

Institute of Theoretical Computer Science

Lecturer: Prof. Jack Snoeyink

Assistant: Yves Brise

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Geometric Computations in Molecular Biology SS07

Exercise Set 4

Course Webpage: <http://www.ti.inf.ethz.ch/ew/courses/GCMB07/>

Due date: -

Classroom Exercise MolProbity Toolbox

The goal of today's exercise session is to take a critical look at the accuracy of structures in the PDB using tools offered by the MolProbity website (<http://molprobity.biochem.duke.edu>). MolProbity pulls together a suite of free open-source software developed and maintained by the Richardson laboratory at Duke University. We are going to use the web interface today, but these tools can also be downloaded and installed on Linux or Mac OS X computers.

MolProbity is designed to check structures that are being refined from data obtained by X-ray crystallography or other techniques. Its forte is "all atom contact analysis", which essentially treats atoms as balls with their corresponding van der Waals radii and looks for good overlaps (e.g. hydrogen bonds) and bad overlaps (e.g. steric clashes). It also evaluates bond lengths, angles, and torsions, and reports when these are outside of normal ranges.

We will walk through MolProbity on two structures of myoglobin (a small all-alpha protein) and one of Human alcohol dehydrogenase (a larger protein). We ask you to run it on your favorite protein as well.

Part A: Myoglobin (1mbn, 1mbo)

Myoglobin is the main oxygen storage protein in muscle cells. We are going to compare two different structures of this protein. One is the 1mbn entry, the first deposited structure in the pdb database, in 1973. The other one is a later structure of Myoglobin showing the position of the stored oxygen atom, deposited in 1981.

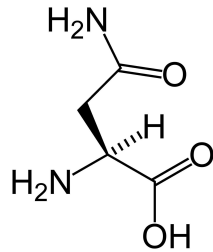
- Load 1mbn.pdb and 1mbo.pdb.
- What are their resolutions: 1mbn ____ Å, and 1mbo ____ Å?
- Add hydrogen atoms to the structure.
- Generate "all atom contact analysis" and explore.

Part B: Human alcohol dehydrogenase (1ht0)

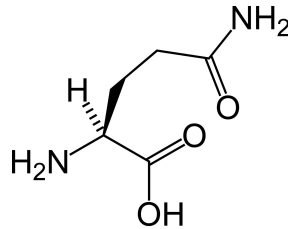
1ht0 is one of several variations of alcohol dehydrogenase, which are all enzymes that metabolize alcohol in our body. The potentially dangerous alcohol molecule is turned into acetate and other molecules that can be utilized by our cells.

- Load 1ht0.pdb and add hydrogen atoms.

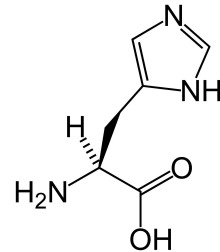
- Because it is hard to distinguish different types of heavy atoms in X-ray structures, amino acids that are symmetric up to atom types (especially asparagine (N), glutamine (Q), and histidine (H)) can be incorrectly placed, and may need to be flipped when adding hydrogens breaks the symmetry.



(a) Asparagine



(b) Glutamine



(c) Histidine

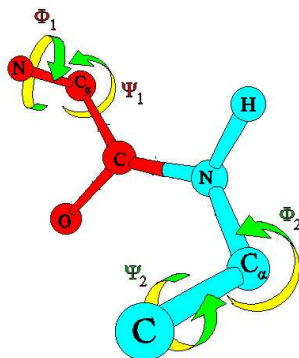
Part C: Your favourite molecule

Have a look at your favourite molecule in MolProbity.

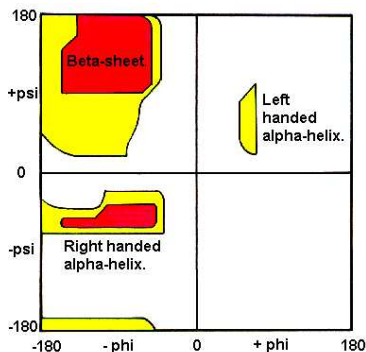
- What is the resolution of your structure?
- Add hydrogens and inspect proposed flips.
- Look at the Ramachandran plot. Are there any outliers that are not GLY?
- Look at trouble spots. Are there bad contacts among or between sidechain/mainchain? Are there any bad C_β angles?

Ramachandran plot

In a polypeptide the main chain $N-C_\alpha$ and $C_\alpha-C$ bonds are free to rotate relatively. These rotations are represented by the torsion angles Φ and Ψ , respectively. If we plot these two angles in a diagram, for all amino acids, we get the Ramachandran plot.



(d) Backbone



(e) Ramachandran plot