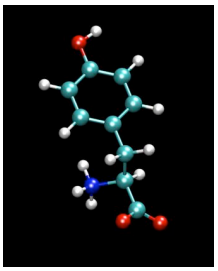
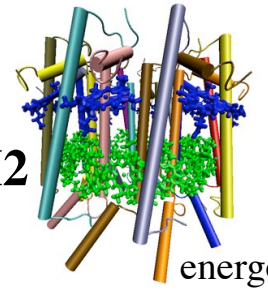
Lecture 1a

Introduction to Protein Structures - Molecular Graphics Tool

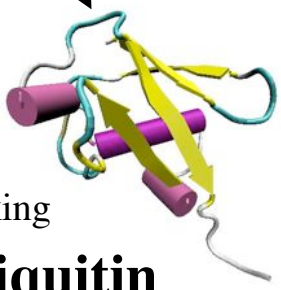


amino acid tyrosine



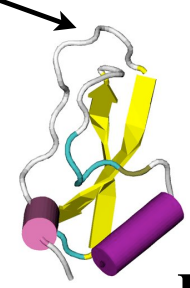
LH2

energetics



traficking

Ubiquitin

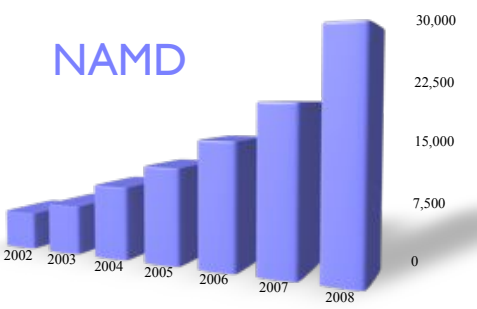


enzymatic control

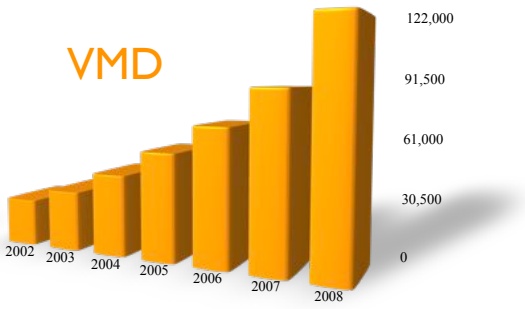
BPTI

Software Widely Used by Scientific Community

Sustained professional software development effort shipping products used by over 150,000 researchers/students worldwide



28,898 registered users
13,160 website visitors/month
1,200 citations



121,391 registered users
22,600 website visitors/month
3,000 citations

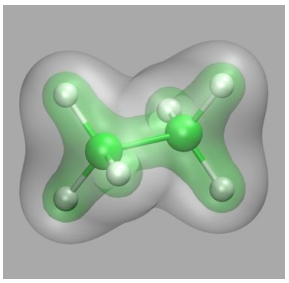
Team: K. Schulten (Physics), L. Kalé (Computer Sciences), Z. Schulten (Chemistry), R. Brunner, J. Phillips, J. Stone, K. Vandivort, D. Hardy, C. Harrison, B. Isralewitz, J. Saam, P. Freddolino, L. Trabuco

National Center for Research Resources

Center for the Physics of Living Cells

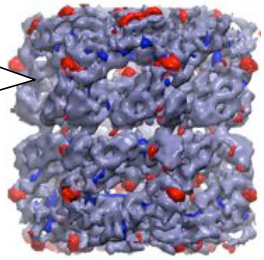
ILLINOIS
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

VMD – A Tool to Think



Volumetric Data:
Density maps,
Electron orbitals,
Electrostatic potential,
Time-averaged occupancy, …

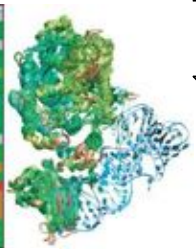
23,000 Users



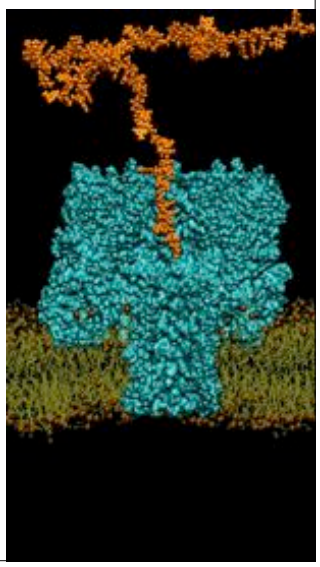
Sequence Data:
Multiple Alignments,
Phylogenetic Trees

VMD

Annotations

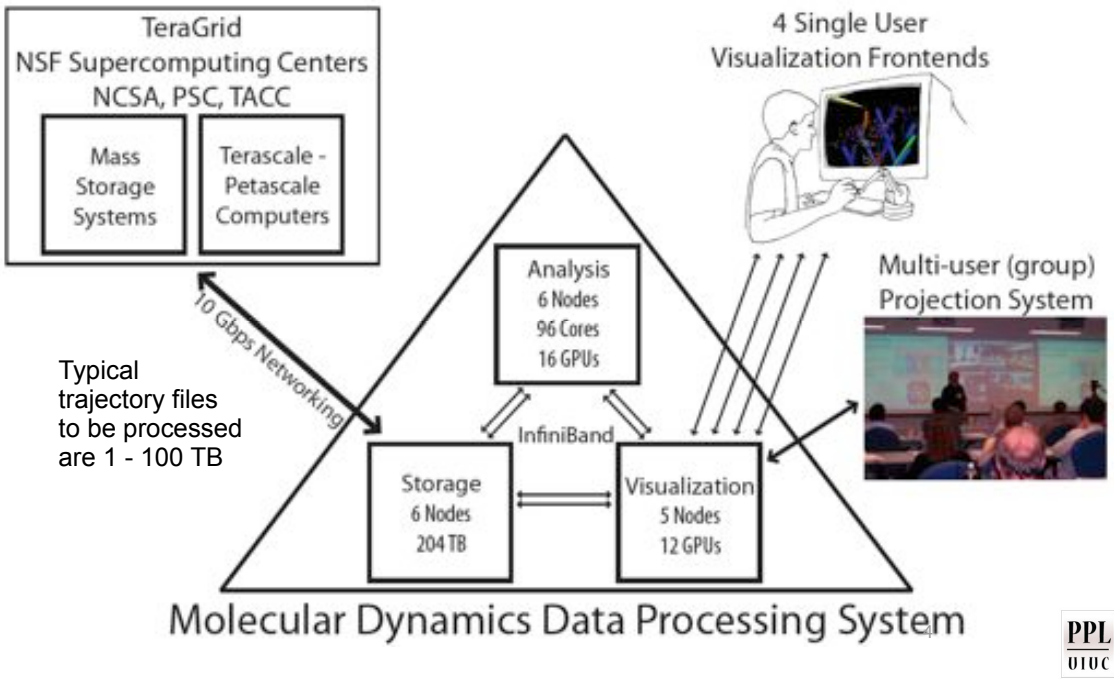


Atomic Data:
Coordinates,
Trajectories,
Energies,
Forces, …

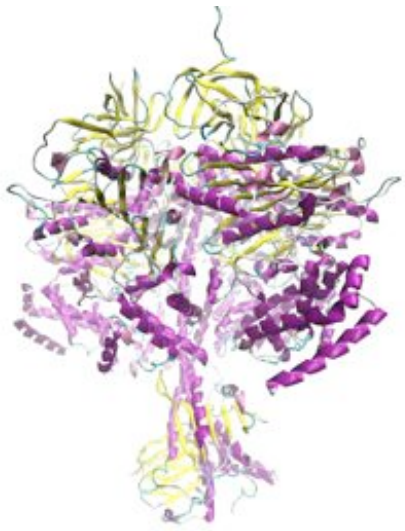


National Center for Research Resources

Biomolecular Modeling Requires Data Processing with VMD



Highlights of the VMD Molecular Graphics Program



- > 120,000 registered users
- Platforms:
  - Unix / Linux
  - Windows
  - MacOS X
- Display of large biomolecules and simulation trajectories
- Sequence browsing and structure highlighting
- Multiple sequence - structure analysis
- User-extensible scripting interfaces for analysis and customization

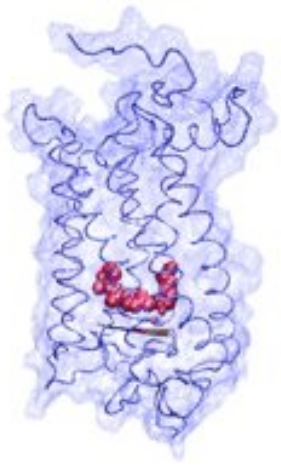
The program is used today more for preparation and analysis of modeling than for graphics

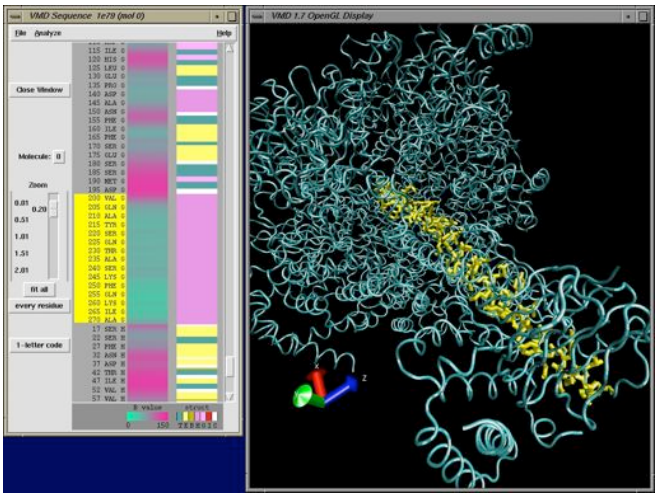
Key Features of VMD

- General 3-D molecular visualization with extensive drawing and coloring methods
- Extensive atom selection syntax for choosing subsets of atoms for display
- Visualization of dynamic molecular data
- Visualization of volumetric data
- Supports all major molecular data file formats
- No limits on the number of molecules or trajectory frames, except available memory
- Molecular analysis commands
- Rendering high-resolution, publication-quality molecule images
- Movie making capability
- Building and preparing systems for molecular dynamics simulations
- Interactive molecular dynamics simulations
- Extensions to the Tcl/Python scripting languages
- Extensible source code written in C and C++

Molecular Graphics Perspective of Protein Structure and Function

see tutorial at http://www.ks.uiuc.edu/Training/Tutorials/



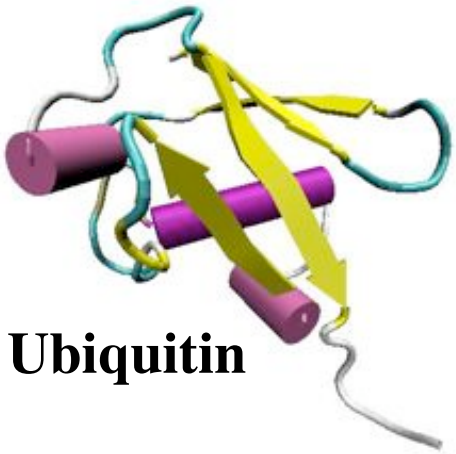


animation sequence structure

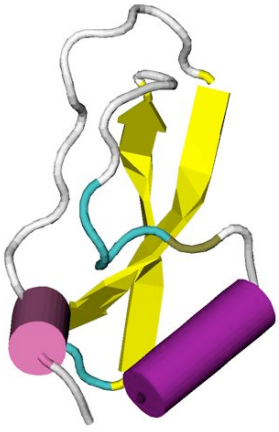
Focus on two proteins

Ubiquitin (used in VMD Tutorial)

Bovine Pancreatic Trypsin Inhibitor (BPTI, available as a case study, www.ks.uiuc.edu)



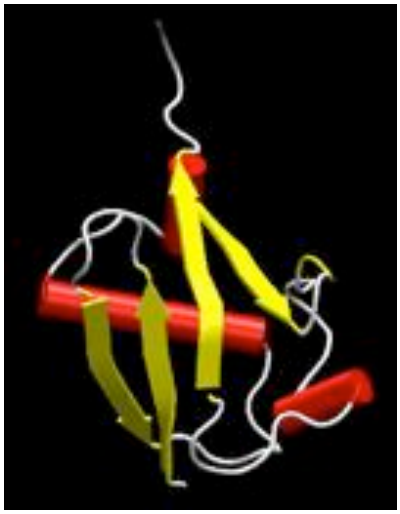
Ubiquitin



BPTI

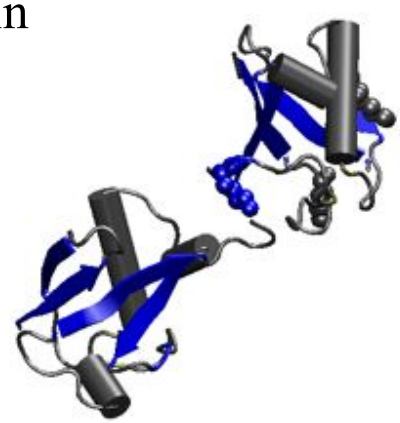
Ubiquitin

- 76 amino acids
- highly conserved
- covalently attaches to proteins and tags them for degradation
- other cell traficking



- Glycine at C-terminal attaches to the Lysine on the protein by an isopeptide bond.
- it can attach to other ubiquitin molecules and make a polyubiquitin chain.

There are 7 conserved lysine residues in ubiquitin.

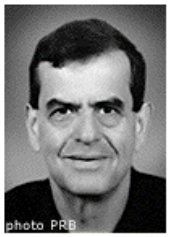


Two ubiquitins attached together through LYS 48. LYS 63 and LYS 29 are also shown there.

Ubiquitination Pathway

The Nobel Prize in Chemistry 2004

"for the discovery of ubiquitin-mediated protein degradation"



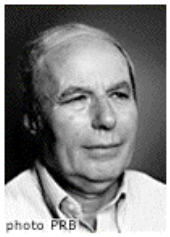
Aaron Ciechanover

1/3 of the prize

Israel

Technion – Israel Institute of Technology
Haifa, Israel

b. 1947



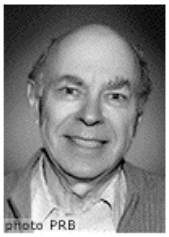
Avram Hershko

1/3 of the prize

Israel

Technion – Israel Institute of Technology
Haifa, Israel

b. 1937
(in Karcag, Hungary)



Irwin Rose

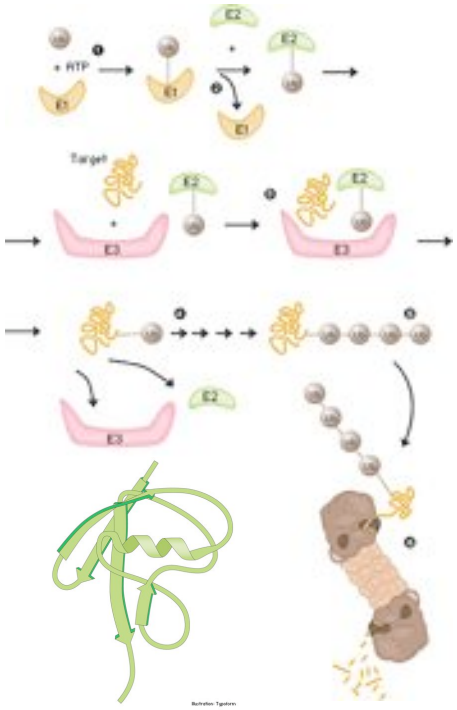
1/3 of the prize

USA

University of California
Irvine, CA, USA

b. 1926

Ubiquitin-mediated protein degradation

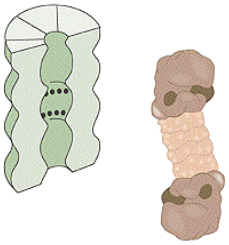


Ubiquitin Functions

• tagging misfolded proteins to be degraded in the proteasome (kiss of death).

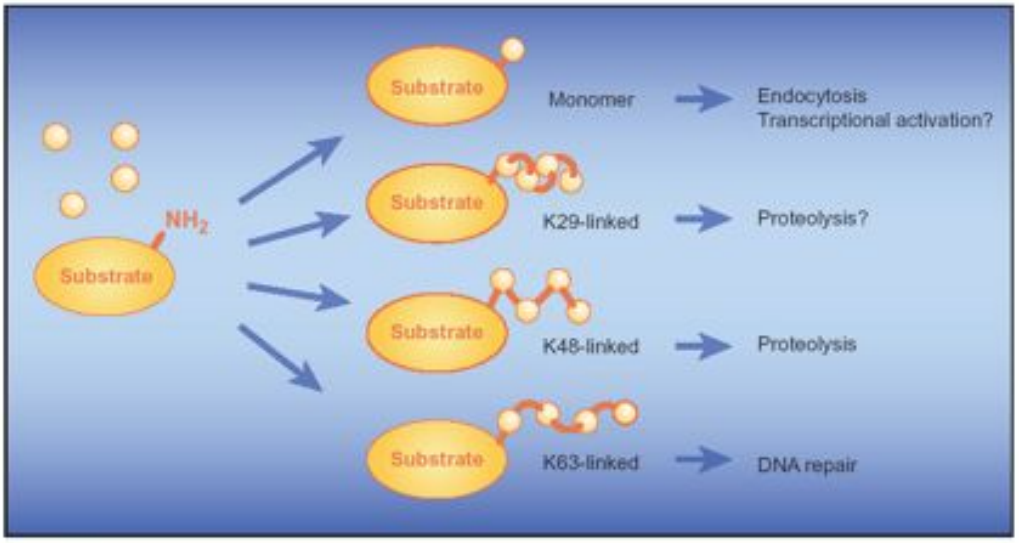
• regulates key cellular processes such as cell division, gene expression, ...

A chain of at least four ubiquitins is needed to be recognized by the proteasome.



The cell's waste disposer, the proteasome. The black spots indicate active, protein-degrading surfaces.

Mono-ubiquitylation versus multi-ubiquitylation



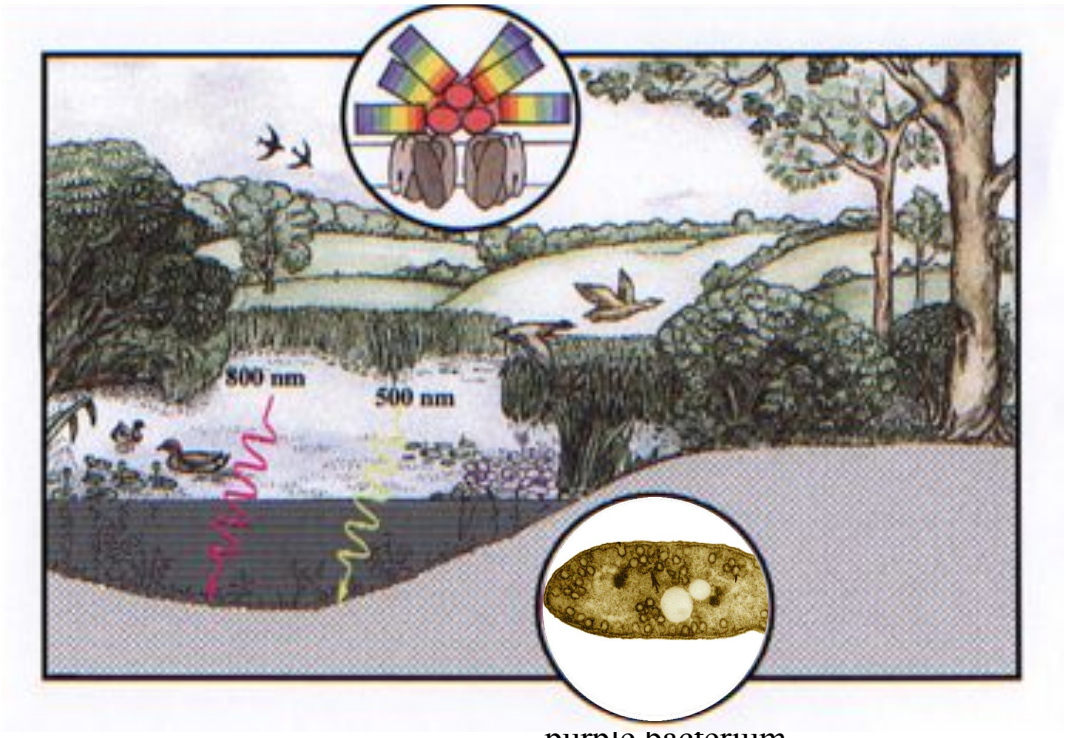
Multifaceted. Ubiquitin can attach to its various substrate proteins, either singly or in chains, and that in turn might determine what effect the ubiquitination has. (K29, K48, and K63 refer to the particular lysine amino acid used to link the ubiquitins to each other.)

Marx, J., Ubiquitin lives up its name, Science 297, 1792-1794 (2002)

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

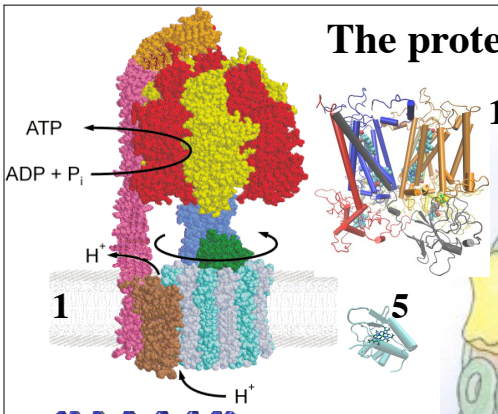
Klaus Schulten
Dept. Physics
U. Illinois at Urbana-Champaign

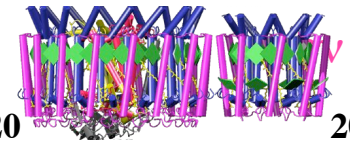
Habitats of Photosynthetic Life Forms



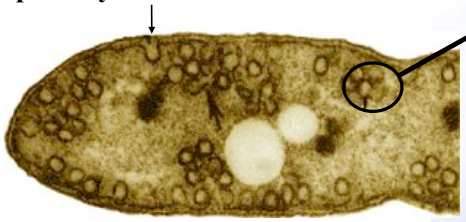
purple bacterium

The proteins that make up the chromatophore of photosynthetic bacteria

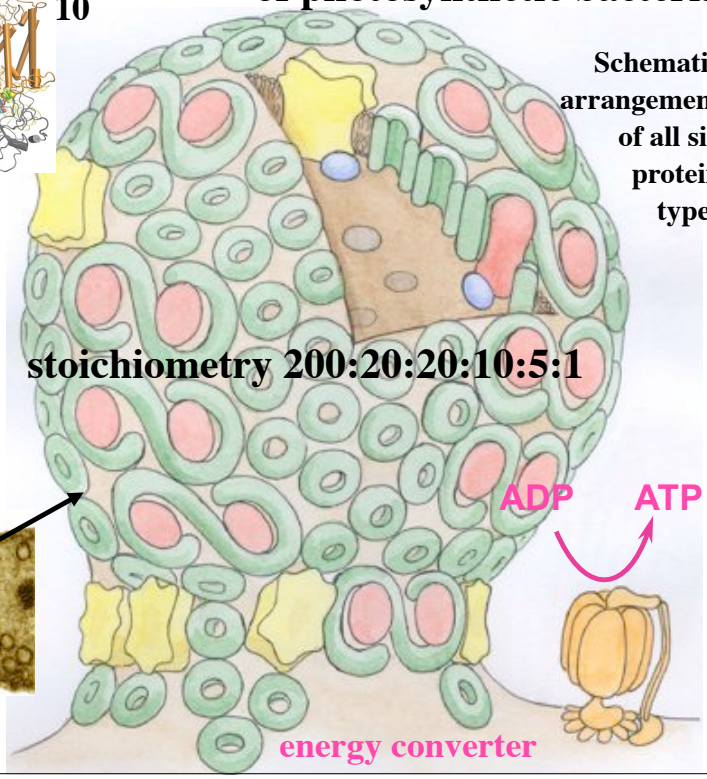




photosynthetic unit

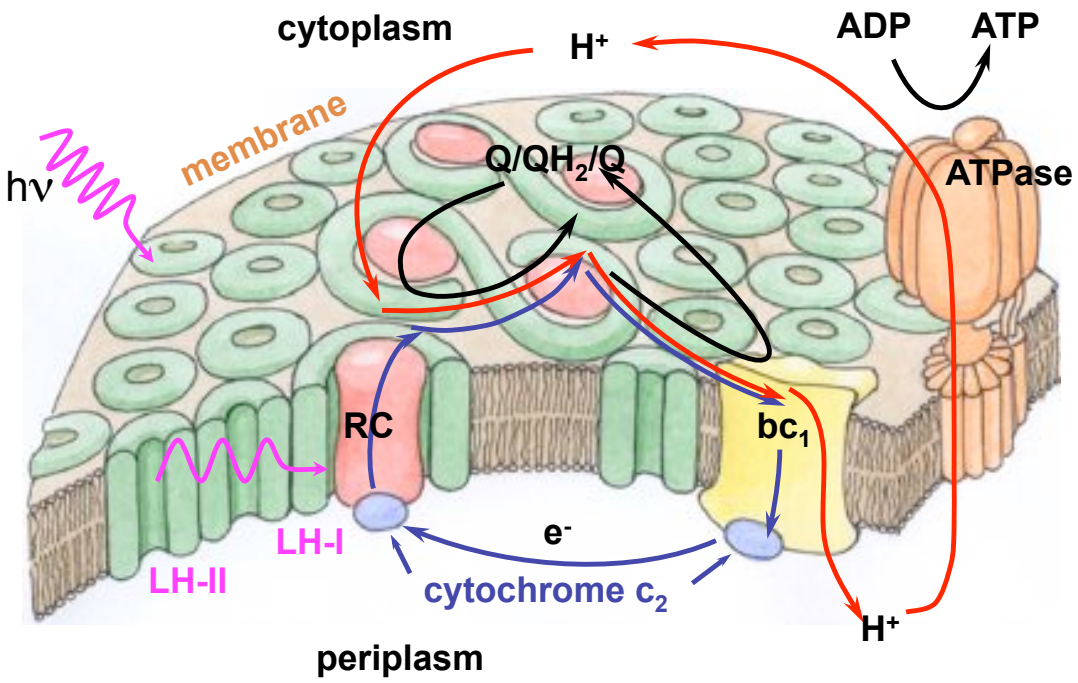


purple bacterium cell



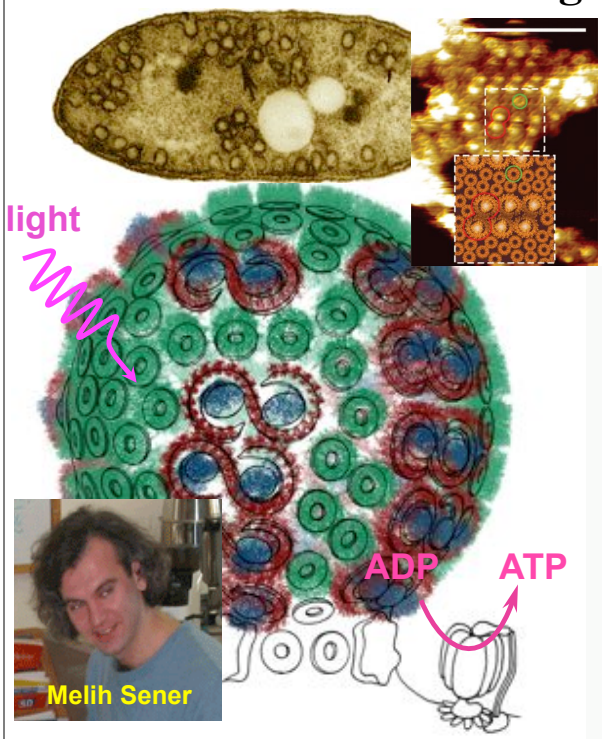
Chromatophore of Purple Bacteria

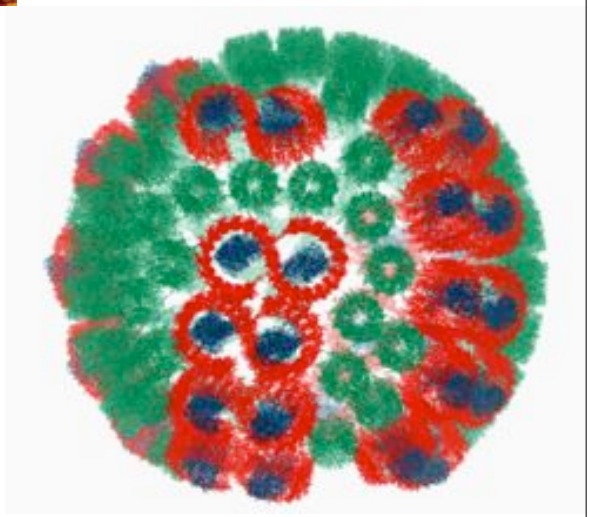
(section of the chromatophore membrane)



Knowing the Atomic Level Structure

of the chromatophore, one can systematically describe its physical mechanism



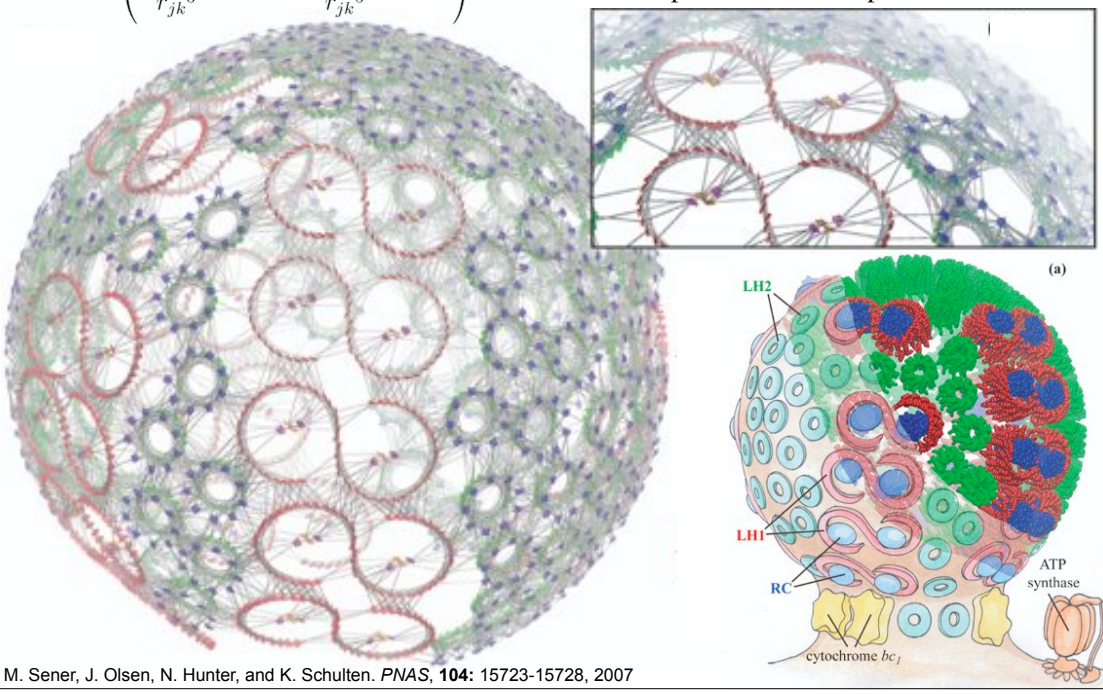


M. Sener, J. Olsen, N. Hunter, and K. Schulten. *PNAS*, **104:** 15723-15728, 2007

The "Physics" of Light Harvesting in the Chromatophore

Calculated Energy Transfer Rates Determine Optimal Placement of Proteins in Chromatophore

$$W_{jk} = C\left(\frac{\vec{d}_j \cdot \vec{d}_k}{{r_{jk}}^3} - \frac{3(\vec{r}_{jk} \cdot \vec{d}_j)\,(\vec{r}_{jk} \cdot \vec{d}_k)}{{r_{jk}}^5}\right)$$ links: induced dipole - induced dipole interaction



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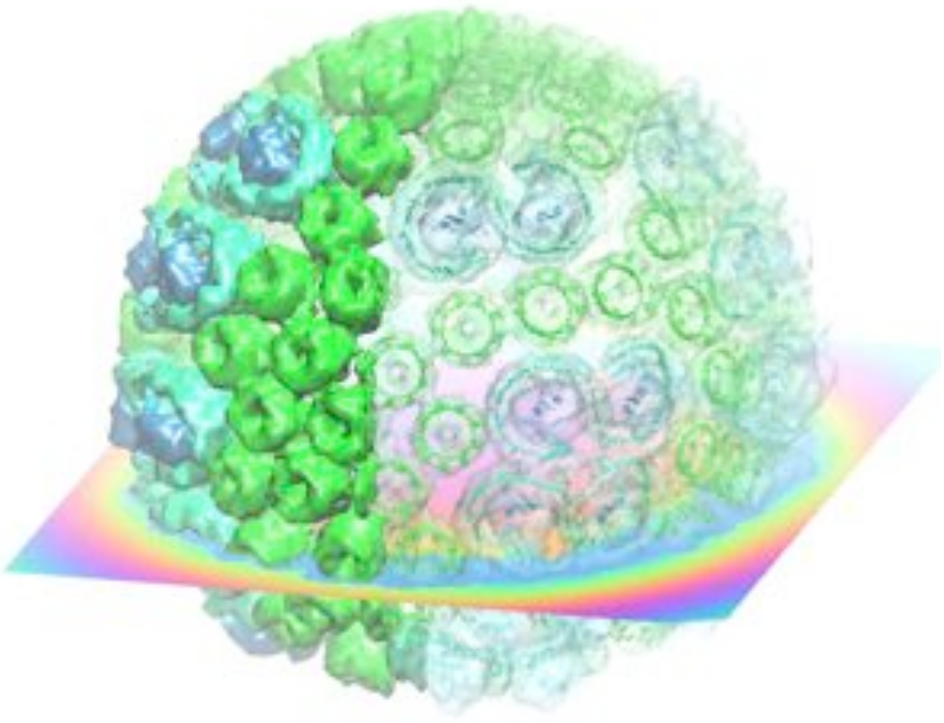
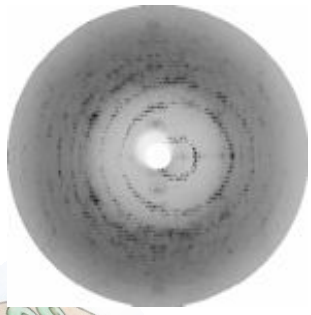
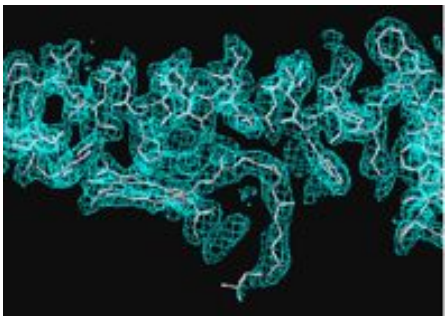
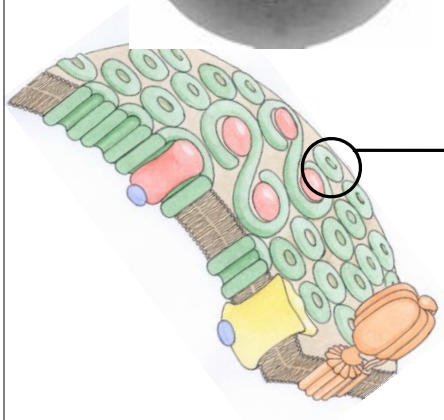


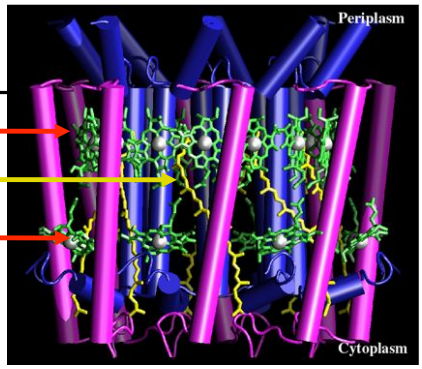
Structure of LH 2 of *Rs. molischianum*



molecular replacement







B850 band

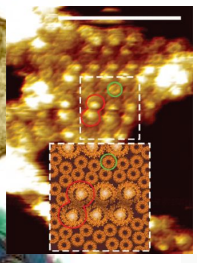
B500 band

B800 band

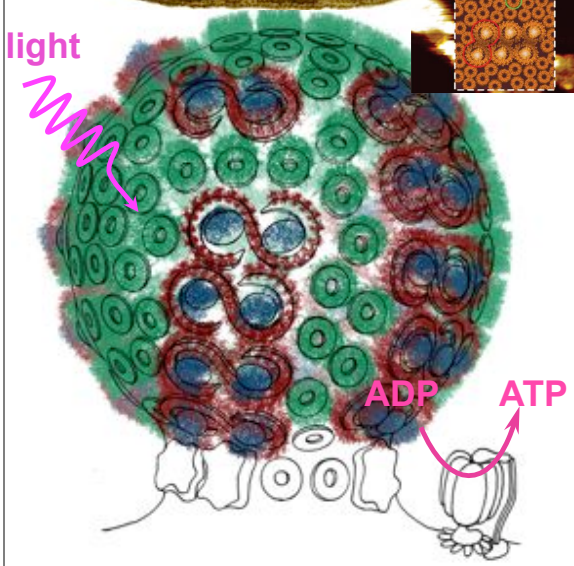
optical spectrum

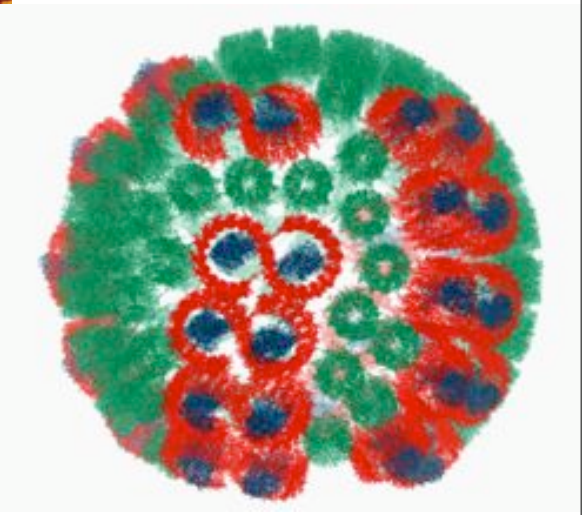
Koepke et al., Structure, **4**, 581 (1996)

Summary: Knowing the Atomic Level Structure



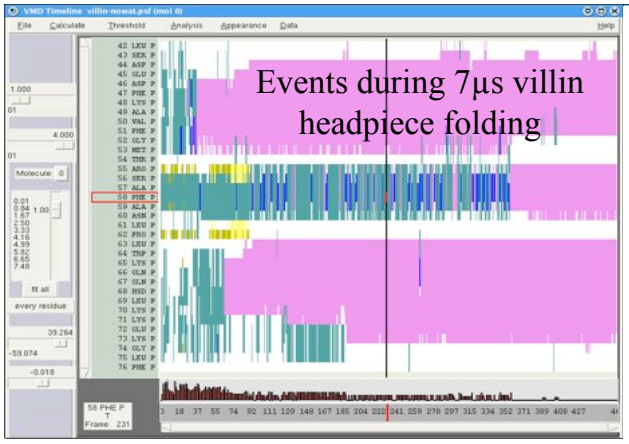
of the chromatophore, one can systematically describe its physical mechanism

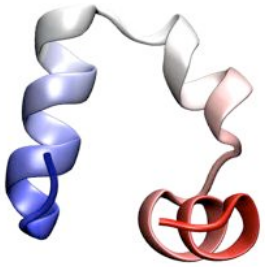




M. Sener, J. Olsen, N. Hunter, and K. Schulten. *PNAS*, **104:** 15723-15728, 2007

VMD New Timeline plug-in





Alpha helix Extended beta Isolated bridge 3-10 helix Beta turn None (coil)

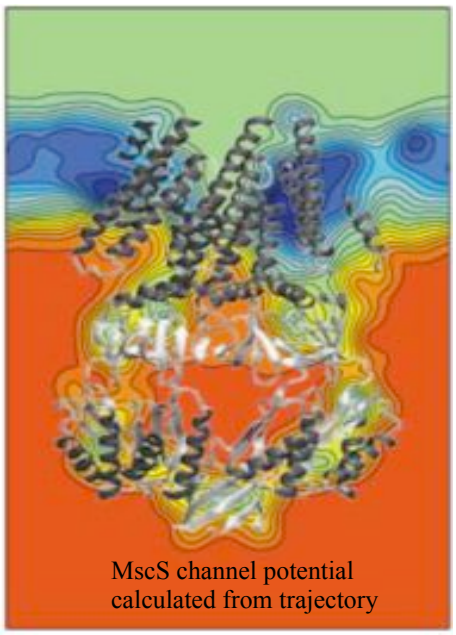
Per-residue secondary structure: villin headpiece folding from a fully denatured state.
7μs simulation; 654 atoms; over 1 million frames to examine

VMD **Timeline plug-in**: graphing and analysis tool to identify events in an MD trajectory
- a single picture shows changing properties across entire structure, entire trajectory.
- explore time vs. attribute (per-residue or per-selection) linked to molecular structure
- many analysis methods available; user-extendable

Electrostatic Potential Maps

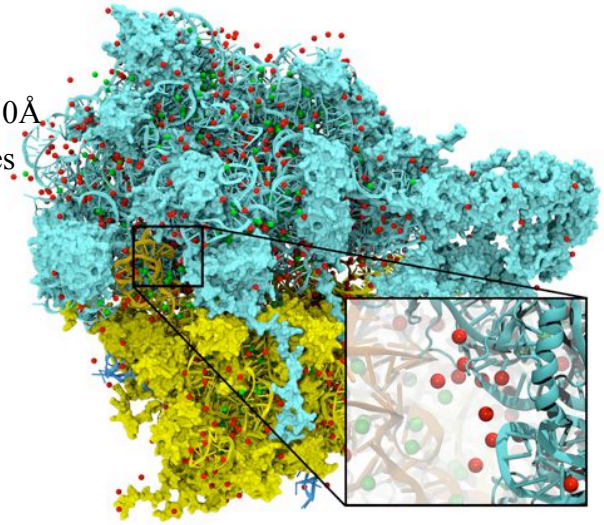
New VMD features made possible through GPU computing

- Electrostatic potentials evaluated on 3-D lattice
- Applications include:
  - Ion placement for structure building
  - Time-averaged potentials for simulation
  - Visualization and analysis



Time-averaged Electrostatic Potential Calculation for the Ribosome with VMD

- Direct Coulomb summation ~580,000 atoms
  - Lattice spacing 1.0Å, padding 10Å
  - Time-average from 1,000 frames
- 3 GPUs: 49 hours
- 3 CPUs: 0.23 years (est.)

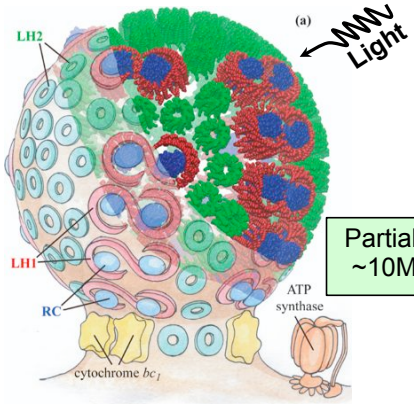


This was one of our early results, using the multi-GPU direct Coulomb summation algorithm, showing the benefit it gave at the time. Now that we have MSM (multilevel summation) we would get much faster performance since it is a linear-time algorithm, but we haven't yet re-run these tests using MSM.

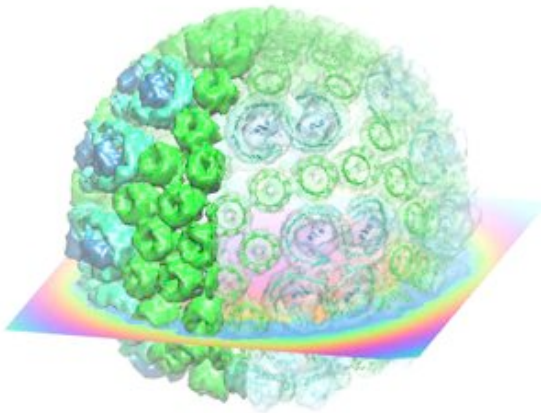
Stone et al. (2007) *J Comp Chem* 28:2618-2640

Photobiology of Vision and Photosynthesis

Investigations of the chromatophore, a photosynthetic organelle



Partial model: ~10M atoms

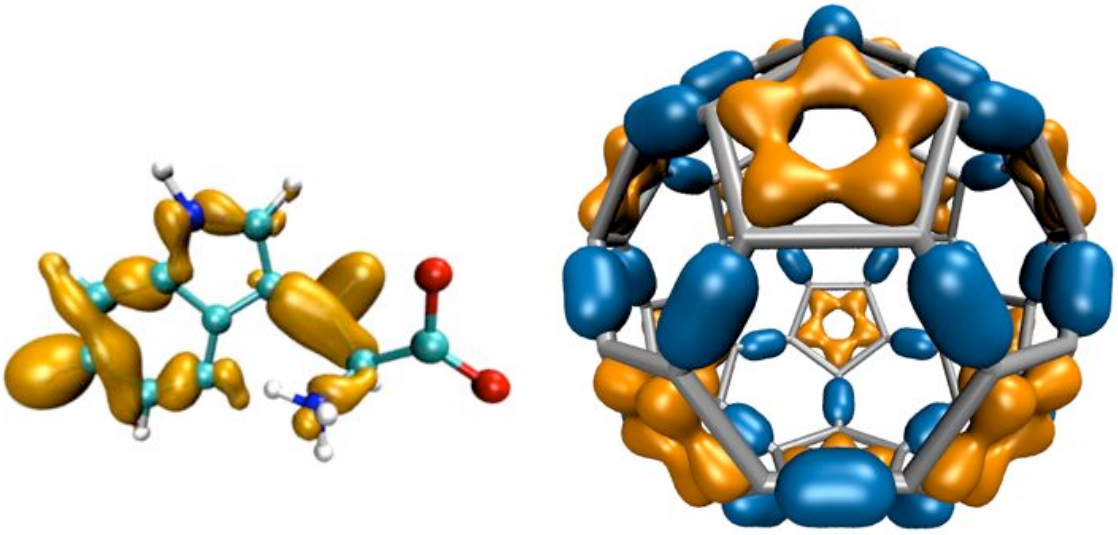


Electrostatics needed to build full structural model, place ions, study macroscopic properties

Electrostatic field of chromatophore model from multilevel summation method: computed with 3 GPUs in ~90 seconds, 46x faster than single CPU core

Full chromatophore model will permit structural, chemical and kinetic investigations at a structural systems biology level

Interactive display of molecular orbitals



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VMD team

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