Basics of Molecular Modeling & Computer-Aided Drug design

Prof. Giulio Poli
Dep. of Pharmacy, University of Pisa, Italy
E-mail: giulio.poli@unipi.it
Web site: http://www.mmvsl.it/wp/group-members/poli/

Introduction & Graphical Representation

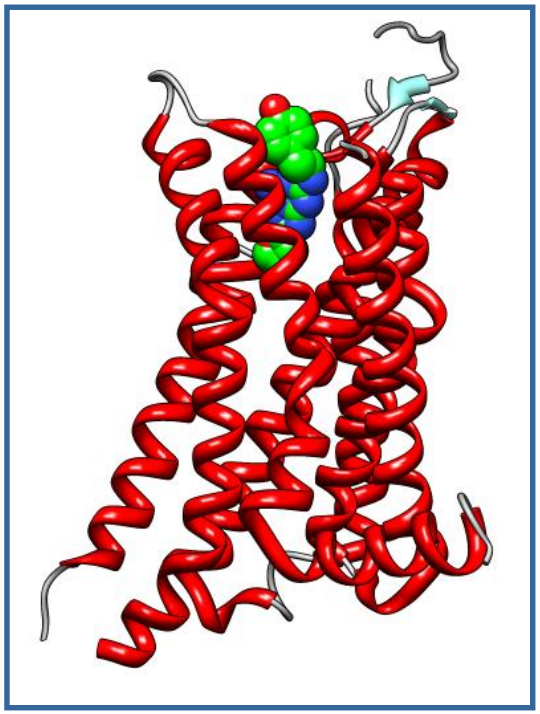
Introduction

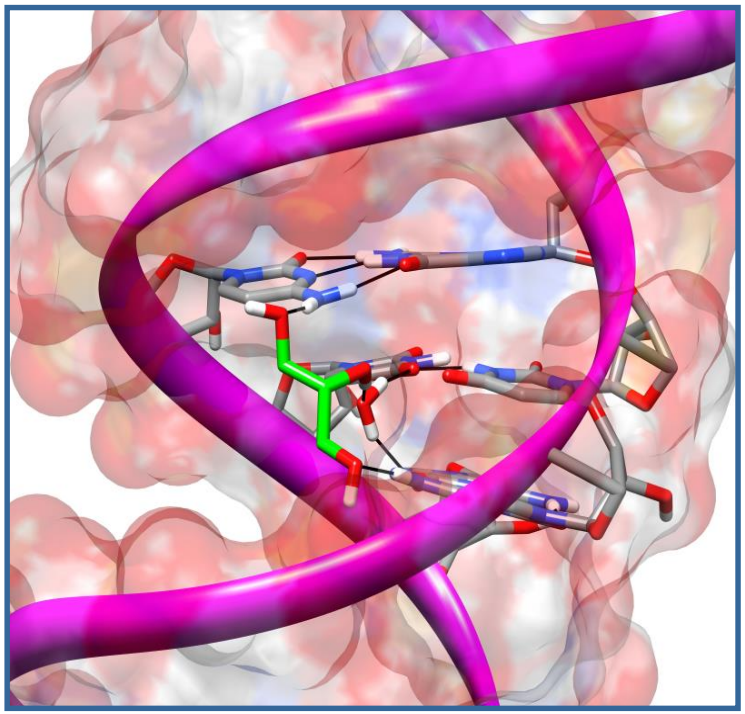
Computational chemistry is a branch of chemistry that uses principles of computer science to assist in solving chemical problems. It uses the results of theoretical chemistry, incorporated into efficient computer programs, to calculate the structures and properties of **molecules** and solids. While its results normally complement the information obtained by chemical experiments, it can in some cases predict hitherto unobserved chemical phenomena. It is widely used in the design of new **drugs** and materials.

It covers a range of chemical applications such as quantum chemistry, molecular dynamics, molecular modelling, molecular mechanics and chemoinformatics. In **computer-aided drug design** many of these applications are employed to study and evaluate the (possible) interactions of **small-molecules** with a **biological target (receptor)**.

Receptor definition

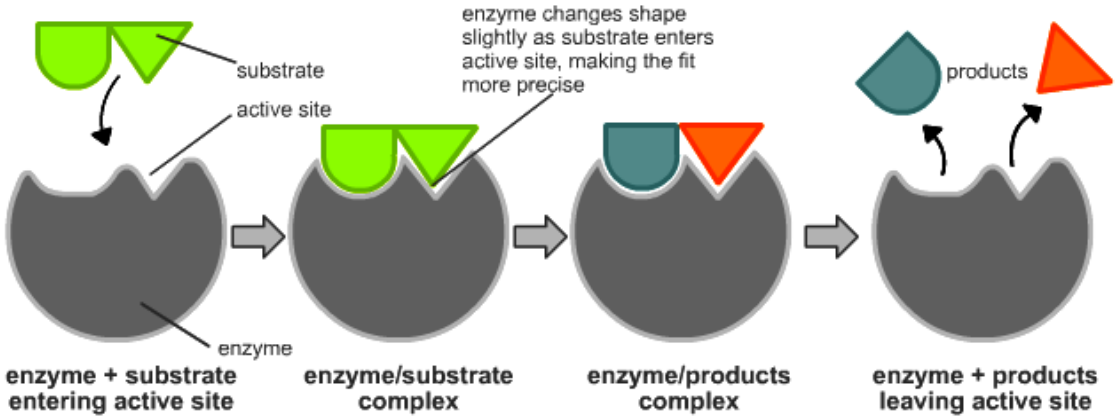
A **receptor** is a biological structure to which one or more specific kinds of signaling molecules may attach. The main receptors are proteins or nucleic acids. A molecule which binds to a receptor is called a **ligand**, and may be a peptide or other small molecule, such as a neurotransmitter, a hormone, a pharmaceutical drug, or a toxin.





Induced-Fit Model

Since enzymes are rather flexible structures, the active site is continually reshaped by interactions with the substrate as the substrate interacts with the enzyme. As a result, the substrate does not simply bind to a rigid active site; the amino acid side chains which make up the active site are modeled into the precise positions that enable the enzyme to perform its catalytic function. In some cases, such as glycosidases, the substrate molecule also changes shape slightly as it enters the active site.



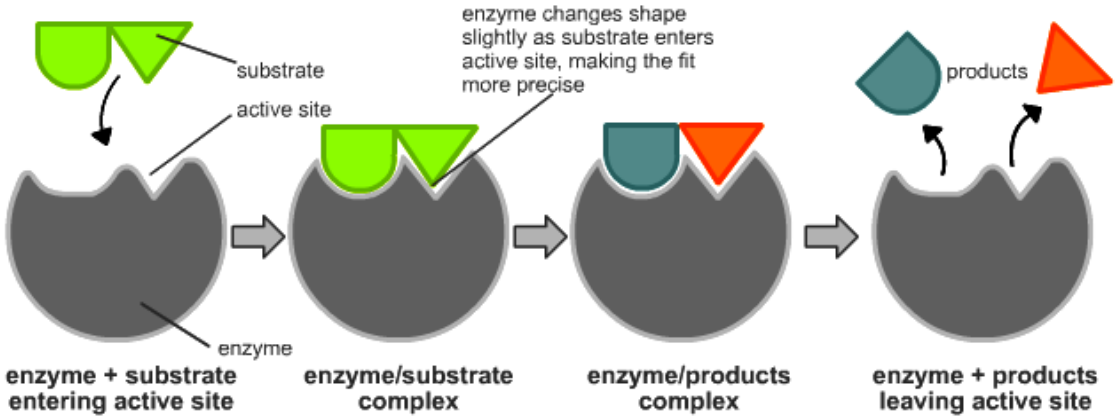
Induced-Fit Model

In the induced-fit model of enzyme action:

- the active site is flexible, not rigid

- the shapes of the enzyme, active site, and substrate/ligand adjust to maximize the fit, which improves catalysis

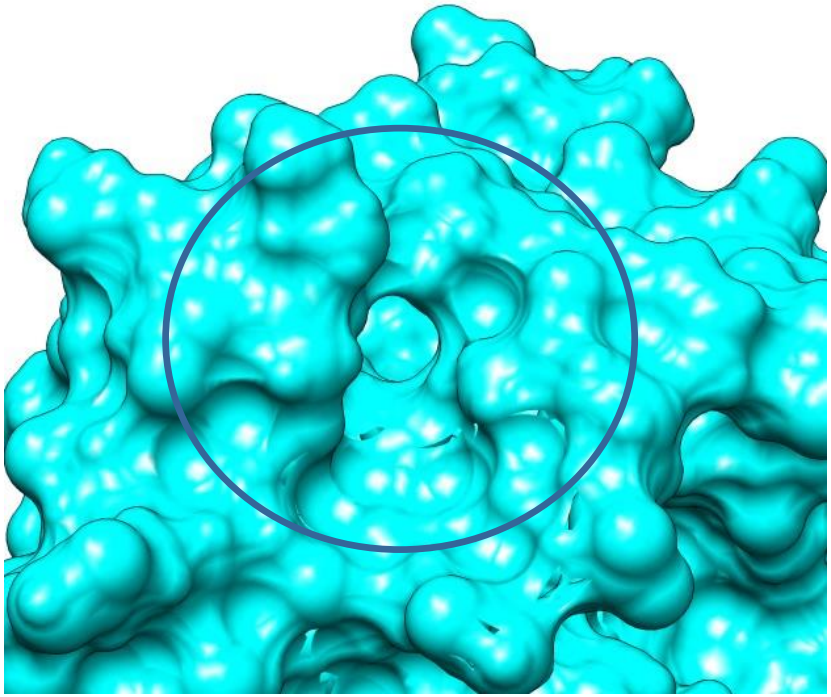
- there is a greater range of substrate specificity



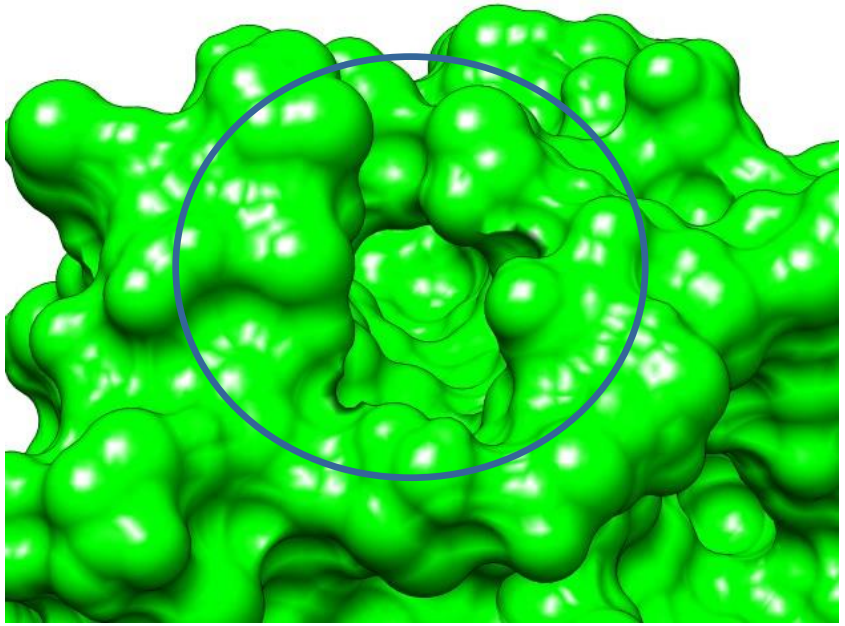
Induced-Fit Model

The active site geometry of a protein complex depends upon conformational changes induced by the bound ligand.

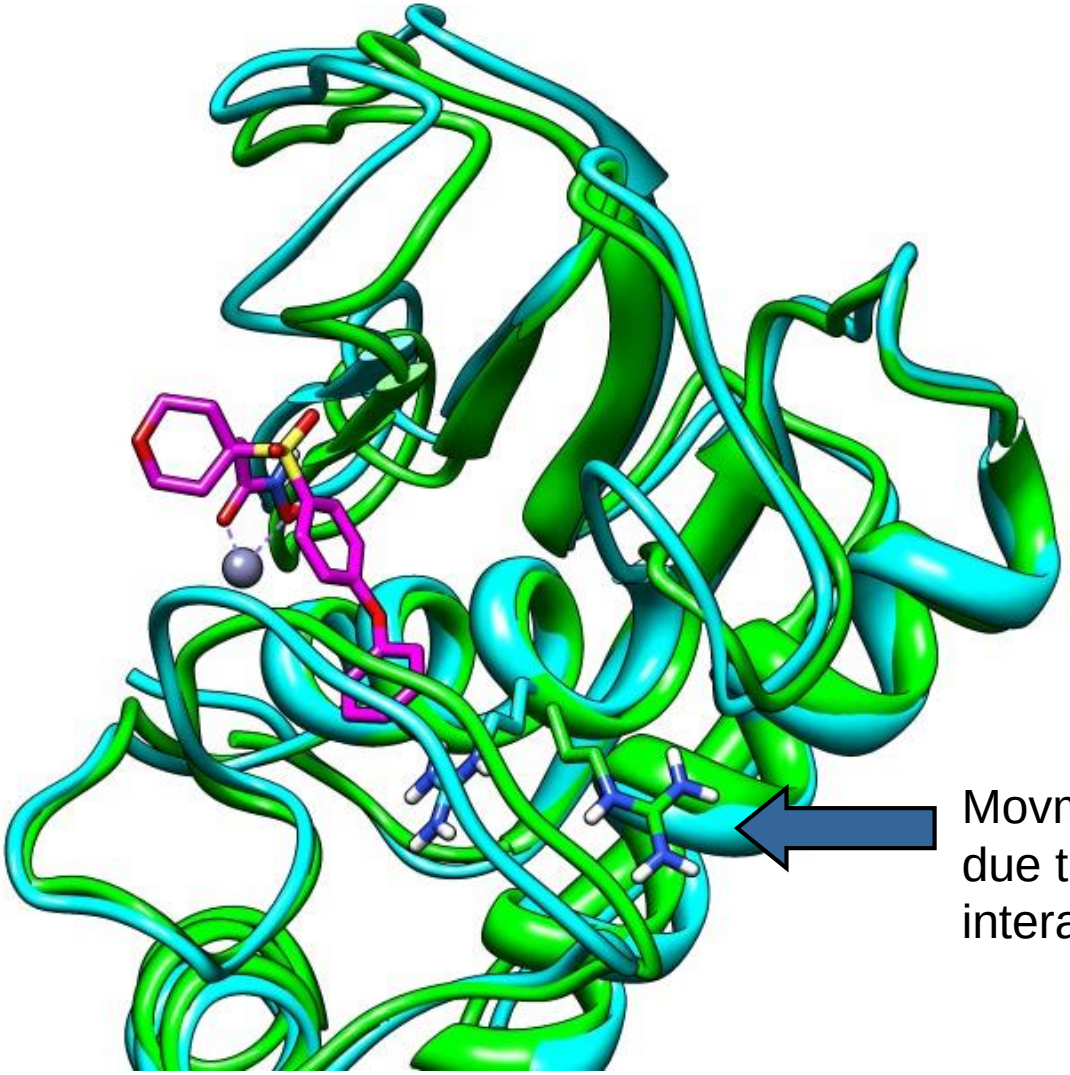
Binding site A



Binding site B



Induced-Fit Model

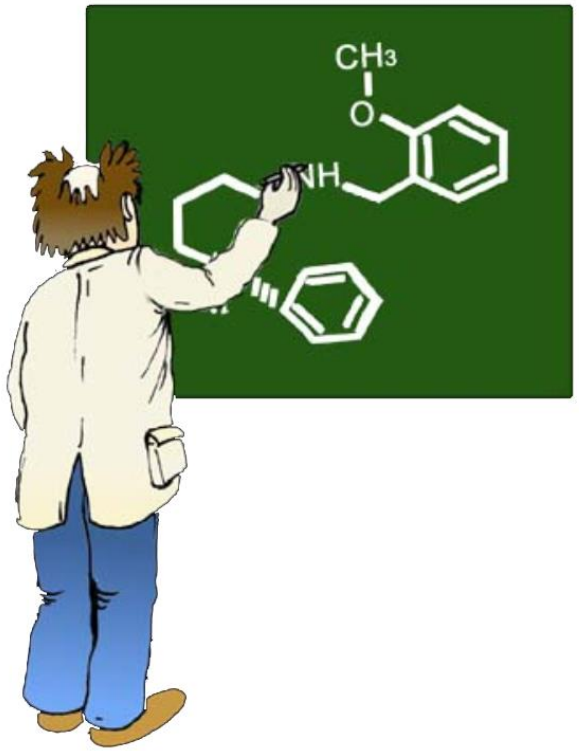


Movment of ARG, due to the ligand interaction

Molecular Modeling

Molecular Geometry

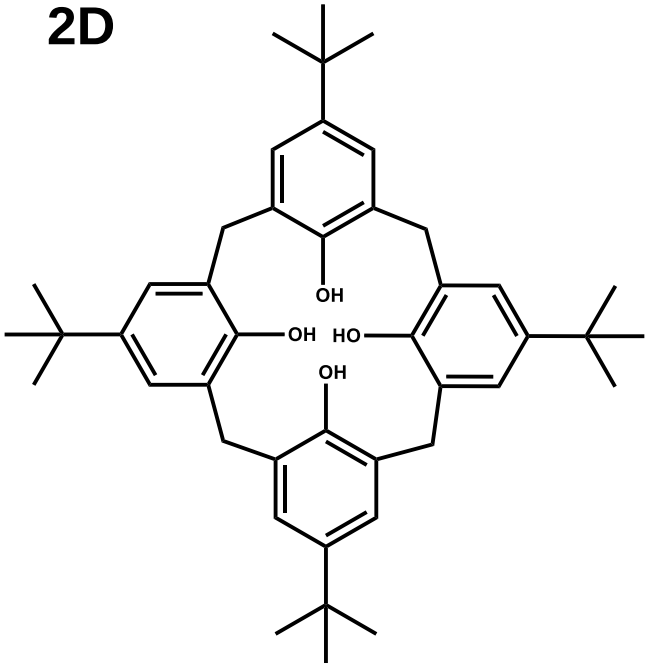
The way molecules have been perceived and defined has changed over the years. In the early 1970s, medicinal chemists considered molecules as mere topological two-dimensional (2D) entities with associated chemical and physicochemical properties.



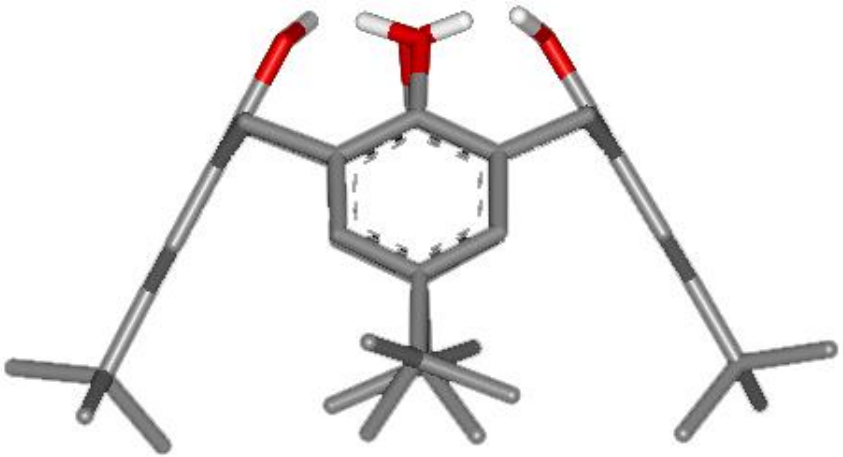
Molecular Geometry

The formula of a molecule can be drawn in two-dimensions, however it really exists in 3D space with precise geometrical features. For example the calix[4]arene showed here has a cone-like structure, a geometry that is not carried by its 2D formula.

2D

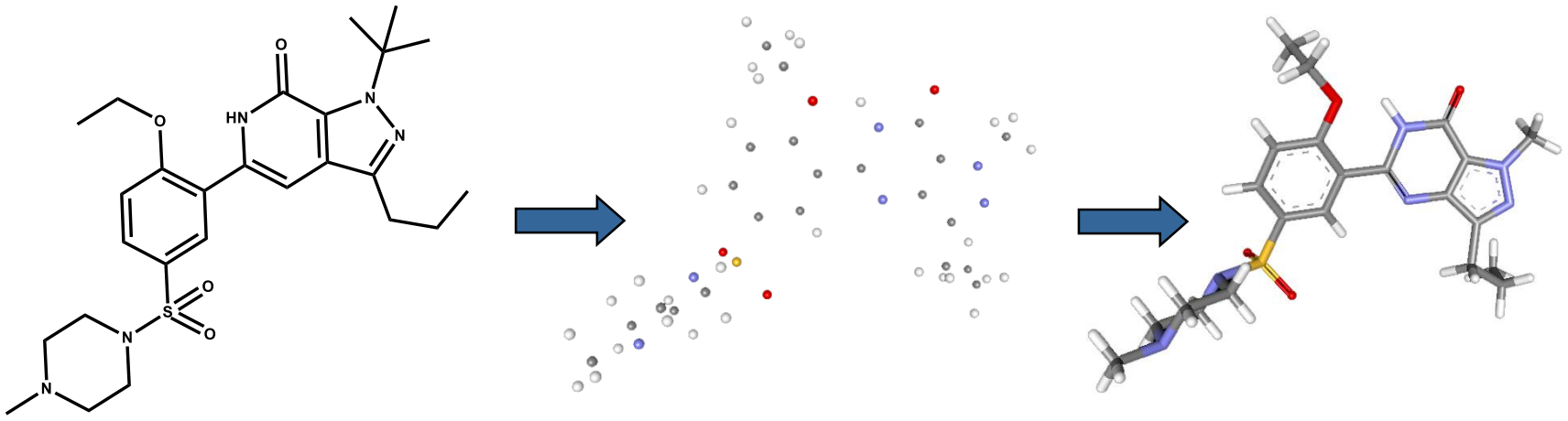


3D



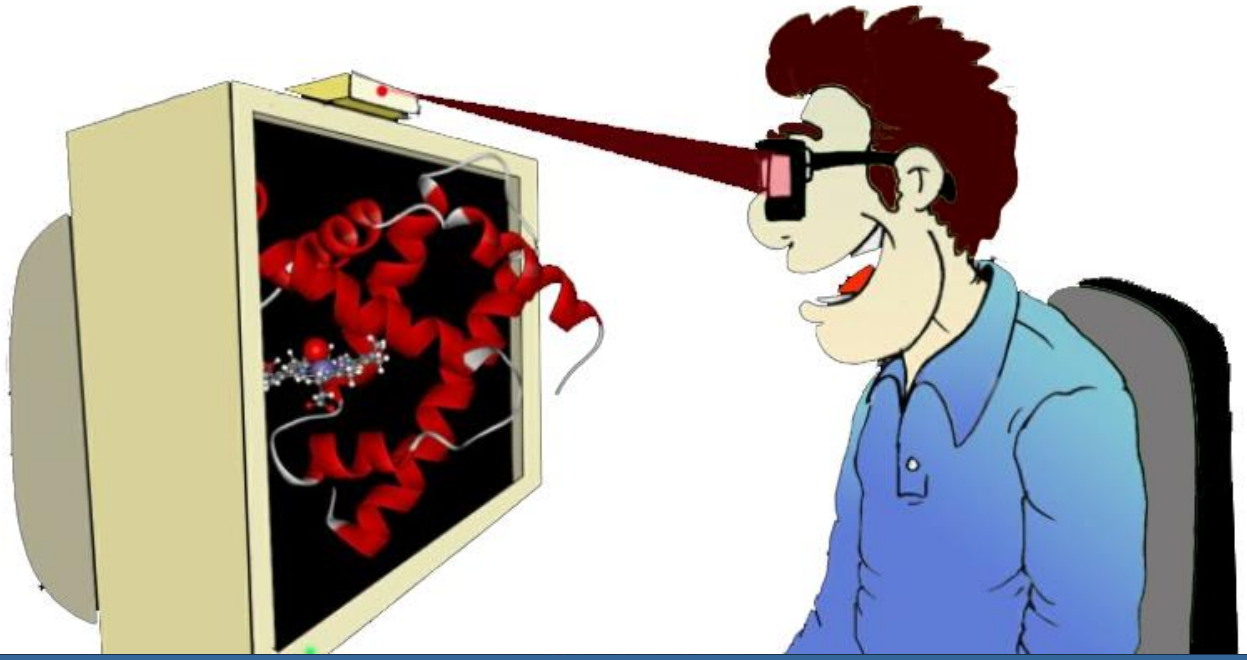
Molecular Geometry

A molecule is an assembly of atoms in 3D. The 2D structure defines the atoms and the connections between them; it becomes 3D when the location of the atoms is considered. The following molecule consists of 63 atoms, 66 bonds and 4 rings.



3D Stereo

Hardware stereo is a trick incorporated in graphics systems. The monitor runs at double frequency so that the screen presents alternate eye views one after another. The user wears a pair of goggles containing liquid crystal shutters and an infrared emitter on the workstation synchronizes the visibility of the screen to each eye.



3D Representation

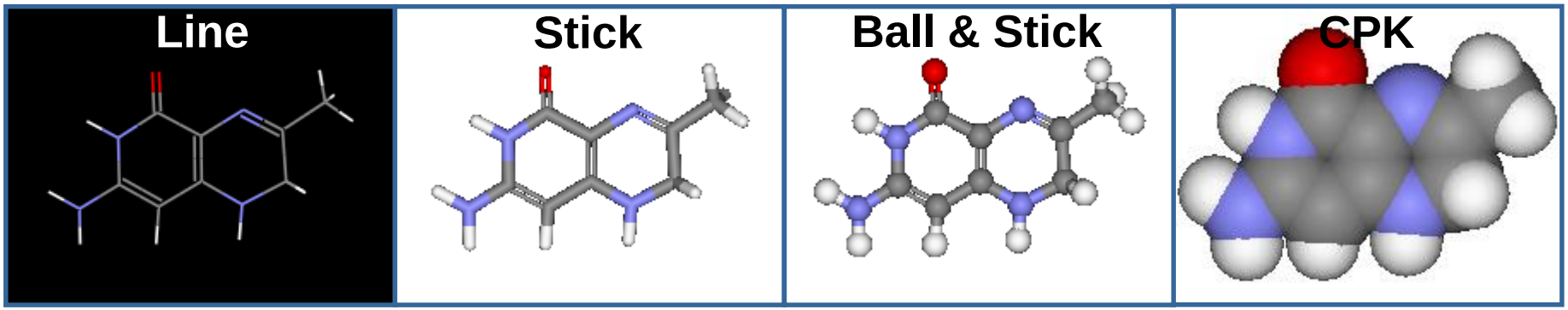
Molecules can be displayed using different rendering techniques.

Line. This is the simplest and most common way to visualize molecules where the bonding arrangment is represented in 3D. This type of representation is also called “wireframe”.

Stick. The bonds are represented as tubes.

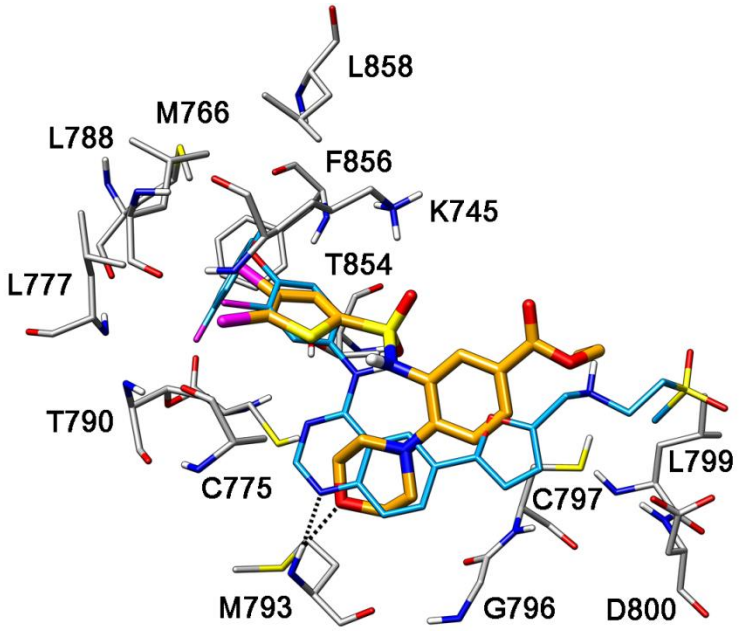
Ball & Stick. The molecule is displayed as the assembly of atoms and bonds. Atoms are represented as small spheres and bonds as tubes.

CPK. The molecule is defined as a set of spheres of van der Walls radii of the individual atoms.



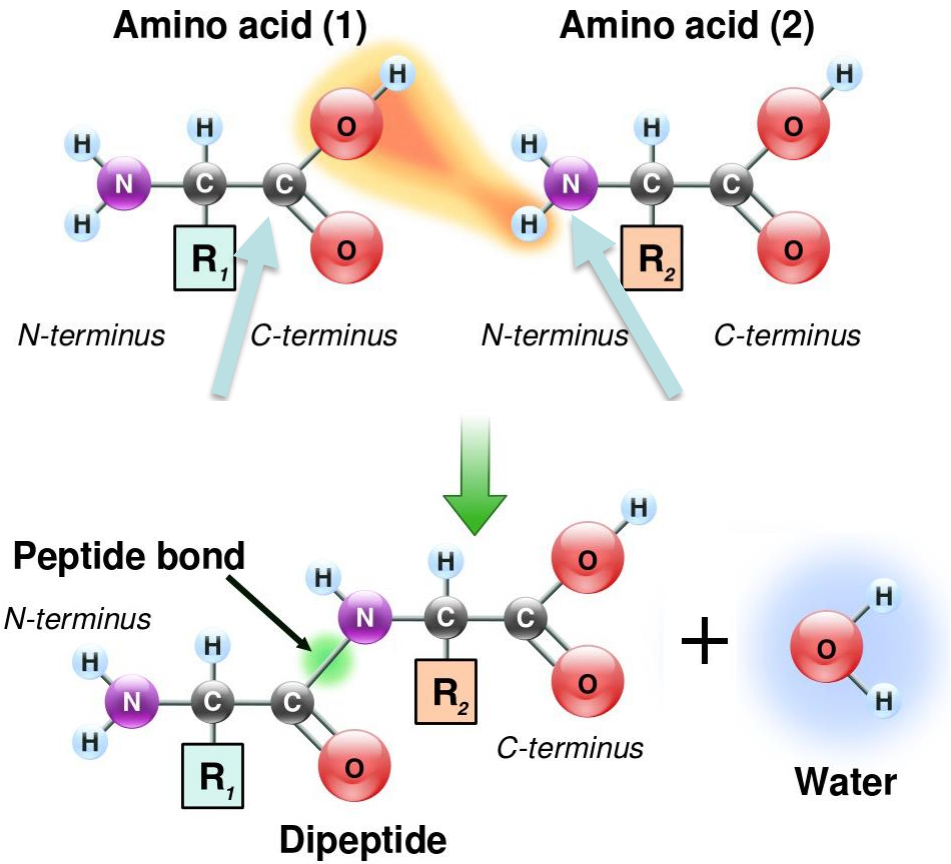
Proteins Representation

Macromolecules are complex entities. They can be displayed as small molecules using various techniques (line, ball and stick, etc.). Other representations are specific to macromolecules and give an overview of the overall molecular architecture of the protein.



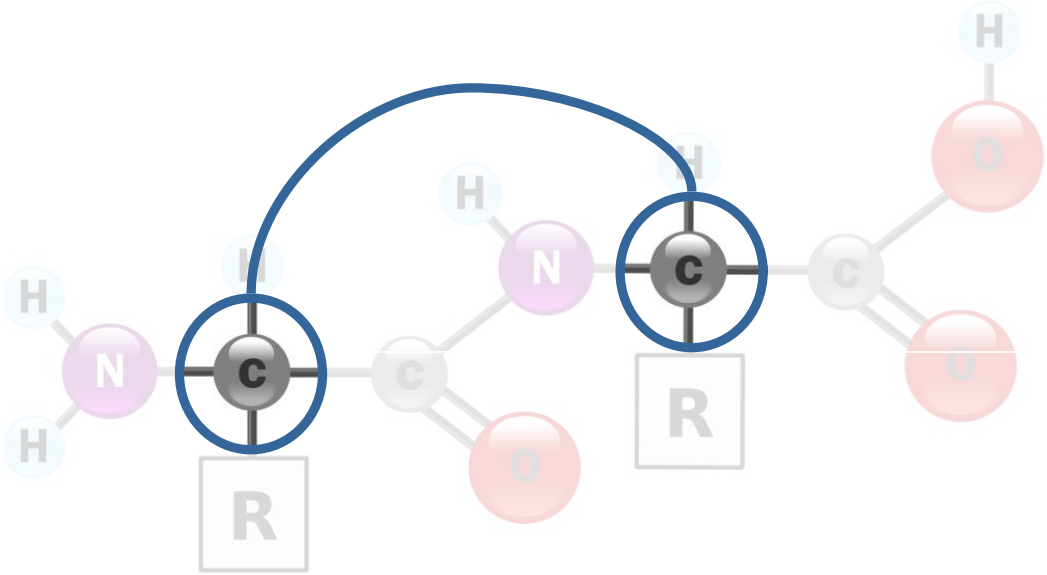
From Amino Acids to Proteins

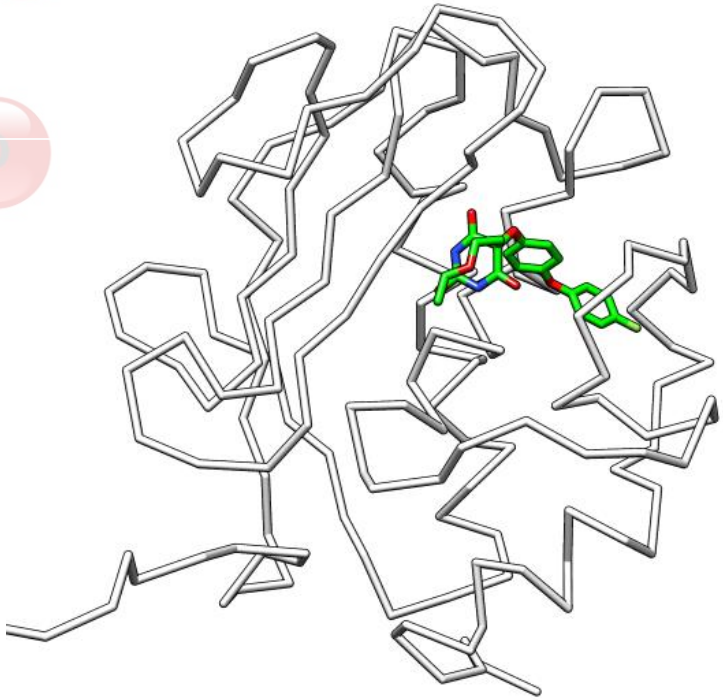
Peptide Bonds



Proteins Representation: Cα trace

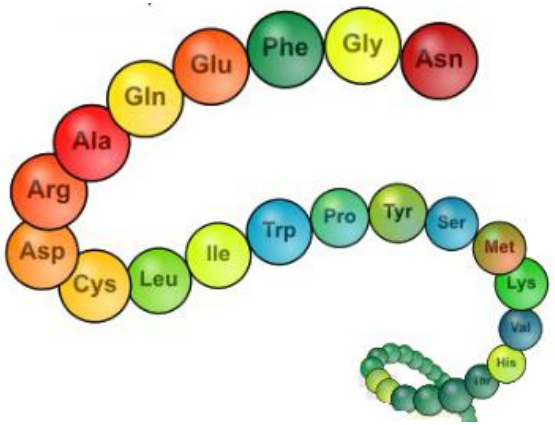
This representation is useful for editing and aligning different proteins.





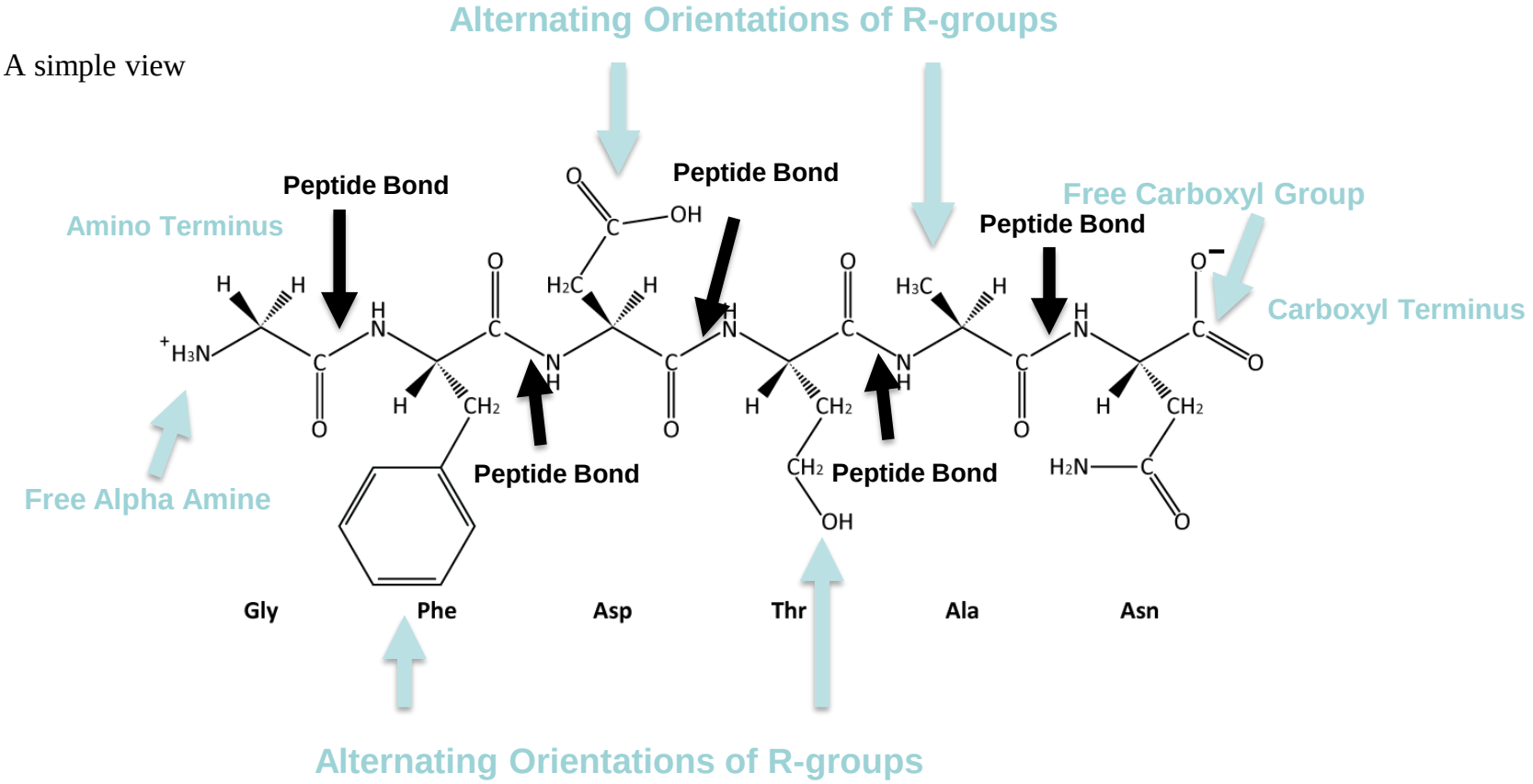
Primary Protein Structure

- Linear sequence of amino acids
- Joined by Peptide Bonds
- Translated from mRNA using Genetic Code
- Synthesis begins at amino-end, and terminates at carboxyl-end
- **<u>Ultimately determines all properties of a protein</u>**



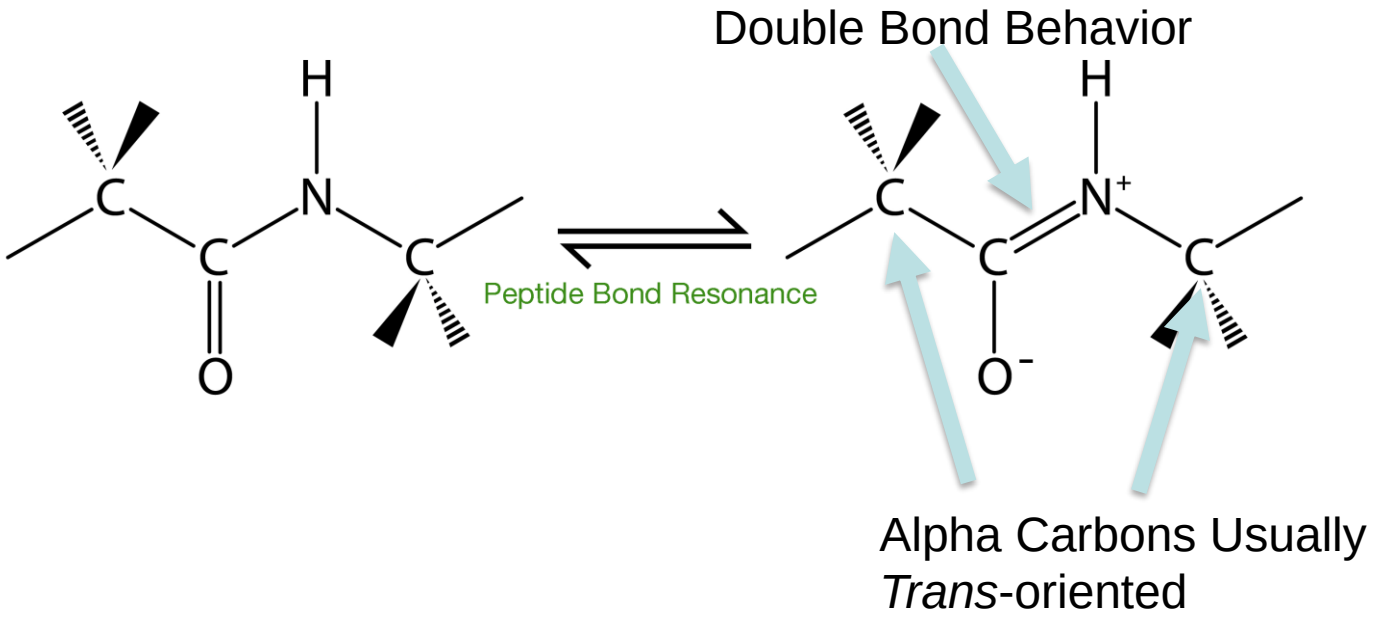
Polypeptides

A simple view



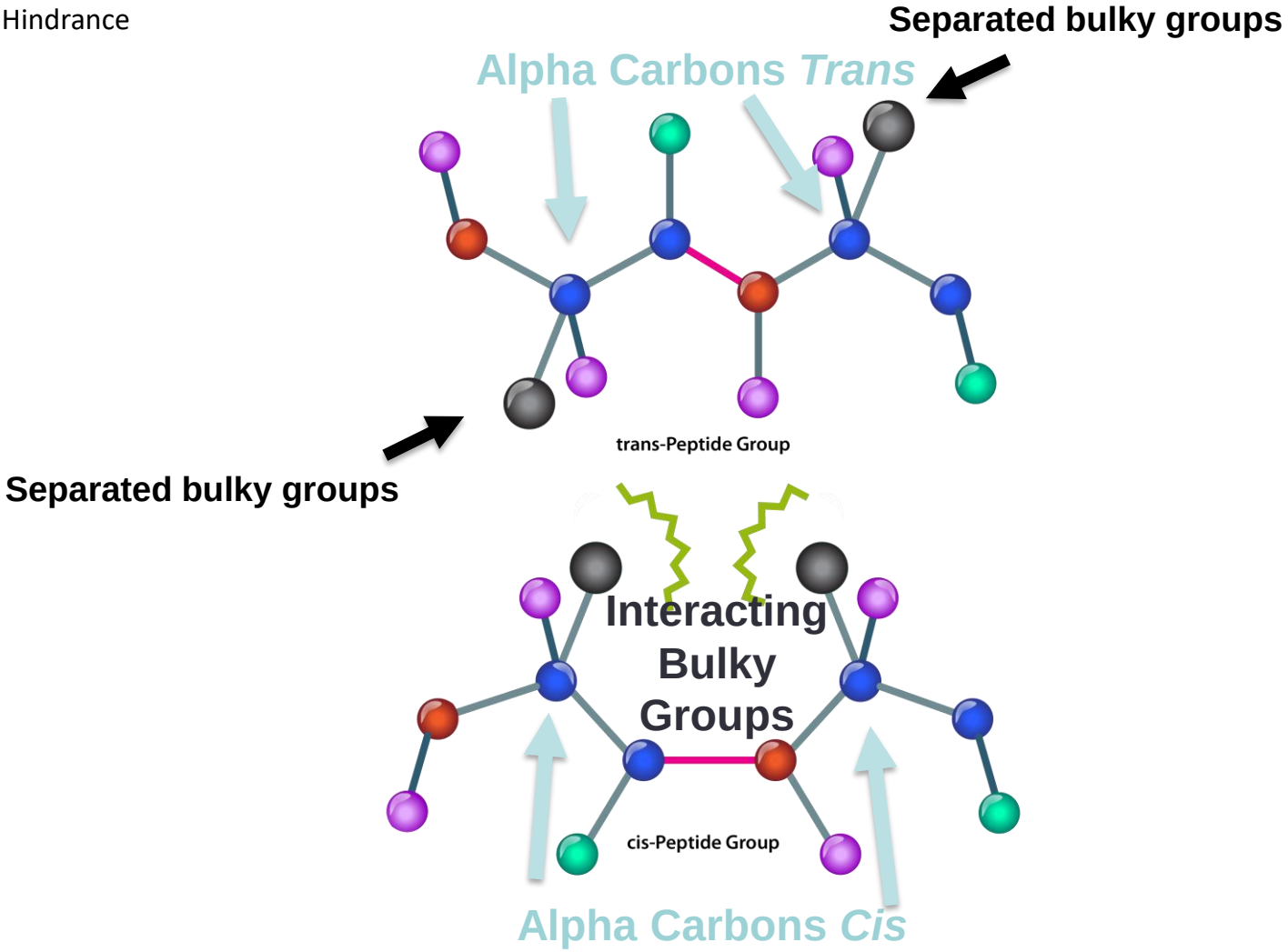
Peptide Bonds

Chemical Character



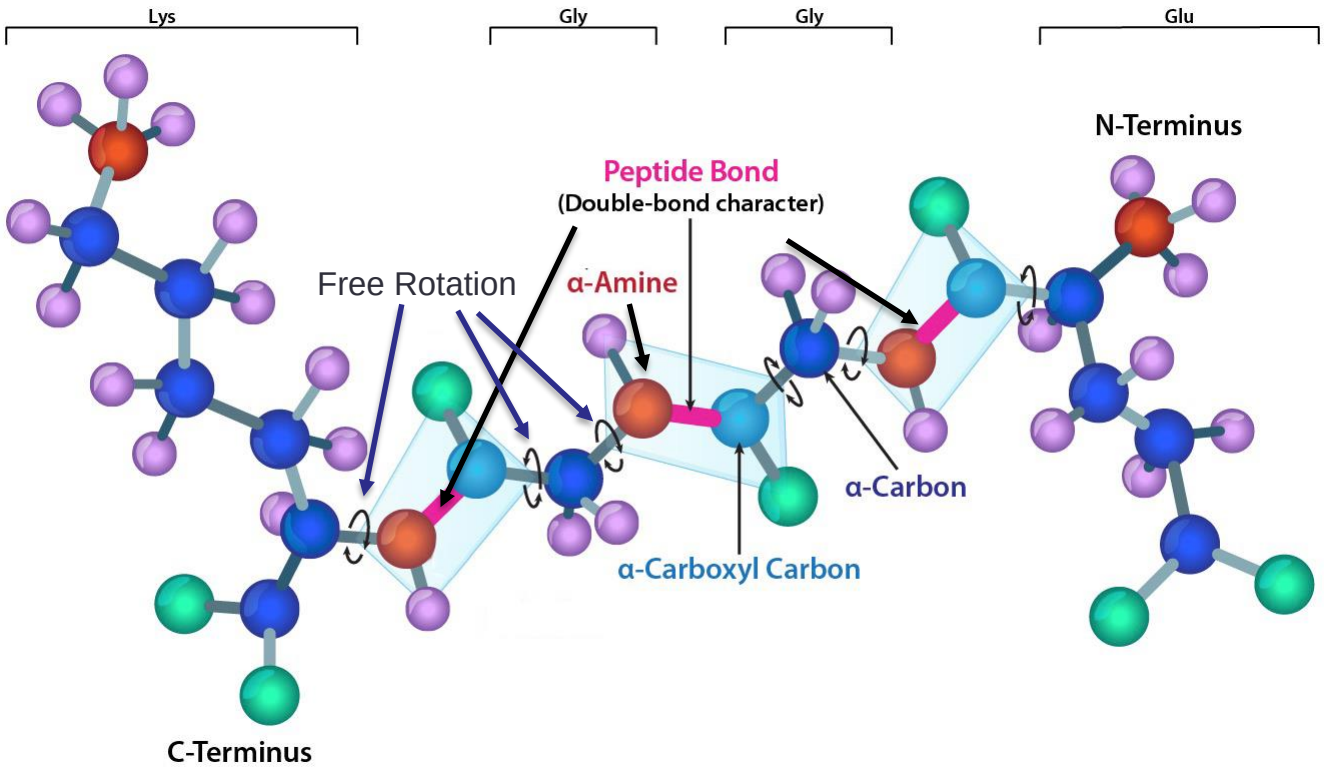
Polypeptides

Steric Hindrance

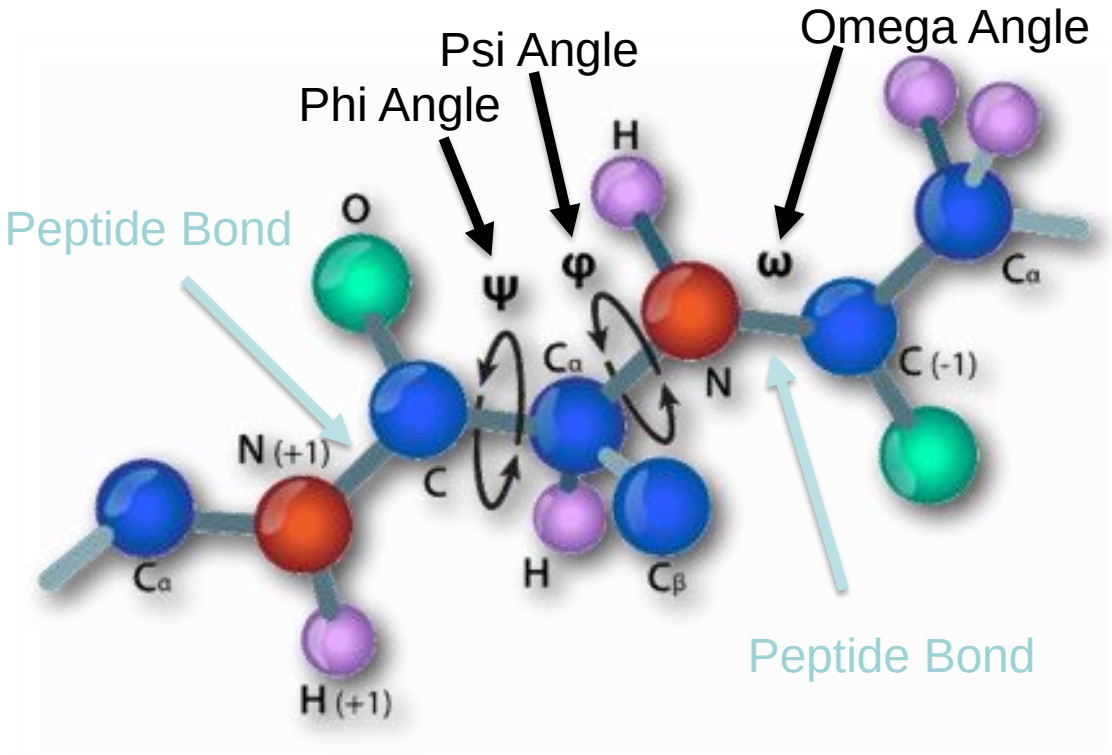


Polypeptides

Multiple Peptide Bond Planes

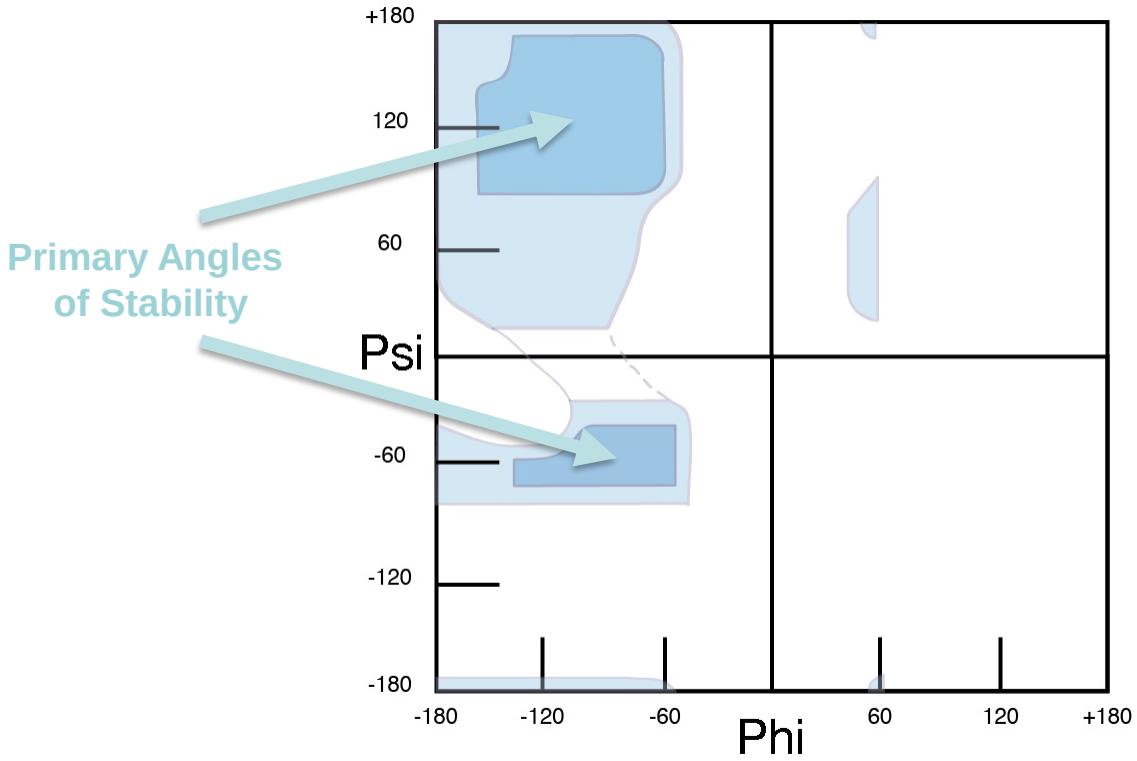


Phi and Psi Angles



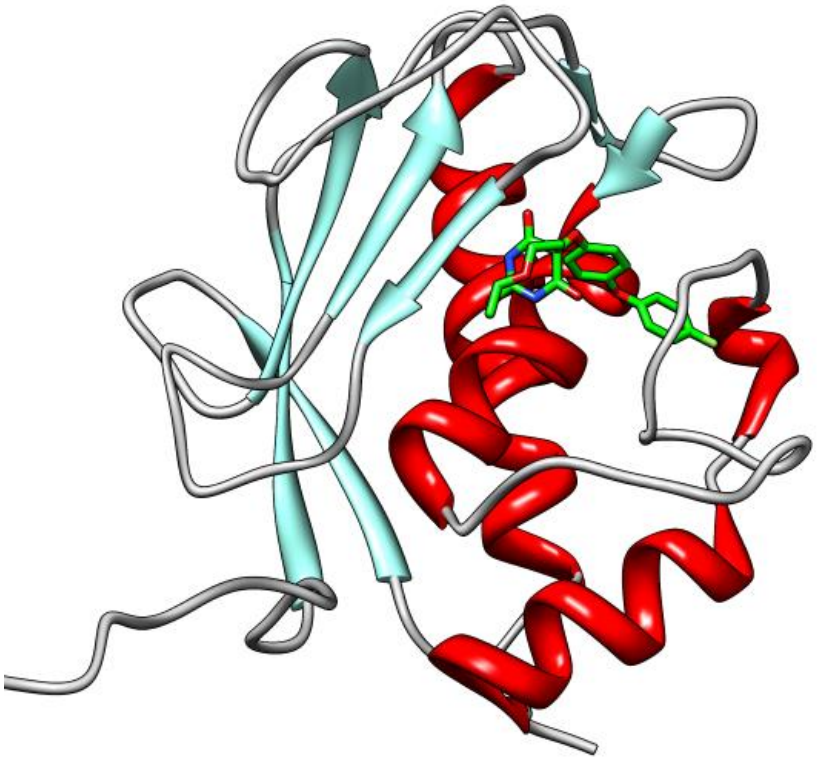
Ramachandran Plot

Bond Angles



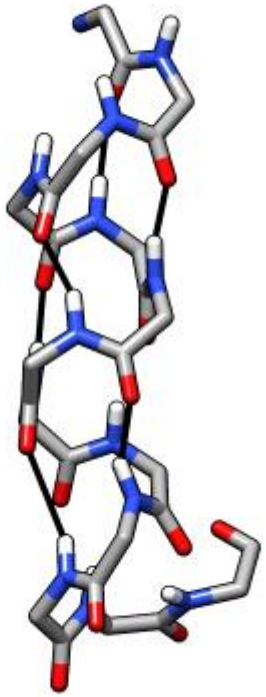
Proteins Representation: Ribbon

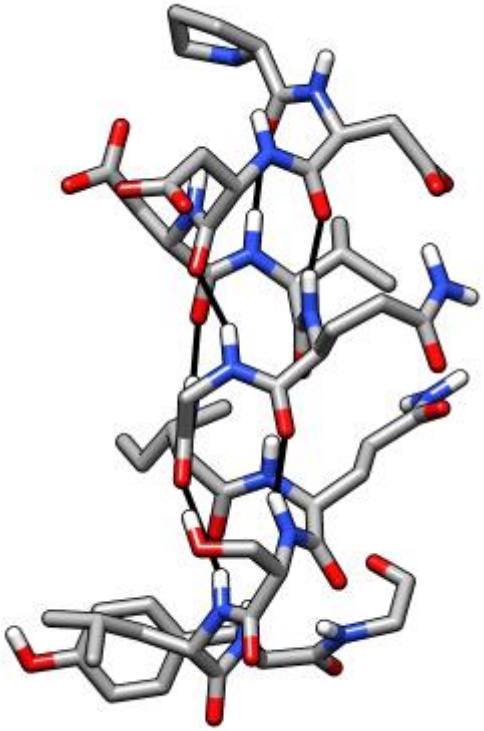
Ribbon representations are specific to proteins and provide an overview of the overall molecular architecture (secondary structure) of the protein. α-helices, β-sheets and β-turns are easily recognized.

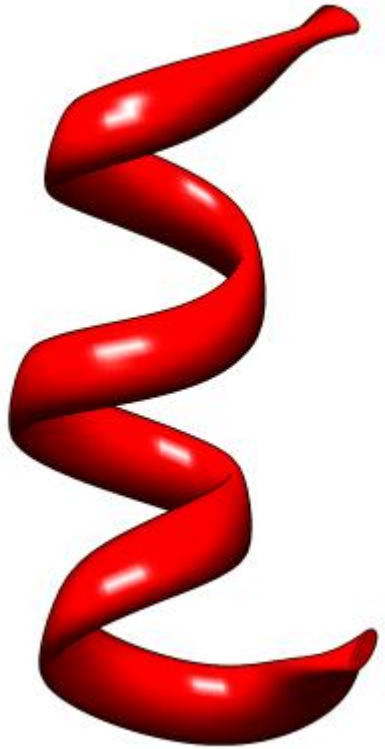


Proteins Representation: α-helices

The **alpha helix** is a right-handed coiled or spiral conformation, in which every backbone N-H group donates a hydrogen bond to the backbone C=O group of the amino acid four residues earlier (i+4→t).



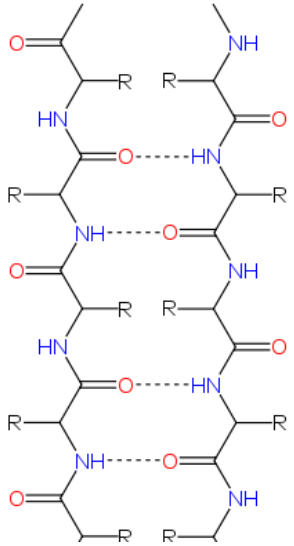




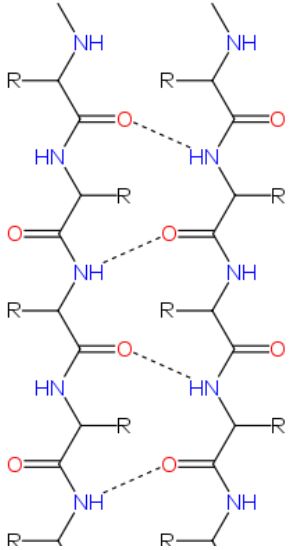
Proteins Representation: β-sheets

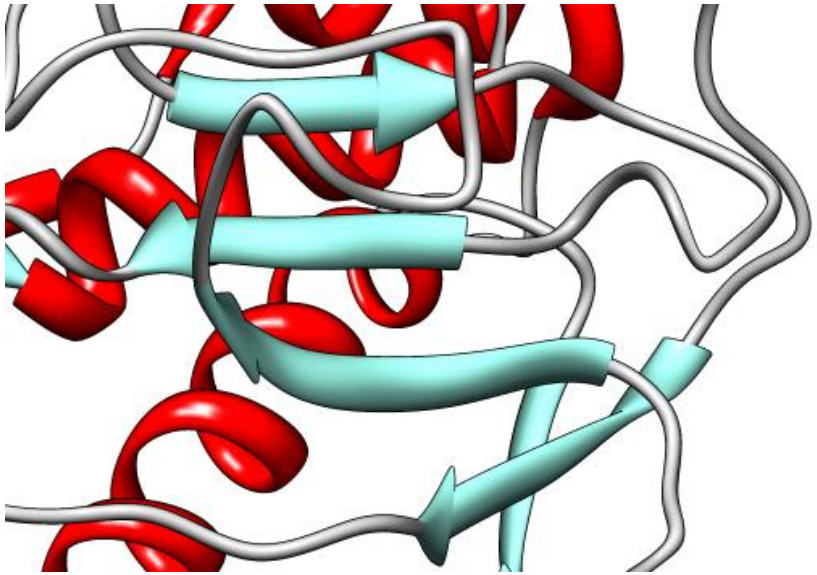
Beta sheet consists of **beta strands** connected laterally by at least two or three backbone hydrogen bonds, forming a generally twisted, pleated sheet. The majority of **beta strands** (typically 3 to 10 amino acids long) are arranged adjacent to other strands and form an extensive hydrogen bond network with their neighbors in which the N-H groups in the backbone of one strand establish hydrogen bonds with the C=O groups in the backbone of the adjacent strands.

Antiparallel Beta sheet

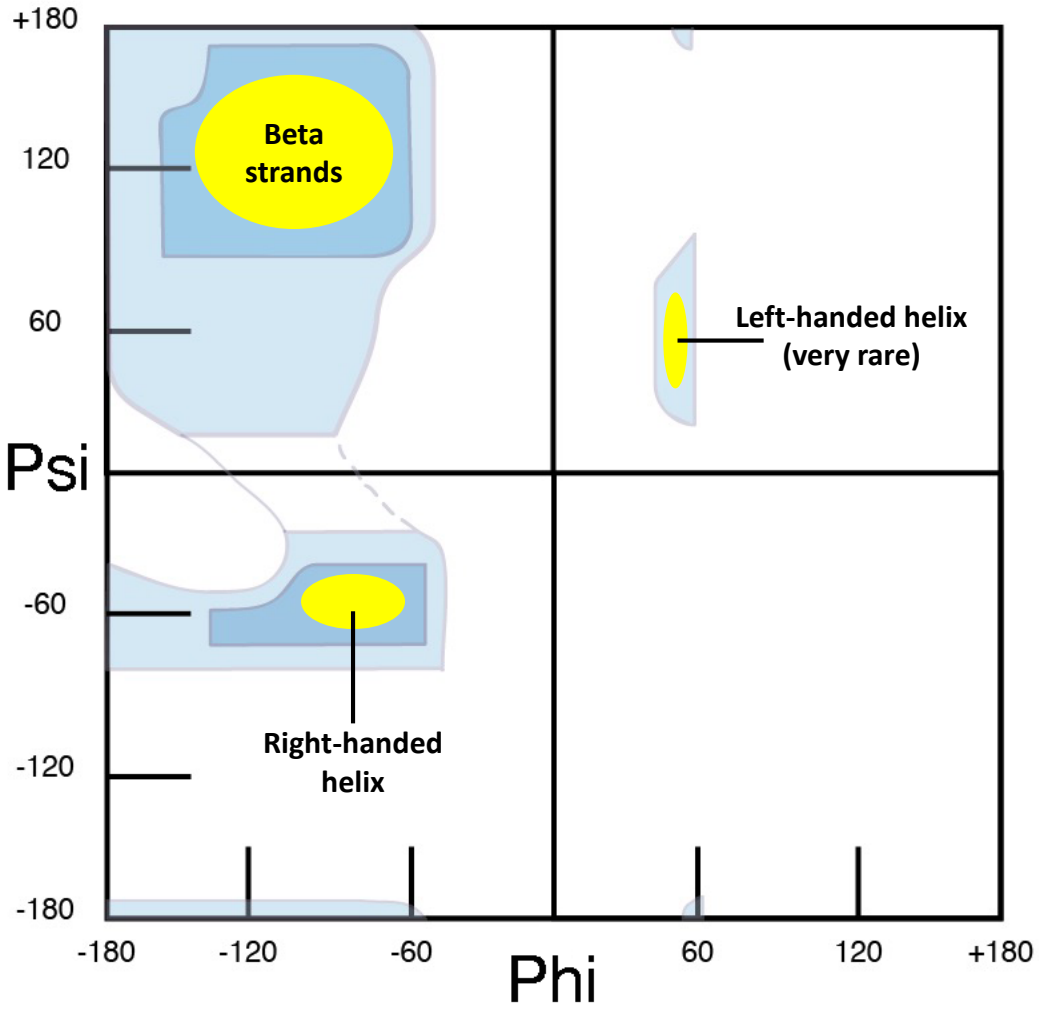


Parallel Beta sheet

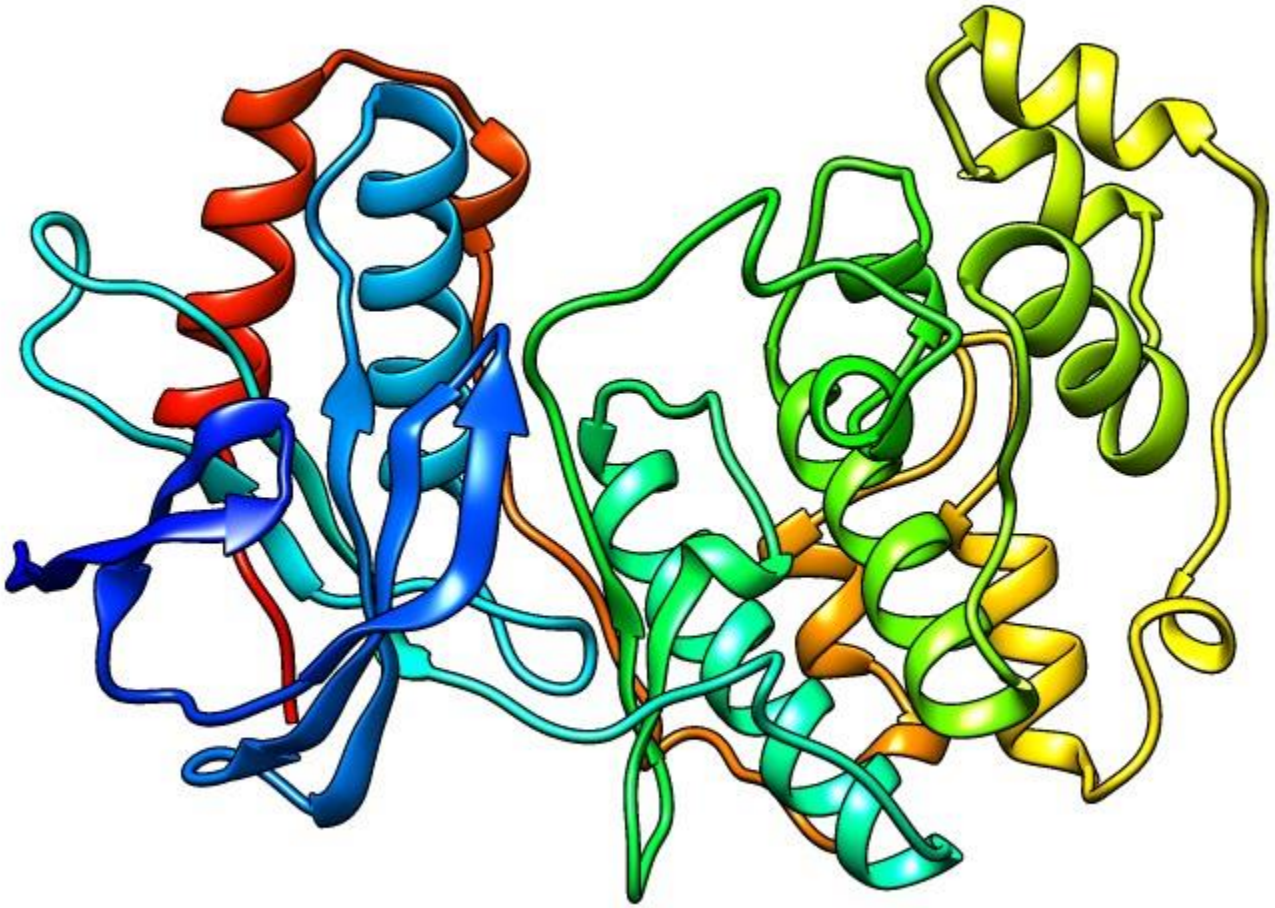




Ramachandran Plot Labeled



Molecule format: PDB



Molecule format: PDB

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ATOM      2  CA  ARG A   5      -1.393   3.612  40.550  1.00 34.02           C
ATOM      3  C   ARG A   5      -0.474   2.718  41.392  1.00 33.04           C
ATOM      4  O   ARG A   5      -0.945   1.957  42.215  1.00 34.00           O
ATOM      5  CB  ARG A   5      -2.020   4.713  41.416  1.00 34.82           C
ATOM      6  CG  ARG A   5      -1.029   5.810  41.901  1.00 35.95           C
ATOM      7  CD  ARG A   5      -1.575   6.691  43.038  1.00 38.02           C
ATOM      8  NE  ARG A   5      -0.657   7.728  43.548  1.00 37.74           N
ATOM      9  CZ  ARG A   5       0.091   7.610  44.656  1.00 38.04           C
ATOM     10  NH1 ARG A   5       0.065   6.479  45.378  1.00 38.47           N
ATOM     11  NH2 ARG A   5       0.878   8.619  45.048  1.00 35.72           N
ATOM     12  N   PRO A   6       0.840   2.782  41.166  1.00 31.98           N
ATOM     13  CA  PRO A   6       1.790   2.041  42.004  1.00 30.33           C
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ATOM     18  CD  PRO A   6       1.520   3.510  40.073  1.00 31.67           C
ATOM     19  N   THR A   7       2.537   1.874  44.291  1.00 27.45           N
ATOM     20  CA  THR A   7       2.900   2.386  45.608  1.00 27.35           C
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ATOM     22  O   THR A   7       5.198   2.609  44.897  1.00 26.31           O
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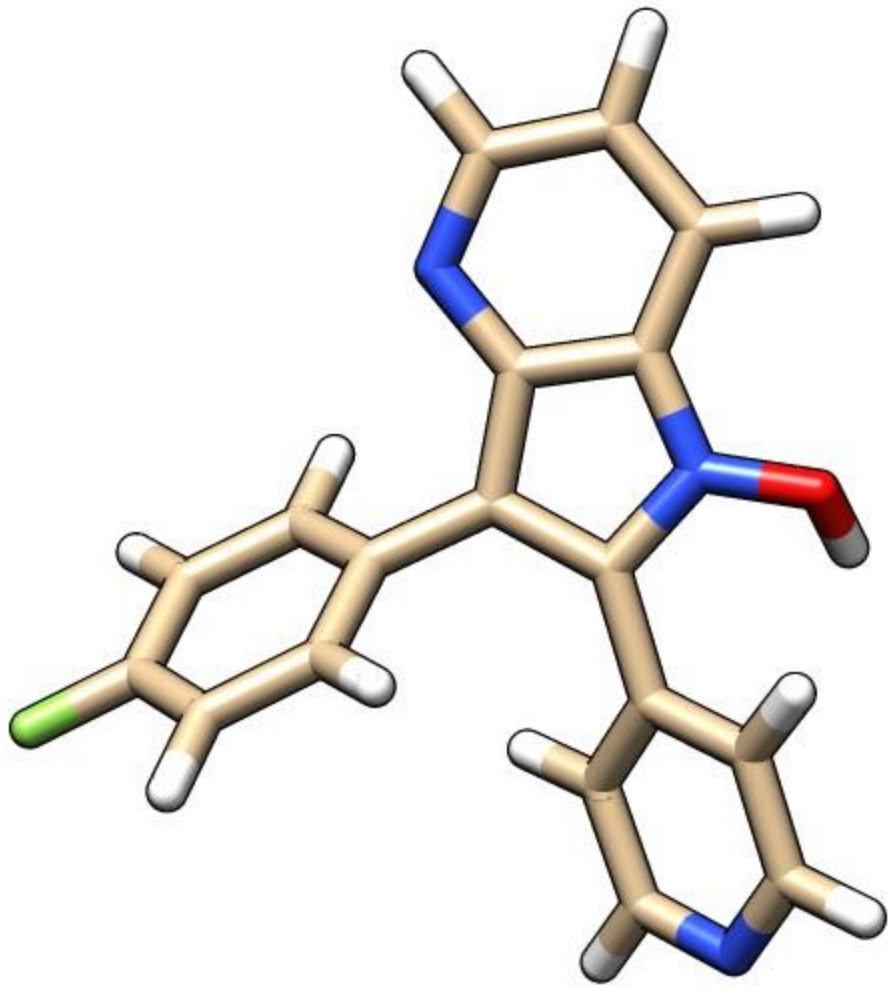
ATOM     34  CE1 PHE A   8       3.210   6.870  42.857  1.00 26.15           C
ATOM     35  CE2 PHE A   8       5.302   8.062  42.562  1.00 25.15           C
ATOM     36  CZ  PHE A   8       4.056   7.658  42.058  1.00 25.39           C
```

ATOM/HETATM

Molecule format: MOL2



Molecule format: MOL2

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1oz1
35 38 1 0 0
PROTEIN
AMBER ff14SB


@<TRIPOS>ATOM
      1 O12         22.9580   13.8160   33.2690 O.3       1 FPH    -0.4462
      2 N07         21.6960   14.0160   33.0600 N.ar      1 FPH     0.0275
      3 C01         21.1480   15.2740   33.0560 C.ar      1 FPH    -0.1626
      4 C06         21.6920   16.5690   33.2740 C.ar      1 FPH    -0.0710
      5 C05         20.7940   17.6450   33.2060 C.ar      1 FPH    -0.2353
      6 C04         19.4490   17.3950   32.9130 C.ar      1 FPH     0.3872
      7 N03         18.9110   16.1640   32.6780 N.ar      1 FPH    -0.6260
      8 C02         19.7840   15.0960   32.7640 C.ar      1 FPH     0.3193
      9 C08         19.5260   13.6820   32.5980 C.ar      1 FPH    -0.0162
     10 C24         18.2190   13.0650   32.3100 C.ar      1 FPH    -0.0548
     11 C25         17.7200   12.0650   33.1830 C.ar      1 FPH    -0.0780
     12 C26         16.4790   11.4420   32.9480 C.ar      1 FPH    -0.1720
     13 C27         15.7220   11.8500   31.8500 C.ar      1 FPH     0.1329
     14 F32         14.5350   11.2560   31.6140 F         1 FPH    -0.1399
     15 C28         16.1900   12.8430   30.9700 C.ar      1 FPH    -0.1720
     16 C29         17.4320   13.4490   31.2020 C.ar      1 FPH    -0.0780
     17 C13         20.7700   13.0000   32.7920 C.ar      1 FPH     0.0008
     18 C14         21.1970   11.5670   32.7220 C.ar      1 FPH    -0.0118
     19 C19         22.2090   11.0690   33.5820 C.ar      1 FPH    -0.2228
     20 C18         22.6200    9.7380   33.4590 C.ar      1 FPH     0.3882
     21 N17         22.0850    8.8740   32.5420 N.ar      1 FPH    -0.6550
     22 C16         21.1230    9.3570   31.7230 C.ar      1 FPH     0.3882
     23 C15         20.6600   10.6740   31.7710 C.ar      1 FPH    -0.2228
     24 H06         22.7416   16.7170   33.4811 H         1 FPH     0.1500
     25 H05         21.1371   18.6545   33.3779 H         1 FPH     0.1470
     26 H04         18.7837   18.2446   32.8694 H         1 FPH     0.0261
     27 H25         18.3030   11.7756   34.0448 H         1 FPH     0.1480
     28 H26         16.1205   10.6635   33.6052 H         1 FPH     0.1510
     29 H28         15.5941   13.1372   30.1187 H         1 FPH     0.1510
     30 H29         17.7896   14.2145   30.5293 H         1 FPH     0.1480
     31 H19         22.6579   11.7117   34.3248 H         1 FPH     0.1575
     32 H18         23.3951    9.3751   34.1178 H         1 FPH     0.0261
     33 H16         20.6899    8.6890   30.9932 H         1 FPH     0.0261
     34 H15         19.8956   11.0066   31.0843 H         1 FPH     0.1575
     35 H12         23.2990   13.2073   32.6096 H         1 FPH     0.4300
@<TRIPOS>BOND
@<TRIPOS>BOND
     1    1    2 1
     2    2    3 ar
     3    2   17 ar
     4    3    4 ar
     5    3    8 ar
     6    4    5 ar
     7    5    6 ar
     8    6    7 ar
     9    7    8 ar
    10    8    9 ar
    11    9   10 1
    12    9   17 ar
    13   10   11 ar
    14   10   16 ar
    15   11   12 ar
    16   12   13 ar
    17   13   14 1
    18   13   15 ar
    19   15   16 ar
    20   17   18 1
    21   18   19 ar
    22   18   23 ar
    23   19   20 ar
    24   20   21 ar
    25   21   22 ar
    26   22   23 ar
    27   24    4 1
    28   25    5 1
    29   26    6 1
    30   27   11 1
    31   28   12 1
    32   29   15 1
    33   30   16 1
    34   31   19 1
    35   32   20 1
    36   33   22 1
    37   34   23 1
    38   35    1 1
@<TRIPOS>SUBSTRUCTURE
     1 FPH     1 RESIDUE           4 A     FPH      0 ROOT
```
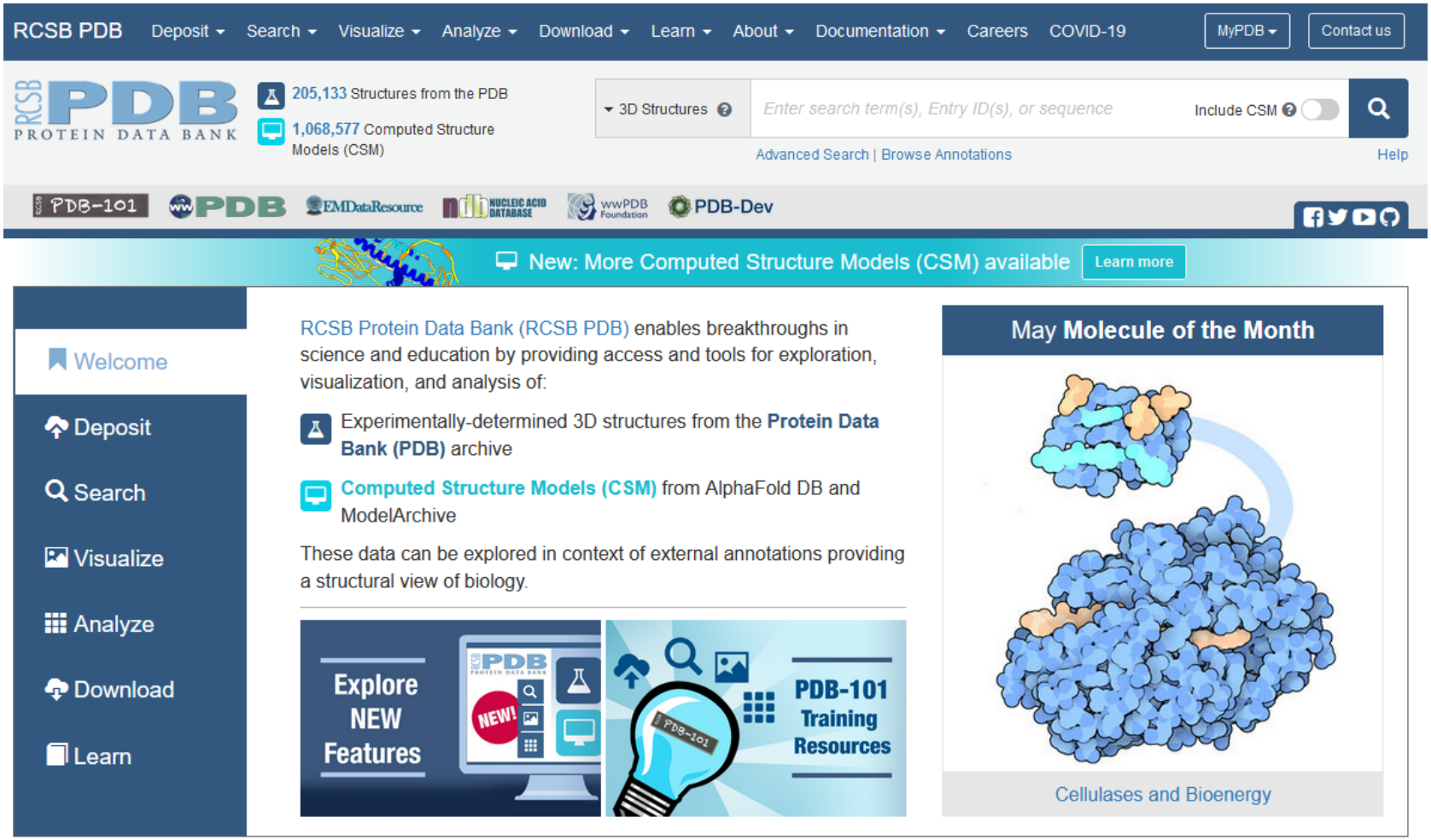
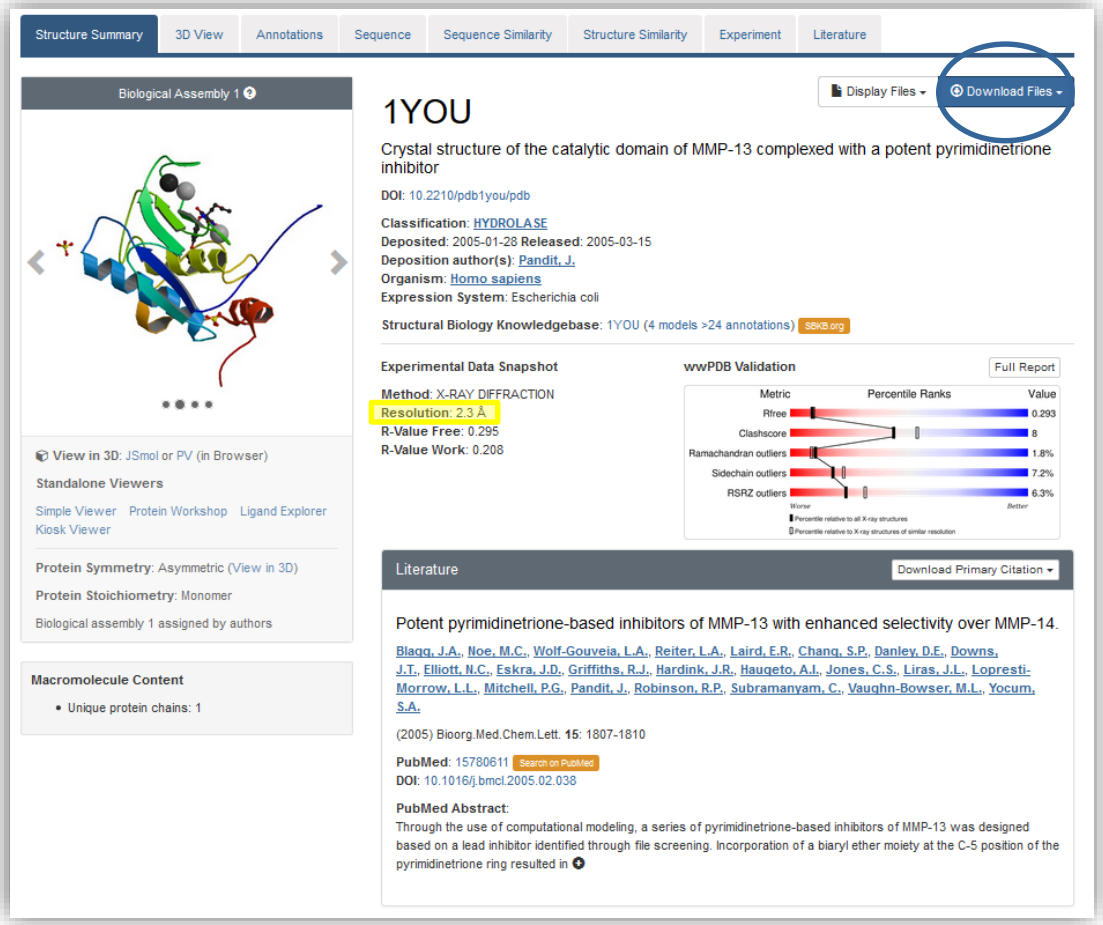

Protein Data Bank

www.rcsb.org



Protein Data Bank

If you insert for example the 1YOU PDB code you will obtain the following results:



X-ray Resolution

Protein Data Bank

Macromolecules

Find similar proteins by: Sequence (by identity cutoff) | Structure

Entity ID: 1

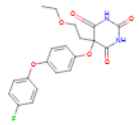
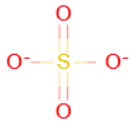
Molecule	Chains	Sequence Length	Organism	Details
Collagenase 3	A, B	168	Homo sapiens	**Mutation(s)**: 0 **Gene Names:** MMP13 **EC:** 3.4.24

Find proteins for P45452 *(Homo sapiens)* Explore P45452

Protein Data Bank

Small Molecules

Ligands 4 Unique

ID	Chains	Name / Formula / InChI Key	2D Diagram	3D Interactions
PFD Query on PFD Download CCD File	A, B	**5-(2-ETHOXYETHYL)-5-[4-(4-FLUOROPHENOXY)PHENOXY]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONE** C_{20} H_{19} F N_2 O_6 XRSYNYGEEYTXJV-UHFFFAOYSA-N		Ligand Interaction
SO4 Query on SO4 Download CCD File	A, B	**SULFATE ION** O_4 S QAOWNCQODCNURD-UHFFFAOYSA-L		Ligand Interaction
ZN Query on ZN Download CCD File	A, B	**ZINC ION** Zn PTFCDOFLOPIGGS-UHFFFAOYSA-N	Zn^{+2}	Ligand Interaction
CA Query on CA Download CCD File	A, B	**CALCIUM ION** Ca BHPQYMZQTOCNFJ-UHFFFAOYSA-N	Ca^{+2}	Ligand Interaction

External Ligand Annotations

ID	Binding Affinity (Sequence Identity %)
PFD	IC50: 0.8700000047683716 nM Binding MOAD
PFD	IC50 : 0.8700000047683716 nM PDBBind
PFD	IC50: 0.6000000238418579 nM BindingDB