MBV-INF x410 ----- Docking tutorial

It's not possible to perform a full docking within the short period of this tutorial. The process starts starts with preparing input files of receptor and ligand(s). Several tools needs to be used in that process to perform the following general steps:

I. Prepare receptor
- Fix missing atoms (if any) in model
- Add hydrogen atoms to protein
- Select protonation state for His residues
- Select rotamers for Gln, Ans residues

II. Calculate grid
- Select region in receptor to define docking site

III. Prepare ligand(s)
- If data are 2D only, generate 3D low-energy conformation(s)

IV. Dock
- Start docking job(s)
- Select level of accuracy, scoring function and level of output

So in this tutorial, we will focus on analysing docking results. These are results published by the designers of the web based docking tool ParDOCK (http://www.scfbio-iitd.res.in/index.html). This is an automated server for one-receptor-one-ligand docking, which is different from a docking program that uses a library of ligands for one receptor. However, the results presented here are still good examples of docking results and the process of predicting good and bad ligands.

Case I - Trypsin inhibitors

Trypsin is a protease that digests proteins by cleaving the peptide bond between amino acids. Many structures of trypsin in complex with ligands have been published and made accessible in the PDB data base (www.pdb.org). Here, we will examine 4 different protein-ligand complexes.

Load the following pdb-files into the same Pymol window:

1f0ucomplex.pdb; 1tnhcomplex.pdb, 3ptbcomplex.pdb; 1tnicomplex.pdb

These complexes must be aligned first to ease the comparison. Give the following commands:

align 1tnhcomplex, 1f0ucomplex
align 3ptbcomplex, 1f0ucomplex

align 1tnicomplex, 1f0ucomplex

Turn on sequence display (Meny Display -> Sequence). The ligand is called "DRG" in the residue list in all structures.

Focus on the DRG ligand in the 1f0u complex. Look at all four complexes and try to answer the following questions.

A. Two ligands have low affinites, one has middle affinity and one has high affinity. Try to predict which ligands belong to which group. Can you find any explanation that supports your answer? Think in terms of strength, number and type of interactions between ligands and protein.

B. Can you also find a plausible explanation for the difference in affinity for the two ligands with lowest affinity? Hint: Look at protein conformation.

C. List 3-4 features that could contribute to a strong interaction for the high-affinity ligand. Optional: Make an illustration showing these interactions

Case II - HIV-1 protease

The HIV-1 protease is a target for several HIV drugs on the market. Many structures of HIV-1 protease in complex with ligands have been published and made accessible in the PDB data base (www.pdb.org). Here, we will examine 5 different protein-ligand complexes.

Load the following pdb-files into the same Pymol window:

1a30complex.pdb; 1a9mcomplex.pdb, 1aaqcomplex.pdb; 1hvjcomplex.pdb; 1hxwcomplex.pdb

These complexes must be aligned first to ease the comparison. Give the following commands:

align 1a9mcomplex, 1a30complex
align 1aaqcomplex, 1a30complex
align 1hvjcomplex, 1a30complex
align 1hxwcomplex, 1a30complex (This is almost in place; only minor corrections needed)

Turn on sequence display (Meny Display -> Sequence). The ligand is called "DRG" in the residue list in all structures. NB! Because of a strange PDB file format for these structures, atoms are sorted into element type and "DRG" is listed several times, one for each of hydrogen, carbon, oxygen, nitrogen etc ....

Focus on the DRG ligand in the 1a30 complex ("turn off" the four other complexes).

A. Which class of compunds does the ligand in 1a30 belong to? Hint: find the chain ....

B. Why do you think this is not a good drug (with respect to stability, not by it's affinity to the receptor)?

Turn on the 1a9m complex. Find the ligand.

C. Do you think this is a better/stronger ligand than 1a30? Why/why not?

Turn on the 1aaq, 1hvj and 1hxw complexes (Turn off the other compelxes)

D. How many H-bond donors and acceptors do you find in these three ligands? Do they all obey the Lipinisk rules with respect to these parameters?

E. Two of these ligands have much better affininty then the third one. Can you suggest which one and give a plausible explanation?