Screening the binding trajectory of two datasets of inhibitors via tunnels and channels using novel software CaverDock

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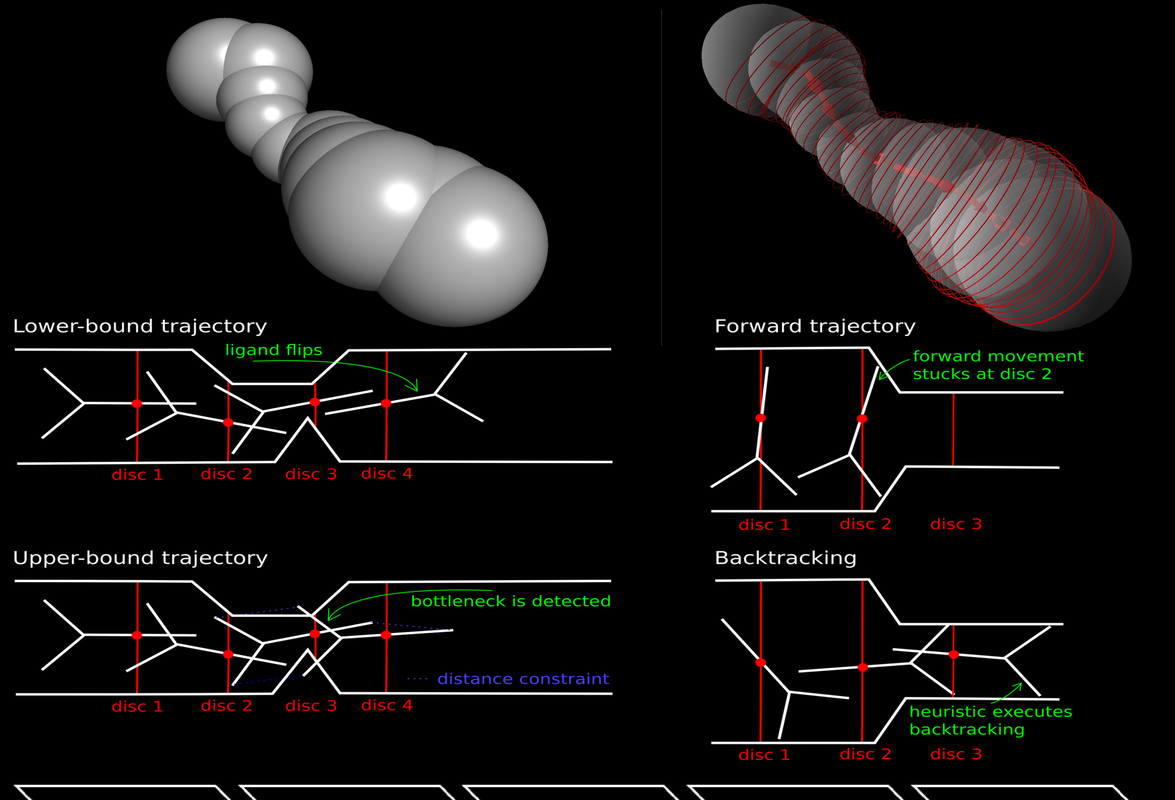
ABSTRACT

Protein tunnels, channels and gates represent attractive targets for drug design. The inhibitors blocking the access of natural substrates into the protein active site are very efficient modulators of biological activity[1]. Here we illustrate the application of newly developed *in-house* software CaverDock[2-3] for virtual screening of large databases of drugs against two pharmacologically relevant targets. CaverDock models the transportation of a ligand from outside environment into the protein active or binding site and *vice versa*. The current version uses Caver[4] for pathway identification and heavily modified Autodock Vina[5] as a docking engine.

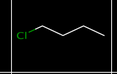
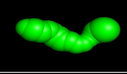
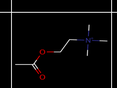
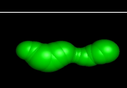
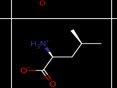
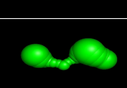
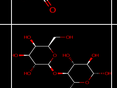
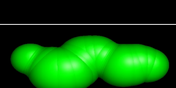
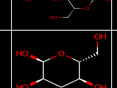
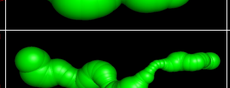
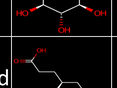
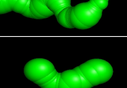
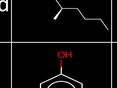
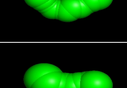
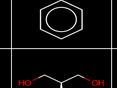
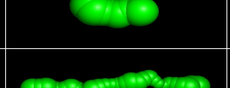
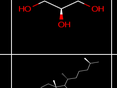
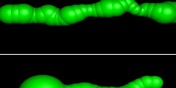
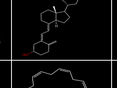
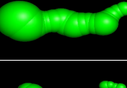
We have used FDA-approved drugs for two targets: (i) cytochrome P450 17A1 and (ii) leukotriene A4 hydrolase/aminopeptidase. Oncological drugs (133 molecules) from the National Institute of Health website and anti-inflammatory drugs (56 molecules) from the DrugBank website were used as the libraries of ligands. The screening took less than an hour per molecule on average and successfully calculated trajectories for more than 90% studied cases. We conclude that CaverDock is sufficiently fast, robust and accurate to allow screening of binding and unbinding processes for pharmacologically important targets containing molecular tunnels or channels.

CaverDock is available free of charge at the website https://loschmidt.chemi.muni.cz/caverdock/.

METHOD

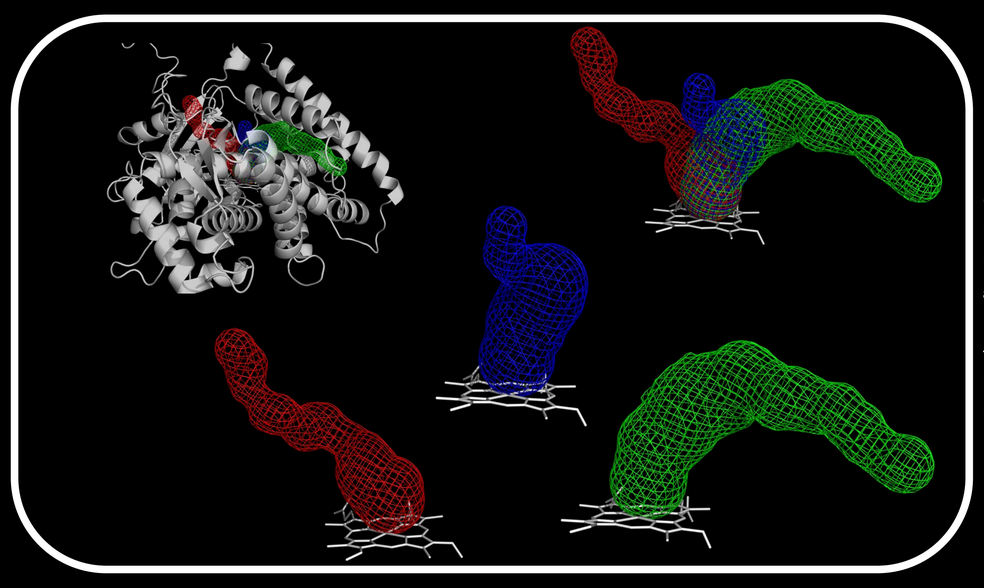


VALIDATION

Enzyme	Ligand	Ligand	Tunnel geometry	CaverDock	SLITHER	MOMA-LigPath
Haloalkanedehalogenase DhaA	1-Chlorobutane			YES	YES	YES
Acetylcholinesterase	Acetylcholine			YES	YES	YES
Leucine transporter	Leucine			YES	YES	YES
Lactose permease	Lactose			YES	YES	YES
Glucose transporter I	α-D-Glucopyranose			YES	YES	NO
Lipase B	4-Methyloctanoic acid			YES	NO	YES
Insuline hexamer	Phenol			YES	NO	YES
Aquaporin Z	Glycerol			YES	NO	NO
Vitamin D receptor	1,25-dihydroxyvitamin D3			YES	NO	NO
Cytochrome P450 2E1	Arachidonic acid			YES	NO	NO

SCREENING

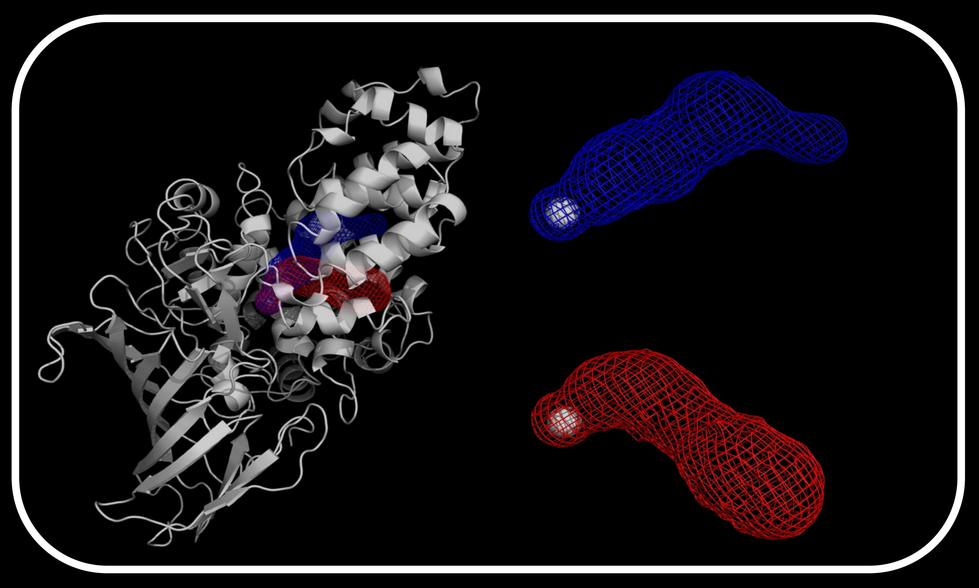
A CaverDock protocol starts with the finding of tunnels by using Caver. For the cytochrome P450 17A1, that has an heme-group in the active-site, the iron atom was chosen as the point of origin for tunnel calculation. For the leukotriene A4 hydrolase/aminopeptidase, that has a zinc atom in the active-site, the zinc was chosen as the point of origin for tunnel calculation. For the cytochrome P450 17A1, a dataset with 133 cancer FDA-approved drugs was used and for the leukotriene A4 hydrolase/aminopeptidase, we used a dataset of 56 anti-inflammatory FDA-approved drugs. A CaverDock input file is similar to an AutoDock Vina input. We add the information for the tunnel, from Caver, to allow the search of a "docking" conformation along the tunnel.

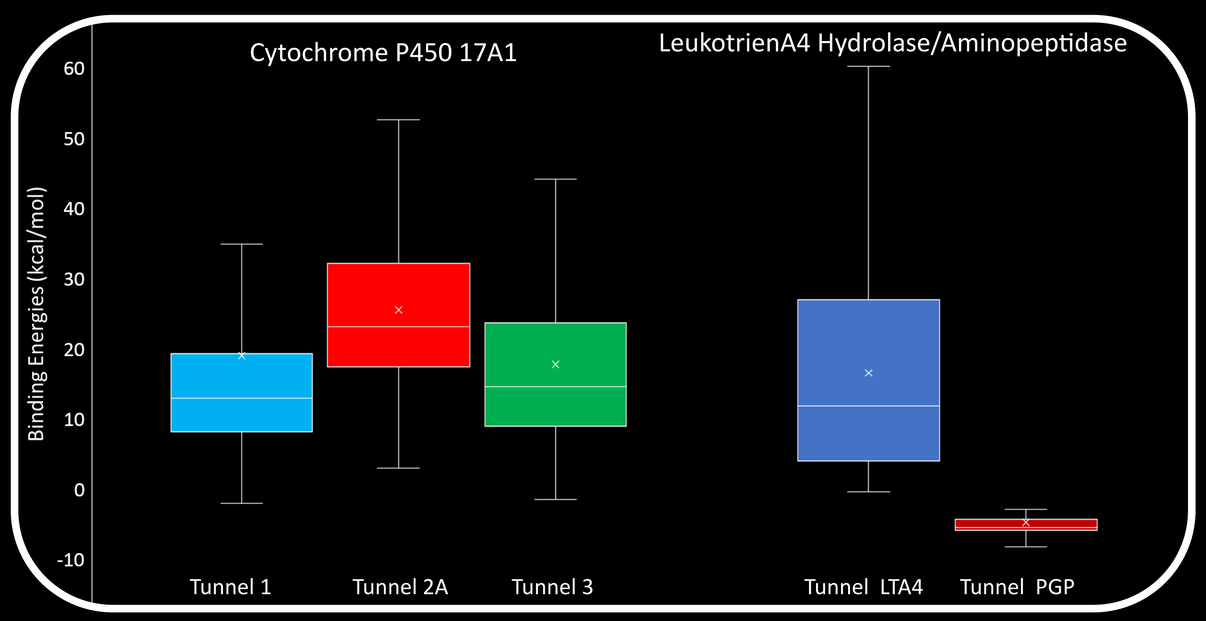


Proteins and Tunnels studied

Cytochrome 17A1, protein and tunnels on the left. Tunnel 1 represented in blue, Tunnel 2 represented in red and Tunnel 3 represented in green.

Leukotriene A4 hydrolase/aminopeptidase, protein and tunnels on the right. Tunnel LTA4 represented in blue and Tunnel PGP represented in red.





	Cytochrome P450 17A1			Leukotriene A4 hydrolase/ aminopeptidase	
	Tunnel 1	Tunnel 2A	Tunnel 3	Tunnel LTA4	Tunnel PGP
Size of Library	105	105	105	54	54
Continuous	41	42	42	20	21
Lower Bound	100	91	93	48	50
Stopped at Bottleneck	5	14	11	6	4
Time Average (s)	2510	4138	3131	2177	1343
Length (Å)	15.1	24.9	28.2	20.4	25.4
Maximum Bottleneck (Å)	1.4	1.3	1.3	1.9	1.7

CONCLUSION

- CaverDock is a newly developed software for fast simulation of ligand binding and unbinding. Resulted as a best predictor in comparison tests with two other available tools. Can be used for comparing transition of different ligands and the transition of ligand through different tunnels.
- Easy to run with a 5 step protocol using the data formats well established for Caver and Autodock Vina. CaverDock is sufficiently fast, providing the results within 1 hour on a computer with four processors.
- Calculations are very robust and provided successful runs for 90% of cases studies thus far. CaverDock is available and free to everyone at the web site https://loschmidt.chemi.muni.cz/caverdock/.

REFERENCES

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[4] Chovancova, E., et al. 2012: CAVER 3.0: Analysis of Transport Pathways in Dynamic Protein Structures. PLOS 8: e1002708.

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