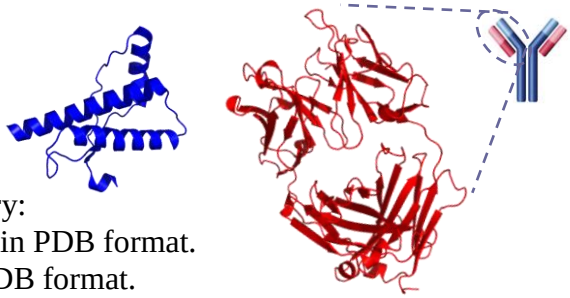
Tutorial: A suite of tools for protein-protein docking

All the servers are available at: http://bioinfo3d.cs.tau.ac.il/

Exercise 1: **Rigid Docking**

Prion diseases are deadly neurodegenerative pathologies affecting numerous mammal species.[1] The key event in the pathogenesis is the conversion of the α-helix-rich host prion protein (PrP^C) into a pathogenic isoform (PrP^{Sc}) characterized by its insolubility, its high content in β-sheet, and its protease resistance.
In this exercise you will solve **Target 19** of the CAPRI challenge[2], by using the PatchDock server. You will try to predict the structure of a complex of a prion protein in its PrP^C conformation and an antibody that cross-reacts with PrP^C and PrP^{Sc}.[3]



A. Submitting a PatchDock job:

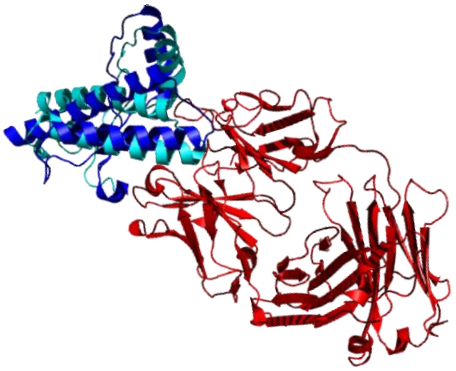
1. Download and unzip the tutorial directory and look at the files in the "Ex1" sub-directory:
   antibody.pdb – The structure of the antibody in PDB format.
   ovine.pdb – The structure of the antigen in PDB format.
   NativeComplex.pdb – The structure of the correct native complex.
   * View the molecules using Rasmol
   (For a clear visualization use: Display→Cartoons, Colours→Chain).
2. Go to the webserver of PatchDock:
   http://bioinfo3d.cs.tau.ac.il/PatchDock/index.html
3. Fill out the following fields in the web-server:

Receptor Molecule:	Upload the *antibody.pdb* file
Ligand Molecule:	Upload the *ovine.pdb* file
e-mail address:	Fill out your e-mail, to which the results will be sent.
Clustering RMSD:	4.0
Complex Type:	Choose "Antibody-antigen"

4. Submit the form.

B. Checking the results:

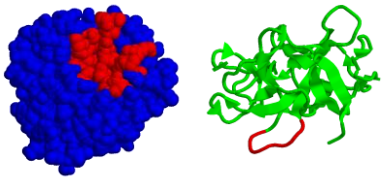
1. Look at the output page and examine the results.
2. Solution number 6 is an accurate prediction of the complex.
3. Compare it to the structure of *NativeComplex.pdb*.



References:
1. Prusiner, S. B. (1998) Proc. Natl. Acad. Sci. USA 95:13363–13383.
2. Janin J. (2005) Proteins. 1;60(2):170-5.
3. Eghiaian et al. (2004) Proc Natl. Acad. Sci. USA. 101(28):10254-9.

Exercise 2: **Flexible Docking**

Savinase is a secreted microbial serine protease, with a catalytic triad consisting of Asp32, His64 and Ser221, situated in a shallow groove on the surface.[1] BASI is a Savinase inhibitor in plants which protects the seed from pathogen-derived serine proteases (e.g. Savinase). A low resolution structure of a homologue of BASI (WASI) in a complex with proteinase K has indicated an important role of a loop (residues 85-96) in the inhibition process.[2]
In this exercise you will solve **Target 32** of the CAPRI challenge, by using the PatchDock server and the FireDock server. You will need to dock the inhibitor BASI to protease savinase, using the biological knowledge above.



A. Submitting a PatchDock job:

1. Look at the files in the "Ex2" sub-directory:
   BASI.pdb – The structure of the inhibitor in PDB format.
   savinase.pdb - The structure of the protease in PDB format.
   NativeComplex.pdb – The structure of the correct native complex.
2. Prepare two binding-site files according to the given biological information.
3. Go to the webserver of PatchDock:
   http://bioinfo3d.cs.tau.ac.il/PatchDock/index.html
4. Fill out the following fields in the web-server:

Receptor Molecule:	Upload the *savinase.pdb* file
Ligand Molecule:	Upload the *BASI.pdb* file
e-mail address:	Fill out your e-mail, to which the results will be sent
Clustering RMSD:	4.0
Complex Type:	Choose: "Enzyme-inhibitor"

5. In the advanced option, fill out the following fields:

Receptor Binding Site:	Upload the binding-site file of savinase
Ligand Binding Site:	Upload the binding-site file of BASI
Distance Constraints:	Leave empty

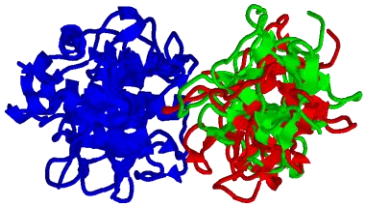
6. Submit the form.

B. Refining the results by FireDock:

1. Transfer up to 1000 of the best solutions to FireDock for refinement and re-scoring.

C. Checking the results:

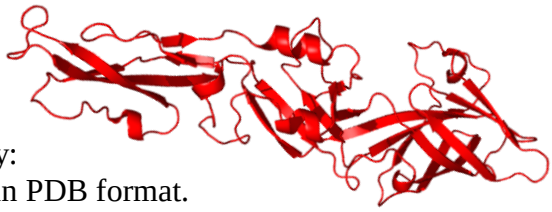
1. Look at the output page and examine the results.
2. Compare the top 10 solutions to the structure of *NativeComplex.pdb*.
3. Did you succeed in predicting the interaction?



References:
1. Micheelsen et al. (2008) JMB 380(4):681-690.
2. Nielsen et al. (2003) Biochim Biophys Acta. 1696(2):157-64.

Exercise 3: **Symmetric Docking**

Enveloped viruses enter cells via a membrane fusion reaction driven by conformational changes of specific viral envelope proteins.[1] The envelope glycoproteins from tick-borne encephalitis virus assemble metastable homodimers on the viral surface and due to membrane fusion it forms very stable homotrimers. The energy released during the transition from the dimers at the viral surface to the target-membrane-inserted homotrimers is used to drive the merging of the viral and cellular membranes.
In this exercise you will solve **Target 10** of the CAPRI challenge[2], using SymmDock.
You will need to predict the homo-trimer structure of the above envelope glycoprotein.

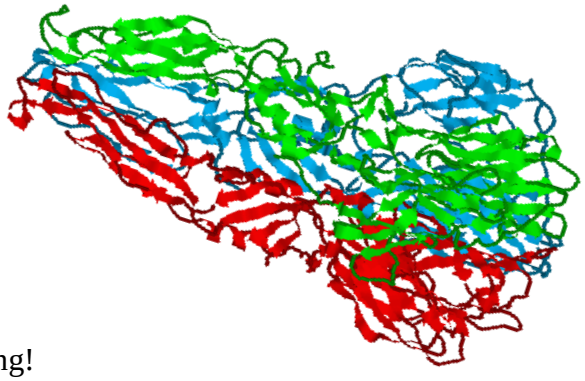


A. Submitting a SymmDock job:
   1. Look at the files in the "Ex3" sub-directory:
      1svb.pdb – The structure of the monomer in PDB format.
      NativeComplex.pdb – The structure of the correct native complex.
   2. Go to the webserver of SymmDock:
      http://bioinfo3d.cs.tau.ac.il/SymmDock/index.html
   3. Fill out the following fields in the web-server:

Unit Molecule:	Upload the *1svb.pdb* file
Symmetry Order:	3 (since we want to predict a homo-trimer)
e-mail address:	Fill out your e-mail, to which the results will be sent.

   4. Submit the form.

B. Checking the results:
   1. Look at the output page and examine the results.
   2. Solution number 1 is an accurate prediction of the complex.
   3. Compare it to the structure of *NativeComplex.pdb*.
   4. What is the main difference between the two structures?



Good luck,
and enjoy the docking!

References:
1. Bressanelli et al. (2004) EMBO J. 23(4): 728–738.
2. Janin J. (2005) Proteins. 1;60(2):170-5.