P59 Lessons learned from docking with the presence of water molecules – is it worth it?

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Water molecules play an important role in many aspects of ligands binding and can be at least considered to be the next dimension in understanding of effects triggered by the creation of a ligand-receptor complex. Ideally, computational approaches should create and incorporate water networks in ligand docking and binding mode analysis. With the releasing of appropriate software, approaches incorporating water molecules were applied for e.g. explanation of SAR studies, justification of *in vitro* results or evaluation if a presence of water molecules improve docking studies. Nevertheless, the presence of water molecules in GPCR's binding site and their influence on different aspects of ligand binding are not explored yet [1].
In this study, for every single crystallized target from GPCR's class A aminergic and peptide families water networks were generated in WaterFLAP [2]. Several issues related to the application of water molecules for docking studies were considered: (i) energy and location of the water molecules within the binding site and the correspondence to the water molecules present in the crystal structures, (ii) recreation of binding mode observed in crystal complexes by docking with presence of predicted water, (iii) how the results of screening experiments depend on incorporation of water molecules.
The results show a rather surprisingly insignificant role of the water molecules for enhancement of the performed docking studies. Moreover, comparison of docking and crystal complexes show some trends as e.g. that not always favorable value of ΔG of water molecule guaranties turning into the bridging water. The results indicate that application of water molecules for docking studies is still challenging and should not be treated as black box must-do procedure, and it requires a careful supervision.

Acknowledgments
The work was supported by the National Science Centre (Poland) grant no. 2016/21/N/NZ2/01725.

References
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