Structural bioinformatics

Voroprot: an interactive tool for the analysis and visualization of complex geometric features of protein structure

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ABSTRACT

Summary: We present Voroprot, an interactive cross-platform software tool that provides a unique set of capabilities for exploring geometric features of protein structure. Voroprot allows the construction and visualization of the Apollonius diagram (also known as the additively weighted Voronoi diagram), the Apollonius graph, protein alpha shapes, interatomic contact surfaces, solvent accessible surfaces, pockets and cavities inside protein structure.

Availability: Voroprot is available for Windows, Linux and Mac OS X operating systems and can be downloaded from http://www.ibt.lt/bioinformatics/voroprot/.

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1 INTRODUCTION

The ability to analyze and visualize geometric features of 3D protein structure is fundamental for studies of protein folding, residue packing, docking, protein–protein interactions, etc. Considering protein structure to be a set of points, each point corresponding to an atom, the use of the Voronoi diagram (Voronoi, 1908) and its dual, the Delaunay triangulation (Delaunay, 1934), offers a powerful approach in such analysis (Poupon, 2004). However, a more realistic representation of an atom is not a point, but the sphere of a Van der Waals radius. Considering protein structure to be a set of spheres, the more appropriate geometric data structures are the Apollonius diagram (also known as additively weighted Voronoi diagram) (Emiris and Karavelas, 2006) and its dual, Apollonius graph. Yet, so far both have been exploited for protein structure analysis only to a limited extent.

One of the few available tools, Voronoia (Rother *et al.*, 2009), uses the additively weighted Voronoi diagram to investigate protein structure packing. It is mainly a console tool, which provides a simplified drawing of inner cavities through a PyMOL plug-in, but does not allow a more advanced visualization. We are aware of two other reports describing the use of the Apollonius diagram for the visualization and analysis of protein structure (Kim *et al.*, 2005; Will, 1998), but the corresponding software is not publicly available. Other reported tools do not exploit the Apollonius diagram. For example, Voro3D (Dupuis *et al.*, 2005) uses an extension of the Voronoi tessellation of points. Its main drawback is that it represents each residue by a single point. Another program, PROVAT (Gore *et al.*, 2005), integrates Qhull (a tool used to compute Voronoi diagram of points) and PyMOL into a pipeline. Unfortunately, it

seems to be no longer publicly available. PyDeT (Ordog, 2008) also uses Qhull and PyMOL, but it only provides visualization of the Delaunay triangulation of protein structure.

Thus, although the Apollonius diagram and the Apollonius graph are powerful geometric constructs, their potential in studies of protein structure is far from being fully utilized. To remedy this situation, we developed Voroprot, a versatile protein structure analysis and visualization tool.

2 METHODS

Protein atoms are represented as spheres of Van der Waals radii. Accordingly, protein 3D structure is a geometric object formed by such spheres. We subdivide this object into quadruples of spheres, making sure that no tangent sphere of any quadruple overlaps any atom sphere. The subdivision is similar to the Delaunay triangulation, except that spheres are used instead of points and tangent spheres are used instead of circumspheres. We then construct a graph with atoms as vertices, where atoms are linked if they share at least one quadruple. This graph is known as the Apollonius graph (Emiris and Karavelas, 2006). It unequivocally defines a set of neighbors for each atom.

For each pair of neighboring atoms, we can define a hyperboloid, such that any point belonging to it is equidistant from both atoms. For each atom α, intersection of all the hyperboloids between α and its neighbors defines a space area, called the Voronoi cell (Goede *et al.*, 1997), consisting of all points closer to α than to any other atom. Such a tessellation, known as the additively weighted Voronoi diagram or the Apollonius diagram (Emiris and Karavelas, 2006), is similar to the Voronoi tessellation, except that spheres are used instead of points and hyperboloids are used instead of planes. Notably, the vertexes of each Voronoi cell are the centers of tangent spheres of quadruples from the previously described subdivision. For atoms at the protein surface, tangent spheres can be very large and Voronoi cells can be unbounded extending away from the protein surface.

We use the Apollonius graph and the Apollonius diagram to construct interatomic contact surfaces and a solvent-accessible surface. Having a protein structure subdivided into quadruples of atoms, we can also find internal cavities and pockets. A quadruple is a part of a cavity only if its tangent sphere cannot be accessed from the outside by a probe of the size of the solvent molecule (a larger probe can be used to find pockets). We also use a concept of Alpha Shape (Edelsbrunner and Mücke, 1994) in combination with the Apollonius graph to construct a triangulated representation of 3D protein structure. This representation is useful in the analysis of the curvature of protein structure surface.

In Voroprot, every constructed geometric object can be visualized. Voroprot is also capable of producing publication-quality images. The software is a stand-alone application written in C++ using Qt framework; 3D rendering is implemented using OpenGL.

3 USAGE EXAMPLES

Let us explore the 3D structure of recombinant human muscle fatty acid-binding protein (PDB id: 2HMB) with Voroprot. We load the

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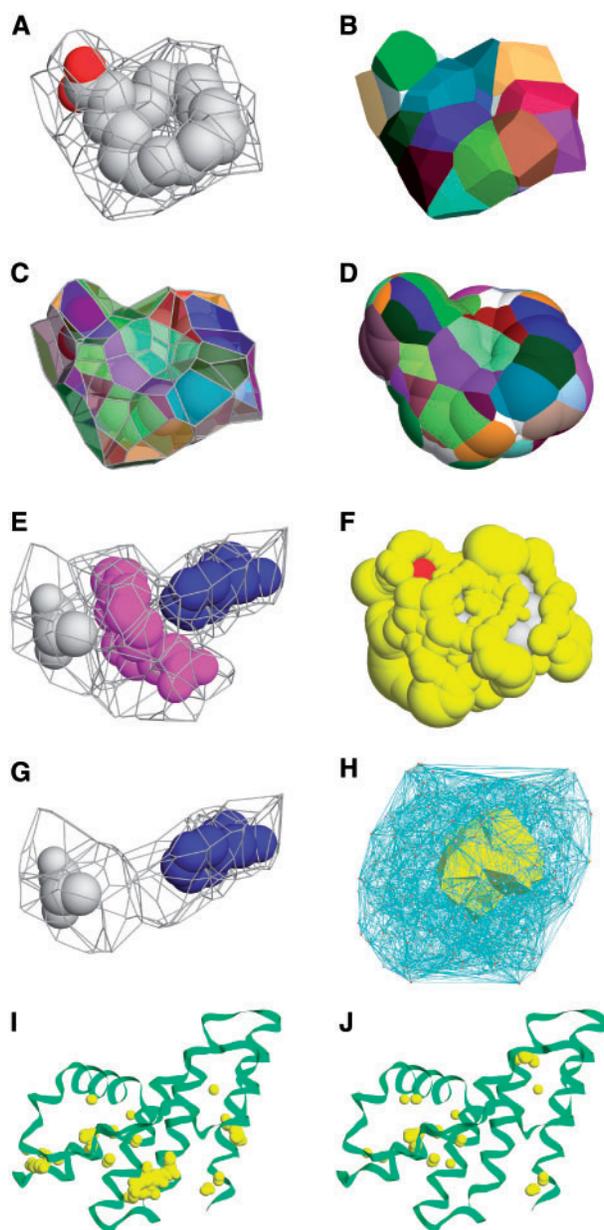
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Fig. 1. Images (**A**–**J**) created by Voroprot. See text for description.

structure file directly from PDB and construct an Apollonius diagram for it. We then select the ligand and display the Voronoi cells of its atoms colored in several ways (Fig. 1A–C). By clicking on the faces of Voronoi cells, we can identify the atoms that are the ligand neighbors. We also construct and display interatomic contact surfaces (Fig. 1D). We select and display two amino acids, Phe16 and Ala75, which have relatively large contact areas with the ligand (Fig. 1E). Additionally, we display the unoccupied space around the ligand using tangent spheres representation (yellow, Fig. 1F). Now let us load the same structure without the ligand. We construct the Apollonius diagram and display the Voronoi cells for Phe16 and Ala75 to see how the space is distributed between them (Fig. 1G).

Then we construct inner cavities and pockets with rolling probes of various sizes to find possible ligand binding sites. As expected, we find a big cavity, whose shape resembles the ligand and which is located in the place of the ligand (Fig. 1H).

Another example illustrates the level of detail that can be analyzed with Voroprot. Let us compare the cavities of the two crystal structures of prokaryotic phospholipase A2, 1FAZ and 1LWB, solved correspondingly at 1.4 and 1.05 Å resolution. The structures are very similar, producing the backbone root mean square deviation (RMSD) of 0.09 Å and the all-atom RMSD of 0.40 Å. We use Voroprot to find cavities inside these structures with a rolling probe of 0.8 Å radius (smaller than the radius of a water molecule, 1.4 Å). The identified cavities of 1LWB (Fig. 1I) differ significantly from the cavities of 1FAZ (Fig. 1J). Voroprot allows us to explain the observed differences. For example, if we select the residues surrounding the largest cavity in 1LWB and compare their side chain conformations with the conformations of the same residues in 1FAZ, we discover that the residue Ile84 acts as a gate. In 1LWB, its side chain blocks the rolling probe of 0.8 Å radius from entering the inter-residue space, which is thus treated as a cavity, while in 1FAZ a different rotamer of Ile84 does not hinder the probe from entering.

4 CONCLUSION

The Apollonius graph and the Apollonius diagram extensively exploited by Voroprot not only enable various representations of protein structure but also provide powerful analytical methods of solving complex computational geometry problems such as the detection of inner cavities, the delineation of interatomic contact areas and the surface curvature analysis.

Conflict of Interest: none declared.

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