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Research review paper

Software tools for identification, visualization and analysis of protein tunnels and channels

Jan Brezovsky [a], Eva Chovancova [a], Artur Gora [a], Antonin Pavelka [a,b,c], Lada Biedermannova [a,1], Jiri Damborsky [a,c,*]

[a] Loschmidt Laboratories, Department of Experimental Biology and Research Centre for Toxic Compounds in the Environment, Faculty of Science, Masaryk University, Kamenice 5/A13, 625 00 Brno, Czech Republic
[b] Human Computer Interaction Laboratory, Faculty of Informatics, Masaryk University, Botanicka 68a, 602 00 Brno, Czech Republic
[c] International Clinical Research Center, St. Anne's University Hospital Brno, Pekarska 53, 656 91 Brno, Czech Republic

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ABSTRACT

Protein structures contain highly complex systems of voids, making up specific features such as surface clefts or grooves, pockets, protrusions, cavities, pores or channels, and tunnels. Many of them are essential for the migration of solvents, ions and small molecules through proteins, and their binding to the functional sites. Analysis of these structural features is very important for understanding of structure–function relationships, for the design of potential inhibitors or proteins with improved functional properties. Here we critically review existing software tools specialized in rapid identification, visualization, analysis and design of protein tunnels and channels. The strengths and weaknesses of individual tools are reported together with examples of their applications for the analysis and engineering of various biological systems. This review can assist users with selecting a proper software tool for study of their biological problem as well as highlighting possible avenues for further development of existing tools. Development of novel descriptors representing not only geometry, but also electrostatics, hydrophobicity or dynamics, is needed for reliable identification of biologically relevant tunnels and channels.

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* Corresponding author at: Loschmidt Laboratories, Department of Experimental Biology, Faculty of Science, Masaryk University, Kamenice 5/A4, 625 00 Brno, Czech Republic. Tel.: +420 549493467; fax: +420 549496302.
E-mail address: jiri@chemi.muni.cz (J. Damborsky).
[1] Present address: Laboratory of Biomolecular Recognition, Institute of Biotechnology AS CR, Videnska 1083, 142 20 Prague 4, Czech Republic.

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1. Introduction

The three dimensional structure of a protein is composed of tightly packed atoms (Richards, 1977). The packing is not perfect, and gives rise to the highly complex system of voids containing many specific features such as surface clefts or grooves, pockets, protrusions, cavities, channels or pores, and tunnels (Fig. 1). These features play an essential role in many biological processes, since they represent sites of interactions with ligands, ions, solvent molecules and other proteins or nucleic acids (Janin and Chothia, 1990; Rhodes and Burley, 2000; Zvelebil and Thornton, 1993). Channels through transmembrane proteins enable the selective transport of ions, small molecules and even large macromolecules across biological membranes (Bezanilla, 2008; Gold et al., 2007). The channel selectivity is determined by its geometry and composition of amino acid residues (Gouaux and Mackinnon, 2005). Channel dysfunctions have been related to various human diseases (Niemeyer et al., 2001). Protein cavities, clefts, grooves and pockets provide a suitable micro-environment for biochemical reactions. In many enzymes, the cavities are buried deeply inside the protein core, shielded from water molecules and accessible from the bulk solvent via tunnels (Petrek et al., 2006). The enzyme specificity is determined not only by protein-substrate interactions in the active site, but is also influenced by the selectivity of these access tunnels (Chaloupková et al., 2003). Similarly to the channels, the selectivity of the tunnels is governed by the size, shape, and physico-chemical properties of the residues lining it.

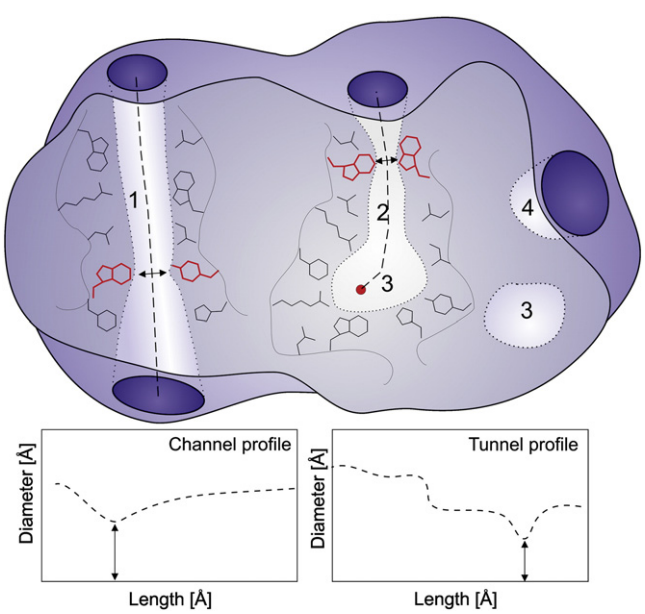

Fig. 1. Schematic representation of a protein with a channel/pore (1), a tunnel (2), a buried cavity (3) and a surface cleft/groove (4). Void interior is light purple, channel and tunnel entrance is dark purple, channel- and tunnel-lining residues are in black and bottleneck residues are in red. Arrows indicate a bottleneck; channel and tunnel profiles are shown at the bottom and correspond to the dashed line. The red dot in the buried cavity represents the starting point for the tunnel calculation.

The importance of pockets and cavities for protein function has been recognized for a long time, therefore, many tools for their identification and analysis have been developed, e.g., POCKET (Levitt and Banaszak, 1992), VOIDOO (Kleywegt and Jones, 1994), SURFNET (Laskowski, 1995), LIGSITE (Hendlich et al., 1997), CAST (Liang et al., 1998), PASS (Brady and Stouten, 2000), Q-SiteFinder (Laurie and Jackson, 2005), LigandFit (Venkatachalam et al., 2003), CASTp (Binkowski et al., 2003), SITEHOUND (Ghersi and Sanchez, 2009), SplitPocket (Tseng et al., 2009), Fpocket (Le Guilloux et al., 2009), and POCASA (Yu et al., 2010). A detailed discussion of the strengths, weaknesses and usability of some of these tools can be found in the review of Laurie and Jackson (Laurie and Jackson, 2006). These tools were designed to find functional pockets on the protein surface or cavities inside the protein, often overlooking tunnels connecting these cavities with the surrounding solvent. However, to study the ligand migration through the tunnels and channels, the molecular dynamics (MD) simulations can be recommended as a method of choice. Readers interested in the comparison of various MD simulation methods for the investigation of transport processes in proteins should refer to the recent review of Arroyo-Mañez and co-workers (Arroyo-Mañez et al., 2011). Setup, computation and analysis of such MD simulations usually require a lot of time and expertise. Therefore, several approximate methods for a direct study of tunnel and channel geometry have been recently developed (Coleman and Sharp, 2009; Ho and Gruswitz, 2008; Pellegrini-Calace et al., 2009; Petrek et al., 2006; Petrek et al., 2007; Smart et al., 1996; Voss and Gerstein, 2010; Yaffe et al., 2008a), representing another possibility to analyze ligand pathways in proteins. This review aims to critically compare these geometry-based methods, point out advantages and pitfalls in their usage, provide users with guidance on how to select appropriate tools for a particular problem and outline their possible practical applications.

2. Software tools for analysis of protein tunnels and channels

The current tools for analysis of protein tunnels and channels (Table 1) can be divided according to their aim to: (i) study of tunnels connecting buried cavities with bulk solvents—CAVER (Petrek et al., 2006), MOLE (Petrek et al., 2007) and MOLAXIS (Yaffe et al., 2008a); (ii) study of channels or pores penetrating throughout the proteins—HOLE (Smart et al., 1996), MOLAXIS (Yaffe et al., 2008a), CHUNNEL (Coleman and Sharp, 2009) and POREWALKER (Pellegrini-Calace et al., 2009); and (iii) analysis of overall voids in proteins—HOLLOW (Ho and Gruswitz, 2008) and 3V (Voss and Gerstein, 2010).

2.1. Software tools specialized in analysis of protein tunnels

These tools calculate tunnels connecting occluded protein cavities with the surrounding bulk solvent. Since finding a pathway from the protein surface to the internal cavity is not an easy task, all current tools are designed to solve the inverse definition of this problem—tracing the pathway from the internal cavity to the protein surface (Petrek et al., 2006, 2007; Yaffe et al., 2008a). All these methods employ Voronoi diagram (Fig. 2A) to describe a skeleton of voids within the protein structure. In this way, all possible pathways connecting the starting point in the internal cavity with the bulk solvent are

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