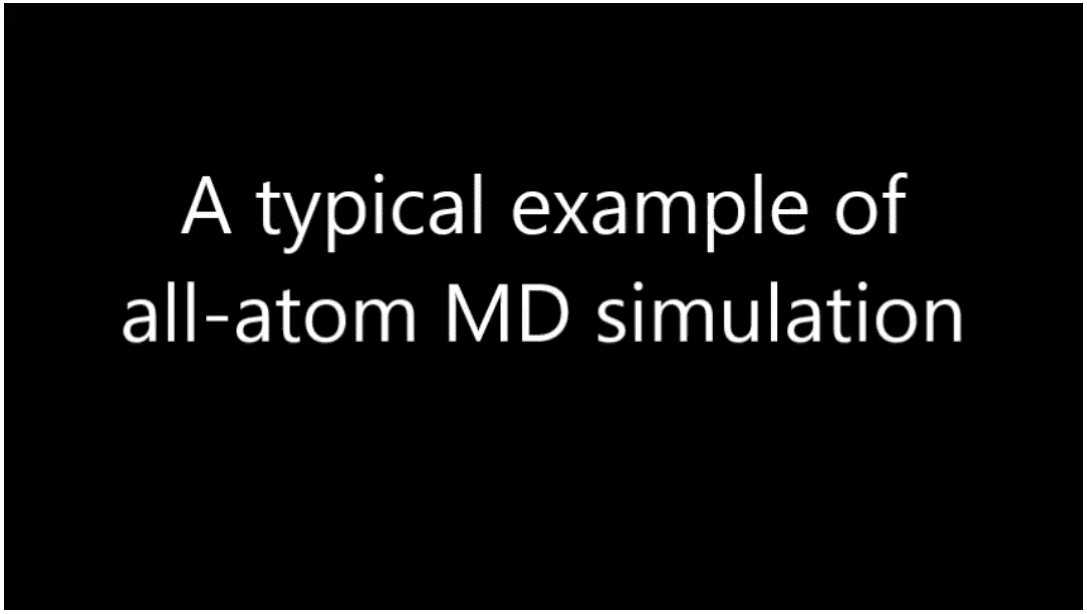
All-atom and coarse-grained molecular simulations of a bacterial cytoplasm

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 protein + solvent molecules

↓

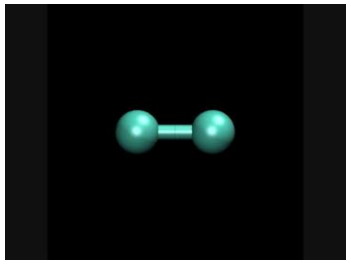
Numerically solve the Newton's equations of motion for the atoms

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

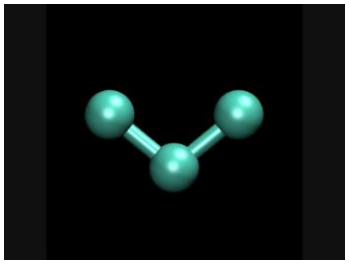
↓

Analyze MD results

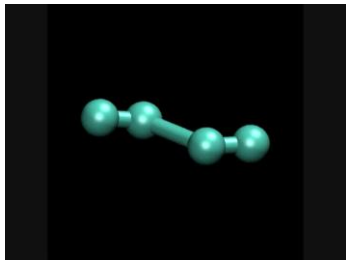
Empirical potential function for MD



Bond stretching term



Angle bending term

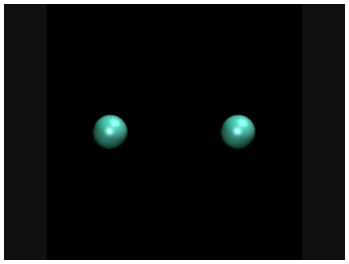


Dihedral term

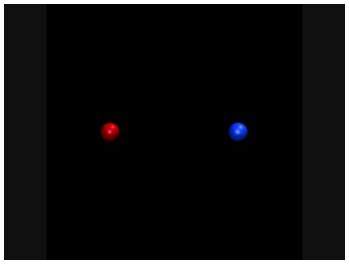
$$V_{\text{total}} = \sum_{\text{bonds}} K_b\left(r - r_0\right)^2 + \sum_{\text{angles}} K_\theta\left(\theta - \theta_0\right)^2 + \sum_{\text{dihedrals}} K_\phi\left[1 + \cos\left(n\phi - \gamma\right)\right]$$

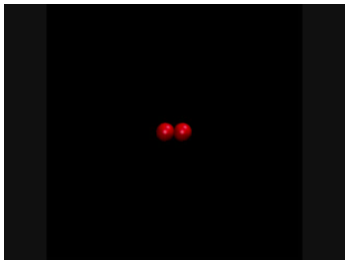
$$+ \sum_{\substack{\text{van der Waals} \\ i,\ j \text{ pairs}}} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) + \sum_{\substack{\text{electrostatic} \\ i,\ j \text{ pairs}}} \frac{q_i q_j}{\varepsilon r_{ij}}$$

van der Waals term

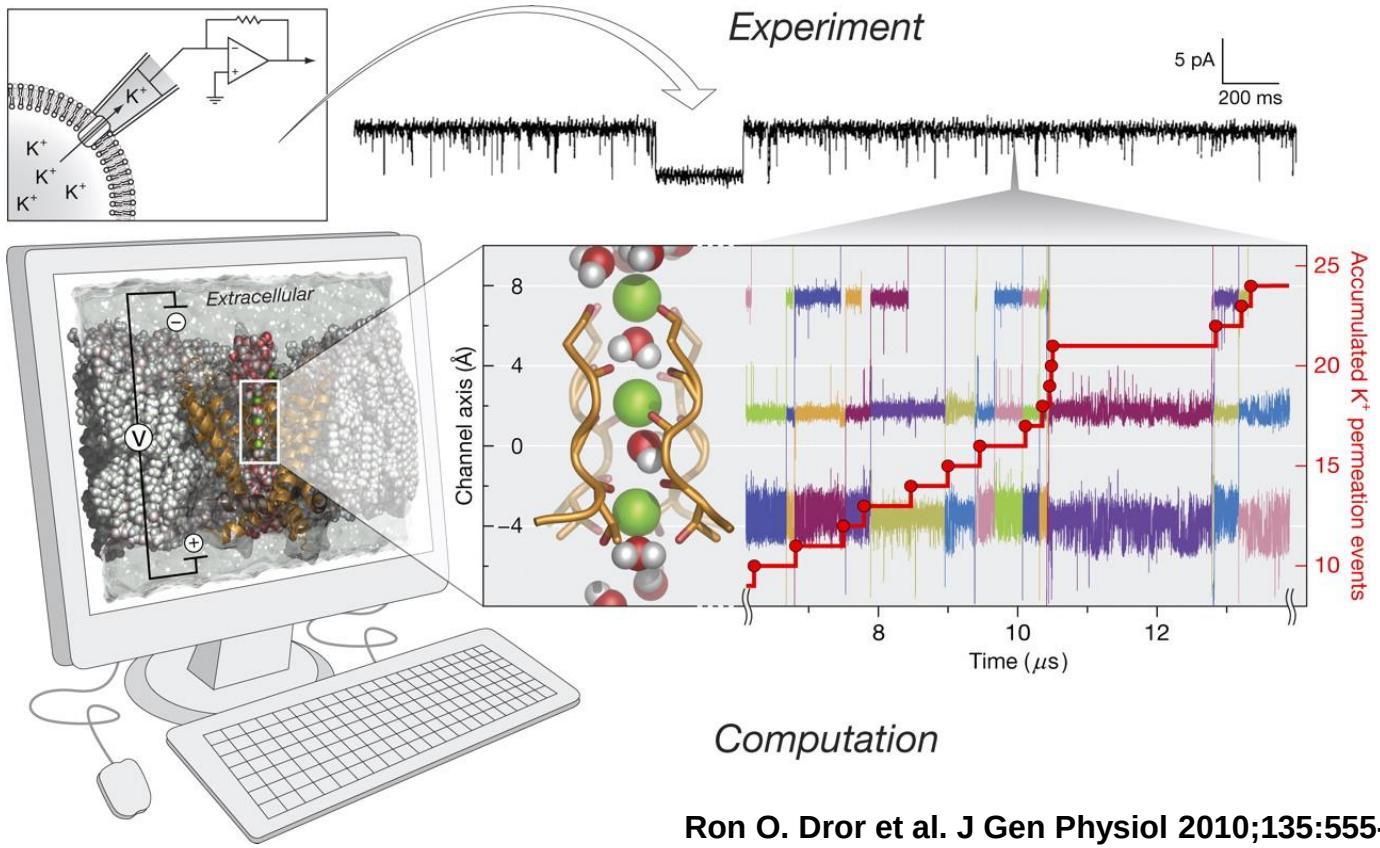


Electrostatic term





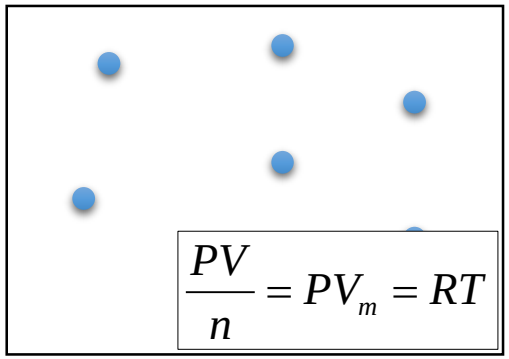
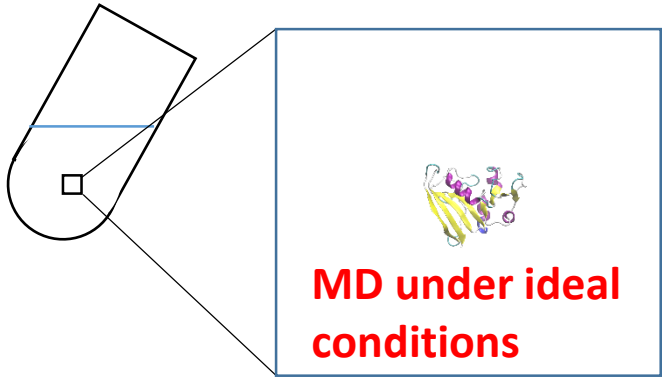
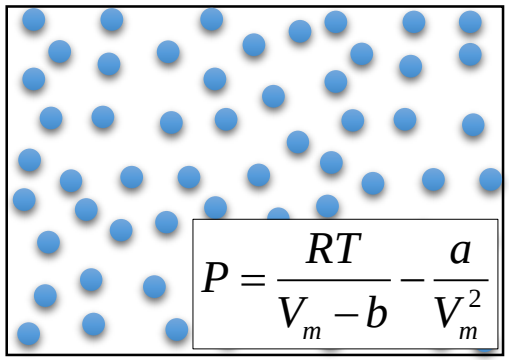
MD in biology



Ron O. Dror et al. J Gen Physiol 2010;135:555-562

MD has played an important role for understanding dynamics of biomolecules at atomic detail.

Ideal and real conditions in physics and biology

Condition	Physics	Biology
Ideal • Isolated or diluted • No intermolecular interactions • homogeneous	Ex.) Ideal gas equation  $\frac{PV}{n} = PV_m = RT$	In test tubes  **MD under ideal conditions**
Real • Denser • Intermolecular interactions • inhomogeneous	Ex.) van der Waals equation  $P = \frac{RT}{V_m - b} - \frac{a}{V_m^2}$	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

Image of inside of cell

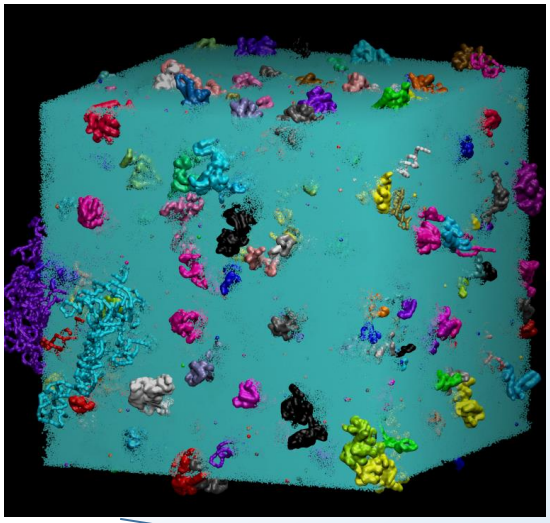
The cellular interior is crowded, where 20-40% in volume fraction are occupied by macromolecules. This means that the environment of cells is far different from the conditions found in most of biochemical experiments and conventional MD simulations.

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**.

Illustration by David S. Goodsell

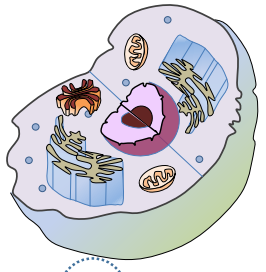
Simulation model: Cytoplasm of *Mycoplasma genitalium*

Model for simulation



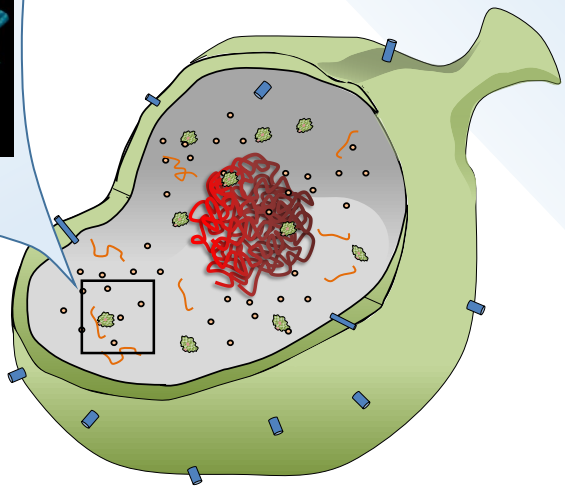
50 nm

Animal cell



10 μm

Mycoplasma genitalium



300 nm

# of atoms: 11,737,298

# of macromolecules: 216 (43 types)

# of metabolites: 4,212 (89 types)

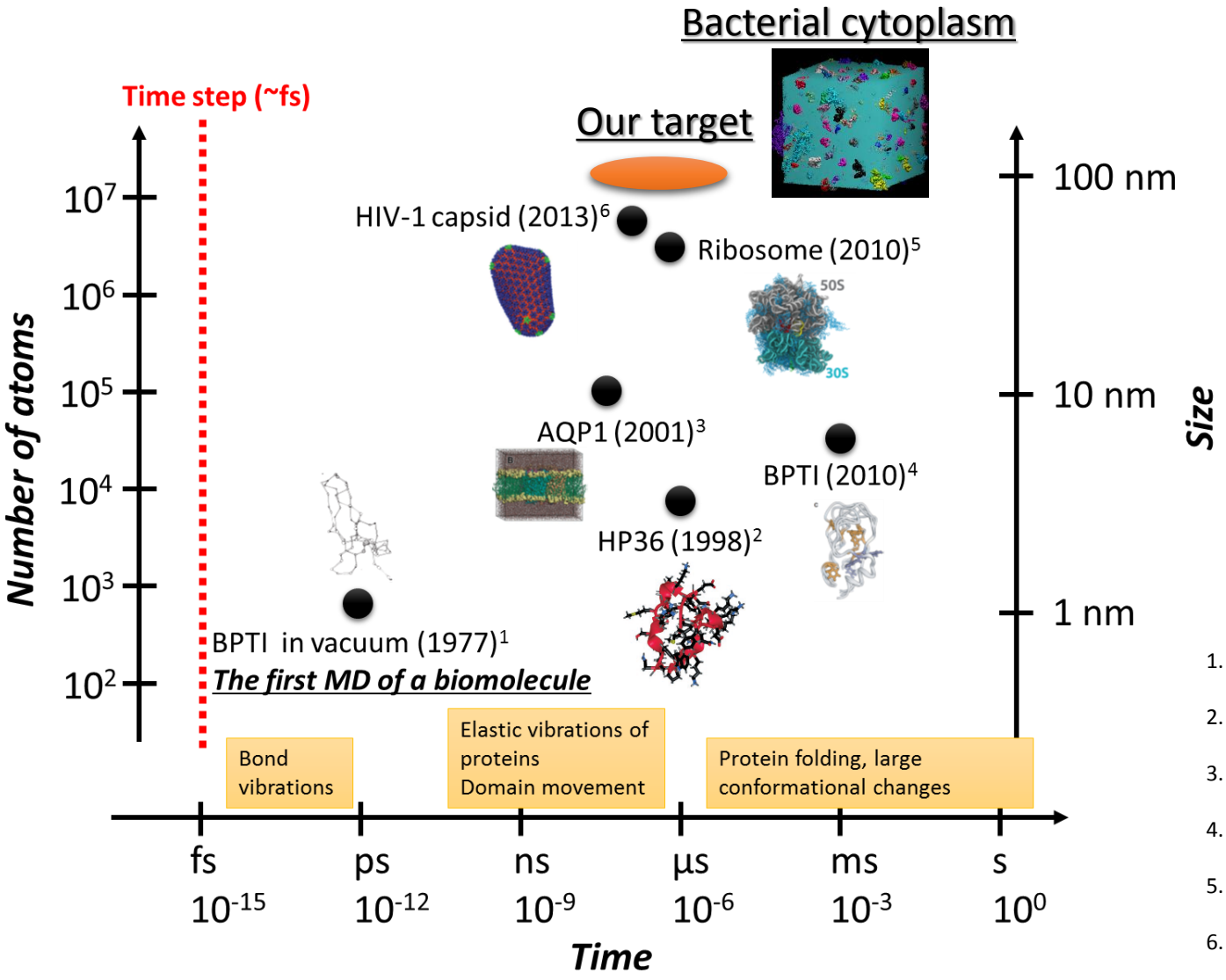
Conc.: 298 mg/ml

Vol. fraction: 0.287

Number of genes is ~ 500.

Figures were created by Dr. Yu

Necessity of a new MD simulator



New algorithms and parallelization of MD have increased accessible simulation time and size.

But, we still need a further speed-up in MD!

1. McCammon *et al.*, *Nature*, 267, pp585-590 (1977)
2. Duan *et al.*, *Science*, 282, pp740-3744 (1998)
3. de Groot *et al.*, *Science*, 294, pp2353-2357 (2001)
4. Shaw *et al.*, *Science*,330, pp341-346 (2010)
5. Whitford *et al.*, *PLOS Comput. Biol.*, 9, e1003003 (2013)
6. Zhao et al., *Nature*, 497, pp643-646 (2013)

GENESIS

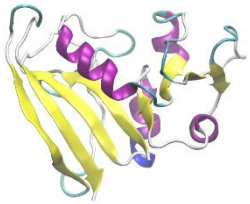
Our team has developed a molecular dynamics and modeling software "GENESIS" for large-scale biomolecular systems (Jung et al, *WIREs Comput Mol Sci* 2015. doi: 10.1002/wcms.1220).

- 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

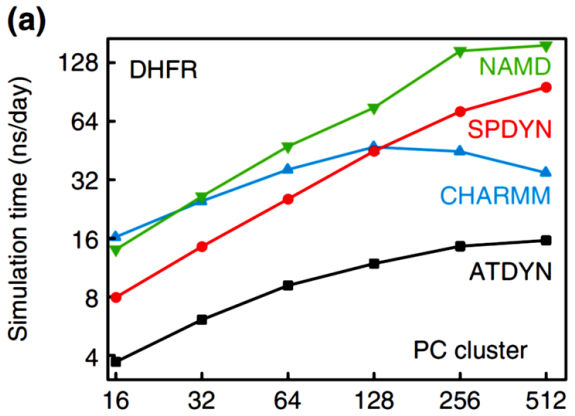
GENESIS is highly parallelized

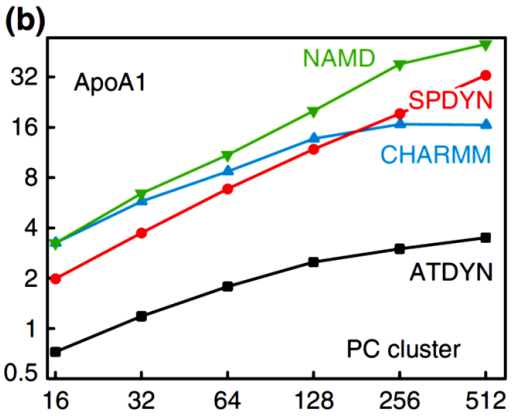
SPDYN is the name of GENESIS module, which is highly parallelized based on a spatial decomposition scheme.

An enzyme

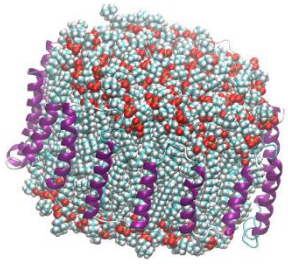


24 K atoms



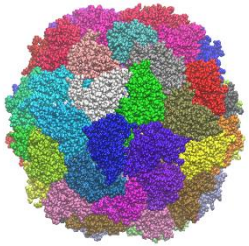


Proteins + lipids

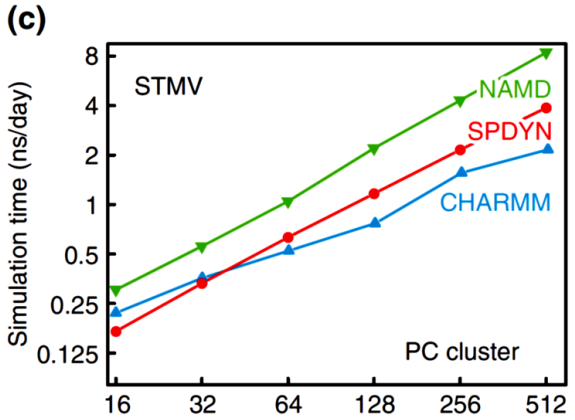


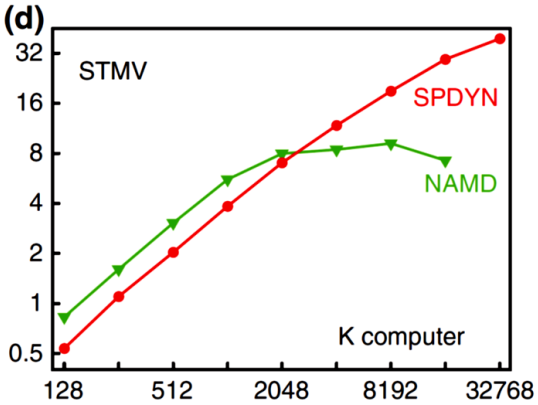
92 K atoms

Virus



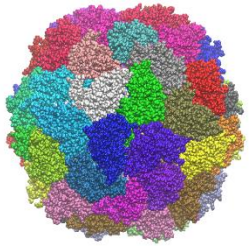
1 M atoms





Number of CPU cores

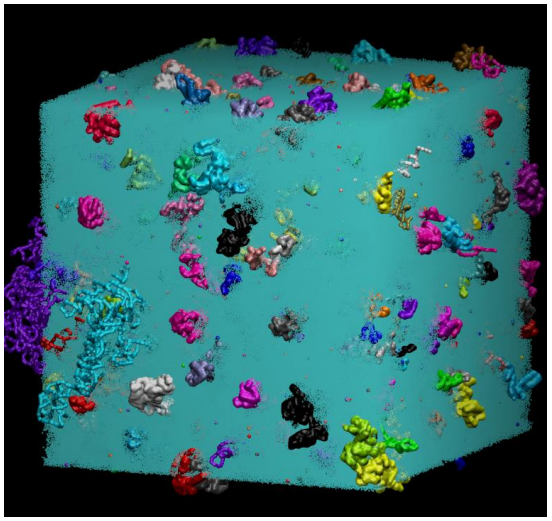
Virus



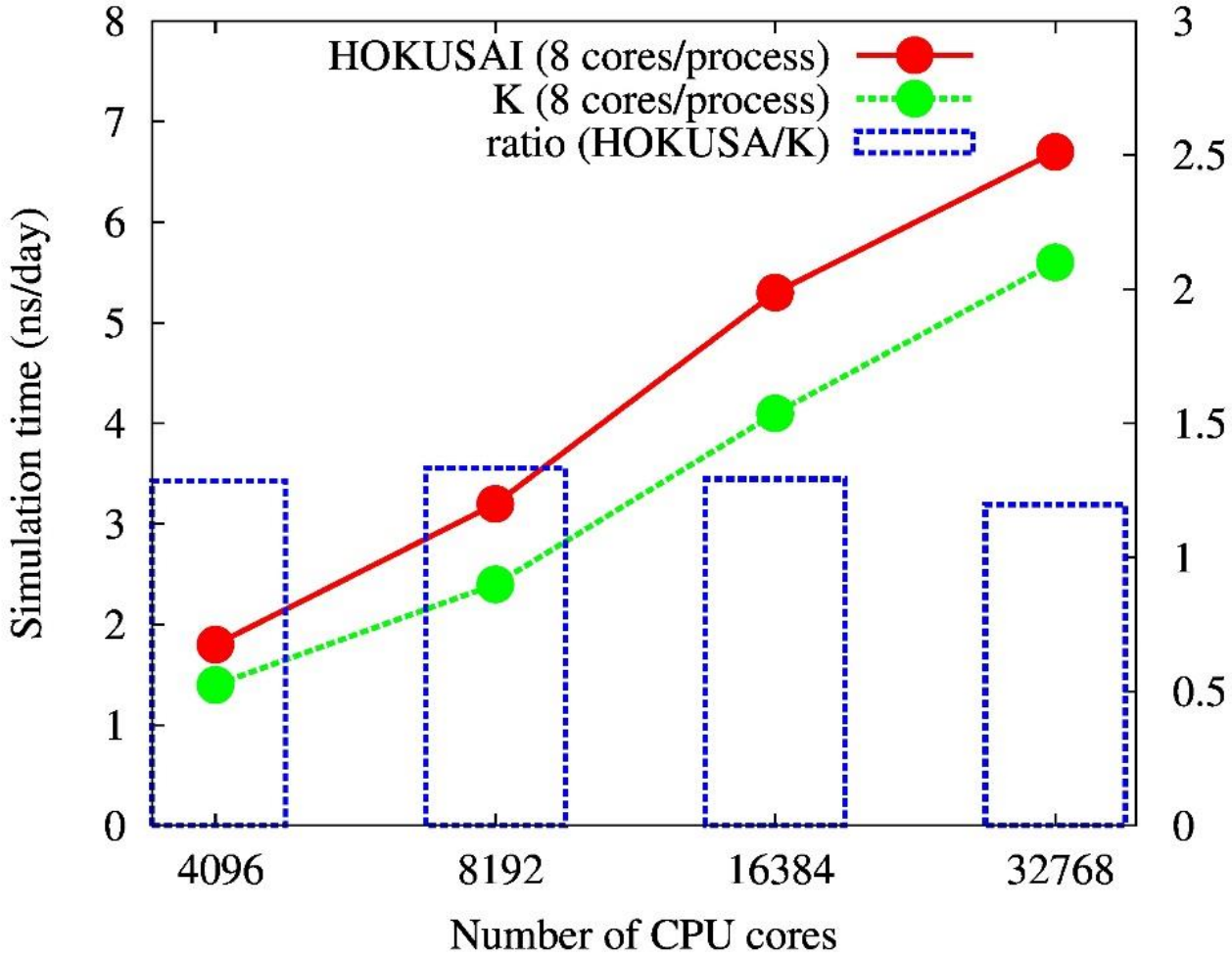
1 M atoms

NAMD and **CHARMM** are names of existing MD software packages.

Timing test using the 12 M-atom system



Bacterial cytoplasm
12 M atoms

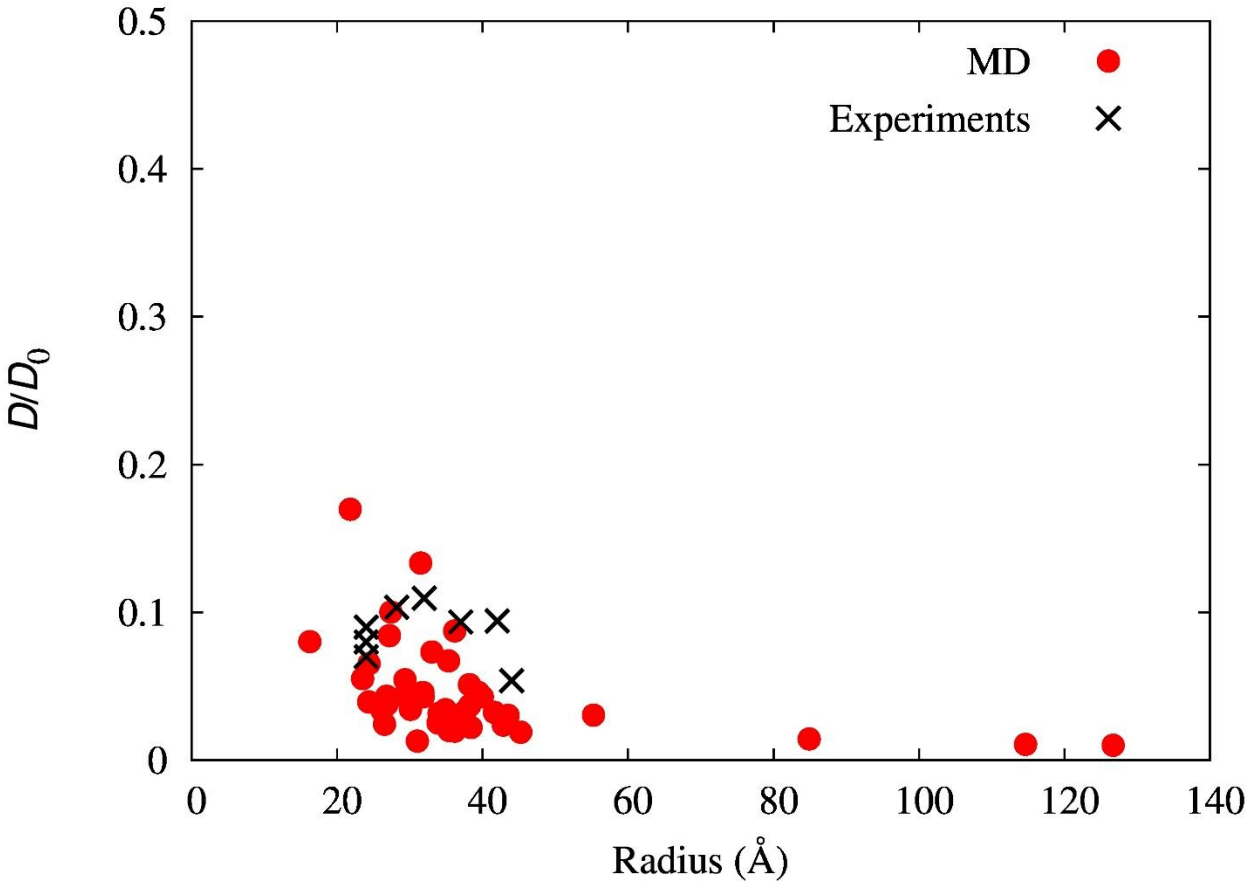


HOKUSAI GW-MPC

- FUJITSU FX100
- 1,080 nodes
- 32 cores/node
- Total 34,560 cores

HOKUSAI GW-MPC is 1.3 times faster than K

Large reduction of macromolecular diffusivities in cells



All-atom MD in the modeled bacterial cytoplasm gives diffusion coefficients of macromolecules consistent with experiments.

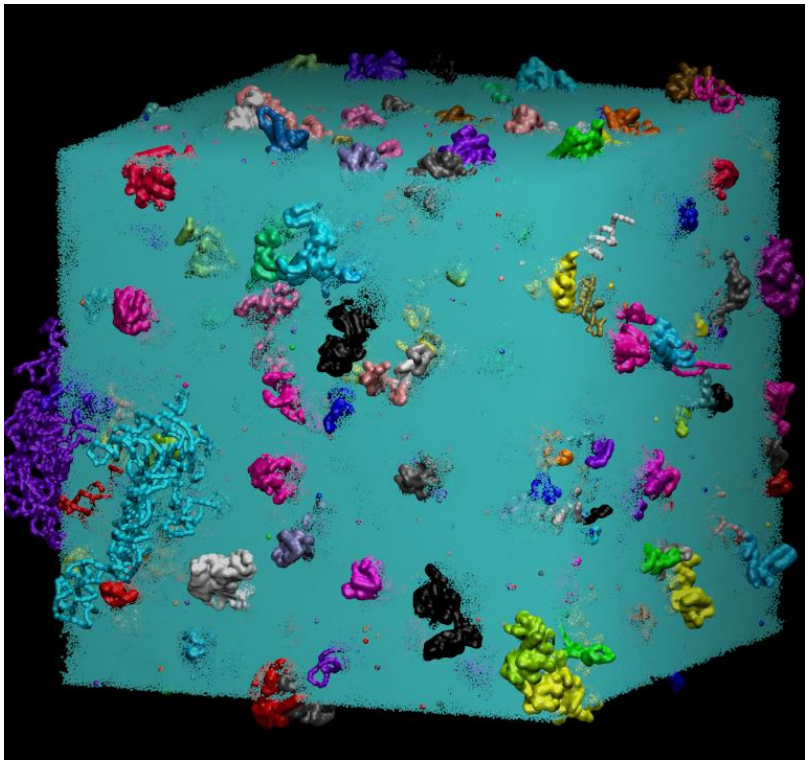
D: observed diffusion coefficient.

D_0: diffusion coefficient in the infinite dilution.

What are mechanisms responsible for the large reduction of macromolecular diffusivity observed in living cells and in MD?

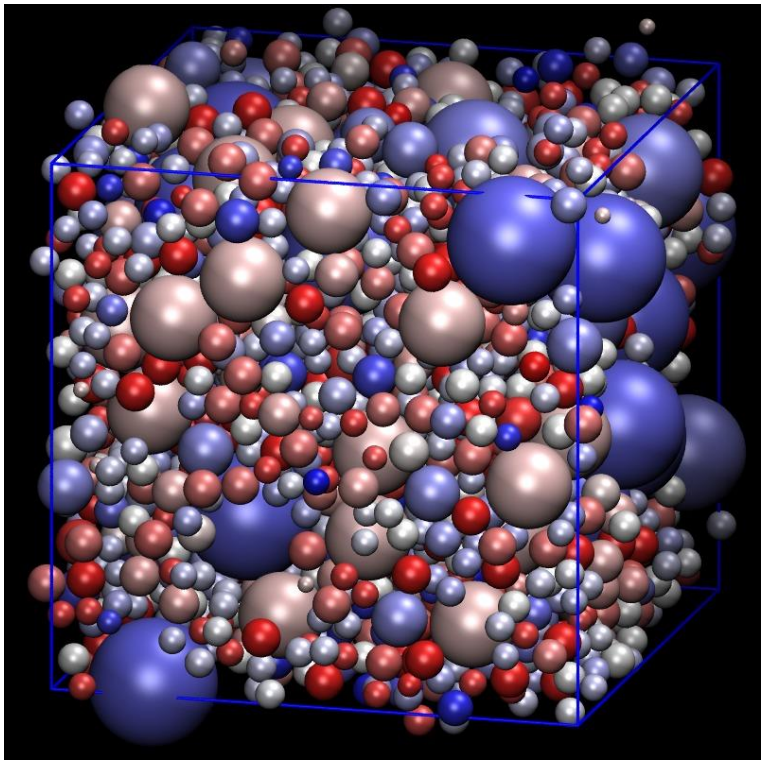
Coarse-graining (CG) idea is useful for understanding physical principles

All-atom simulation system



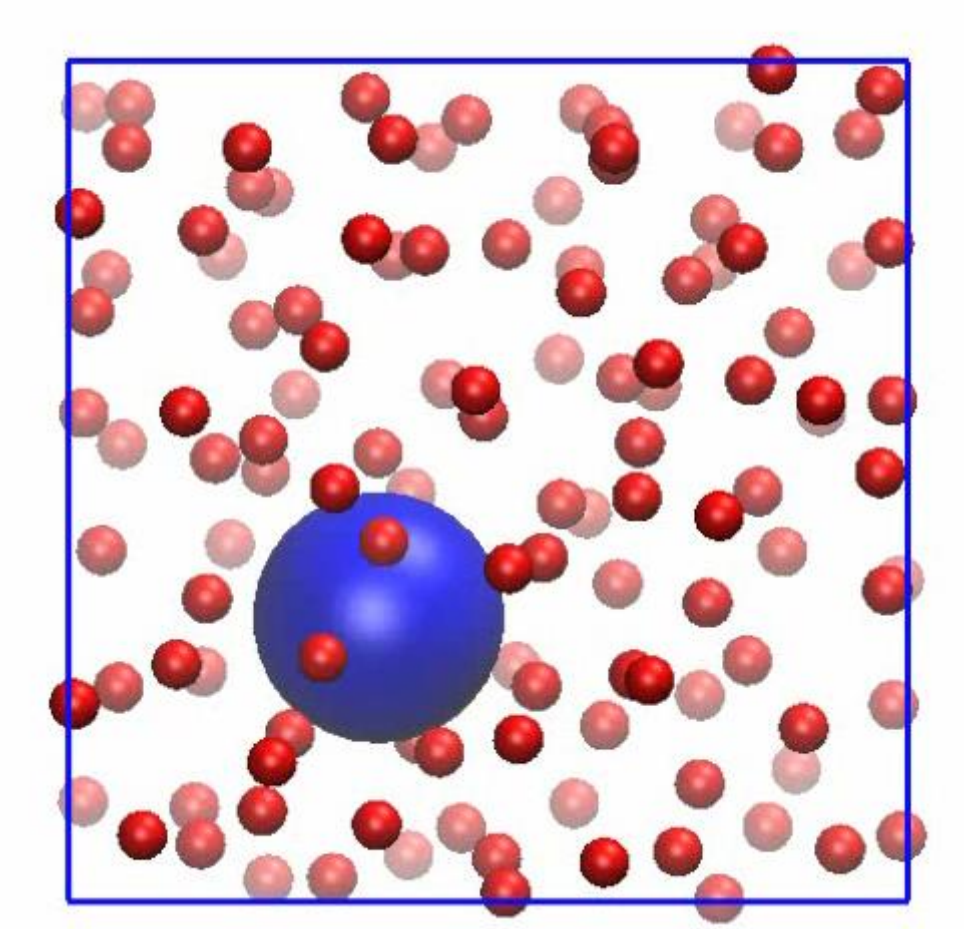
Number of atoms: ~12 M

CG simulation system



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

$$\Delta r = \frac{D_0}{k_B T} f \Delta t + \sqrt{2 D_0 \Delta t}\, z$$

Δr: particle displacement
Δt: time step
f: force
D_0 (= $k_B T/6\pi\eta a$): diffusion coefficient of particle with radius a at infinite dilution with water viscosity η
z: Gaussian random number

Turn HI on! ***Turn HI off!***

BD w/ HI

$$\Delta \mathbf{r} = \left(\nabla \cdot \mathbf{D}\right)\Delta t + \frac{\mathbf{D}}{k_B T}\mathbf{f}\Delta t + \mathbf{X}\left(\Delta t\right),$$

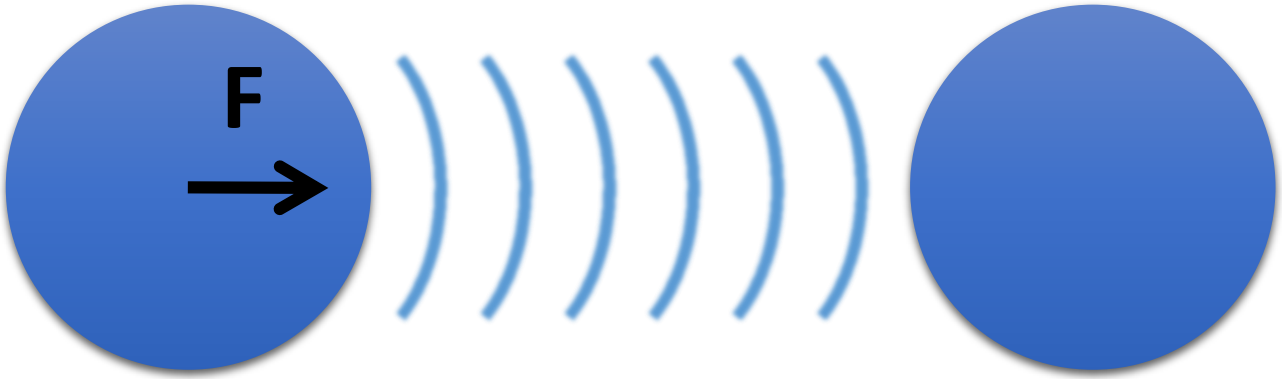
$$\mathbf{X}\left(\Delta t\right) = \sqrt{2\Delta t}\,\mathbf{B}\mathbf{z}, \text{ and } \mathbf{B}\mathbf{B}^T = \mathbf{D}$$

$\Delta \mathbf{r}$: $3N \times 1$ particle displacement vector, where N is the number of particles
$\mathbf{f}$: $3N \times 1$ force vector
$\mathbf{D}$: $3N \times 3N$ position dependent diffusion matrix
$\mathbf{z}$: $3N \times 1$ Gaussian random noise vector

Comparing BD simulations w/ and w/o HI can elucidate effects of HI on macromolecular dynamics.

What are hydrodynamic interactions (HI)?

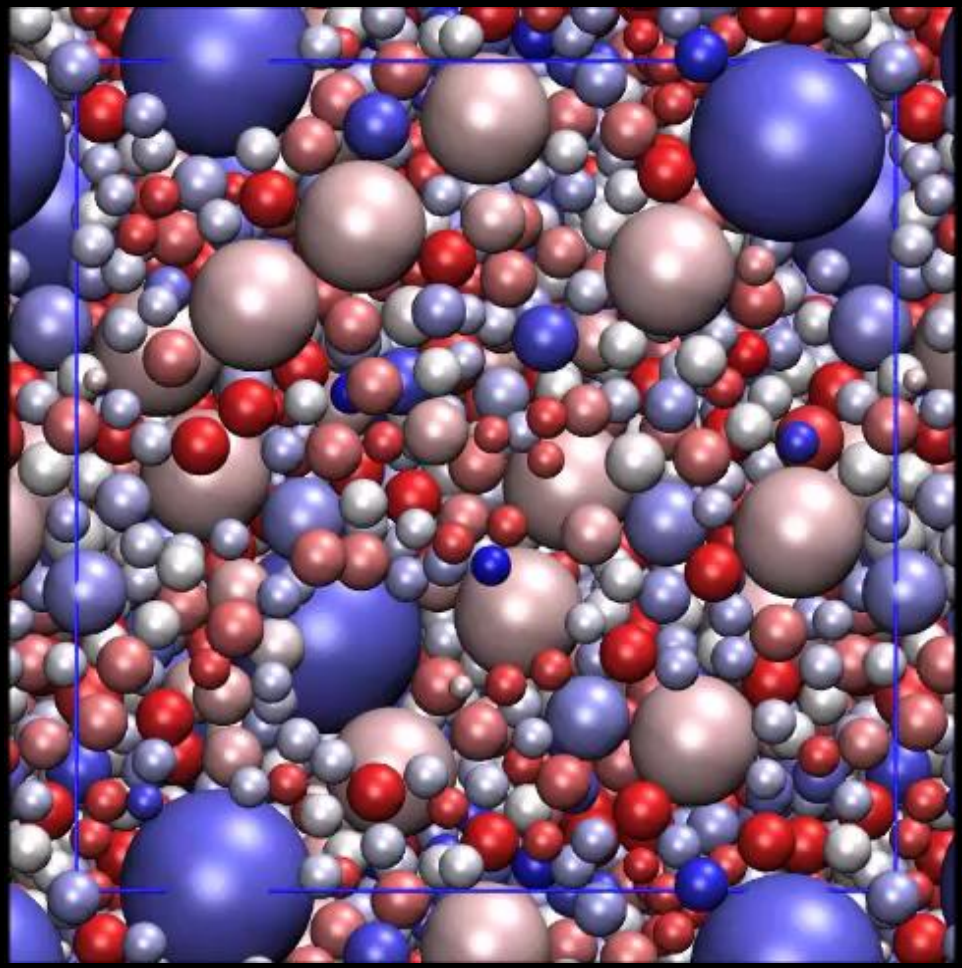
Each particle's force changes the solvent flow, and this in turn affects forces on other particles through the frictional forces affecting them.

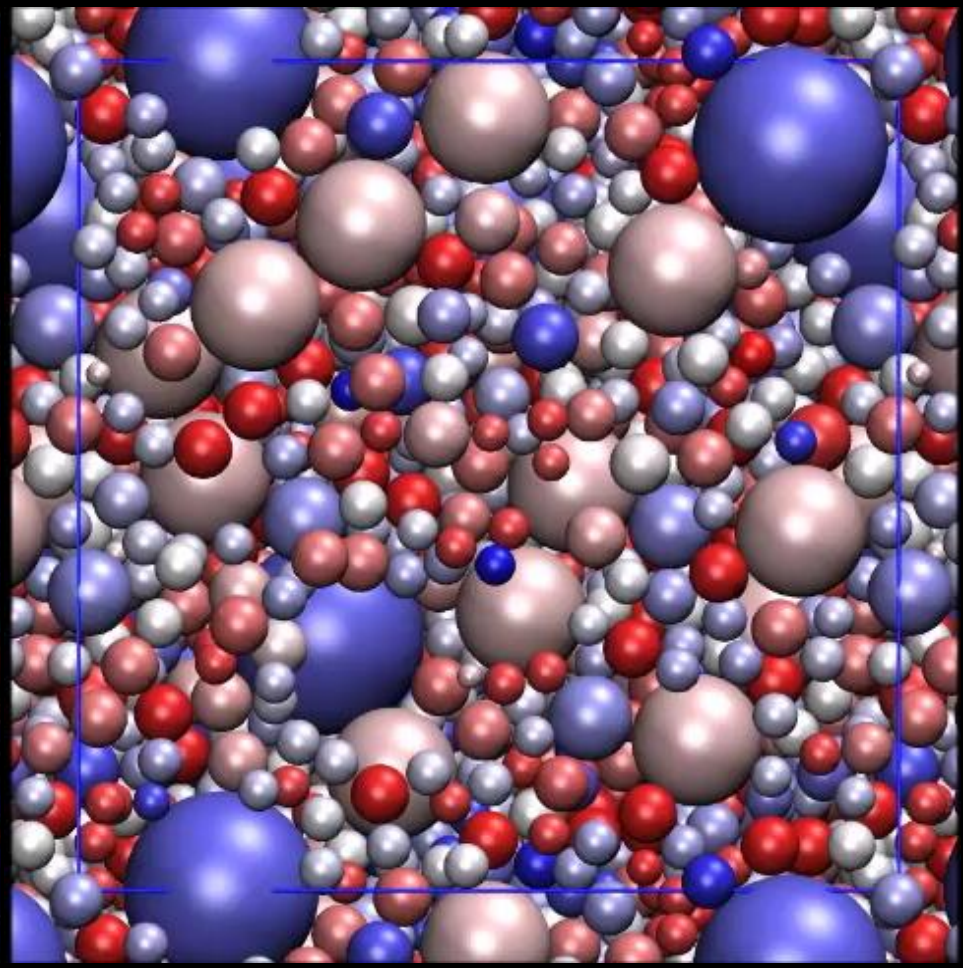


Hydrodynamics are what make a fluid a fluid!

BD without HI

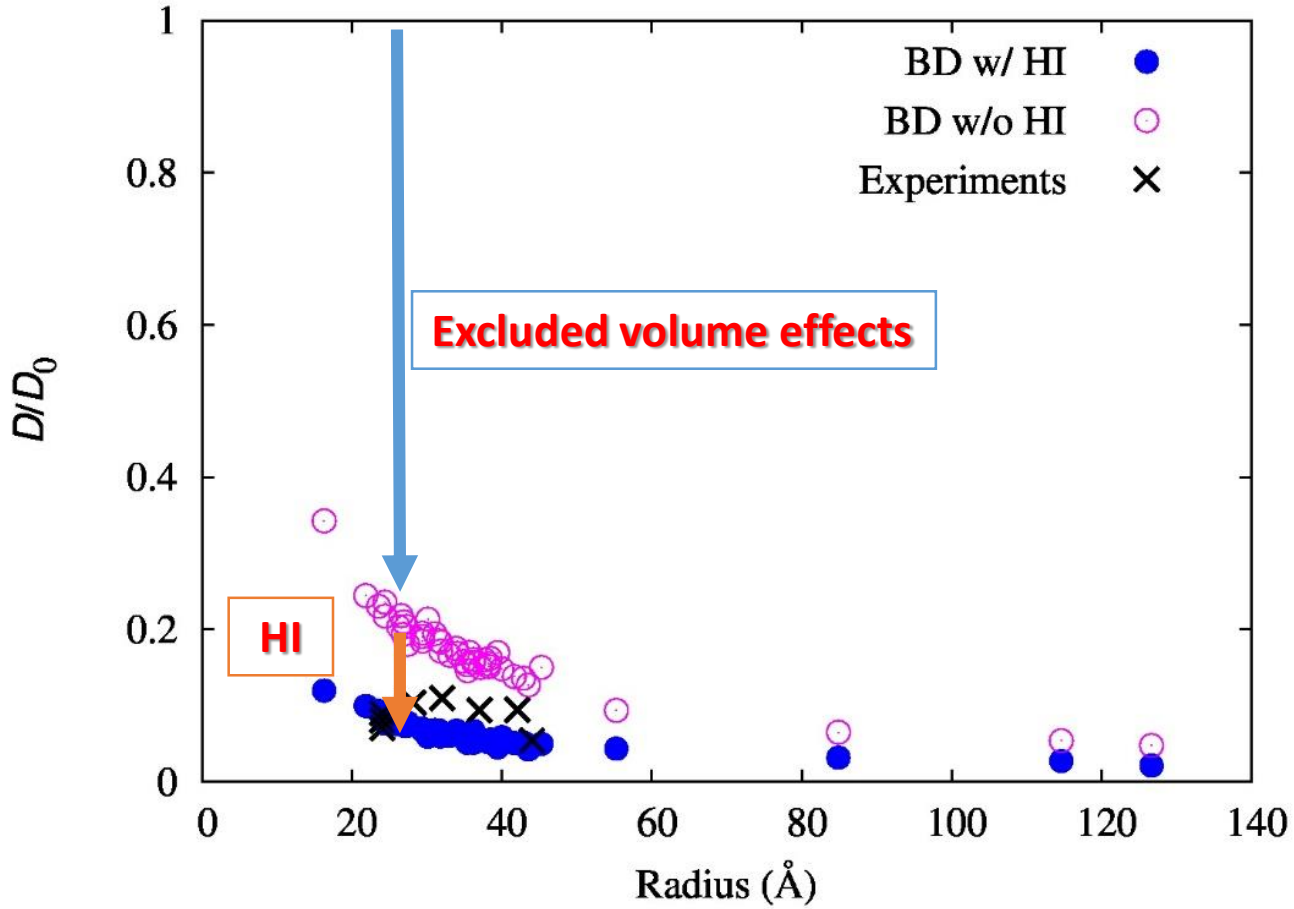
BD with HI





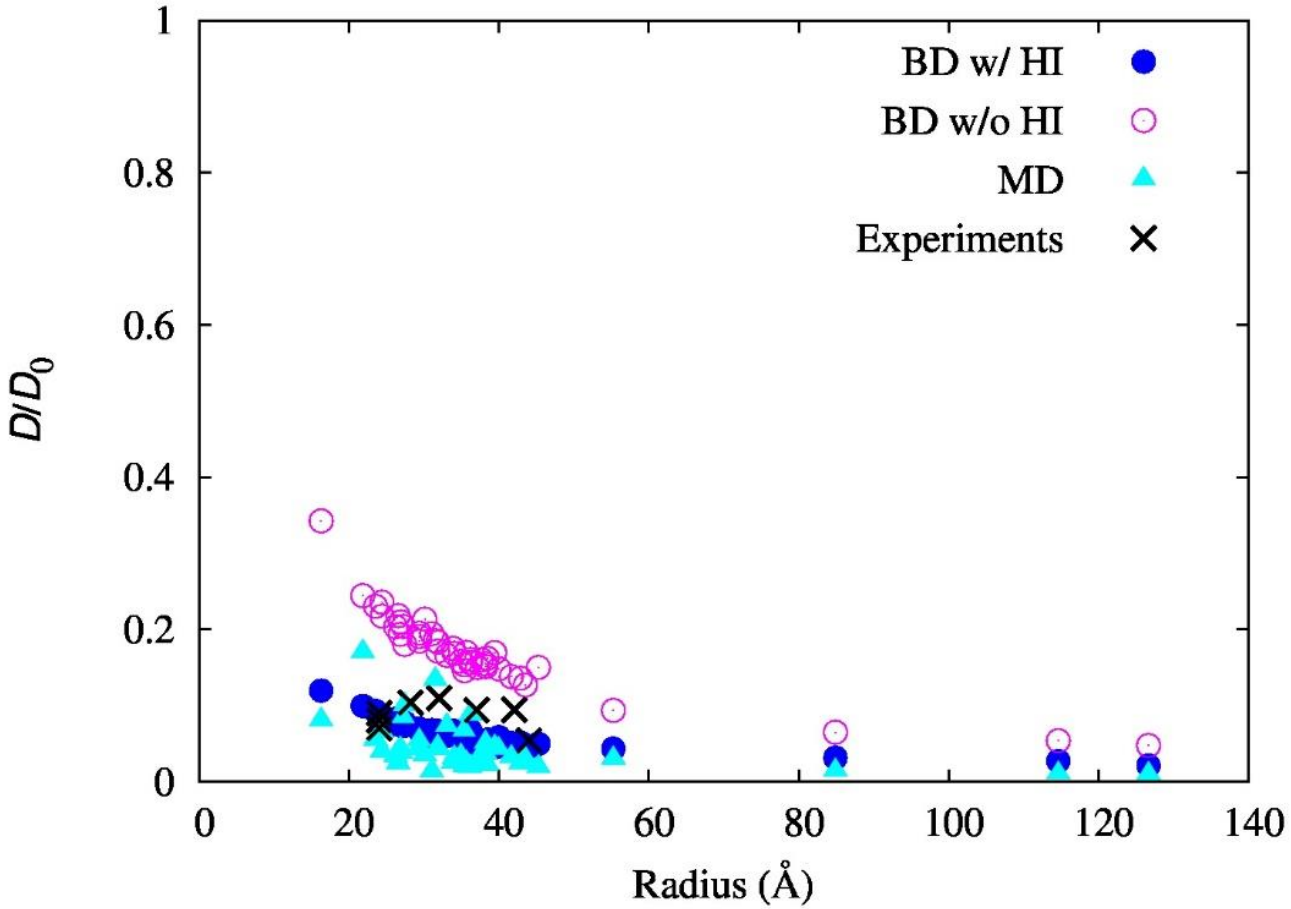
Simulations were performed on RICC

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)