Dr. Hibbs group at UTSW published the first structure of the GABAA receptor in June of 2018. Excitingly, their structure was bound to both the endogenous agonist (γ-amino-butanoic acid – GABA) and a benzodiazepine. In addition, they captured two conformations of the receptor, which provides important information about how the motions of the protein contribute to function.

GABAA receptor: GABAAR.pse

This file contains both conformations (A and B) of the GABAR solved by the Hibbs group.

1) The GABAAR is a chloride channel. Looking at the structure, can you identify the pore (i.e. where the ions flow; it might help to show a surface or mesh)?

2) The GABAAR is a heteropentamer; it has five similar but nonidentical subunits. Each of the different subunits is colored differently in this file. In building the structure, it was essential to be able to tell these apart – how did the Hibbs group solve that problem (hint: click on the 'Antibody' object to show it – what are antibodies and how do they work?).

3) What does the specificity of the antibody for the α1 subunit suggest about how its sequence and structure compare to the other subunits where the antibody is binding? The “aligned\_B2-A1 and aligned\_A1-B2” objects were created by aligning the β2 and α1 subunits (using the 'align' command in pymol; you can check the PyMOL wiki for more information) to compare their overall fold. Hide everything but these two and the antibody object and look for differences in the fold. You can also look for specific differences in the sequence by, *e.g.*, click on the region near the antibody and look in “display sequence” – you can also show “lines” or “sticks” and looking near the antibody.

4) Locate the GABA molecules in the structure (e.g. by “showing” spheres on the selection). What subunits are they interacting with? Are they on the surface or buried?

5) Locate the benzodiazepine molecule (Benzo). What subunits is it interacting with? Is it close to the GABA? Would you expect them to work directly or allosterically?

6) Load the lipid bilayer pdb from the first worksheet (not the session – go to raw\_pdbs and open lipid\_bilayer.pdb). Comparing the bilayer with the GABAAR, can you guess where the transmembrane portion of the protein is? (You can move the lipid bilayer around by clicking the <A> button near the object, then <drag> and then hold shift while you move the mouse with a button held).

7) Let's look at the conformational changes between the 'A' and 'B' states (looking only at the cartoon representation and setting the color of each state to be all one color might help)? Where are the biggest changes? How big are the movements (structural biologists might measure the maximum displacement or e.g. the angle of movement of a helix's rotation)?

8) If we hypothesize that these changes are coupled to some function, what might these conformational states represent? Do either of them have an entirely open pore (look down the poor with a surface or mesh representation)? What might this mean?