All-atom and coarse-grained molecular simulations of a bacterial cytoplasm

Laboratory for Biomolecular Function Simulation,
RIKEN QBiC

Tadashi Ando

RIKEN Symposium “ペタスケールシステムHOKUSAI GreatWaveとアプリケーションの研究開発への針路”
@ Wako
June 19, 2015
Molecular Dynamics (MD)

A typical example of all-atom MD simulation

A protein + solvent molecules

Numerically solve the Newton’s equations of motion for the atoms

\[ f = m \frac{d^2r}{dt^2} \]

Analyze MD results
Empirical potential function for MD

\[ V_{\text{total}} = \sum_{\text{bonds}} K_b(r - r_0)^2 + \sum_{\text{angles}} K_{\theta}(\theta - \theta_0)^2 + \sum_{\text{dihedrals}} K_\phi[1 + \cos(n\phi - \gamma)] \]

\[ + \sum_{\text{van der Waals \atop i, j pairs}} \left( \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} \right) + \sum_{\text{electrostatic \atop i, j pairs}} \frac{q_i q_j}{\varepsilon r_{ij}} \]
MD has played an important role for understanding dynamics of biomolecules at atomic detail.

Ron O. Dror et al. J Gen Physiol 2010;135:555-562
Ideal and real conditions in physics and biology

**Condition**

**Ideal**
- Isolated or diluted
- No intermolecular interactions
- homogeneous

**Real**
- Denser
- Intermolecular interactions
- inhomogeneous

**Physics**

- Ex.) Ideal gas equation
  \[
  \frac{PV}{n} = PV_m = RT
  \]

- Ex.) van der Waals equation
  \[
  P = \frac{RT}{V_m - b} - \frac{a}{V_m^2}
  \]

**Biology**

- In test tubes
- MD under ideal conditions

- In living cells

We need MD simulations under real conditions!

Let’s look at an inside of cell in next slide!
Inside of cell is crowded

The cellular interior is crowded, where 20-40% in volume fraction are occupied by macromolecules. This means that the environment of cells is far different from the conditions found in most of biochemical experiments and conventional MD simulations.

We need to examine how the cellular crowding alters the thermodynamics and kinetics of biological processes, which is a necessary step towards understanding living systems.
Simulation model: Cytoplasm of *Mycoplasma genitalium*

Number of genes is ~500.

# of atoms: 11,737,298
# of macromolecules: 216 (43 types)
# of metabolites: 4,212 (89 types)
Conc.: 298 mg/ml
Vol. fraction: 0.287

Figures were created by Dr. Yu
The necessity of a new MD simulator

New algorithms and parallelization of MD have increased accessible simulation time and size. But, we still need further speed-up in MD!

Our team has developed a molecular dynamics and modeling software “GENESIS” for large-scale biomolecular systems (Jung et al, WIREs Comput Mol Sci 2015. doi: 10.1002/wcms.1220).

- Highly parallelized and very fast, running on “K(京)” and “HOKUSAI”.
- We are implementing many functions into GENESIS (multiple time stepping, meta-dynamics, reaction-path sampling, coarse-grained model, Brownian dynamics, etc).
- We are tuning the program for HOKUSAI (FX100).
- We are also developing a GPU version, which would be much faster than CPU version.
- It’s FREE!
- Supporting in Japanese is also OK! (日本語でも対応いたします!)
- Register @ http://www.riken.jp/TMS2012/cbp/en/research/software/genesis/index.html
GENESIS is highly parallelized

**SPDYN** is the name of GENESIS module, which is highly parallelized based on a spatial decomposition scheme.

NAMD and CHARMM are names of existing MD software packages.
Timing test using the 12 M-atom system

HOKUSAI GW-MPC is 1.3 times faster than K

- FUJITSU FX100
- 1,080 nodes
- 32 cores/node
- Total 34,560 cores
Large reduction of macromolecular diffusivities in cells

$D$: observed diffusion coefficient.

$D_0$: diffusion coefficient in the infinite dilution.

All-atom MD in the modeled bacterial cytoplasm gives diffusion coefficients of macromolecules consistent with experiments.
What are mechanisms responsible for the large reduction of macromolecular diffusivity observed in living cells and in MD?
Coarse-graining (CG) idea is useful for understanding physical principles.

All-atom simulation system

CG simulation system

Number of atoms: ~12 M

Number of particles: ~2,000
Each macromolecule is represented by an equivalent sphere Stokes radius without any attractive interaction.
Simulating CG molecules: Brownian Dynamics (BD)

Simulating Brownian particles in a fluid without explicitly considering solvent molecules.
The power of BD is the ability to include hydrodynamic interactions (HI)

BD w/o HI
\[ \Delta r = \frac{D_0}{k_B T} f \Delta t + \sqrt{2D_0 \Delta t} \mathbf{z} \]

BD w/ HI
\[ \Delta \mathbf{r} = \left( \nabla \cdot \mathbf{D} \right) \Delta t + \frac{\mathbf{D}}{k_B T} f \Delta t + \mathbf{X}(\Delta t), \]
\[ \mathbf{X}(\Delta t) = \sqrt{2\Delta t \mathbf{B}} \mathbf{z}, \quad \text{and} \quad \mathbf{B} \mathbf{B}^T = \mathbf{D} \]

\[ \begin{align*}
\Delta r & \text{: particle displacement} \\
\Delta t & \text{: time step} \\
f & \text{: force} \\
D_0 & = k_B T/(6\pi \eta a): \text{diffusion coefficient of particle with radius } a \text{ at infinite dilution with water viscosity } \eta \\
\mathbf{z} & \text{: Gaussian random number} \\
\end{align*} \]

Comparing BD simulations w/ and w/o HI can elucidate effects of HI on macromolecular dynamics.
What are hydrodynamic interactions (HI)?

Each particle’s force changes the solvent flow, and this in turn affects forces on other particles through the frictional forces affecting them.

*Hydrodynamics are what make a fluid a fluid!*
Simulations were performed on RICC
BD with HI gives diffusion coefficients close to experiments

Large reduction in diffusivity of macromolecules in living cells can be explained by excluded volume effects and HI.
BD w/ HI, MD, and experiments give consistent values of diffusion coefficients.

Results of BD with HI, MD, and experiments are qualitatively consistent. → all-atom MD reasonably well reproduces the excluded volume effects and HI even at the high macromolecular density, which is a good news for further analysis of MD result.
Conclusions and outlook

• We performed the all-atom MD simulation of the interior of *M. genitalium* to investigate macromolecular dynamics in living cells.

• HOKUSAI GW-MPC has a great capacity to simulate a very large system. Our benchmark test of GENESIS MD software using the cytoplasmic model shows that MD performance on HOKUSAI GW-MPC is 1.2 times better than K.

• Diffusion coefficients of some of macromolecules in intracellular space evaluated by all-atom MD, CG-BD, and experiments were consistent each other.

• We are now analyzing other quantities from all-atom MD simulation, such as diffusions of water, metabolites, ions, and conformational dynamics of macromolecules, which cannot be obtained from CG-BD.
Members and collaborators

• Yuji Sugita (Team leader)
• Jung Jaewoon (AICS, Kobe)
• Chigusa Kobayashi (AICS, Kobe)
• Yasuhiro Matsunaga (AICS, Kobe)
• Takaharu Mori (TMS, Wako)
• Isseki Yu (TMS, Wako)
• Michael Feig (MSU, USA)
Acknowledgements

• Hiroo Kenzaki (ACCC)
• Gen Masumoto (ACCC)
• Motoyoshi Kurokawa (ACCC)