

# Using Cavity Triangulation to Solve Different Problems in Protein Modeling

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Native structures of many proteins have cavities. A number of experiments has shown that changes in the size and the shape of the cavities influence considerably the stabilization energy of the protein structures.

Computational algorithms for detection and quantitative characterization of the cavities are usually based on the space filling geometry model of the protein by Lee and Richards [1] which interprets a protein as a union of mutually interpenetrating balls.

The first computational investigation of the cavities has been reported by Lee and Richards [1]. Rashin, et al. [2] have developed a program for detection of the internal cavities and for prediction of the positions of buried water molecules. Zhang and Hermans [3] used the molecular surface calculation algorithm [4] to calculate energies and free energies of a water molecule in cavities and discuss the hydrophobicity of protein cavities. In [5] is described an analytically exact method for computing the metric properties of macromolecules. Later this method has been applied to study quantitatively the inaccessible cavities in proteins [6].

Recently we have suggested a new efficient analytical algorithm for detection and analysis of internal cavities [7, 8]. The basic idea of the proposed method lies in the construction of a special *enveloping triangulation* such that the conclusion if any point from the space belongs or does not belong to the cavity depends only on the relation between the point and the triangulation, see Fig. 1. Our objective for this work has been to develop our own cavity detection software for the protein simulation package SMMP [9] which has been used widely to study structures and thermal properties of proteins.

Based on this method, we develop an algorithm and a fortran package, CAVE, for computing volumes and surface areas of cavities in proteins. We first test our method and algorithm in some artificial systems of spheres and find that the calculated results are consistent with exact results. Then we apply the package to compute volumes and surface areas of cavities for some protein structures in the Protein Data Bank. We compare our calculated results with those obtained by some other methods

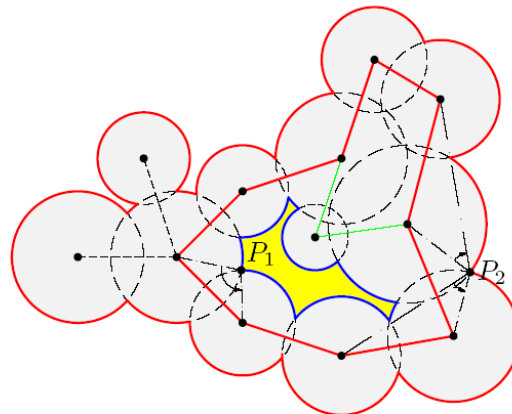


Figure 1: 2D analogy for triangulation

and find that our approach is reliable [7].

Electrostatic potential  $u$  is described by nonlinear Poisson-Boltzmann equation:

$$-\nabla \cdot [\varepsilon(\vec{r}) \nabla u(\vec{r})] + k^2(\vec{r}) \sinh [u(\vec{r})] = \\ = \frac{4\pi e_c^2}{k_B T} \sum_{i=1}^{N_m} z_i \delta(\vec{r} - \vec{r}_i), \quad u(\infty) = 0,$$

$$\text{dielectric constant } \varepsilon = \begin{cases} 2 & \text{inside molecule,} \\ 80 & \text{in water.} \end{cases}$$

Numerical solutions to the Poisson-Boltzmann equation (both linear and nonlinear form) for molecules of arbitrary shape and charge distribution provides, e.g., software DelPhi using finite difference algorithm [10, 11, 12, 13, 14]. The ‘molecular’ value of dielectric constant  $\varepsilon$  should be set at all grid points inside the molecular surface of a molecule.

The idea of molecular surface was defined by [15], when the authors introduced the contact surface. The contact surface is the part of the van der Waals surface that can be touched by a water-sized probe sphere. Soon afterwards, Richards introduced the reentrant surface, which together with the contact surface form the *molecular surface* [16]. The reentrant surface consists of the inward-facing part of the probe sphere when it is in contact with more than one atom.

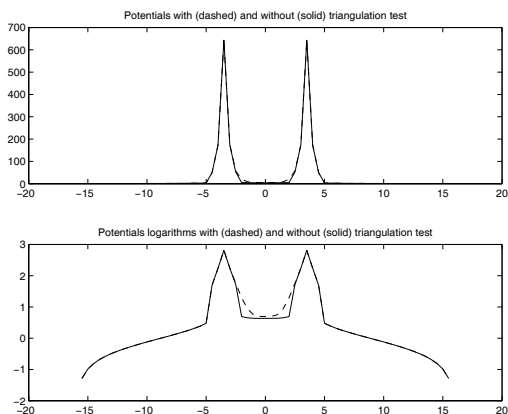


Figure 2: Potentials calculated for six atoms with radii  $r_a = 1.501$ , and probe radius  $r_w = 1.401$

Consider the van der Waals space area of a molecule as the union of a system of intersected balls  $\mathcal{B}_i$  representing atoms which are given by their centers  $C_i = (x_i, y_i, z_i)$  in a Cartesian coordinate system and radii  $r_i$ . A molecule of solvent is taken as an additional ball of given radius  $r_s$  outside of the van der Waals area which is forbidden to intersect by the solvent sphere. The solvent is allowed to roll over its outer surfaces at most. The question is: “How to identify if a given point is or not accessible to any point of a wandering solvent ball?” Videlicet, we are looking for an indicator of the part of space which is inaccessible by solvent sphere flying around. This area is bounded by the outermost part of the molecular surface.

In [17] we proposed four tests to identify the position of any grid point. The **first class** of points are internal points of the van der Waals area. The **second class** consists of such points  $X = (x, y, z)$  that there are two different balls  $\mathcal{B}_i$  and  $\mathcal{B}_j$  that are close to point  $X$  and each to other less than diameter  $2r_s$  of the solvent sphere. If point  $X = (x, y, z)$  belongs to the **third class** then there are three different balls  $\mathcal{B}_i, \mathcal{B}_j, \mathcal{B}_k$  generating a wall triangle that are close to point  $X$  at the distance less than  $2r_s$ . The **fourth class** is constituted by such points  $X$  which are inside the envelope triangulation (see [7, 8]) but accessible neither from any outer intersection point  $E_{ijk}$  nor from any arc with radius less than  $r_s$  on the outer accessible surface connecting two such points.

Fig. 2 shows potentials calculated for six atoms with radii  $r_a = 1.501$  placed at the distance 3.5 from the origin on the  $x, y,$  and  $z$  axes, and for probe radius  $r_w = 1.401$ . The results show that there are significant differences between the potential values calculated with and without including cavities test for the fourth class. The recent version of the program is not so efficient like the Sanner et al. approach to the reduced surface construction [20].

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