Detecting channels in proteins

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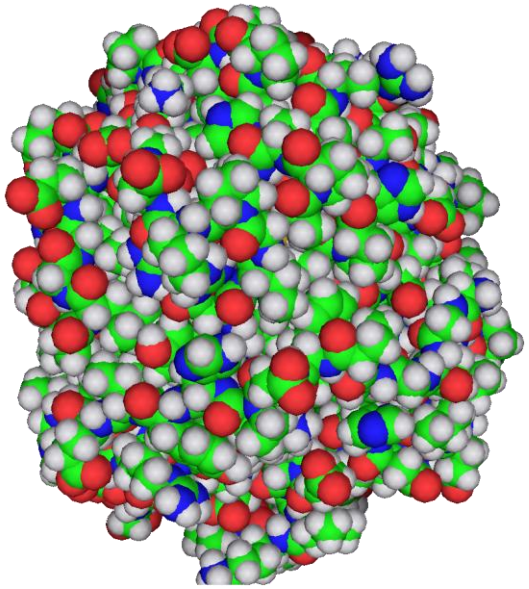
outline

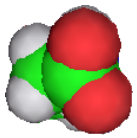
- biochemical background
- what a channel in a protein is
- what we have so far
- what another directions should be (in relation to my PhD. thesis)
- how are our algorithms available to common public
- conclusion

biochemical background

- **protein molecule**
  - for us thousands of atoms (spheres) with different radii (diferent chemical item)

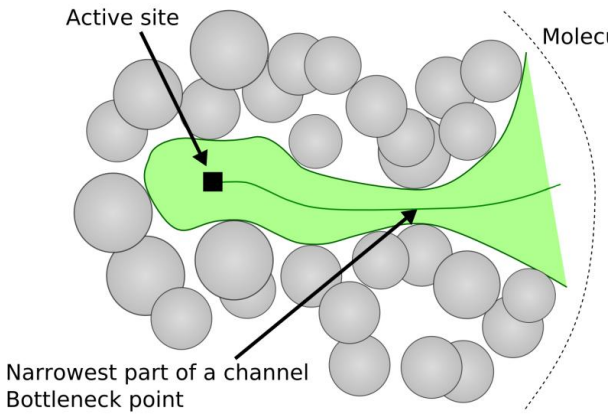


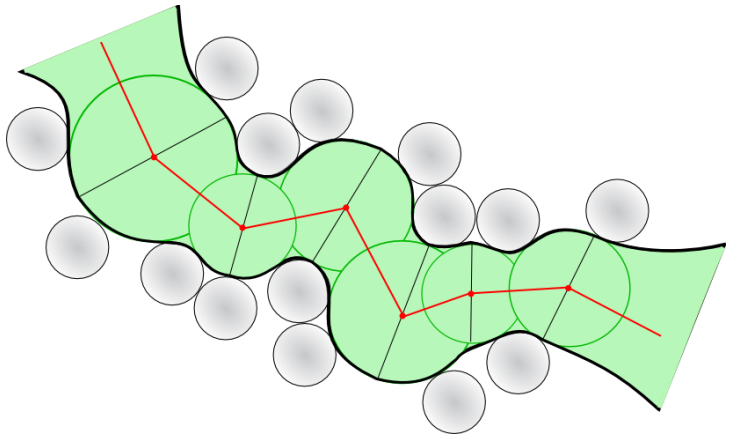
- **substrate**
  - small protein molecule (tens of atoms)



channel

- union of spheres with centres on the path that connect an active site with the boundary of the molecule and not intersect any atom

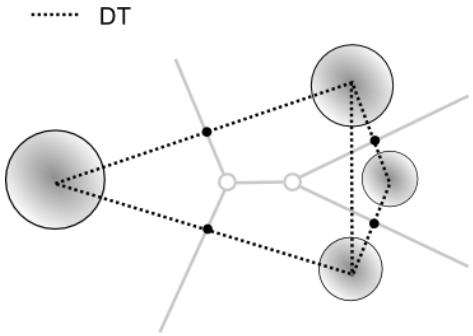




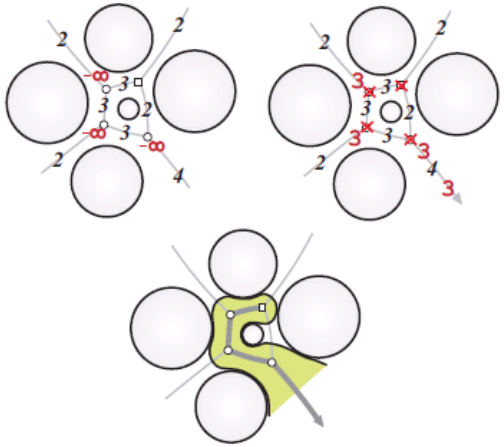
- channels are used by substrate to penetrate into protein
- existence of channels provide to chemists important information about protein behaviour and may emphasise places where the empty space is
- substrate penetration is important for instance during drug design

channel detection algorithms

- based on computational geometry
- utilizing Voronoi diagram and it's dual Delaunay triangulation

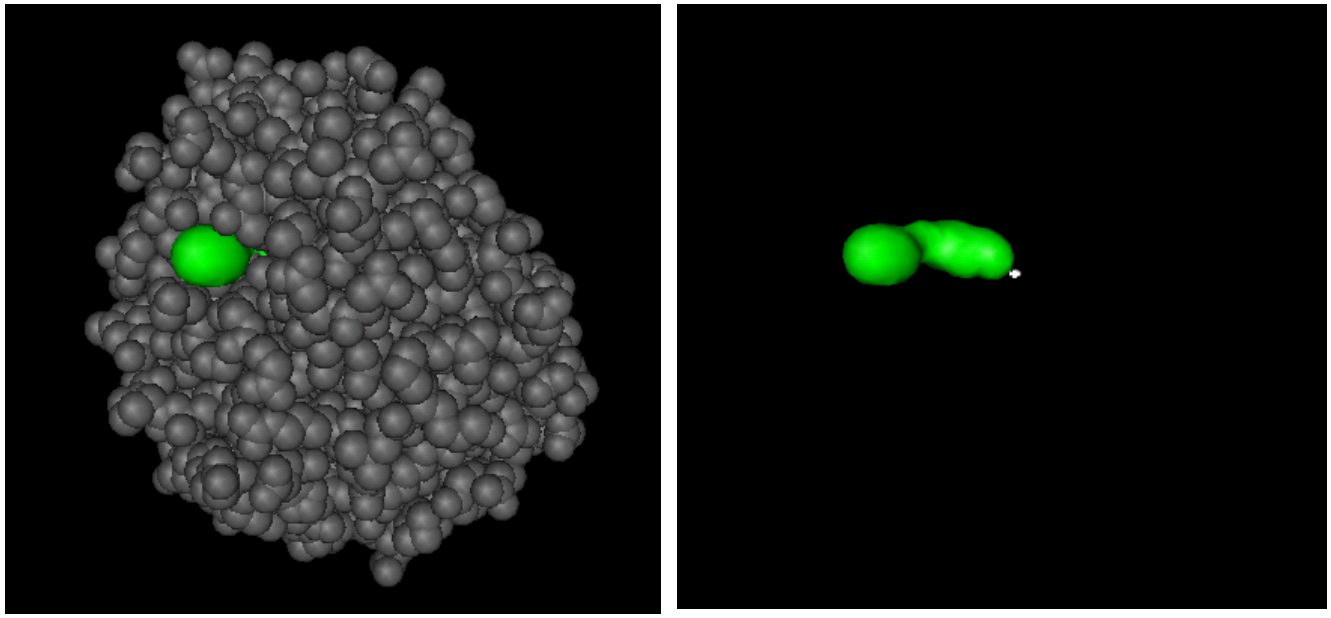


- and Dijkstra's algorithm (maximizing cost function)



channels in a single snapshot

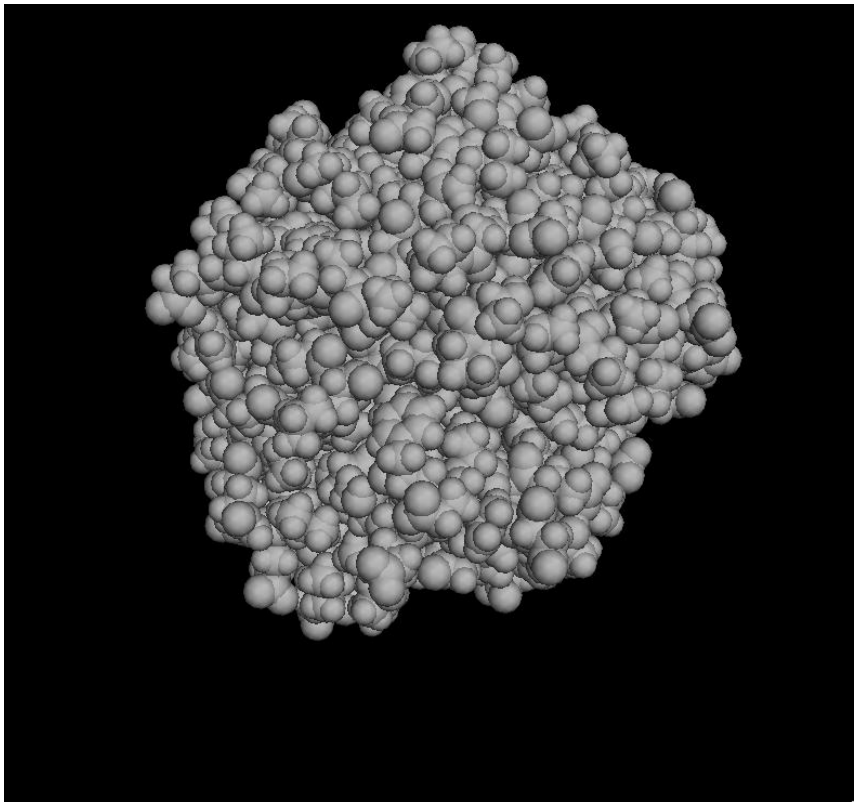
- we are able to detect channels in one snapshot (stored positions of all atoms in given time)



- a number of detecting channels is defined by the user

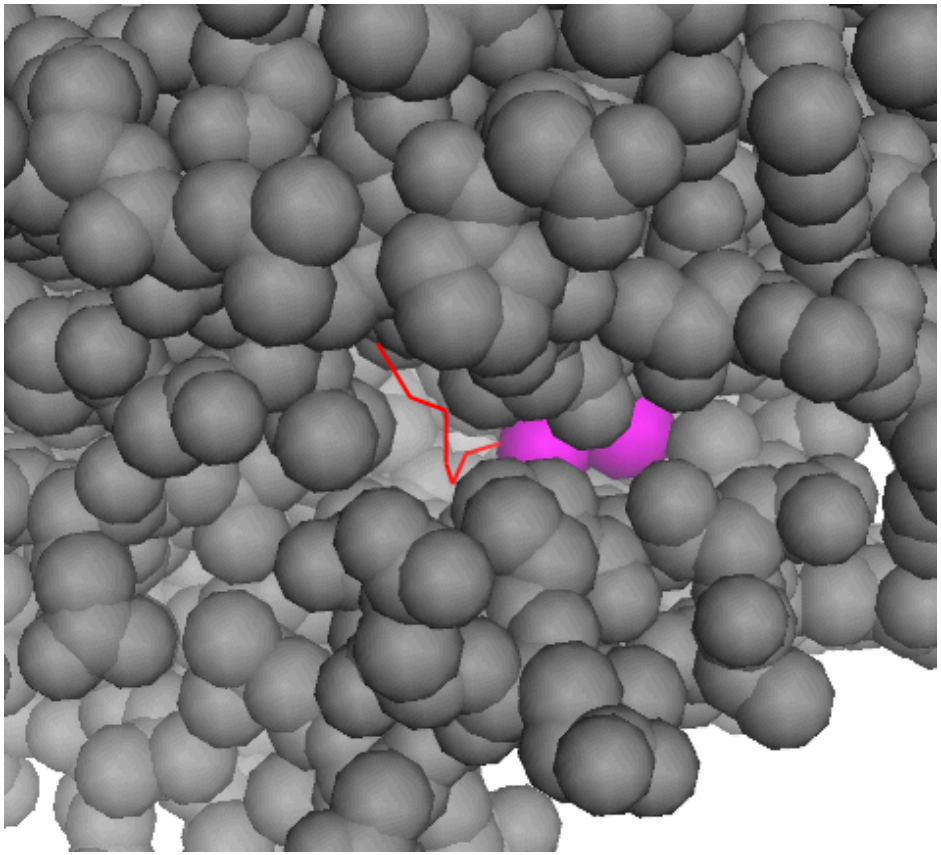
biochemical background

- in real life atoms in the protein do not remain still



channels in molecular dynamics

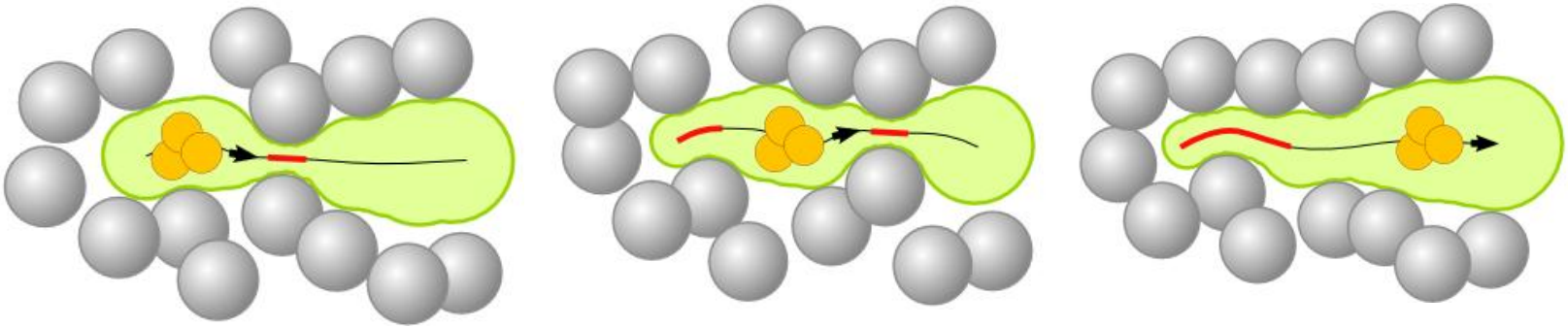
- sequence of snapshots – sampling frequency in [ns]



clustering

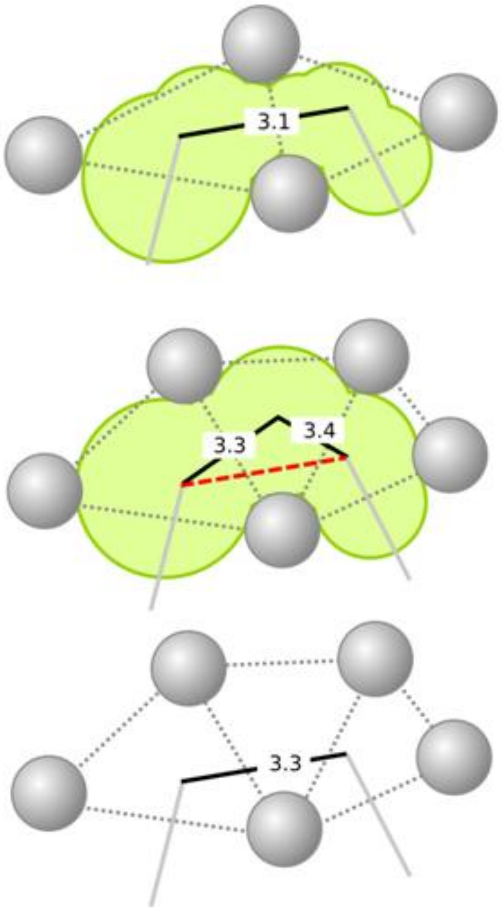
- more channels may seem to be similar – there may be only small differences in their path **in different snapshots**
- two channels which are closer than user-defined threshold are marked as similar and as members of one cluster
- clustering gives additional information about the parts in the protein where empty space is pulsing

channels in molecular dynamics



channels in molecular dynamics

1) create initial graph from a given snapshot
2) process another snapshot
   - track all edges
   - update the edge value where necessary
3) process Dijkstra's algorithm

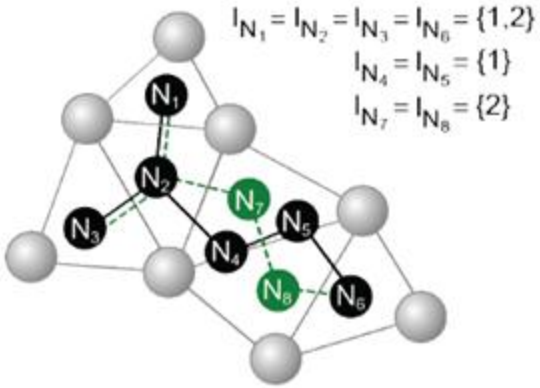


- number of edges remain the same
- emphasize pulsing parts

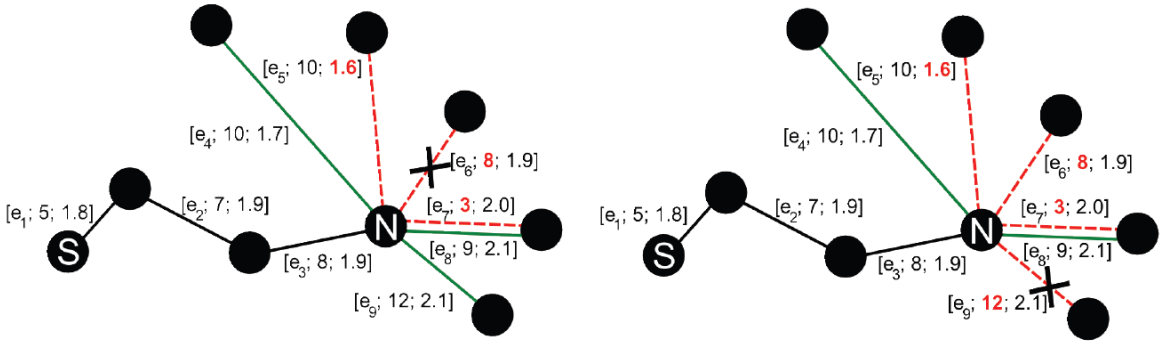
BENEŠ Petr, MEDEK Petr, STRNAD Ondřej, SOCHOR Jiří - Computation of Dynamic Channels in Proteins [BIOTECHNO 2011]

channels in molecular dynamics – constrained channels

- building one large multi-edge graph
  - generate huge amount of edges



- defining constraints in order to decrease the total number of traversing edges



BENEŠ Petr, STRNAD Ondřej, SOCHOR Jiří, New path planning method for computation of constrained dynamic channels in proteins [WSCG 2011]

current research

- continue with validation of biochemical relevance on different proteins
- with the increase of computational power, the chemists are capturing larger and larger proteins and longer sequence of snapshots
- try to investigate behaviour of our algorithms on very large proteins (hundreds of thousands of atoms) - optimization

another identified directions of research

- include some biochemical properties during the channel computation (van der Waals forces, …)
- channels with different shape of cross-section – maximizing the channel
- put the simulation of penetration of substrate into haptic environment (currently solved by Dr. Křenek and his team) and use it with our algorithms

availability of our algorithms

- Caver viewer
  - software developed by Caver team (HCI and Loschmidt laboratories)
  - available as Java-applet (www.caver.cz)

- Caver plugin for PyMOL

conclusion

- detecting channels in proteins is very important for biochemists
- we are able to detect channels in the single snapshot or sequence of snapshosts
- nowadays we are focusing on molecules with large amount of atoms
- results of our work are accessible for general public via Caver Viewer software

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Questions?