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Building a system: general rules

1. Selecting the structure

- Take a curated structure:

GPCRdb

https://gpcrdb.org/

- Check that the receptor has the canonical human sequence: sometimes they resolve the receptor of another organism or introduce thermostabilizing mutations.

2. Dealing with missing loops

- If they are shorter than 15 amino acids, you may consider modeling then.
- Otherwise, leave the gap making sure that both ends are capped.

3. Disulfide bonds

- Check them in UniProt or GPCRdb and incorporate them into your structure if they are missing!

4. Protonating the structure

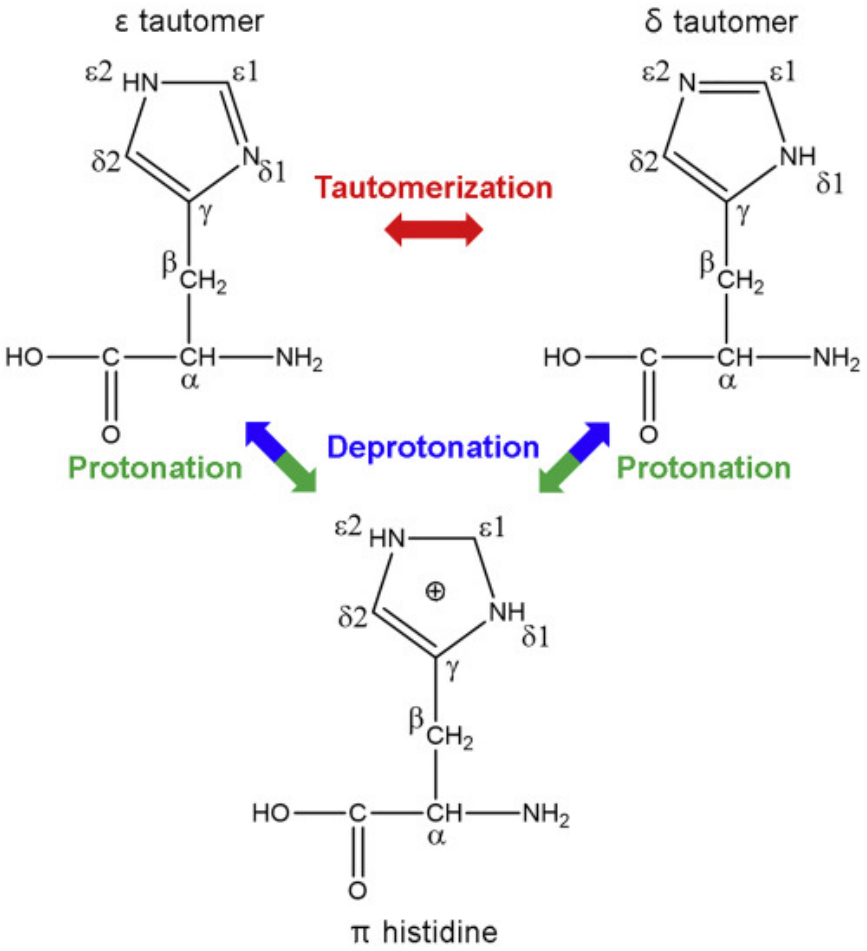
- For most amino acids, take the majority species at physiological pH.

4.1. Asp and Glu

- If they are facing the membrane, they are normally protonated.

4.2. His

- Histidine has two neutral tautomers at physiological pH. The most important ones are the ones near the ligand. It is advisable to visually check which tautomer would cause less steric impediment and provide a better hydrogen bonding netowrk.



Tomek 2:20 PM

hmm

you need to look at the ligand pose and check if there is a possible hydrogen bond interraction

i.e. if you se a histidine veeery close to an oxygen you might try and put in the protonation differently

but in all honesty

sometimes after simulations you see that you should ahve done the protonations differently

5. Na^+ ion near Asp2.50.

- It is typical in class A GPCRs.

Inactive structures

Should have the Asp deprotonaned, interacting with the Na^+.

Active structures

Should have the Asp protonated and no Na^+ ion near.