CONFORMATIONAL SELECTION AND INDUCED FIT ROLES IN ENSEMBLE DOCKING APPLICATIONS

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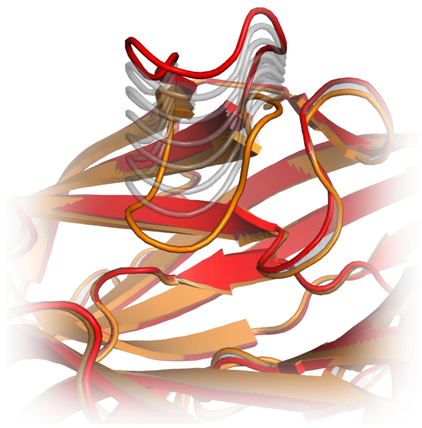
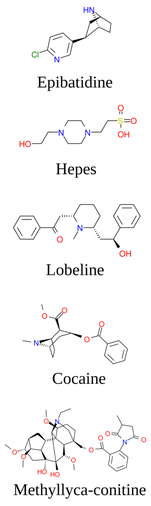
Protein dynamics plays a critical role in ligand binding and different models have been proposed to explain the relationships between protein motions and molecular recognition.[1] Here we present a study of ligand-binding processes associated with large conformational changes of the protein aimed at investigating the distinctive features that may lead to a conformational selection mechanism or the interplay of conformational selection and induced fit. Starting from MD simulations of the protein apo conformation, an ensemble-docking approach[2] was used to predict the holo structures, investigating the most appropriate choices for each scenario.

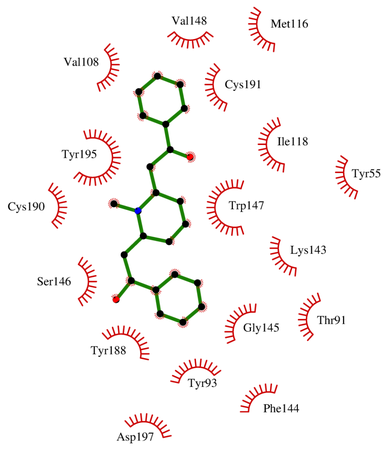
Acetylcholine Binding Protein[3]



Moderate Conf. Changes

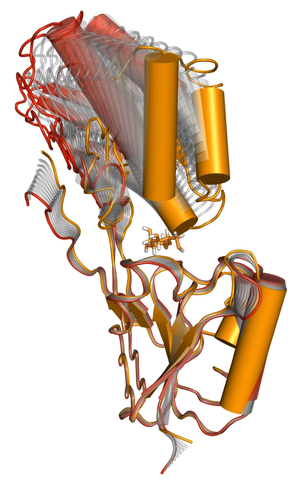


Promiscuous

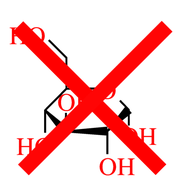


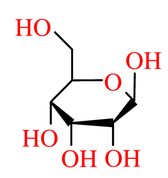
Dispersive Interactions

Allose Binding Protein[4]

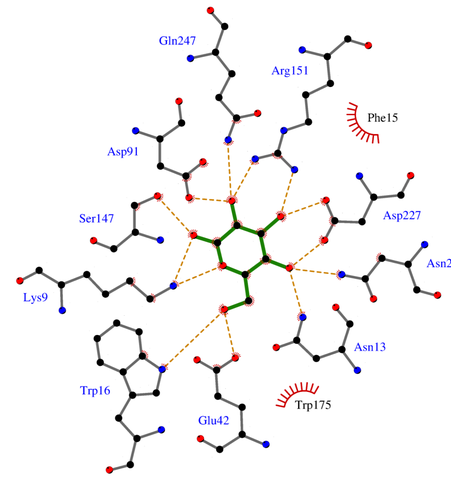


Large Conf. Changes





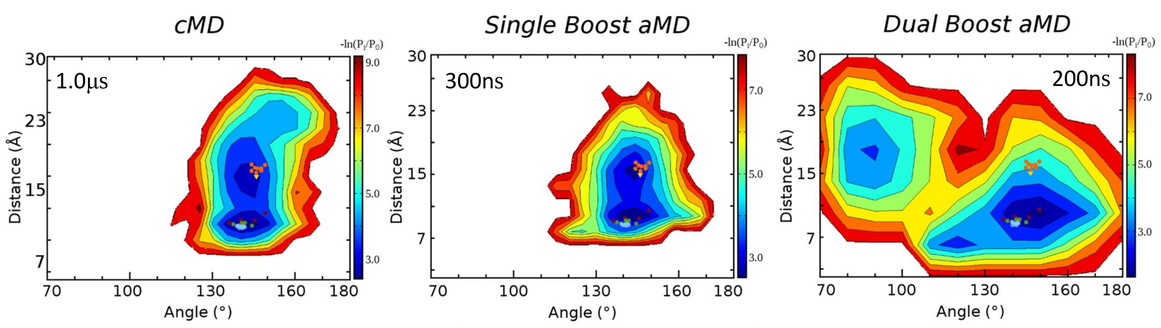
Selective



Polar Interactions

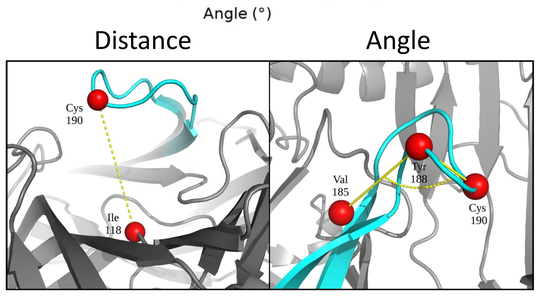
Sampling

Conformational states probability in the sub-space of two selected variables



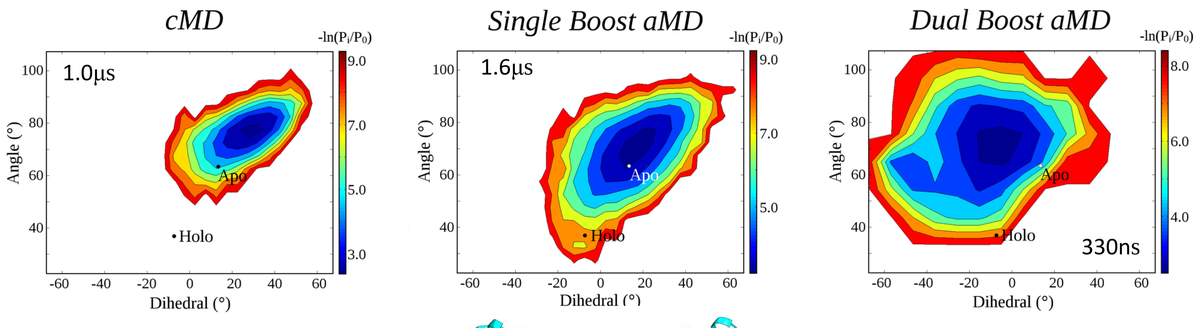
cMD: Conventional MD

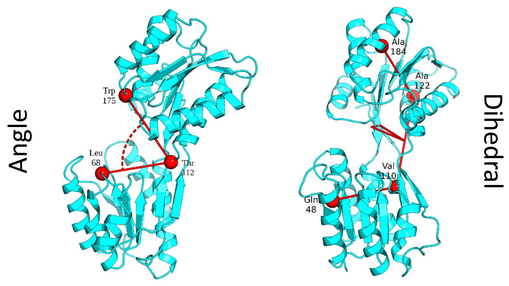
aMD: Accelerated MD[5]



- Epibatidine
- Hepes
- Lobeline
- Cocaine
- Methyllyca-conitine

Conformational states probability in the sub-space of two selected variables



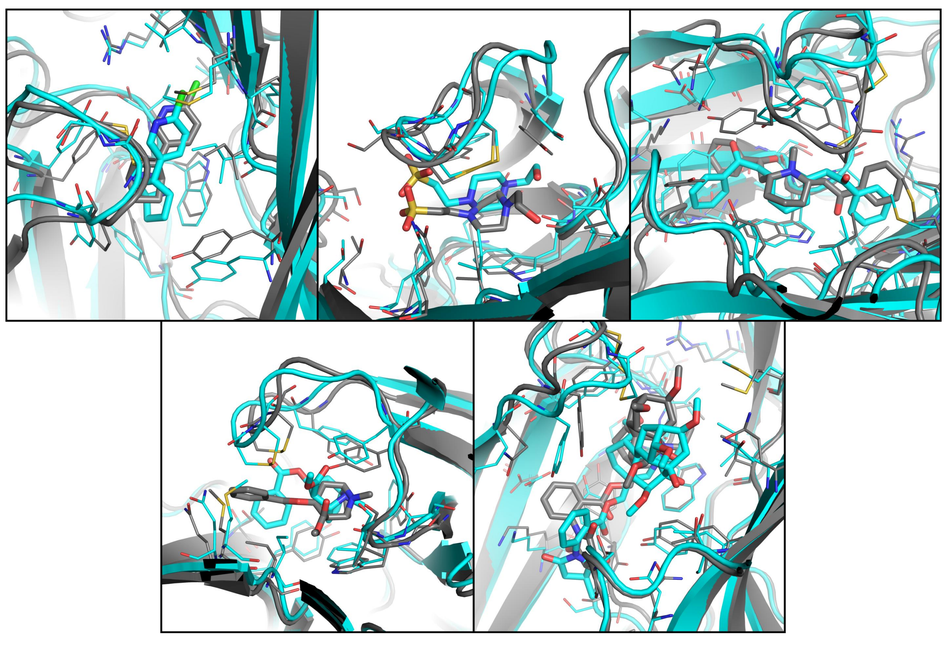


cMD: Conventional MD

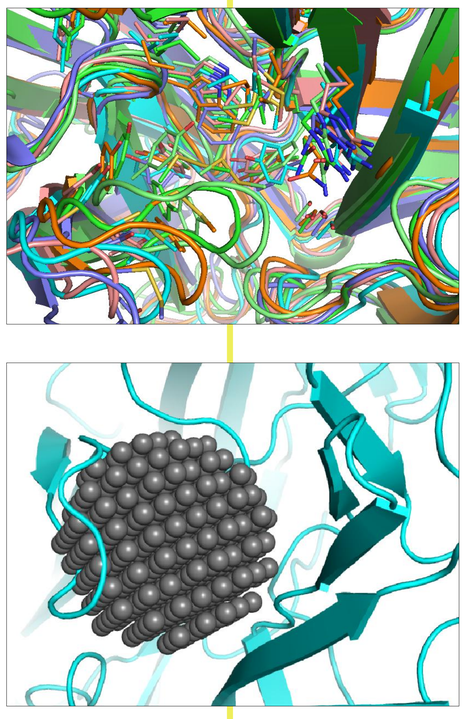
aMD: Accelerated MD[5]

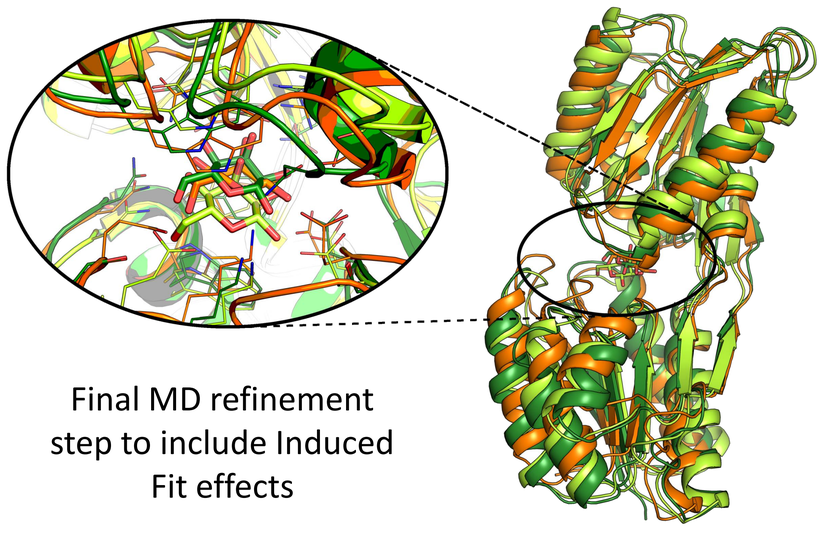
Clustering and Docking

Soft Docking ← **Binding Site oriented Clustering** → **Docking** → **MD Refinement**



Good reproduction of experimental geometries





Final MD refinement step to include Induced Fit effects

Conclusions

The presented study shows how distinctive features of the system influence the interplay between Induced Fit and Conformational Selection: weak dispersive interactions are mostly associated to conformational selection, while strong long-range interactions involve an induced fit component. Two different effects can explain these findings. The first one is energetic: in a conformational selection mechanism, where the apo and holo states are similar in energy, the population shift can be induced by weak interactions with ligands, while during an induced fit event, characterized by a higher energy gap, stabilization by strong interactions with ligands are needed. The second effect is entropic: since strong interactions are often directional (for example H-bonds), finding the correct orientation of all the interacting groups is less likely than in the case of dispersive interactions. Based on these findings, we provided clear indication that the ensemble-docking technique can better predict the structure of ligand-protein complexes when suitable methodological choices are made according to the different mechanistic scenarios.

References

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2. Sinko, W.; Lindert, S.; McCammon, J. A. *Chem Biol Drug Des.* ***2013, 81, 41-49***
3. Hansen, S. B.; Sulzenbacher, G.; Huxford, T.; Marchot, P.; Taylor, P.; Bourne, Y. *EMBO J.* ***2005, 24, 3635-46.***
4. Magnusson, U.; Chaudhuri, B. N.; Ko, J.; Park, C.; Jones, T. A.; Mowbray, S. L *J Biol Chem.* ***2002, 277, 14077-84***.
5. Doshi, U.; Hamelberg, D. *Biochim Biophys Acta J.* ***2015, 1850, 878-88.***