Protein Binding Sites Dynamics in Drug Discovery

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We have developed new methodological solutions for prediction and study of protein binding sites, based on graph theoretical approaches, combined with molecular dynamics simulations. Protein binding sites have been subject of intensive research, due to their key role in binding of drugs, and also, because they allow us to understand biochemical processes of a cell. For efficient drug development, one should know structure of the binding site and its dynamics, that is, one should be able to predict how the process of binding a molecule will change the binding site. The research of protein binding sites is also driven by scientific field named structural genomics, whose goal is to determine three-dimensional structures of representatives of all known proteins and their biochemical functions. Because biochemical functions of proteins are closely related to protein binding sites, further development of computational approaches to predict protein binding sites is needed.

We have developed a freely available ProBiS web tools enabling the discovery of molecules relevant to pharmaceutical research. These new tools enable researchers to predict molecules that could bind to their investigated proteins using ProBiS, and also enable them to obtain a quantitative measure of how firmly the predicted molecules bind to a protein using molecular dynamics simulation. Here, we review these algorithms and their use in pharmaceutical discovery. In particular:

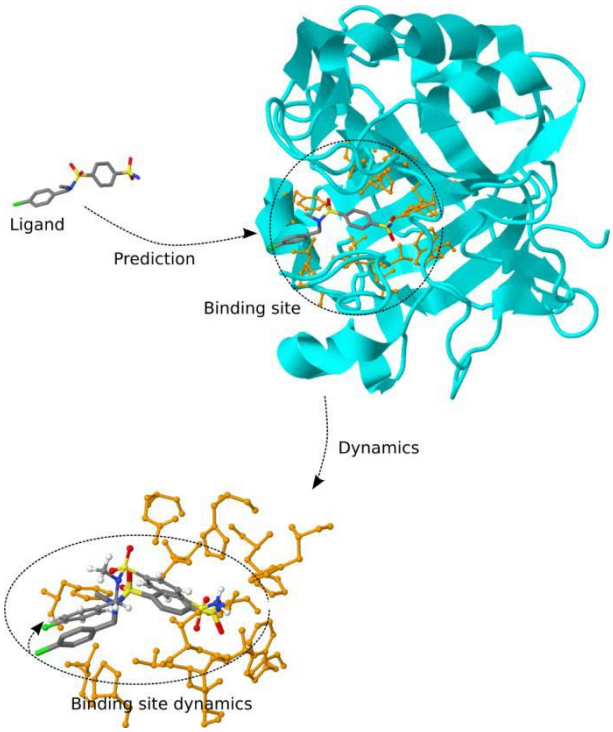

Fig. 1. *Prediction of the protein binding site, the ligand, and their binding dynamics. Depicted here is a small-molecule ligand (CPK colors, sticks) binding to the predicted binding site (orange, balls and sticks) in human carbonic anhydrase protein (cyan, cartoon).*

- **ProBiS Algorithm**: for detection of structurally similar protein binding sites by local structural alignment (J. Konc and D. Janežič, *Bioinformatics* 26 (**2010**) 1160-1168). ProBiS enables binding sites & ligands prediction based on detection of similar evolutionary patterns in proteins.

- **ProBiS-CHARMMing Web Server** @ http://probis.nih.gov for prediction and energy optimization of ligands (J. Konc, B.T. Miller, T. Štular, S. Lešnik, H.L. Woodcock, B.R. Brooks, D. Janežič, *J. Chem. Inf. Model.* 55 (**2015**) 2308-2314). ProBiS-CHARMMing predicts & minimizes ligands for any protein and can be used to generate holo protein structures from apo proteins (or prepare ligand-receptor complex for molecular dynamics simulation).

- **ProBiS - Use in drug discovery** (Angew Chem. Int. Ed. 2016, JMC 2016, PBMB, 2016).