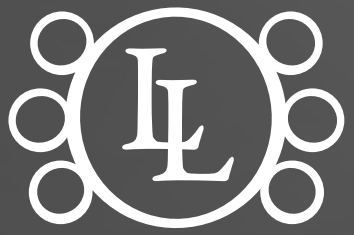
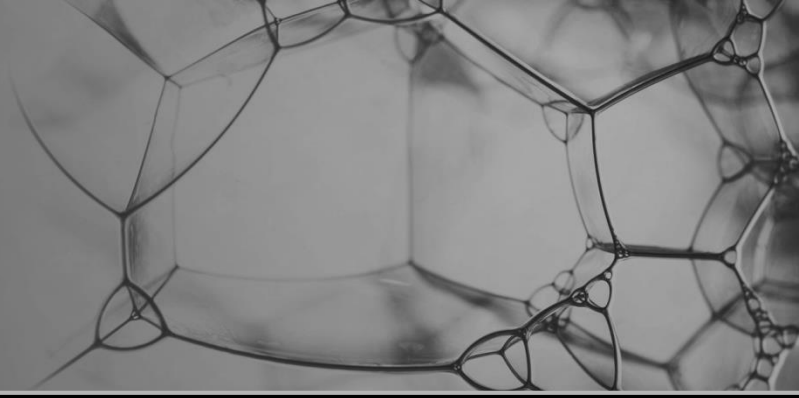


LOSCHMIDT
LABORATORIES



Computational Tools to Aid Modelling, Analysis, and Virtual Screening

Gaspar Pinto @ EJIBCE 2018

Introduction

- Who we are

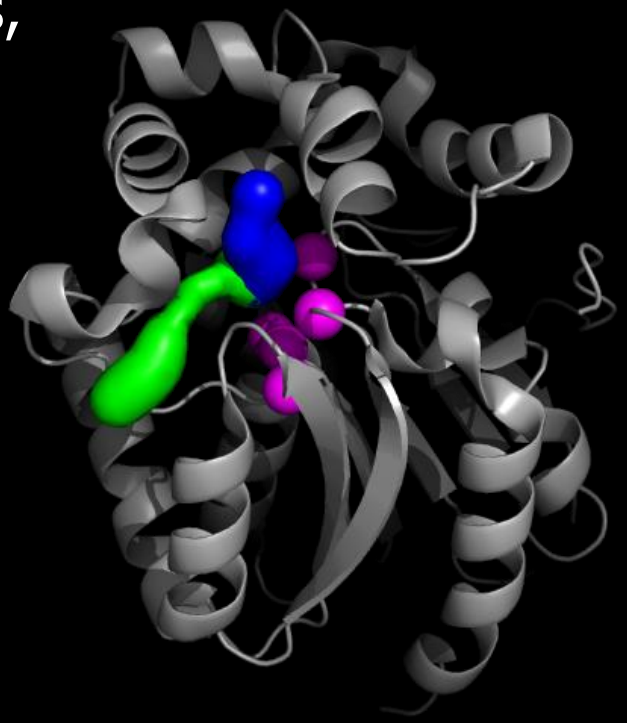
Introduction

- Enzymes with buried active site

Haloalkane dehalogenase DhaA

Introduction

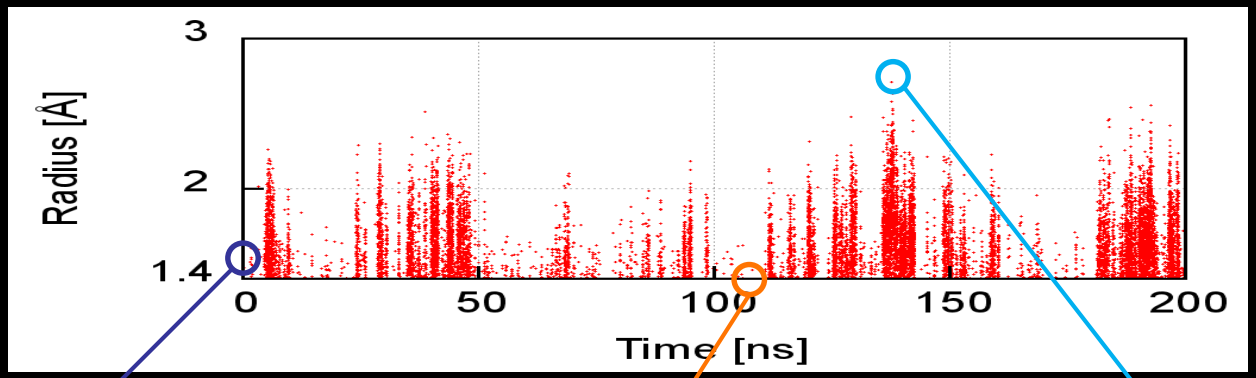
- Enzymes with buried active site… need tunnels
  - Transport of substrates, products, solvent, cofactors
  - Wide-spread features
    - 64% of known enzymes
    - All 6 enzyme classes

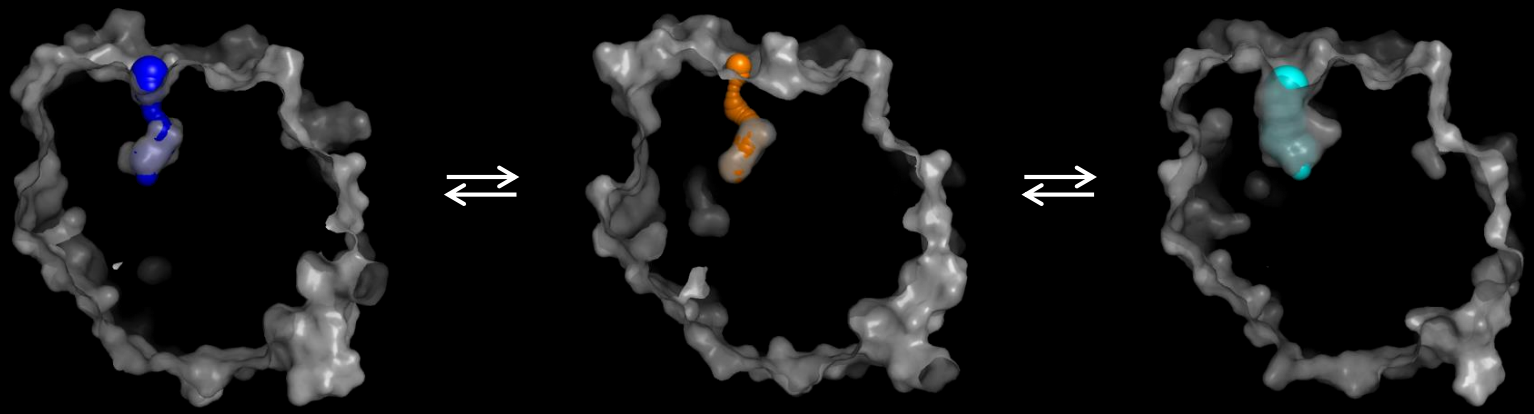


Haloalkane dehalogenase DhaA

Introduction

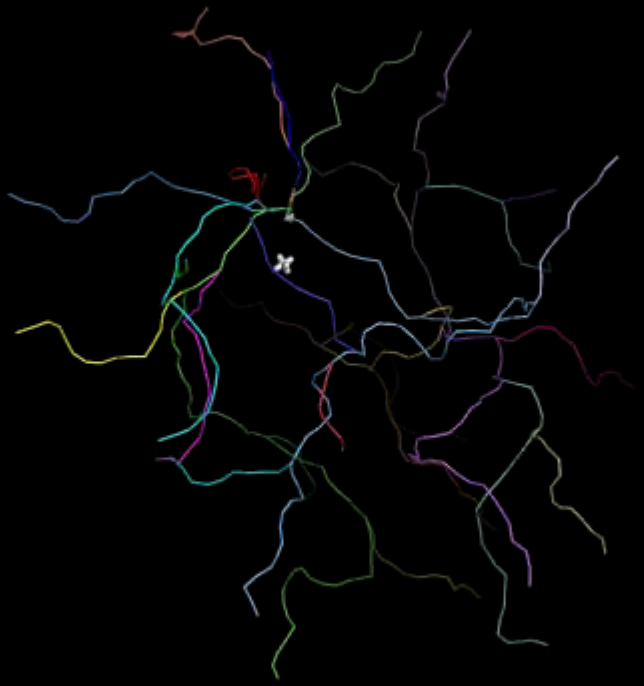
- Protein tunnels: dynamic features





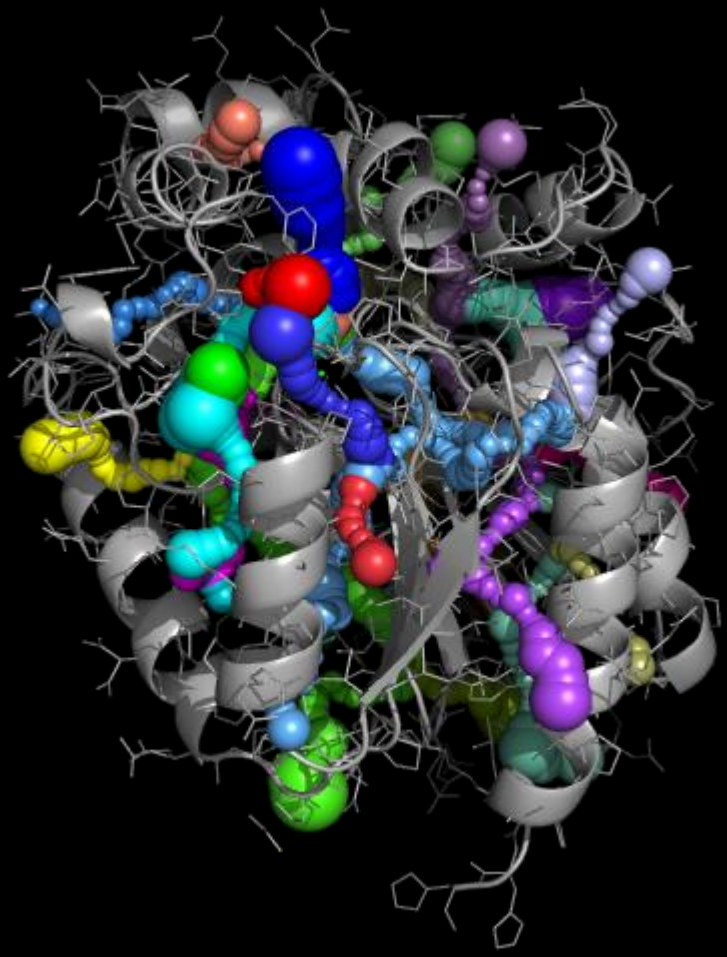
CAVER

- Tool for tunnel computation
  - Space characterization
  - Voronoi diagrams
  - Search for pathways
    - Origin, probe radius,
      shell radius,
      clustering threshold



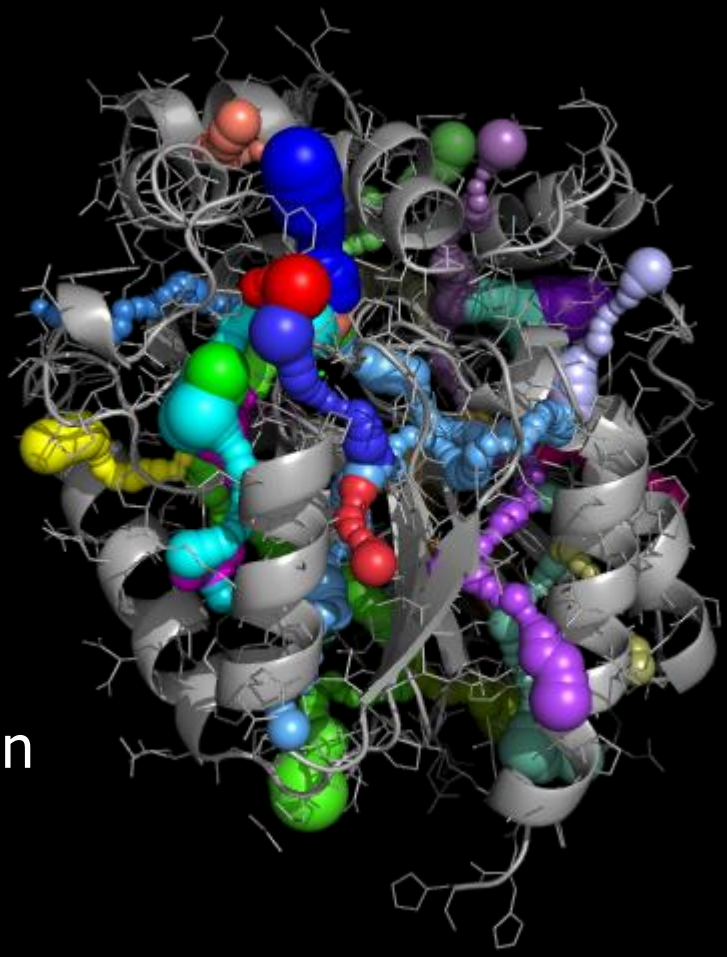
CAVER

- Tool for tunnel computation
  - Space characterization
  - Voronoi diagrams
  - Search for pathways
    - Origin, probe radius,
      shell radius,
      clustering threshold



CAVER

- Tool for tunnel computation
  - Space characterization
  - Voronoi diagrams
  - Search for pathways
  - Ranking of tunnels
    - Based on bottleneck radius, length, curvature
  - Command-line, PyMOL plugin



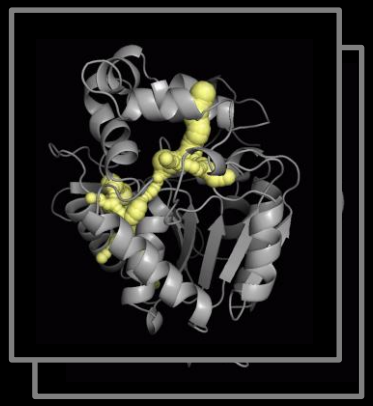
CAVER

- Dynamic tunnels
  - Structure ensemble

identification of tunnels
in each snapshot

CAVER

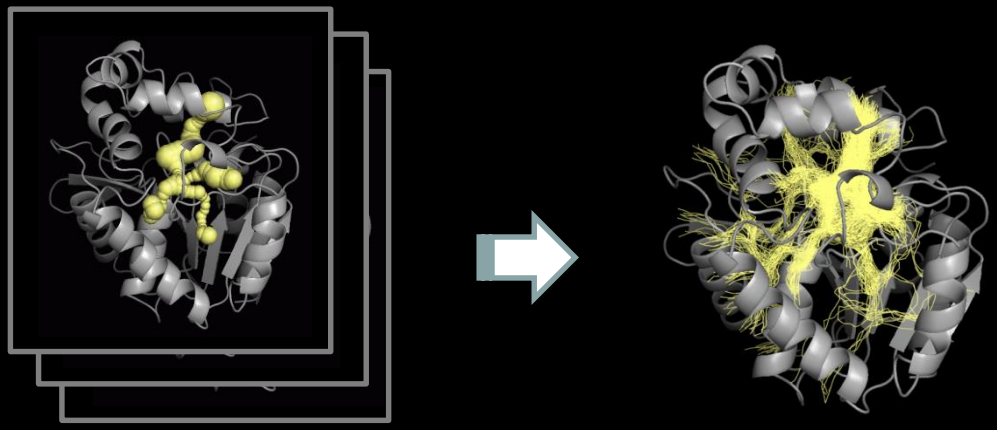
- Dynamic tunnels
  - Structure ensemble



identification of tunnels
in each snapshot

CAVER

- Dynamic tunnels
  - Structure ensemble

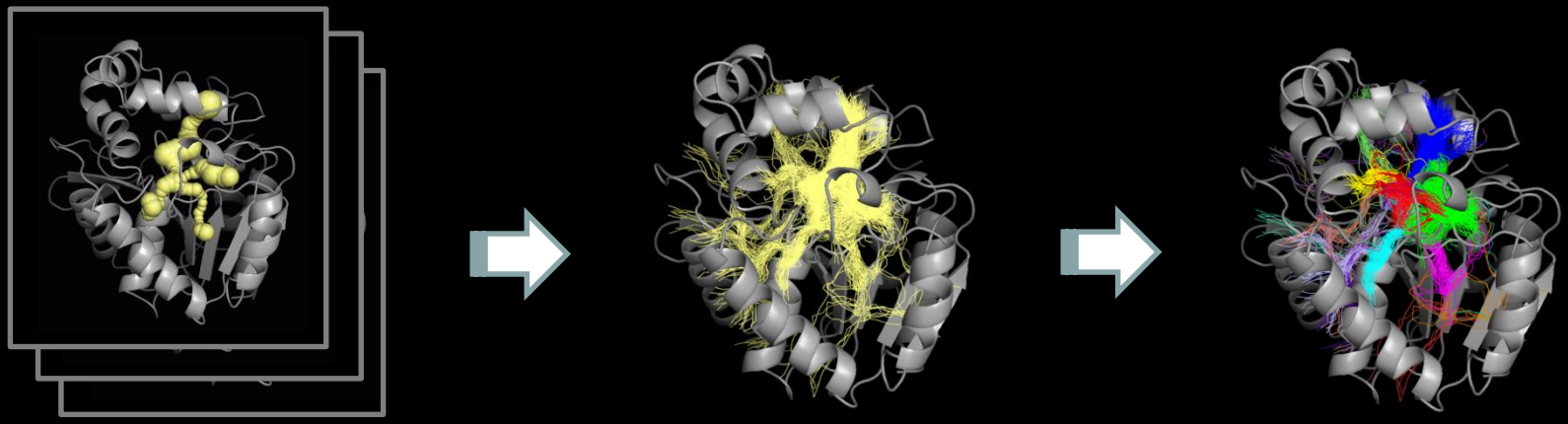


identification of tunnels in each snapshot

merging all identified tunnels

CAVER

- Dynamic tunnels
  - Structure ensemble
  - Clustering of tunnels



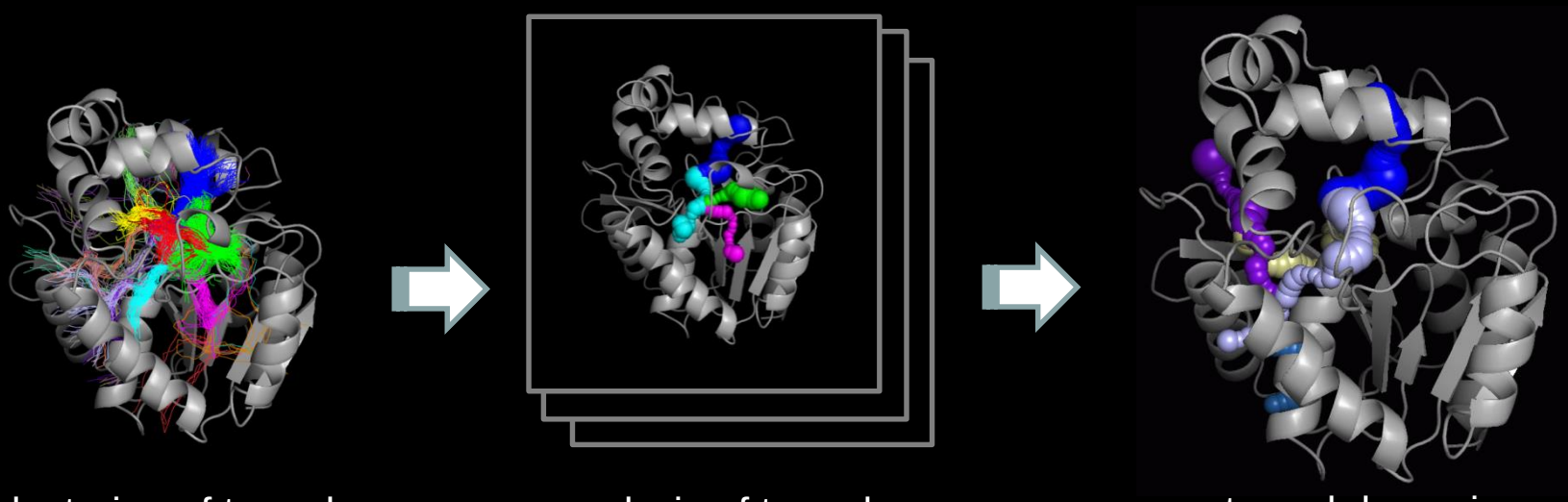
identification of tunnels in each snapshot

merging all identified tunnels

clustering of tunnels

CAVER

- Dynamic tunnels
  - Analysis of tunnel dynamics
  - Statistics, analysis and visualization output



clustering of tunnels

analysis of tunnels

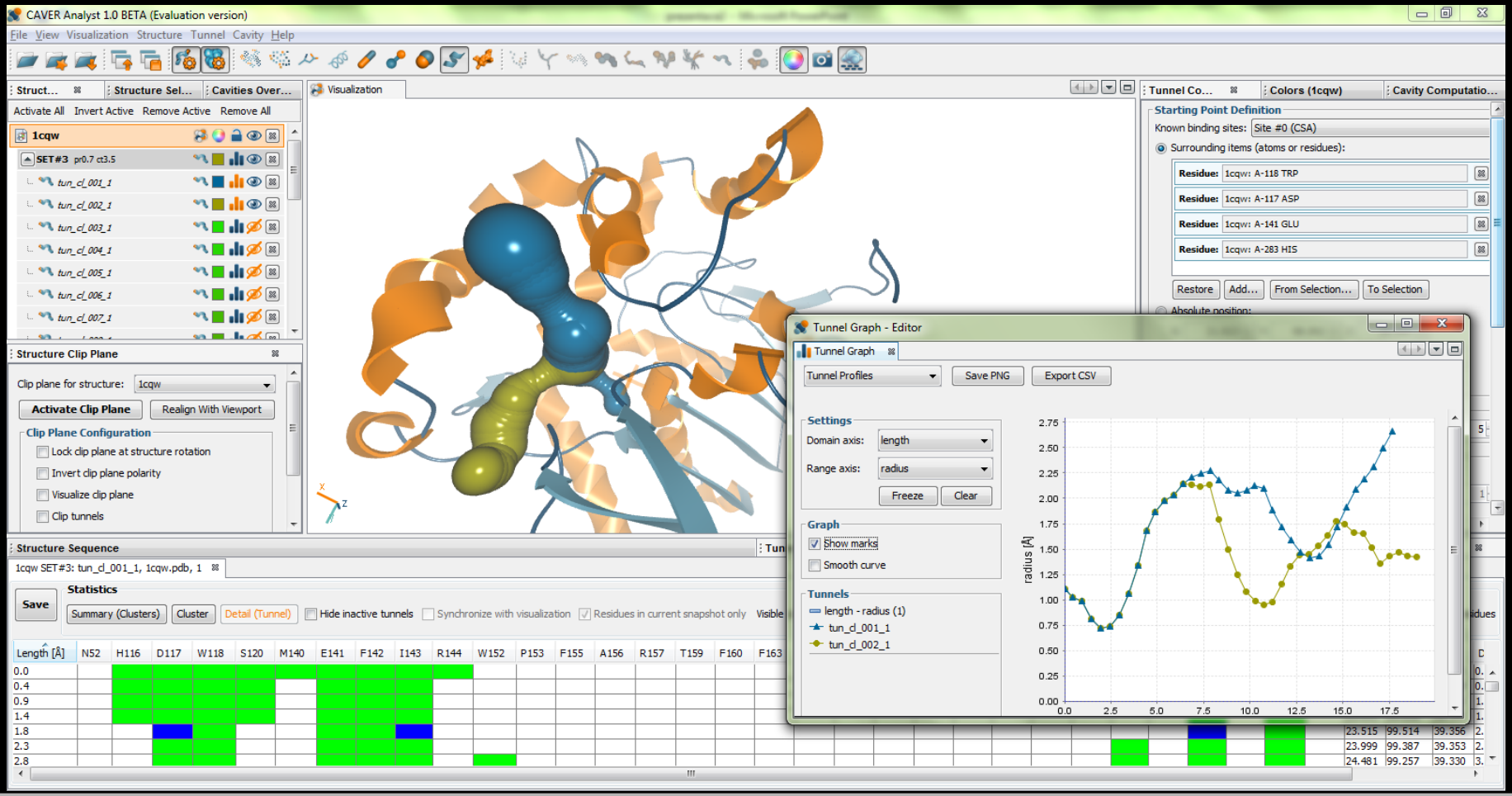
tunnel dynamics

Caver Analyst

- Graphical interface to CAVER
  - User-friendly
  - Static and dynamic structures
  - Versatile representations

Caver Analyst

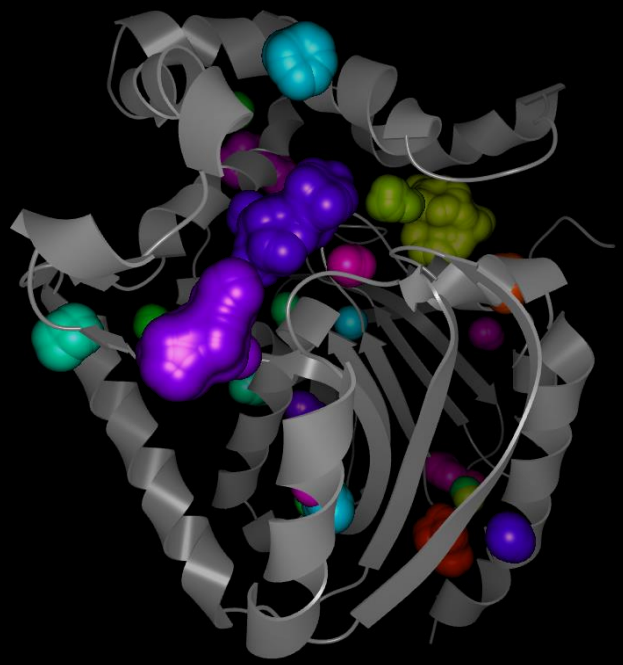
- Graphical interface to CAVER



Computational Tools to Aid Modelling, Analysis and Virtual Screening

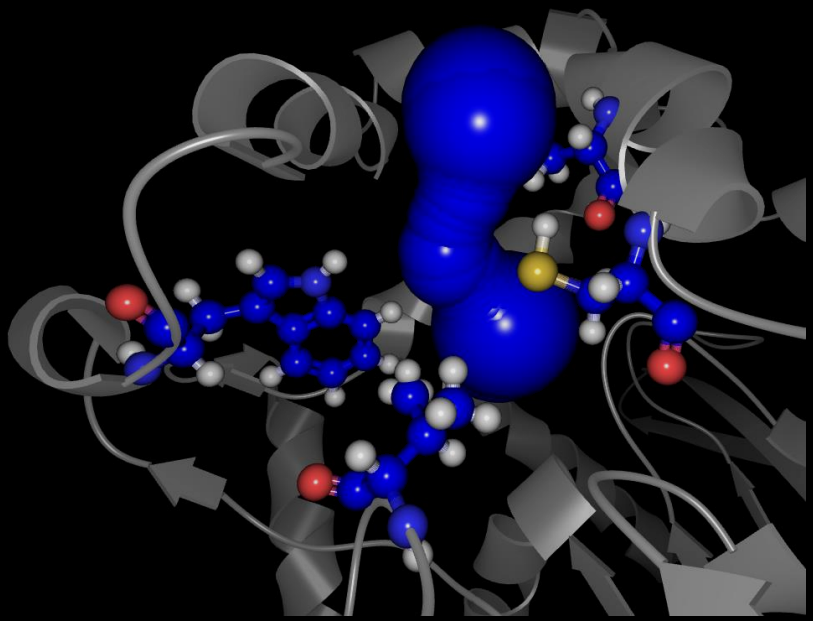
Caver Analyst

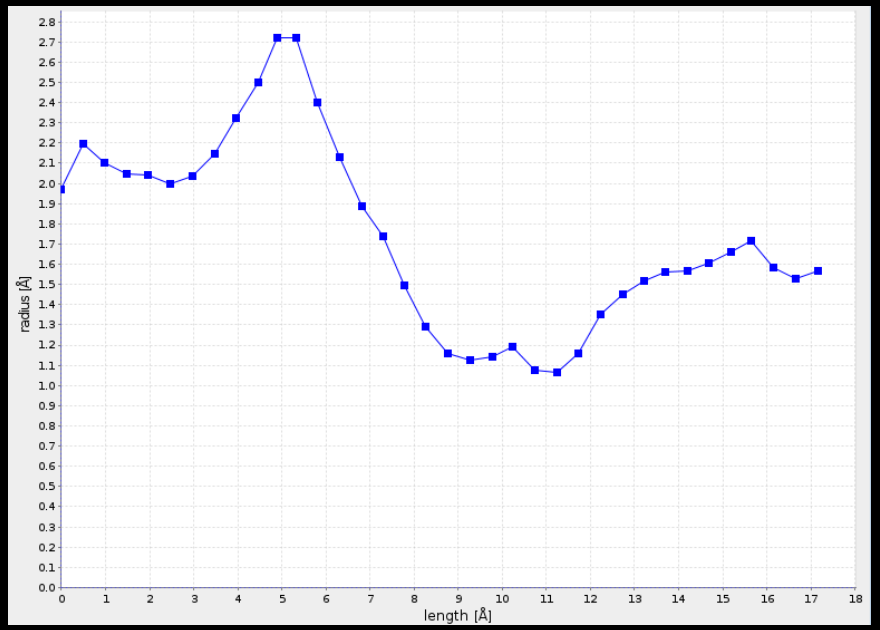
- Graphical interface to CAVER
  - User-friendly
  - Static and dynamic structures
  - Versatile representations
  - Compute protein cavities



Caver Analyst

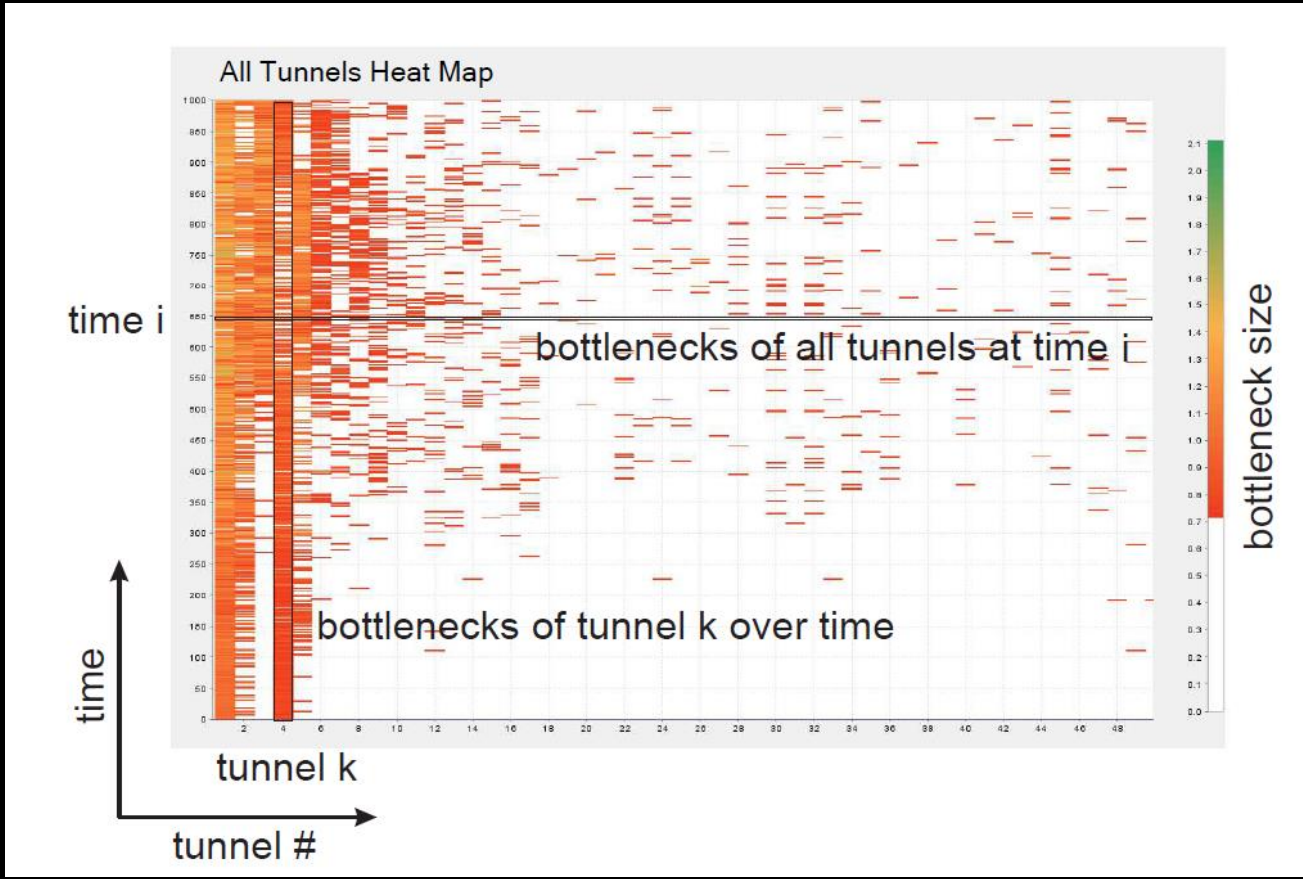
- Graphical interface to CAVER





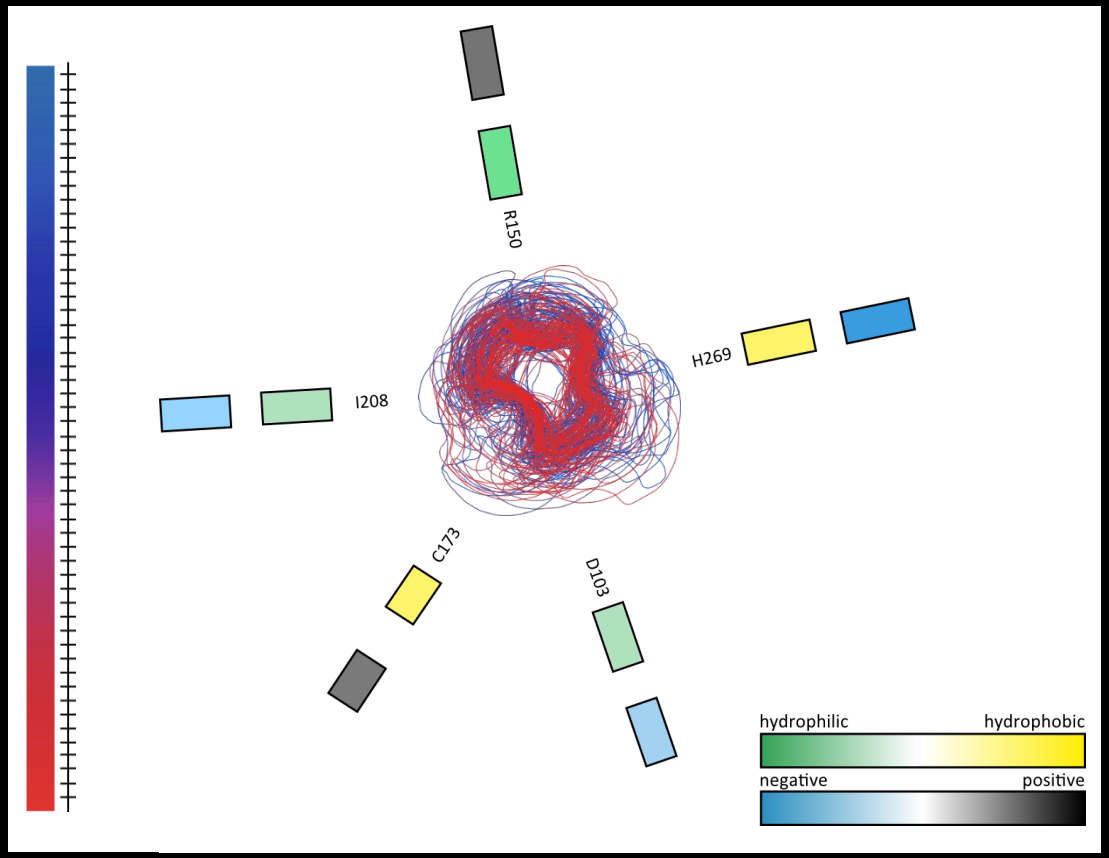
Caver Analyst

- Graphical interface to CAVER



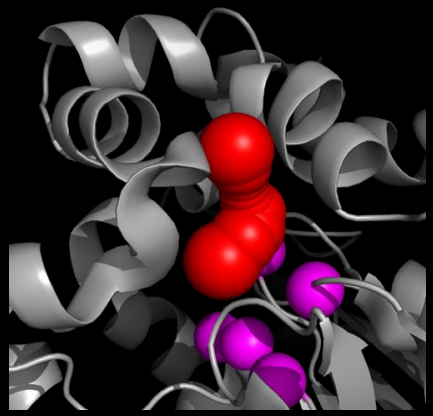
Caver Analyst

- Graphical interface to CAVER

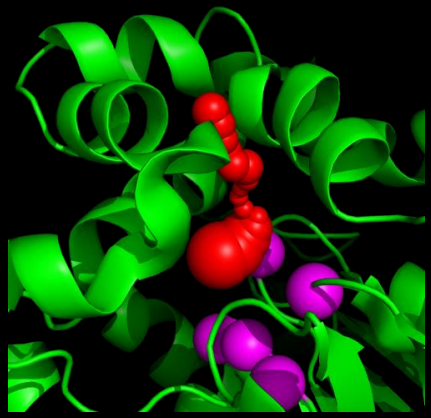


Caver Analyst – case study

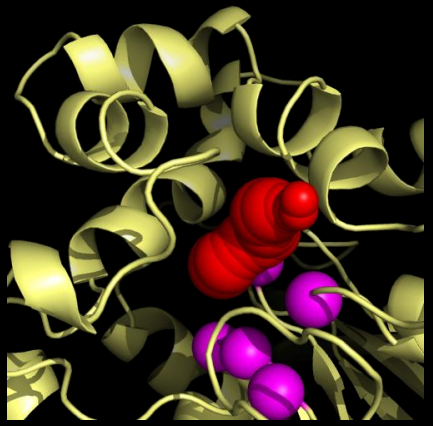
DhaA

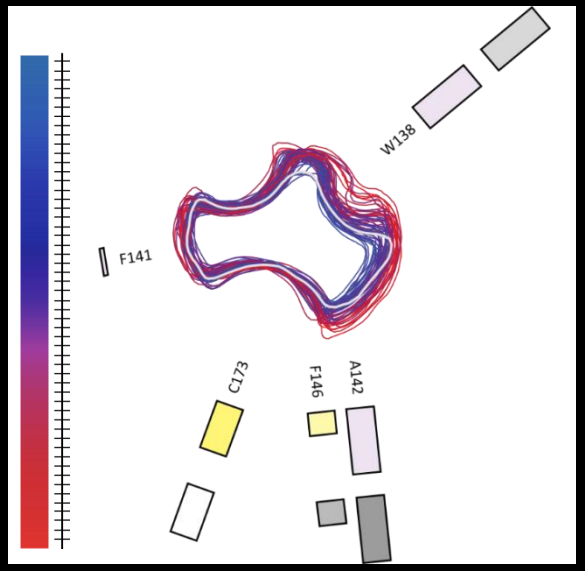


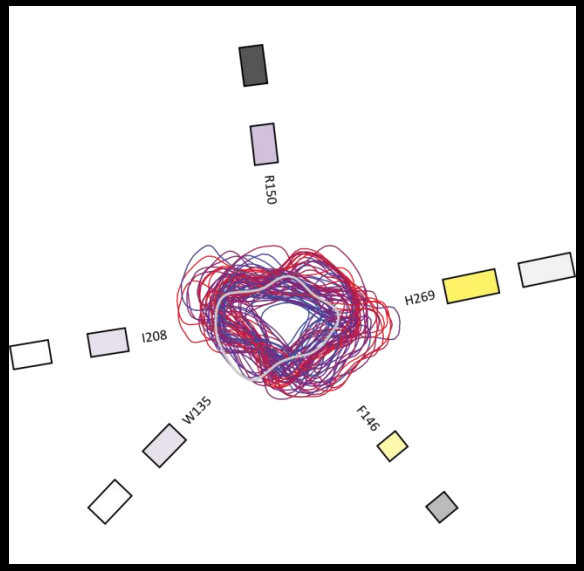
DhaA80

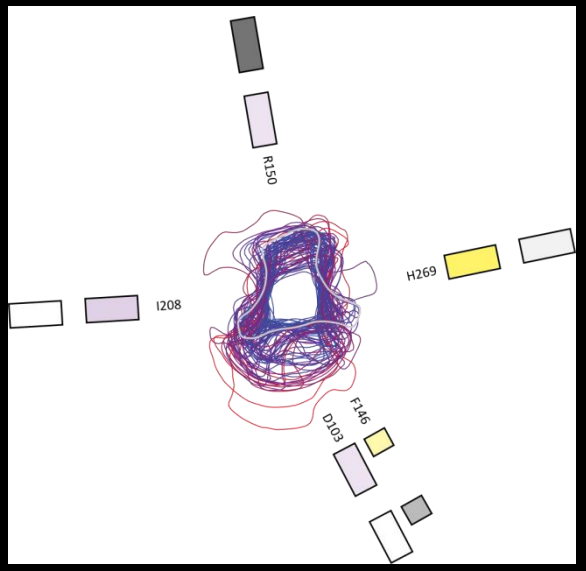


DhaA106







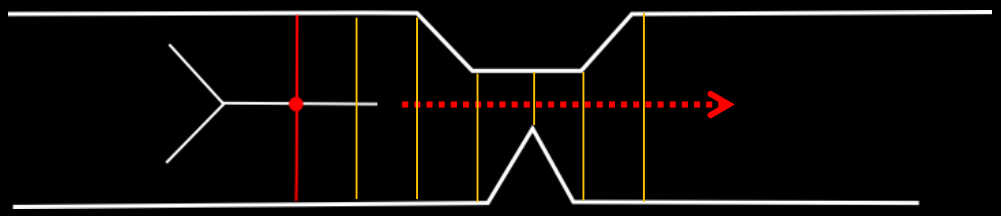


Caver Analyst

- Caver Analyst 2.0
  - Improved tunnel analysis
  - Mutagenesis
  - Enhanced visualization
  - Video recording
  - Saving images with no background
  - www.caver.cz

CaverDock

- Tool to study ligand transport through tunnels
  - Substrate, products, inhibitors
  - Based on CAVER and AutoDock Vina
  - Trajectory computation



CaverDock

- Tool to study ligand transport through tunnels
  - Substrate, products, inhibitors
  - Based on CAVER and AutoDock Vina
  - Lower-bound trajectory

CaverDock

- Tool to study ligand transport through tunnels
  - Substrate, products, inhibitors
  - Based on CAVER and AutoDock Vina
  - Continuous movement

CaverDock

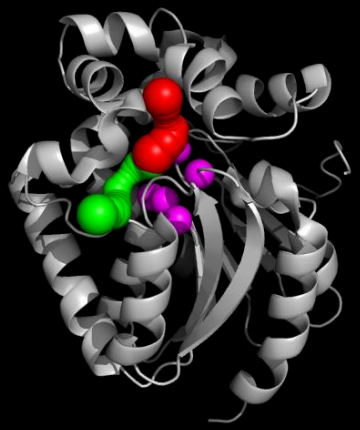
- Tool to study ligand transport through tunnels
  - Substrate, products, inhibitors
  - Based on CAVER and AutoDock Vina
  - Optimized trajectory

CaverDock

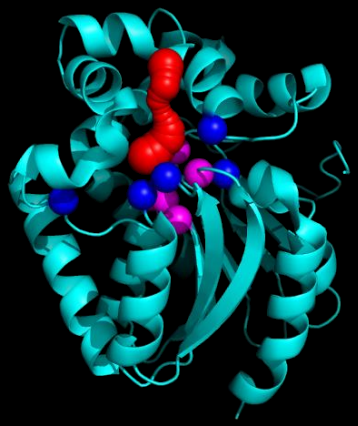
- Tool to study ligand transport through tunnels
  - Substrate, products, inhibitors
  - Based on CAVER and AutoDock Vina
  - Flexibility can be added
  - Trajectory and binding energy along tunnel

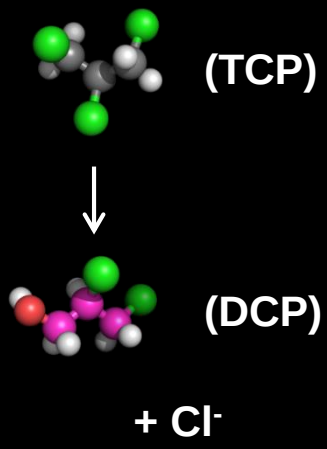
CaverDock – case study

DhaA



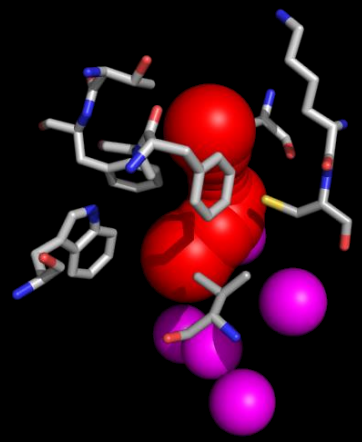
DhaA31



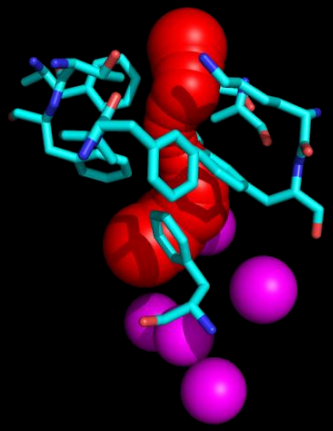


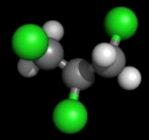
CaverDock – case study

DhaA

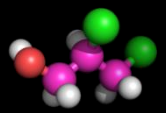


DhaA31



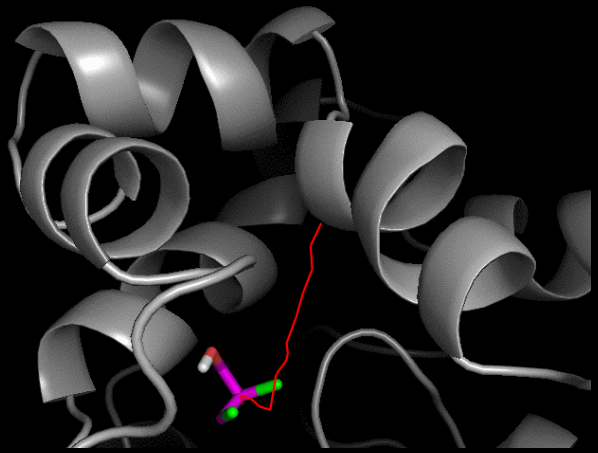


(TCP)



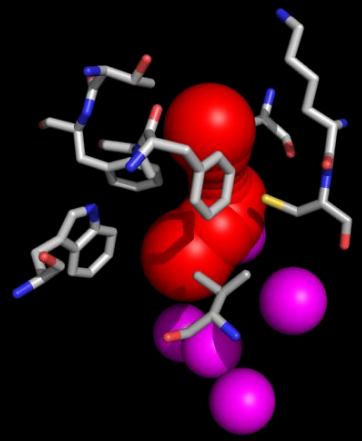
(DCP)

+ Cl^-

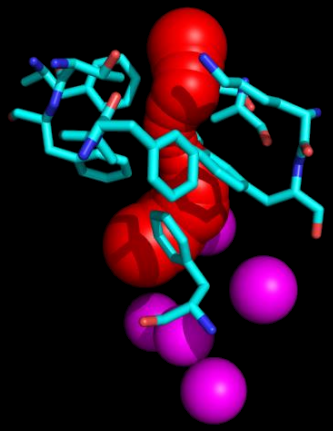


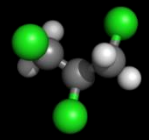
CaverDock – case study

DhaA

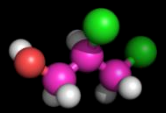


DhaA31



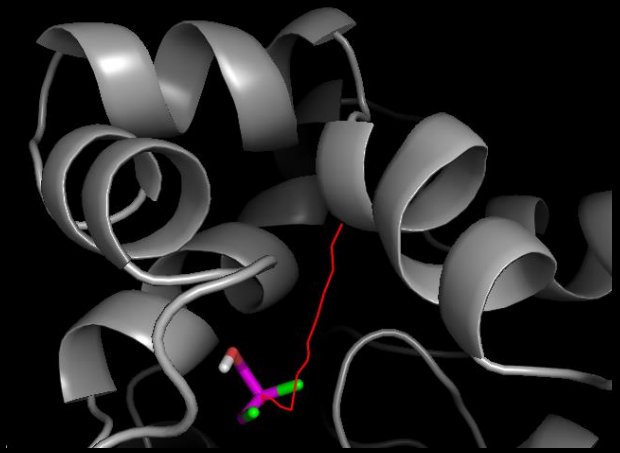


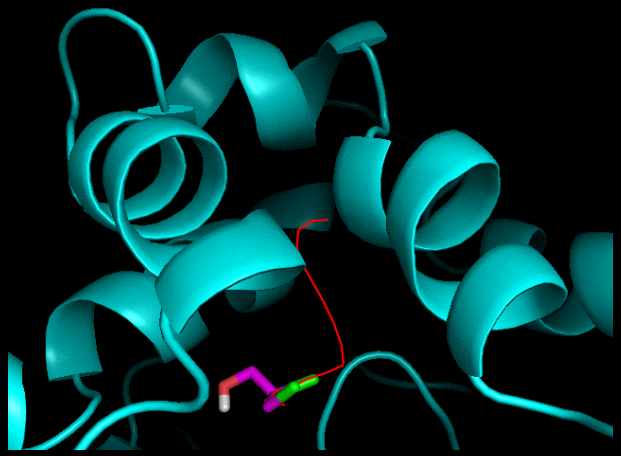
(TCP)



(DCP)

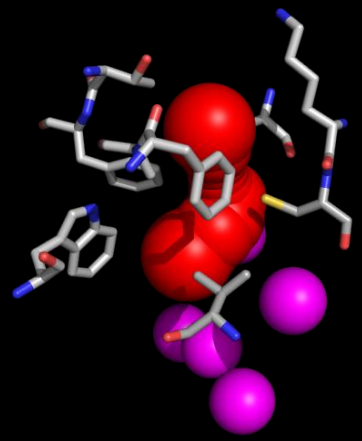
+ Cl^-



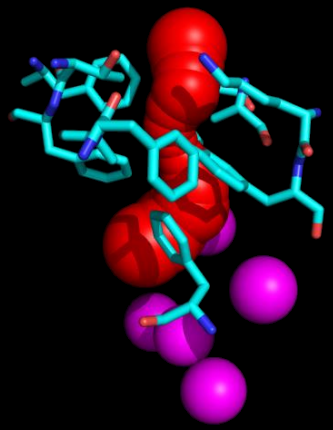


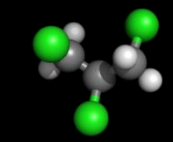
CaverDock – case study

DhaA

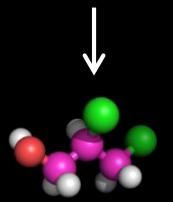


DhaA31



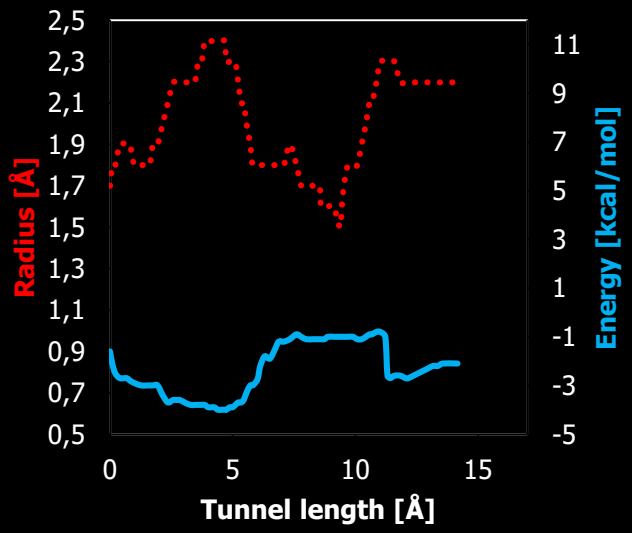


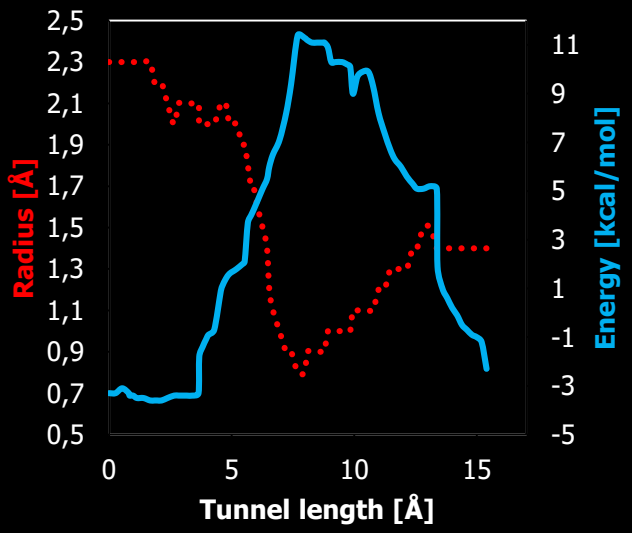
(TCP)



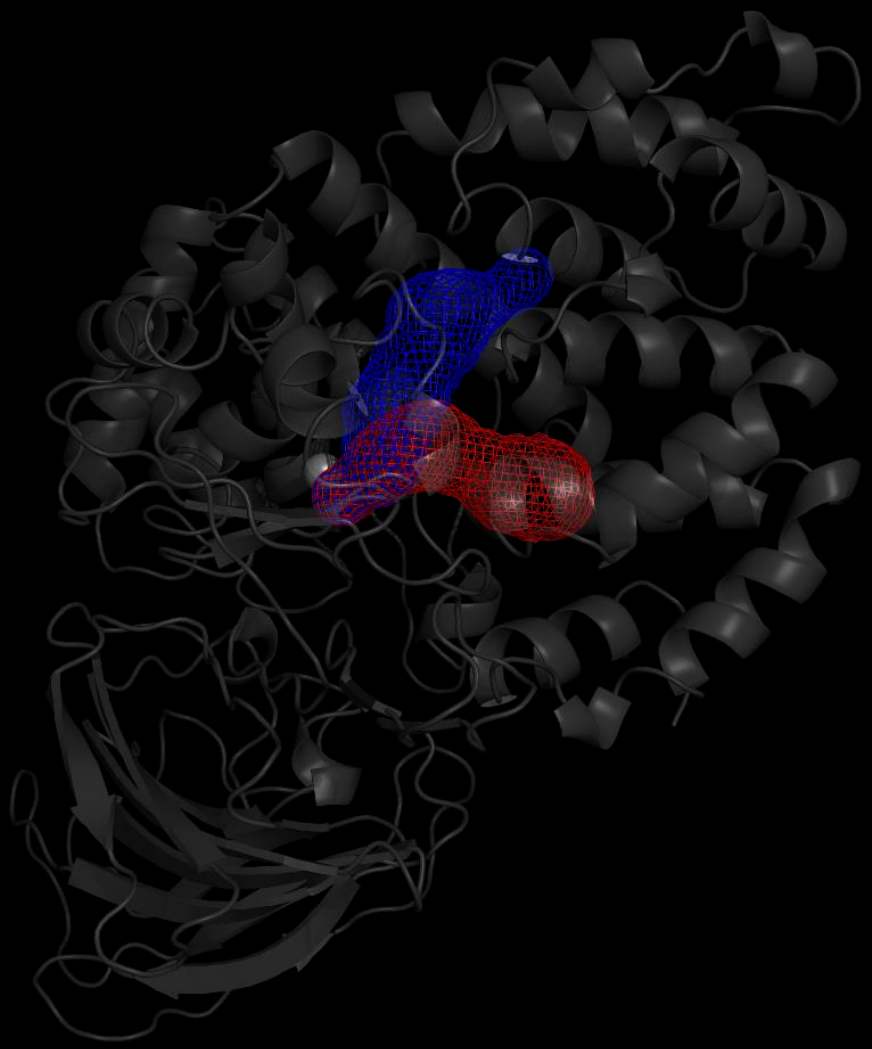
(DCP)

+ Cl^-





Virtual screening – Caver Analysis

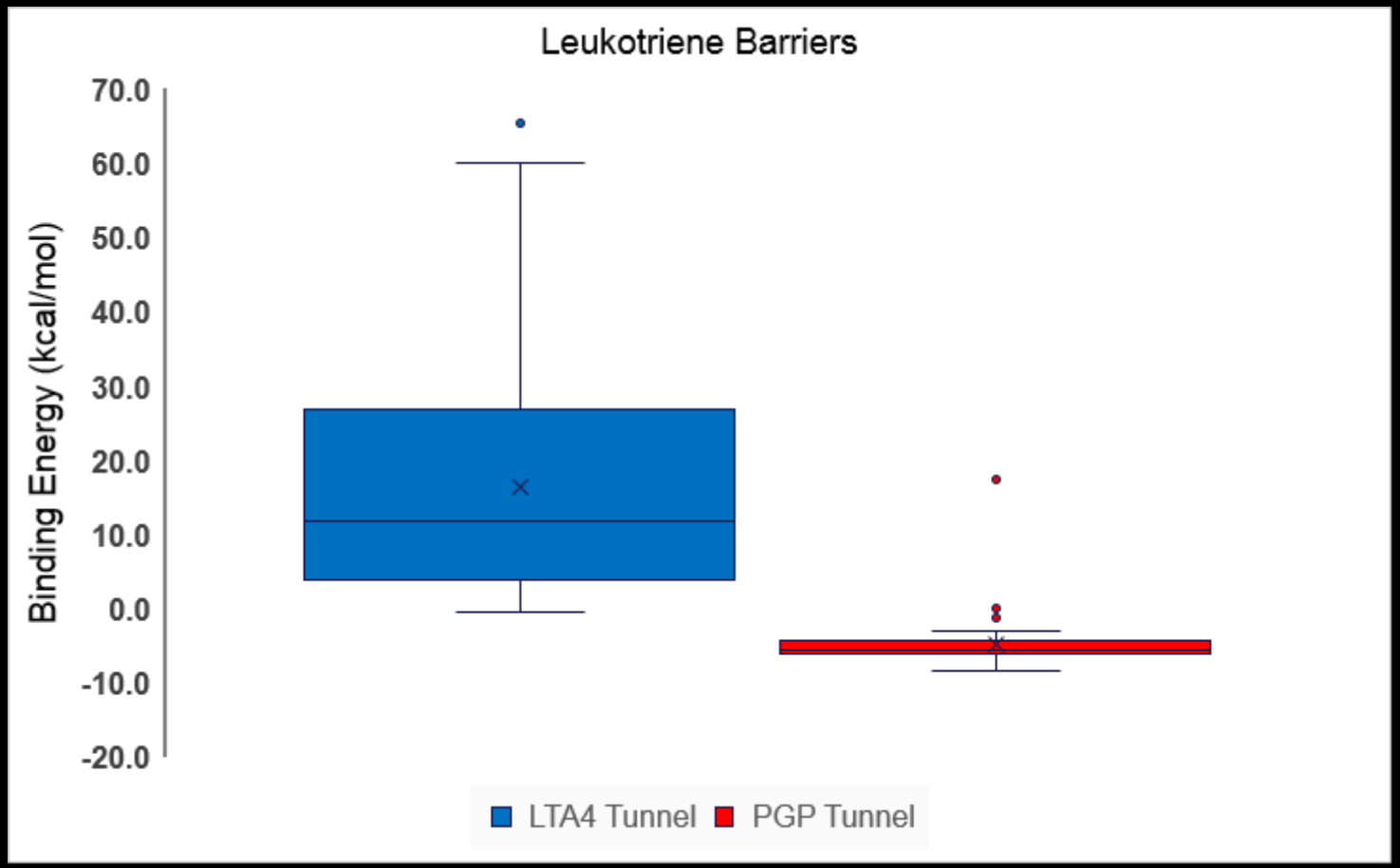


Leukotriene A4

- Biosynthesis of a pro-inflammatory mediator

- Screening library:
  - Anti-inflammatory agents
  - 56 molecules
  - 2 ligands discarded from the set

Virtual screening – Data Analysis



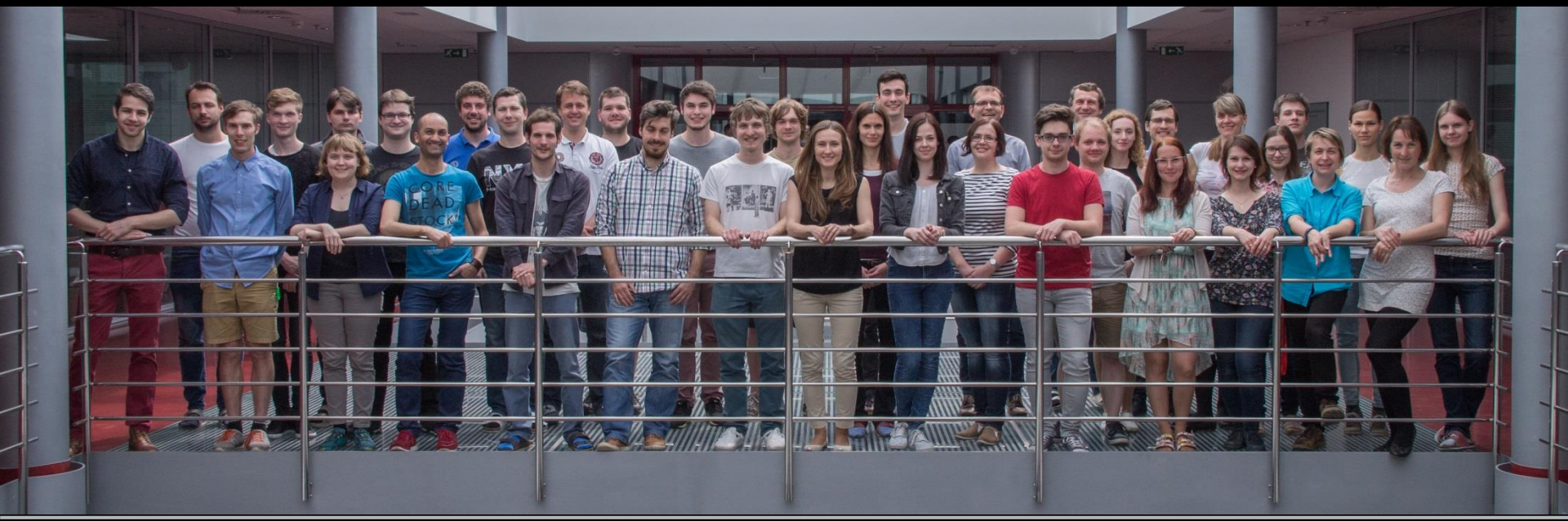
Acknowledgements

FNUSA ICRC

ST. ANNE'S UNIVERSITY HOSPITAL BRNO

INTERNATIONAL CLINICAL RESEARCH CENTER

LOSCHMIDT LABORATORIES



Software tools by LL & Co.

CAVER, Caver Analyst

http://www.caver.cz

FireProt

http://loschmidt.chemi.muni.cz/fireprot

Hotspot Wizard

http://loschmidt.chemi.muni.cz/hotspotwizard

Predict SNP

http://loschmidt.chemi.muni.cz/predictsnp

CalFitter

http://https://loschmidt.chemi.muni.cz/calfitter