Docking homework

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Table 1: Binding Affinities of Various Ligands to Human Serum Albumin (HSA) Sites

Ligand	Target Protein Site	Binding Affinity (kcal/mol)
Warfarin	HSA Site 1	-8.62
2-Phenylchromone	HSA Site 1	-8.06
2-Phenylchromone	HSA Site 2	-7.35
Ibuprofen	HSA Site 2	-8.37

1 Warfarin in site 1 of HSA

Can the redocking with AutoDock reproduce the experimental binding mode?

Is the experimental binding mode found in the best scored pose?

What are the main interactions that mediate the binding for the predicted pose?

Since redocking was performed on the basis of crystallographic data of HSA with warfarin, the quality of docking can be judged by the reference RMSD, which for the best pose is 1.01 angstroms, which is less than the threshold value of 2 angstroms, which means that it was possible to reproduce more or less experimental binding mode.

Nevertheless, molecular docking correlation is about 0.6 [1], which means that by definition, this method cannot give results of affinity that are the same as the experimental ones. Considering that we make a number of assumptions (no solvent, protein fixation, etc.), we cannot expect to reproduce experimental data on this feature.

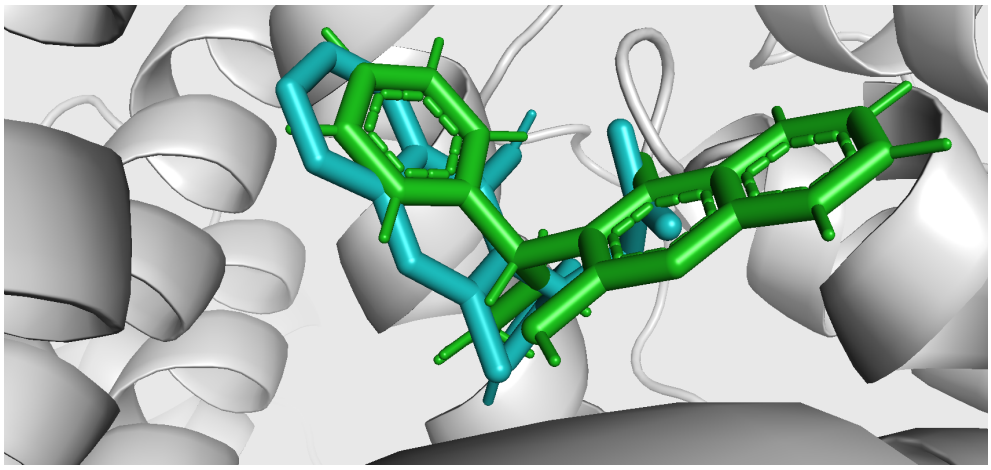

Figure 1: Green – experimental binding mode of warfarin, cyan – redocked

Albumin contains hydrophobic residues as well as aromatic residues. Crossing the surface of the ligand with the region of hydrophobic residues (e.g., alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, and glycine) will result in hydrophobic interactions. Intersection of the ligand surface with the region of aromatic amino acid residues (e.g., phenylalanine, tyrosine, tryptophan, and histidine) may indicate potential Pi-Pi stacking interactions, given that warfarin has inherent aromatic rings. In the case of warfarin, non-polar (hydrophobic) interactions usually enhance binding to proteins such as human serum albumin (HSA). Warfarin contains hydrophobic aromatic structures that can interact with hydrophobic pockets of proteins. These hydrophobic interactions help stabilize warfarin in the binding space, increasing its affinity for the protein. Hydrogen bonds also play a role, which can also increase the affinity of the ligand for the protein pocket. In this particular case, the combination of all these factors is calculated to give a slightly higher affinity of warfarin to the site than it actually is, according to the experiments[2]. Considering also the absence of entropic factors associated with the flexibility of the protein, the absence of taking into account the solution, etc., it all together gives a deviation from the experimental binding affinity value.

2 2-Phenylchromone in site 1 of HSA

Do you think the predicted binding mode is acceptable?

How does the predicted affinity of 2Phe compare with the affinity of warfarin?

Do the binding affinities of warfarin and 2Phe reflect in your view the interactions formed by these compounds?

I guess, according to the binding affinity value in the 1 table, which is not too different from warfarin, we can consider the predicted binding mode to be acceptable. Also, with pymol, it can be seen that more or less this ligand is in the same region as warfarin. It can be seen that the binding location is different, which I suppose can be attributed to the fact that when doing blind docking, getting binding in the same location as for the other ligand is somewhat less likely due to the difference in structures.

2Phe affinity is lower than that of warfarin, but not that significantly. I suppose this may be due to the fact that warfarin has a slightly more branched structure and is therefore more flexible than 2Phe. And the structures are different in the number of functional groups with oxygen, which also affects

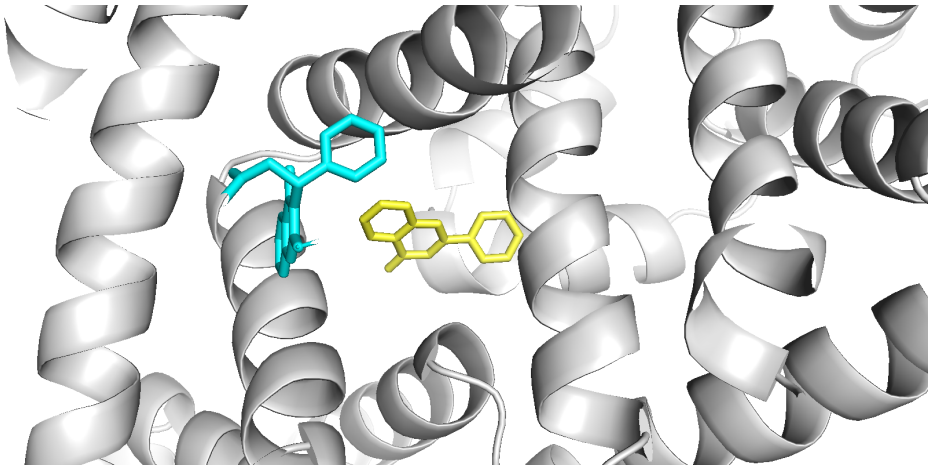

Figure 2: Yellow – binding mode of 2-Phenylchromone, cyan – warfarin

binding affinity (2Phe has them two times less). Overall, this explains the reason why 2phe has a lower affinity than warfarin, but additional calculations using molecular dynamics are needed as the difference in values is not large enough to draw such resounding conclusions.

3 2-Phenylchromone and ibuprofen in site 2 of HSA

Do you think 2Phe may compete with ibuprofen for binding at site 2?

According to the binding affinity results in table 1 (as in the case of warfarin and 2phe, the binding poses of ibuprofen and 2phe are in the same vicinity), ibuprofen has a higher value of binding affinity than 2Phe, which means that these ligands might compete in site 2 of HSA. It is worth noting that the difference is less than 1 kcal/mol, and given the approximity of docking, additional calculations using molecular dynamics methods are required.

References

[1] Liu, J., & Wang, R. (2015). Classification of current scoring functions. Journal of chemical information and modeling, 55(3), 475-482.

[2] Ràfols, C., Amézqueta, S., Fuguet, E., & Bosch, E. (2018). Molecular interactions between warfarin and human (HSA) or bovine (BSA) serum albumin evaluated by isothermal titration calorimetry (ITC), fluorescence spectrometry (FS) and frontal analysis capillary electrophoresis (FA/CE). Journal of Pharmaceutical and Biomedical Analysis, 150, 452-459.