[L8] Pharmacophore-based Analysis of MD Trajectories: Towards Understanding KD of Protein Ligands

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In many different application domains, structure-based pharmacophore models have been proven to be useful as selective *in silico* screening filters.[1]

Recently, we have extended the static pharmacophore approach by a dynamic one, deriving interaction models from molecular dynamics (MD) trajectory snapshots[2] and including also a novel consensus screening approach, which was shown to be superior to previous pharmacophore-based virtual screening methods.[3]

One of the main benefits of performing MD simulations of protein-ligand complexes is the possibility to detect global changes in protein geometry, and thus enabling the observation of emerging pockets of potential interest for the formation of additional ligand-protein interactions. To address this challenge, we have developed a method that is able to detect transient protein pockets and to place pharmacophore features in such empty target binding sites without the guidance of a known bound-state ligand structure. The thus derived dynamic *apo pharmacophore models* provide invaluable information that can be put to good use for the *de novo* design of new ligands as well as for the refinement of existing lead structures in the drug development process.

Details about the algorithm developed together with the results of its validation with a series of protein conformation snapshots obtained from MD simulations of Hsp90 ligand complexes aimed at understanding KD of the ligands will be presented.

Bibliography:

[1] Langer T. Mol. Inf. 2010; 29:470-475.
[2] Wieder M, Perricone U, Boresch S, Seidel T, Langer T. Biochem. Biophys. Res. Comm. 2016; 470:685-689.
[3] Wieder M, Garon A, Perricone U, Boresch S, Seidel T, Almerico AM, Langer T. J. Chem. Inf. Model. 2017; 57:365-385.