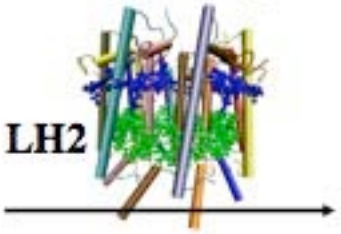
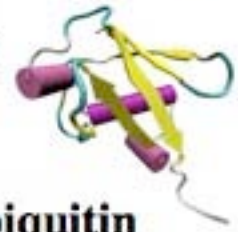
Lecture 1b

Introduction to Protein Structures - Molecular Graphics Tool

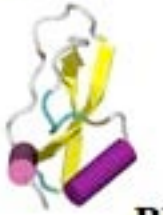
amino acid tyrosine



ATPase



Ubiquitin



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

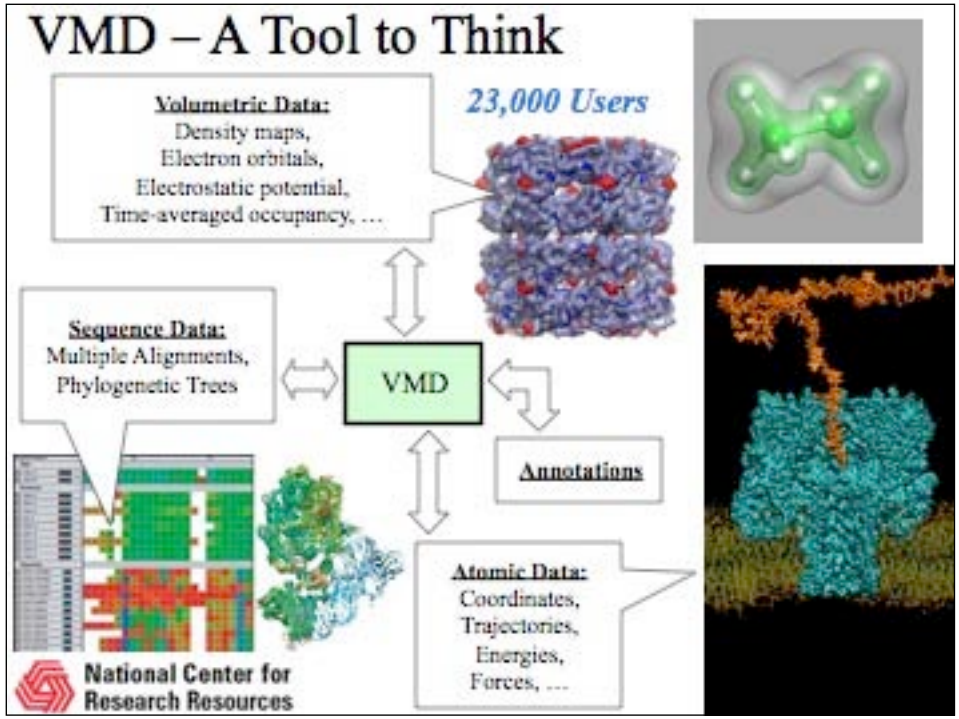
121,391 registered users
22,600 website visitors/month
3,000 citations

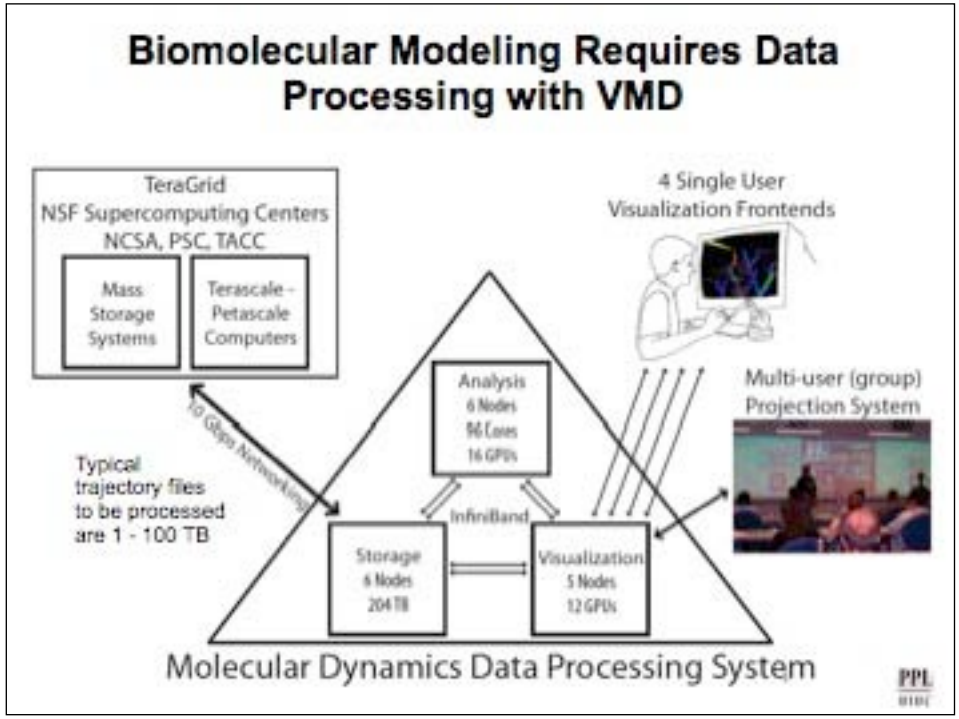
Team: K. Schulten (Physics), L. Kalé (Computer Sciences), Z. Schulten (Chemistry), R. Brunner, J. Phillips, J. Stone, K. Vandivort, D. Hardy, C. Harrison, B. Isralewitz, J. Saam, P. Freddolino, L. Trabuco

National Center for Research Resources

Center for the Physics of Living Cells

ILLINOIS


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
TeraGrid
NSF Supercomputing Centers
NCSA, PSC, TACC
Mass Storage Systems
Terascale - Petascale Computers
4 Single User Visualization Frontends
Multi-user (group) Projection System
Typical trajectory files to be processed are 1 - 100 TB
10 Gbps Networking
Analysis
6 Nodes
96 Cores
16 GPUs
InfiniBand
Storage
6 Nodes
204 TB
Visualization
5 Nodes
12 GPUs
Molecular Dynamics Data Processing System
PPL

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

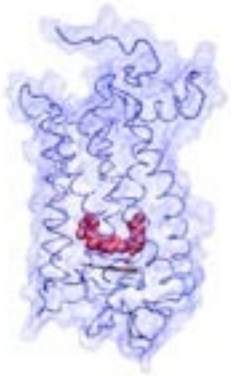
The program is used today more for preparation and analysis of modeling than for graphics

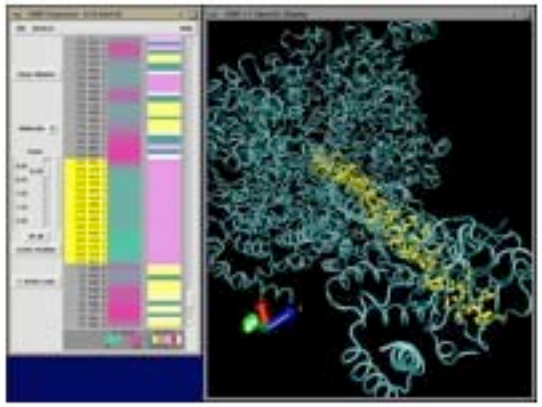
Key Features of VMD

- 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/



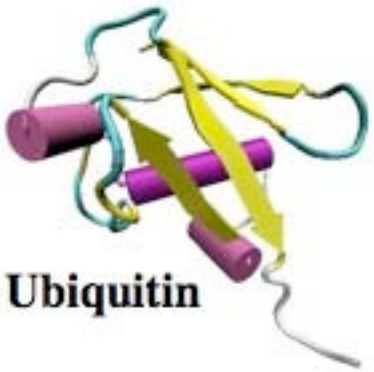


animation sequence structure

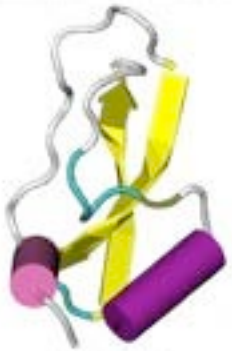
Focus on two proteins

Ubiquitin (used 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

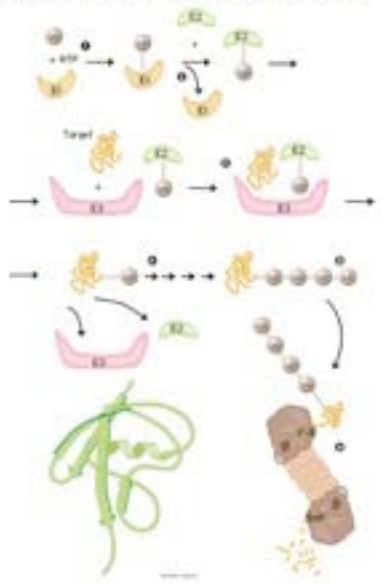
1/3 of the prize

USA

University of California
Irvine, CA, USA

b. 1926

Ubiquitin-mediated protein degradation



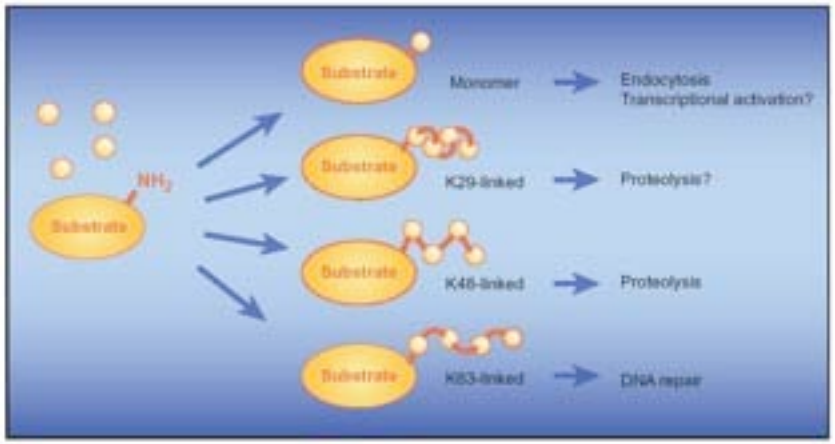
Ubiquitin Functions

- 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



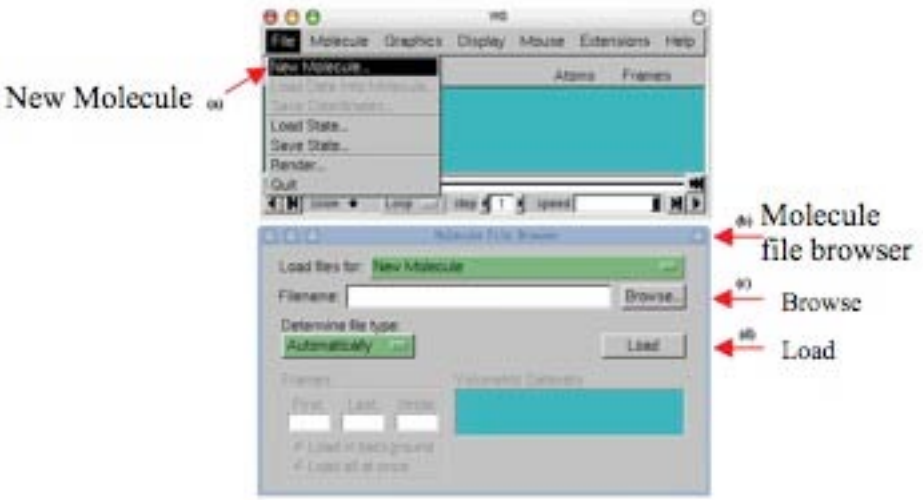
Multifaceted. Ubiquitin can attach to its various substrate proteins, either singly or in chains, and that in turn might determine what effect the ubiquitination has. (K29, K48, and K63 refer to the particular lysine amino acid used to link the ubiquitins to each other.)

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

Inspect ubiquitin with VMD

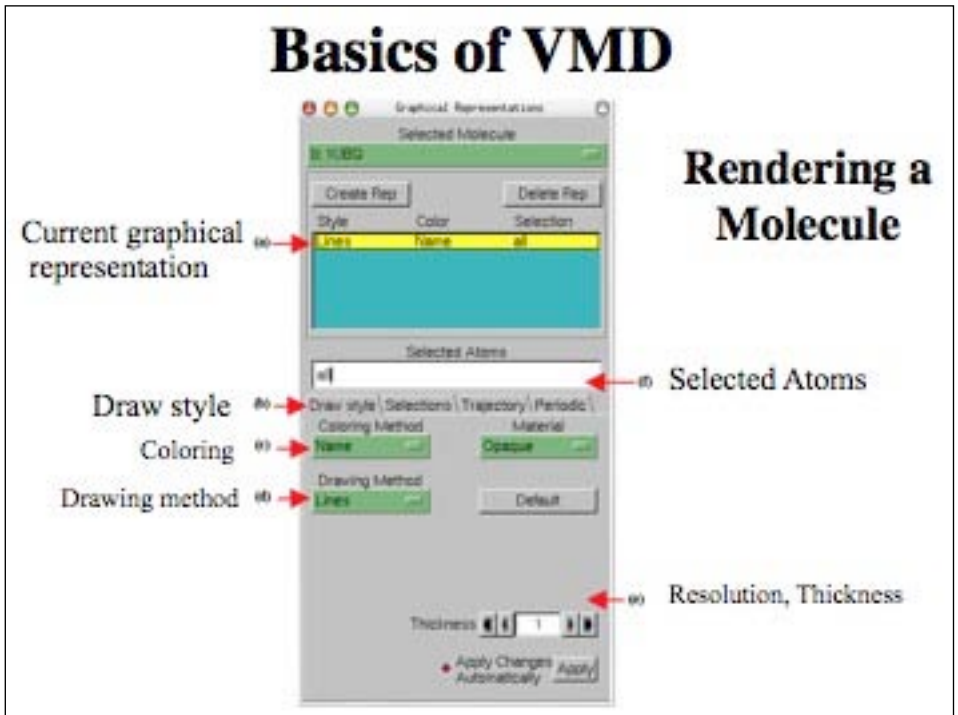
Basics of VMD

Loading a Molecule



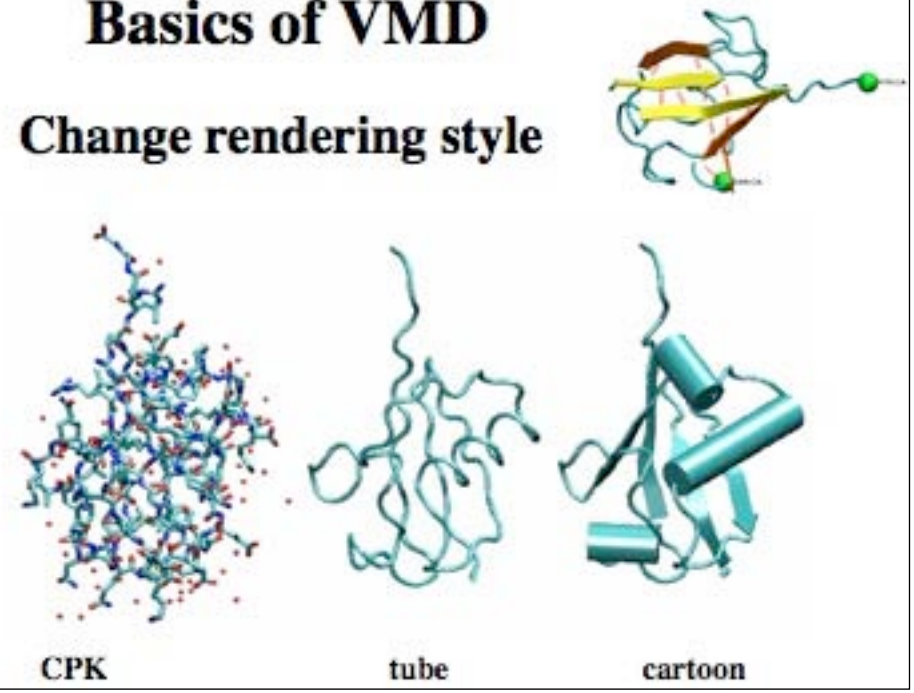
Basics of VMD

Rendering a Molecule

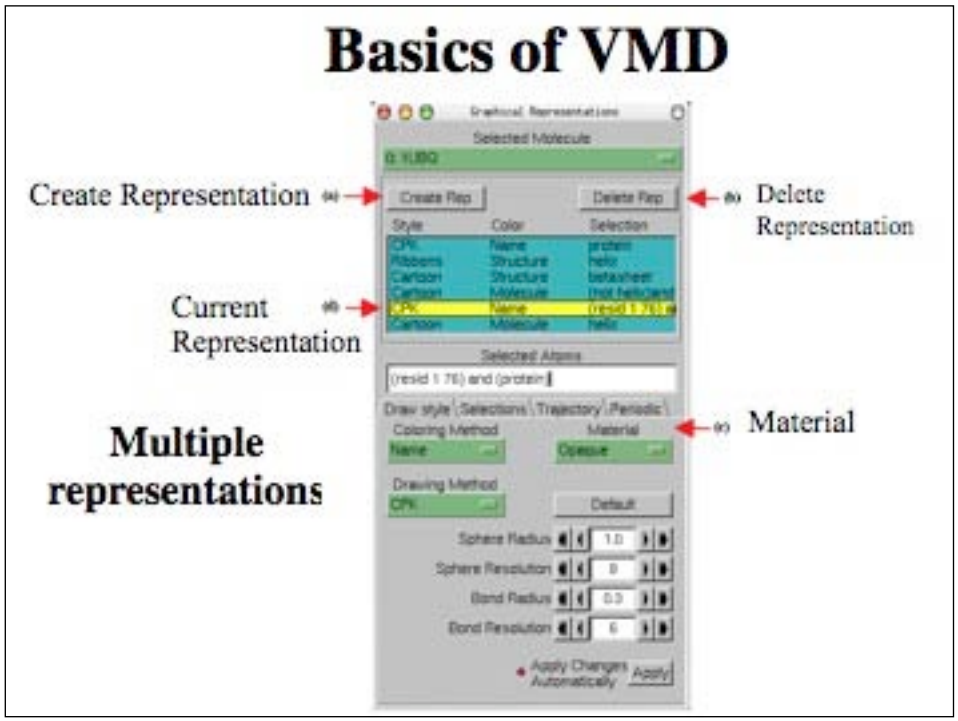


Basics of VMD

Change rendering style



Basics of VMD

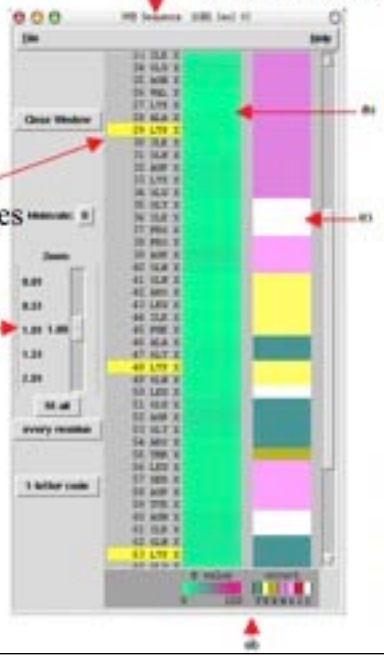


VMD Scripting

Left: Initial and final states of ubiquitin after spatial alignment
Right (top): Color coding of deviation between initial and final

The Color Controls window showing the Color Scale tab.

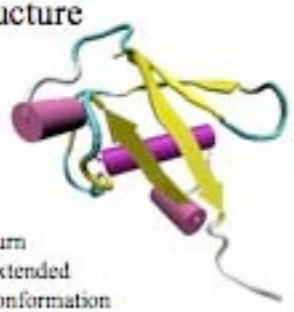
VMD Sequence Window



Beta Value

List of the residues

Structure

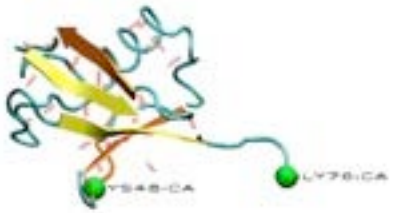


Zoom

T: Turn
E: Extended conformation
H: Helix
B: Isolated Bridge
G: 3-10 helix
I: Phi helix

VMD Macros to Color Beta Strands

Use VMD scripting features to color beta strands separately; show hydrogen bonds to monitor the mechanical stability of ubiquitin



Ubiquitin stretched between the C terminus and K48 does not fully extend!

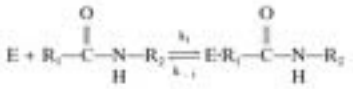
Discovering the Mechanical Properties of Ubiquitin

Ubiquitin stretched between the C and the N termini extends fully!

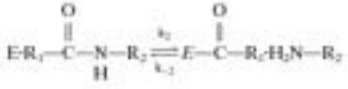
Discover BPTI on your own!

bovine pancreatic trypsin inhibitor

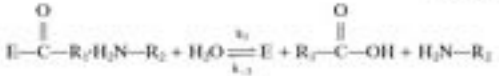
- small (58 amino acids)
- rigid
- binds as an inhibitor to Trypsin
  (a serine proteolytic enzyme, that appears in digestive system of mammalians.)
- blocks its active site.



(Michaelis complex)



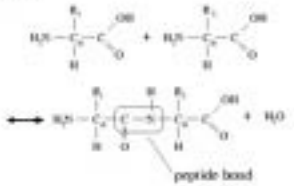
(Acyl–enzyme with leaving peptide noncovalently bound)



(Free enzyme and products)

Mechanism of cleavage of peptides with serine proteases.
Radisky E. and Koshland D. Jr., Proc. Natl. Acad. Sci., USA, 99, 10316-10321

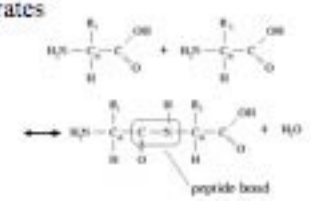
Trypsin: A proteolytic enzyme that hydrolyzes peptide bonds on the carboxyl side of Arg or Lys.



BPTI: A "standard mechanism" inhibitor

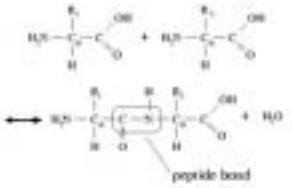
- Binds to Trypsin as a substrate.
  forms an acyl-enzyme intermediate rapidly.
- Very little **structural changes** in trypsin or BPTI.
  several H-bonds between backbone of the two proteins change,
  little reduction in conformational entropy → binds tightly
- Remains uncleaved.
  hydrolysis is 10^{11} times slower than for other substrates

Structures of the protease binding region, in the proteins of all 18 families of standard mechanism inhibitors are similar.



Why does Trypsin cleave BPTI so slowly?

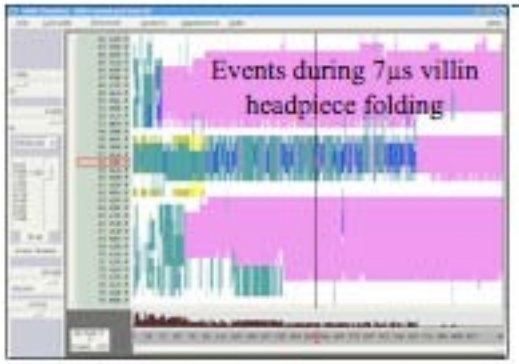
- Disruption of the non-covalent bonds in the tightly bonded enzyme-inhibitor complex increases the energy of transition states for bond cleavage.
- Water molecules do not have access to the active site, because of the tight binding of Trypsin and BPTI.
- After the cleavage of the active-site peptide bond, the newly formed termini are held in close proximity, favoring reformation of the peptide bond.
- The rigidity of BPTI may also contribute by not allowing necessary atomic motions.



Inspect BPTI with VMD in a Case Study (there is also a ubiquitin case study)

Go to: http://www.ks.uiuc.edu/Training/CaseStudies/

VMD New Timeline plug-in



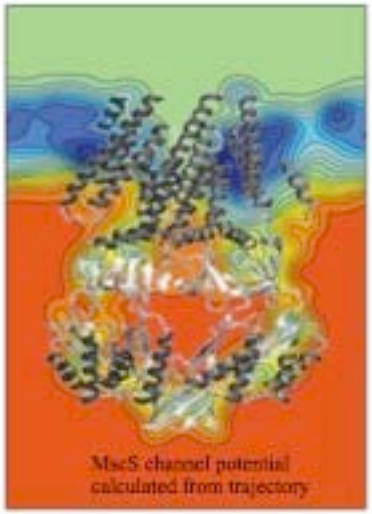
Per-residue secondary structure: villin headpiece folding from a fully denatured state.
7μs simulation; 654 atoms; over 1 million frames to examine

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

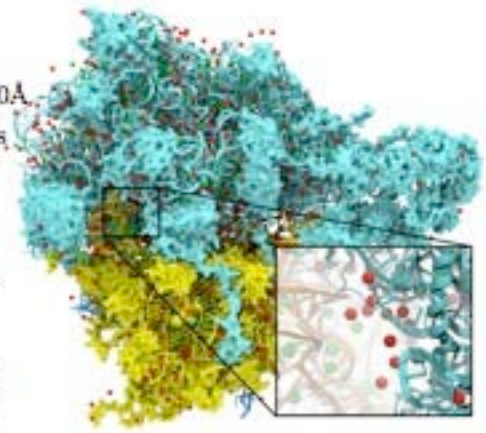
New VMD features made possible through GPU computing

- 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.)

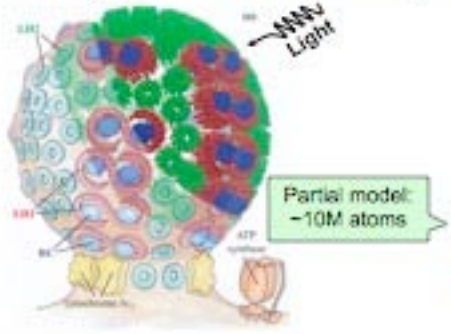


This was one of our early results, using the multi-GPU direct Coulomb summation algorithm, showing the benefit it gave at the time. Now that we have MSM (multilevel summation) we would get much faster performance since it is a linear-time algorithm, but we haven't yet re-run these tests using MSM.

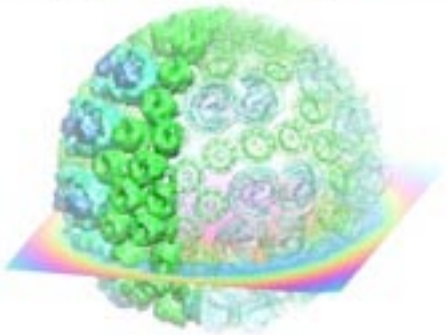
Stone et al. (2007) *J Comp Chem* 28:2618-2640

Photobiology of Vision and Photosynthesis

Investigations of the chromatophore, a photosynthetic organelle



Partial model:
~10M atoms

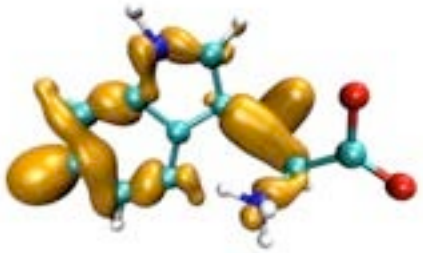


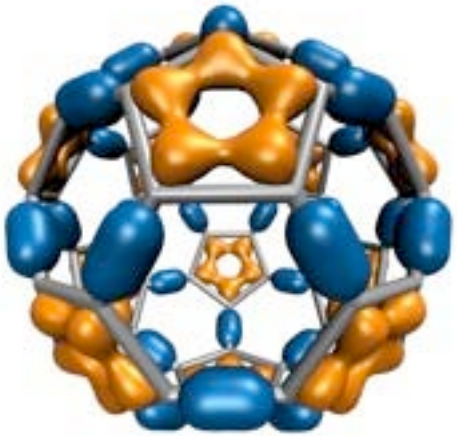
Electrostatics needed to build full structural model, place ions, study macroscopic properties

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





Acknowledgements

VMD team
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K. Vandivoort
R. Brunner

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National Center for Research Resources

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