Eurographics Workshop on Visual Computing for Biology and Medicine (2019)
J. Byška and G. Mistelbauer (Poster Chairs)

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

Kokkonen, P.[1], Stourac, J.[1,2], Filipovic, J.[3], Vavra, O.[1], Pinto, G.[2], Bednar, D.[1,2], Damborsky, J.[1,2]

[1]Loschmidt Laboratories, Department of Experimental Biology and RECETOX, Faculty of Science, Masaryk University, Czech Republic
[2]International Clinical Research Center, St. Anne's University Hospital Brno, Czech Republic
[3]Institute of Computer Science, Masaryk University, Czech Republic

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 only 1-2 min for a single protein structure. The ligand transport analysis 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.*

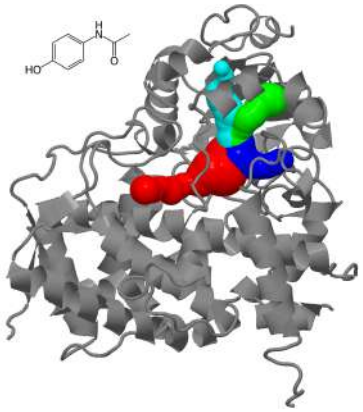

Figure 1: *Paracetamol and the CYP3A4 enzyme that metabolizes it in humans. Different identified tunnels are show in colors.*

References

[CPB*12] Chovancova E., Pavelka A., Benes P., Strnad O., Brezovsky J., Kozlikova B., Gora A., Sustr V., Klvana M., Medek P., et al.: Caver 3.0: a tool for the analysis of transport pathways in dynamic protein structures. *PLoS computational biology 8*, 10 (2012), e1002708. 1

[FVP*19] Filipovič J., Vávra O., Plhák J., Bednář D., Marques S. M., Brezovský J., Matyska L., Damborský J.: Caverdock: A novel method for the fast analysis of ligand transport. *Manuscript submitted* (2019). 1

[MDB*17] Marques S. M., Daniel L., Buryska T., Prokop Z., Brezovsky J., Damborsky J.: Enzyme tunnels and gates as relevant targets in drug design. *Medicinal research reviews 37*, 5 (2017), 1095–1139. 1

[PVK*19] Pinto G., Vavra O., Kokkonen P., Filipovic J., Jurcik A., Kozlikova B., Bednar D., Damborsky J.: Screening of the binding trajectories of inhibitors via tunnels using novel software caverdock. *Manuscript submitted* (2019). 1

[TO10] Trott O., Olson A. J.: Autodock vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry 31*, 2 (2010), 455–461. 1

[VFP*19] Vavra O., Filipovic J., Plhak J., Bednar D., Marques S., Brezovsky J., Matyska L., Damborsky J.: Caverdock: A new tool for analysis of ligand binding and unbinding based on molecular docking. *Manuscript submitted* (2019). 1