A glimpse of computational methods in biological physics:

Case study on three proteins and a cellular organelle

Klaus Schulten
Theoretical and Computational Biophysics Group
February 15, 2012

Administrative issues

- Assignment from this lecture: read the case study on ubiquitin and choose THREE out of the six exercises to complete: http://www.ks.uiuc.edu/Training/CaseStudies/index.html#ubqcs
- You will have to download and install the software VMD: http://www.ks.uiuc.edu/Research/vmd/
- For any questions and assistance on the assignment, email Marco Tjioe at tjioe2@illinois.edu
- Assignments should be given to Professor Selvin before class on January 30, 2012 (next Wednesday).

Case Study: Ubiquitin

Eduardo Cruz-Chu and JC Gumbart

1 Introduction

Without a doubt, the most organized and coordinated machine known is the biological cell. Inside its micrometer-scale diameter, a wide variety of macromolecules (DNA, proteins, sugars, lipids, etc.) work together in a co-operative way, balancing energy and matter to keep the cell alive. Within the cell, proteins are the overachievers. They allow the movement of water and ions through the cell membrane, help ATP to store energy, assist DNA during replication, recognize foreign infections, and more. However, all of these functions don't work independently of each other. To maintain harmony and efficiency between various functions, most processes have to be turned on or off according to different cellular stages and changes within the environment.

To this end, together with the mechanisms to assemble functional proteins and to turn on their functions, there should be counterparts to suppress and disassemble proteins when they are no longer needed. The cellular machine depends on assembly and disassembly to regulate the effective concentration of proteins and their corresponding activities [1]. Furthermore, defective

1

Introduction to Protein Structures - Molecular Graphics Tool

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        10         20         30         40         50         60
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        70
IQKESTLHLV LRLRGG
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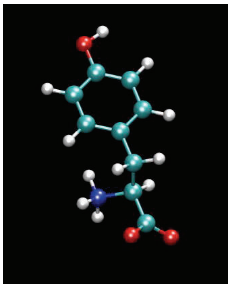
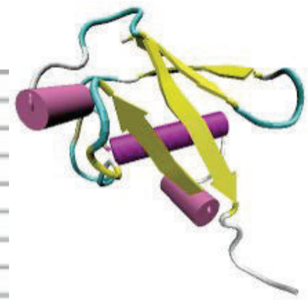


amino acid tyrosine, Y

Amino Acid	SLC	DNA codons
Isoleucine	I	ATT, ATC, ATA
Leucine	L	CTT, CTC, CTA, CTG, TTA, TTG
Valine	V	GTT, GTC, GTA, GTG
Phenylalanine	F	TTT, TTC
Methionine	M	ATG
Cysteine	C	TGT, TGC
Alanine	A	GCT, GCC, GCA, GCG
Glycine	G	GGT, GGC, GGA, GGG
Proline	P	CCT, CCC, CCA, CCG
Threonine	T	ACT, ACC, ACA, ACG
Serine	S	TCT, TCC, TCA, TCG, AGT, AGC
Tyrosine	Y	TAT, TAC
Tryptophan	W	TGG
Glutamine	Q	CAA, CAG
Asparagine	N	AAT, AAC
Histidine	H	CAT, CAC
Glutamic acid	E	GAA, GAG
Aspartic acid	D	GAT, GAC
Lysine	K	AAA, AAG
Arginine	R	CGT, CGC, CGA, CGG, AGA, AGG
Stop codons	Stop	TAA, TAG, TGA

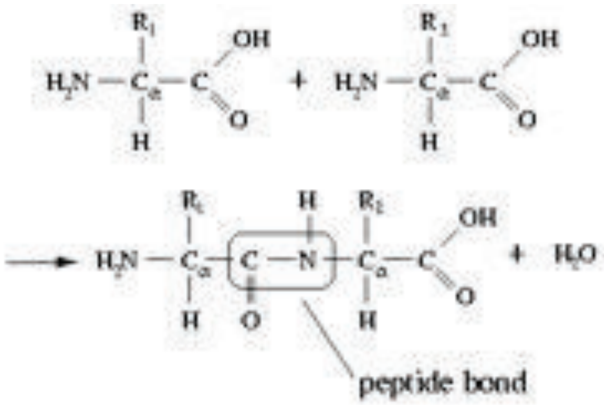


Ubiquitin

Quick Overview of Protein Structure

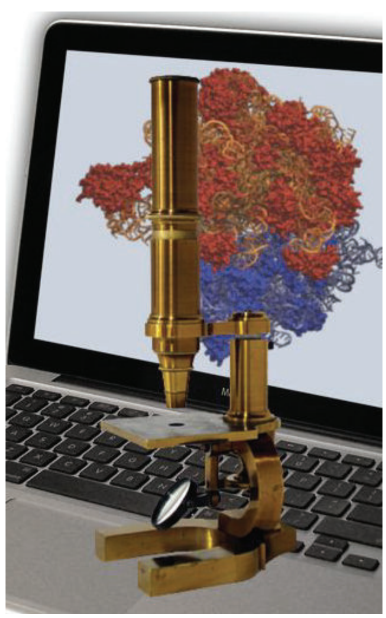
What Proteins are Made of:
Primary Structure (Sequence) of Amino Acids

Proteins: polymeric molecules linking amino acids through peptide bonds



Peptide bond linking two amino acids

Looking at Proteins Through the Program VMD

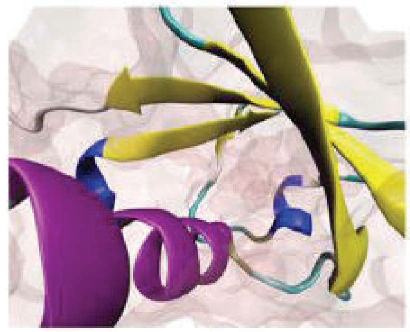


Learn to use VMD from the
"Using VMD" tutorial available at
http://www.ks.uiuc.edu/Training/Tutorials/

VMD for Mac OS X, Unix, and
Windows is available for download at
http://www.ks.uiuc.edu/Research/vmd/

University of Illinois at Urbana-Champaign
Beckman Institute for Advanced Science and Technology
Theoretical and Computational Biophysics Group
Computational Biophysics Workshop

Using VMD



VMD Developer:
John Stone

Tutorial Contributors:
Alek Aksimentiev, Anton Arkhipov, Robert Brunner, Jordi Cohen, Brijeet Dhaliwal, John Eargle, Jen Hsin, Fatemeh Khalili, Eric H. Lee, Zan Luthey-Schulten, Patrick O'Donoghue, Elijah Roberts, Anurag Sethi, Marcos Sotomayor, Emad Tajkhorshid, Leonardo Trabuco, Elizabeth Villa, Yi Wang, David Wells, Dan Wright, Ying Yin

July 2009

VMD Demo 0

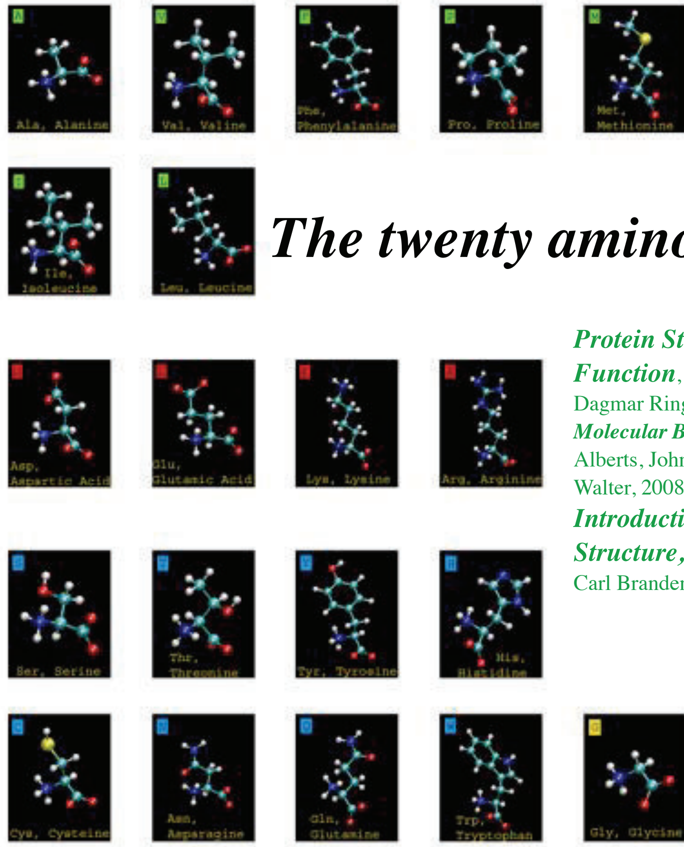
Protein Primary Structure

The twenty amino acids

non-polar

charged

polar



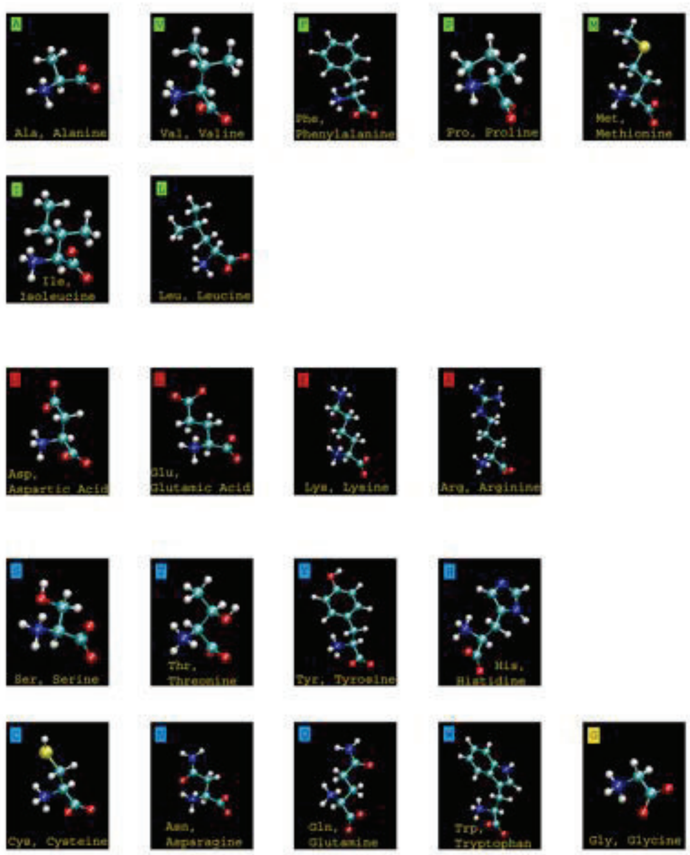
Protein Structure and Function, Gregory Petsko and Dagmar Ringe, 2004

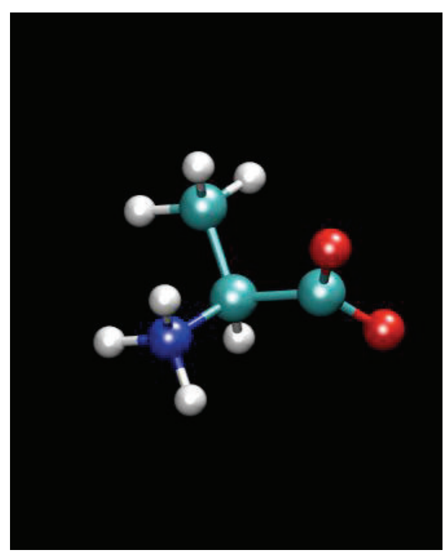
Molecular Biology of The Cell Alberts, Johnson, Lewis, Raff, Roberts, Walter, 2008, 3rd Ed.

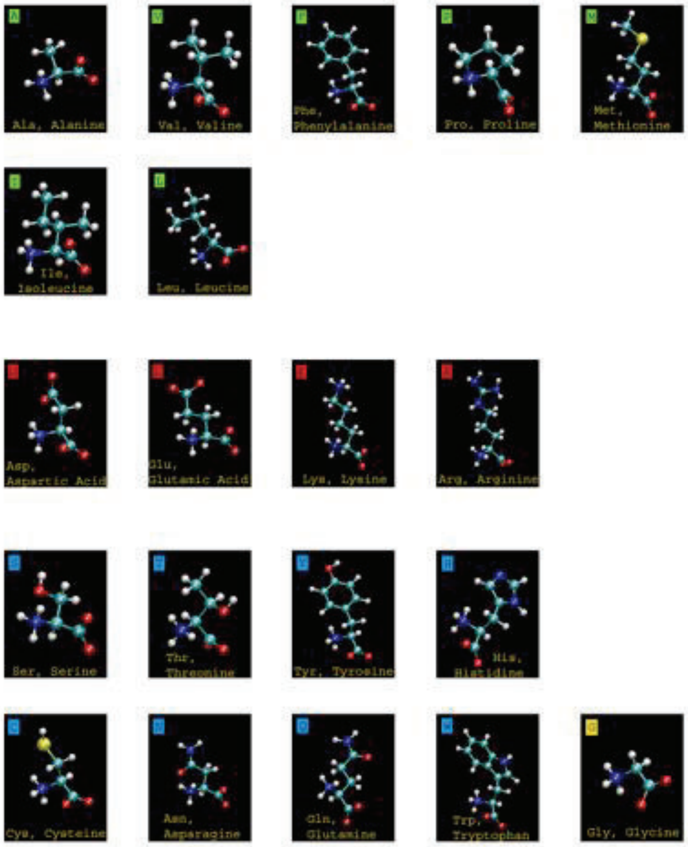
Introduction to Protein Structure, *2nd ed.* Carl Branden & John Tooze, 1999

URL: http://lectures.molgen.mpg.de/ProteinStructure

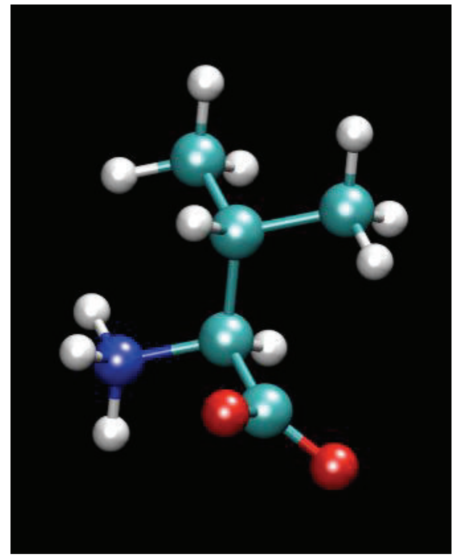
Alanine

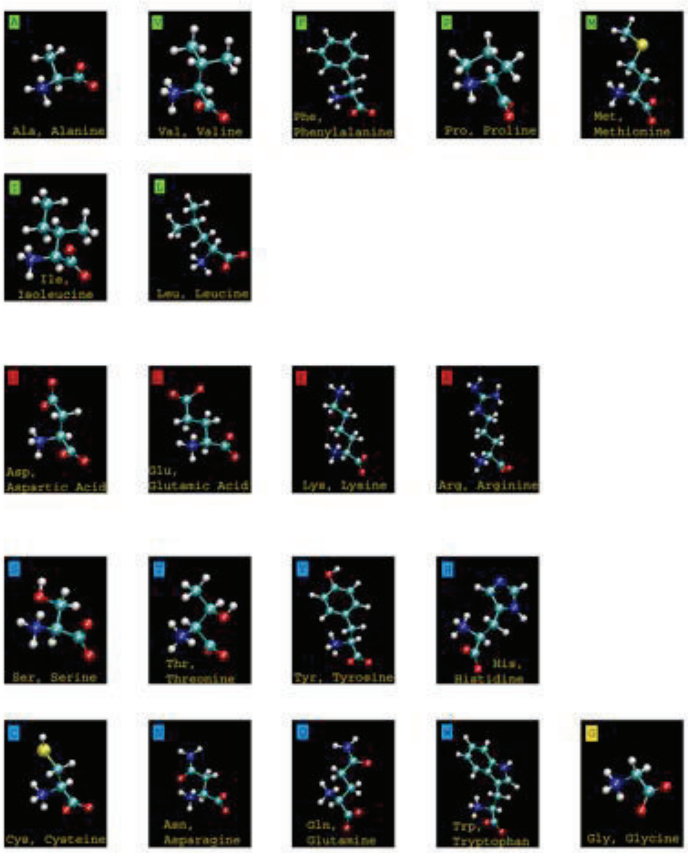




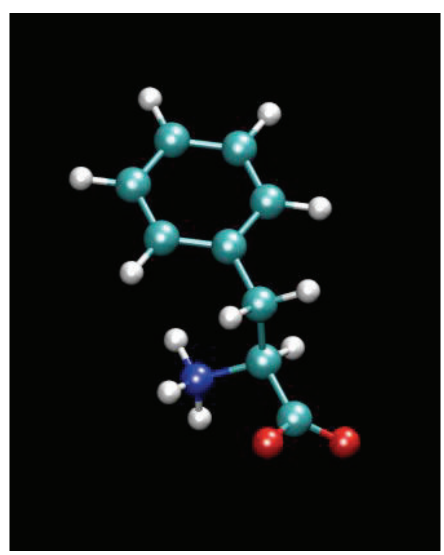


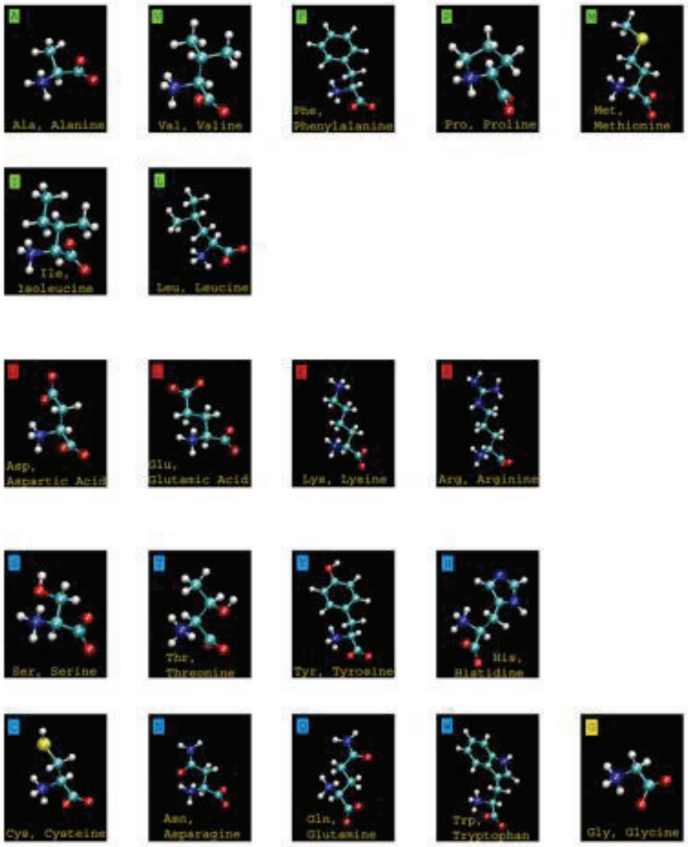
Valine



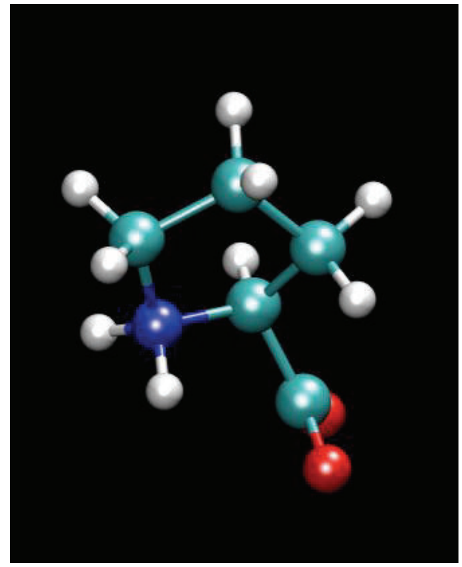


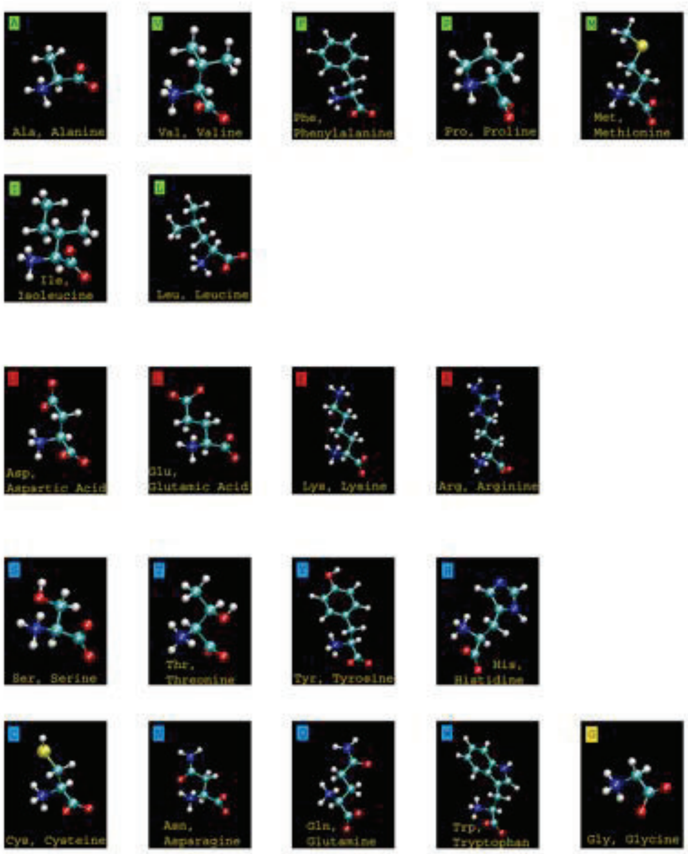
Phenylanaline



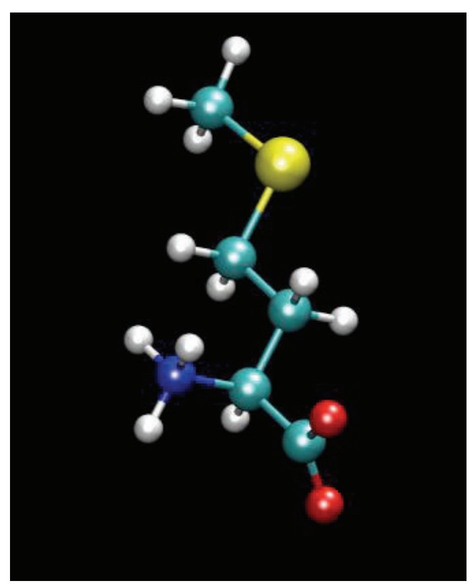


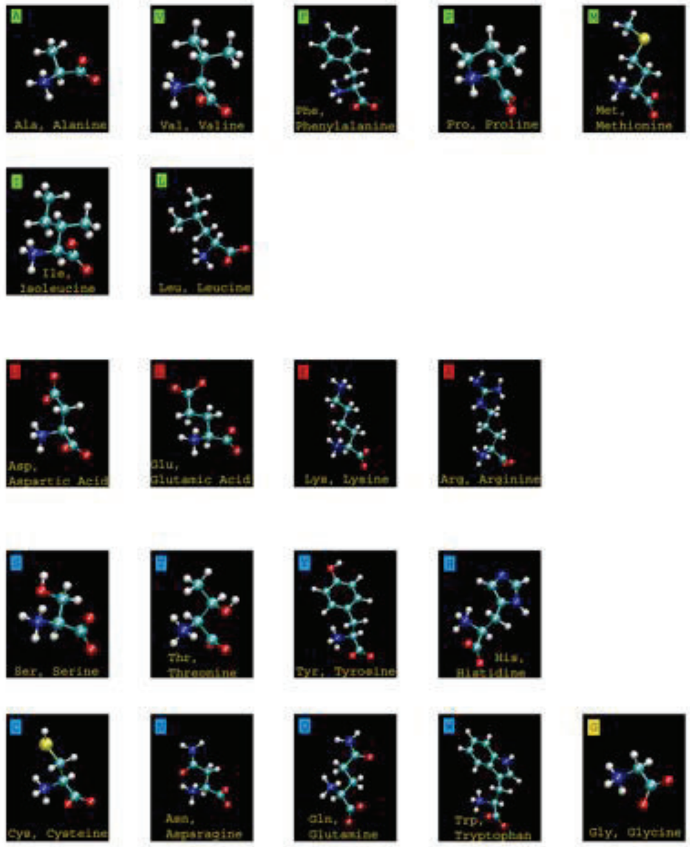
Proline



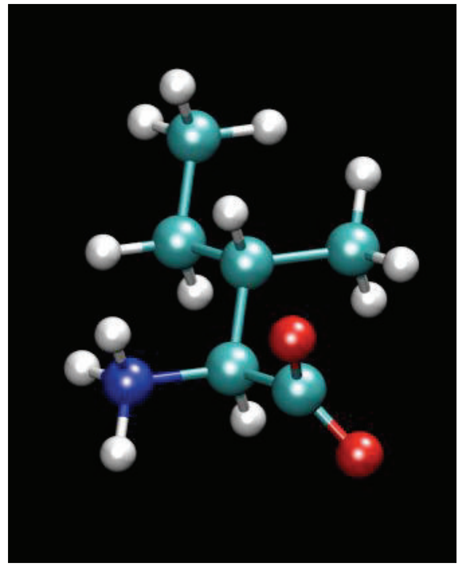


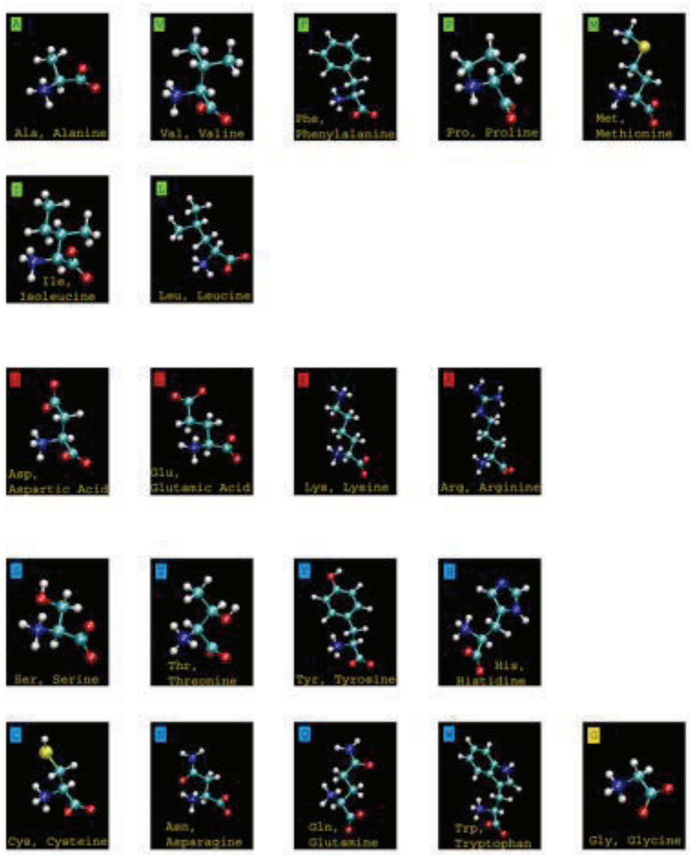
Methionine



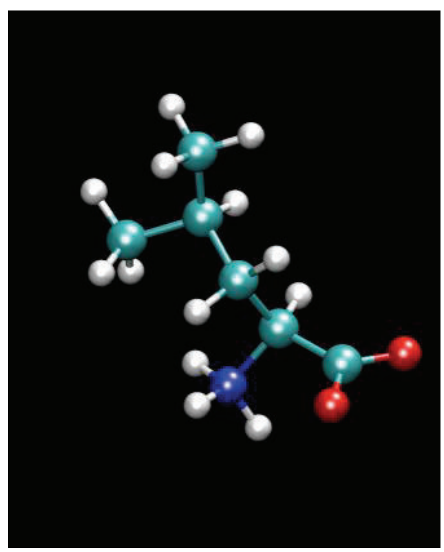


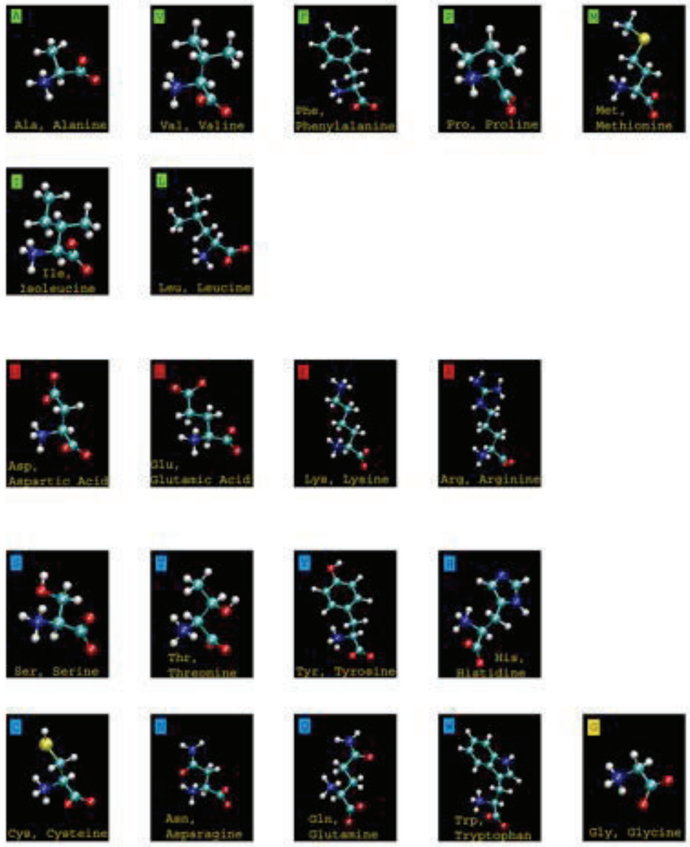
Isoleucine



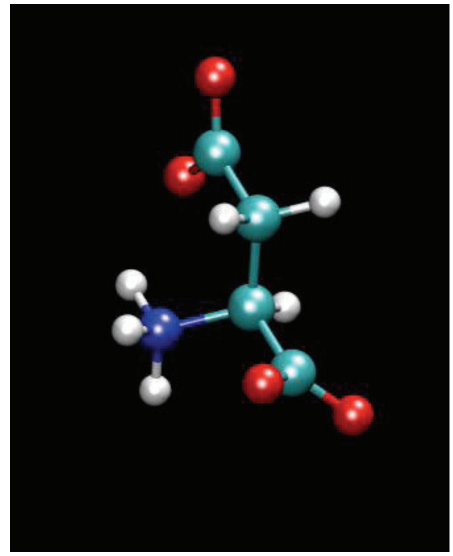


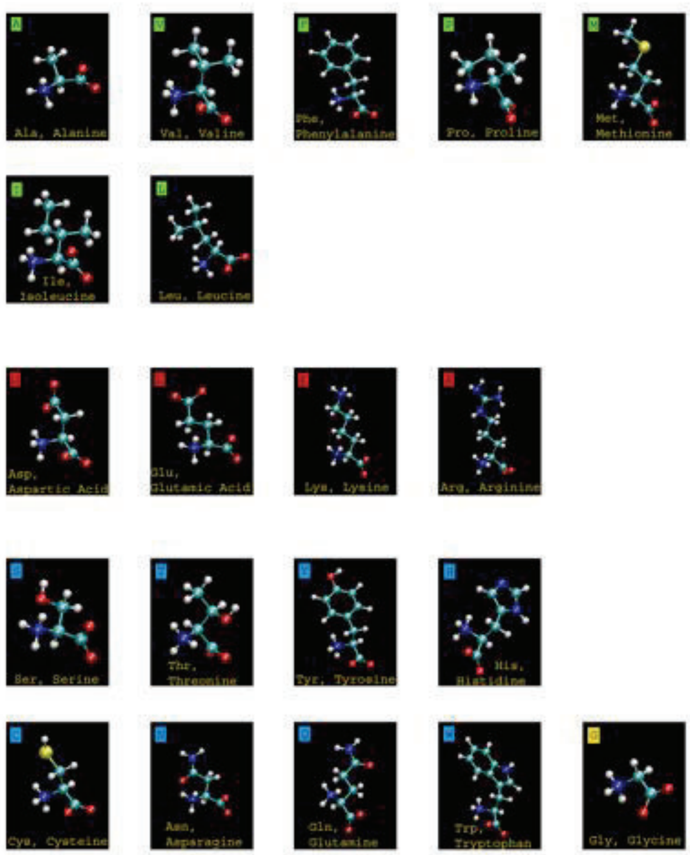
Leucine



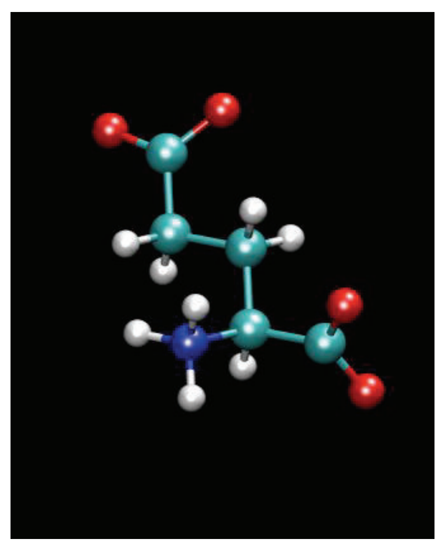


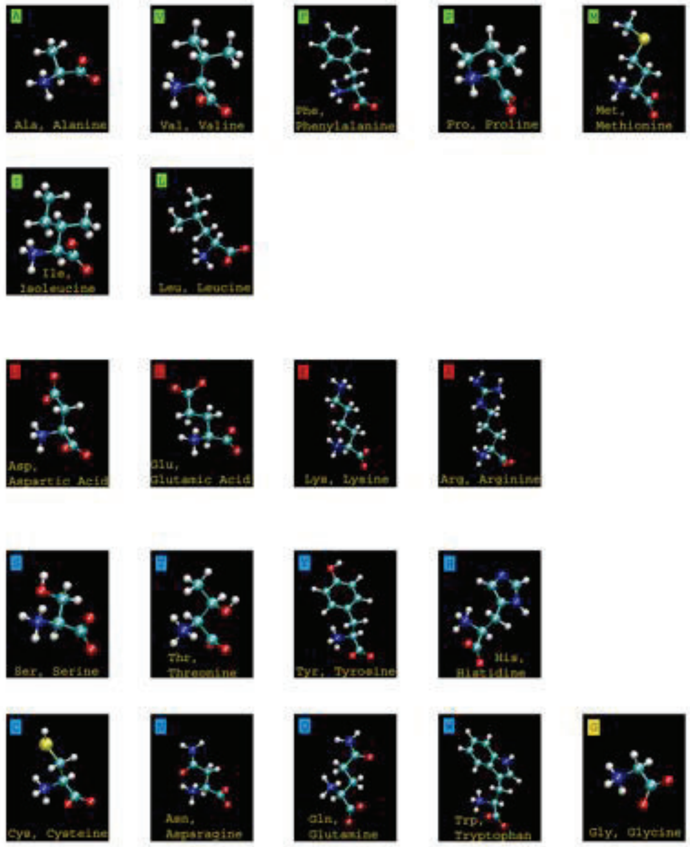
Aspartate



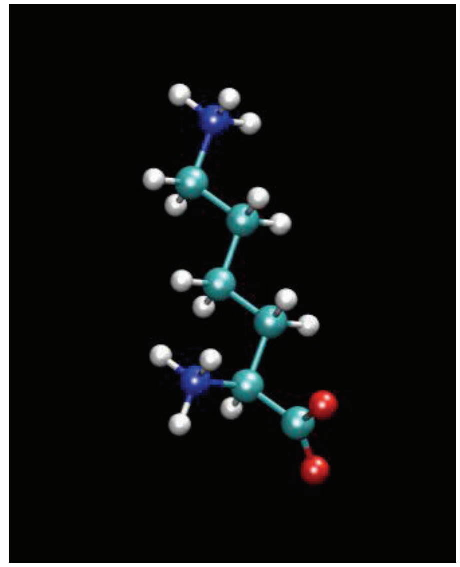


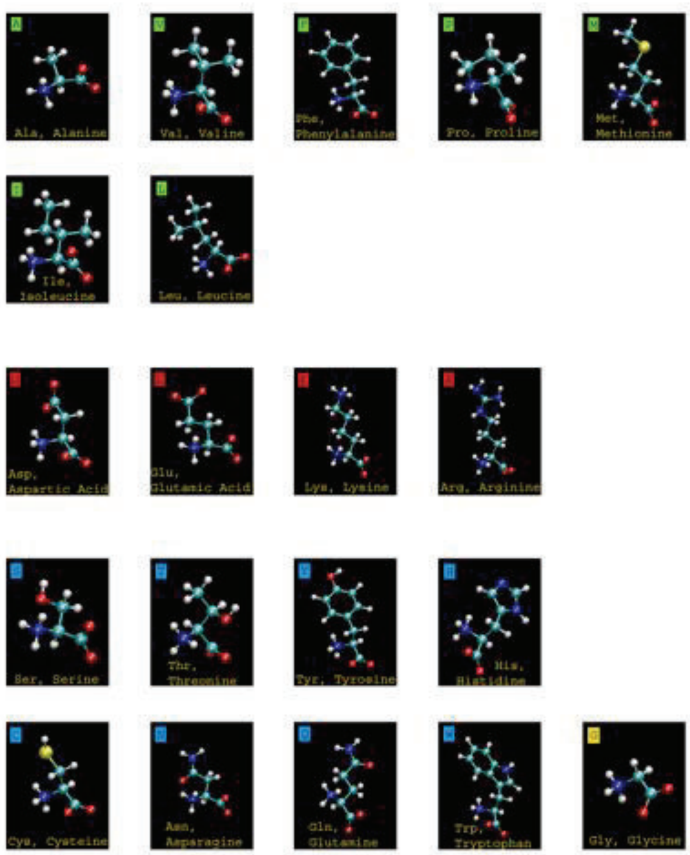
Glutamate



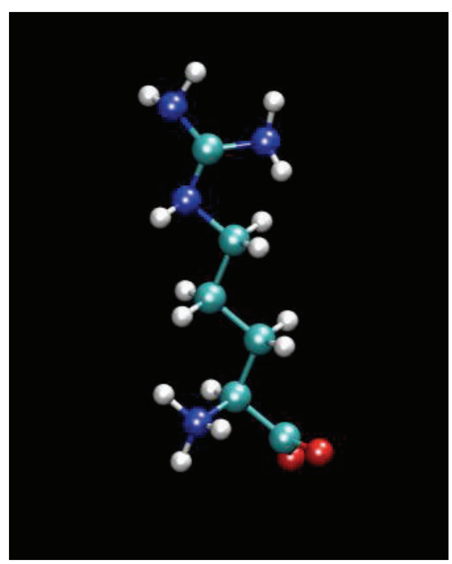


Lysine

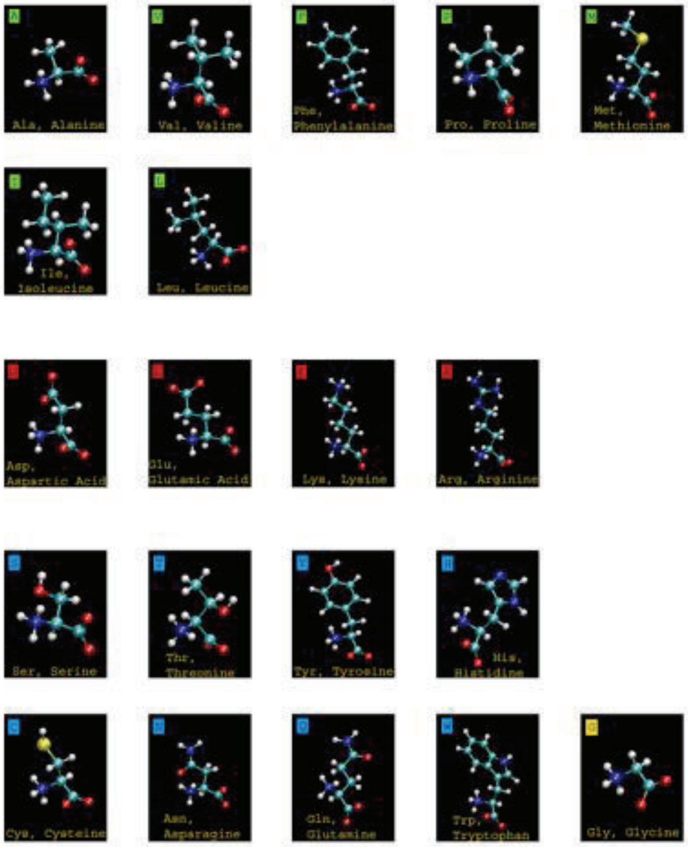


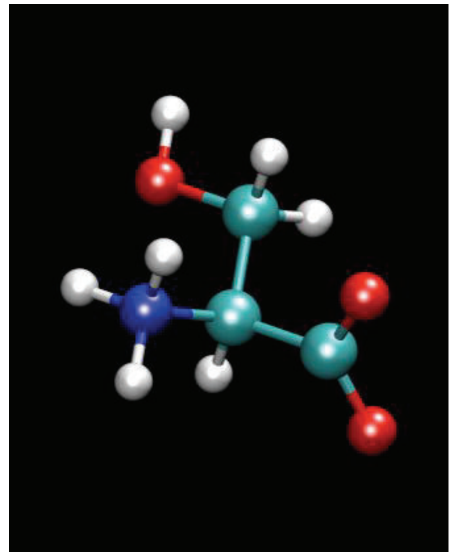


Arginine

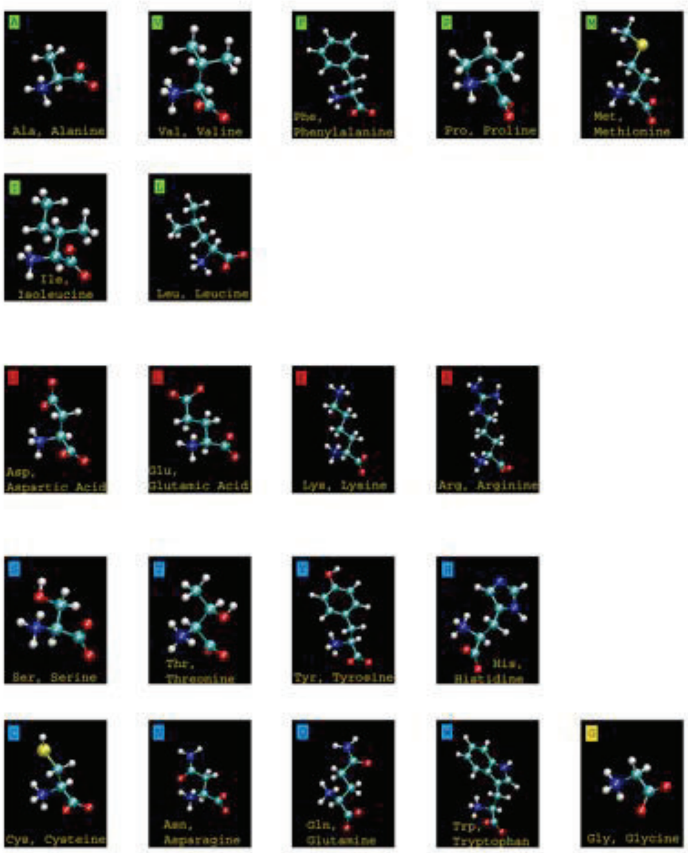


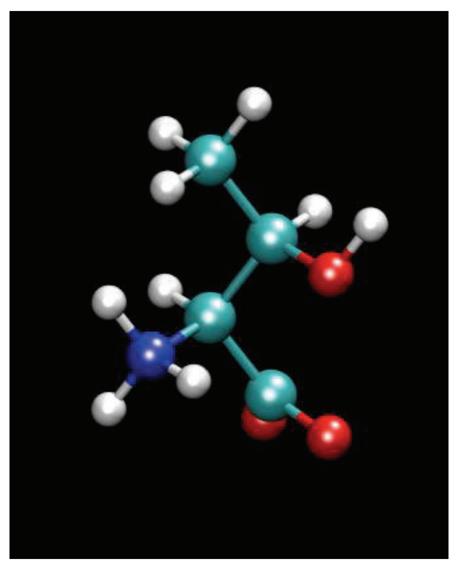
Serine

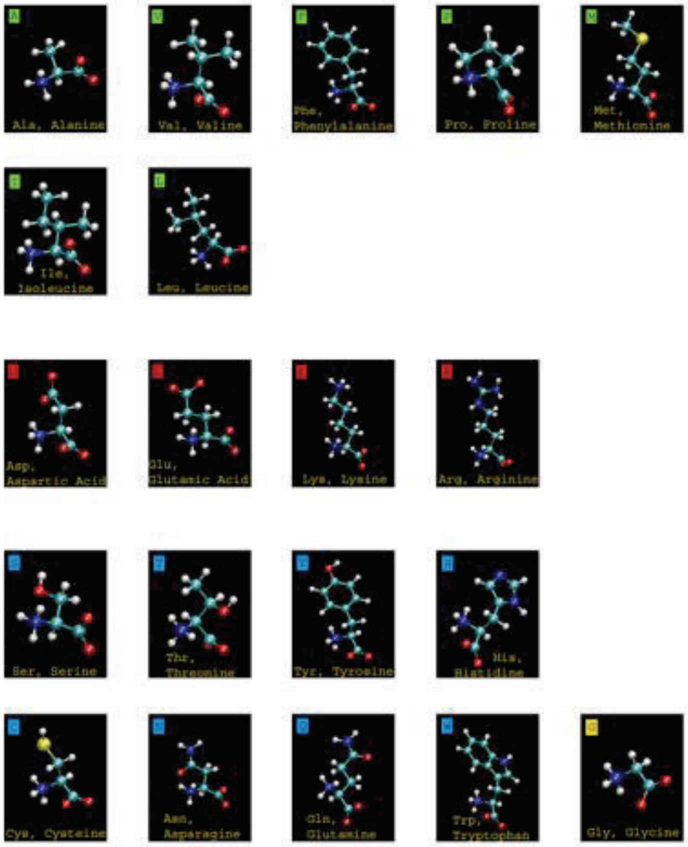




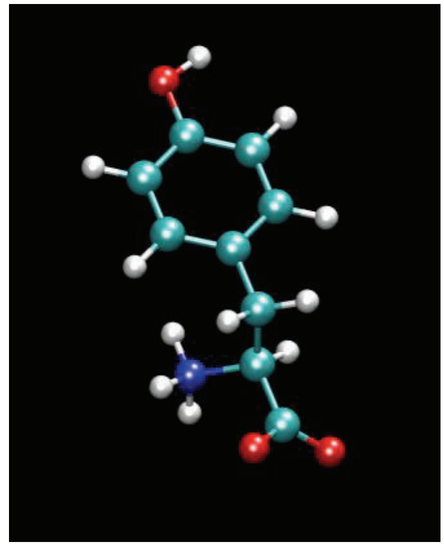
Threonine

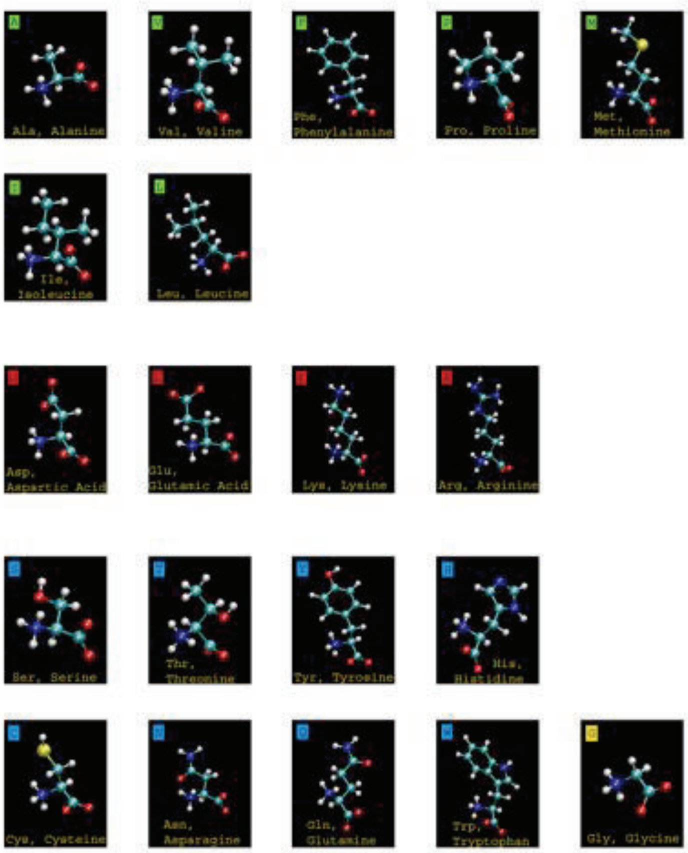




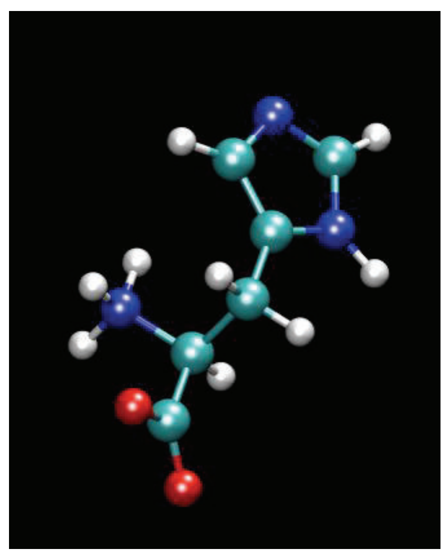


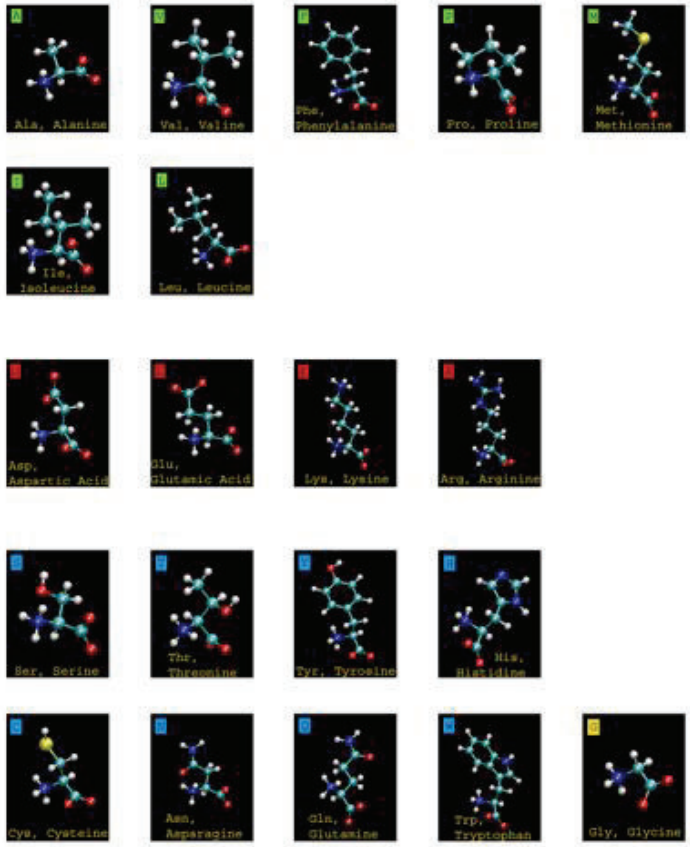
Tyrosine



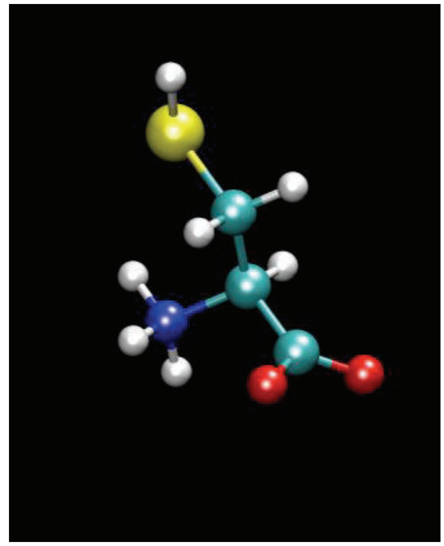


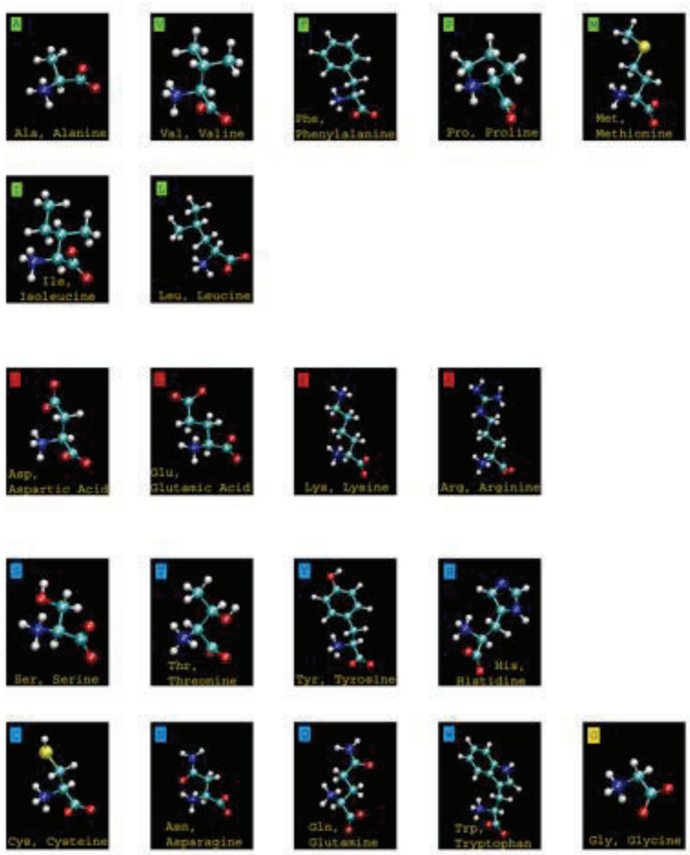
Histidine



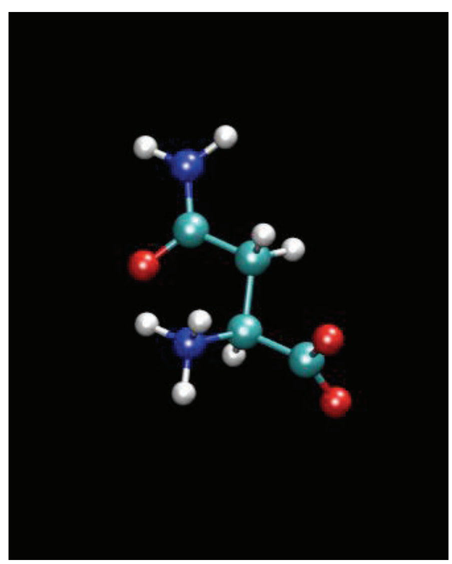


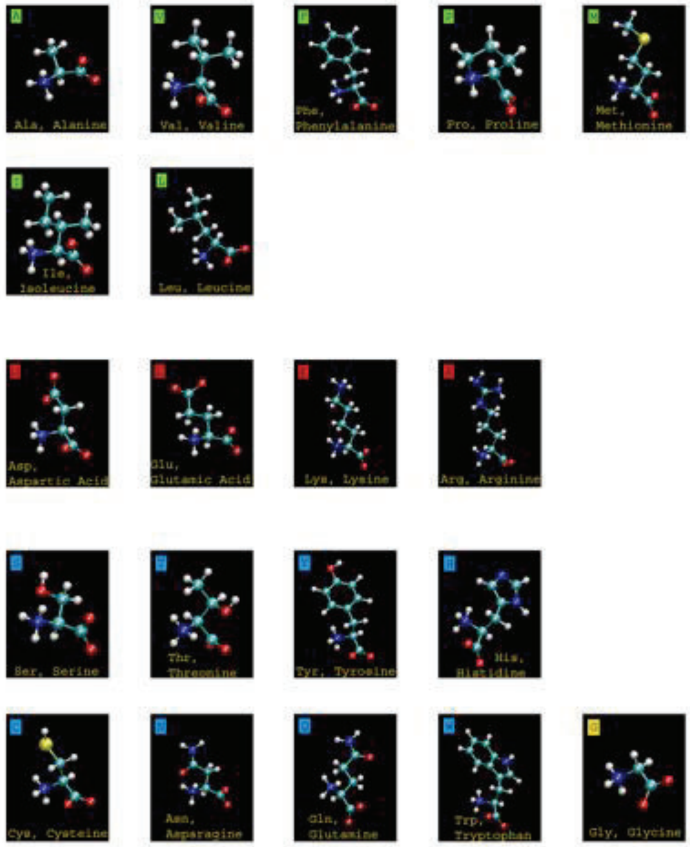
Cysteine



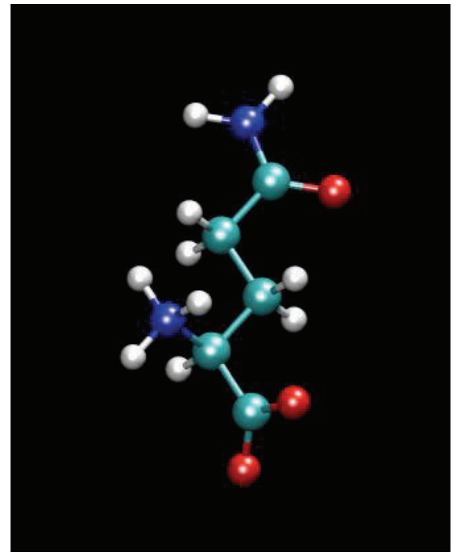


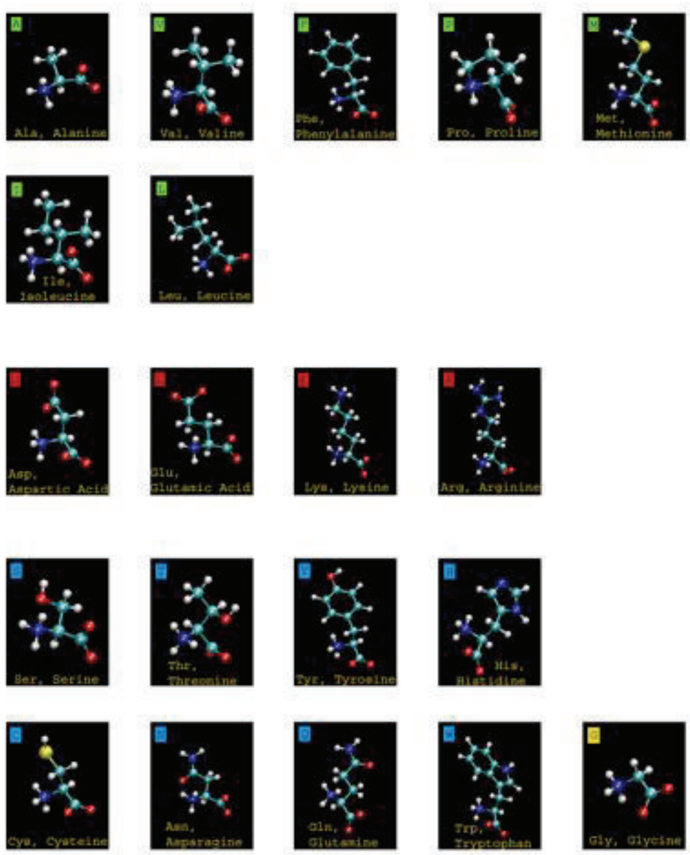
Asparagine



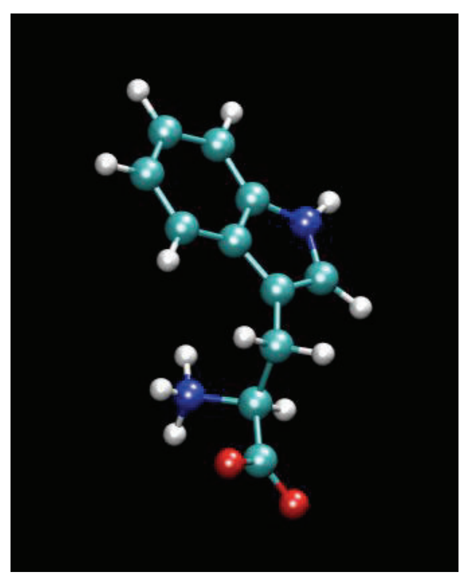


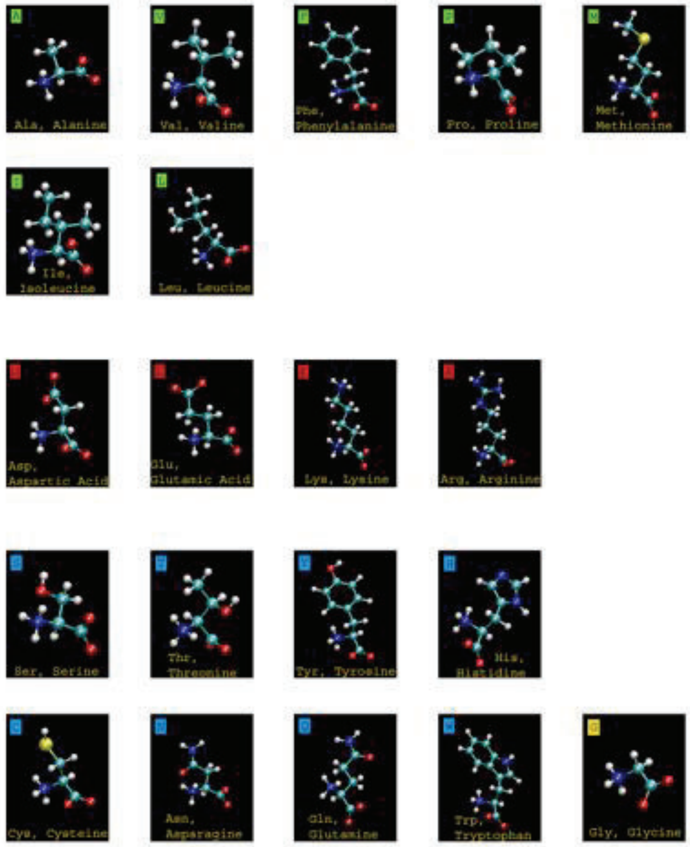
Glutamine



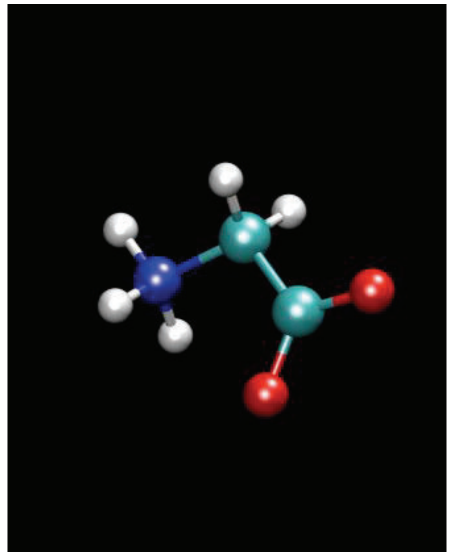


Tryptophane

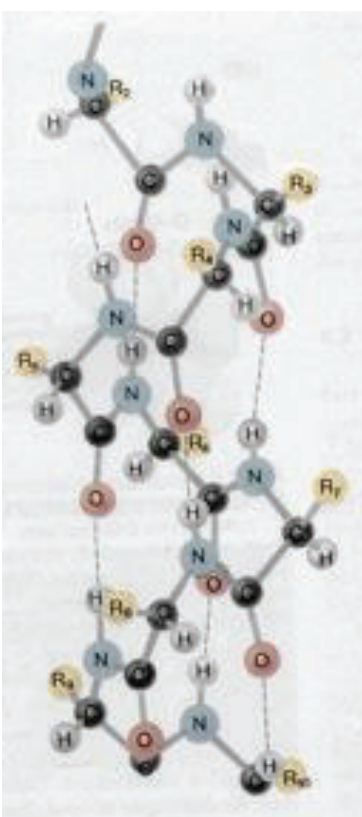




Glycine

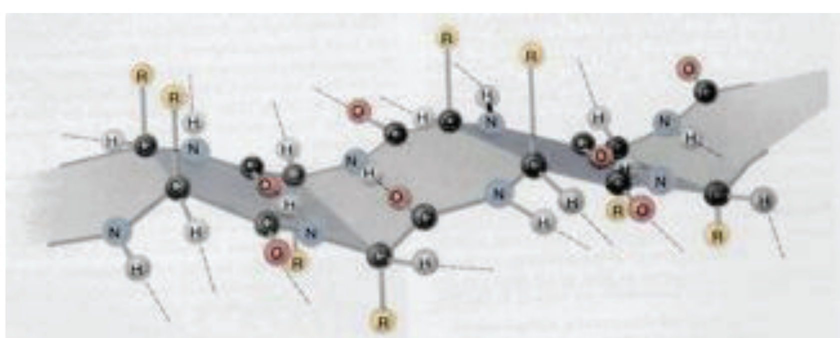


Protein Secondary Structure



An antiparallel beta sheet

Beta sheets are created, when atoms of beta strands are hydrogen bound. Beta-sheets may consist of parallel strands, antiparallel strands or out of a mixture of parallel and antiparallel strands.



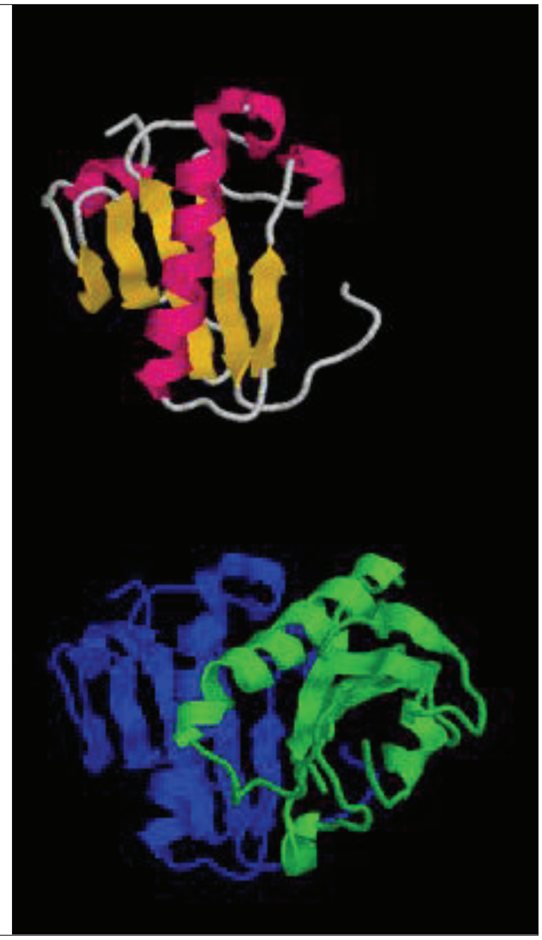
An alpha helix

The backbone is formed as a helix. An ideal alpha helix consists of 3.6 residues per complete turn. The side chains stick out. There are hydrogen bonds between the carboxy group of amino acid and the amino group of another amino acid n+4. The mean phi angle is -62 degrees and the mean psi angle is -41 degrees

Tertiary and Quarternary Structures of Proteins

Tertiary structure describes the packing of alpha-helices, beta-sheets and random coils with respect to each other on the level of one whole polypeptide chain.

Quaternary structure only exists, if there is more than one polypeptide chain present in a complex protein. Then quaternary structure describes the spatial organization of the chains

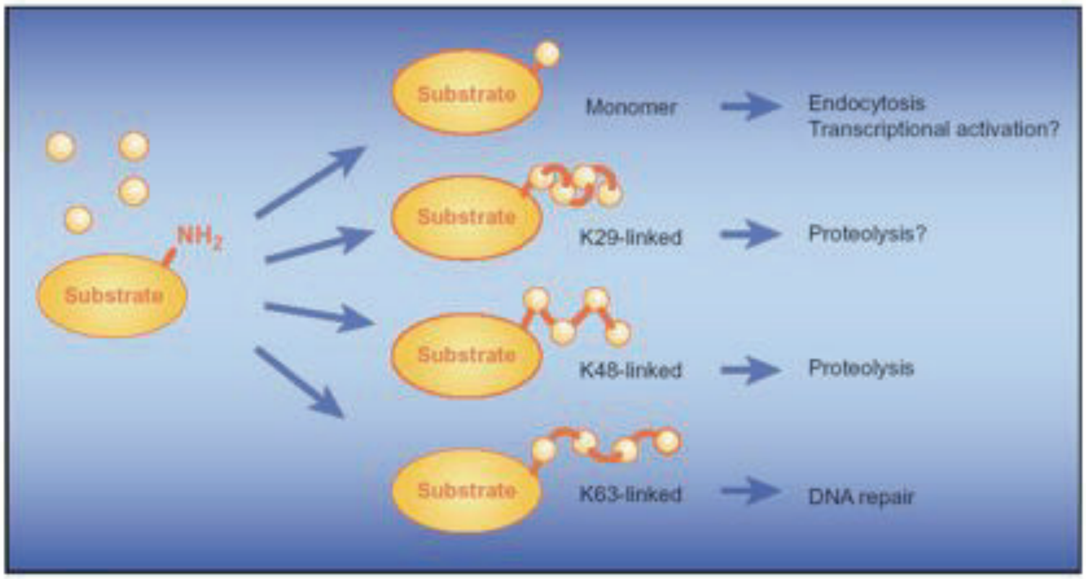


Focus on one protein

Ubiquitin

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

Mono-ubiquitylation versus multi-ubiquitylation



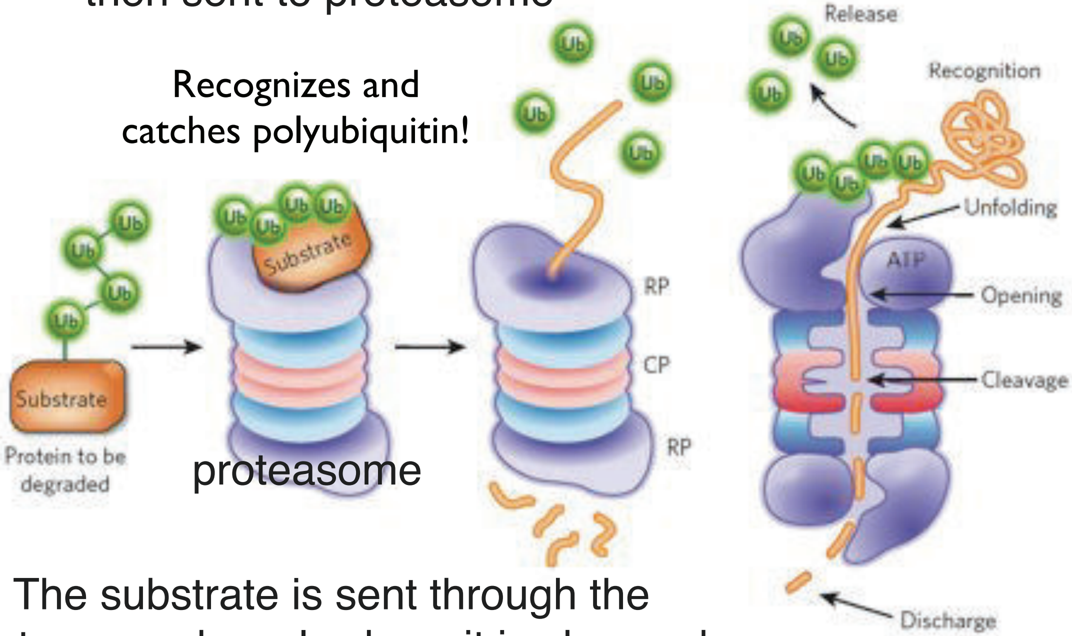
Multifaceted. Ubiquitin can attach to its various substrate proteins, either singly or in chains, and that in turn might determine what effect the ubiquitination has. (K29, K48, and K63 refer to the particular lysine amino acid used to link the ubiquitins to each other.)

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

Ubiquitin's role in protein degradation

The substrate-polyubiquitin complex is then sent to proteasome

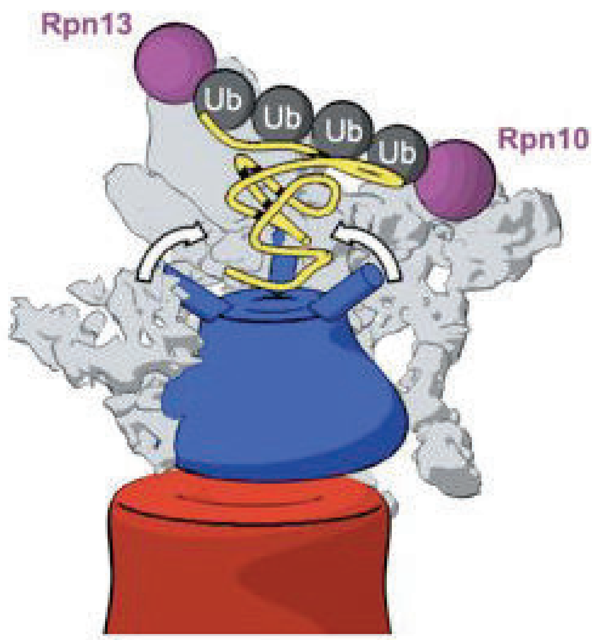
Recognizes and catches polyubiquitin!



The substrate is sent through the proteasome barrel, where it is chopped up and recycled

M. Hochstrasser, *Nature*, 458. (2009)

Polyubiquitine Ruler of the Proteasome



Ubiquitin's role in protein degradation

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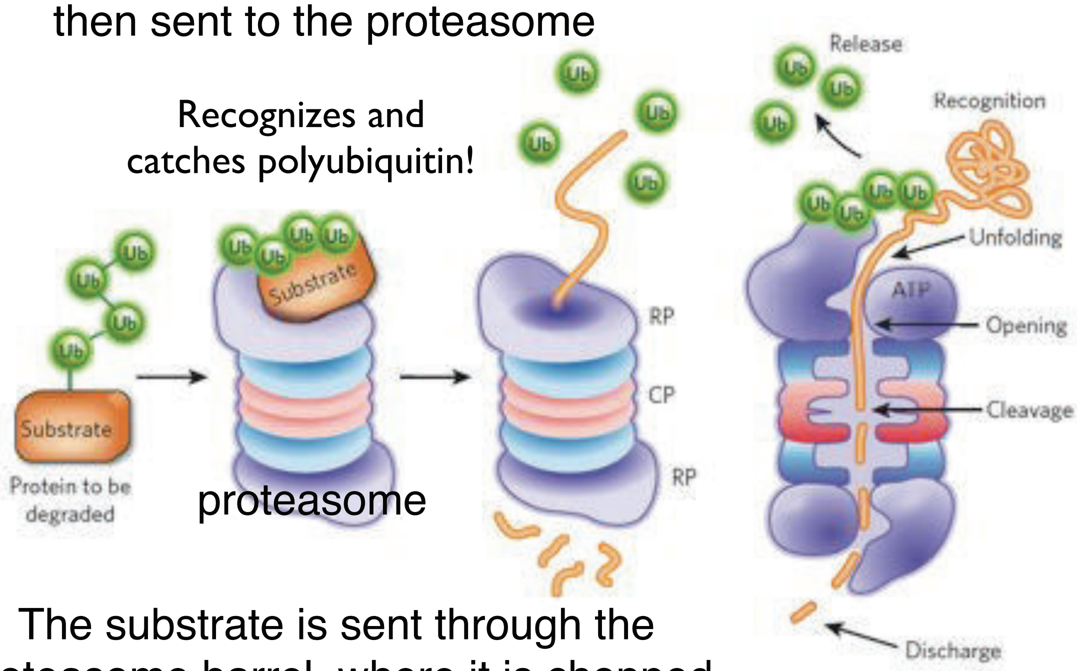
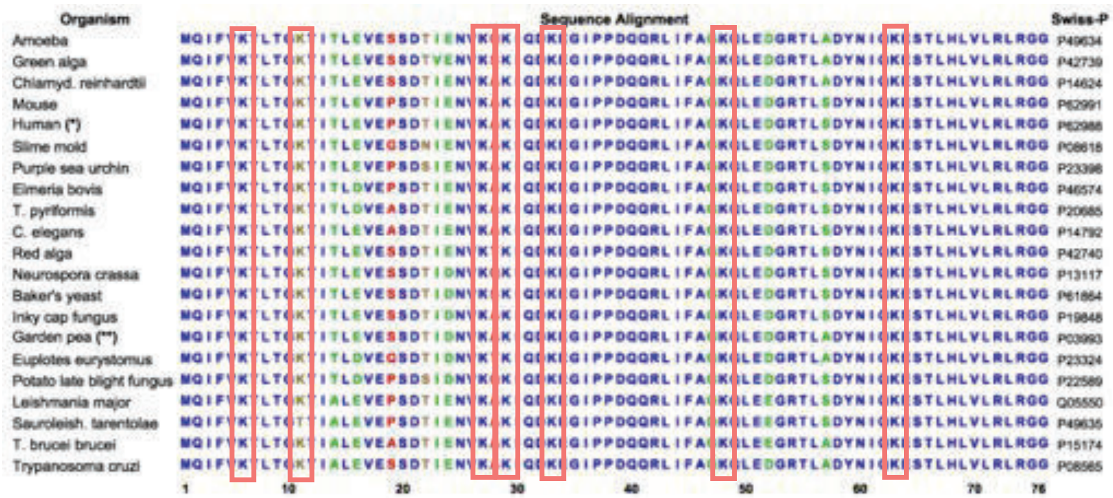


The substrate is sent through the proteasome barrel, where it is chopped up and recycled

M. Hochstrasser, *Nature*, 458. (2009)

Highly conserved ubiquitin chain

- The sequence of ubiquitin is highly conserved, in particular the seven lysine residues
- A lysine residue in a ubiquitin can be linked to the C-terminus of another ubiquitin
- By using different lysine for such linkage, ubiquitin is used for different cellular purposes



VMD Demo 1

Some readings

http://en.wikipedia.org/wiki/Ubiquitin

J. Marx, "Ubiquitin lives up to its name." *Science*, 297. (2002)

M. Hochstrasser, "Origin and function of ubiquitin-like proteins." *Nature*, 458. (2009)

A. Varshavsky, "The early history of the ubiquitin field." *Protein Science*, 15. (2006)

C. M. Pickart, "Back to the future with ubiquitin." *Cell*, 116. (2004)

M. Carrion-Vazquez et al., "The mechanical stability of ubiquitin is linkage dependent." *Nature Structure Biology*, 10. (2003)

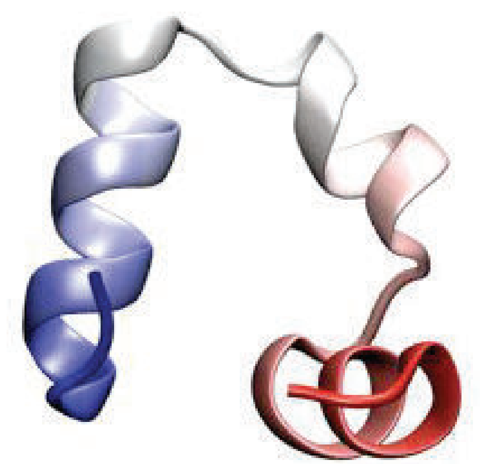
http://nobelprize.org/nobel_prizes/chemistry/laureates/2004/

If you need to get a quick lesson on VMD, here is a short tutorial:

http://www.ks.uiuc.edu/~jhsin/papers/HSIN2008.pdf

Protein Folding

- Folding of the Protein called Villin Headpiece
- First protein folded in computer simulation
- Visualization of the "trajectory" of the folding protein reveales how this protein finds it native conformation from an initially stretched-out conformation

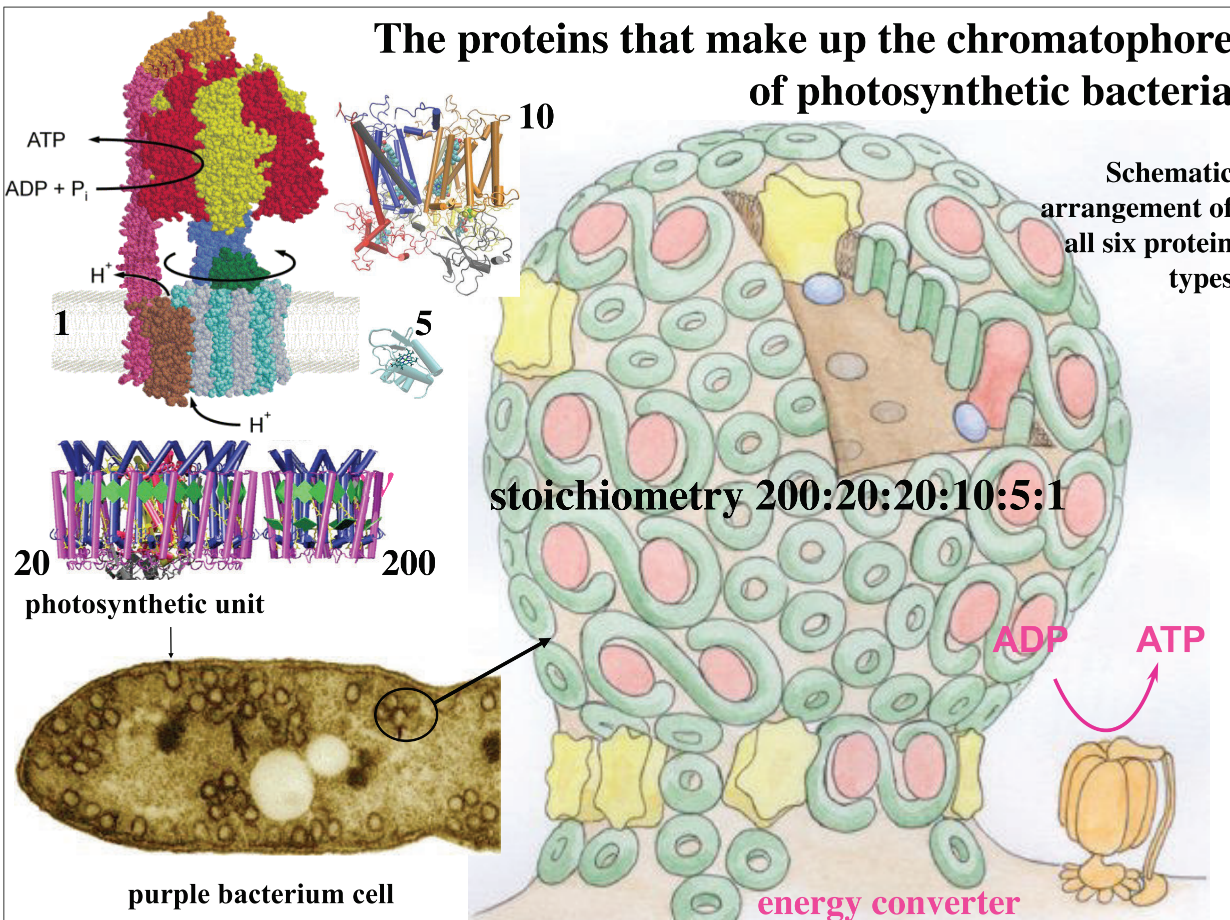


villin headpiece

Observe folding process in unprecedented detail

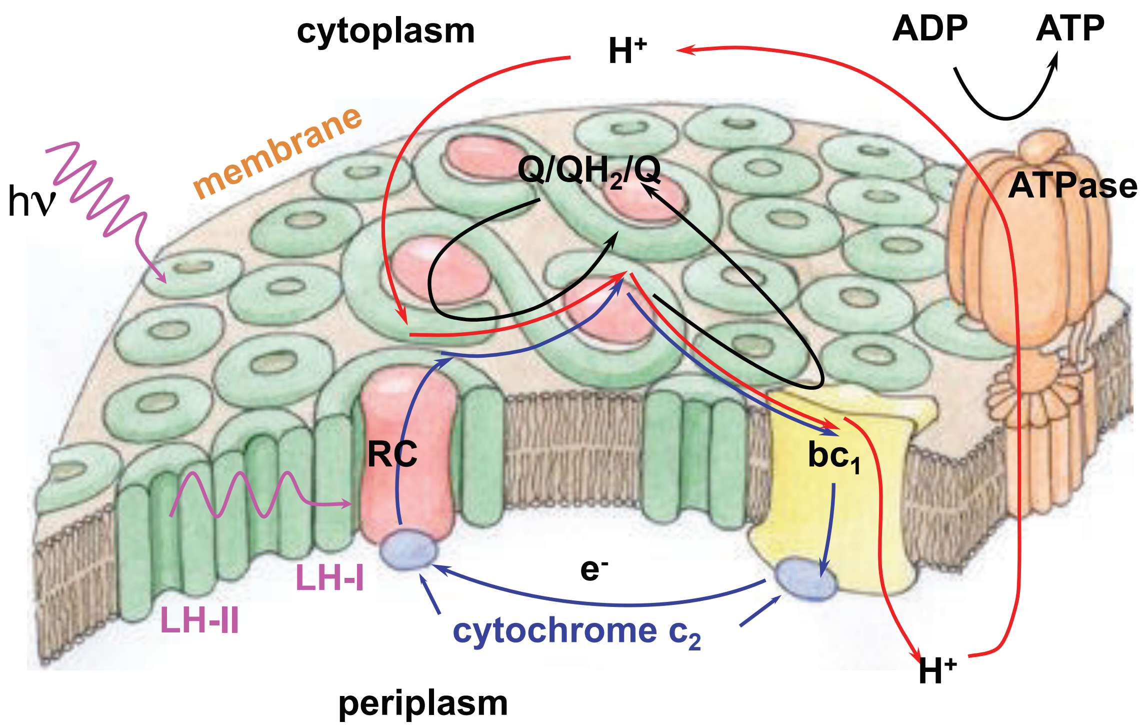
VMD Demo 2

The proteins that make up the chromatophore of photosynthetic bacteria



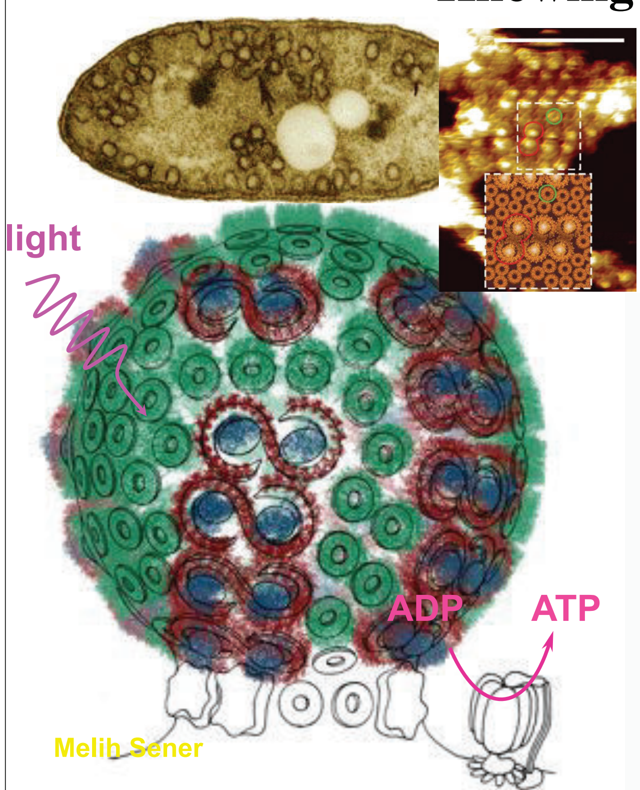
Chromatophore of Purple Bacteria

(section of the chromatophore membrane)



Knowing the Atomic Level Structure

of the chromatophore, one can systematically describe its physical mechanism

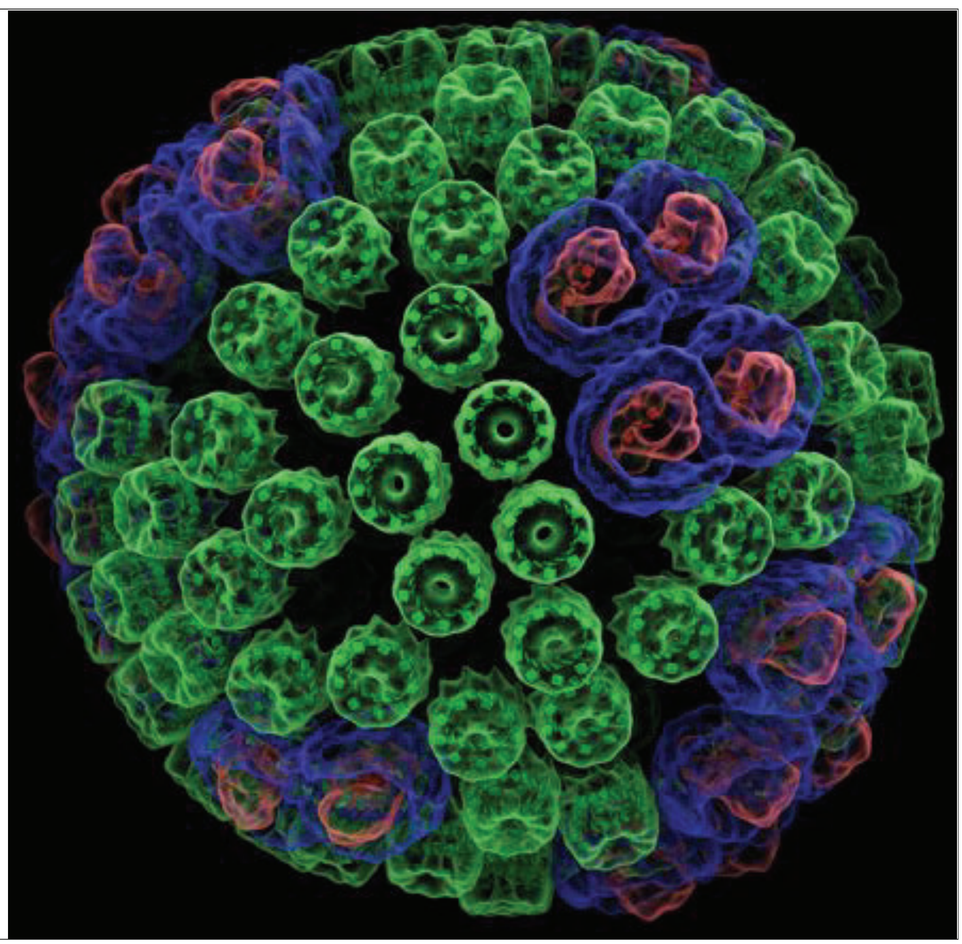


M. Sener, J. Olsen, N. Hunter, and K. Schulten. *PNAS*, **104:** 15723-15728, 2007

VMD Demo 3

QuickSurf Representation w/ Angle-Modulated Transparency

Chromatophore 10M atoms

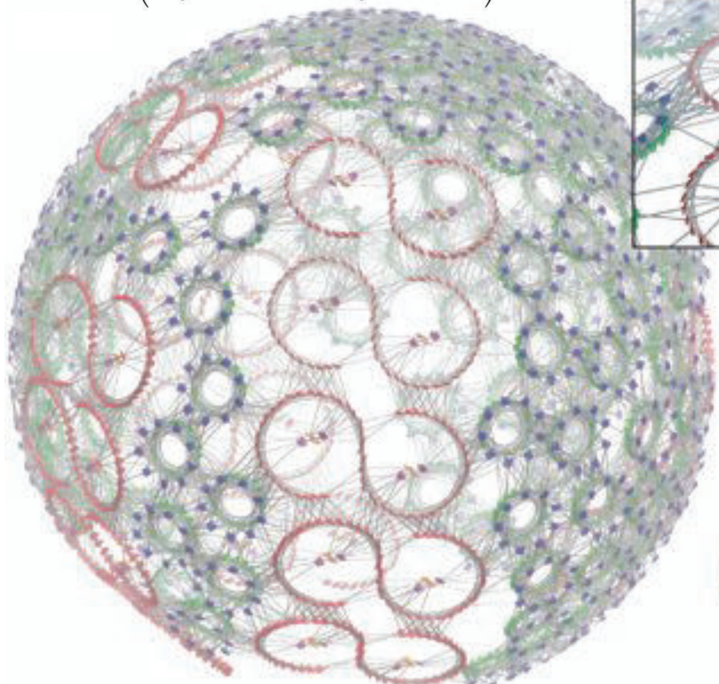


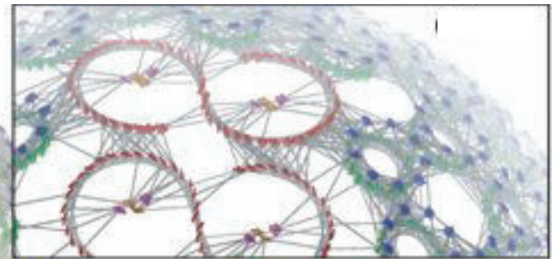
National Center for Research Resources

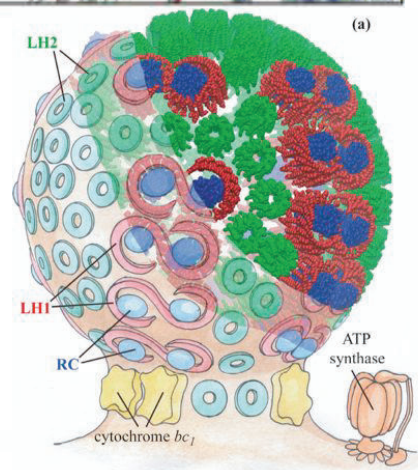
The "Physics" of Light Harvesting in the Chromatophore

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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