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Probing dynamic water molecules with rigid-ligand complexes

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It is long known that water molecules play an important role in protein-ligand interactions. Nevertheless, most of today's computer-aided drug design methods are hardly able to predict whether upon protein-ligand complex formation a water molecule is displaced or remains in the binding pocket bridging the interaction between the binding partners. To the same extent it is challenging to accurately estimate the corresponding energetic and entropic contributions.

Since information about water effects in protein-ligand complexes are inherently difficult to obtain, we resort to a well-suited model system to study the role of water molecules by means of molecular dynamics simulations. This system consists of complexes between the cytochrome c peroxidase W191G mutant [1] and a set of structurally similar, small and rigid ligands with completely different interaction patterns to crystal water molecules. The engineered binding cavity is known to be polar, solvated and deeply buried. This allows to study the effects of structural water without taking into account the influences from the bulk phase. Various aspects of this model system have been the subject of earlier theoretical studies [2][3][4].

We use our simulation data to investigate (1) why very similar ligands show very different water interactions in the complex and (2) how the binding mode and water interaction pattern of new ligands in this cavity can be predicted. A fundamental methodical question in this context is how to properly analyse the dynamic nature of the water molecules for which for instance different metrics were calculated and tested. Finally, thermodynamic properties evaluated from the ensembles generated by MD can help to quantify the corresponding structural observations.

References

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