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A combined combinatorial and pKa-based approach to ligand protonation states

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The protonation of the ligand molecule and the protein binding site has a significant influence on the results obtained by protein-ligand docking. Due to the inability of X-ray crystallography to resolve the hydrogen atom in protein and protein complex structures, the correct protonation for the protein and the ligand has to be assigned on a theoretical basis before the structures can be used. Because of the local environment inside the binding site and because of the influence of the ligand and the protein onto each other, the ligand protonation can differ from the protonation one would expect for the ligand in solution under physiological conditions. Hence for protein-ligand docking different protonation states of the ligand have to be taken into account.

Our recently introduced structure preparation tool SPORES [1] used a rule based method to generate a standard protonation for each ligand molecule and afterwards generated different protonation states in a combinatorial way by adding and removing single hydrogen atoms belonging to predefined functional groups. Docking of all these protonation states of a given ligand molecule often led to scoring problems due to the different number of hydrogen interactions formed by the different protomers of the ligand molecule. To overcome these problems two methods to filter highly charged and unstable protonation states from the docking were implemented. One based on the difference between the standard protonation of the ligand and the actual protonation state and one based on pKa values calculated with ChemAxon's MARVIN software [2]. Here we present a new approach in which the ligand atoms considered for the combinatorial method not chosen from predefined functional groups but according to the calculated pKa values which leads to a wider variety but with a smaller overall number of protonation states.

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References

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