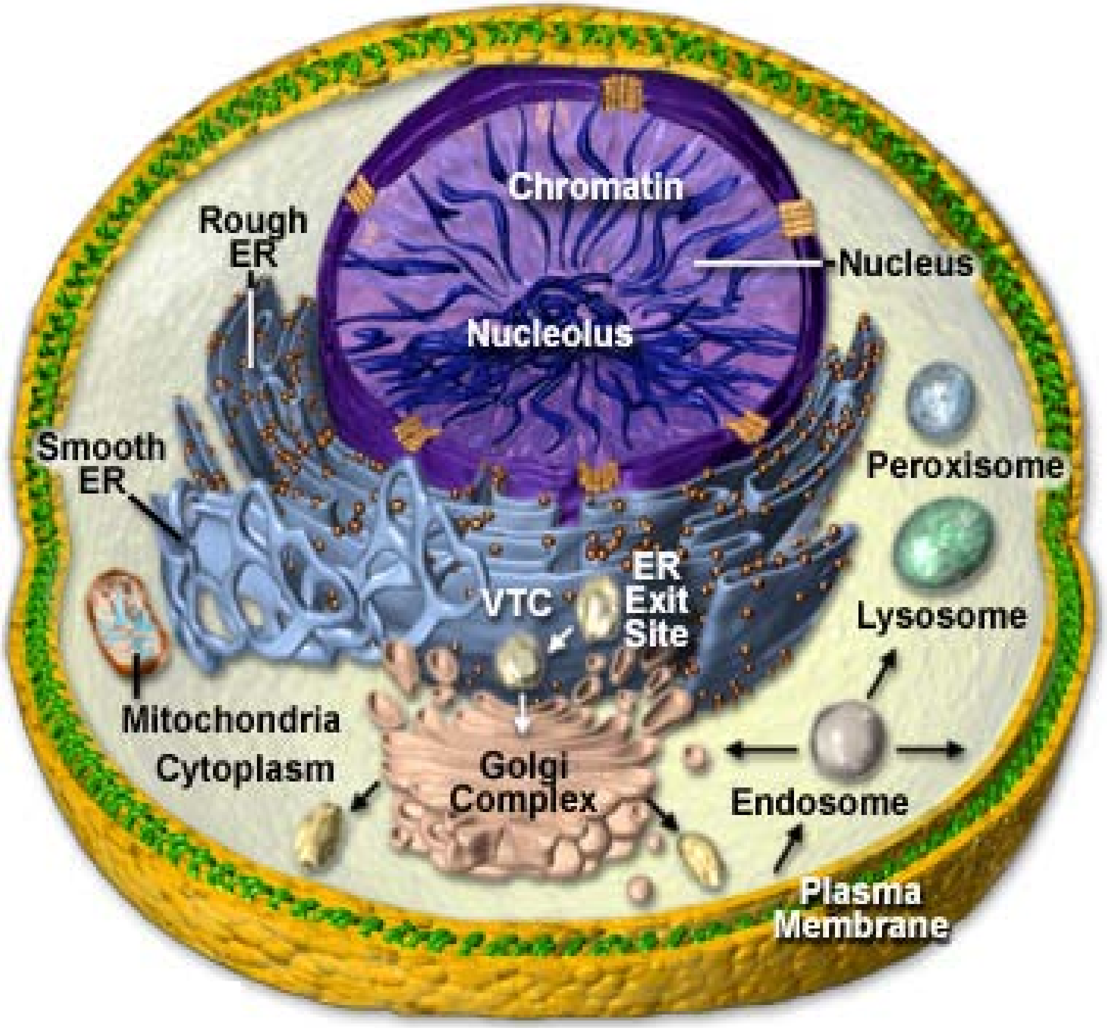
Computational microscope views the cell

100 - 1,000,000 processors

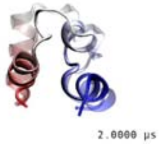


http://micro.magnet.fsu.edu/cells/animals/images/animalcellsfigure1.jpg

The living cell is a society of molecules: molecules assembling and cooperating bring about life!

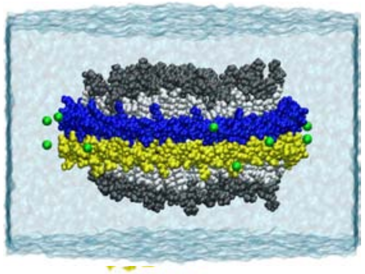
100 - 1,000,000 processors

Computational microscope views the cell

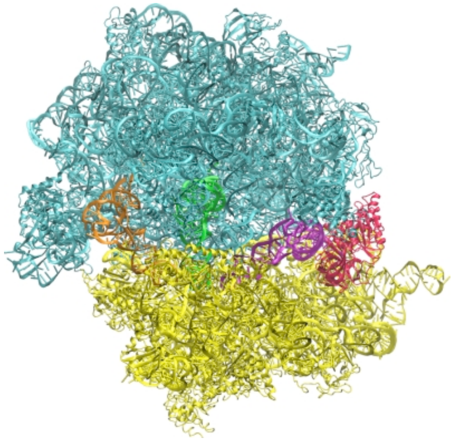


protein folding (**10^4 atoms**)

fibrinogen (**10^6 atoms**)

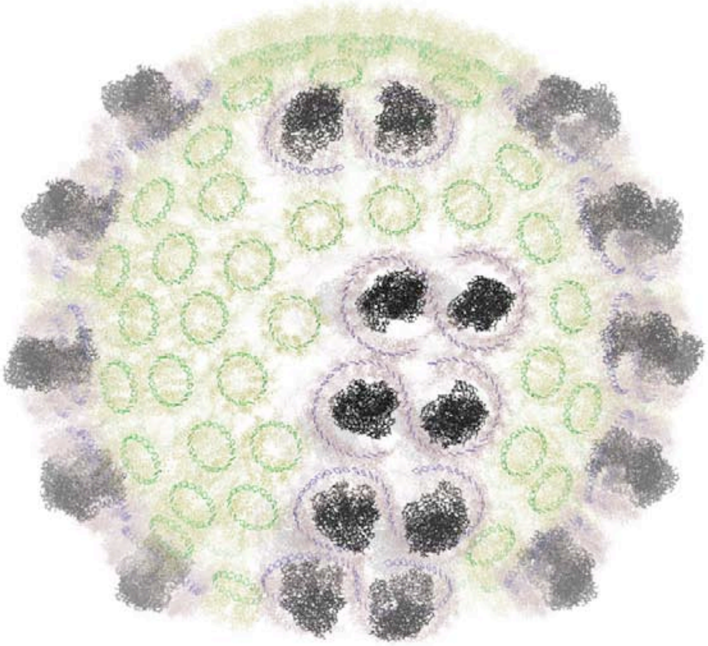


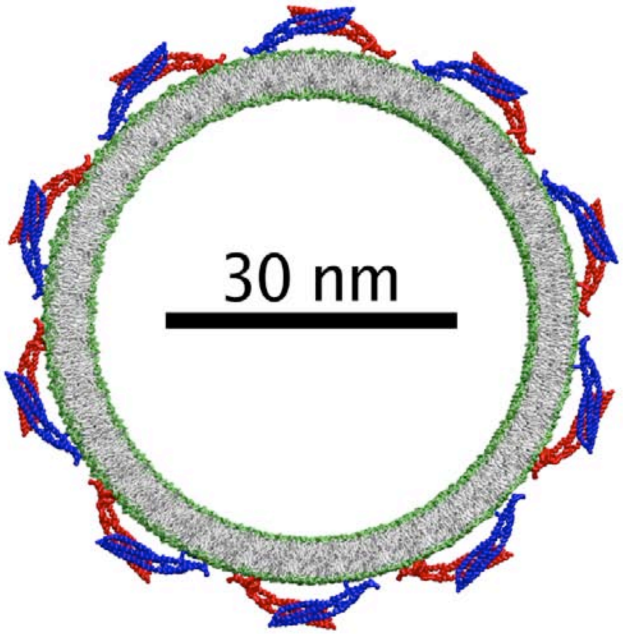
lipoprotein (**10^5 atoms**)



ribosome (**10^6 atoms**)

photosynthetic chromatophore (**10^8 atoms**)

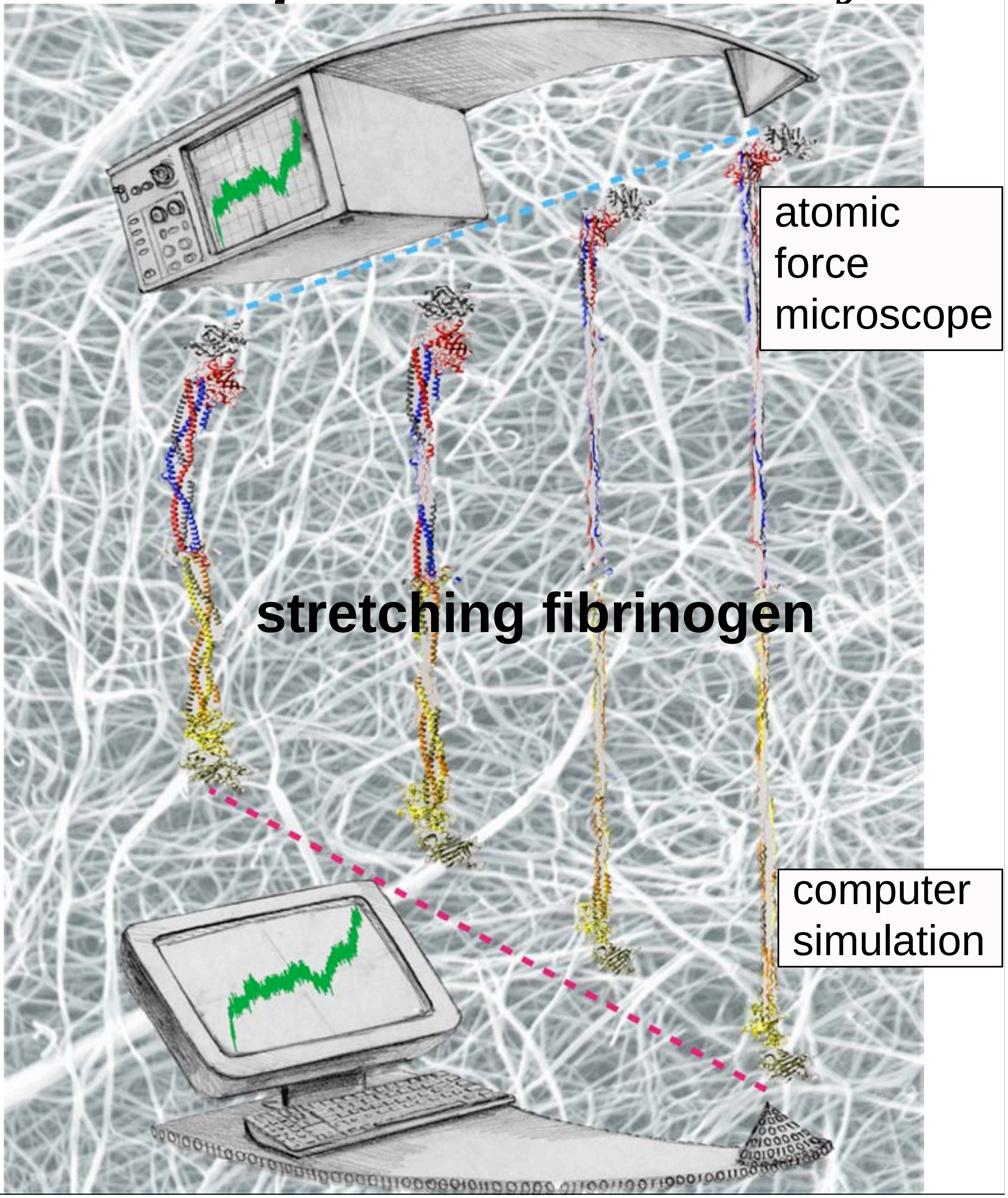




vesicle formed by BAR domains (**5x10^7 atoms**)

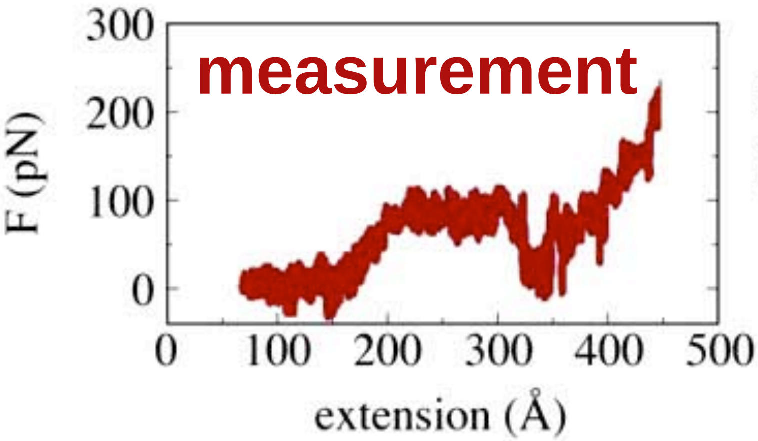
100 - 1,000,000 processors

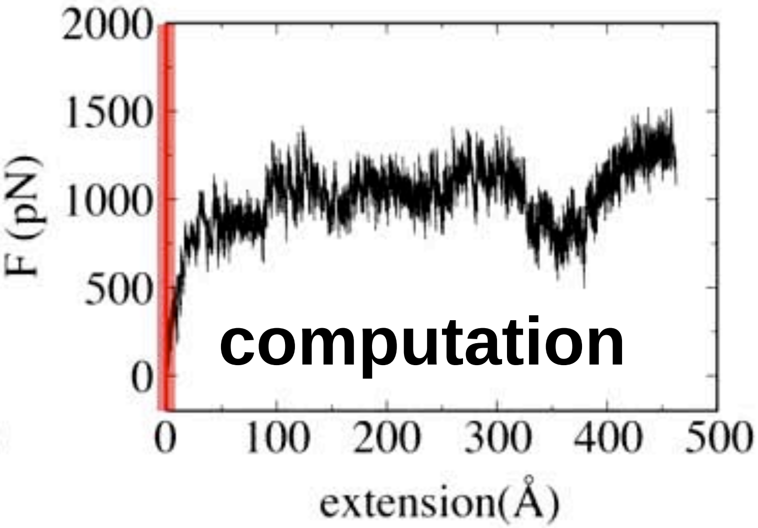
View of blood clot elasticity



Mechanical Strength of a Blood Clot

Collaborator: Bernard C. Lim (Mayo Clinic College of Medicine)





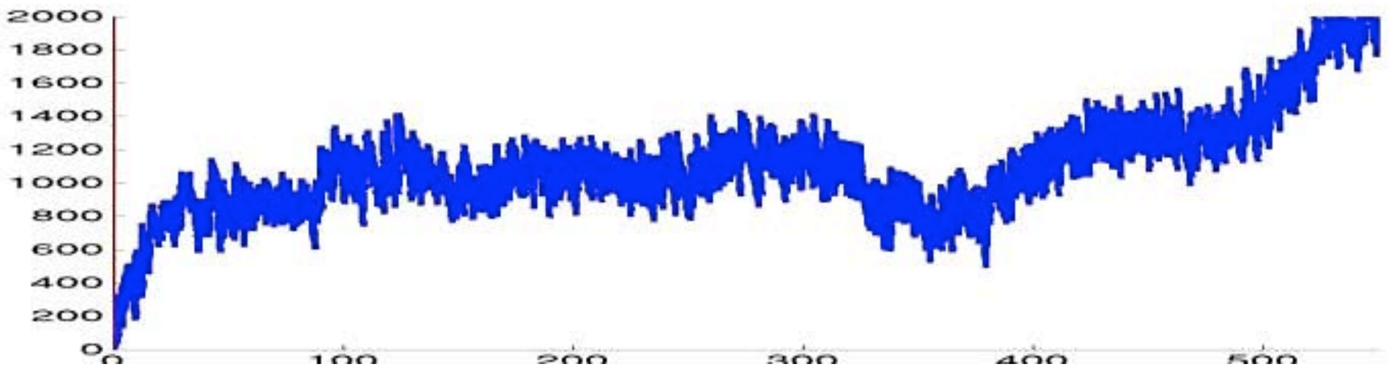
A Blood Clot

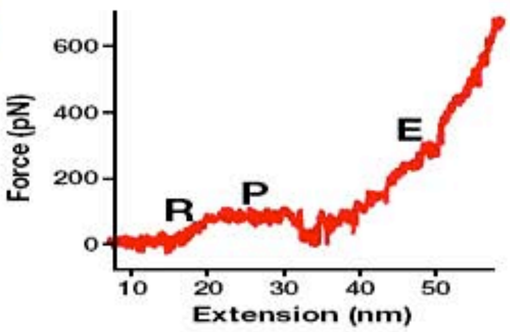
Red blood cells within a network of fibrin fibers, composed of polymerized fibrinogen molecules.

B. Lim, E. Lee, M. Sotomayor, and K. Schulten. **Molecular basis of fibrin clot elasticity.** *Structure*, 16:449-459, 2008.

Mechanical Strength of a Blood Clot

An even closer look



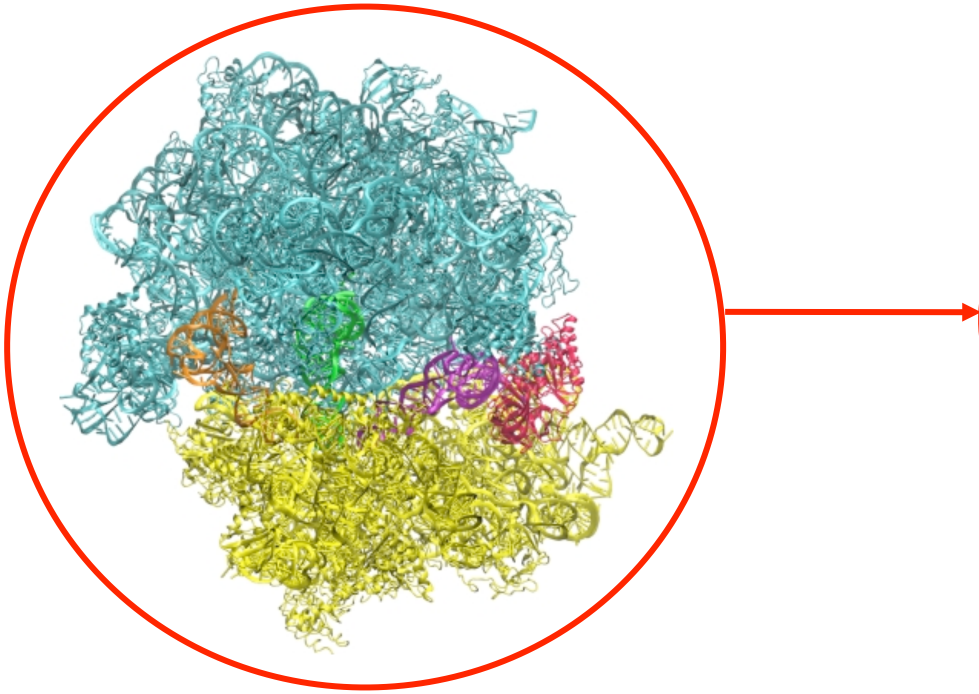


B. Lim, E. Lee, M. Sotomayor, and K. Schulten. **Molecular basis of fibrin clot elasticity.** *Structure*, 16:449-459, 2008.

Application to Ribosome

X-ray crystallography

High resolution (3-5Å)
Crystal packing makes it difficult
to determine functional state

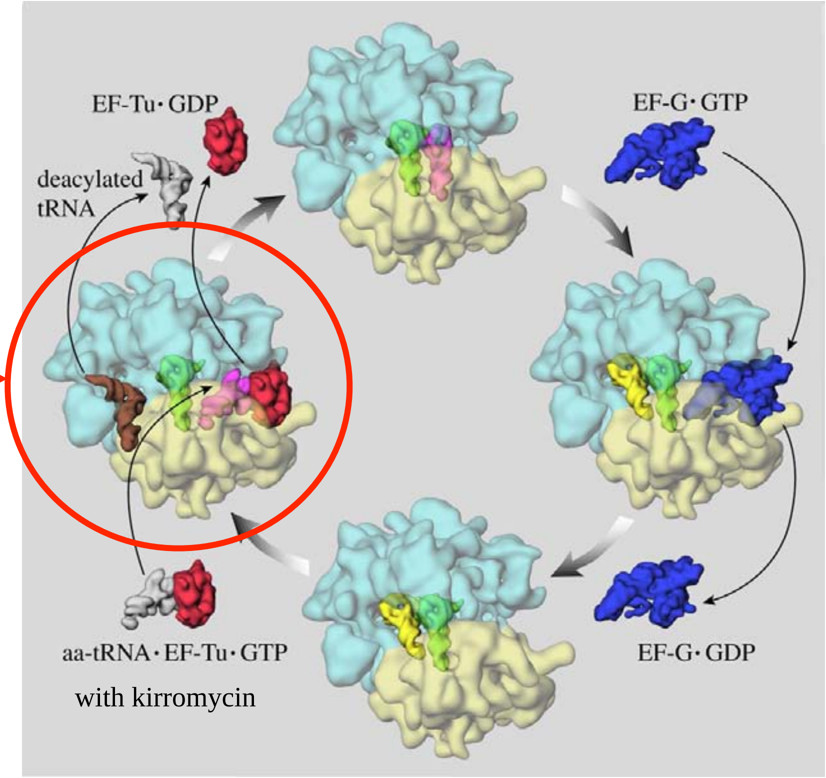


Crystal structures of ribosome and ligands

30S and 50S from 2I2U/2I2V (Berk et al., 2006); L1 protuberance based on 1MZP (Nikulin et al., 2003); L1 protein using MODELLER (Sali and Blundell, 1993) with 1ZHO as template (Nevskaya et al., 2006); A-site finger using 1TWB (Tung and Sanbonmatsu, 2004) as template; tRNAs from Selmer et al., 2006; ternary complex from 1OB2 (P.Nissen ,unpublished)

Cryo-EM

Lower resolution (typically 8-12Å)
Many functional states can be obtained



Structures of the ribosome at different stages of the elongation cycle obtained by Cryo-EM

(J. Frank. The dynamics of the Ribosome inferred from Cryo-EM, in Conformational Proteomics of Macromolecular Architectures, 2004)

Application to Ribosome

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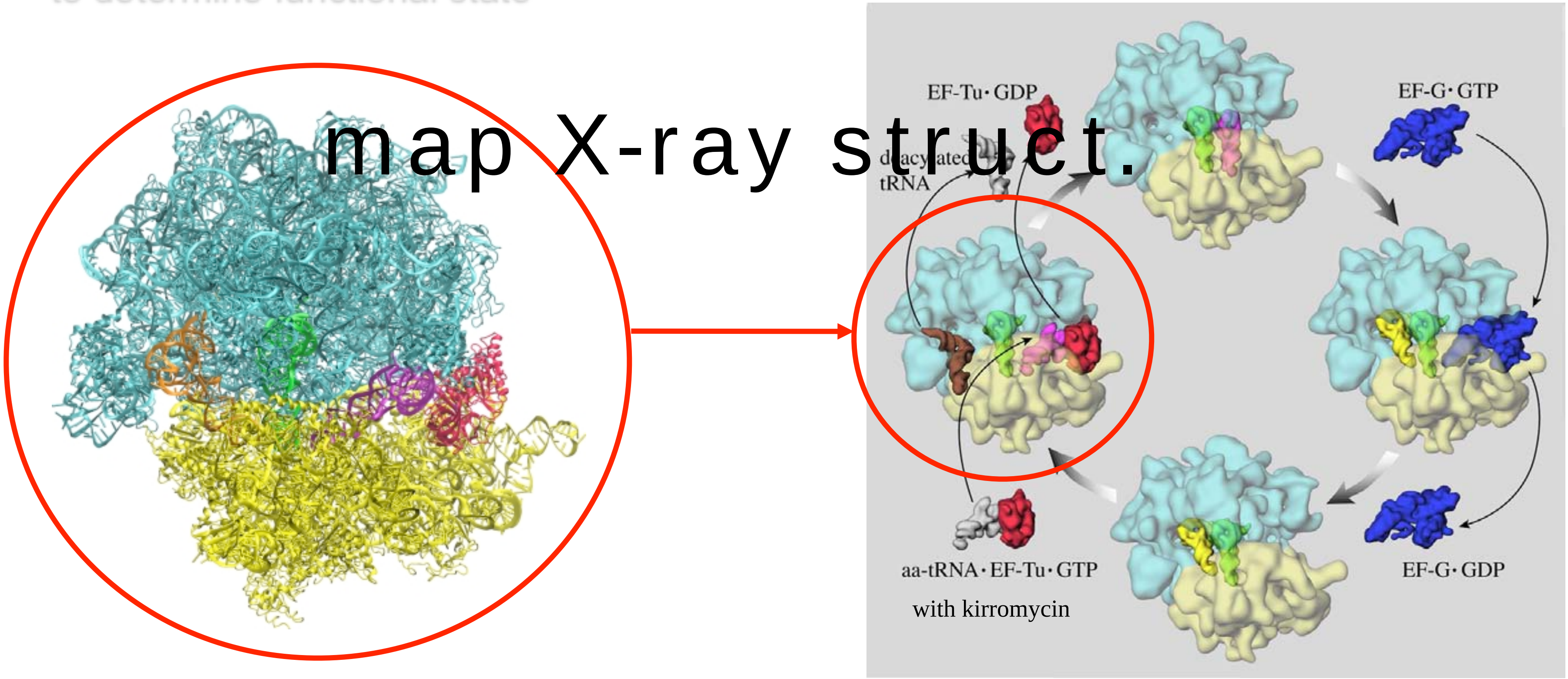

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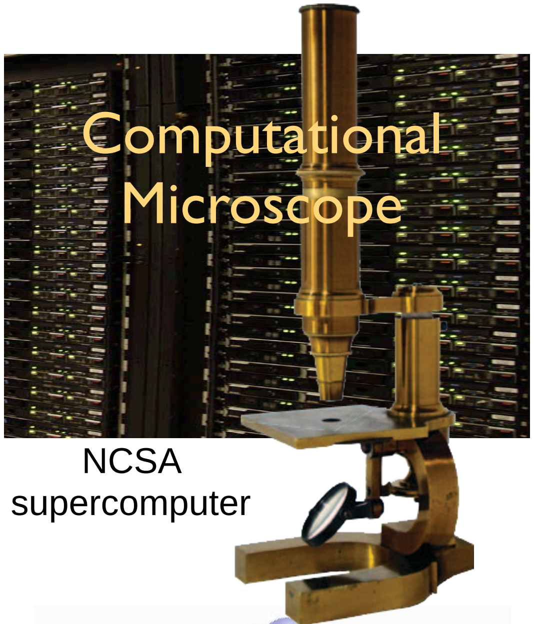
(J. Frank. The dynamics of the Ribosome inferred from Cryo-EM, in Conformational Proteomics of Macromolecular Architectures, 2004)

Hybrid Microscopy with X-rays, Electrons, and Bits

X-ray crystallography

APS at Argonne

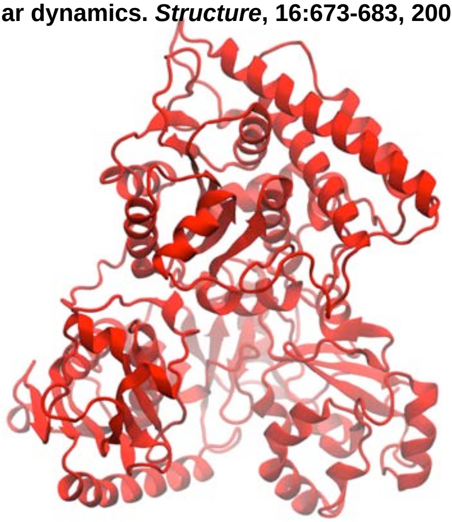


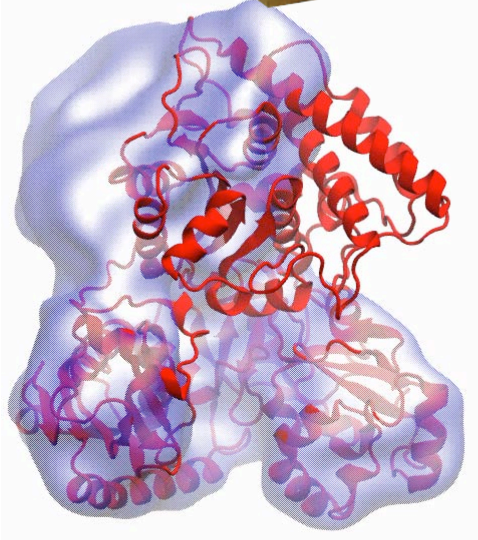
NCSA
supercomputer

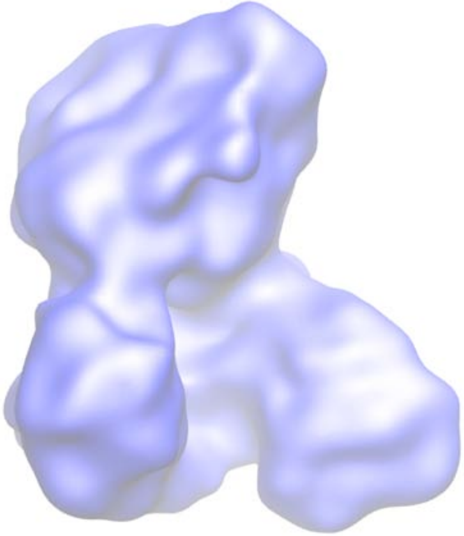
Electron microscopy

FEI microscope

L. Trabuco, E. Villa, K. Mitra, J. Frank, and K. Schulten. Flexible fitting of atomic structures into electron microscopy maps using molecular dynamics. *Structure*, 16:673-683, 2008.







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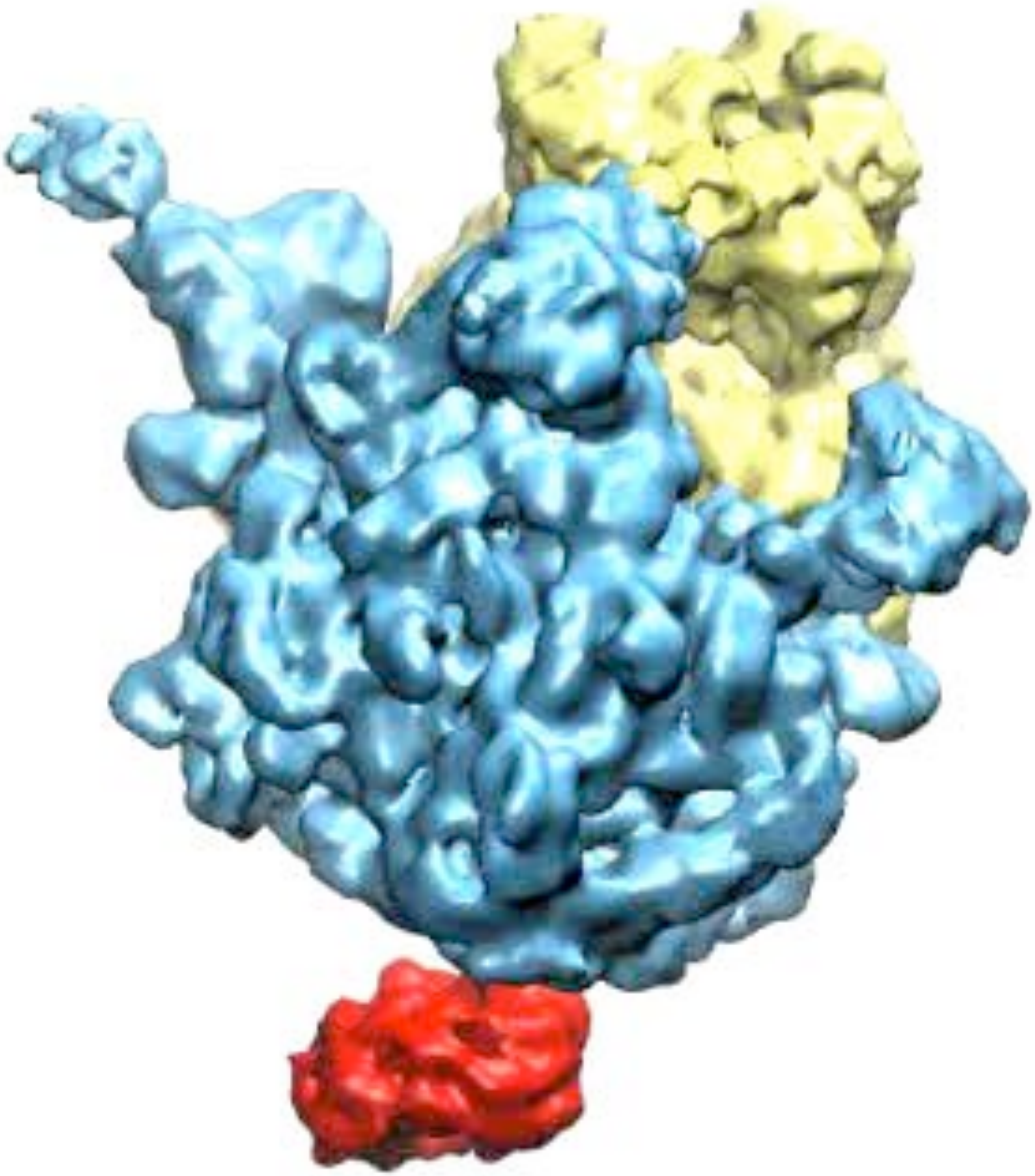
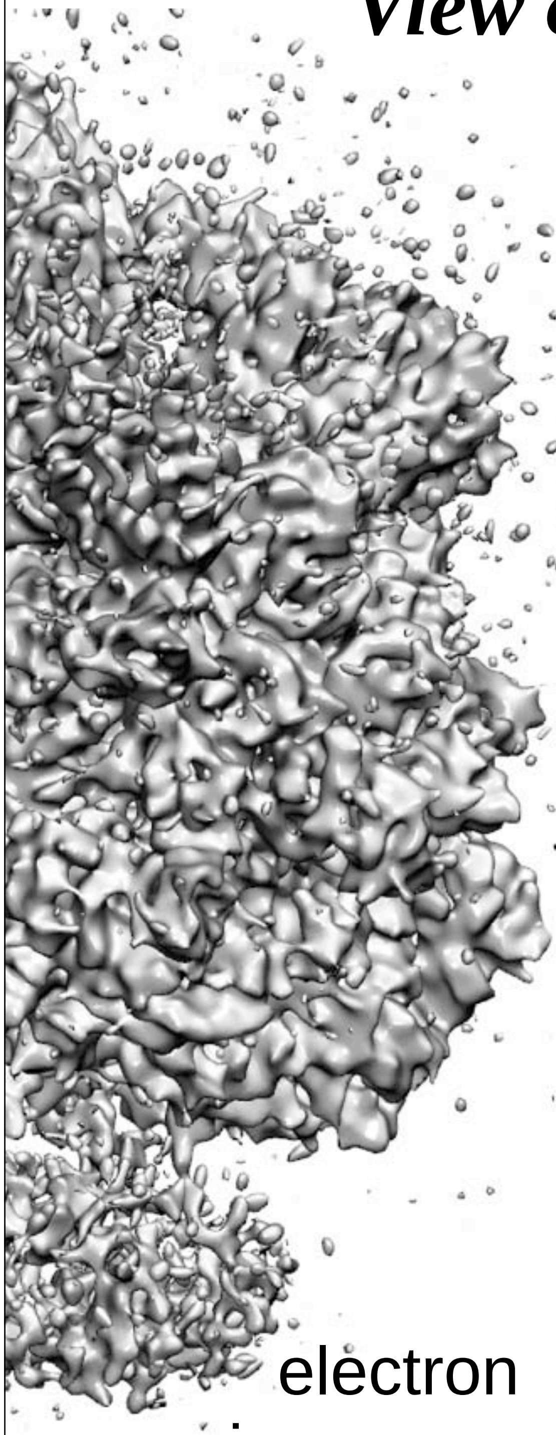
Computational microscope recognizes atomic resolution picture of ribosome in action



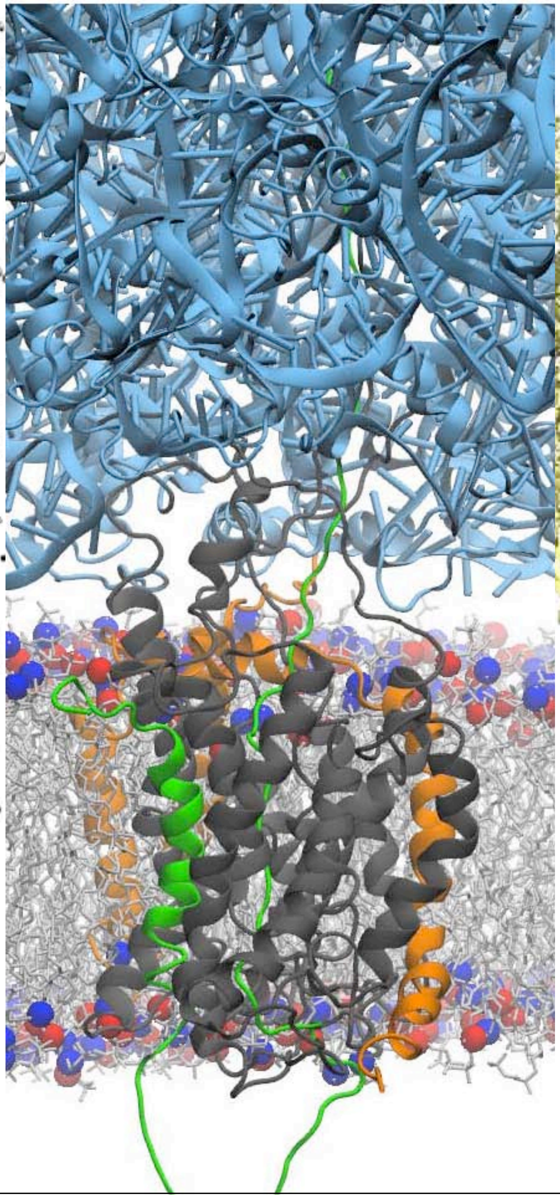
300,000 atoms structurally assigned

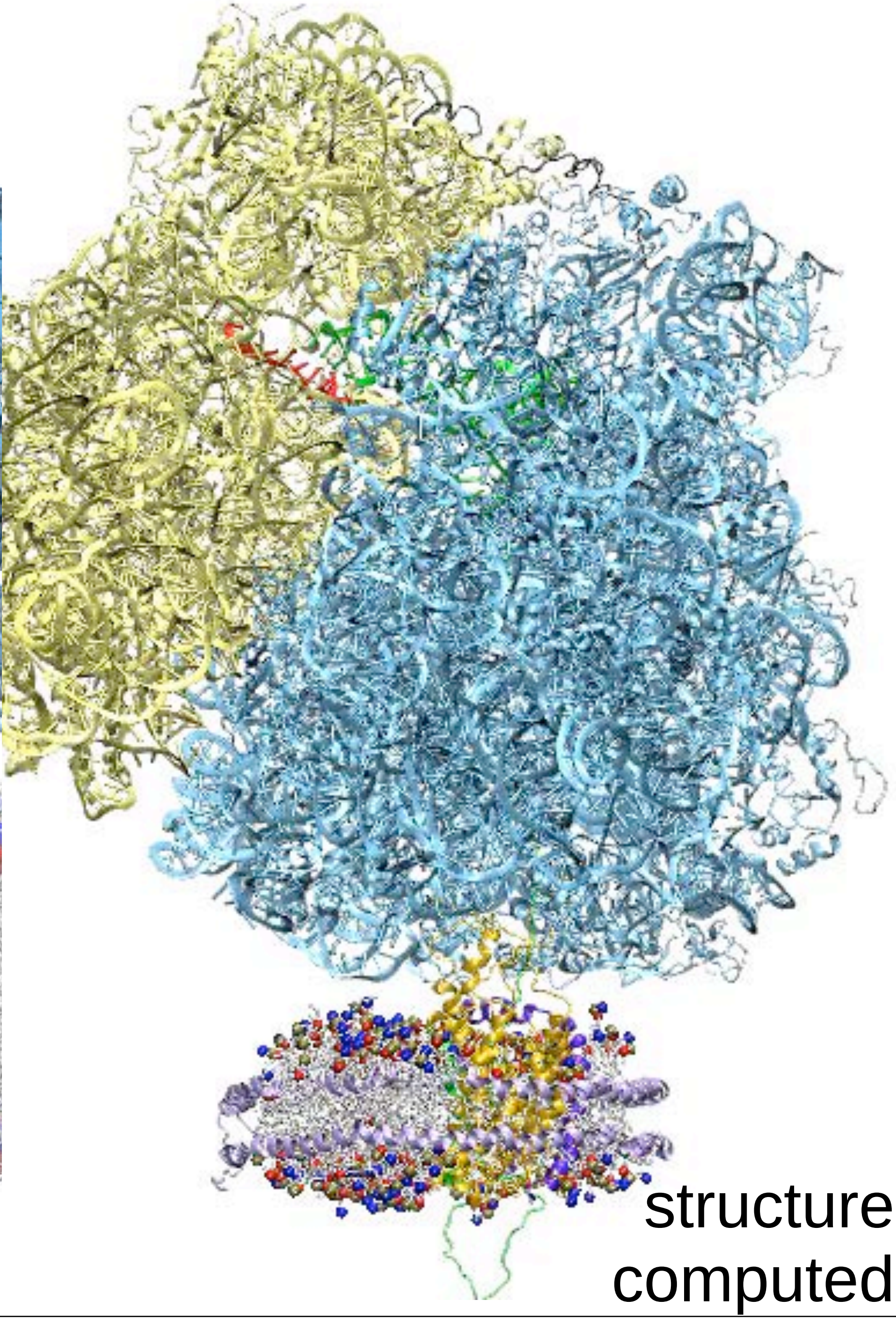
View of a ***Protein Being Born***



electron
microscope

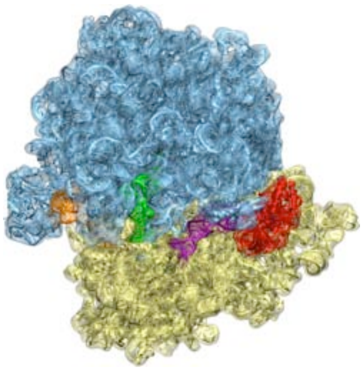
close view





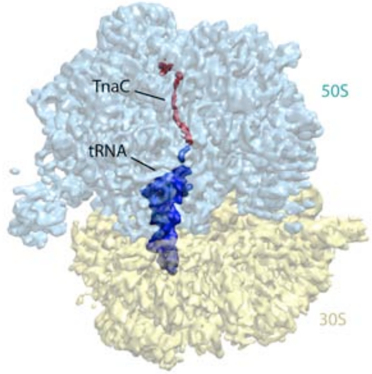
structure
computed

Current MDFF Applications



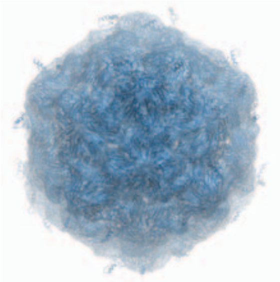
Genetic decoding [1]

J. Frank (Columbia U.)



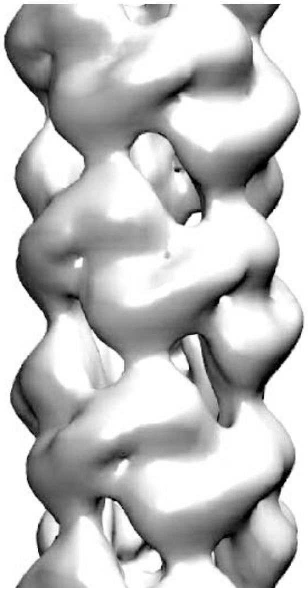
Regulatory nascent chain [7]

R. Beckmann (U. Munich)



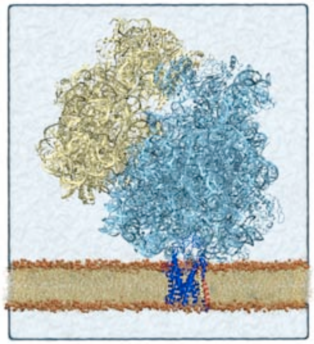
Poliovirus

J. Hogle (Harvard U.)



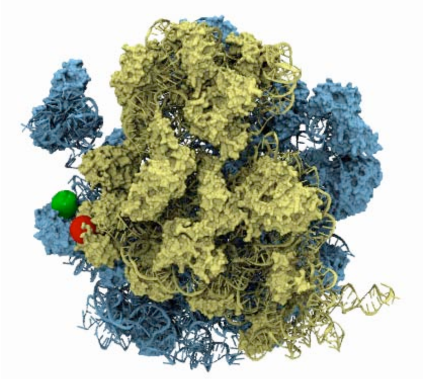
B. pumilus cyanide dihydratase

T. Sewell (U. Cape Town)



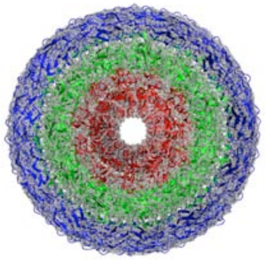
Protein translocation [6,8]

C. Akey (Boston U.)
R. Beckmann (U. Munich)



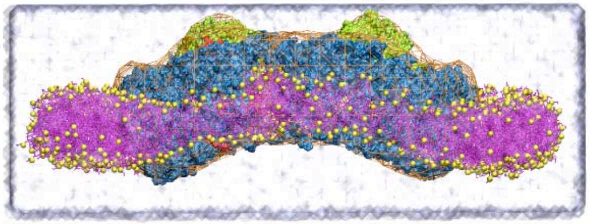
Ribosome ratcheting

J. Frank (Columbia U.)
T. Ha (UIUC)



Flagellar hook

K. Namba (Osaka U.)



Membrane curvature [3,5]

N. Hunter (Sheffield U.)

[1] Trabuco et al. *Structure* (2008) 16:673-683.

[2] Villa et al. *PNAS* (2009) 106:1063-1068.

[3] Sener et al. *Chem Phys* (2009) 357:188-197.

[4] Trabuco et al. *Methods* (2009) 49:174-180.

[5] Hsin et al. *Biophys J* (2009) 97:321-329.

[6] Gumbart et al. *Structure* (2009) 17:1453-.1465.

[7] Seidelt et al. *Science* (2009) 326: 1412-1415.

[8] Becker et al. *Science* (2009) 326: 1369-1373.

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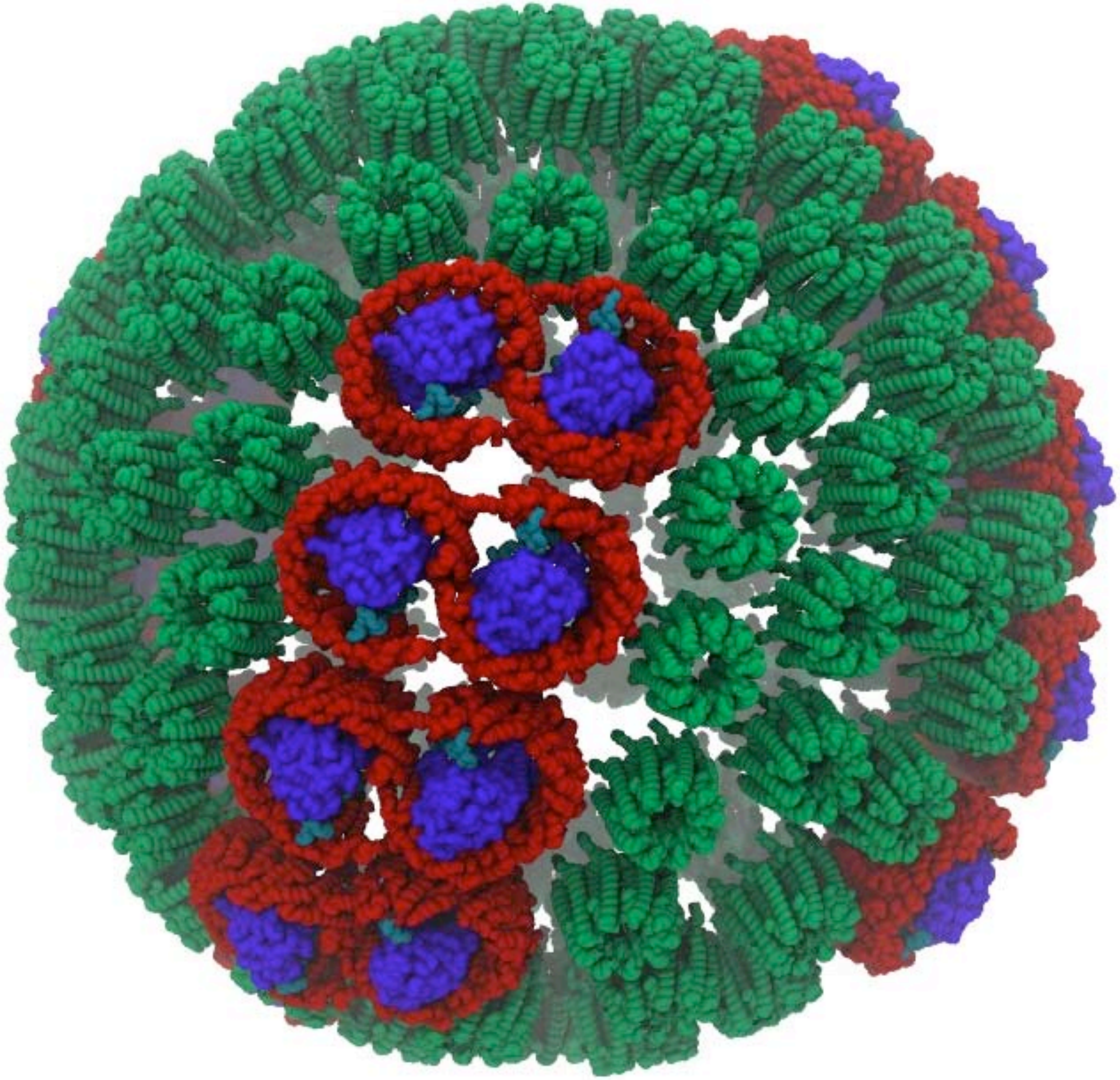
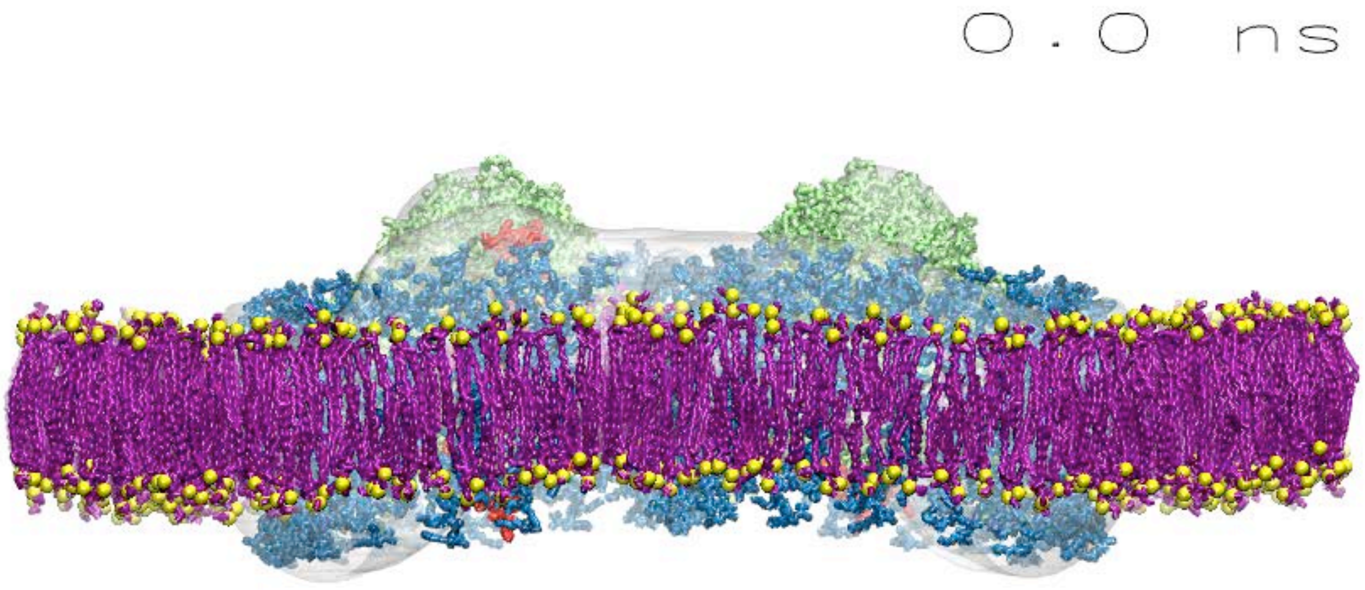
Computational microscope recognizes atomic resolution picture of photosynthetic apparatus

**100 - 1,000,000
processors**



Molecular Dynamics Flexible Fitting (MDFF) Simulation

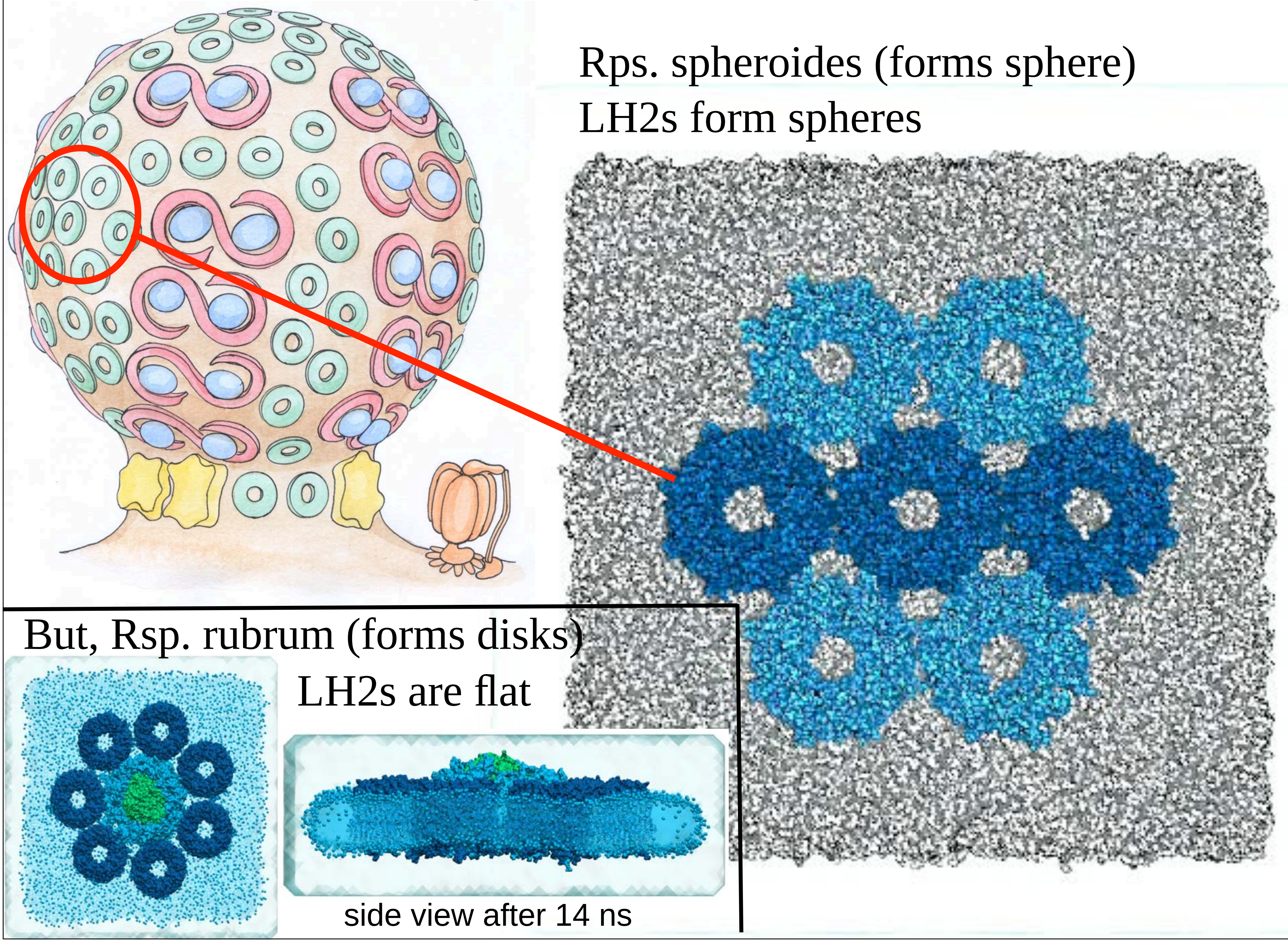
- In an MDFF simulation, RC-LH1-PufX dimer atoms are steered into high-density regions of the EM map
- 5 ns of MDFF, followed by a 29 ns of equilibration was performed



- The entire lipid patch became arched
- Curvature is anisotropic
- Lipid patch is “twisted”

Jen Hsin, James Gumbart, Leonardo G. Trabuco, Elizabeth Villa, Pu Qian, C. Neil Hunter, and Klaus Schulten. **Protein-induced membrane curvature investigated through molecular dynamics flexible fitting.***Biophysical Journal*, 97:321-329, 2009.

LH2 Packing Induces Curvature



Rps. spheroides (forms sphere)
LH2s form spheres

But, Rsp. rubrum (forms disks)
LH2s are flat

side view after 14 ns

Acknowledgements

NAMD leaders
L. Kale
J. Phillips
S. Kumar (IBM)

fibrinogen
E. Lee
B. Lim (Mayo)

lipoprotein
A. Shih
S. Sligar (UIUC)

10 μs folding
P. Freddolino
M. Gruebele (UIUC)

BAR domain
Y. Yin
A. Arkhipov

Chromatophore
J. Hsin
D. Chandler
JC. Gumbart
J. Strumpfer
M. Sener

ribosome
Elizabeth Villa
L. Trabucco
J. Gumbart
J. Frank (Columbia U.)
R. Beckman (Gene Center Munich)

Funding: NIH, NSF

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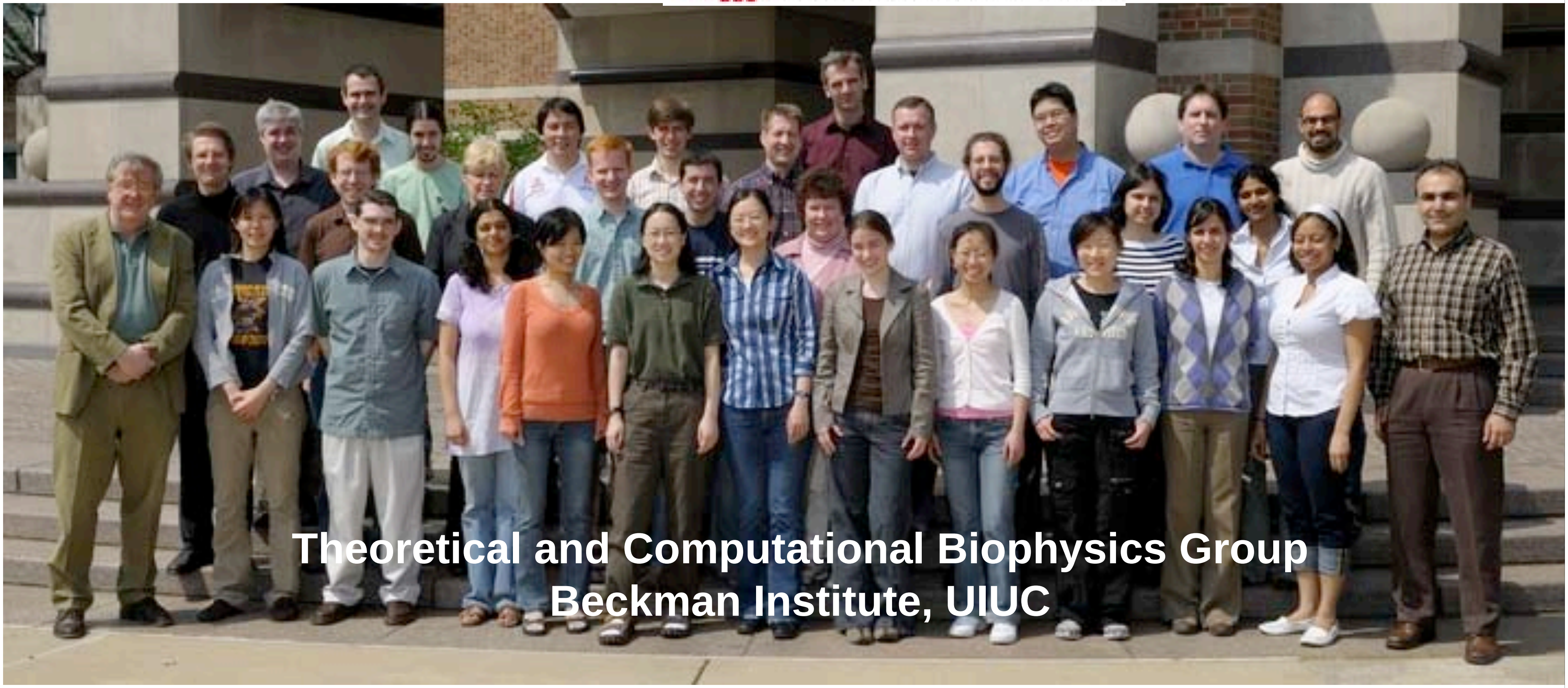
DOE - Incite



Theoretical and Computational Biophysics Group
Beckman Institute, UIUC