**CAVERDOCK: A New Tool for Analysis of Ligand Transport Processes in Proteins Using Molecular Docking**

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Understanding the mechanisms of ligand binding and unbinding into the proteins’ is crucial for drug design and protein engineering. Since many proteins have their active/binding sites buried inside the protein core, properties of access paths connecting the protein surface with the active site can heavily influence the whole binding mechanism [1]. We developed a novel software tool called CaverDock to study the ligand passage through such pathways [2, 3]. The tool is based on the idea of slicing the access tunnels into the small disks followed by iterative molecular docking calculation by AutoDock Vina [5], employing the constraints to every single disk. The software requires protein structure, tunnel topology from CAVER [4] and ligand structure as the inputs. The outputs are continuous ligand trajectory, estimated free energy of binding along the pathway, activation barrier of the transport process and the energy difference between bound and unbound states. CaverDock is easy to setup and very fast - a typical calculation time in dozens of minutes makes it suitable even for a large scale virtual screenings. CaverDock is available free of charge at the website <https://loschmidt.chemi.muni.cz/caverdock/>.

[1] Marques, S.M., et al. 2016: Enzyme Tunnels and Gates as Relevant Targets in Drug Design. *Medicinal Research Reviews* 37: 1095-1139.

[2] Vavra, O., et al. CAVERDOCK: A New Tool for Analysis of Ligand Binding and Unbinding Based on Molecular Docking. In preparation.

[3] Filipovic, J., et al. A Novel Method for Analysis of Ligand Binding and Unbinding Based on Molecular Docking. In preparation.

[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] Trott, O. & Olson, A.J., 2010: AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization and Multithreading. *Journal of Computational Chemistry* 31: 455-461.