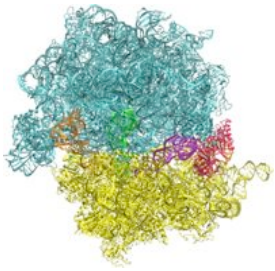
100 - 1,000,000 processors

Computational microscope views the cell

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

fibrinogen (**10^6 atoms**)



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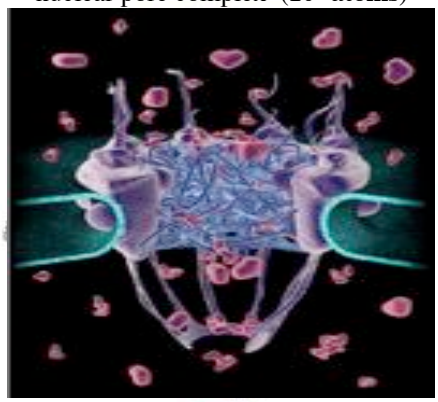
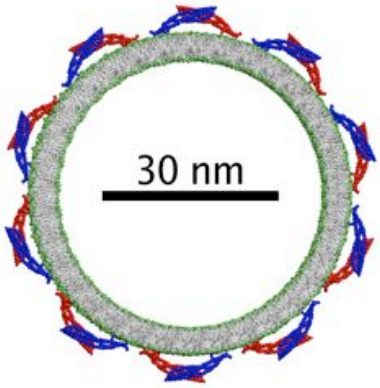
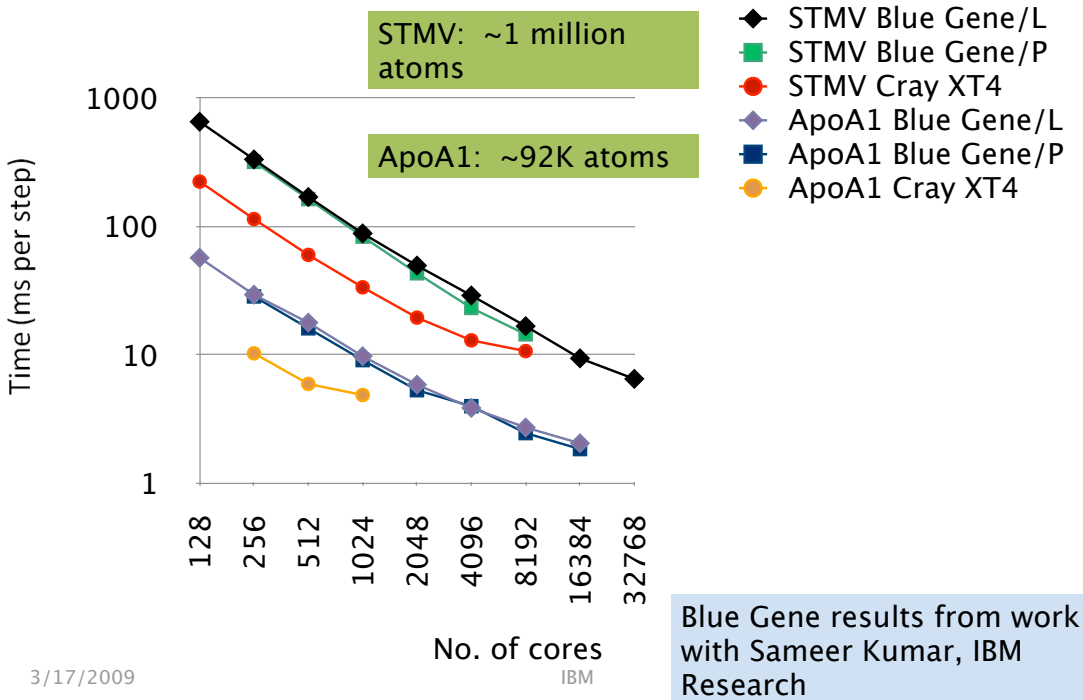




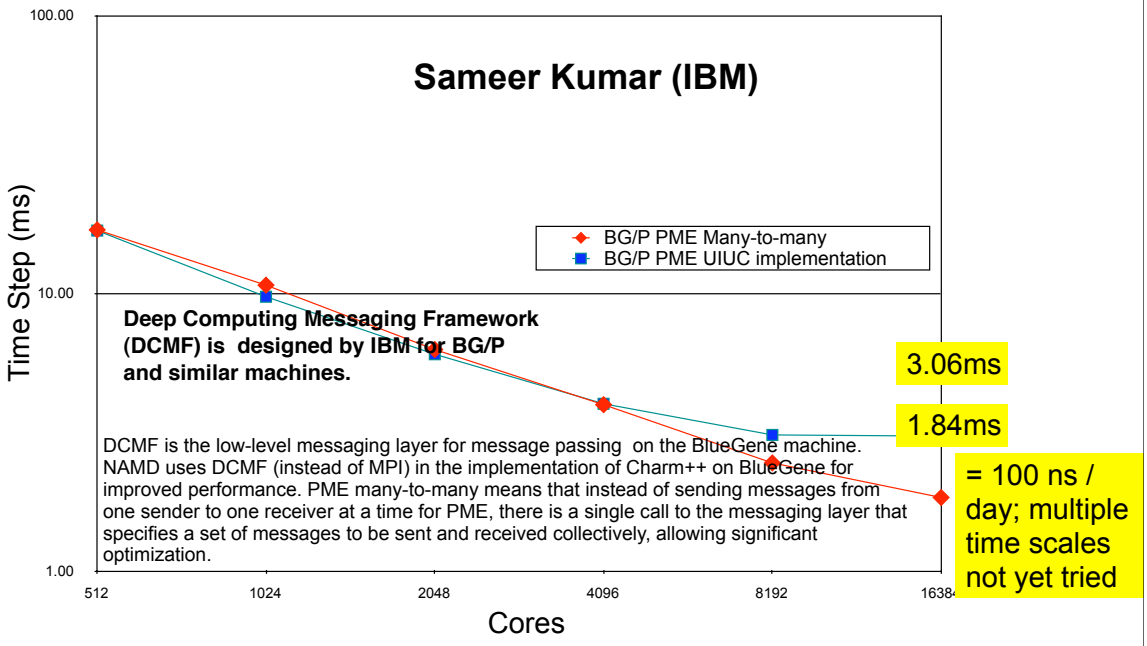
vesicle formed by BAR domains (**$5x10^7$ atoms**)

Blue Gene / Cray XT4 Performance of NAMD



Blue Gene results from work with Sameer Kumar, IBM Research

PME Optimized by DCMF Many-to-many



92K Atom APoA1 Benchmark with PME every step in Quad Mode (4 cores used)

PPL UIUC

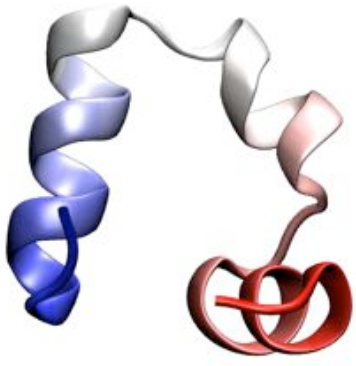
Viewing the 10 μs Folding of a Protein

- Solvated system is ~30,000 atoms
- Simulated in NAMD using CHARMM22/ CMAP
- ~100 ns/day on 329 processors
- Starting conformations either fully extended or thermally denatured
- Three independent WT simulations done
- Six mutant simulations
- Altogether over 50 μs of simulation
- Simulations of WW domain reveal deficit of force field

Protein dynamics in cells go out to a millisecond and longer. We recently increased computational time scales from 100 ns to 60 microseconds!

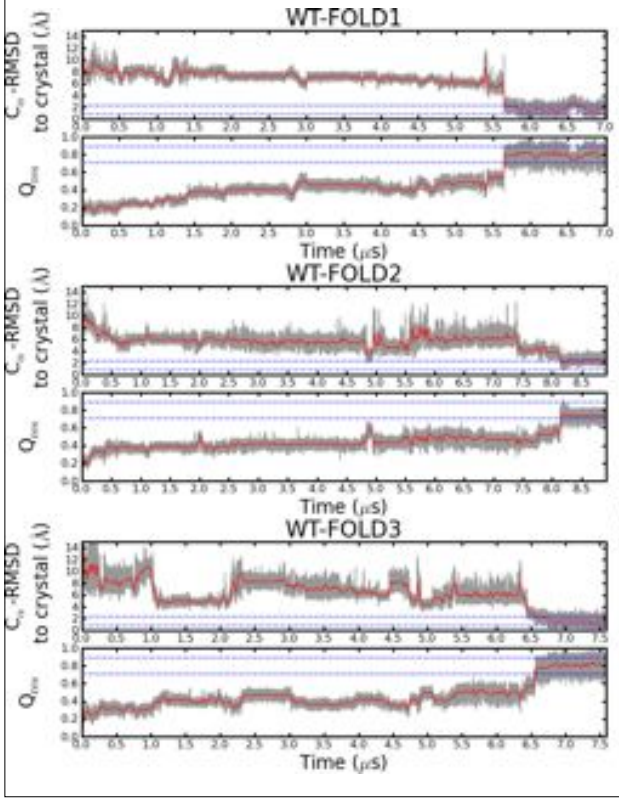
Over **50 microsecond** of protein folding

WT villin head piece; exp 4 μs, sim 6 μs

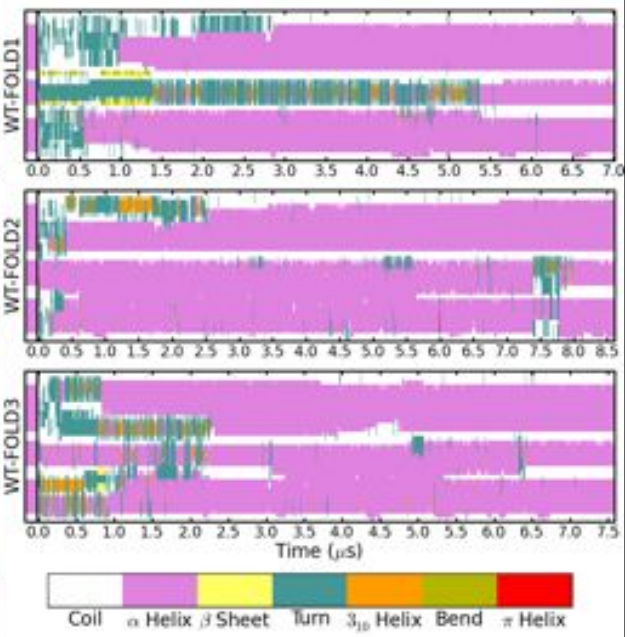


Folding WT villin *in silico*

Three folding simulations reach native state within 5-8 μs



Use VMD TimeLine tool!



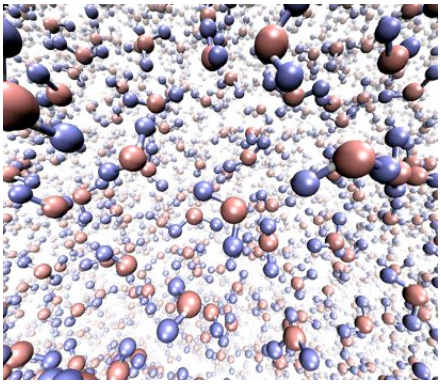
FAQ: Did you test if states reached remain stable? Yes, for 1 μs.

100 - 1,000,000 processors

Implementing Polarizable Force Fields into NAMD

Atomic polarizability not yet accounted for in modeling. Respective force fields are being developed; here the fluctuating charge model of Brooks et al.

Polarizable water; fluct. charge



Goal: Realize polarizable force fields in our modeling program effectively.

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Computational microscope views the cell

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

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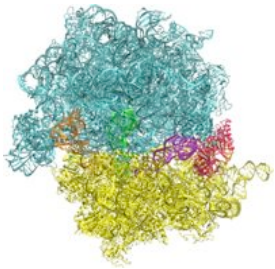

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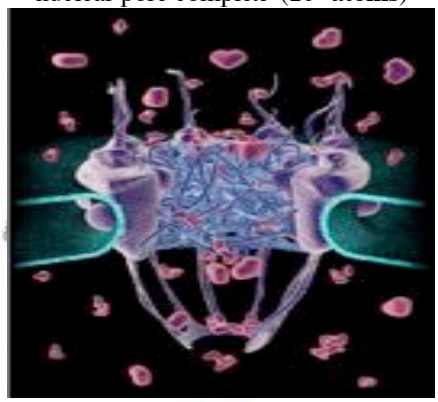

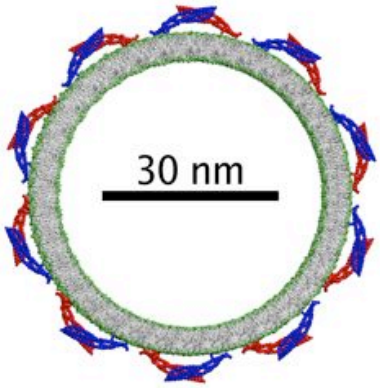

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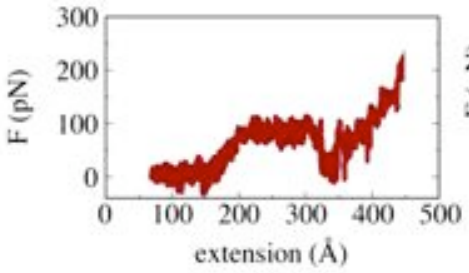
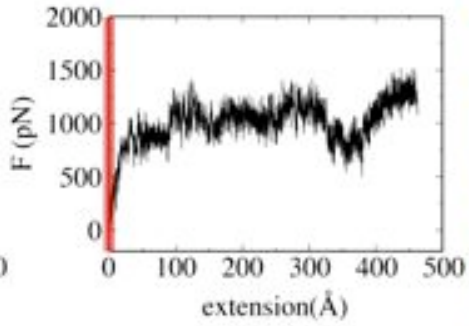
Inspecting the mechanical Strength of a blood clot

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





20ns SMD Simulation of fibrinogen, *1.06 million atoms, 1.2 ns/day with pencil decomposition, 15 days on PSC XT3 Cray (1024 processors)*

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

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

NIH Center for Research Resources

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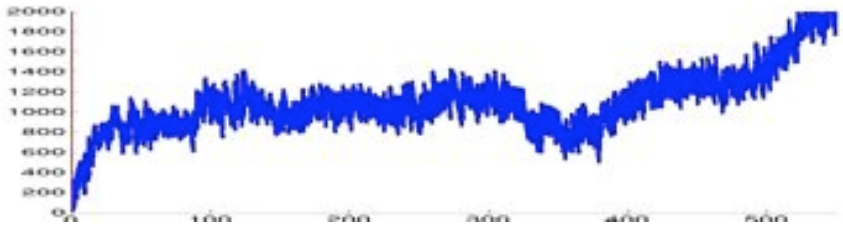

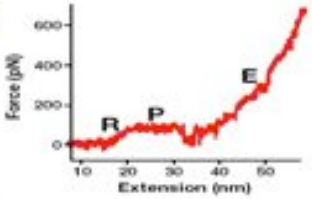

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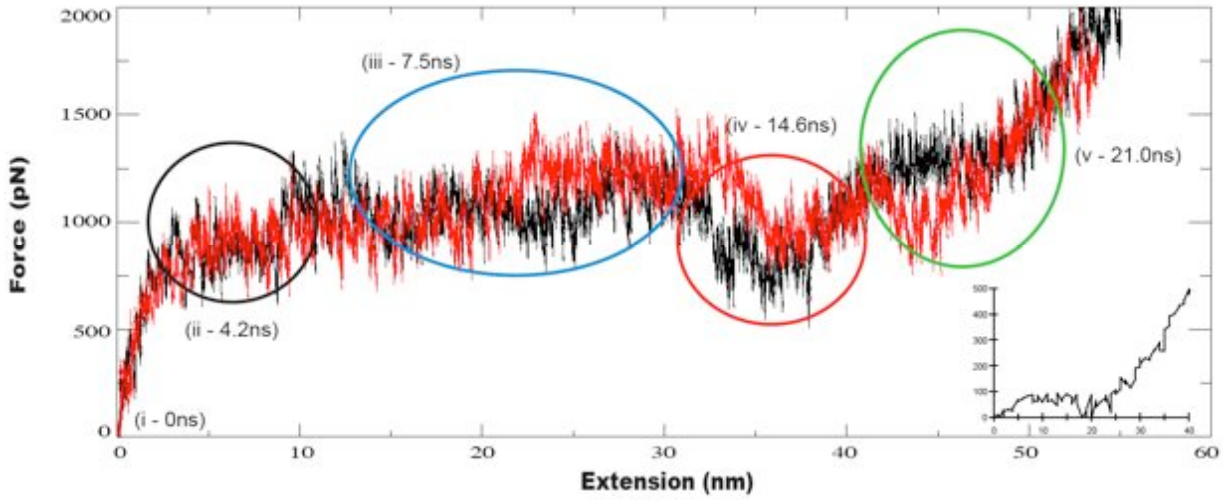
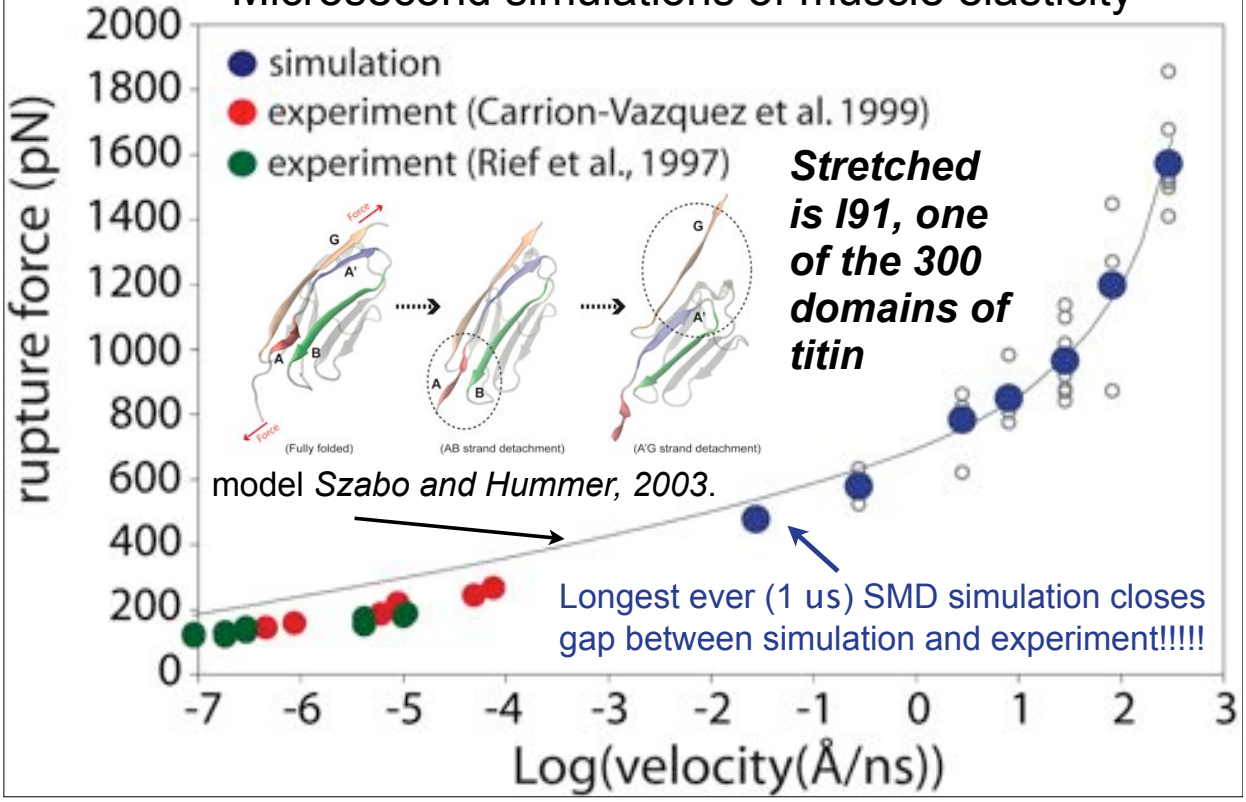
Petascale simulations will Permit Sampling

For Example Carrying out a Second Simulation Required by a Referee



Reaching for Overlapping Time Scales

Microsecond simulations of muscle elasticity



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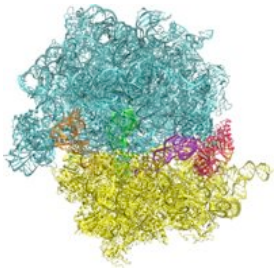

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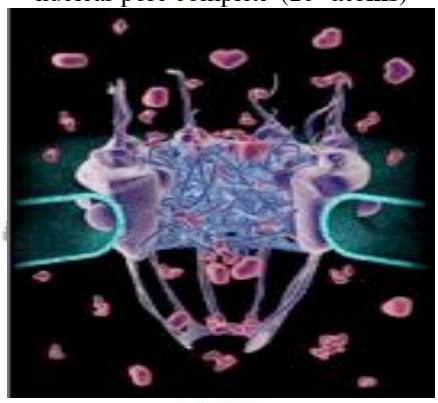

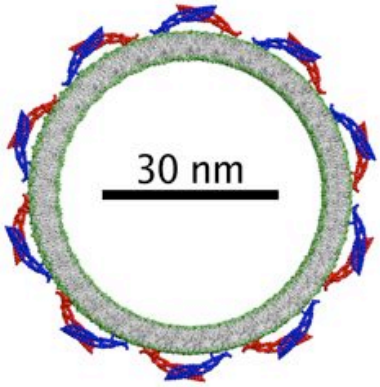

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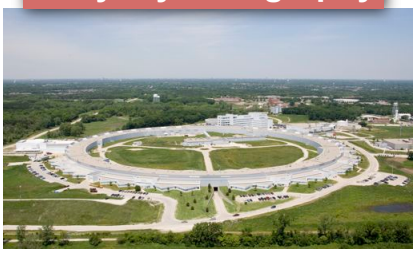
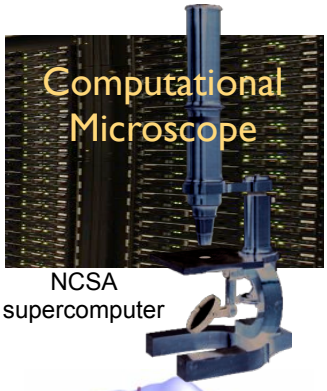
Petascale Simulations Support Hybrid Microscopy

Advance through combination of ***X-ray*** *and* ***EM***

X-ray crystallography



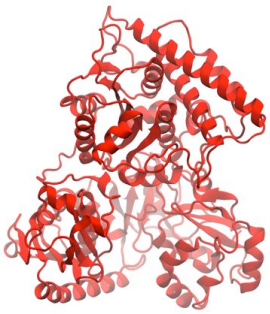
APS at Argonne

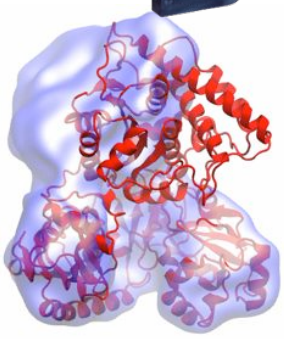


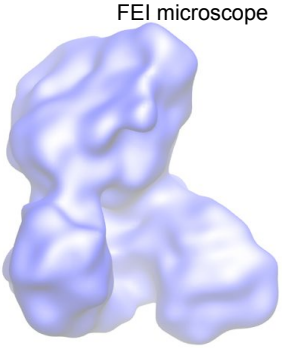
NCSA supercomputer

Electron microscopy

FEI microscope







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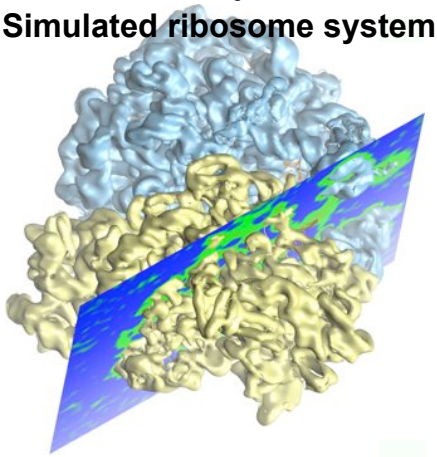
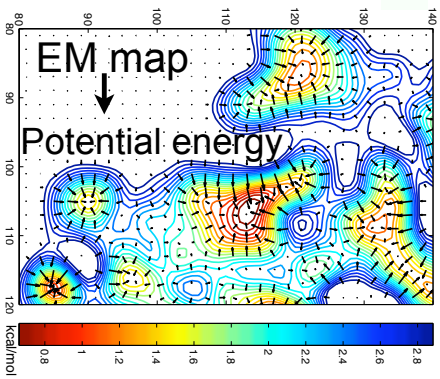
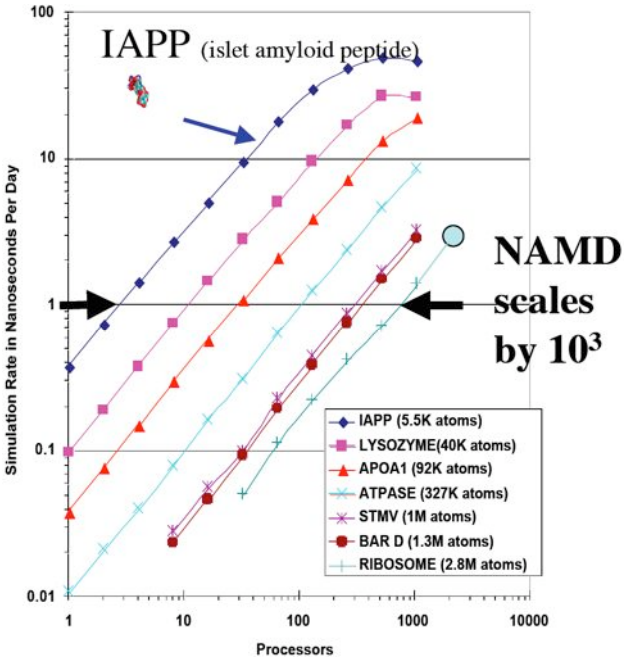
Molecular Dynamics Flexible Fitting with NAMD

Simulated ribosome system





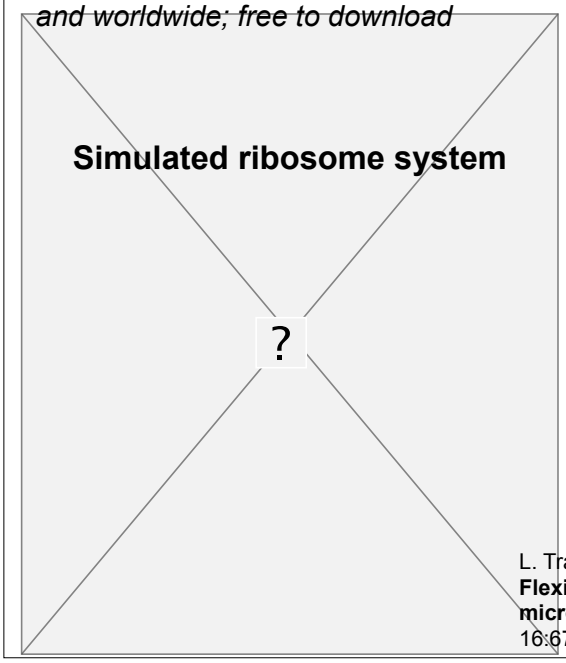
Performance on NCSA Abe



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.

Molecular Dynamics Flexible Fitting with NAMD

NAMD is a molecular dynamics program running efficiently on single processors up to thousands of processors; achieves 100 ns / day speed on 1K - 1 million K systems; available at all NSF-DOE centers in the US and worldwide; free to download



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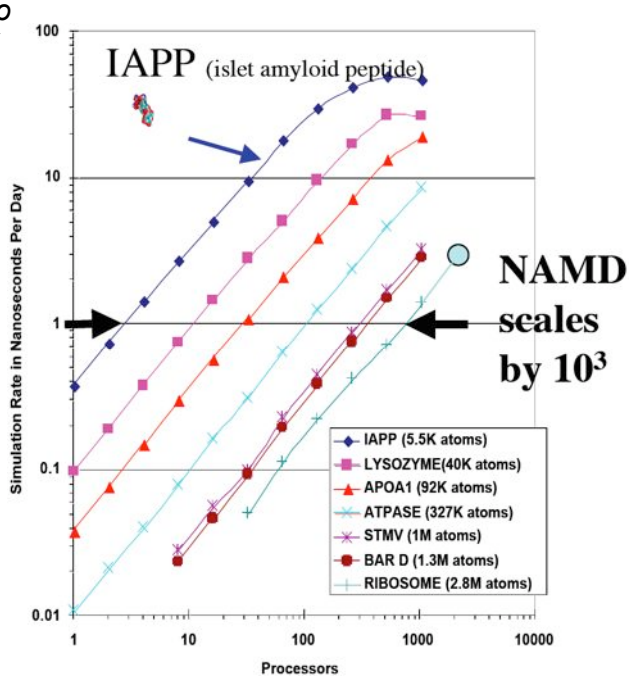

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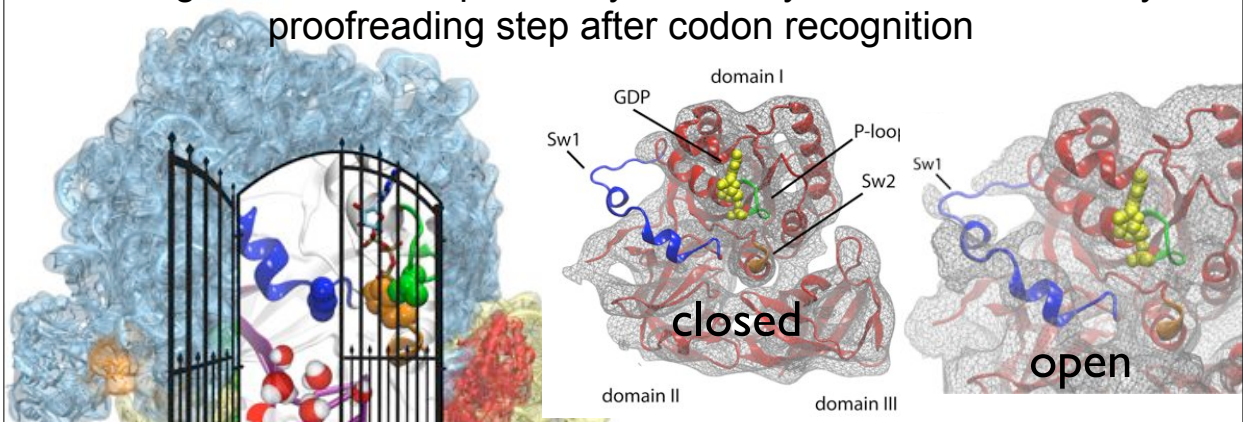
Discovery Through the Computational Microscope

Gating mechanism of protein synthesis by the ribosome as key proofreading step after codon recognition



J. Frank (Columbia U.)

Villa et al. PNAS (2009)
with PNAS commentary from ribosome expert M. Rodnina

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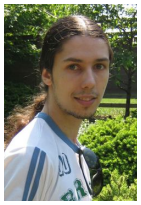
Trabuco

UIUC grad students

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UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Successes of Computational Microscope Prototype

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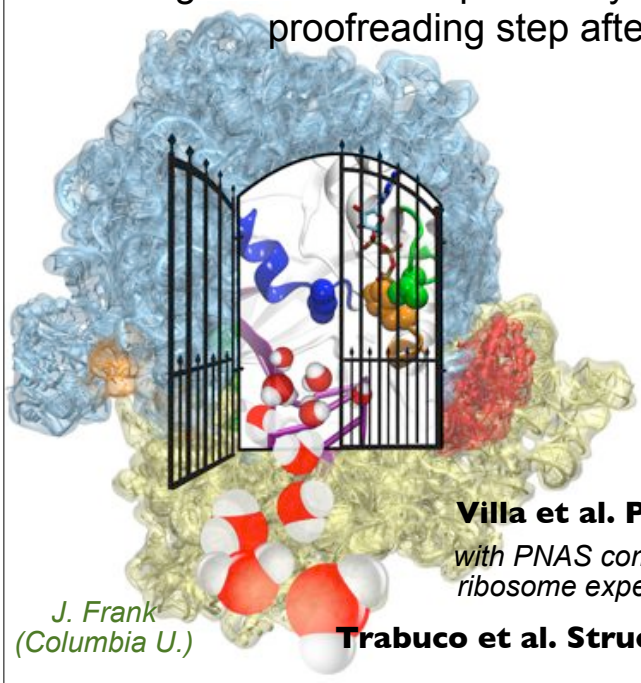

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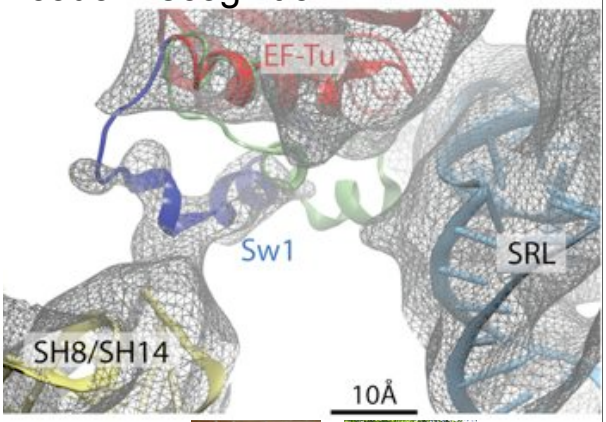

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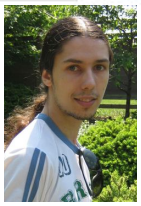

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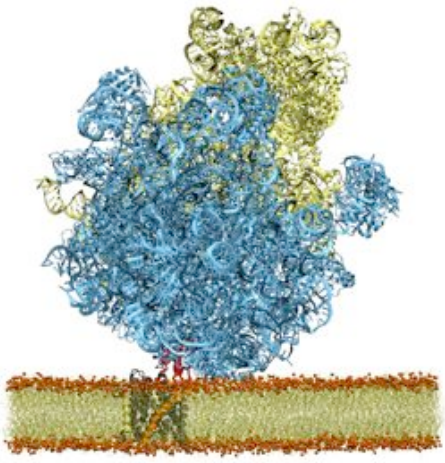
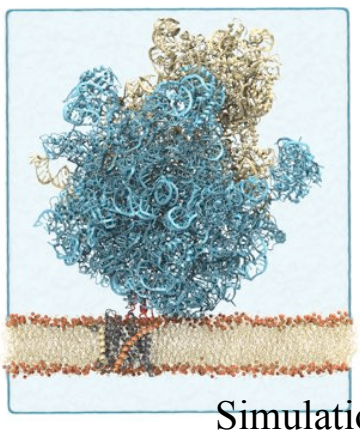
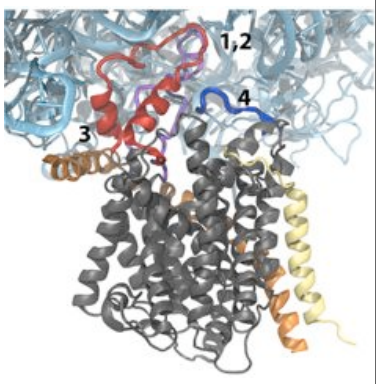
Modeling a ribosome-channel complex



Simulation system
2.7 million atoms
simulated in total for nearly 50 ns

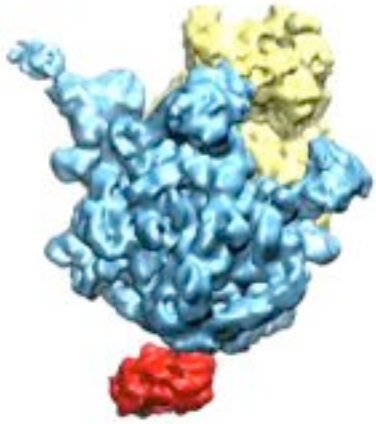
- Ribosome-SecY channel complex: known only from low-resolution density maps (grey outline)
- Used MD Flexible Fitting to fit atomic structures to map





Simulations reveal atomic-scale interactions that maintain complex

Modeling a ribosome-channel complex



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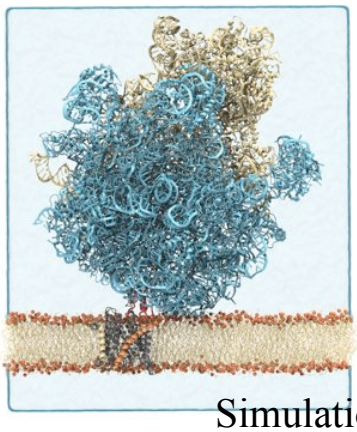

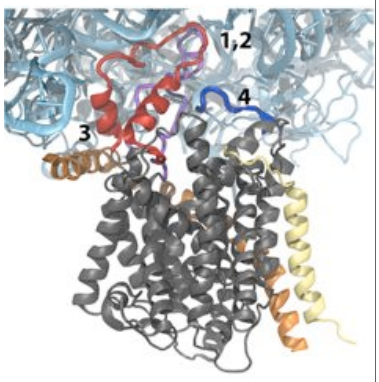

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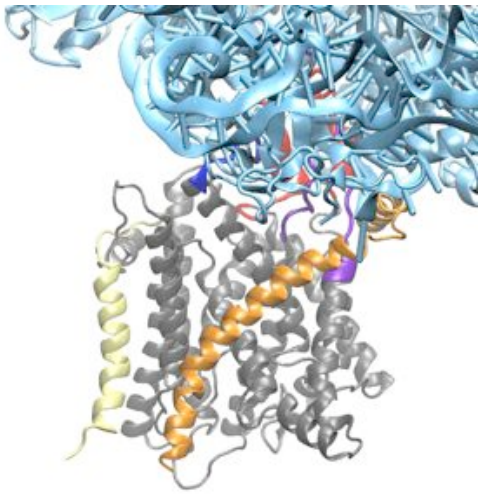

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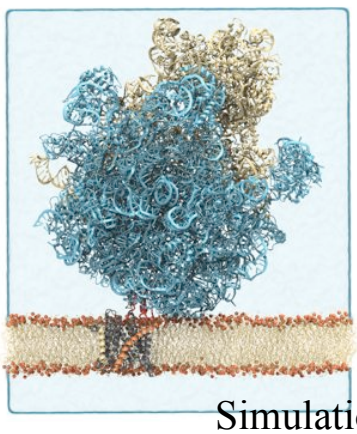
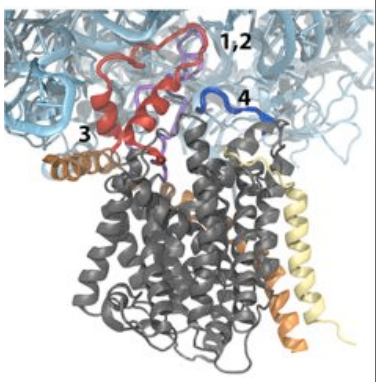
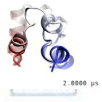




Simulations reveal atomic-scale interactions that maintain complex

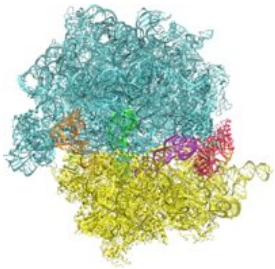
100 - 1,000,000 processors

Computational microscope views the cell



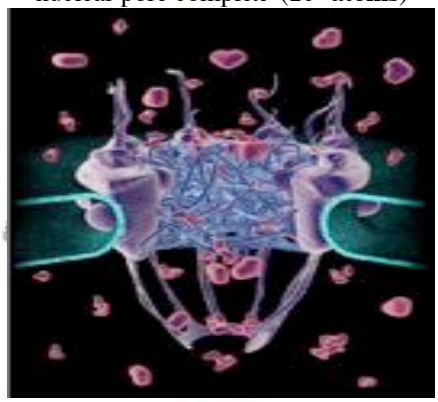
protein folding (**10^4 atoms**)

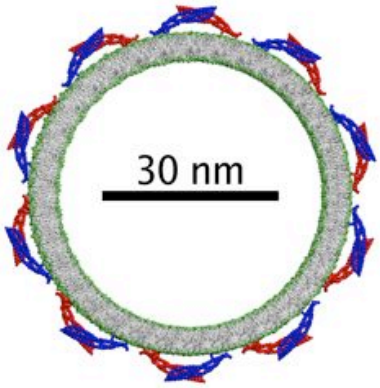
fibrinogen (**10^6 atoms**)



bacterial flagellum (**10^9 atoms**)

nuclear pore complex (**10^8 atoms**)

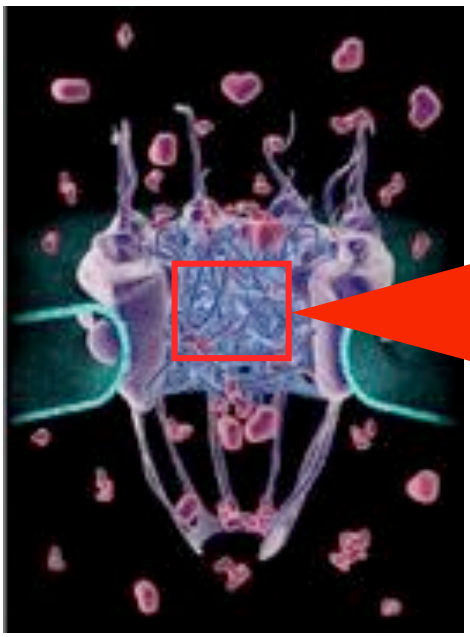




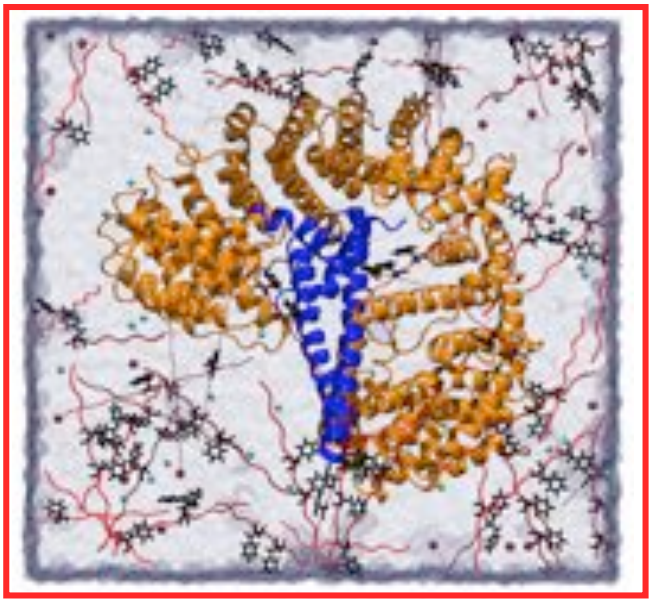
vesicle formed by BAR domains (**$5x10^7$ atoms**)

The Nuclear Pore Complex - What Is It?

NPC



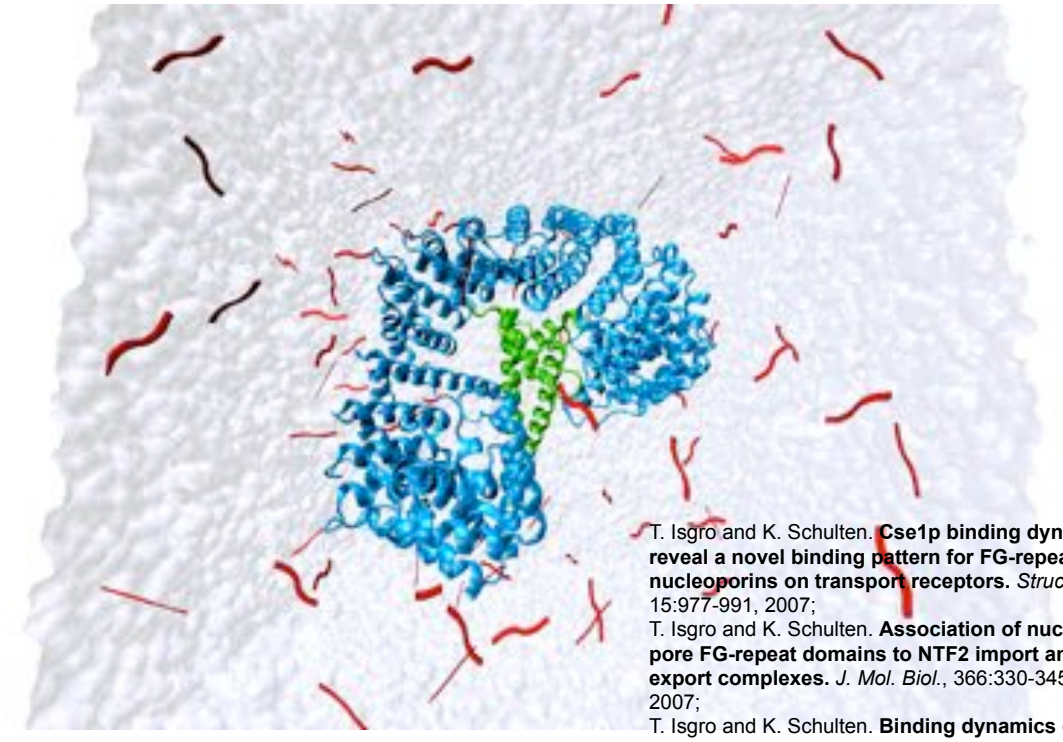
Section to be studied by molecular dynamics



Importin- β; SREBP-2 cargo

transcription factor

Sampling of FG-nup Binding

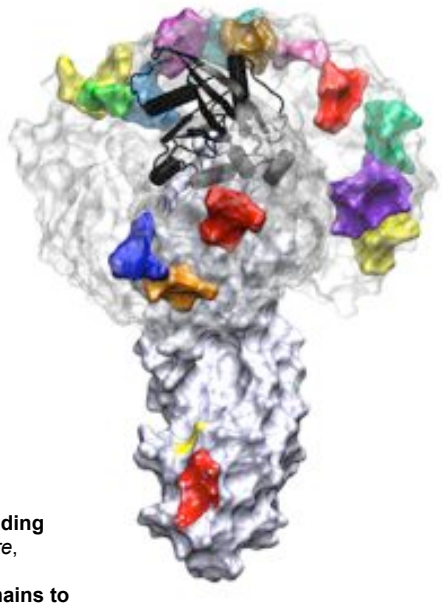


T. Isgro and K. Schulten. **Cse1p binding dynamics reveal a novel binding pattern for FG-repeat nucleoporins on transport receptors.** *Structure*, 15:977-991, 2007;
T. Isgro and K. Schulten. **Association of nuclear pore FG-repeat domains to NTF2 import and export complexes.** *J. Mol. Biol.*, 366:330-345, 2007;
T. Isgro and K. Schulten. **Binding dynamics of isolated nucleoporin repeat regions to importin-β.** *Structure*, 13:1869-1879, 2005.

FG-nup Binding Pattern

How does the NPC distinguish between transport receptors and inert macromolecules?

- Any macromolecule may have random FG-nup binding spots
- Transport receptors exhibit a *particular* surface binding spot *pattern*
  - *Binding spots tend to be clustered with a ~14 Å spacing between spots*



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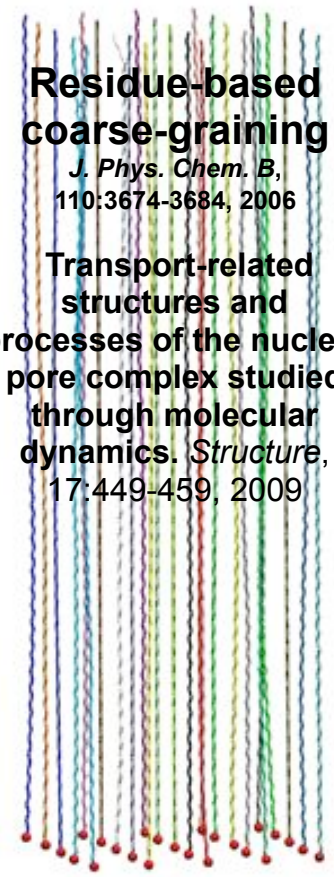
Theoretical and Computational Biophysics Group

ILLINOIS

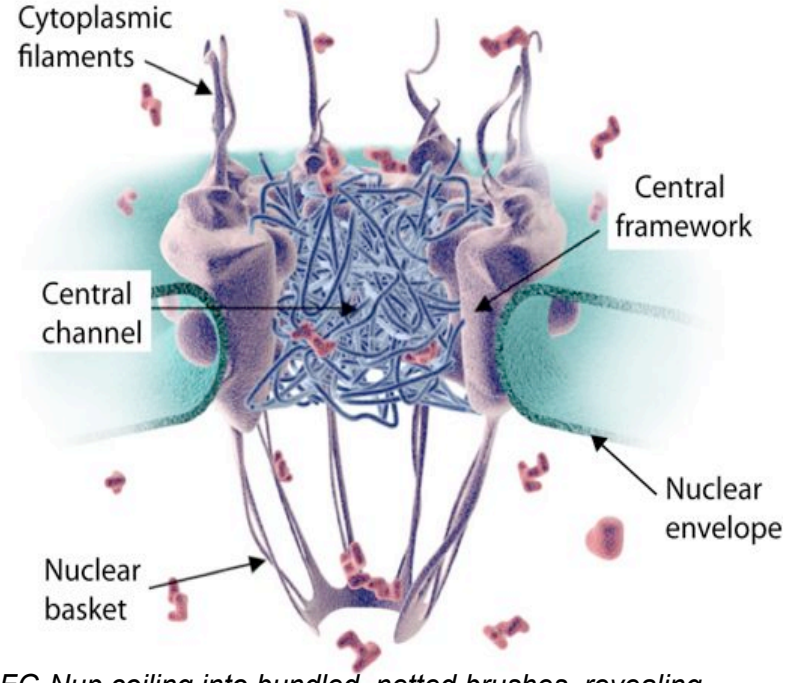


Residue-based coarse-graining

***J. Phys. Chem. B*, 110:3674-3684, 2006**

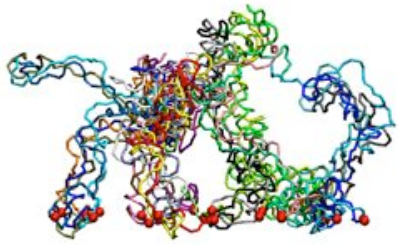
Transport-related structures and processes of the nuclear pore complex studied through molecular dynamics. *Structure*, 17:449-459, 2009

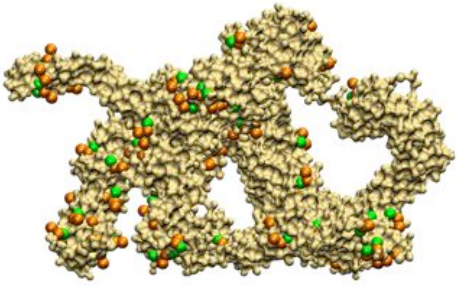
Simulating an Array of Nsp1 Segments Tethered to a Planar Lattice at NPC Density Coarse-Grained



FG-Nup coiling into bundled, netted brushes, revealing the structure of the gel-like gate.

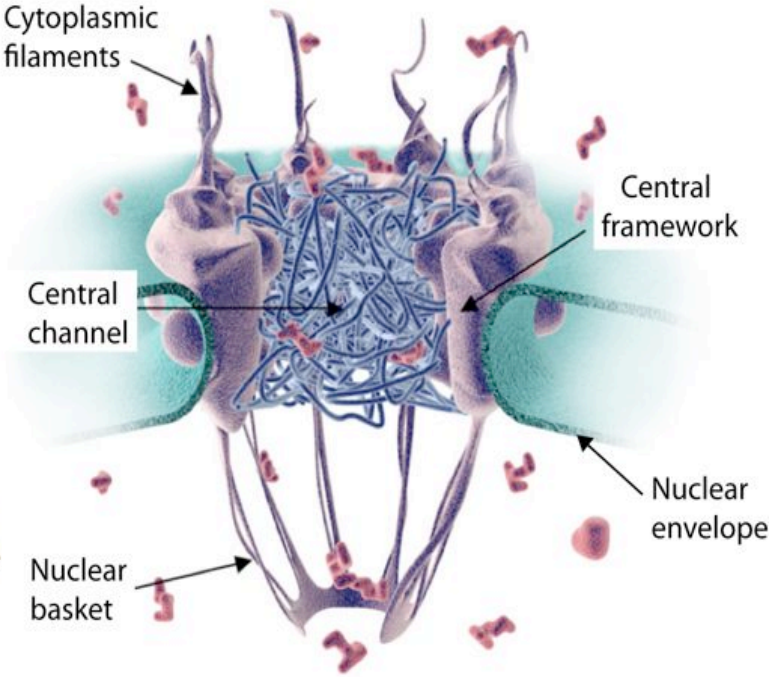
FG-Nup coiling into bundled, netted brushes, revealing the structure of the gel-like gate.





Using the Prior Coarse-Grained Simulation, Reverse Coarse Graining Permits One to Explore at Atomic Level Structure and Dynamics

The Computational Microscope Reveals the NPC Selective Barrier Structure?



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L. Miao and K. Schulten, **Transport-related structures and processes of the nuclear pore complex studied through molecular dynamics.** *Structure*, 17:449-459, 2009

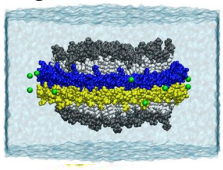
100 - 1,000,000 processors

Computational microscope views the cell

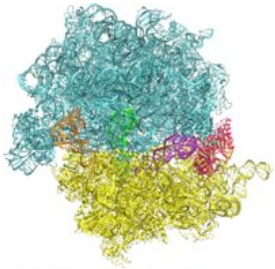
photosynthetic chromatophore (**10^8 atoms**)

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

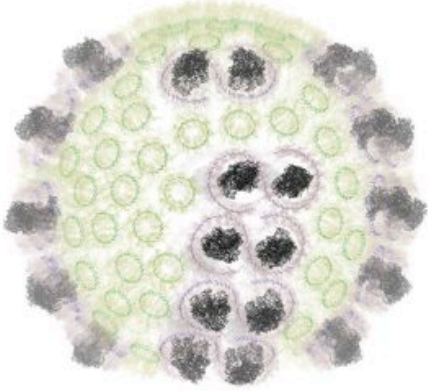
fibrinogen (**10^6 atoms**)

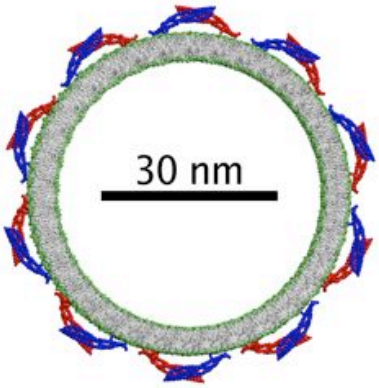


lipoprotein (**10^5 atoms**)

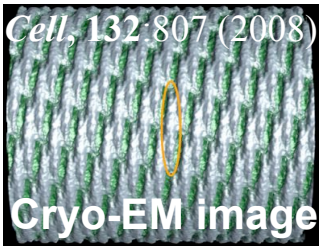


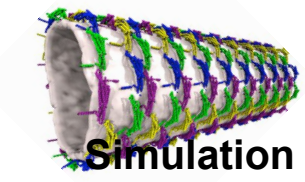
ribosome (**10^6 atoms**)





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

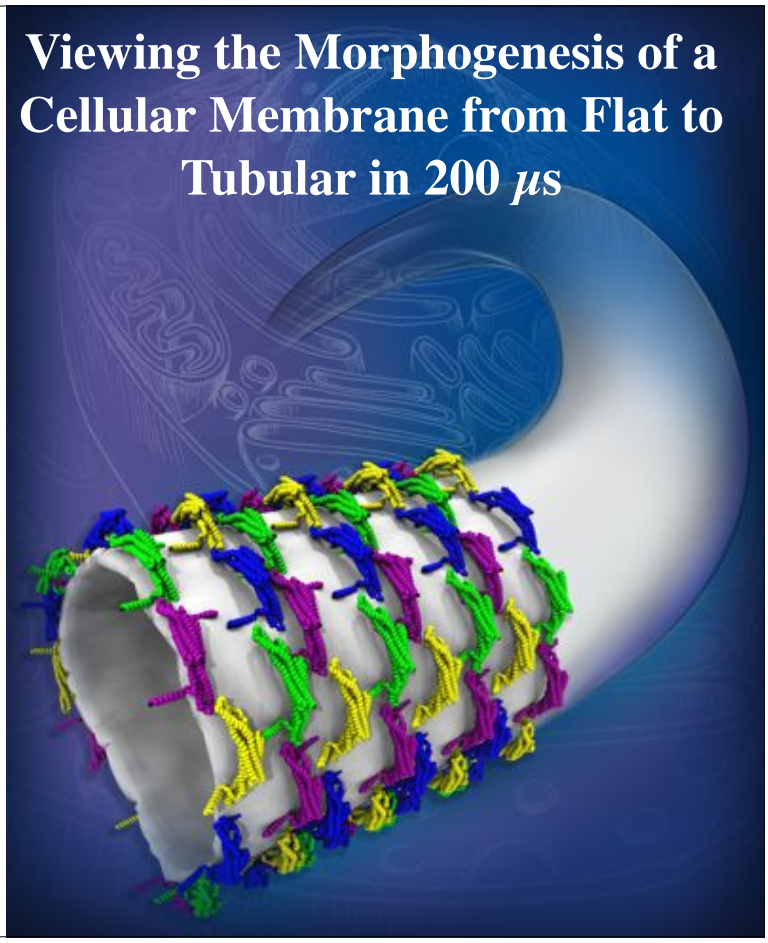




A. Arkhipov, Y. Yin, and K. Schulten. **Four-scale description of membrane sculpting by BAR domains.** *Biophysical J.*, 95: 2806-2821 2008.

Ying Yin, Anton Arkhipov, and Klaus Schulten. **Simulations of membrane tubulation by lattices of amphiphysin N-BAR domains.** *Structure* ***17,*** *882-892,* 2009.

Viewing the Morphogenesis of a Cellular Membrane from Flat to Tubular in 200 μs



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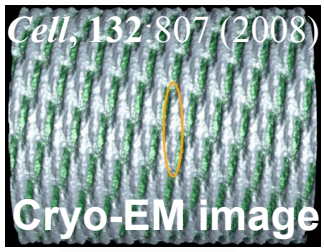

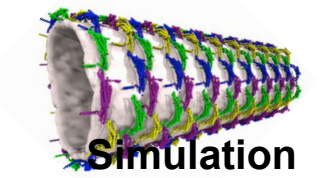

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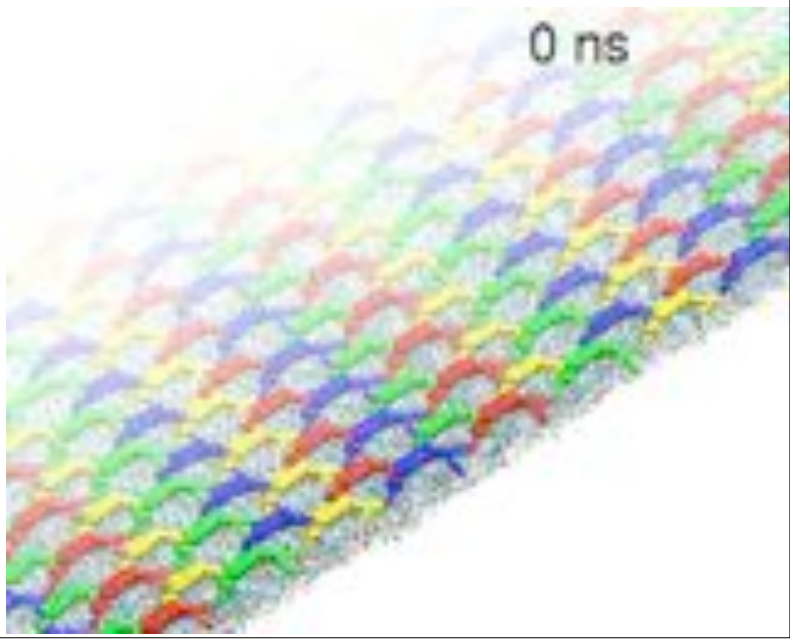
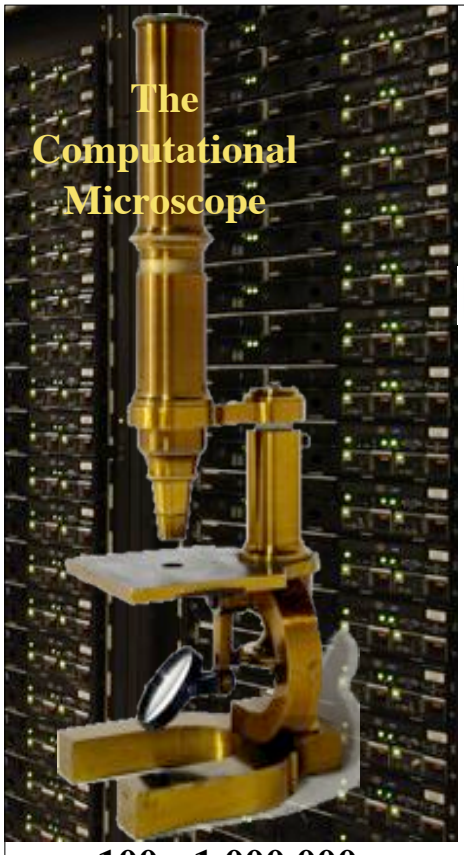
2.3 million atom simulation, .3 microseconds





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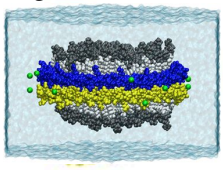

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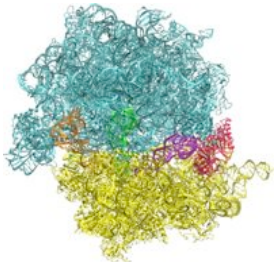
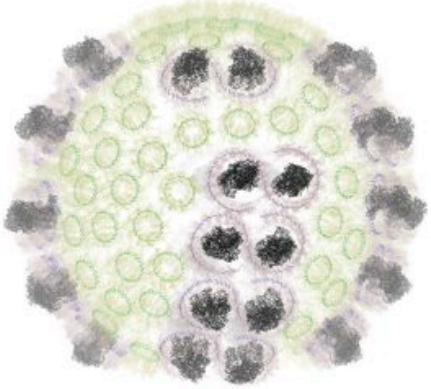
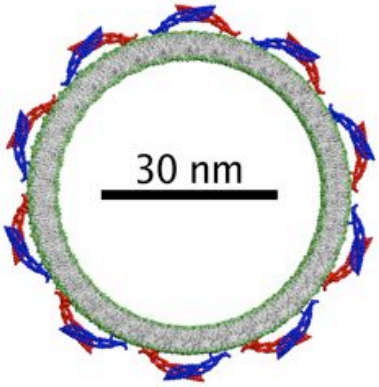


ribosome (**10^6 atoms**)

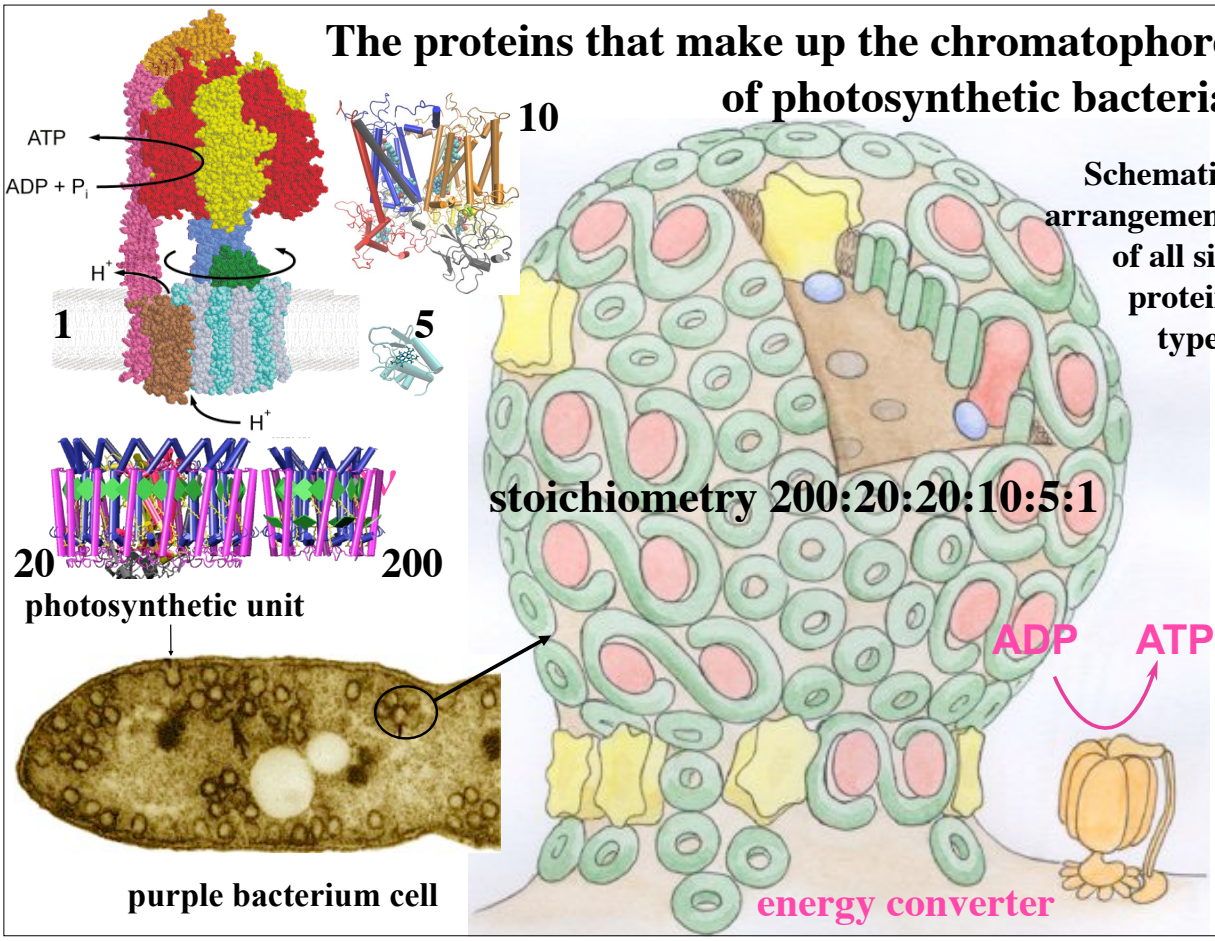
photosynthetic chromatophore (**10^8 atoms**)





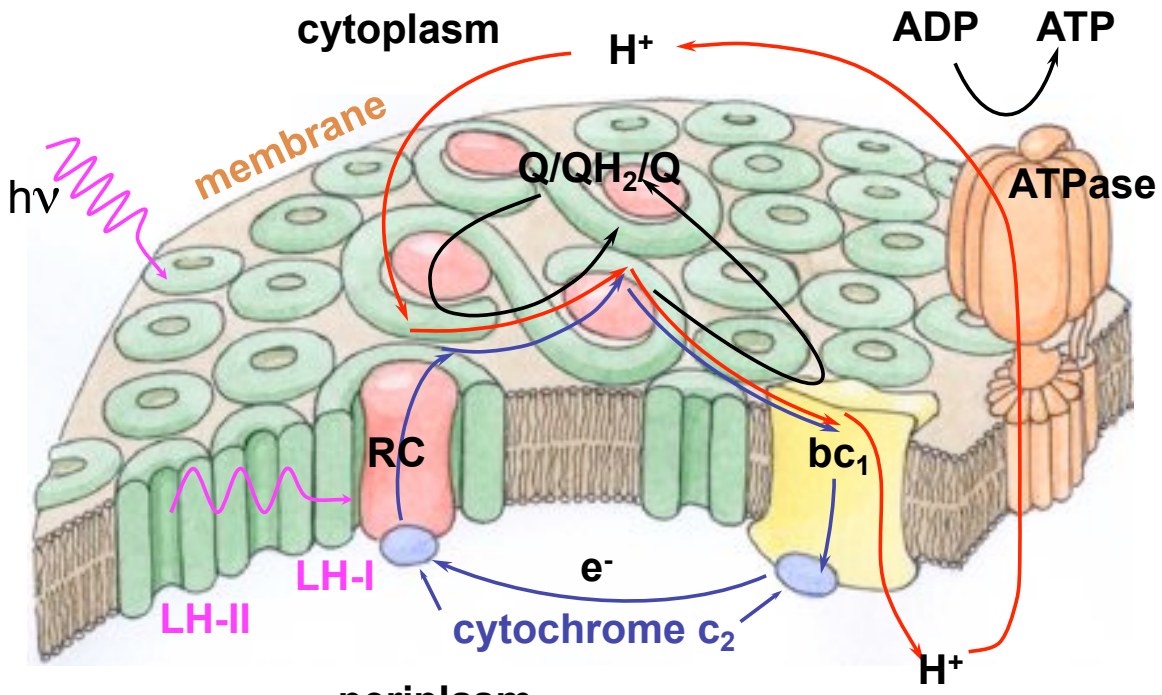
vesicle formed by BAR domains (**$5x10^7$ atoms**)

The proteins that make up the chromatophore of photosynthetic bacteria



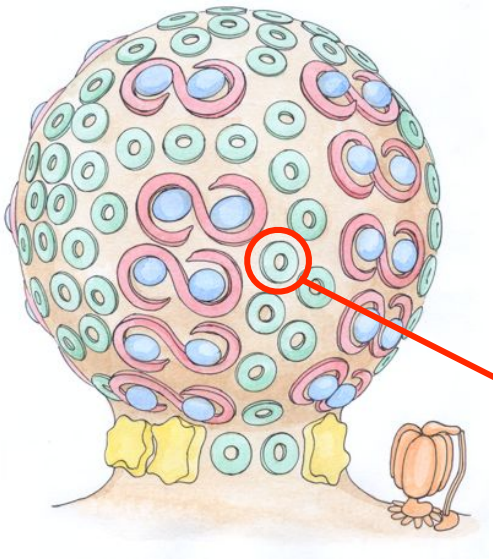
Chromatophore of Purple Bacteria

(section of the chromatophore membrane)



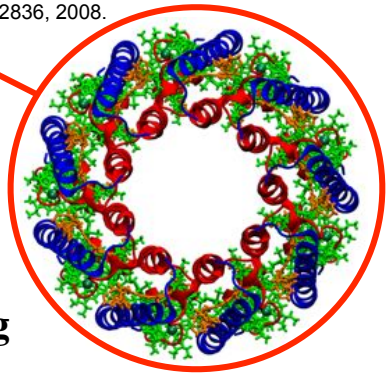
Xiche Hu, Thorsten Ritz, Ana Damjanovic, Felix Autenrieth, and Klaus Schulten. Photosynthetic apparatus of purple bacteria. *Quarterly Reviews of Biophysics*, 35:1-62, 2002.

Component 1: Light Harvesting Complex 2 (LH2)



- **LH2 absorbs light via its bacteriochlorophylls (below in Green)**
- **This energy is transferred to the LH1 where the reaction center utilizes it to pump electrons across the membrane**
- **LH2 complexes form the bulk of chromatophore membranes and are integral to both its structure and function**

Danielle Chandler, Jen Hsin, Christopher B. Harrison, James Gumbart, and Klaus Schulten. **Intrinsic curvature properties of photosynthetic proteins in chromatophores.** *Biophysical Journal*, 95:2822-2836, 2008.



Structure of LH2 established by crystallography & homology modeling

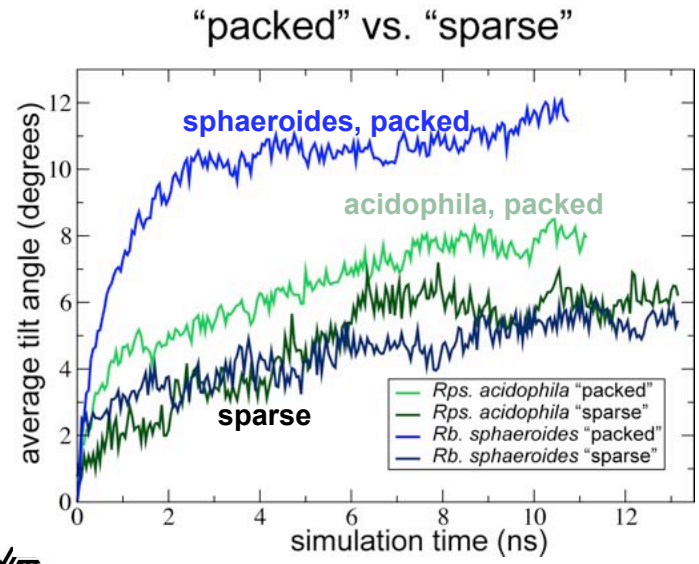
LH2

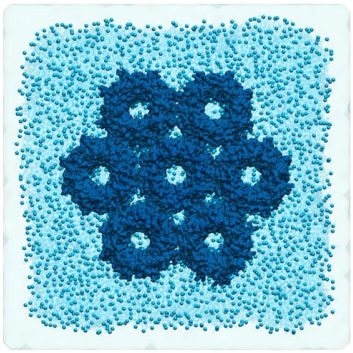
LH2 aggregates induce curvature via packing

7 hexagonally-packed LH2s

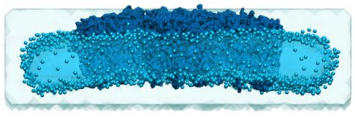
"packed" → no lipids between LH2s

"sparse" → one layer of lipids between LH2s

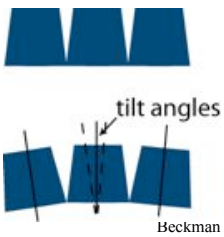




top view

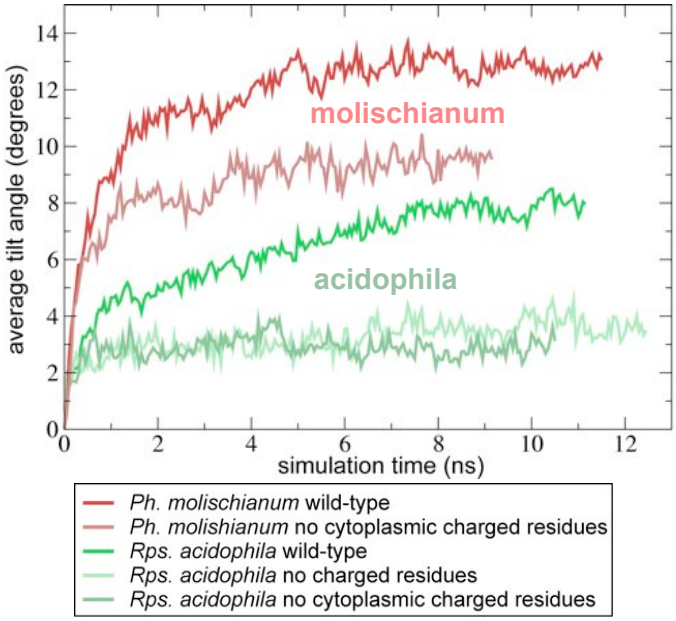


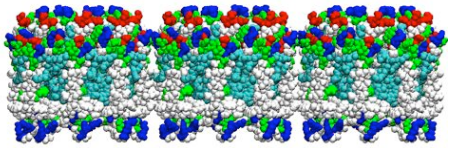
side view after 12 ns



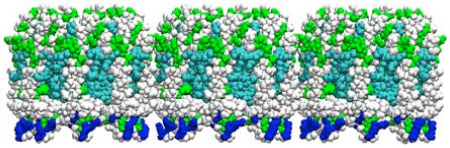
LH2 curvature partially driven by electrostatics

curvature is reduced by removal of conserved cytoplasmic charged residues





Ph. molischianum wild-type

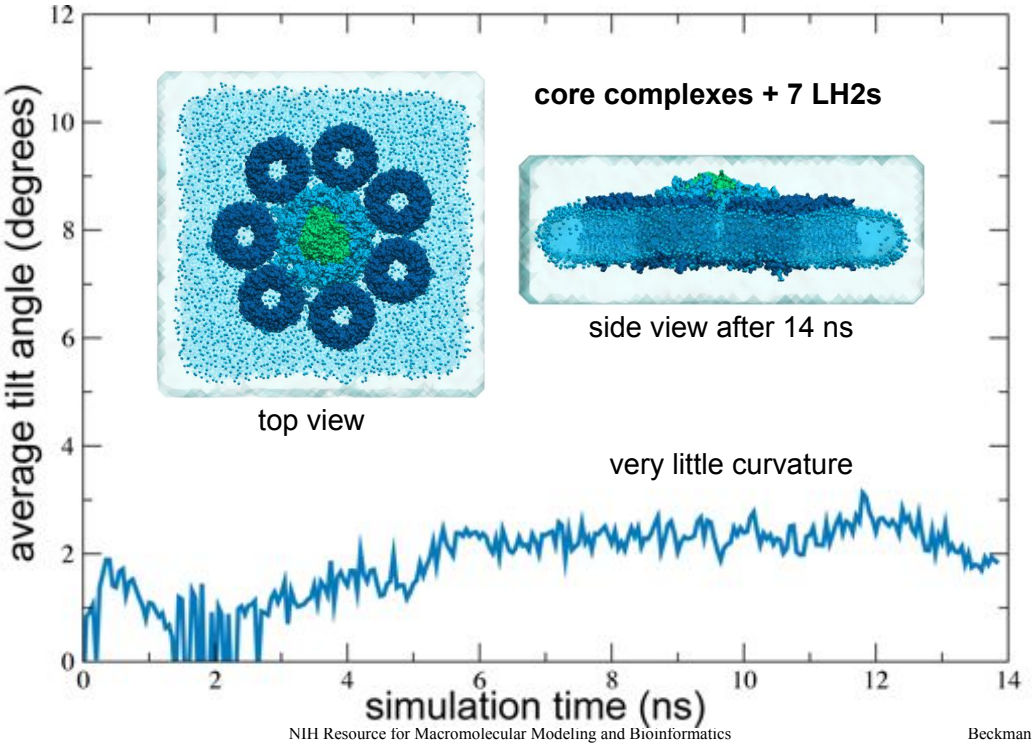


Ph. molischianum modified

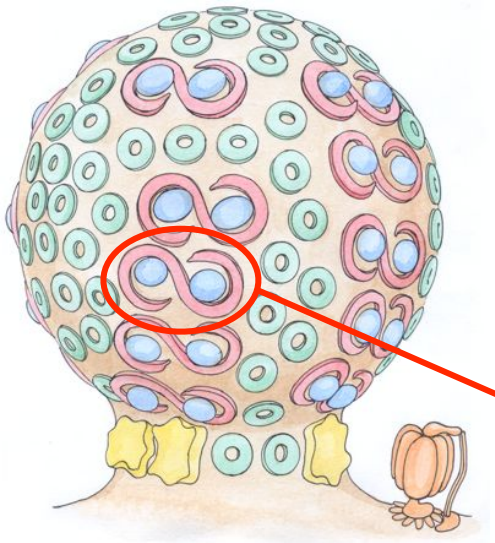
Much reduced curvature in LH1-LH2 mixed system

LH1 monomer surrounded by seven LH2 complexes

(LH1 and LH2 from *Rps. acidophila*, RC from *Rb. sphaeroides*)



Component 2: Light Harvesting Complex 1 (LH1)

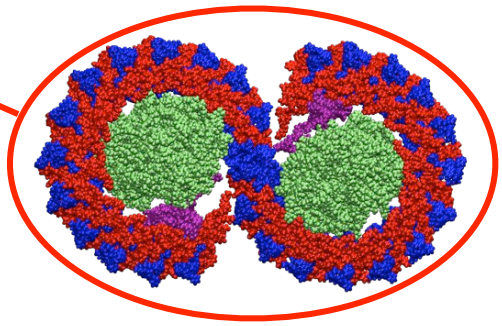


- **LH1s form stacks in spherical chromatophores**

- **LH1 is dimeric multi-protein complex of**
- **•Light Harvesting Complex 1 (LH1)(Blue & Red)**
- **•Reaction Center (RC) (Green)**
- **•Puf X (Purple)**

- **LH1 absorbs light energy, transfers it to RC which uses it to pump electrons across the membrane.**

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*, 2009. In press.

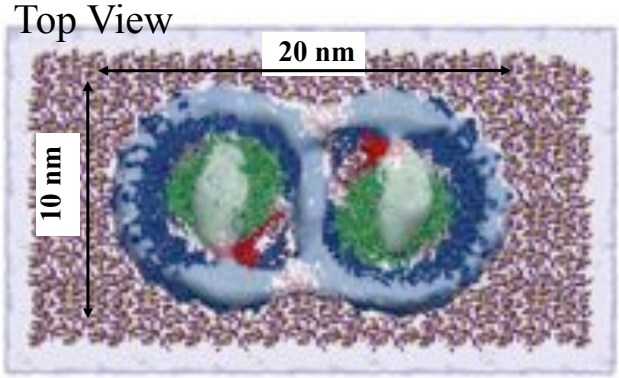


Structure of LH1 established through crystallography and model-fitting to EM densities

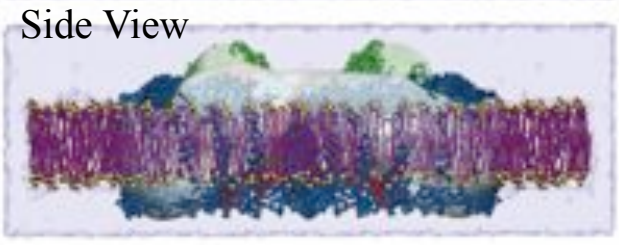
LH1

All-atom Simulations of a Membrane-Bending Protein Complex

Top View



Side View



Photosynthetic core complex:

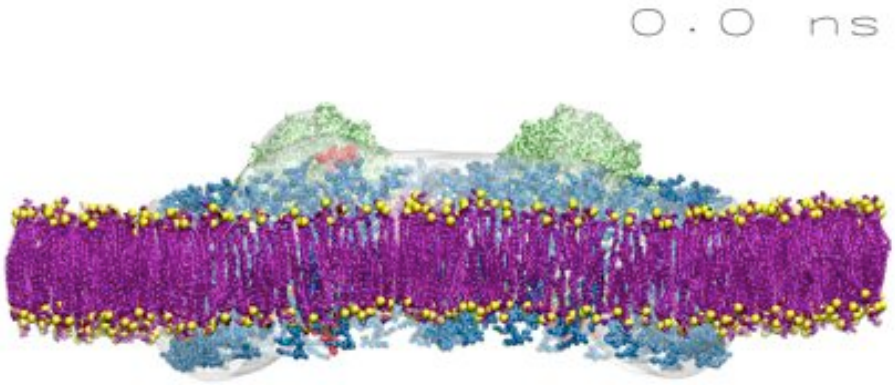
0.9 million atoms
simulated in total for > 51 ns

- Core complex stacks into tubes in bacterial cells

- Each core complex is thought to induce local curvautre in membrane

Sener et al., ***Chem. Phys.* 357:**188-197 (2009)
Hsin et al., ***Biophys. J.***, in press (2009)

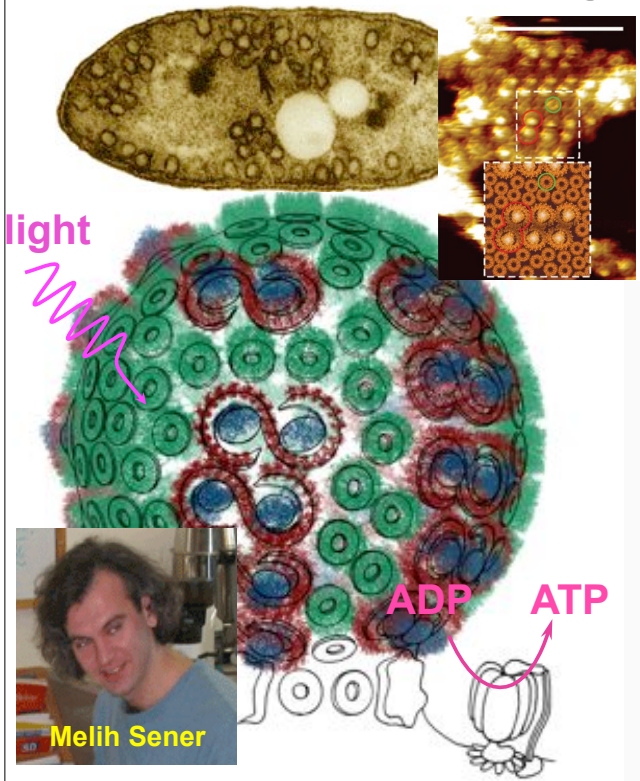
All-atom Simulations of a Membrane-Bending Protein Complex

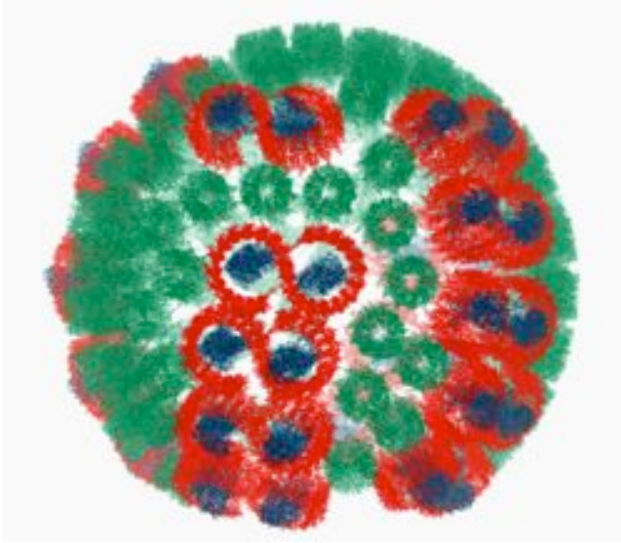


- Simulations revealed the membrane-bending process
- Size of the membrane curvature matched that of experiment
- Local curvature is related to long-range organization of the complex

Sener et al., ***Chem. Phys.* 357:**188-197 (2009)
Hsin et al., ***Biophys. J.***, in press (2009)

Knowing the Atomic Level Structure of the chromatophore, one can systematically describe its physical mechanism





M. Sener, J. Olsen, N. Hunter, and K. Schulten. *PNAS*, **104:** 15723-15728, 2007

Form-follows-function architecture of purple bacterial light harvesting systems

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fibrinogen
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10 μs folding
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BAR domain
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A. Arkhipov

GPU team
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