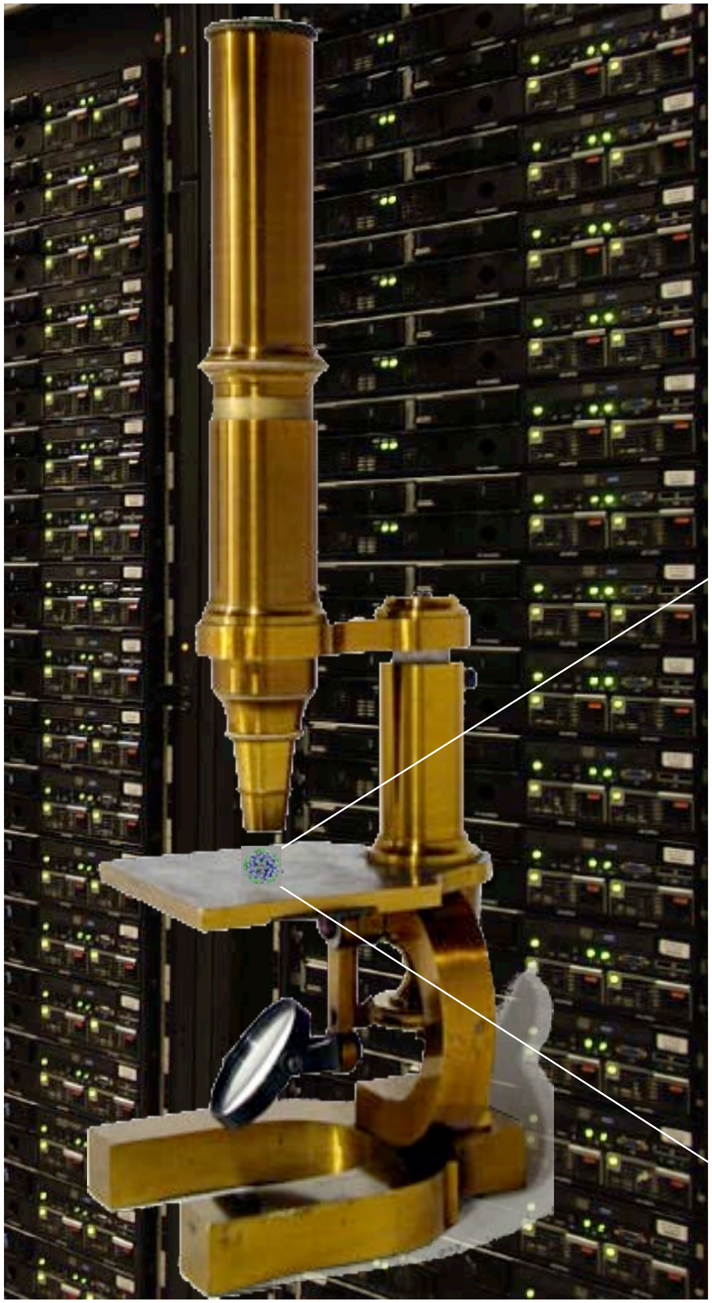
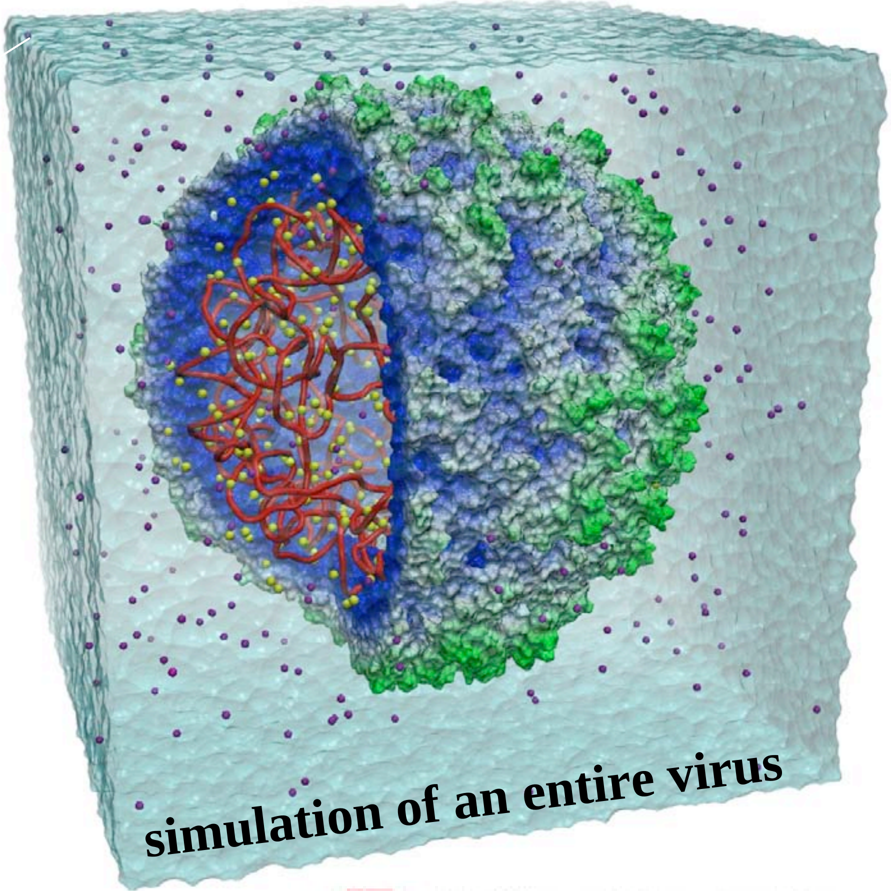


The Computational Microscope

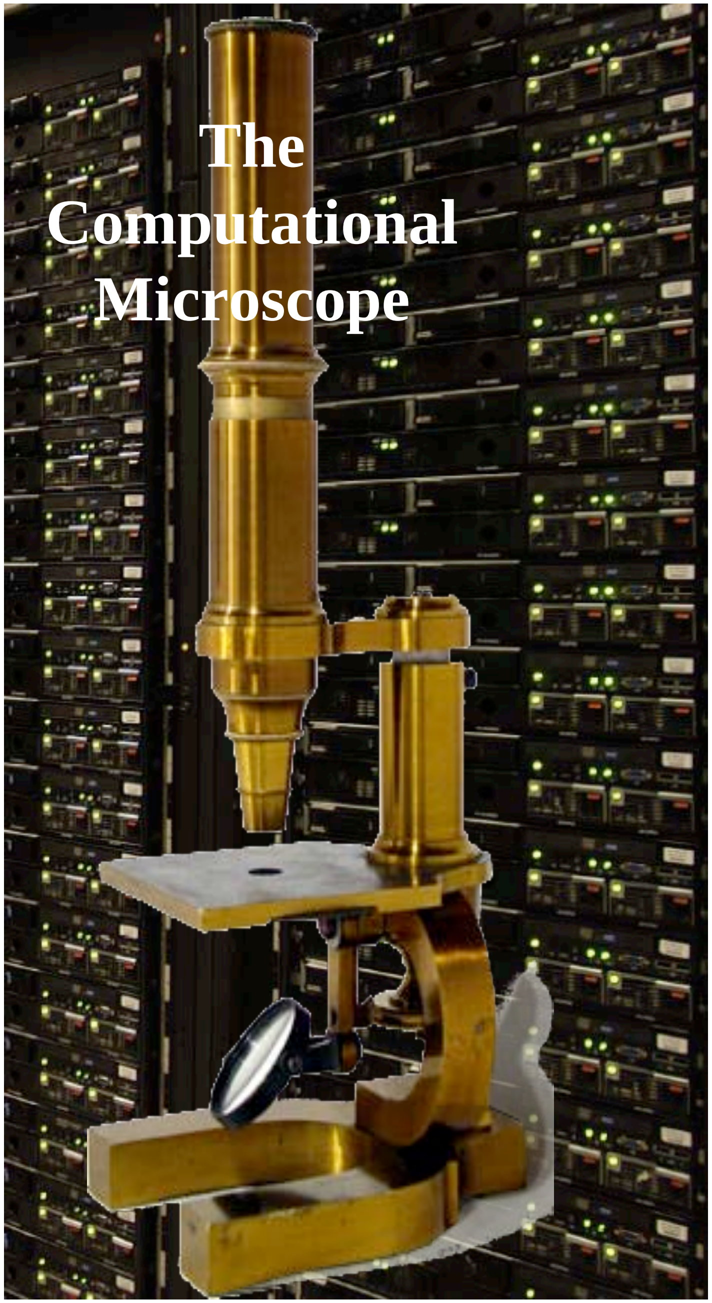
Klaus Schulten
Dept. Physics / Beckman Institute, U. Illinois
NIH., October 2007



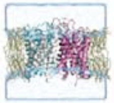
simulation of an entire virus

Main funding: National Center for Research Resources

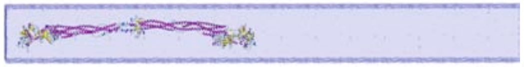
Computational Microscope views the Cell



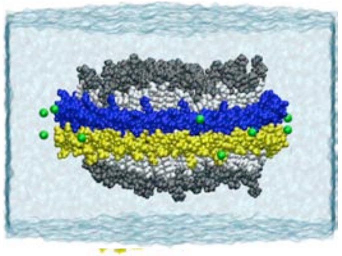
100 - 1,000,000 processors



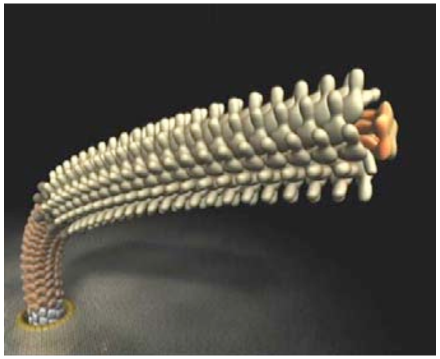
water channel (**10^{5} atoms**)



fibrinogen (**10^{6} atoms**)

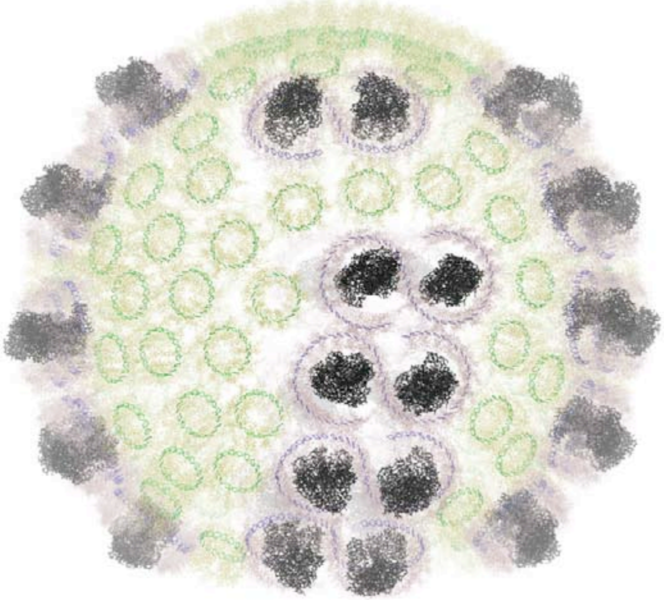


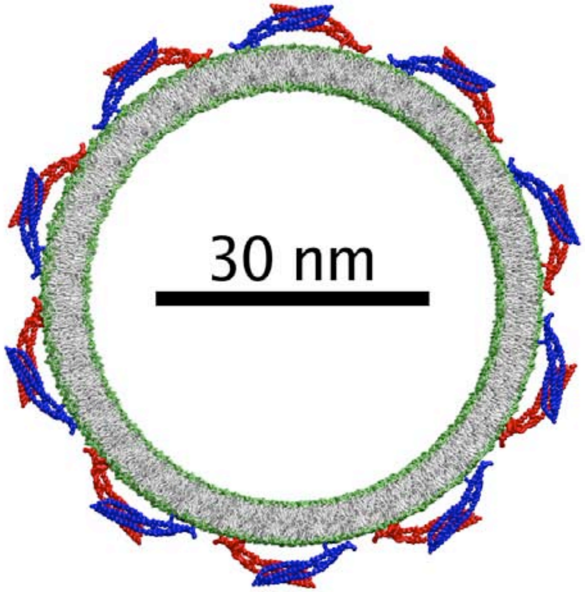
lipoprotein (**10^{5} atoms**)



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

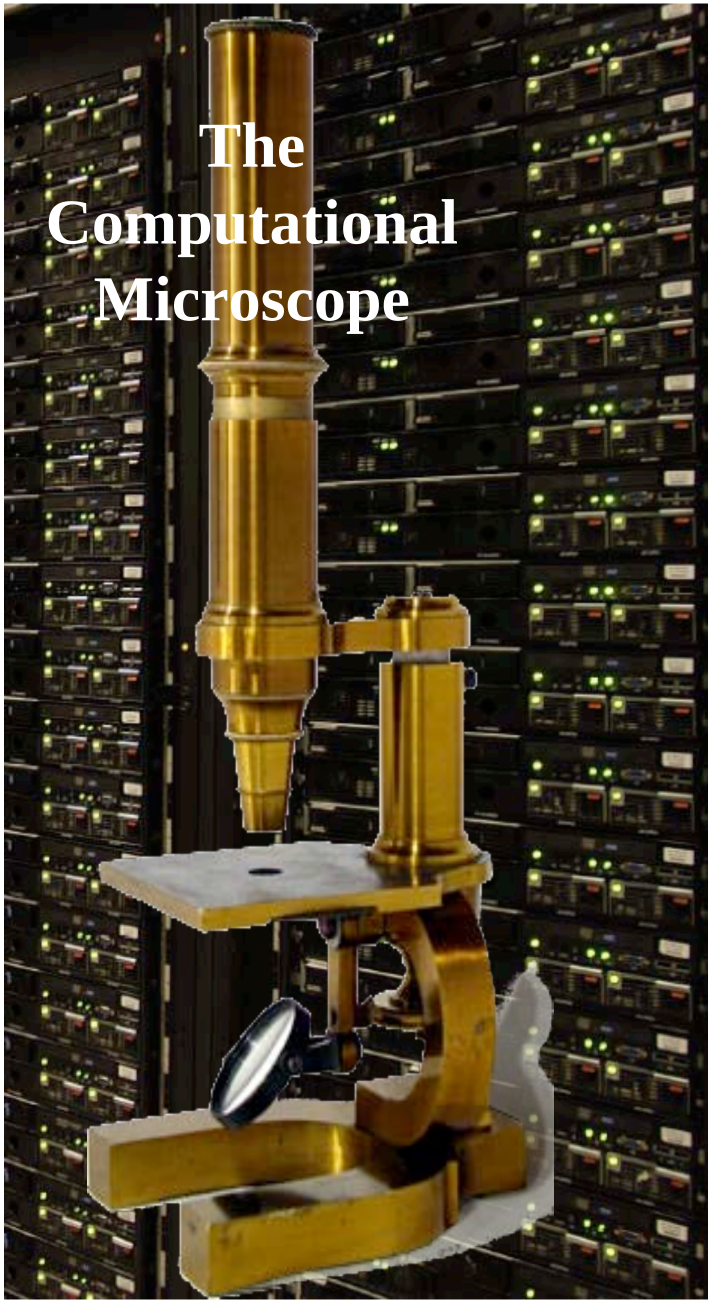
photosynthetic chromatophore (**10^{8} atoms**)



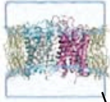


vesicle formed by BAR domains (**$5x10^{7}$ atoms**)

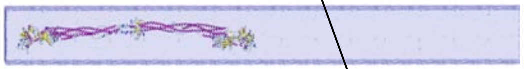
Computational Microscope 2002-2010



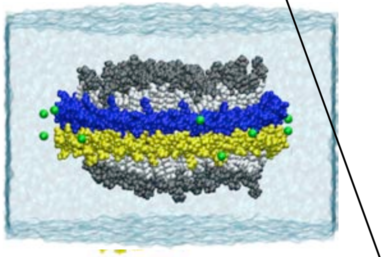
100 - 1,000,000 processors



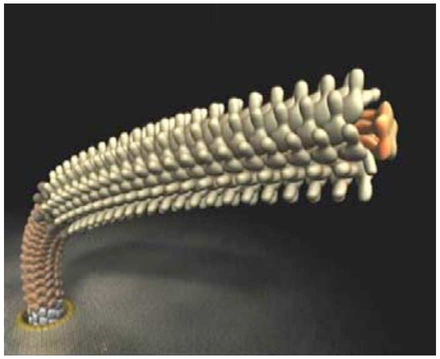
water channel (**10^5 atoms**)



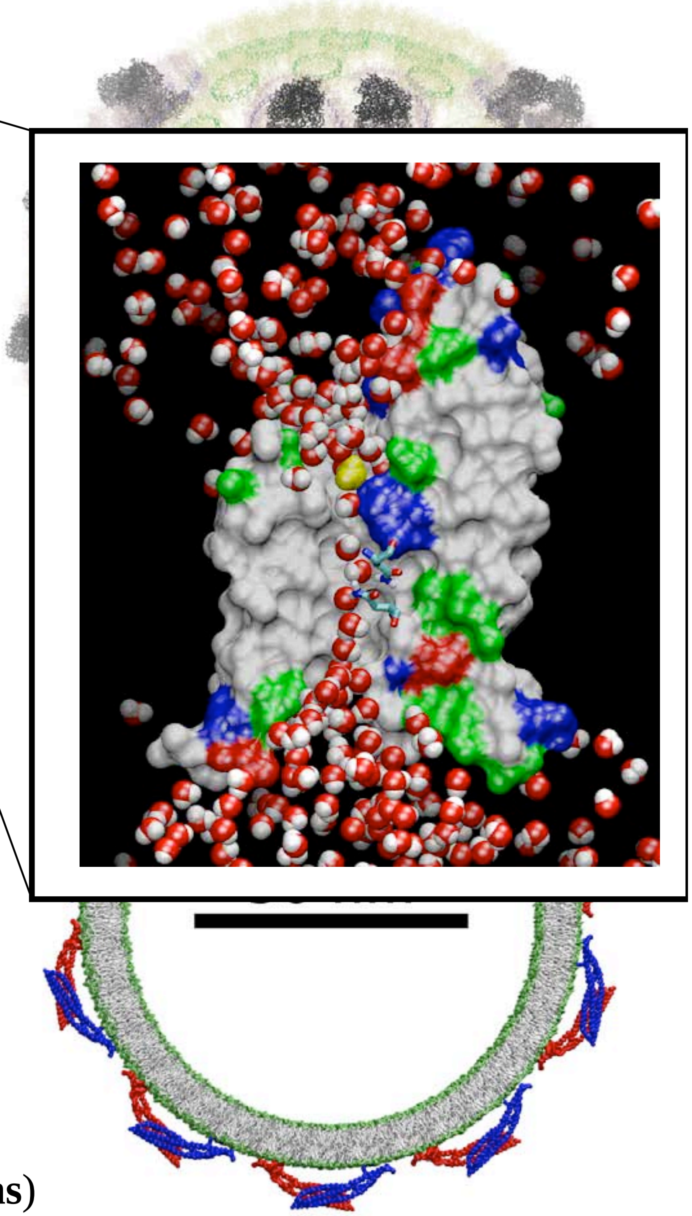
fibrinogen (**10^6 atoms**)



lipoprotein (**10^5 atoms**)



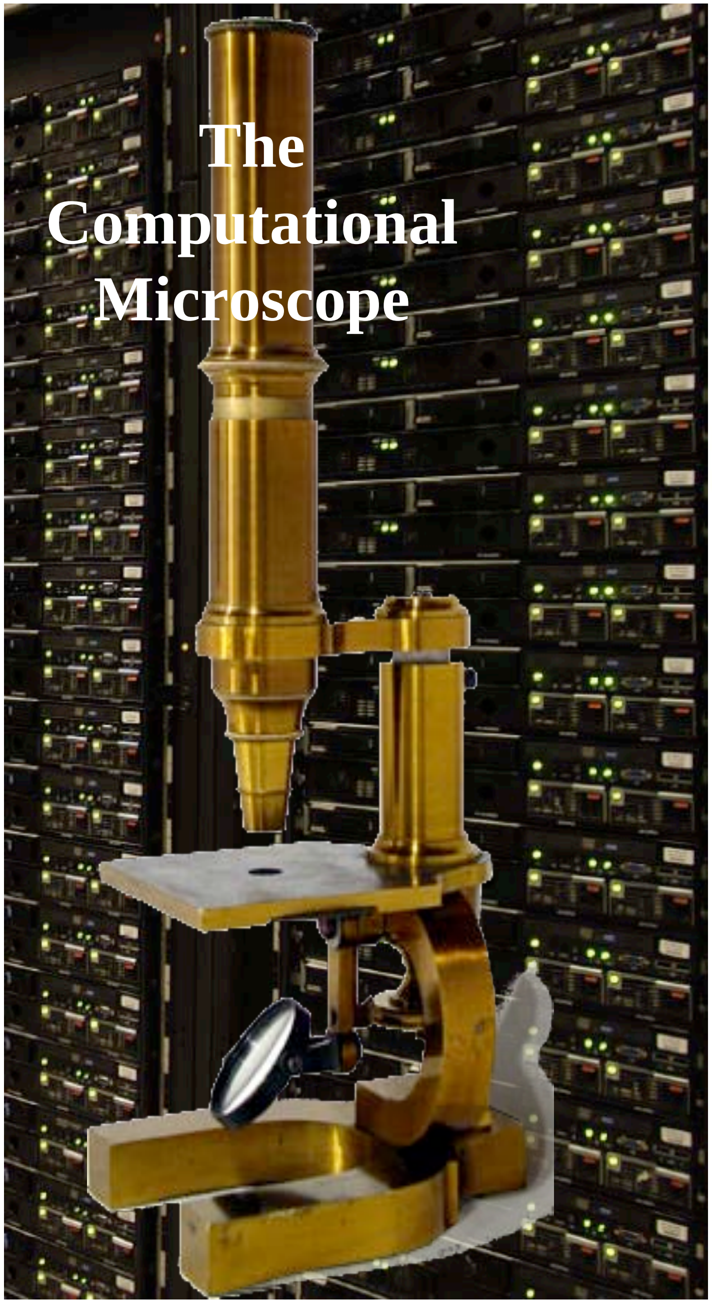
bacterial flagellum (**10^9 atoms**)



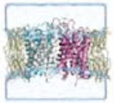
photosynthetic chromatophore (**10^8 atoms**)

vesicle formed by BAR domains (**5×10^7 atoms**)

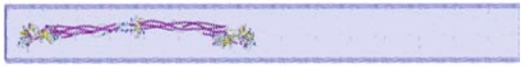
Computational Microscope 2002-2010



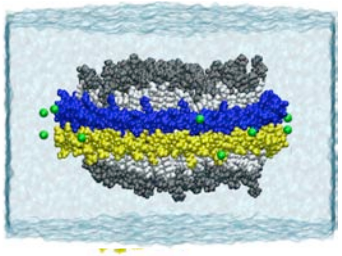
100 - 1,000,000 processors



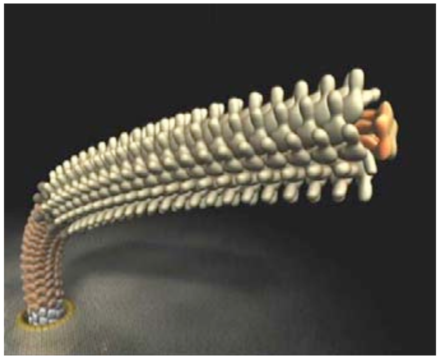
water channel (**10^5 atoms**)



fibrinogen (**10^6 atoms**)

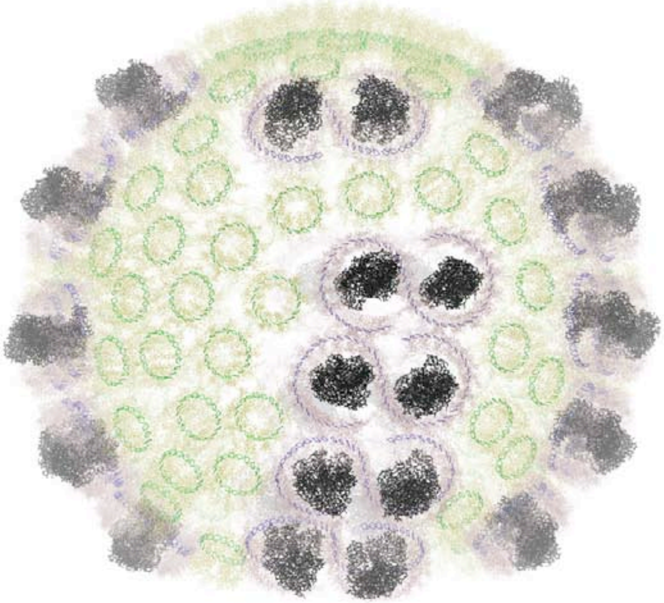


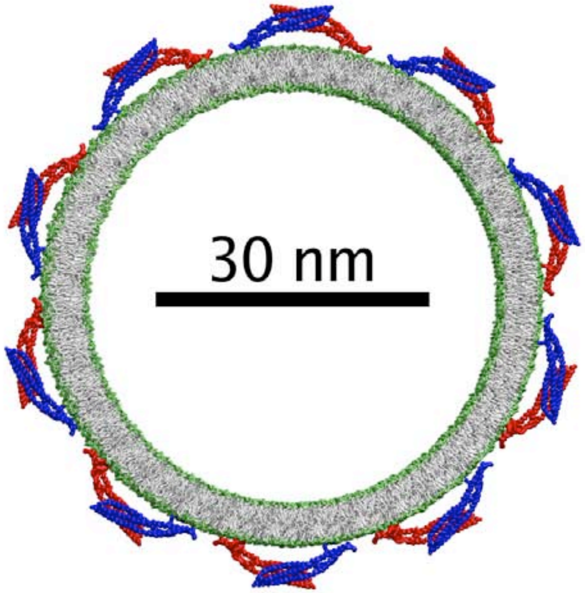
lipoprotein (**10^5 atoms**)



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

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

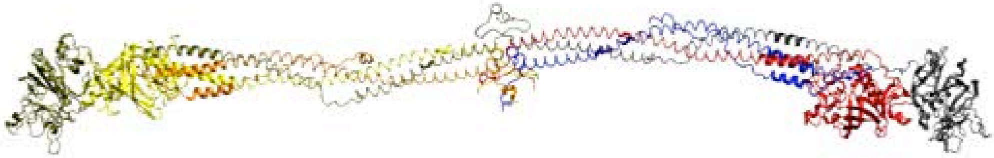


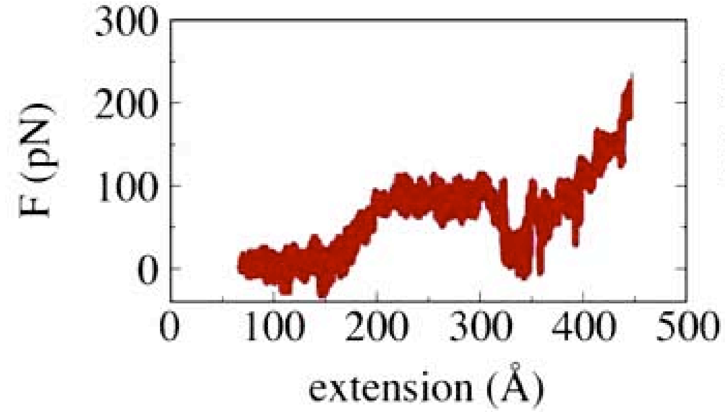


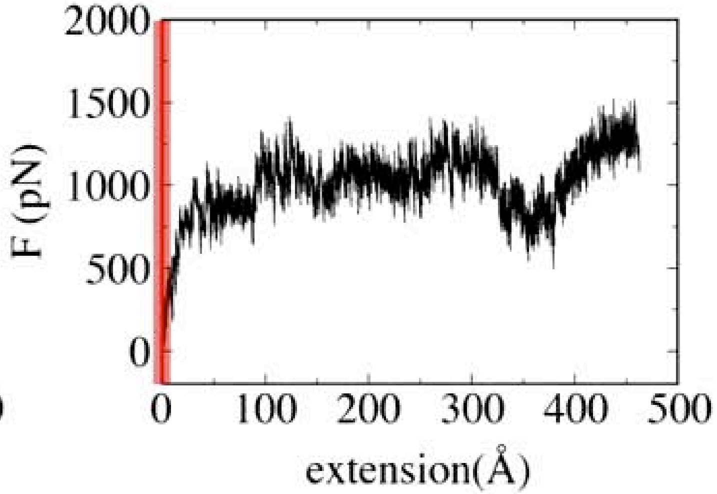
vesicle formed by BAR domains (**$5x10^7$ atoms**)

Mechanical Strength of a Blood Clot

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





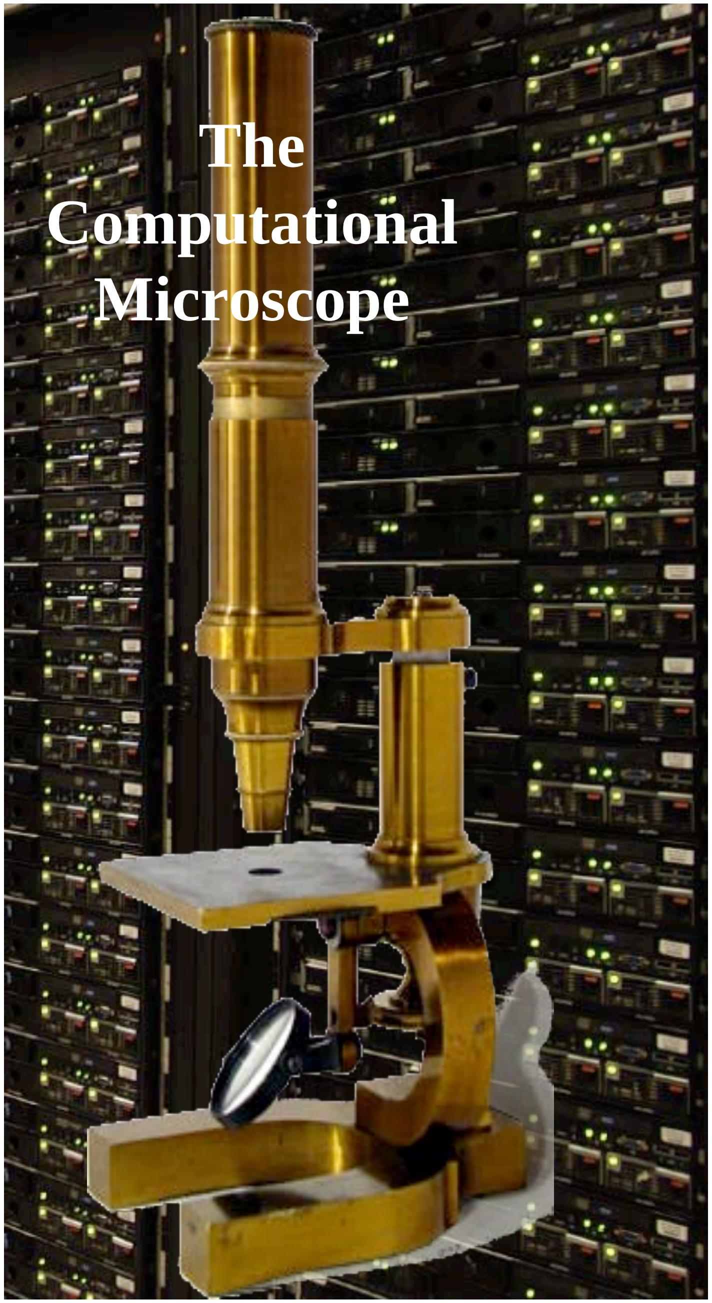


20ns SMD Simulation of fibrinogen, ***1.06 million atoms, 1.2 ns/day with pencil decomposition, 15 days on PSC XT3 Cray (1024 processors)***

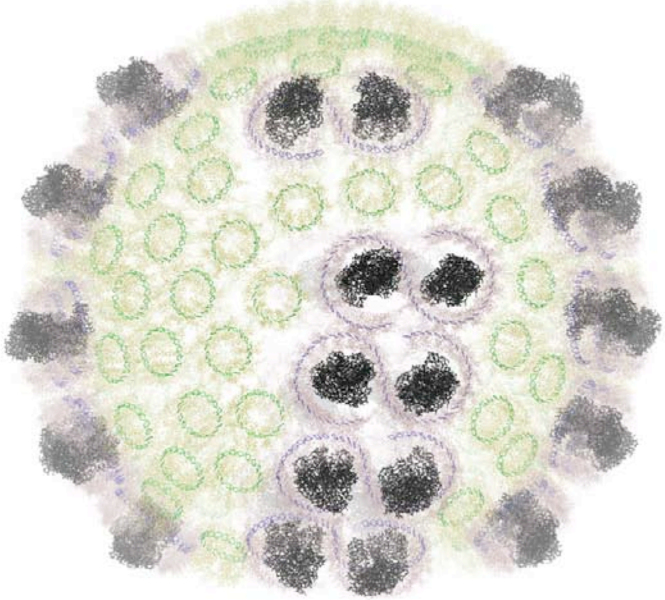
A Blood Clot

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

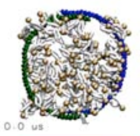
Computational Microscope 2002-2010



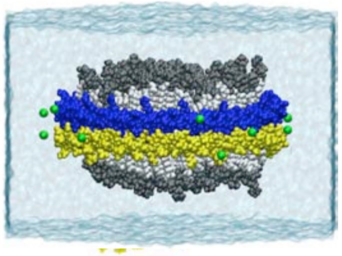
100 - 1,000,000
processors



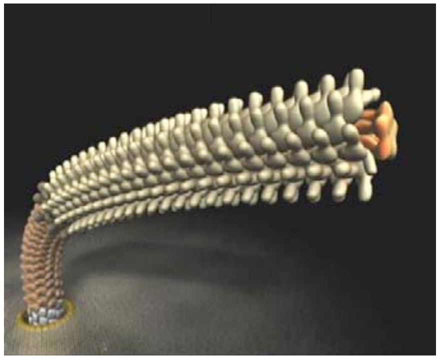
photosynthetic chromatophore (**10^{8} atoms**)



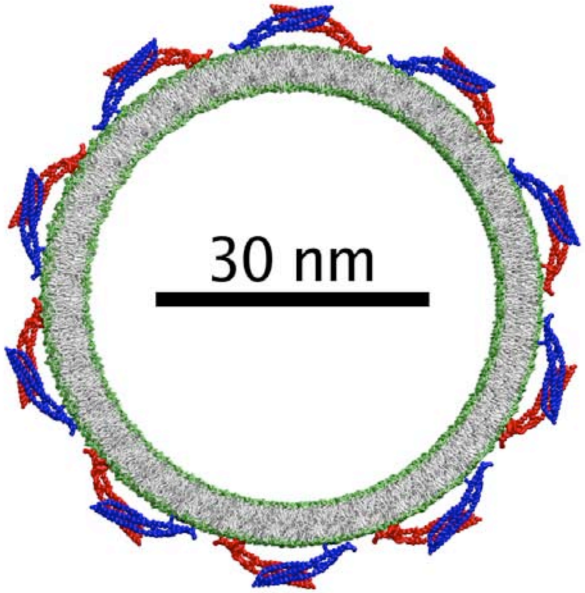
lipoprotein (**1x10^{5} atoms**)



lipoprotein (**10^{5} atoms**)

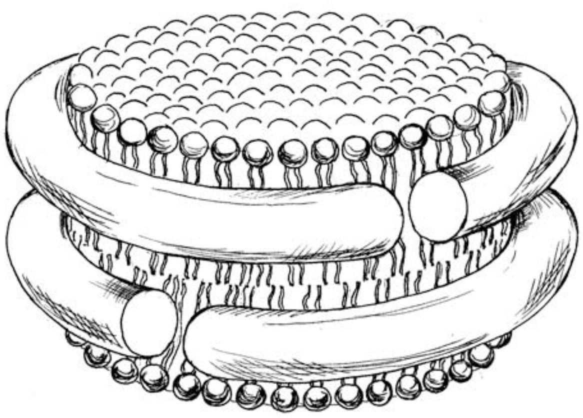


bacterial flagellum (**10^{9} atoms**)



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

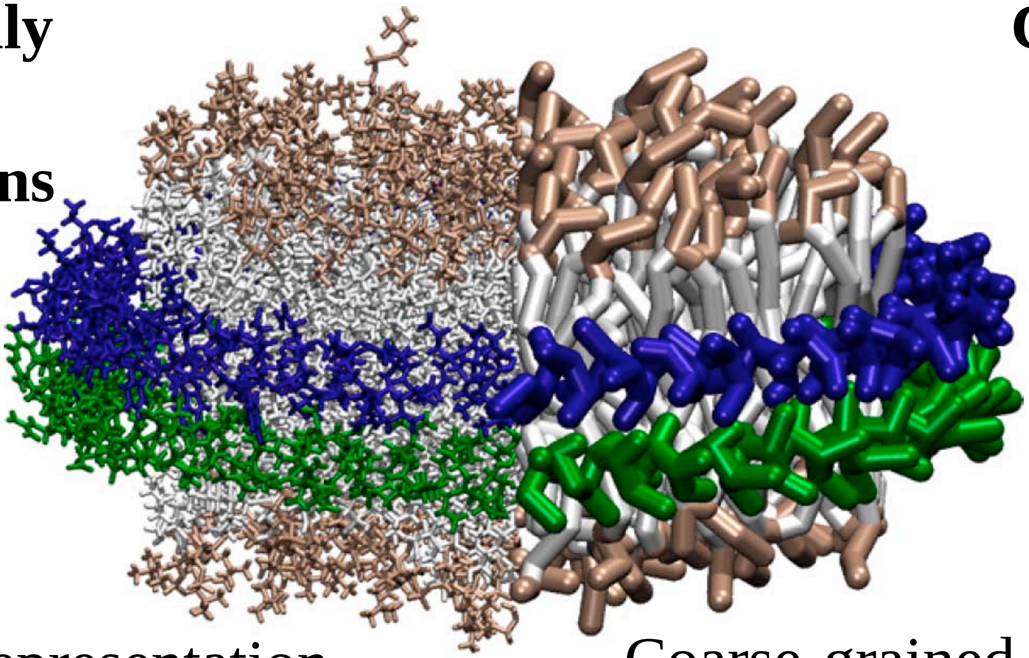
Coarse Grained Molecular Dynamics of Lipid Nanodiscs



Simple scaffold protein

Computationally slow dynamics reaches to 100 ns

Computationally fast dynamics reaches to 10 μs



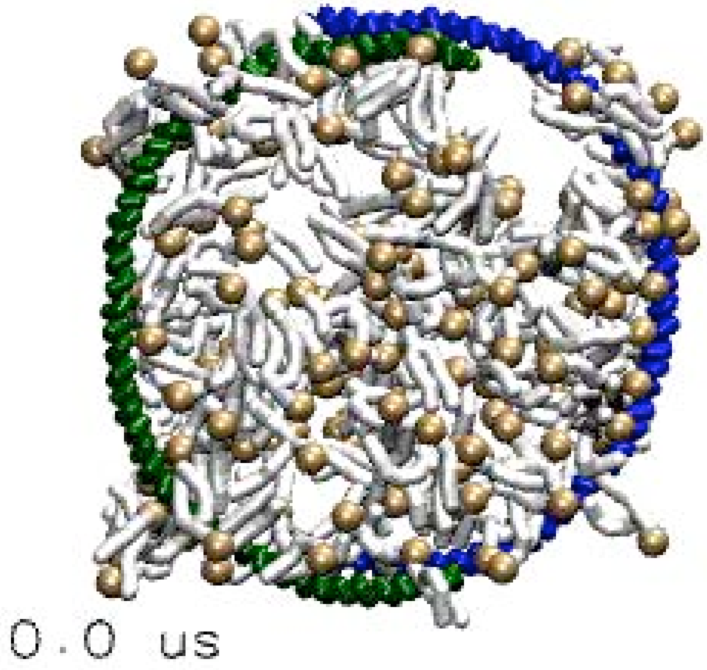
Full atom representation

Coarse-grained representation

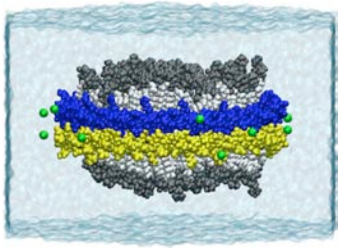
A. Shih, A. Arkhipov, P. Freddolino, and K. Schulten. *J. Phys. Chem. B*, 110:3674–3684, 2006; A. Shih, P. Freddolino, A. Arkhipov, and K. Schulten. *J. Struct. Biol*., 157:579–592,2007; A. Shih, A. Arkhipov, P. Freddolino, S. Sligar, and K. Schulten. *Journal of Physical Chemistry B*, 111: 11095 - 11104, 2007; A. Shih, P. Freddolino, S. Sligar, and K. Schulten. *Nano Letters*, 7:1692-1696, 2007.

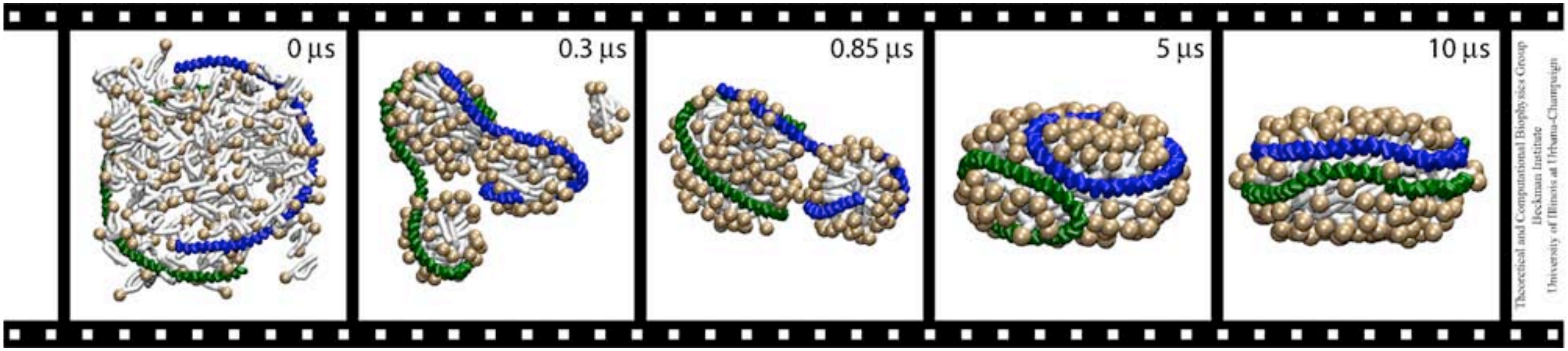
Nanodisc Assembly CG MD Simulation

- 10 μs simulation
- Assembly proceeds in two steps:
  - Aggregation of proteins and lipids driven by the hydrophobic effect
  - Optimization of the protein structure driven by increasingly specific protein-protein interactions
- Formation of the generally accepted double-belt model for discoidal HDL



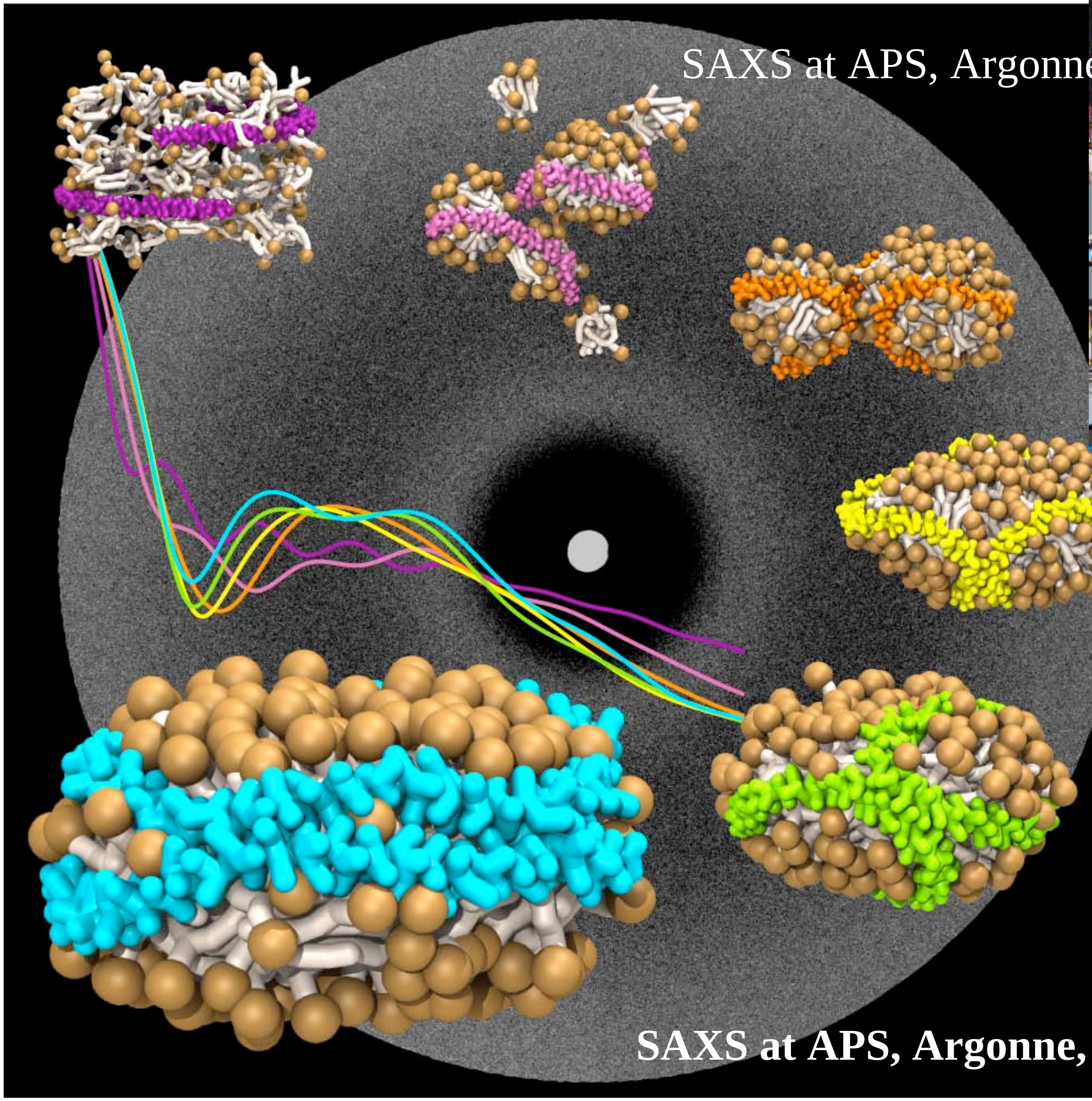
Fully hydrated

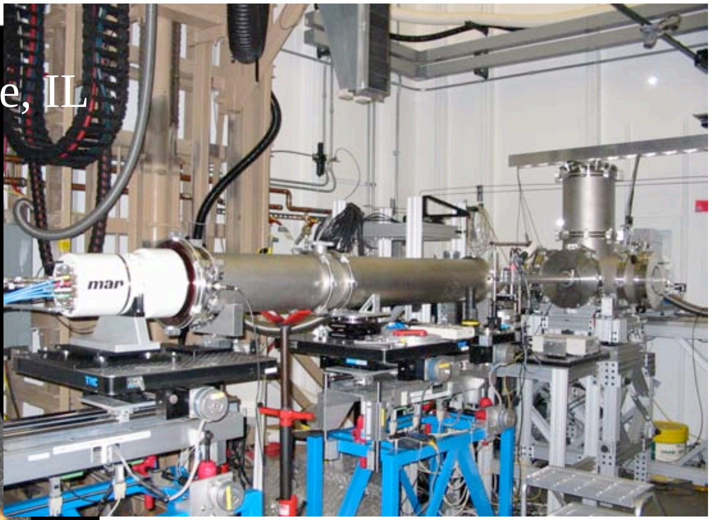




A. Shih, A. Arkhipov, P. Freddolino, and K. Schulten. *J. Phys. Chem. B*, 110:3674–3684, 2006; A. Shih, P. Freddolino, A. Arkhipov, and K. Schulten. *J. Struct. Biol.*, 157:579–592,2007; A. Shih, A. Arkhipov, P. Freddolino, S. Sligar, and K. Schulten. *Journal of Physical Chemistry B*, 111: 11095 - 11104, 2007; A. Shih, P. Freddolino, S. Sligar, and K. Schulten. *Nano Letters*, 7:1692-1696, 2007.

Formation of Nanodiscs Monitored by SAXS and Simulation



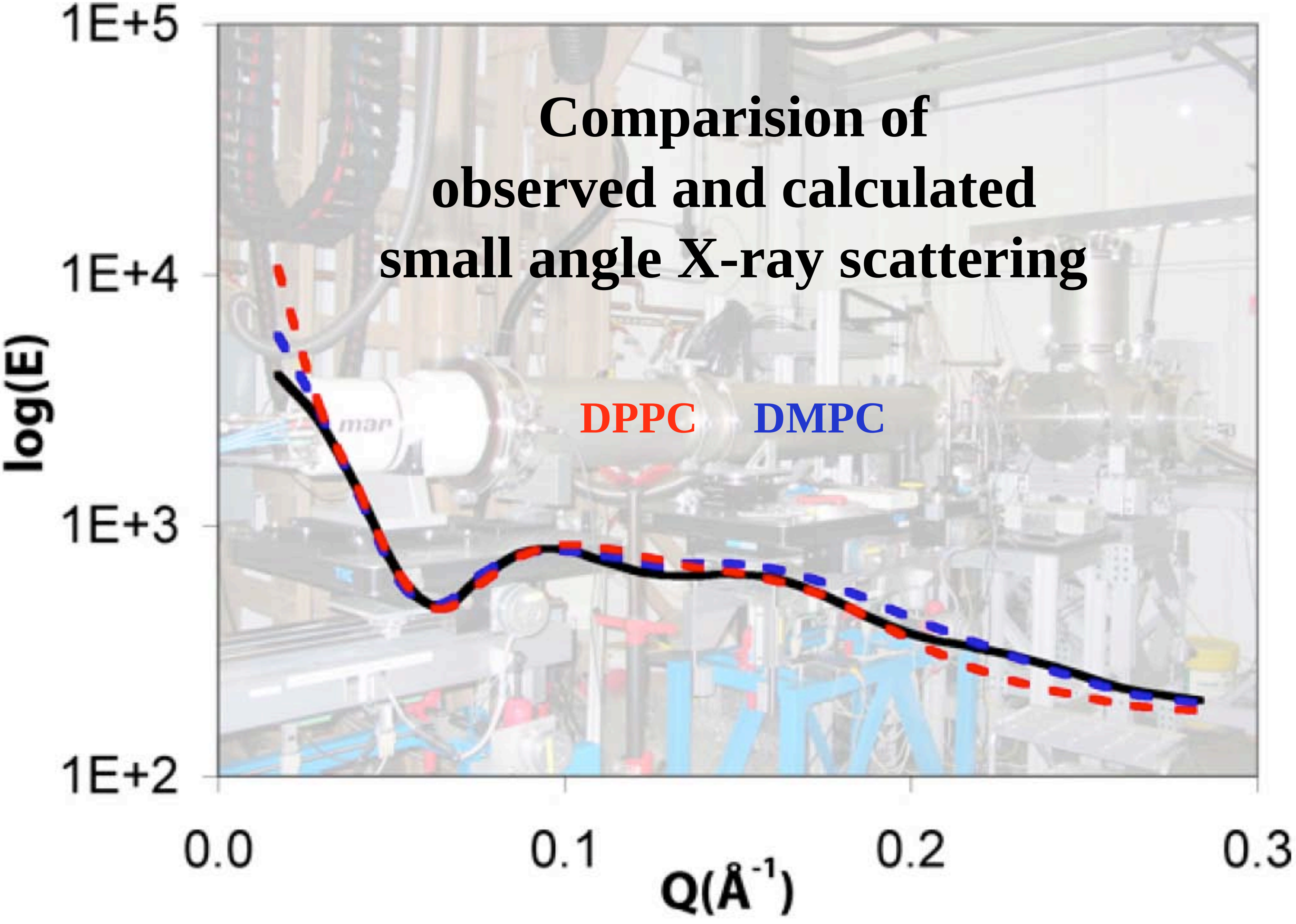


A. Shih, I. Denisov, J. Phillips, S. Sligar, and K. Schulten. *Biophys. J.,* 88: 548–556, 2005

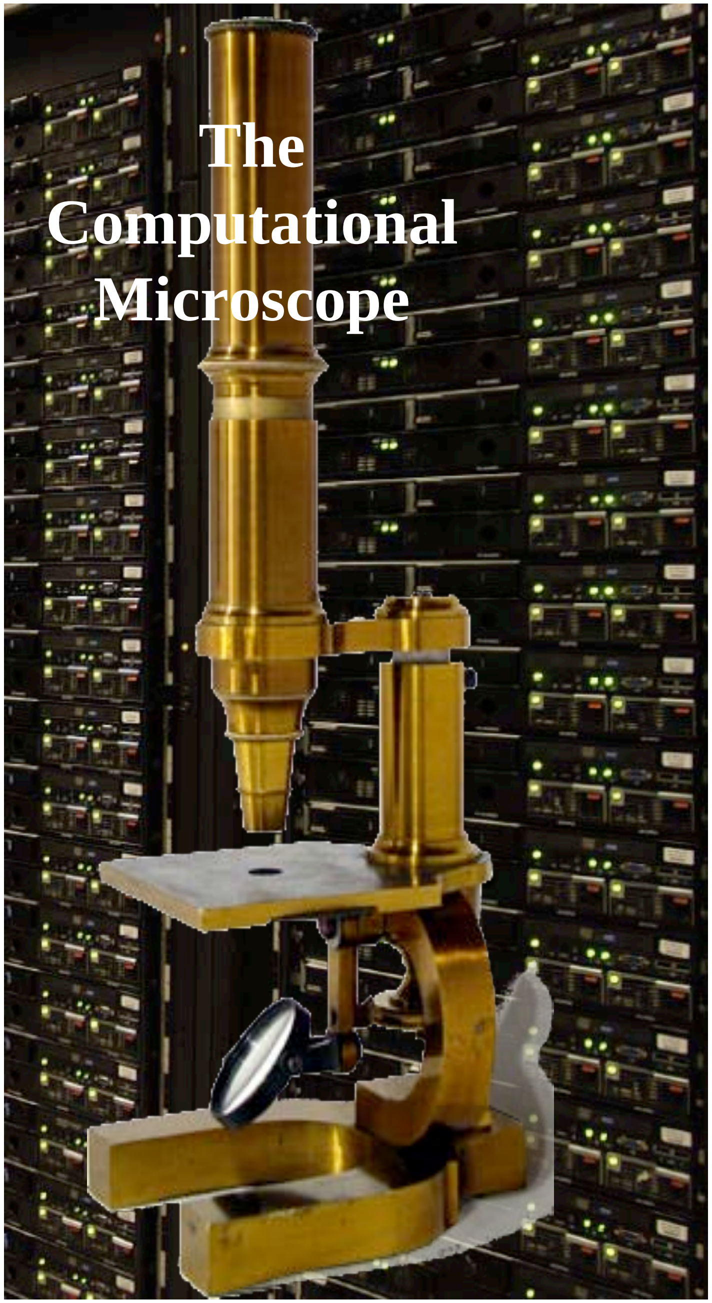
A. Shih, A. Arkhipov, P. Freddolino, S. Sligar, and K. Schulten. *J. Phys. Chem. B*, 111: 11095 - 11104, 2007;

A. Shih, A. Arkhipov, P. Freddolino, S. Sligar, and K. Schulten. *J. Phys. Chem. B*, 111: 11095 - 11104, 2007; A. Shih, P. Freddolino, S. Sligar, and K. Schulten. *Nano Letters*, 7:1692-1696, 2007.

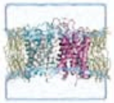
Comparision of observed and calculated small angle X-ray scattering



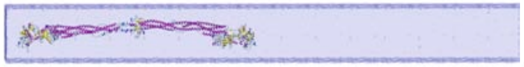
Computational Microscope 2002-2010



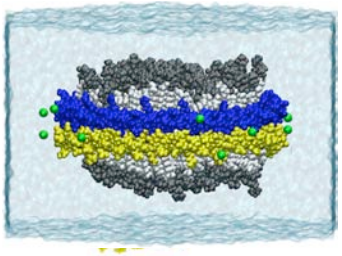
100 - 1,000,000 processors



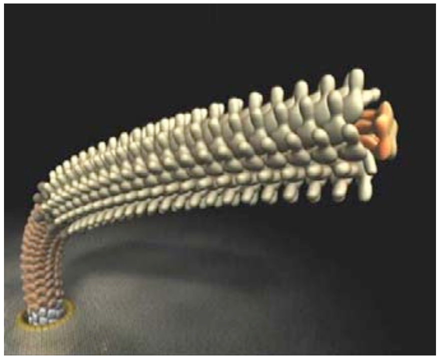
water channel (**10^5 atoms**)



fibrinogen (**10^6 atoms**)

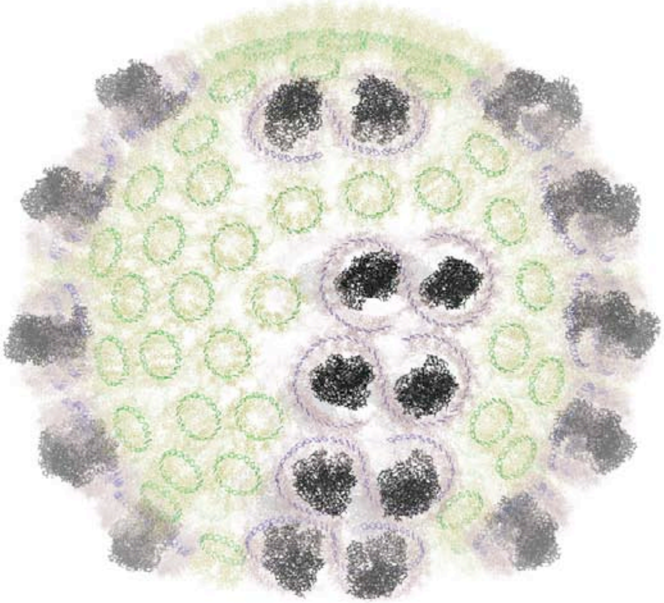


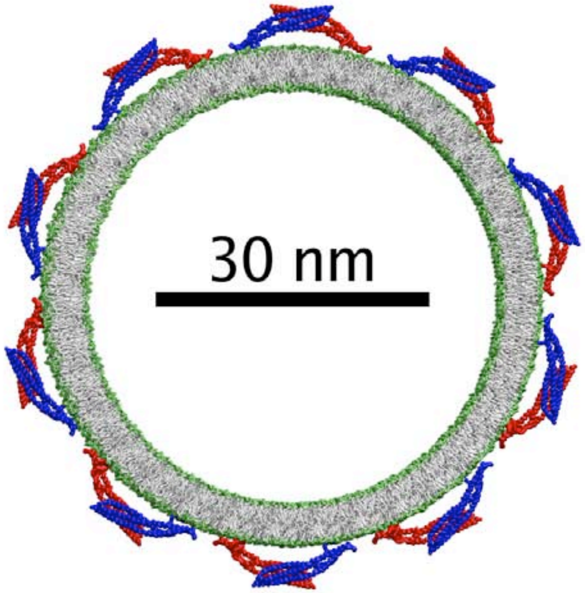
lipoprotein (**10^5 atoms**)



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

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

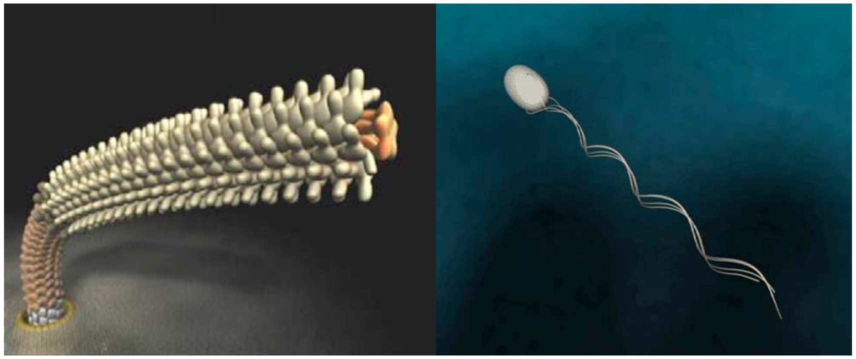


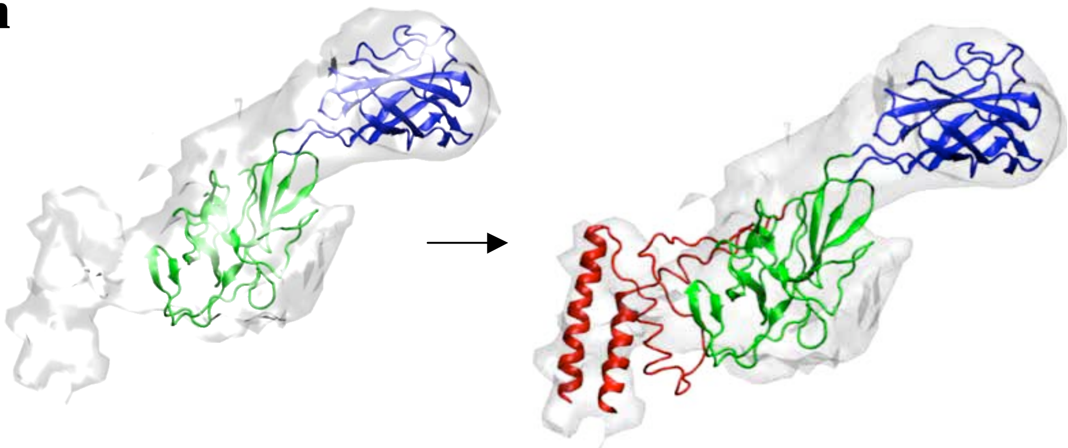


vesicle formed by BAR domains (**$5\text{x}10^7$ atoms**)

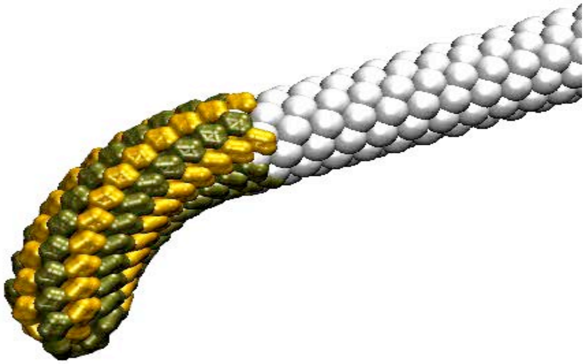
Modeling and Simulating the Flagellar Hook of a Bacterium

Elements of the Bacterial Flagellum

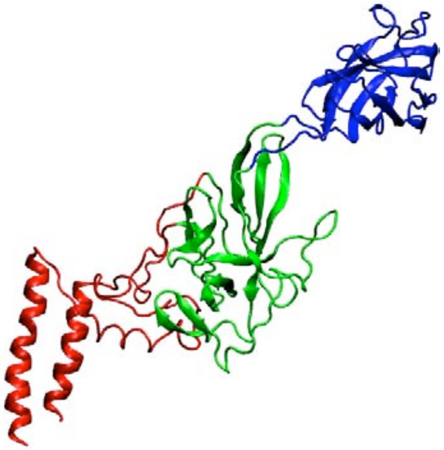




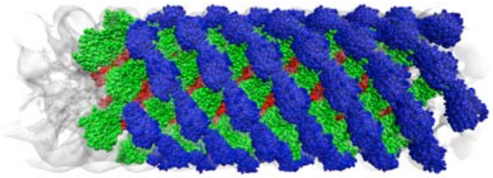
Protein structure prediction adds D0 domain and fits full structure into cryo-EM map



Simulated with all-atom and CG molecular dynamics



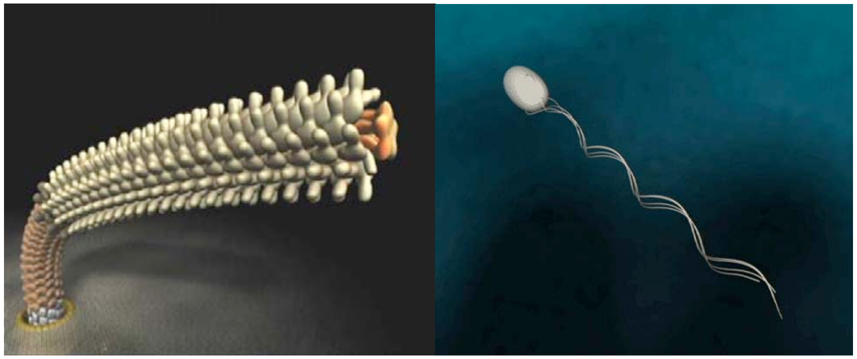
Construction of a Shape-Based Coarse-Grain Model

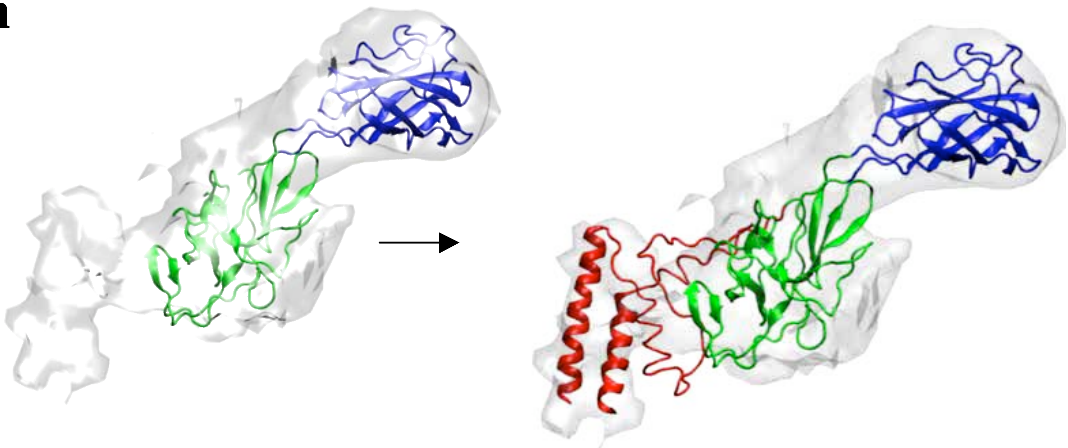


Crystal structure of hook missing interior domain

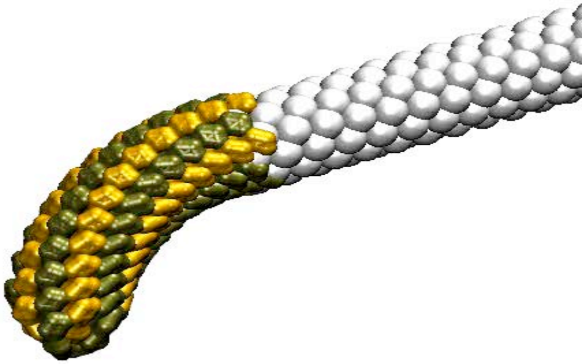
Modeling and Simulating the Flagellar Hook of a Bacterium

Elements of the Bacterial Flagellum

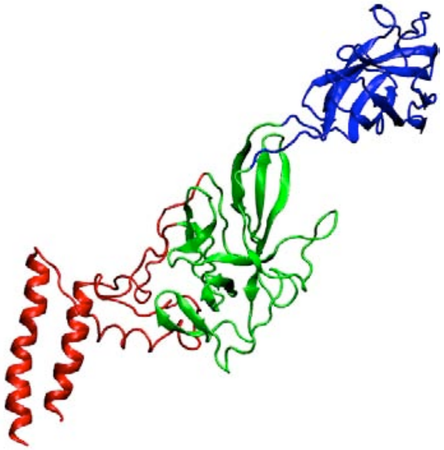




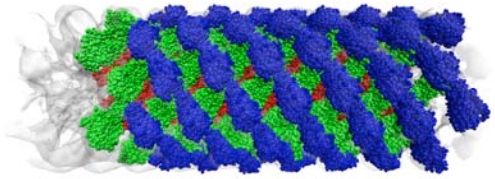
Protein structure prediction adds D0 domain and fits full structure into cryo-EM map



Simulated with all-atom and CG molecular dynamics

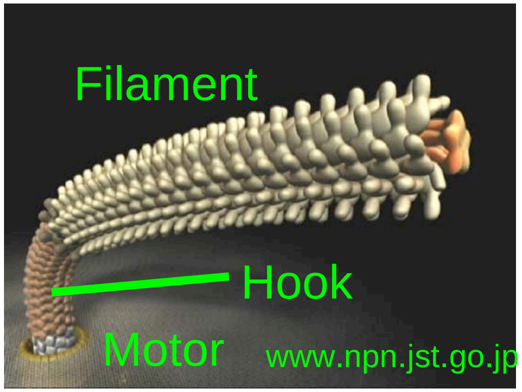


Construction of a Shape-Based Coarse-Grain Model



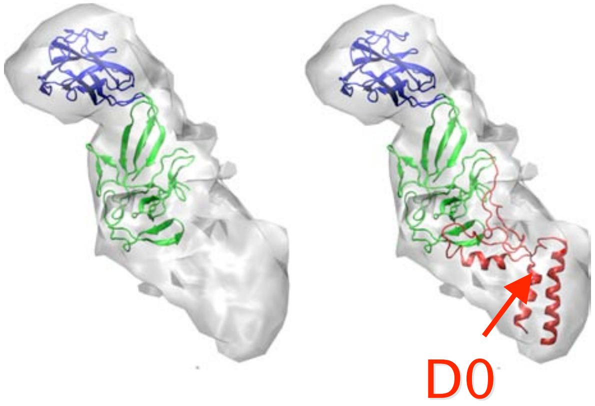
Crystal structure of hook missing interior domain

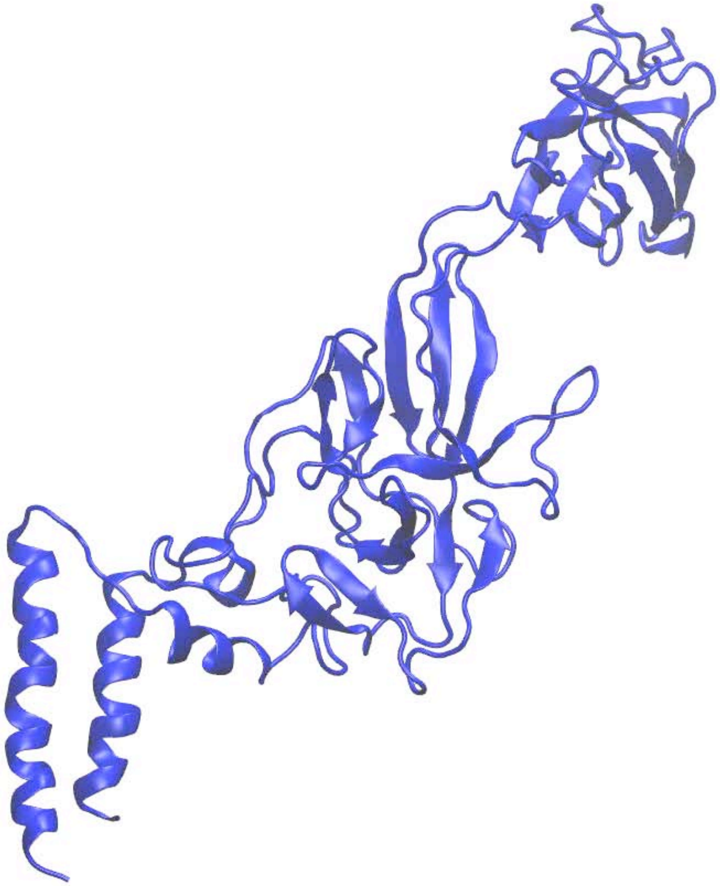
Solving the Structure of the Flagellar Hook Through Crystallography, Electron Microscopy, and Computational Modeling



Cryo-EM map of the hook was obtained at 9.0Å resolution.

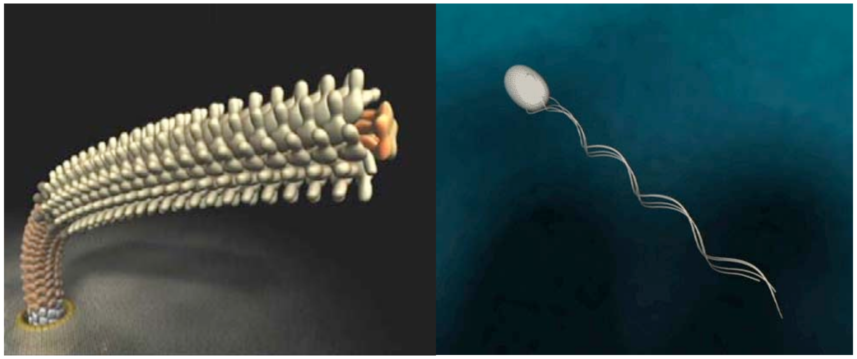
Missing D0 domain modeled

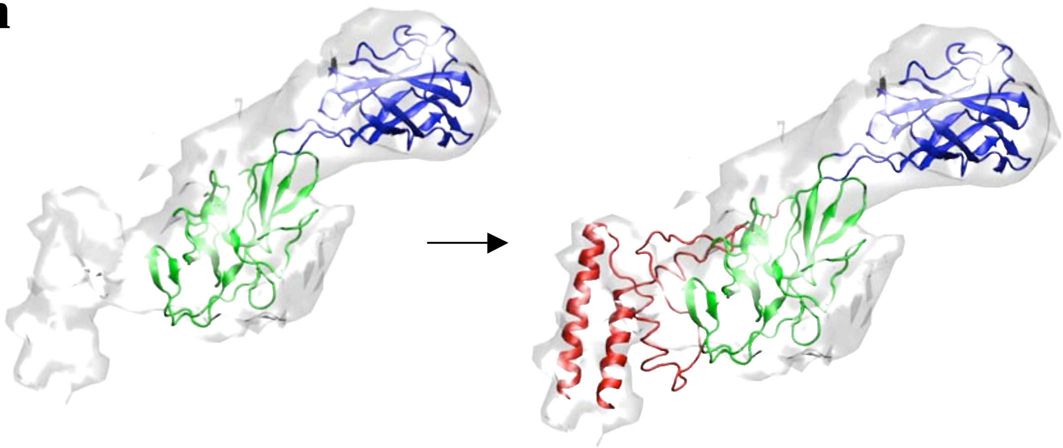




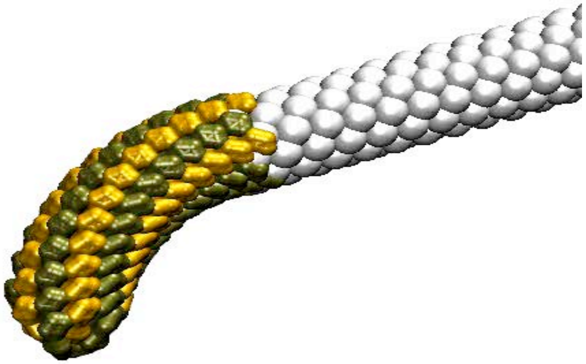
Modeling and Simulating the Flagellar Hook of a Bacterium

Elements of the Bacterial Flagellum

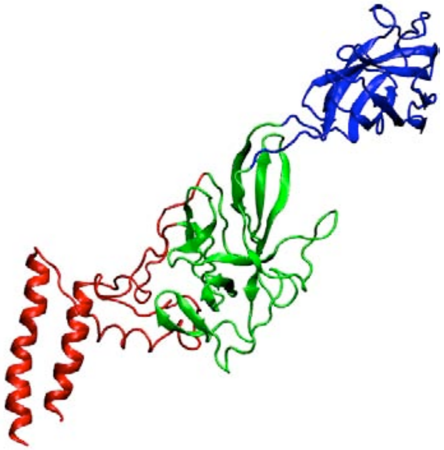




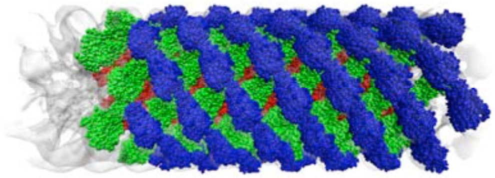
Protein structure prediction adds D0 domain and fits full structure into cryo-EM map



Simulated with all-atom and CG molecular dynamics, needs to stretch to 10 ms

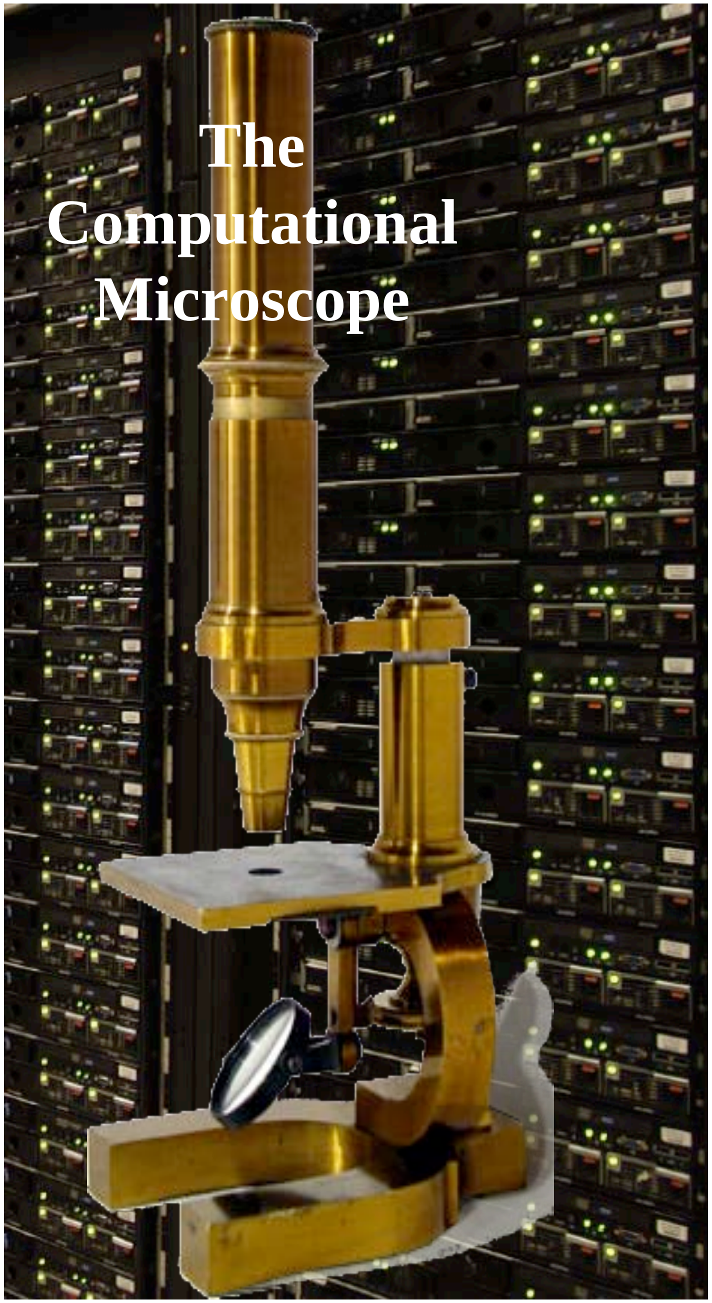


Construction of a Shape-Based Coarse-Grain Model

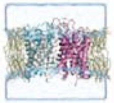


Crystal structure of hook missing interior domain

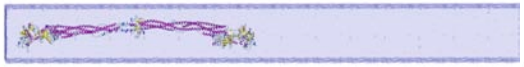
Computational Microscope 2002-2010



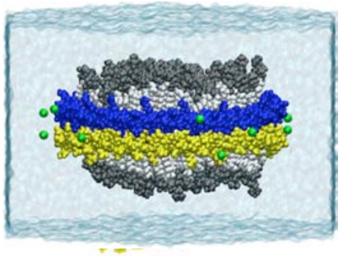
100 - 1,000,000 processors



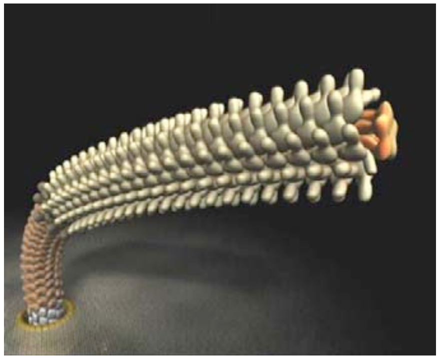
water channel (**10^5 atoms**)



fibrinogen (**10^6 atoms**)

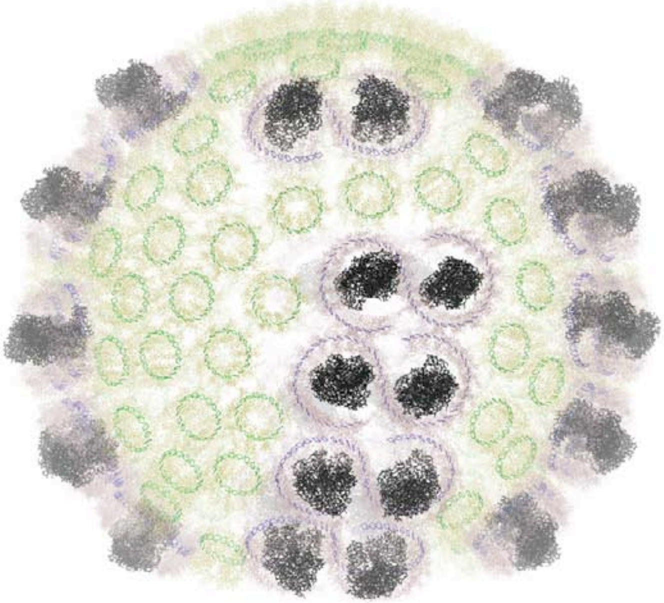


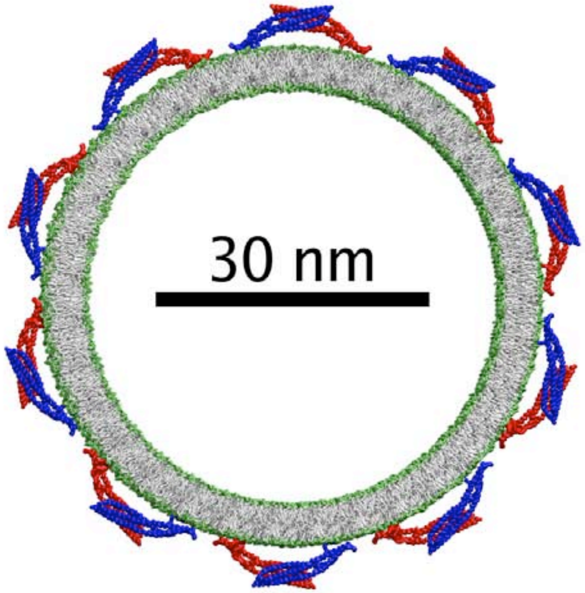
lipoprotein (**10^5 atoms**)



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

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

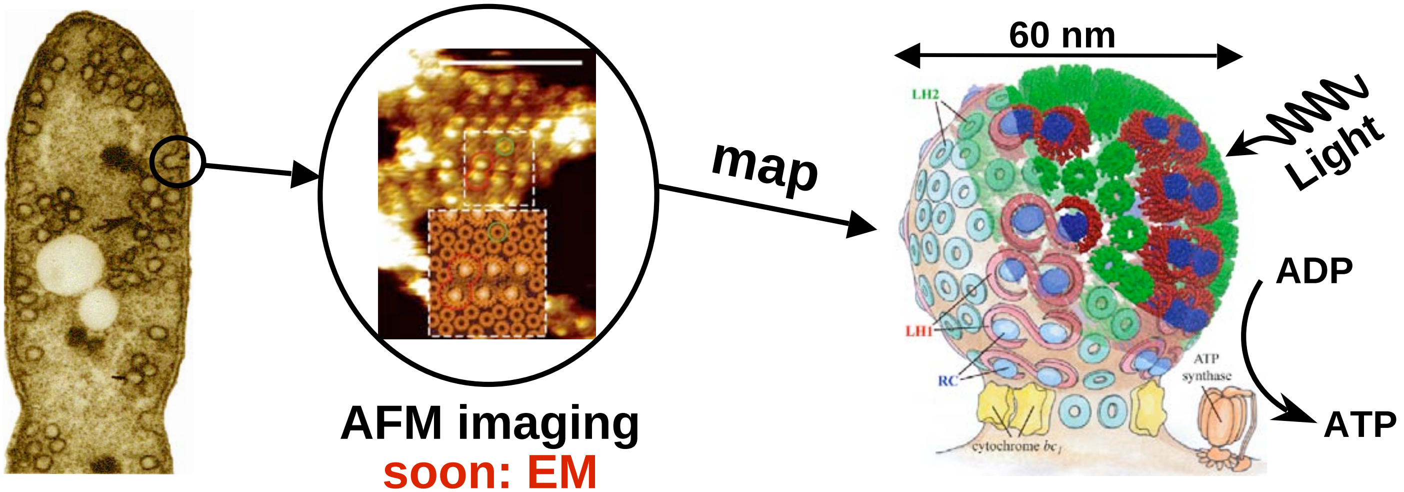




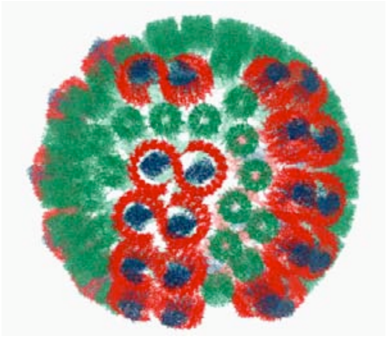
vesicle formed by BAR domains (**$5x10^7$ atoms**)

Photosynthetic Chromatophore

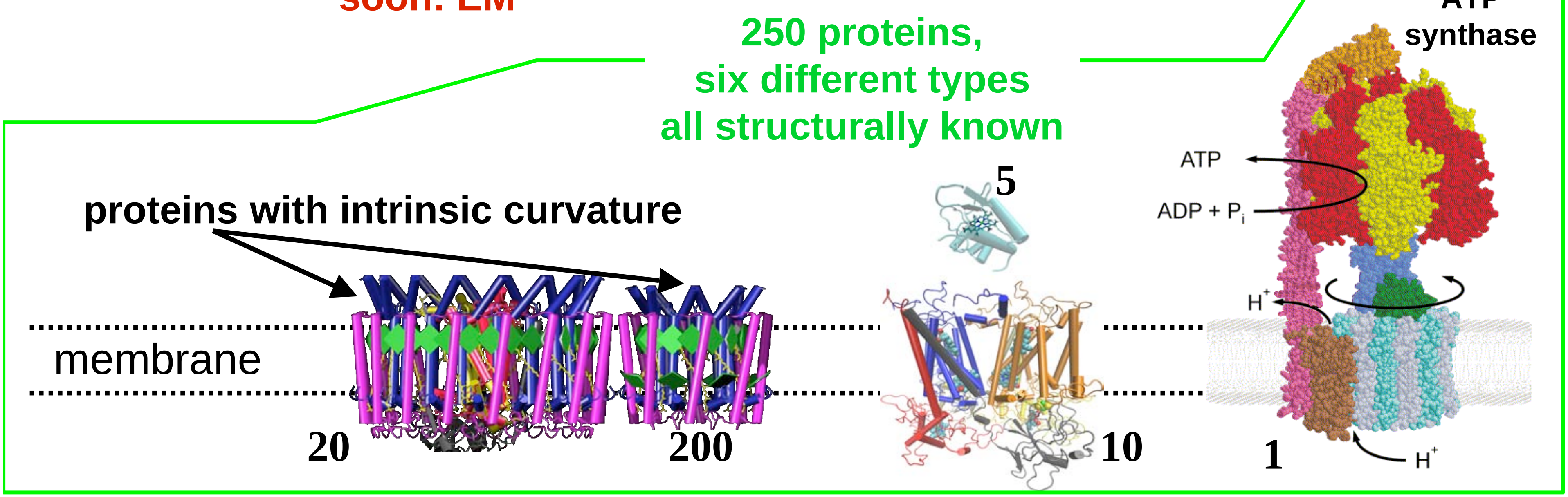
Elucidate assembly and function (`Docking`, `Molefacture`, `Paratool`, `Psfgen`, `Solvate`, `Membrane Builder`, `QM Tools`)



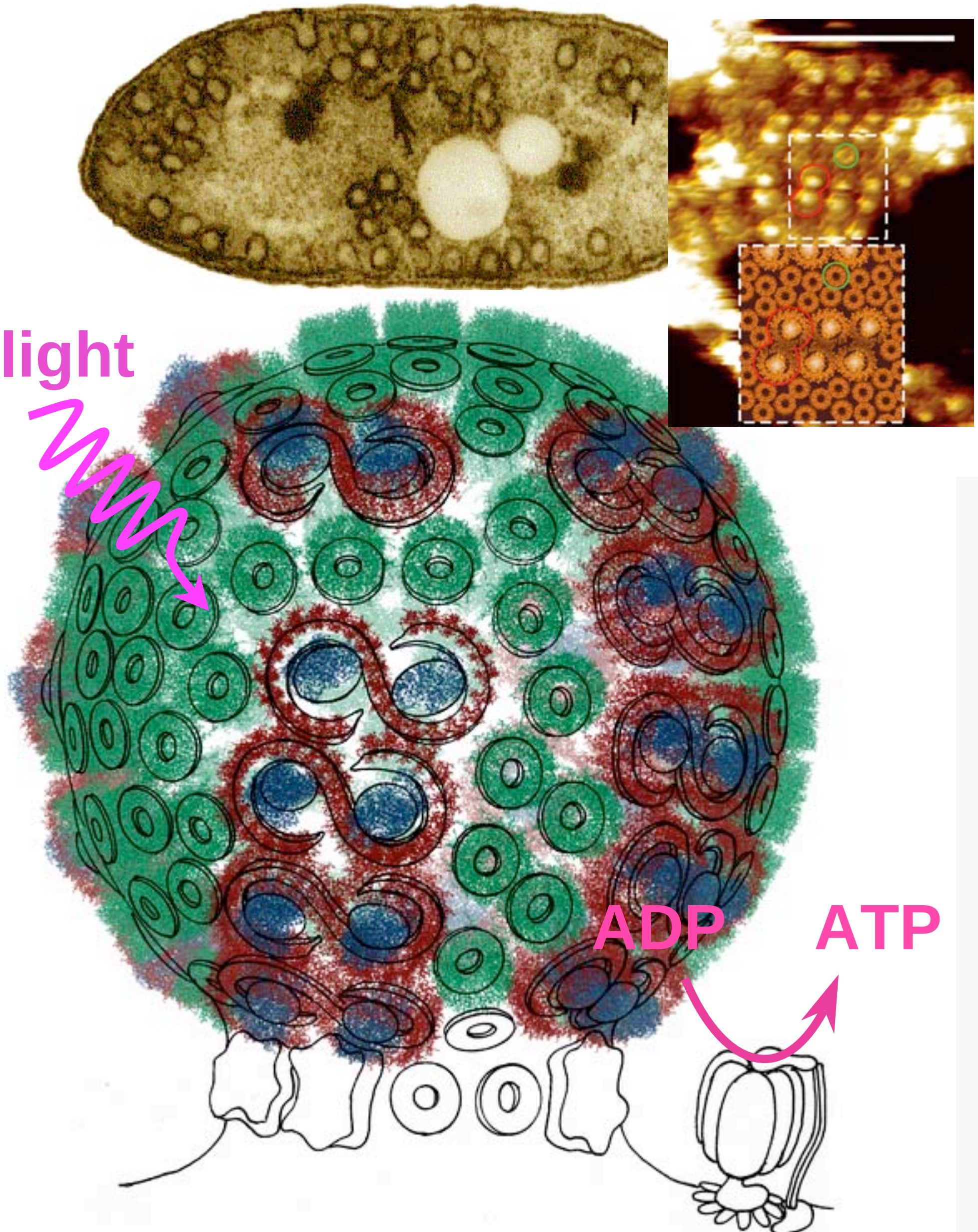
AFM imaging
soon: EM

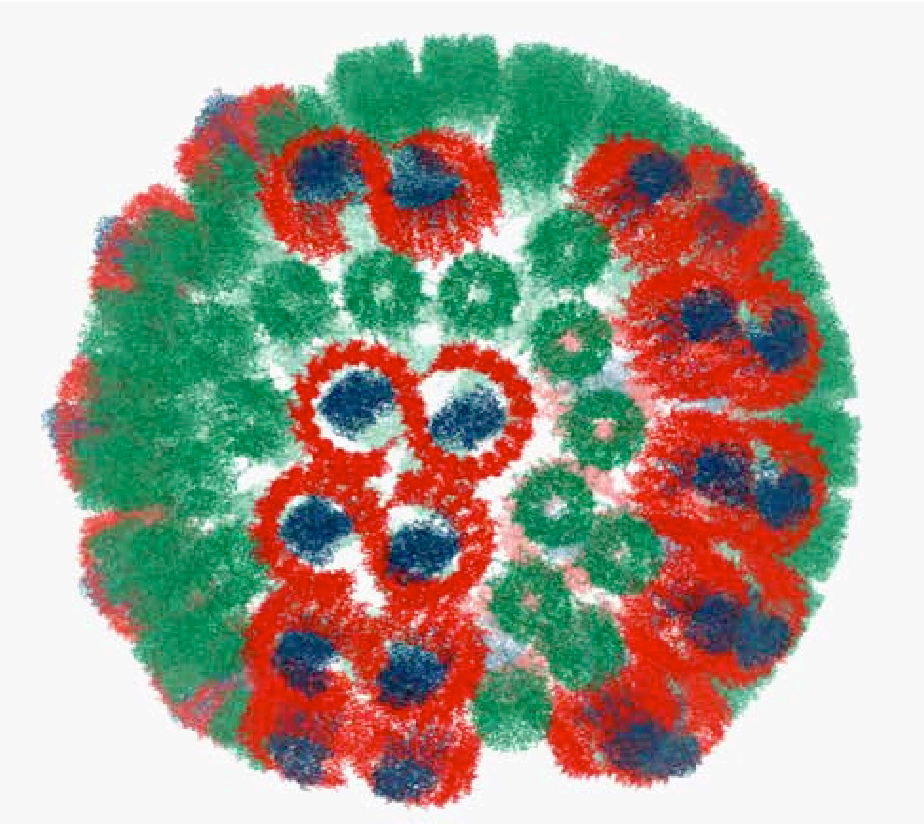


250 proteins,
six different types
all structurally known



Summary: Knowing the Atomic Level Structure of the chromatophore one can systematically describe its physcal mechanism

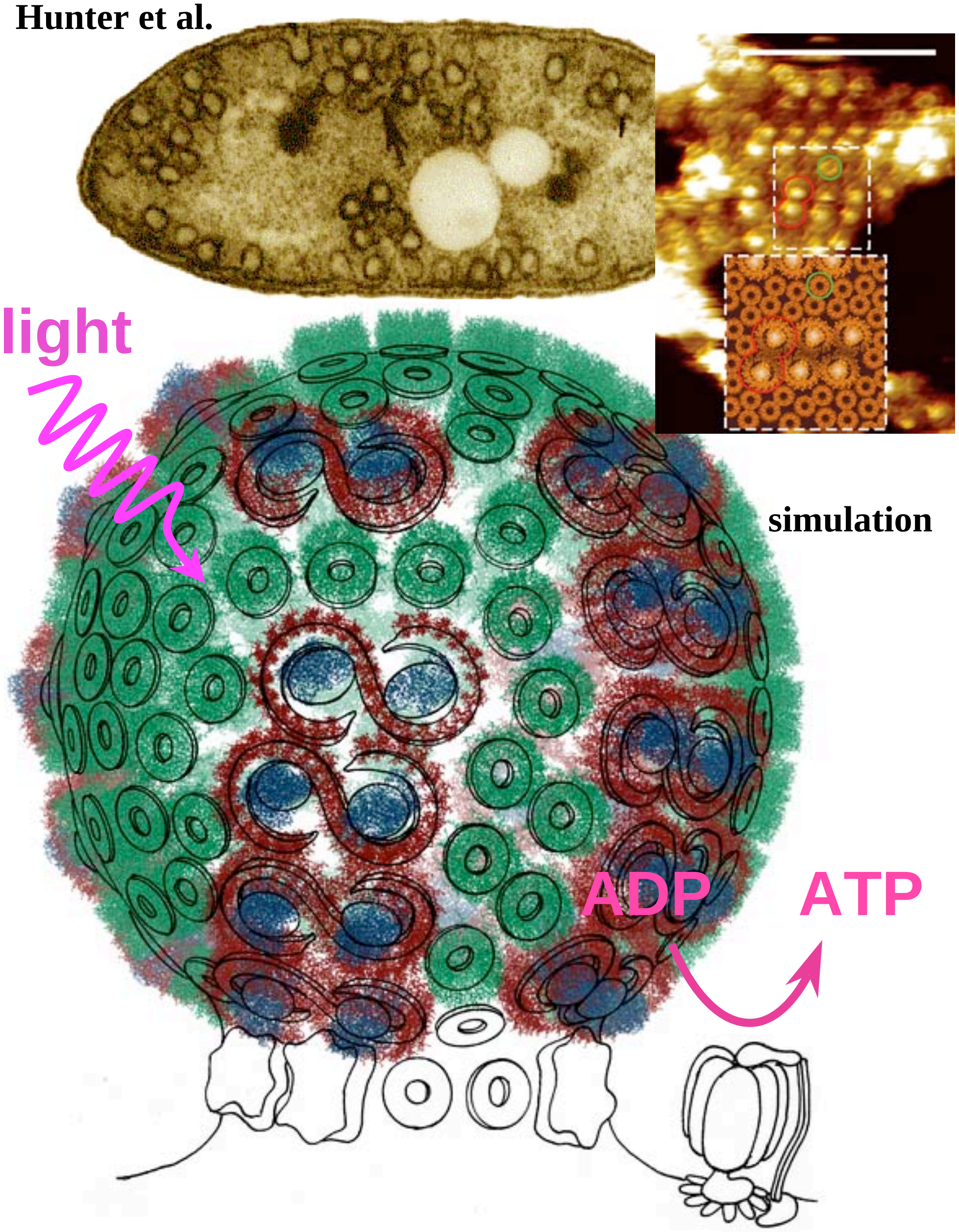




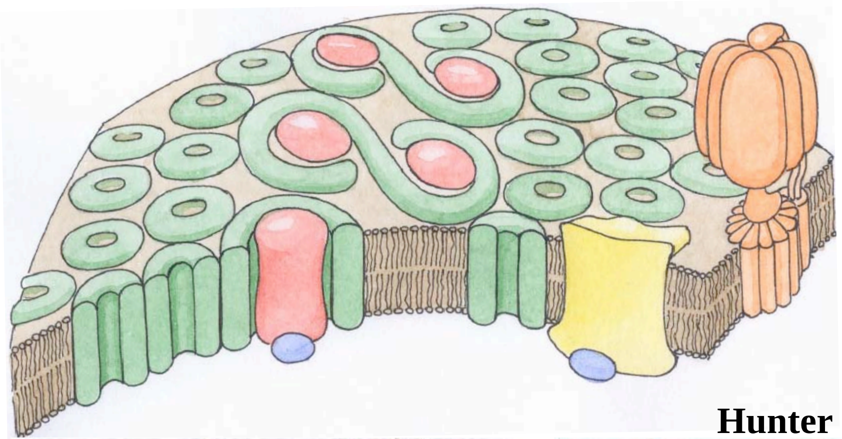
M. Sener, J. Olsen, N. Hunter, and K. Schulten. *PNAS*, **104:** 15723-15728, 2007

Studying the Morphogenesis of a Cellular Organelle

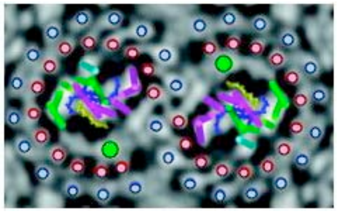
Hunter et al.



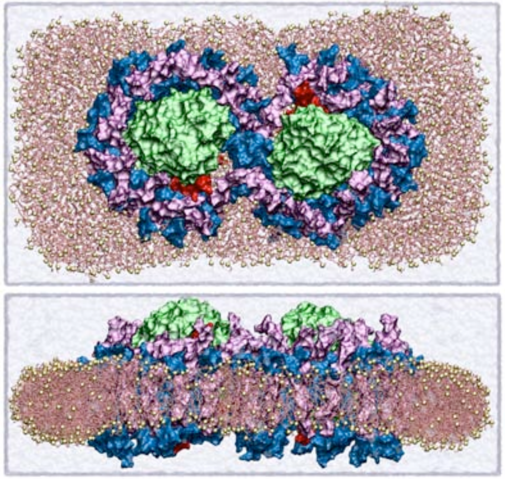
How does membrane curvature develop?



Hunter et al.



EM density



Simulation:
0.7 million atoms
20 ns equilibration

Rhodobacter sphaeroides **RC-LH1-PufX dimer**

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

Protein Packing Induces Membrane Curvature

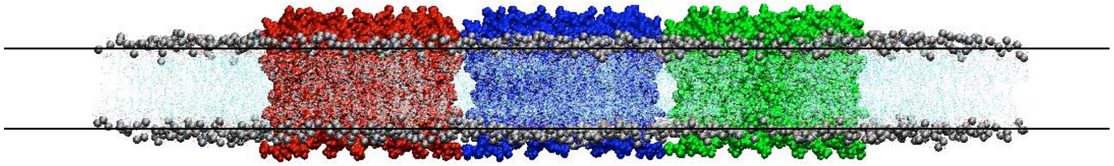
Seven *Rb. sphaeroides* peripheral light harvesting (LH2) complexes in mixed POPE/POPG membrane patch

909830 atoms

~10 ns full equilibration

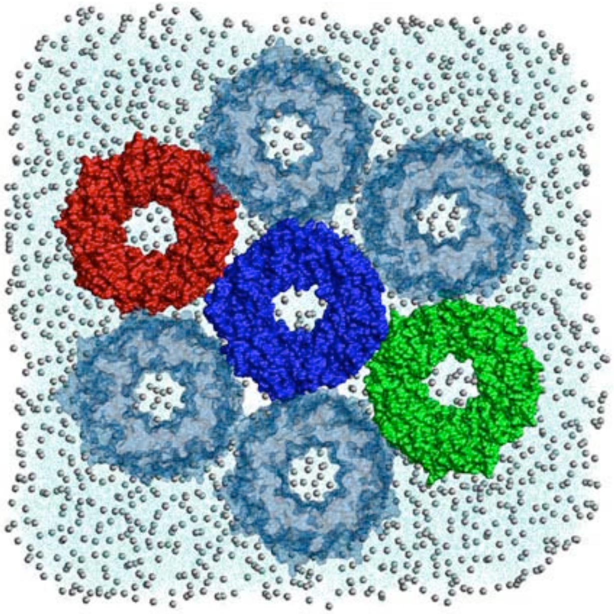
~ 1.2 ns/day on 32 Abe nodes

NPT equilibration, Charmm force field

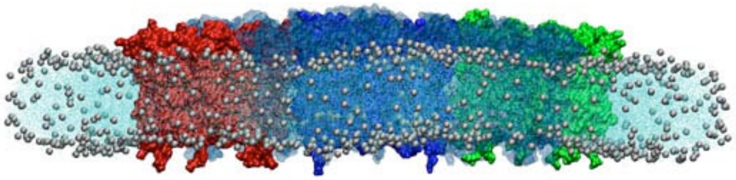


positive curvature

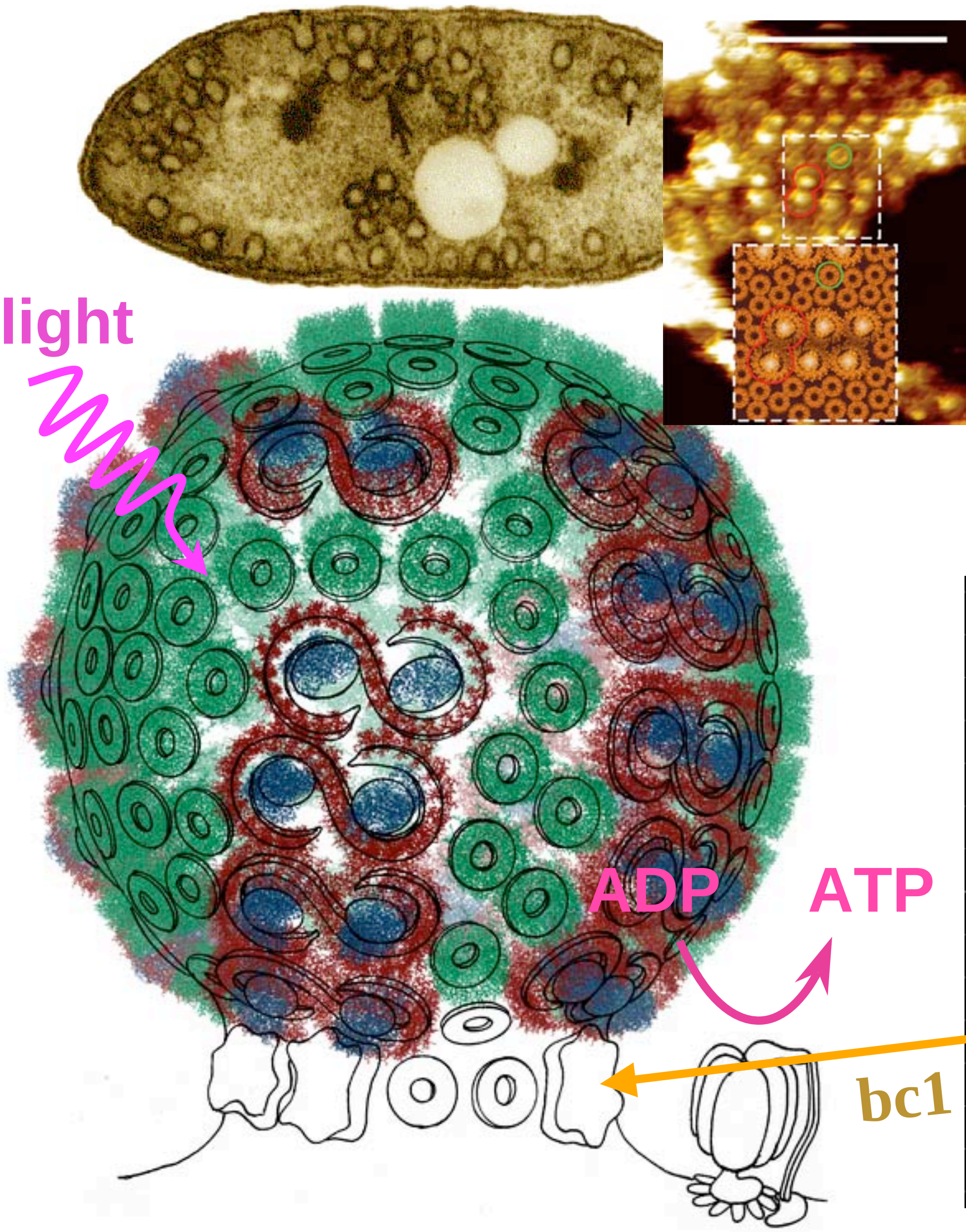
top view



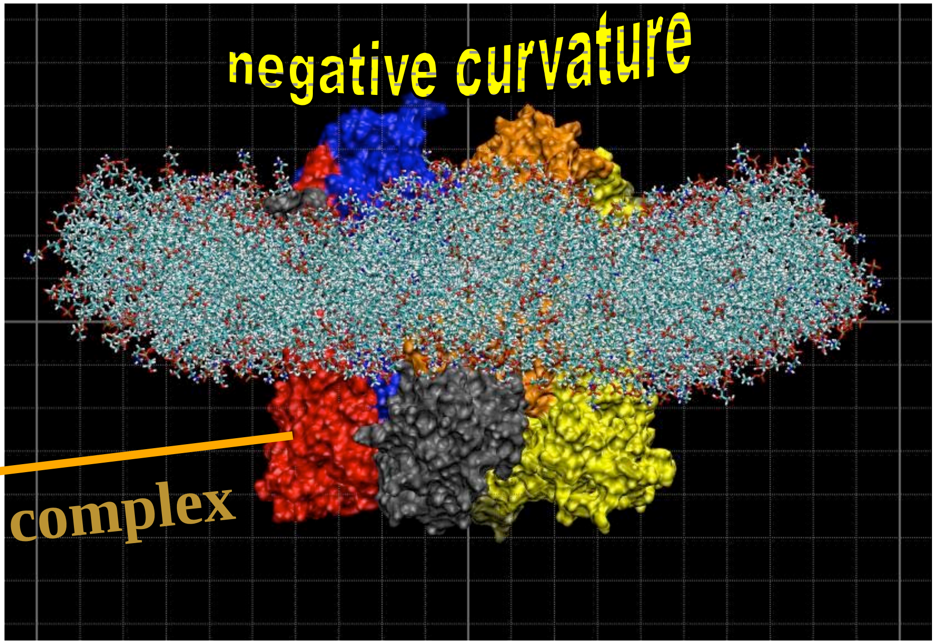
side view



Protein Packing Induces Membrane Curvature



How does membrane curvature develop?



Theoretical and Computational Biophysics Group

Funding: NIH, NSF

- focus on systems biology
- focus on quantum biology
- theoretical biophysics
- computational biophysics
- develops renewable energy
- guides bionanotechnology