

[P44] S4MPLE – Sampler For Multiple Protein-Ligand Entities: Simultaneous docking of several entities.

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S4MPLE is a general conformational sampling tool, based on a hybrid genetic algorithm, simulating one (conformer enumeration) or more molecules (docking). Here, simultaneous docking of multiple entities is addressed in two different important contexts.

First, simultaneous docking of two fragment-like ligands was attempted, as such ternary complexes are the basis of fragment-based drug design by linkage of the independent binders. S4MPLE was successfully challenged to predict locations of fragments involved in ternary complexes by means of multi-entity docking.

Second, the key problem of predicting water-mediated interaction is addressed by considering explicit water molecules as additional entities to be docked in presence of the “main” ligand. Blind prediction of solvent molecule positions, reproducing relevant ligand-water-site mediated interactions, is achieved in 76% cases over saved poses. S4MPLE was also successful to predict crystallographic water displacement by a therefore tailored functional group in the optimized ligand. However, water localization is an extremely delicate issue in terms of weighing of electrostatic and desolvation terms, and also introduces a significant increase of required sampling efforts. Yet, the herein reported results – not making use of massively parallel deployment of the software – are very encouraging.