CAVERDOCK: SOFTWARE TOOL FOR FAST SCREENING OF UN/BINDING OF LIGANDS IN PROTEIN ENGINEERING

Gaspar Pinto, Loschmidt Laboratories, Faculty of Science, Masaryk University, Brno, Czech Republic
International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic
gaspar.pinto@fnusa.cz
Ondrej Vavra, Loschmidt Laboratories, Faculty of Science, Masaryk University, Brno, Czech Republic
International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic
Jiri Filipovic, Institute of Computer Science, Masaryk University, Brno, Czech Republic
Sergio Marques, Loschmidt Laboratories, Faculty of Science, Masaryk University, Brno, Czech Republic
International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic
Piia Kokkonen, Loschmidt Laboratories, Faculty of Science, Masaryk University, Brno, Czech Republic
David Bednar, Loschmidt Laboratories, Faculty of Science, Masaryk University, Brno, Czech Republic
International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic
Jiri Damborsky, Loschmidt Laboratories, Faculty of Science, Masaryk University, Brno, Czech Republic
International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic

Key Words: CaverDock; Caver; Tunnels; Docking;

Protein tunnels, channels and gates are important for enzymatic catalysis and also represent attractive targets for rational protein design and drug design [1]. Drug molecules blocking the access of natural substrate or release of products are very efficient modulators of biological activity. Here we demonstrate the application of newly *in-house* developed software tool CaverDock [2,3] for the analysis of the transport of ligands through tunnels in biomolecular targets. Caverdock is a new addition to the Caver Suite [4-6]. We performed virtual screening of large databases of drugs against two pharmacologically relevant targets. We have used FDA-approved drugs for both targets. Oncological drugs (133 molecules), taken from the NIH website, and anti-inflammatory (56 molecules), taken from the Drugbank website, as the libraries of ligands for the two molecular targets: (i) cytochrome P450 17A1 and (ii) leukotriene A4 hydrolase/aminopeptidase. Moreover, we will also show the unbinding of the 2,3-dichloropropan-1-ol product from a buried active site of an haloalkane dehalogenase and its variant. With this study we identified hot-spots that may be used for directed evolution or site-directed mutagenesis to create new variants for faster 2,3-dichloropropan-1-ol release [7]. Finally, we will show the difference on ligand transportation when a protein is in an open and closed conformations [8]. We will show how CaverDock tackles the problem of protein flexibility.

1. Marques, S.M., et al., 2017: Enzyme Tunnels and Gates as Relevant Targets in Drug Design. Medicinal Research Reviews 37: 1095-1139.
2. Vavra, O., et al., 2019: CaverDock 1.0: A New Tool for Analysis of Ligand Binding and Unbinding Based on Molecular Docking. Bioinformatics (under review).
3. Filipovic, J., et al, 2019: A Novel Method for Analysis of Ligand Binding and Unbinding Based on Molecular Docking. Transactions on Computational Biology and Bioinformatics (under review)
4. Chovancova, E., et al., 2012: CAVER 3.0: A Tool for Analysis of Transport Pathways in Dynamic Protein Structures. PLOS Computational Biology 8: e1002708.
5. Jurcik, A., et al., 2018: CAVER Analyst 2.0: Analysis and Visualization of Channels and Tunnels in Protein Structures and Molecular Dynamics Trajectories. Bioinformatics 34: 3586-3588.
6. Stourac, J., et al., 2019: Caver Web 1.0: Identification of Tunnels and Channels in Proteins and Analysis of Ligand Transport. Nucleic Acids Research (under review).
7. Marques, S.M., et al., 2019: Computational Study of Protein-Ligand Unbinding for Enzyme Engineering. Frontiers in Chemistry 6: 650.
8. Kokkonen, P., et al., 2018: Molecular Gating of an Engineered Enzyme Captured in Real Time. Journal of the American Chemical Society 140: 17999–18008.