Sampling of Ligand-Induced Conformational Changes in Renin and Factor VIIa

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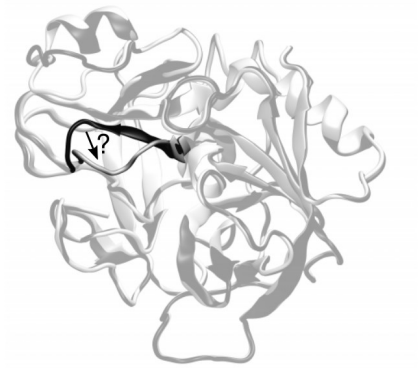
Proteins are dynamic biomacromolecules that can have diverse and nearly isoenergetic conformational states. Ligand binding can shift the equilibrium of this conformational ensemble.

We are studying protein conformational changes upon ligand binding in two different systems: Factor VIIa and Renin. In both systems we know from experiment that a specific group of ligands targeting the orthosteric site can induce conformational changes. The observed conformational changes are the distortion of a beta-sheet structure in the S1 pocket and the opening of a non-functional flap for Factor VIIa and Renin, respectively.

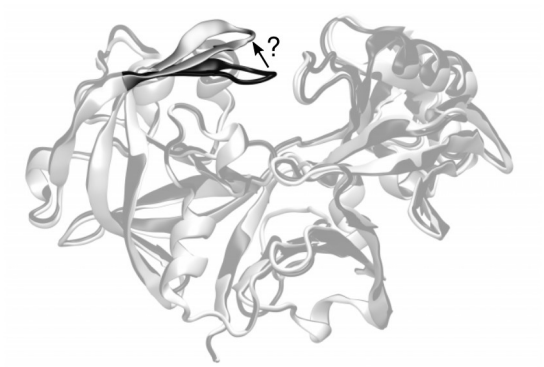
Unbiased MD simulations for Factor VIIa and for Renin (each 4 µs) with removed ligand structures led to contrasting findings. For Factor VIIa the conformational change can be captured with unbiased MD simulations, whereas the transition could not be sampled for Renin within this time scale.

For Factor VIIa starting from the initial beta sheet conformation one or both backbone hydrogen bonds were disrupted leading to the loop-like conformation. Starting with the loop-like conformation the distorted S1 pocket remained distorted.

For Renin starting from the initial closed flap conformation the flap did not open up. Using established biasing protocols for Renin such as increasing the water-protein interaction as established in the group of Gervasio [1] enhanced the protein flexibility, but did not sample the fully open flap. We are working on alternative approaches to disrupt the hydrophobic aromatic cluster holding the Renin flap in place. Starting from the open flap conformation, the open flap of Renin closed again for all eight available X-ray structures.



Factor VIIa:
stable (black) vs. distorted (grey) S1 pocket



Renin:
closed (black) vs. open (grey) flap

[1] Oleinikovas et al., J. Am. Chem. Soc. 2016