

UDC 519.632, 544.139, 538.911

Identification of Internal Points of Macromolecular System for the Definition of the Parameters of a Poisson-Boltzmann Equation

J. Buša*, I. Pokorný*, E. A. Hayryan†, J. Skřivánek‡

* *Technical University in Košice
Letná 9, 04001 Košice, Slovak Republic*

† *Laboratory of Information Technologies
Joint Institute for Nuclear Research
Joliot-Curie 6, 141980 Dubna, Moscow region, Russia*

‡ *SORS Research
Strojársená 3, 040 01 Košice, Slovak Republic*

Systems of overlapping spheres are widely used in macromolecular modeling, where atoms are represented by spheres. Study of geometric properties of such systems, like the surface area, the volume or the existence of internal cavities is important because of their physical applications. In this paper the cavity triangulation is applied to identify internal grid points for the numerical solution of the Poisson-Boltzmann equation describing the electrostatic potential of macromolecule.

Key words and phrases: Poisson-Boltzmann equation, macromolecular modeling, numerical solution.

1. Introduction

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]. 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. Our objective for this work has been to develop our own cavity detection software for the protein simulation package SMMP [8] which has been used widely to study structures and thermal properties of proteins.

Received 28th November, 2009.

The work was supported by grants NSC 96-2911-M 001-003-MY3, AS-95-TP-A07, and National Center for Theoretical Sciences in Taiwan, by VEGA grant 1/0819/08 of Slovak Grant Agency, and by Russian RFBR Grants 08-01-00800-a and 07-01-00738-a.

2. Poisson–Boltzmann Equation

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

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

$$u(\infty) = 0, \quad \text{dielectric constant } \varepsilon = \begin{cases} 2 & \text{inside molecule,} \\ 80 & \text{in water.} \end{cases}$$

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 [9–13]. The “molecular” value of dielectric constant ε should be set at all grid points inside the molecular surface of a molecule.

3. Molecular Surface Identifier

The idea of molecular surface was defined by [14], 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* [15]. The reentrant surface consists of the inward-facing part of the probe sphere when it is in contact with more than one atom.

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.

The **first class** of points which are indicated by value 1 are internal points of the van der Waals area. These points $X = (x, y, z)$ are inside of some balls \mathcal{B}_i and accordingly satisfy the inequality

$$\|X - C_i\| < r_i \text{ for some ball } \mathcal{B}_i, \quad (1)$$

where $\|X - C_i\| = \sqrt{(x - x_i)^2 + (y - y_i)^2 + (z - z_i)^2}$.

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. So, they satisfy inequalities

$$\begin{aligned} \|X - C_m\| &< r_m + 2r_s \text{ for each } m \in \{i, j\}, \\ \|C_i - C_j\| &< r_i + r_j + 2r_s. \end{aligned} \quad (2)$$

If the solvent ball is rolling over balls \mathcal{B}_i , \mathcal{B}_j and touching both, it designs a torus (potentially degenerate). Connecting lines of the solvent center and centers of balls \mathcal{B}_i and \mathcal{B}_j design two conical surfaces. For some couple of balls \mathcal{B}_i , \mathcal{B}_j satisfying (2), the point X is inside of both cones (with the scalar product of vectors on the left side)

and outside of the torus

$$\begin{aligned}
(X - C_i) \cdot (C_j - C_i) &> \frac{\|C_j - C_i\|^2 + (r_i + r_s)^2 - (r_j + r_s)^2}{2(r_i + r_s)} \|X - C_i\|, \\
(X - C_j) \cdot (C_i - C_j) &> \frac{\|C_i - C_j\|^2 + (r_j + r_s)^2 - (r_i + r_s)^2}{2(r_j + r_s)} \|X - C_j\|, \\
\|X - D_{ij}\|^2 + R_{ij}^2 &> 2R_{ij} \text{dist}\left(X, \overleftrightarrow{C_i C_j}\right) + r_s^2,
\end{aligned} \tag{3}$$

where

$$D_{ij} = C_i + \left(\frac{1}{2} + \frac{(r_i + r_s)^2 - (r_j + r_s)^2}{2\|C_j - C_i\|^2} \right) (C_j - C_i)$$

and

$$R_{ij} = \sqrt{\frac{(r_i + r_s)^2 + (r_j + r_s)^2}{2} - \frac{\|C_j - C_i\|^2}{4} - \frac{((r_i + r_s)^2 - (r_j + r_s)^2)^2}{4\|C_j - C_i\|^2}}$$

are the center and the radius of the torus. The distance X from the axis of rotation $\overleftrightarrow{C_i C_j}$ of the torus is

$$\text{dist}\left(X, \overleftrightarrow{C_i C_j}\right) = \frac{\|(X - C_i) \times (C_j - C_i)\|}{\|C_j - C_i\|}$$

(with the cross vector product in the numerator). Membership in several classes is possible.

For purposes of quantification of hydrophobic burial [16], Lee and Richards defined the solvent-accessible surface [1]. The *accessible surface* is traced out by the probe sphere center as it rolls over the protein. It is a kind of expanded van der Waals surface. If you increase each atom's van der Waals radius by the probe radius, you get so-called expanded atom radii. The union of the expanded atoms is what Richmond calls the solvent-excluded volume [17]. It is the region enclosed by the accessible surface.

In order to indicate if a point is or not inside a cavity created by accessible surface area, the authors of [7] introduced the *wall triangle*. It is such triangle $\Delta C_i C_j C_k$ of centers of spheres that there exists a point $F_{ijk} = (x_F, y_F, z_F)$ inside each sphere \mathcal{B}_i , \mathcal{B}_j and \mathcal{B}_k ($\|F_{ijk} - C_m\| < r_m$ for each $m \in \{i, j, k\}$) which satisfies

$$\begin{aligned}
(x_j - x_i)x_F + (y_j - y_i)y_F + (z_j - z_i)z_F &= \\
&= \frac{1}{2} \left((r_i + r_s)^2 - (r_j + r_s)^2 - x_i^2 + x_j^2 - y_i^2 + y_j^2 - z_i^2 + z_j^2 \right),
\end{aligned}$$

$$\begin{aligned}
(x_k - x_i)x_F + (y_k - y_i)y_F + (z_k - z_i)z_F &= \\
&= \frac{1}{2} \left((r_i + r_s)^2 - (r_k + r_s)^2 - x_i^2 + x_k^2 - y_i^2 + y_k^2 - z_i^2 + z_k^2 \right),
\end{aligned}$$

$$\begin{vmatrix} x_F - x_i & y_F - y_i & z_F - z_i \\ x_j - x_i & y_j - y_i & z_j - z_i \\ x_k - x_i & y_k - y_i & z_k - z_i \end{vmatrix} = 0.$$

It means the expanded spheres with the centers C_i , C_j , C_k , and radii $r_i + r_s$, $r_j + r_s$, $r_k + r_s$ have just two different common points E_{ijk} and E'_{ijk} . Moreover, the vectors $C_i - E$, $C_j - E$ and $C_k - E$ are independent for both E_{ijk} and E'_{ijk} in role E .

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 $2r_s$. So, it satisfies inequalities

$$\|X - C_m\| < r_m + 2r_s \text{ for each } m \in \{i, j, k\}. \quad (4)$$

The point X is outside solvent spheres positioned by their centers in E_{ijk} and E'_{ijk} but inside one of tetrahedrons $C_i C_j C_k E_{ijk}$ and $C_i C_j C_k E'_{ijk}$. So, $X - E$ is a convex combination of $C_i - E$, $C_j - E$ and $C_k - E$.

$$\|X - E\| > s, \quad \alpha_m \geq 0 \text{ and } \sum_{m=1}^3 \alpha_m \leq 1, \quad (5)$$

where $X - E = \alpha_1(C_i - E) + \alpha_2(C_j - E) + \alpha_3(C_k - E)$ for some triplet $\mathcal{B}_i, \mathcal{B}_j, \mathcal{B}_k$ satisfying (4) and E_{ijk} or E'_{ijk} in role E .

The method developed in [7] takes the *envelope triangulation* $\Delta\mathcal{M}$ as a system of closed polyhedrons whose facets represent inwardly oriented wall triangles of the outermost balls. A point X inside a cavity of the accessible surface is inside the envelope triangulation too. So, the compound oriented spherical angle $4\pi\chi_X(\Delta\mathcal{M})$ (see, [18–20]) accordant with the envelope triangulation viewed from any point X not included in any ball \mathcal{B}_i is 4π if X is inside the triangulation and the angle is 0 if it is outside.

The **fourth class** is constituted by such points X which are inside the envelope triangulation but accessible neither from any outer intersection point E_{ijk} nor from any arc with radius less than s on the outer accessible surface connecting two such points

$$\chi_X(\Delta\mathcal{M}) = 1, \quad \|X - E_{ijk}\| > r_s \text{ for all } \Delta C_i C_j C_k \in \Delta\mathcal{M}. \quad (6)$$

4. Numerical Result

Fig. 1 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.

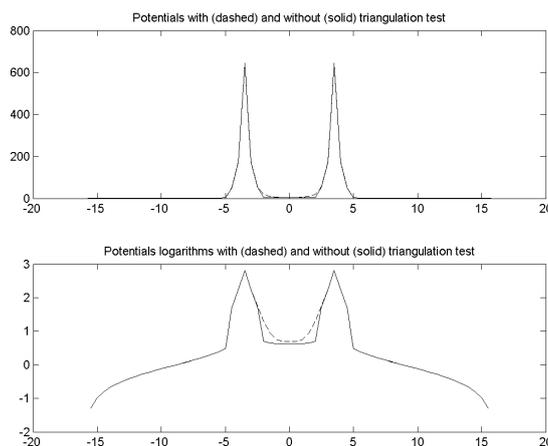


Figure 1. Potentials calculated for six atoms with radii $r_a = 1.501$, and probe radius $r_w = 1.401$

5. Conclusions

The cavity triangulation enables us to get the information about the cavities positions. Using the cavity triangulation one can get the information about the point position with respect to the possible cavities. It may be included into a program for solving Poisson-Boltzmann equation. The recent version of the program is not so efficient like the Sanner et al. approach to the reduced surface construction [21].

References

1. *Lee B., Richards F. M.* The Interpretation of Protein Structures: Estimation of Static Accessibility // *J. Mol. Biol.* — 1971. — Vol. 55. — Pp. 379–400.
2. *Rashin A. A., Iofin M., Honig B.* Internal Cavities and Buried Waters in Globular Proteins // *Biochemistry.* — 1986. — Vol. 25. — Pp. 3619–3625.
3. *Zhang L., Hermans J.* Hydrophilicity of Cavities in Proteins // *Proteins.* — 1996. — Vol. 24. — Pp. 433–438.
4. *Connolly M. L.* Solvent-Accessible Surfaces of Proteins and Nucleic-Acids // *Science.* — 1983. — Vol. 221. — Pp. 709–713.
5. Analytical Shape Computation of Macromolecules: I. Molecular Area and Volume Through Alpha Shape / *J. Liang, H. Edelsbrunner, P. Fu et al.* // *Proteins: Structure, Function, and Genetics.* — 1998. — Vol. 33. — Pp. 1–17.
6. Analytical Shape Computation of Macromolecules: II. Inaccessible Cavities in Proteins / *J. Liang, H. Edelsbrunner, P. Fu et al.* // *Proteins: Structure, Function, and Genetics.* — 1998. — Vol. 33. — Pp. 18–29.
7. Enveloping Triangulation Method for Detecting Internal Cavities in Proteins and Algorithm for Computing Their Surface Areas and Volumes / *J. Buša, S. Hayryan, C.-K. Hu et al.* // *Journal of Computational Chemistry.* — 2009. — Vol. 30, No 3. — Pp. 346–357.
8. [SMMP] A Modern Package for Simulation of Proteins / *F. Eisenmenger, U. H. E. Hansmann, S. Hayryan, C.-K. Hu* // *Comput. Phys. Commun.* — 2001. — Vol. 138. — Pp. 192–212.
9. *Rocchia W., Alexov E., Honig B.* Extending the Applicability of the Nonlinear Poisson-Boltzmann Equation: Multiple Dielectric Constants and Multivalent Ions // *J. Phys. Chem. B.* — 2001. — Vol. 105, No 28. — Pp. 6507–6514.
10. *Honig B., Nicholls A.* Classical Electrostatics in Biology and Chemistry // *Science.* — 1995. — Vol. 268, No 5214. — Pp. 1144–1149.
11. *Nicholls A., Honig B.* A Rapid Finite Difference Algorithm, Utilizing Successive Over-Relaxation to Solve the Poisson-Boltzmann Equation // *J. Comp. Chem.* — 1991. — Vol. 12. — Pp. 435–445.
12. *Gilson M., Honig B.* Calculation of the Total Electrostatic Energy of a Macromolecular System: Solvation Energies, Binding Energies and Conformational Analysis // *Proteins.* — 1998. — Vol. 4. — Pp. 7–18.
13. *Gilson M. K., Sharp K., Honig B.* Calculating the Electrostatic Potential of Molecules in Solution: Method and Error Assessment // *J. Comp. Chem.* — 1987. — Vol. 9. — Pp. 327–335.
14. *Richmond T.J., Richards F.M.* Packing of α -Helices: Geometrical Constraints and Contact Areas // *J. Mol. Biol.* — 1978. — Vol. 119. — Pp. 537–555.
15. *Richards F. M.* Areas, Volumes, Packing and Protein Structure // *Annu. Rev. Biophys. Bioeng.* — 1977. — Vol. 6. — Pp. 151–176.
16. *Chothia C.* Hydrophobic Bonding and Accessible Surface Area in Proteins // *Nature.* — 1974. — Vol. 248. — Pp. 338–339.
17. *Richmond T. J.* Solvent Accessible Surface Area and Excluded Volume in Proteins. Analytical Equations for Overlapping Spheres and Implications for the Hydrophobic Effect // *J. Mol. Biol.* — 1984. — Vol. 178. — Pp. 63–89.
18. Spherical Triangle. — 2008. — <http://mathworld.wolfram.com/SphericalTriangle.html>.

19. Spherical Trigonometry. — 2008. — <http://mathworld.wolfram.com/SphericalTrigonometry.htm>.
20. The Course of Spherical Geometry. — 2008. — <http://www.shef.ac.uk/phys/people/vdhillon/Teaching/>.
21. *Sanner M. F., Olson A. J., Spohner J.-C.* REDUCED SURFACE: an Efficient Way to Compute Molecular Surfaces // Biopolymers. — 1996. — Vol. 38, No 3. — Pp. 305–320.

УДК 519.632, 544.139, 538.911

Идентификация внутренних точек макромолекулярных систем для установления параметров уравнения Пуассона–Больцмана

Я. Буша*, И. Покорны*, Э. А. Айрян†, Я. Скрживанек‡

* *Технический университет Кошице
ул. Летна, д.9, Кошице, 04001, Словакия*

† *Лаборатория информационных технологий
Объединённый институт ядерных исследований
ул. Жолио-Кюри, д.6, Дубна, Московская область, 141980, Россия*

‡ *SORS Research, Строяренска, 3, 04001, Кошице, Словакия*

Системы пересекающихся сфер широко используются в моделировании макромолекул, где атомы представлены сферами. Изучение геометрических свойств таких систем как площадь поверхности и объём области или существование внутренних полостей важно в силу их физических применений. В этой работе применена триангуляция полостей для идентификации внутренних точек сетки для численного решения уравнения Пуассона–Больцмана, описывающего электростатический потенциал макромолекулы.

Ключевые слова: уравнение Пуассона–Больцмана, макромолекулярное моделирование, численное решение.