All-atom molecular dynamics simulations of biological systems using supercomputers

Kavli IPMU - RIKEN iTHES - Osaka TSRP Symposium
"Frontiers of Theoretical Science – MATTER, LIFE and COSMOS – "
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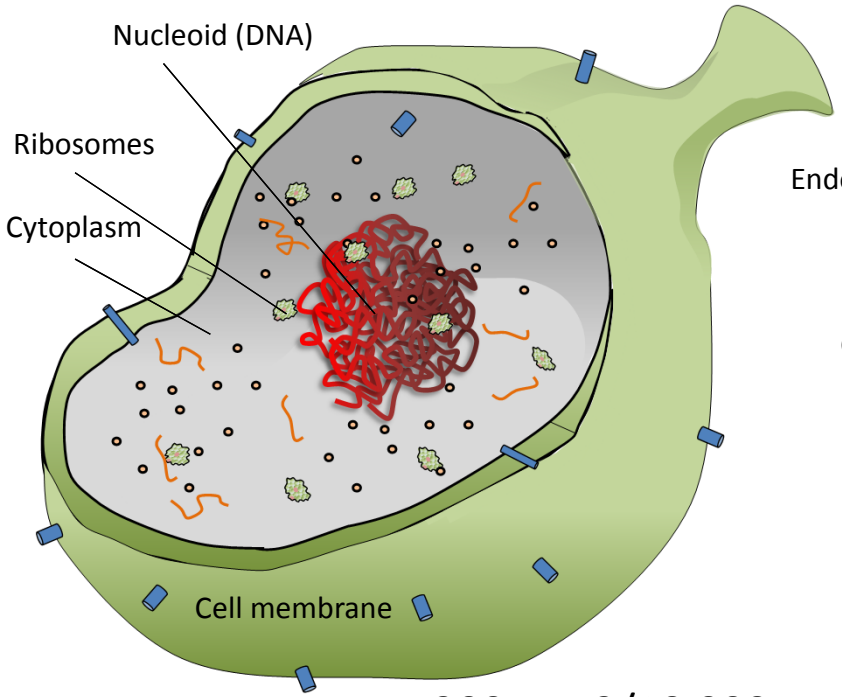
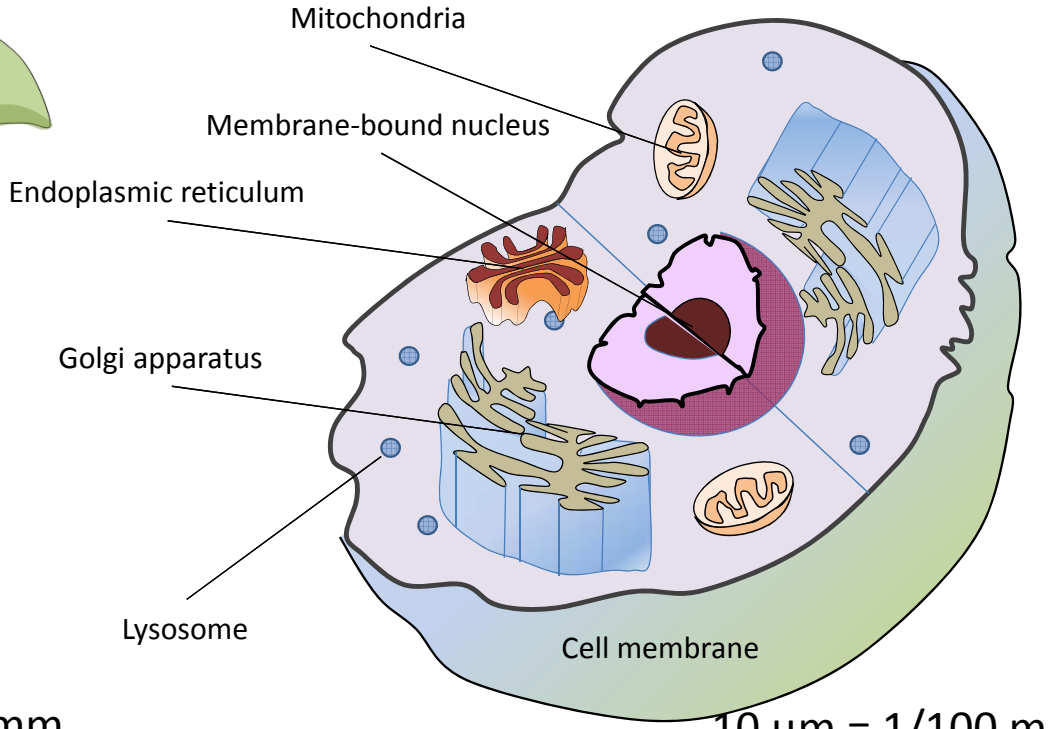
These figures were drawn by Dr. Isseki Yu, using only PowerPoint.

Two different cells: prokaryotic cells and eukaryotic cells



300nm=3/10,000mm

A typical prokaryotic cell（原核細胞）
***(Mycoplasma Genitalium* (bacteria))**

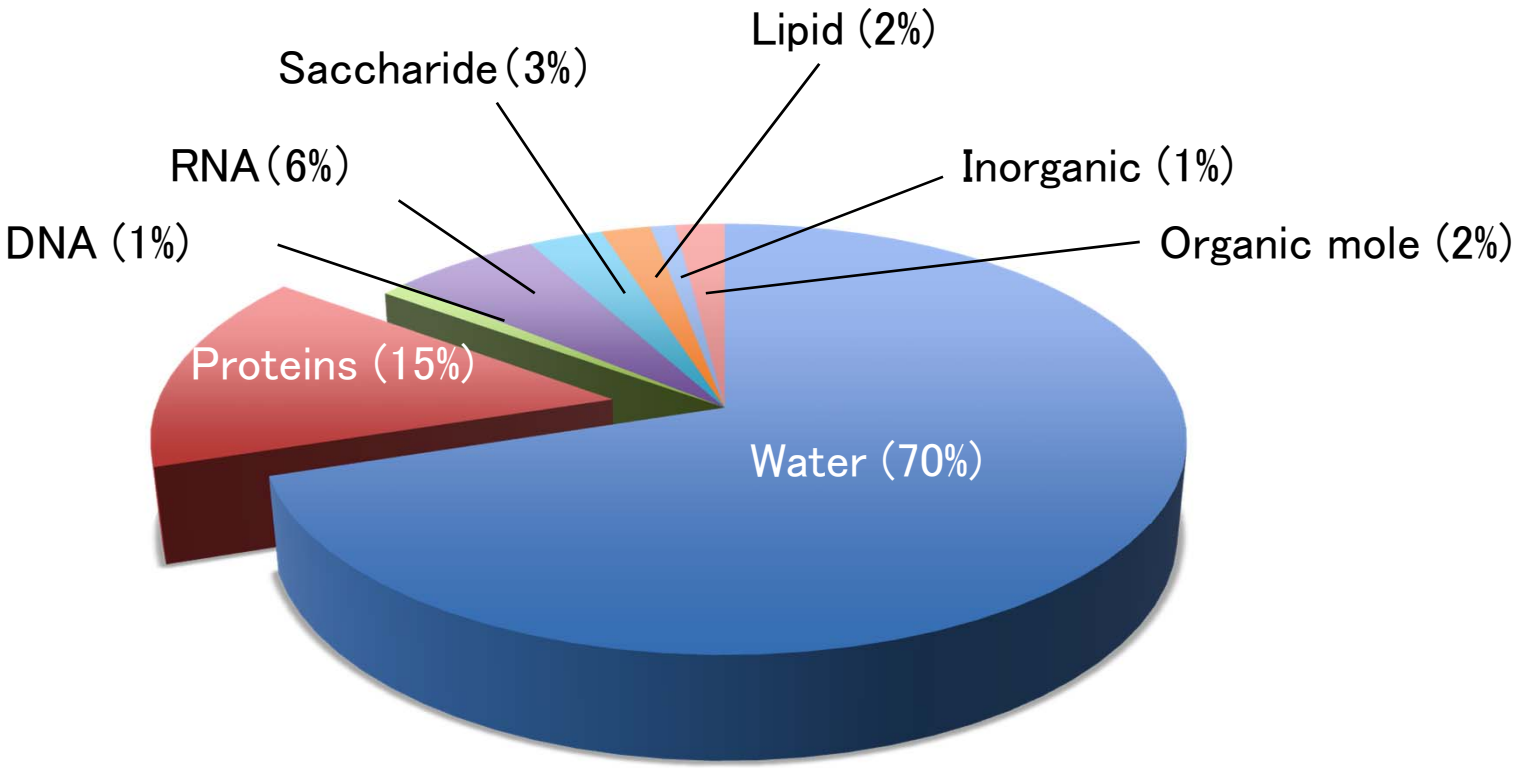


10 µm = 1/100 mm

A typical eukaryotic cell
（真核細胞）

Eukaryotic cells are 100 times larger than simple prokaryotic cells.

Various Molecules in a Cell



（参考：レニンジャー　生化学）

In E. coli

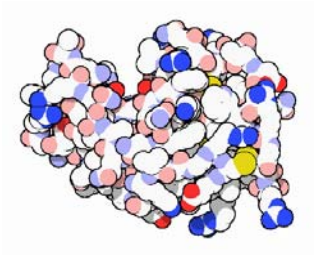
70 % of volume fraction of E. coli cells are occupied by water molecules. However, in this concentration, the inside of cell is crowded with large number of molecules.

Protein Structure and Function

PDBj http://www.pdbj.org/mom/index.php?l=ja

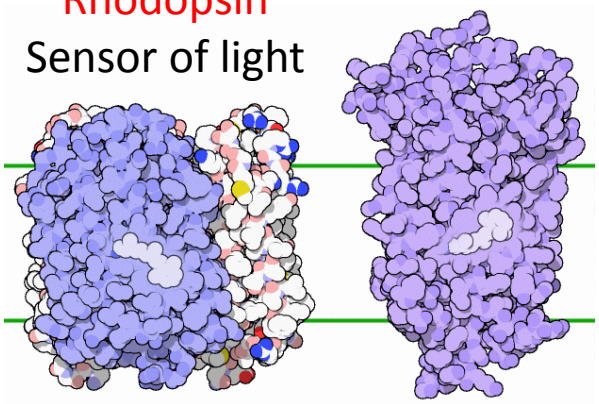
Lysozyme

Protection from bacteria



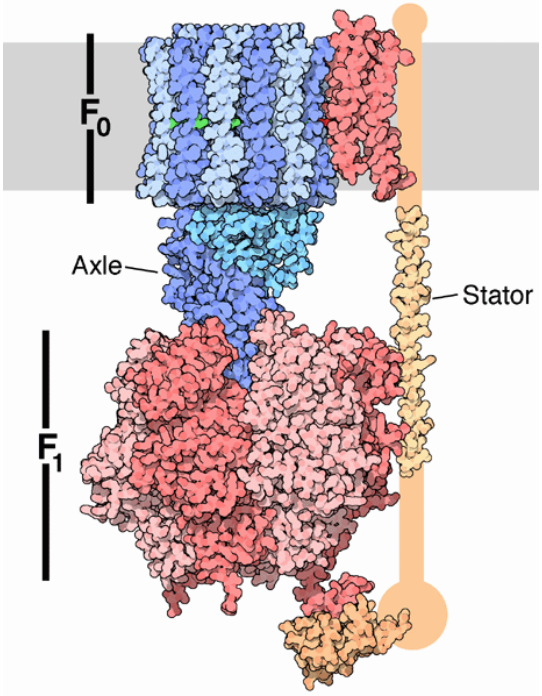
Rhodopsin

Sensor of light



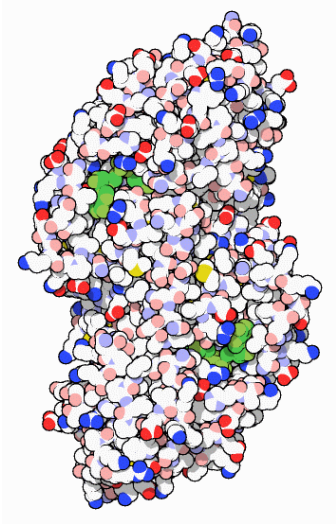
ATP Synthtase

Generate ATP by using proton gradient across membrane



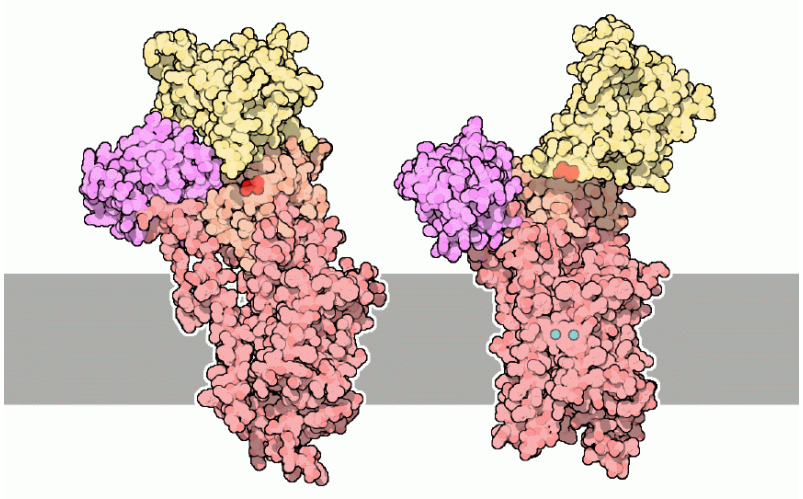
Alcohol Dehydrogenase

Facilitate the interconversion between alcohol and aldehyde



Ca-pump

Muscle relaxation for uptaking Ca^{2+}

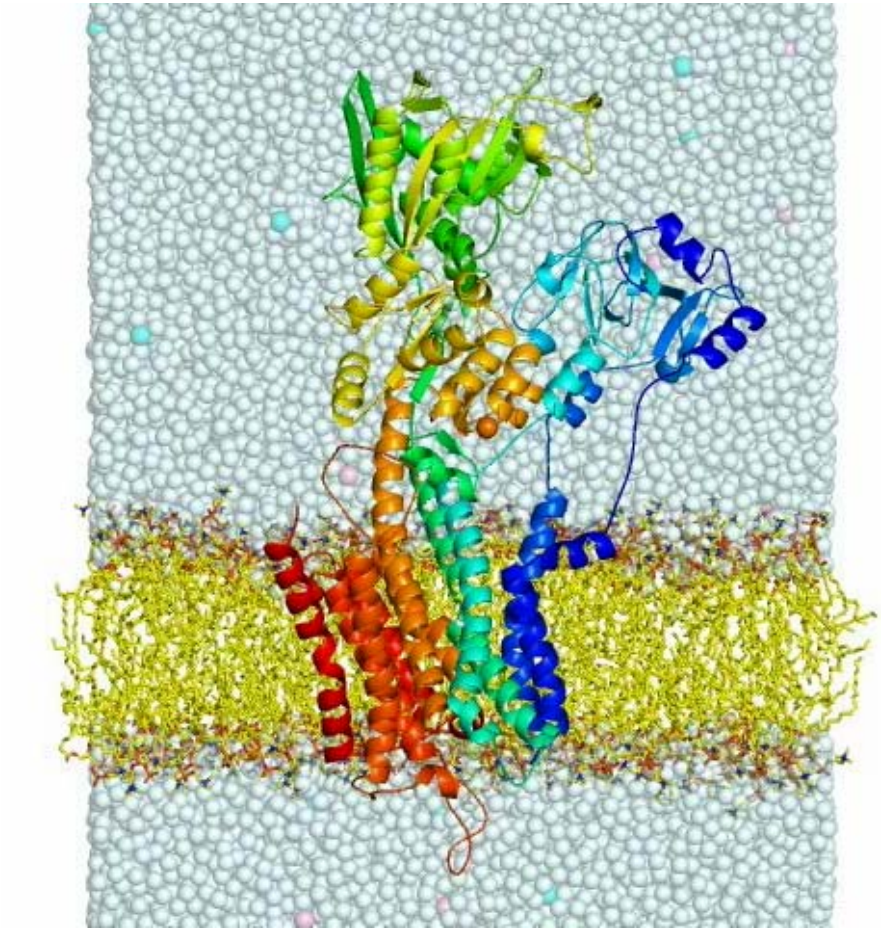


Sugita et al. JACS (2005); Sugita et al. PNAS (2010).

All-atom MD simulation of Ca^{2+}-pump

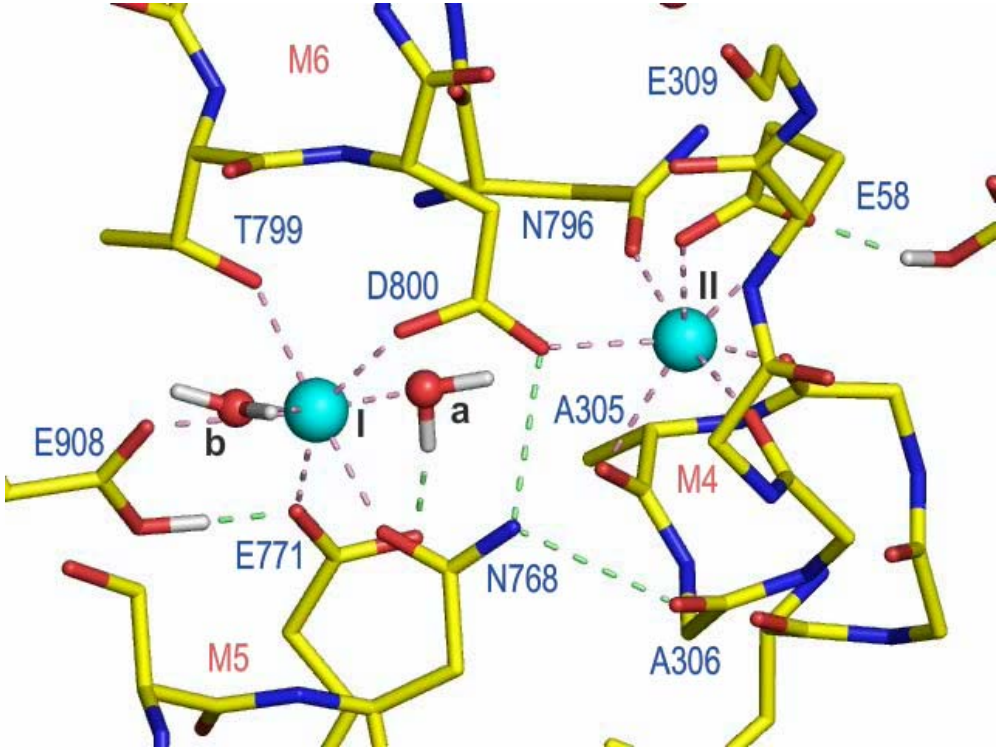
We can visualize how a protein works in cell using computer simulation.

Conformational dynamics of Ca^{2+}-pump (30ns)



10nm

A close-up view of the Ca^{2+}-binding site
Yellow: Carbon, Red: Oxygen, Blue: Nitrogen, Light Blue: Ca^{2+}




Molecular Force Field

A. Warshel M. Levitt S. Lifson

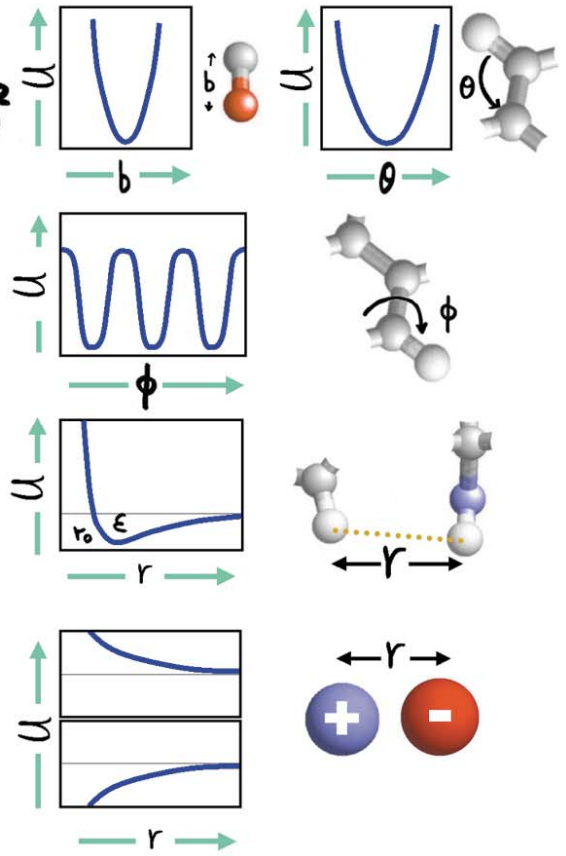
- Warshel and Levitt (Novel prize in chemistry (2013)) contributed the development of molecular force fields that have been commonly used in MD simulations.

$$U = \sum_{\text{All Bonds}} \tfrac{1}{2}K_b(b-b_o)^2 + \sum_{\text{All Angles}} \tfrac{1}{2}K_\theta(\theta-\theta_o)^2$$

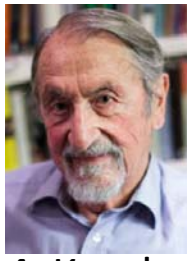
$$+ \sum_{\text{All Torsion Angles}} K_\phi[1-\cos(n\phi+\delta)]$$

$$+ \sum_{\text{All nonbonded pairs}} \epsilon\left[\left(r_o/r\right)^{12} - 2\left(r_o/r\right)^{6}\right]$$

$$+ \sum_{\text{All partial charges}} 332 q_i q_j / r$$



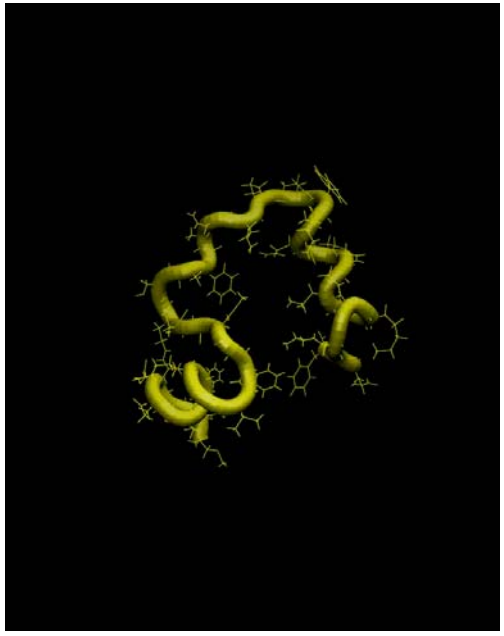
S. Lifson and A. Warshel, J. Chem. Phys. 49, 5116, 1968
M. Levitt and S. Lifson, J. Mol. Biol. 46, 269, 1969

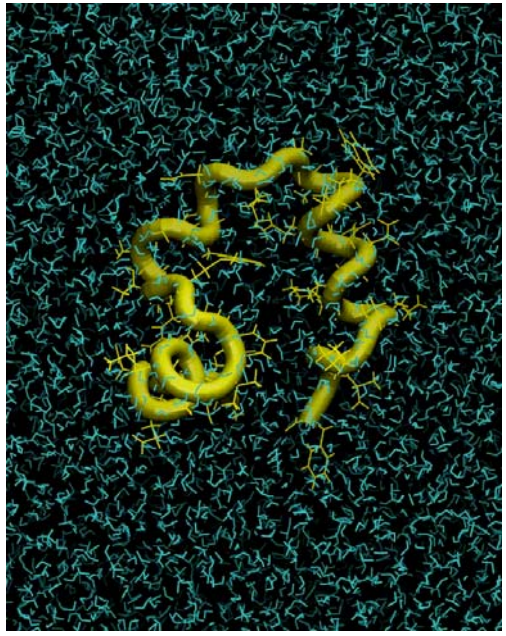


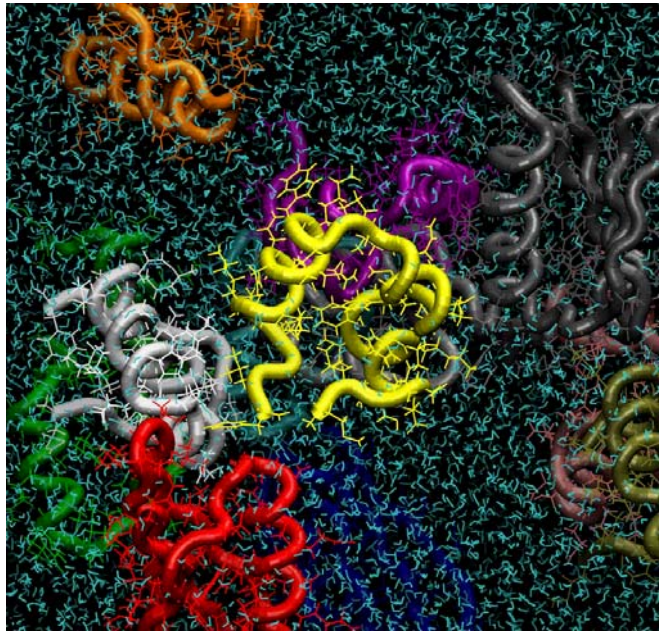
M. Karplus

MD simulations of biomolecules

- In 1977, M. Karplus (Novel prize in chemistry (2013)) and his co-workers performed the first MD simulation of a protein in vacuum. Later, more realistic simulations have become possible.







From 1977

MD in vacuum

From 1990

MD in water

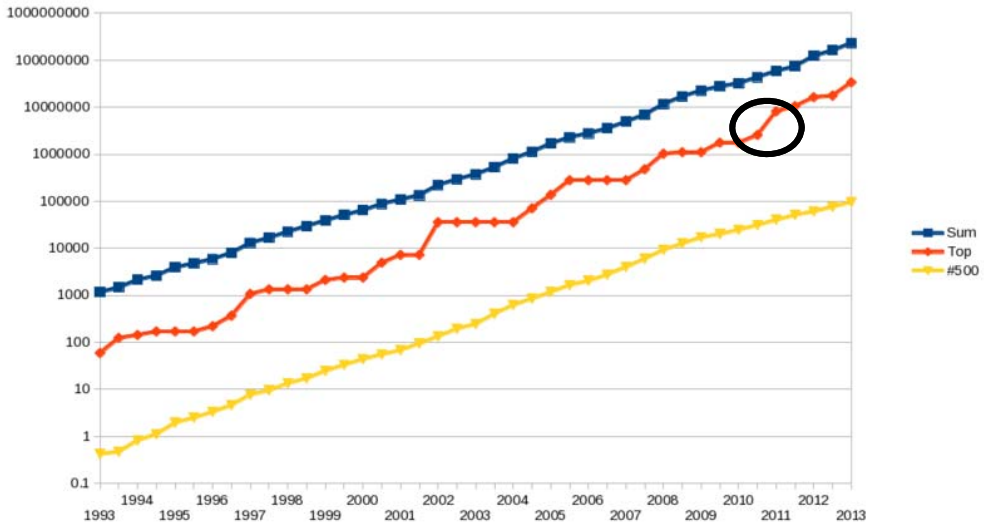
From 2010 (K)

MD in cell

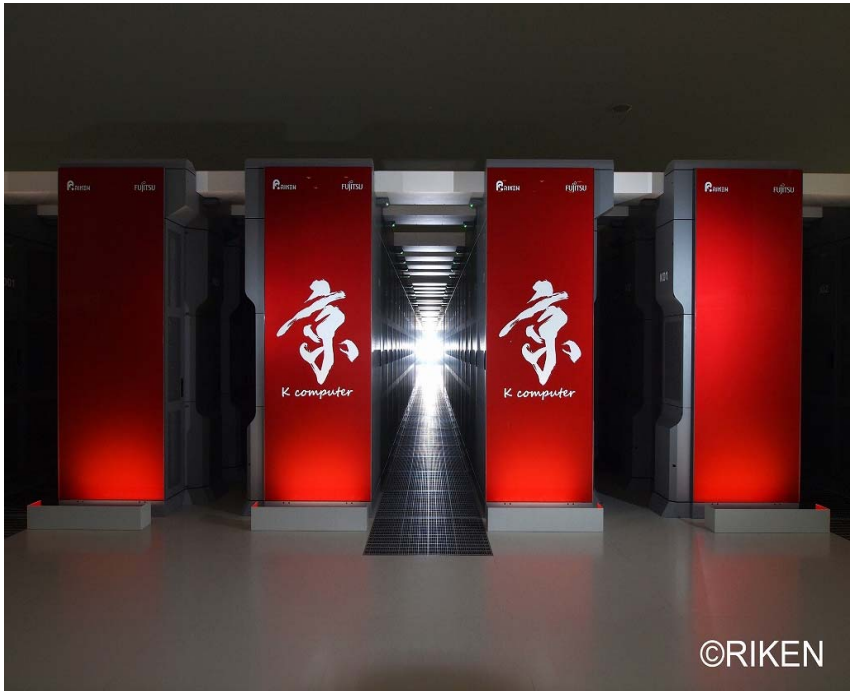
Dev ed

K computer at RIKEN Advanced Institute for Computational Science (AICS)

Performance of SuperComputer (from Top500)



Recently, the performance of supercomputers has been improved significantly. Top machine in 2013 is more than 100,000 times faster than that in 1993.



K computer (The 4th fastest computer)

Peak Performance: 10.51 PFLOPS

# of CPU Cores： 705,024

Total Memory：1.41PB（16GB per node）

Network: Tofu: 6D mesh / Torus

GENESIS (Generalized-Ensemble Simulation Systems)

GENESIS (R1) Development Team

- Project Leader: Yuji Sugita
- Major Developers: **Jaewoon Jung, Takaharu Mori**
- Developers: **Chigusa Kobayashi, Yasuhiro Matsunaga, Takashi Imai,**
  Takao Yoda (Nagahama Bio Institute), Norio Takase (Isogo Soft)
- Other Contributors: Many members in Sugita Group


Y. Sugita


J. Jung


T. Mori


C. Kobayashi


Y. Matsunaga

New Features of GENESIS

- Inverse Lookup Table Scheme for Nonbonded Interaction.
  - J. Jung et al. J.Comp.Chem. 2013, 34, 2412-2420.
- Midpoint Cell Method for Hybrid Parallelization.
  - J. Jung et al. J.Comp.Chem. 2014, 35, 300-308.
- New Replica-exchange molecular dynamics method (Surface-tension REMD).
  - T. Mori et al. J.Chem.Theor.Comp. (2013) **9**, 5629-5640.
- 3D-FFT based on the volumetric decompositions.
  - J. Jung et al. in preparation.

Smooth particle mesh Ewald method for long-range electrostatic calculations

$$U_{elec} = \sum_{i<j} \frac{q_i q_j}{4\pi\varepsilon_0} \frac{\mathrm{erfc}(\alpha_{ij})}{r_{ij}} + \frac{2\pi}{V} \sum_{G\neq 0} \frac{\exp(-|G|^2/4\alpha^2)}{|G|^2} \sum_{ij} \frac{q_i q_j}{4\pi\varepsilon_0} \cos(G \cdot r_{ij}) - \sum_i \frac{q_i q_i}{4\pi\varepsilon_0} \frac{\alpha}{\sqrt{\pi}}$$

Real part | Reciprocal part | Self energy

1. Real part is calculated with cutoff
2. Reciprocal part is rewritten as $\frac{1}{2\varepsilon_0 V} \sum_{G\neq 0} \frac{\exp(-|G|^2/4\alpha^2)}{|G|^2} |S(G)|^2$

$$S(G) = \sum_i q_i \exp(iG \cdot r_i) \approx b_1(G_1) b_2(G_2) b_3(G_3) F(Q)(G_1, G_2, G_3)$$

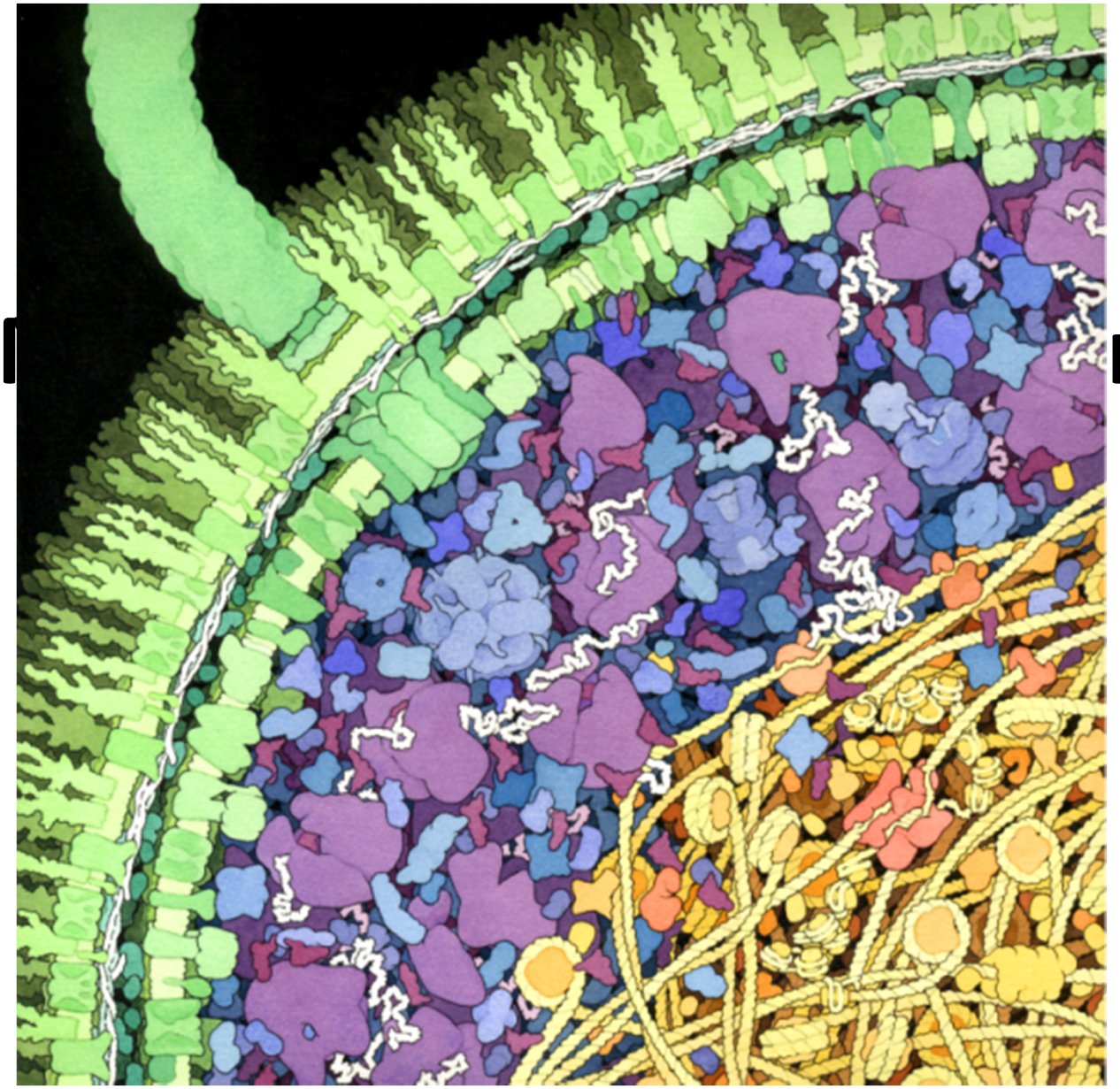
Parallel 3D FFT

Fourier Transform

Using Cardinal B-splines of order n

3D FFT requires all-to-all communications among large number of processors and it becomes a main bottle neck in MD simulations.

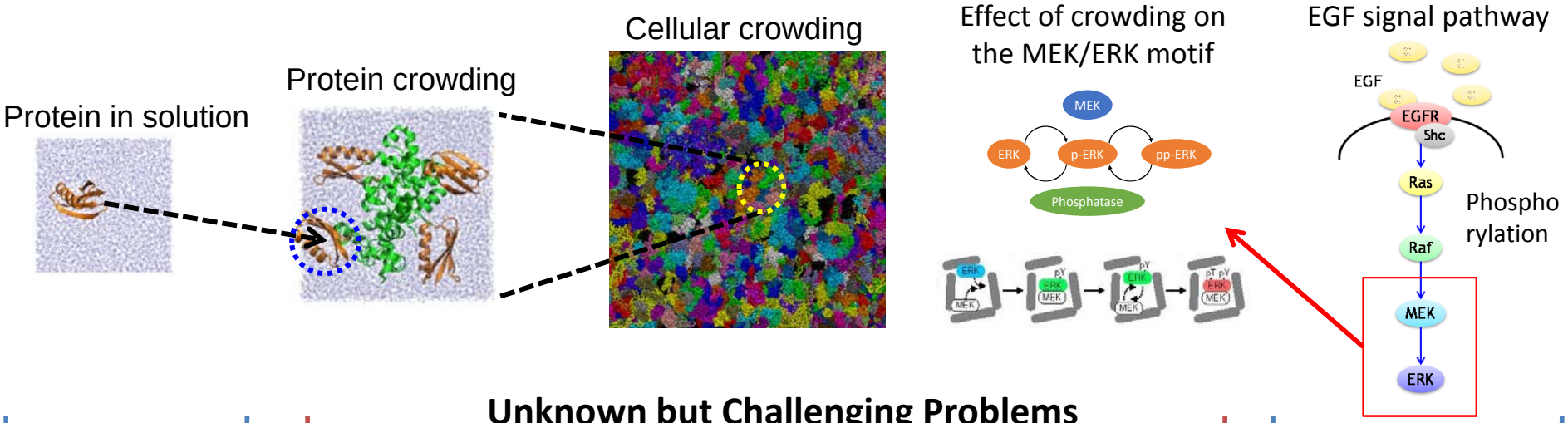
This work has been mainly done by Dr. Isseki Yu (RIKEN) in collaboration with Prof. Michael Feig (Michigan State University).



I. Yu (RIKEN iTHES)

From Biomolecules to Cellular Functions

Biomolecules → **Cell**



Unknown but Challenging Problems

X-ray crystallography
Solution NMR

Conventional MD

Cellular Crowding Environments may affect
→ Protein Stability, Hydration, Diffusion
→ Hydrodynamic effect in the cytoplasm
→ Enzyme reactions in cells
→ Signal transduction pathways in cells

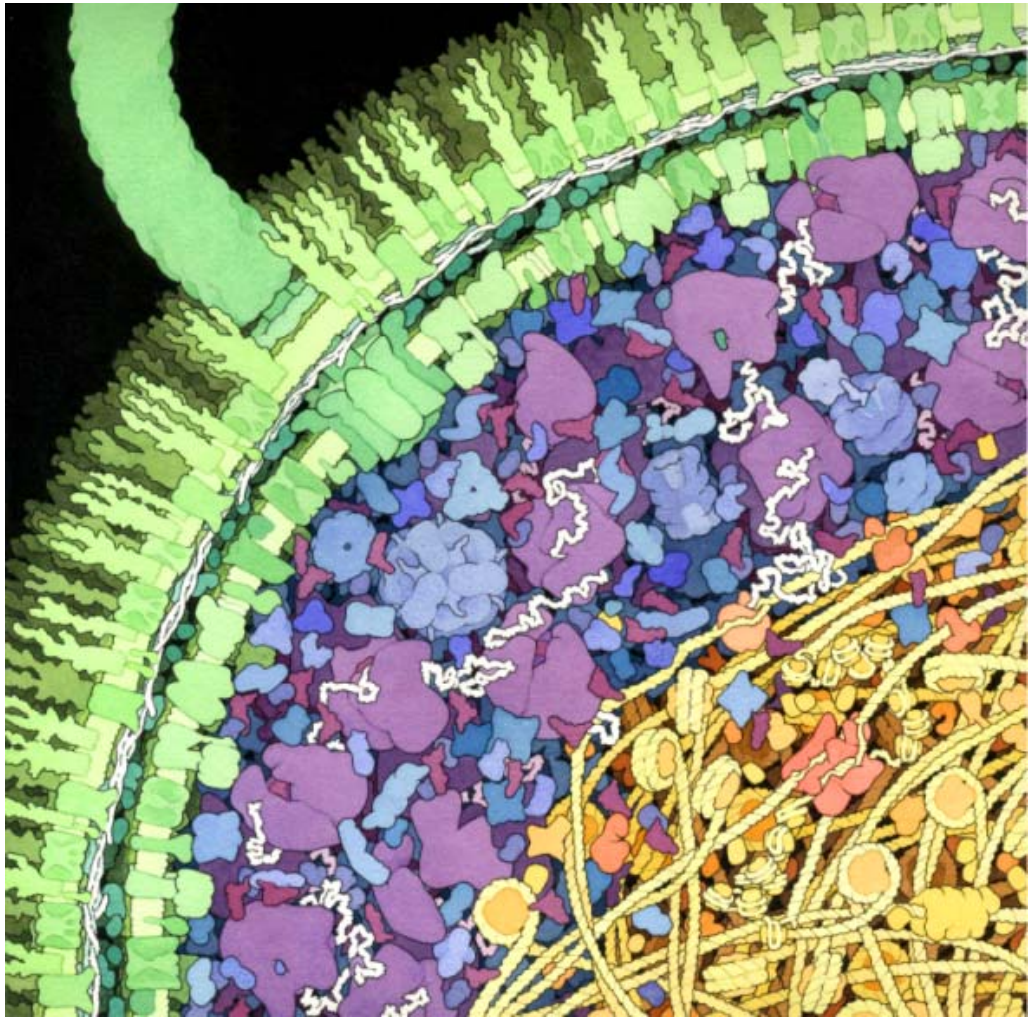
Molecular and Cellular Biology

Systems Biology

1. Multi-Scale Models and Simulations
2. Collaboration between Simulations and Experiments

QBiC

Effect of Macromolecular Crowding



(Illustrated by D. Goodsell)

The interiors of cells is the high total concentration of biological macromolecules (20-40% in volume fraction).

Macromolecular crowding exerts surprisingly large effects on the thermodynamics and kinetics of biological processes.

Understanding macromolecular dynamics in the intracellular environment is a necessary first step towards whole cell modeling.

What can we learn from the simulations ?

- How protein stability is changed between in water and in cytoplasm ?
- How proteins and RNAs can move in the crowded environments ?
- How proteins can bind their ligands in the environments ?

Summary

- We have developed a highly parallel MD program, GENESIS, for the efficient usage of K computer.
- The bacterial cytoplasm was simulated using all-atom MD method. We obtain new insight on protein stability, diffusion, protein-ligand binding, etc.

- We consider that the current MD simulations are too short and therefore we still have so many unsolved questions. We would like to examine them one by one.
- We need to develop a new coarse-grained model to extend the simulation time-scales. In “near” future, we would like to study protein-protein interaction in biological networks in a cell.

Acknowledgement

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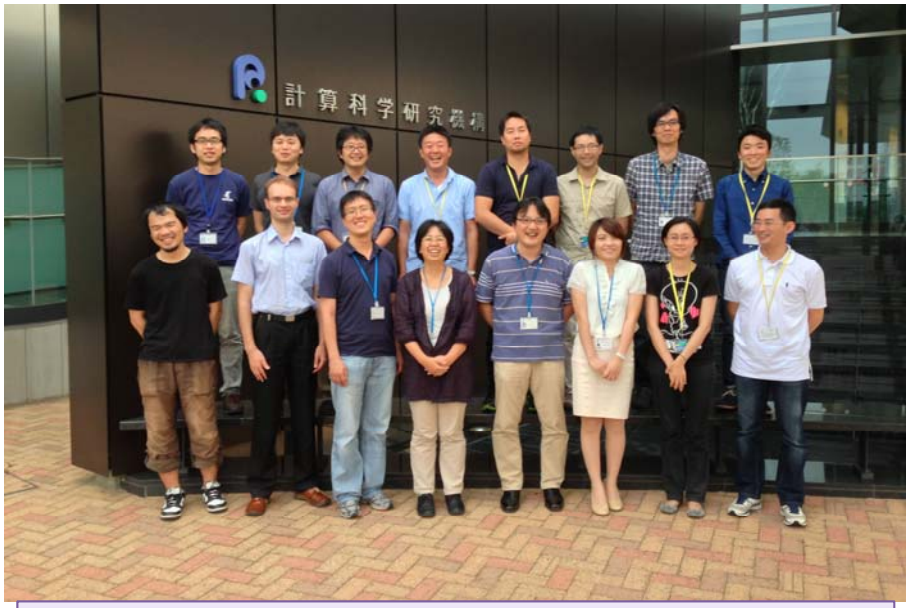
  - Dr. J. Jung
  - Dr. C. Kobayashi
  - Dr. Y. Matsunaga
  - Dr. R. Harada (Tsukuba University)
- RIKEN Theoretical Molecular Science Laboratory
  - Dr. T. Mori
  - Dr. I. Yu (iTHES)
- Michigan State University
  - Prof. M. Feig

- Computer Resources
  - RIKEN RICC
  - Oakleaf FX10 (U. Tokyo)
  - RIKEN K
- Research Grants
  - RIKEN iTHES, QBiC, and AICS
  - JST CREST
  - Strategic Research Field 1



Sugita Lab. Joint Meeting at Kobe (2013/7)