Water Molecules Control Protein Structure and Ligand Affinity to fXa

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The serine protease factor Xa (fXa) is a key enzyme in the blood coagulation cascade, and therefore, considered a promising target for antithrombotic drugs.

An in-depth analysis of the crystallographically resolved water molecules in the available X-ray structures of fXa provide a consensus set of water molecules. We show that this consensus set is necessary for an accurate description of the protein in MD simulations, and we analyze the problems associated with differently derived sets of water molecules. Severe structural distortions in the protein body as well as in the catalytic active binding site are avoided with the presented water network [1].

Unfortunately, not for all proteins as many X-ray structures as for fXa are available. Therefore, an *in silico* alternative, namely molecular interaction field (MIF)-based water positions derived with the GRID program, is tested. Results from comparison with the water network from the clustering approach as well as comparative MD simulations show that GRID is a viable approach for the analysis of protein hydration [2].

Finally, the yielded structural model incorporating the water positions from the clustering approach is used for free energy prediction methods. Results from MM/GBSA, MM/PBSA and LIE are presented. Accurate results are only accessible with an explicit inclusion of decisive water molecules [3].

[1] H. G. Wallnoefer, S. Handschuh, K. R. Liedl, T. Fox. *Journal of Physical Chemistry B,* **2010**, *114*, 7405-7412.

[2] H. G. Wallnoefer, K. R. Liedl, T. Fox. s*ubmitted*.

[3] H. G. Wallnoefer, K. R. Liedl, T. Fox. *Journal of Computational Chemistry,* **2011**, available online, DOI:10.1002/jcc.21758.