase separation by performing multi-scale molecular dynamics simulations, solution NMR, and in-cell NMR spectroscopy. Simulation results are, thus, examined experimentally for improving the reliability of computational models and methods.

Second one is the role of cellular environments in enzymatic reactions. Enzymes can catalyze chemical reactions in a living cell. Before conducting the enzyme catalysis, substrate binding is required for enzyme, which can be affected by the surrounding environments. We study the substrate channeling in tryptophan synthase by computer simulations, such as atomistic molecular dynamics and hybrid QM/MM simulations. The simulation results are compared to the existing experimental results.

【Expected Research Achievements and Scientific Significance】

We can develop unique and useful multi-scale simulation modules in GENESIS. Since GENESIS is freeware under GPLv2 license, the developed methodologies will be released in future version of GENESIS. The multi-scale simulation will be available on Fugaku computer as well as PC-clusters with/without GPUs.

To understand molecular function in crowded cellular environments, substrate binding, protein-protein or protein-substrate interaction, and enzyme catalysis are the essential components. In this research, we will study molecular mechanisms underlying these essential functions and propose new insights as well as research strategies combining simulations with experiments.

【Publications Relevant to the Project】

・Yu, I. et al., Biomolecular interactions modulate macromolecular structure and dynamics in atomistic model of a bacterial cytoplasm. *eLife* **5**, e19274 (2016).
・Sakakibara, D. et al., Protein structure determination in living cells by in-cell NMR spectroscopy. *Nature* **458**, 102-105 (2009).

【Term of Project】

FY2019-2023

【Budget Allocation】

152,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www2.riken.jp/TMS2012/tms/ja/index.html
sugita@riken.jp