Often, we have biochemical information about an interaction but limited structural information. For example, we might know the K_D for a binding interaction, but not the exact molecular contacts made between a ligand and a protein. This can be solved using a "docking" calculation in which we try different chemically plausible orientations of the ligand. We can use the same tools for rational drug design, by docking drugs into a pocket, tweaking their chemistry, and then calculating their energies. Two commonly used pieces of software for this purpose are ROSETTA and AutoDock.

In this lab, we are going to investigate four different orientations of a ligand computationally docked into a receptor. In a docking calculation, these orientations are known as "poses." To gain a better understanding of the functions used for the calculation, we are going to do the calculations manually, rather than relying on complex software.

The molecules we are going to investigate are the small molecule *estradiol* interacting with its biological target, the *estrogen receptor* (ER). Estradiol is a master regulator of secondary sexual characteristics in vertebrates. It is also up-regulated in breast cancer, driving tumorogenesis. The drug *tamoxifen* binds in the same pocket as estradiol, regulating ER activity and limiting tumor growth (at least for some cancer types).

Goal

Rank-order the four estradiol poses *a, b, c,* and *d* from the most likely to the least likely. Use whatever energetic calculations you think necessary to rank the poses.

Information available

1. Structures:
   (a) ER.pdb has the protein alone
   (b) a.pdb, b.pdb, c.pdb, and d.pdb have the structures of estradiol, alone, in the four different poses.
   (c) ER_with-x-docked.pdb with has estradiol in pose x docked into the ER.
2. x_vdw.csv: has ϵ_i, ϵ_j, σ_i, σ_j, and r_{ij} for the protein-ligand contacts necessary for calculating the van der waal's interaction.
3. *aminoacids.rtp* has properties for the atoms in amino acids. Most importantly, the third column under each "[atoms]" entry has the *partial charge* on each amino acid.
4. *est.rtf* has properites for the atoms in estradiol. The format is a bit different than the *rtp* file. The partial charges are in the fourth column of the "ATOM" lines.

Questions

1. What is the rank-order for these ligand poses?
2. What energetic term is the strongest determinantt of rank-order?
3. What mutation(s) could you make to the protein to test your best predicted pose?
4. What chemical modification could you make to estradiol to test your best predicted pose?