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Multi-body interactions in molecular docking: treatment of water molecules and multiple ligands

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In the last years, the importance of water molecules in pose prediction experiments has been widely recognized and several approaches to integrate water molecules into the docking process have been proposed [1,2]. The inclusion of water molecules extends the classical two-body problem of docking a flexible ligand into a protein receptor to a multi-body docking problem as protein-ligand, protein-water, water-ligand and water-water interactions need to be taken into account. Our Ant Colony Optimization [4] based protein-ligand docking algorithm PLANTS [3] has been extended by a general multi-body docking kernel, which is able to handle interactions arising between several molecules. This kernel allows us, on the one hand, to include essential water molecules located in the binding site into docking experiments and, on the other hand, also to score interactions between multiple ligands that are docked concurrently into the binding site. Water molecules are modeled as rigid bodies that are allowed to move and rotate inside a predefined spherical domain making it possible to adapt to structural deviations in cross-docking experiments. Additionally, water molecules can be displaced by ligands or flexible protein side-chains. All ligands considered in the docking experiment are treated fully flexible.

We present the water model parameterization carried out on a set of benchmark complexes and show some preliminary results for docking multiple ligands concurrently.

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