Usage Report for Fiscal Year 2024

Project Title:

Development of multi-scale simulation methods for large biomolecular systems

Name:
○Cheng Tan (1), Yangyang Zhang (1), Diego Ugarte La Torre (1), Jaewoon Jung (1,2), and Chigusa Kobayashi (1)

Laboratory at RIKEN:
(1) RIKEN Center for Computational Science, Computational Biophysics Research Team
(2) RIKEN Cluster for Pioneering Research, Theoretical Molecular Science Laboratory

1. Background and purpose of the project, relationship of the project with other projects

Molecular dynamics (MD) simulations are essential for investigating biological processes by leveraging computational models and algorithms. In our current project (RB230018), we have advanced MD methodologies within the GENESIS software, enabling the modeling of large-scale biomolecular systems (Figure 1). Our work includes integrating multi-scale models and optimizing GENESIS for high-performance execution across diverse computing platforms.

A key focus of our research is biomolecular phase separation, a fundamental mechanism regulating molecular compartmentalization in cells. We aim to develop and apply multi-scale computational models to simulate liquid-liquid phase separation (LLPS) and to gain deeper insights into the physicochemical principles governing phase-separated condensates and their biological functions.

Additionally, we investigate lipid systems to explore their role in biological processes and simulate different cellular environments. Improving lipid models enhances our understanding of membrane-associated phase separation, lipid-protein interactions, and how environmental conditions influence biomolecular organization.

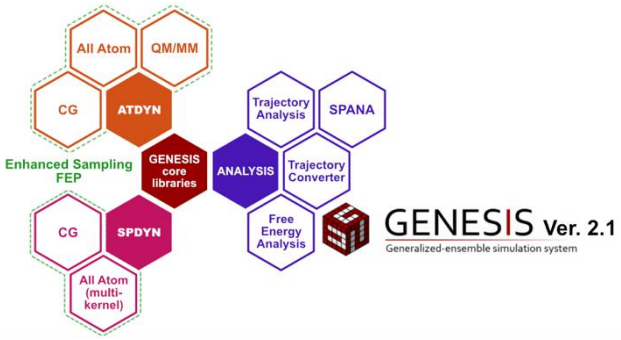

Figure 1. Development of multi-scale simulation and analysis tools in the framework of GENESIS (Jung *et al. JPCB* 2024).

Specifically, we have conducted the following studies:

1) Enhancement of the coarse-grained lipid model, iSoLF, by increasing lipid diversity and incorporating electrostatic interactions (by Ugarte).

2) Development of efficient parallelization for coarse-grained MD simulations (by Jung).

3) Implementation of a coarse-grained method to model domain motions of multi-domain/multi-chain proteins (by Kobayashi).

4) Application of explicit solvent coarse-grained MD simulations to study salt effects on TDP-43 condensation (by Zhang).

5) Application of multiscale MD simulations to investigate the regulation of TDP-43 condensation

by Hero11 (by Tan).

2. System Usage and Computational Methods

1) iSoLF Lipid Model: We expanded lipid diversity in GENESIS and incorporated electrostatic interactions. Molecular dynamics simulations at different scales were performed to evaluate the quality of the force field parameters.

2) Parallelization of Coarse-Grained MD Simulations: A new parallelization scheme was developed for multi-scale biological simulations using coarse-grained models with implicit solvents. The system is partitioned into domains of varying volumes to minimize load imbalance, and this scheme has been implemented in the new GENESIS MD engine, CGDYN, enabling large-scale biomolecular simulations (Figure 2).

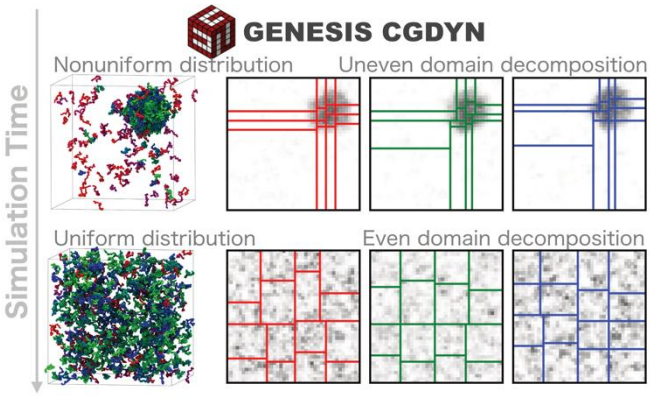

Figure 2. GENESIS CGDYN: large-scale CG simulations with dynamic load balancing (Jung *et al. Nat Commun* 2024).

3) Modeling Domain Motion in Multi-Domain Proteins: To represent domain motions, we used central points for domains, hinges between them, and rotational points. The method extends Henderson's approach (Nat. Str. Mol. Biol. 2020, Science 2021) by optimizing rotational points using MD trajectories. The approach was applied to three multi-domain proteins, effectively capturing their domain motions.

4) Salt Effects on TDP-43 Condensates: Using the Martini 3 coarse-grained model in GROMACS, we studied salt effects on TDP-43 condensates. By calibrating protein-water van der Waals interactions at 0.15 M NaCl to match dense-phase protein density from all-atom simulations, we achieved realistic protein-water distributions. Simulations across different salt concentrations revealed key dependencies of condensate behavior on salt levels.

5) Regulation of TDP-43 Condensation by Hero11: Using GENESIS SPDYN, we conducted all-atom simulations on TDP-43 and Hero11. Simulations covered single-chain systems, dimers, and large condensates, providing insights into the regulatory effects of Hero11 on TDP-43 condensation.

3. Result

The enhanced iSoLF model exhibited improved phase-separation in multi-component bilayers and shorter equilibration times compared to all-atom counterparts.

The coarse-grained domain motion model effectively captured large-scale structural changes in multi-domain proteins using a reduced representation, improving computational efficiency while preserving accuracy.

The Martini 3-based study of salt effects on protein condensates demonstrated key phase behaviors across a range of NaCl concentrations. However, deviations in ion distributions and unexpected behavior at near-zero salt levels indicate areas for further refinement of explicit solvent CG models.

Simulations of TDP-43 condensation regulation by Hero11 revealed electrostatic interactions influencing condensate density and ion distribution, providing mechanistic insights into biomolecular

phase separation.

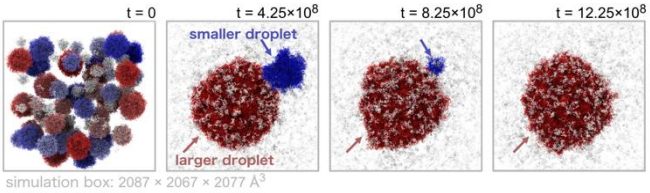

Figure 3. Residue-level description of droplet fusion dynamics using CGDYN (Jung *et al. Nat Commun* 2024).

Using CGDYN, we successfully simulated multi-droplet systems and observed Ostwald ripening at residue-level resolution, marking a significant advancement in large-scale condensate modeling (Figure 3).

4. Conclusion

Our work in the Hokusai project has led to significant advancements in multi-scale MD simulations within GENESIS, including:

1) Extension and validation of the iSoLF coarse-grained lipid model.

2) Development of an efficient parallelization scheme in CGDYN, improving computational scalability for large-scale MD simulations.

3) A novel approach for modeling domain motion in multi-domain proteins, capturing key structural dynamics with reduced representations.

4) Refinement of the Martini 3 coarse-grained model to study salt effects on protein condensates, highlighting key phase behaviors while identifying limitations for further improvement.

5) CG and all-atom simulations of biomolecular condensates, uncovering regulatory mechanisms of highly charged proteins in LLPS.

5. Schedule and prospect for the future

Moving forward, we aim to refine our multi-scale implementation for improved computational efficiency. Additionally, we will expand our all-atom and coarse-grained simulation framework to study a broader range of multi-domain proteins and their interactions with lipid membranes. These advancements will enable a more comprehensive evaluation of biomolecular phase separation mechanisms and their biological implications.

6. If no job was executed, specify the reason.

Usage Report for Fiscal Year 2024

Fiscal Year 2024 List of Publications Resulting from the Use of the supercomputer

[Paper accepted by a journal]

- Jaewoon Jung, Kiyoshi Yagi, Cheng Tan, Hiraku Oshima, Takaharu Mori, Isseki Yu, Yasuhiro Matsunaga, Chigusa Kobayashi, Shingo Ito, Diego Ugarte La Torre, Yuji Sugita, "GENESIS 2.1: High-Performance Molecular Dynamics Software for Enhanced Sampling and Free-Energy Calculations for Atomistic, Coarse-Grained, and Quantum Mechanics/Molecular Mechanics Models." The Journal of Physical Chemistry B 128, 25 (2024): 6028-6048.

- Jaewoon Jung, Cheng Tan, and Yuji Sugita. "GENESIS CGDYN: large-scale coarse-grained MD simulation with dynamic load balancing for heterogeneous biomolecular systems." Nature Communications 15, 3370 (2024).

[Oral presentation]

- Cheng Tan, "Large-scale Molecular Dynamics Simulations of Multicomponent Biomolecular Condensation Reveals a Regulatory Mechanism by Highly Charged Proteins." The 38th Molecular Simulation Symposium, Himeji, Japan. Wed, Dec 4, 2024

[Poster presentation]

- Cheng Tan, "Regulating Biomolecular Condensation: Insights from Multi-Scale Simulations of Hero11 and TDP43 Interactions." ACS Fall 2024, Denver, USA. Tue, Aug 20, 2024

- Chegn Tan, "Highly Charged Proteins and Their Repulsive Interactions in Regulation of Biomolecular Condensation." IUPAB 2024, Kyoto, Japan. Tue, Jun 25, 2024

- Cheng Tan, "Multiscale Molecular Dynamics Simulations Reveal the Regulatory Functions of Highly Charged Proteins in Biomolecular Condensation." The 24th Annual Meeting of the Protein Science Society of Japan, Sapporo, Japan. Thr, Jun 13, 2024

[Others (Book, Press release, etc.)]

- "細胞内生命現象を計算機で観察 －粗視化分子動力学プログラム GENESIS CGDYN の開発－"

https://www.riken.jp/press/2024/20240510_3/index.html