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S4MPLE – SAMPLER FOR MULTIPLE PROTEIN-LIGAND ENTITIES: SIMULTANEOUS DOCKING OF SEVERAL ENTITIES

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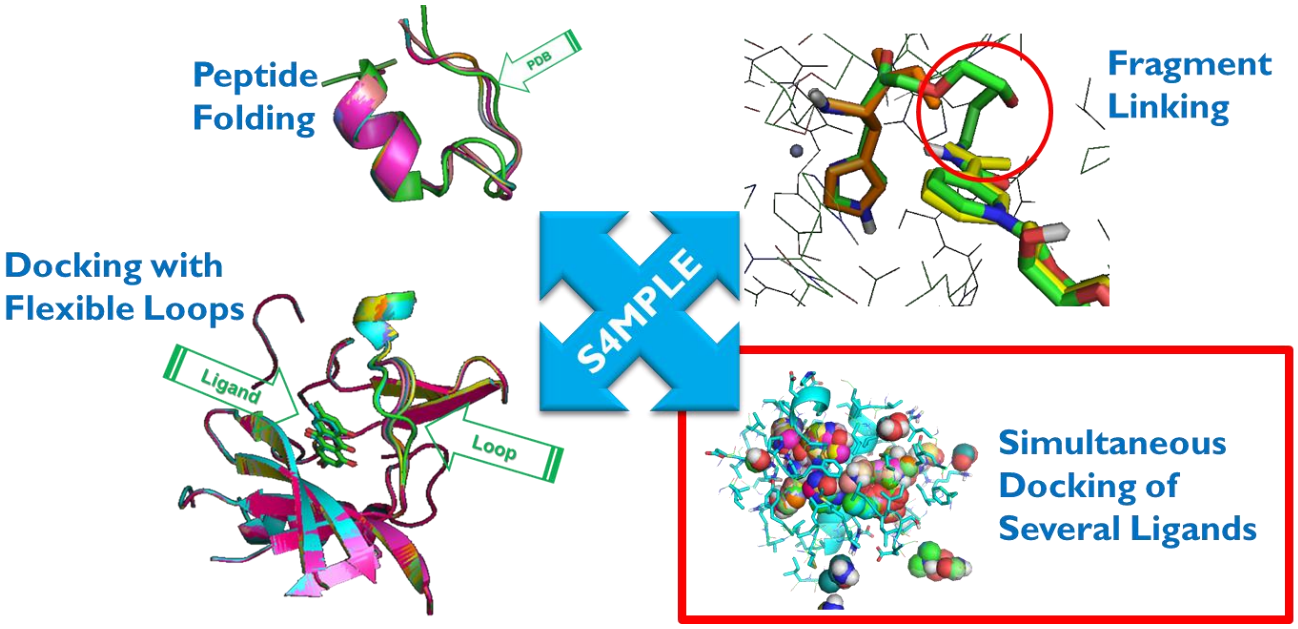
S4MPLE [1,2] a conformational sampling tool based on a genetic algorithm coupled to an AMBER/GAFF core force field competed by a continuum desolvation term, is able to address various problems, from folding/sampling of individual molecules to simultaneous docking of multiple entities. This latter, original ability is assessed in two different important contexts:

First, 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 purposely added functional group. However, water localization is a delicate issue in terms of weighing of electrostatic and desolvation terms, and also introduces a significant increase of required sampling efforts.

Second, 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. The herein reported results – not making use of massively parallel deployment of the software – are very encouraging.



1. Hoffer L. et al. *J Chem Inf Model*, 2012, **53**: 88-102.
2. Hoffer L. et al. *J Chem Inf Model*, 2013, **53**: 836-51