PockDrug-Server: a web server for predicting pocket druggability and its applications

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Abstract

Therapeutical molecules bind to to the disease-modifying protein target at a specific binding site, called "pocket"[1]; it corresponds to a region of a "cavity" or a "binding site", on the protein surface, where drug-like molecules bind. Drug-like molecules are orally bio-available small molecules and possess optimal physicochemical properties[2]. Therefore, estimation and characterization of pockets are major issues for drug discovery projects. Namely, predicting protein pocket's ability to bind drug-like molecules with high target affinity, i.e. druggability, is a key step of the modern drug design process[3]. Existing druggability prediction models involve only one pocket estimation method at a time, despite pocket estimation uncertainties[4]. Here we describe the evolution of druggability concept[4] and our pocket druggability prediction web server PockDrug-Server[5]. It is efficient on both (i) estimated pockets guided by the ligand proximity (extracted by proximity to a ligand from a holo protein structure using several distance thresholds), and (ii) estimated pockets only based on protein 3D structure. In order to provide a mean druggability, PockDrug-Server involves a consensus model based on a combination of 7 linear discriminant analysis models using 9 pocket descriptors[6]. It provides consistent and robust druggability results using different pocket estimation methods; thus it is efficient when using *apo* pockets difficult to estimate. It accurately distinguishes druggable from undruggable pockets prioritizing thus target selection, outperforming recent druggability models for *apo* pocket. It can be carried out from one or a set of *apo*/*holo* proteins. PockDrug-Server is publicly available at: http://pockdrug.rpbs.univ-paris-diderot.fr. A case study showing the advantage to combine different draggability prediction will be also presented[4].

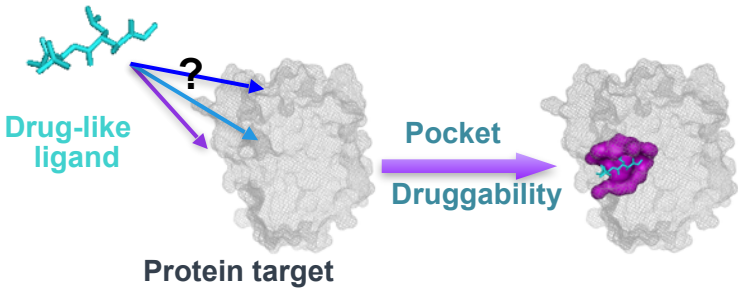


Fig. 1. The interaction between a drug-like molecule and a draggable pocket of the protein target.

Publications

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5. Abi Hussein, H., Borrel, A., Geneix, C., Petitjean, M., Regad, L.,and Camproux, A.-C. (2015). PockDrug-Server: a new web server for predicting pocket druggability on holo and apo proteins. Nucleic Acids Research, 43:1-7.
6. Borrel, A., Regad, L., Xhaard, H., Petitjean, M., and Camproux, A.-C. (2015). PockDrug: A Model for Predicting Pocket Druggability That Overcomes Pocket Estimation Uncertainties. Journal of Chemical Information and Modeling, 55(4):882-895.



Biography

Dr. Hiba Abi Hussein has expertise in structural bioinformatics, data analysis and machine learning methods. She works on protein characterization and statistical models that aim to accelerate the drug discovery projects. She has developed PockDrug web-server during her PhD studies in the National Institute of Health and Medical Research of France (Inserm, UMRS-973, pharmacological profiling using computational approaches team, Paris VII university). This open access web-server implements different pocket estimation methods and a model of draggability prediction that allows an accurate selection of druggable drug targets. Currently, she is still conducting structural-based research studies.

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