Caver Web: Analysis of Protein Tunnels and Ligand Binding Trajectories in Drug Design

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Abstract

Objectives: Protein tunnels and gates are attractive targets for drug design [MDB*17]. Tunnels are important for the transport of ligands, solvent and ions, and can be found in many enzymes, ion channels and membrane proteins. Here, we wanted to create a user-friendly web tool to analyse the tunnels and channels of proteins, and the transport of ligands through these pathways.

Methods: Caver Web 1.0 uses the Caver 3.02 [VFP*19] for tunnel detection and the new CaverDock 1.0 [FVP*19, CPB*12] for ligand transport analysis. CaverDock is a fast, robust and accurate tool, which allows the screening of binding and unbinding processes for pharmacologically interesting compounds. It is based on a heavily modified AutoDock Vina algorithms [TO10] and we have previously successfully tested it with many pharmaceutically interesting targets, such as cytochrome P450 17A1 and leukotriene A4 hydrolase/aminopeptidase [PVK*19].

Results: The identified tunnels, their properties, energy profiles and trajectories for the passage of ligands can be calculated and visualized using the Caver Web tool. The calculation of tunnels takes generally 2-20 min per one ligand-tunnel pair and thus the tool is applicable even for virtual screening purposes. The three tutorials presented on the web page describe three different use cases: (i) comparing tunnels of a family of enzymes, (ii) comparing the passage of a single ligand through multiple tunnels and (iii) comparing the passage of different ligands through a single tunnel.

Conclusions: The simple setup and graphical user interface make the tool accessible for all users who are interested in tunnel or channel identification and ligand binding analysis. Caver Web is freely available at https://loschmidt.chemi.muni.cz/caverweb.

References


Figure 1: Paracetamol and the CYP3A4 enzyme that metabolizes it in humans. Different identified tunnels are show in colors.