BioISI - Biosystems & Integrative Sciences Institute

Improved drug discovery: towards an energy-based criterion to characterize protein-ligand interactions

Place of work/: BioISI, Chemistry for Biological Systems Group, Computational Laboratory, 8.5.55D

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The characterization of protein-ligand complexes is essential for research in structural biochemistry, drug discovery, and biology [1]. These protein–ligand interactions comprise hydrophobic interactions, hydrogen bonds, aromatic stacking, salt bridges, and even halogen bonds [2]. There are several tools that automatically assign the presence of non-covalent protein–ligand interactions in PDB structures such as the freely available Protein-Ligand Interaction Profiler [https://plip-tool.biotec.tu-dresden.de/plip-web/] [1]. This is extremely useful in drug design since in the initial stages, prior to library screening or molecule design, a comparative analysis of binding patterns in a target is often performed, thus helping to identify key residues [1]. To assign the existence of a bond (such as hydrogen or a halogen bonds, Fig. 1), these tools verify if certain geometric requirements are fulfilled, i.e., they use angle and distance thresholds. This might be problematic since the thresholds are empiric and might be excluding (or erroneously including) interactions. Therefore, the use of an energy based criterion is a great advantage, as previously shown with the Define Secondary Structure of Proteins (DSSP) algorithm [3], which is a popular standard method for assigning the secondary structure to the amino acids of a protein. Based on previous work by our group [4,5] which showed the existence of energy thresholds for the identification of these interactions, in this project, by using computational and modeling tools such as mining the Protein Data Bank and the usage of force field methods, we aim at developing a robust energy-based criterion to assign noncovalent interactions involving protein-ligand complexes. In other words, having a given protein-ligand structure, our method will identify the presence or absence of such interactions (with a particular emphasis on the less studied ones such as halogen bonds), thus hopefully contributing to the improvement of computational drug discovery tools. This project requires someone motivated to study biochemical systems using computational methods. The results will be used not only for the Master Thesis but also to be published in a peer-review journal.

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[4] Nunes, R.; Vila-Viçosa, D.; Machuqueiro, M.; Costa, P. J. Biomolecular Simulations of Halogen Bonds with a GROMOS Force Field. J. Chem. Theory Comput. 2018, 14, 5383–5392
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