# Identification of Internal Points of Macromolecular System for Statement of Parameters of Poisson-Boltzmann Equation

Ján Buša[a,b,c], Edik Hayryan[b,c], Shura Hayryan[c], Chin-Kun Hu[c], Imrich Pokorný[a,b], Jaroslav Skřivánek[b,c,d]

[a] Technical University in Košice, 040 01 Košice, Slovak Republic
[b] Joint Institute for Nuclear Research, 141 980 Dubna, Moscow Region, Russia
[c] Institute of Physics, Academia Sinica, Nankang, Taipei 11529, Taiwan
[d] SORS Research, 040 01 Košice, Slovak Republic

Back

Close

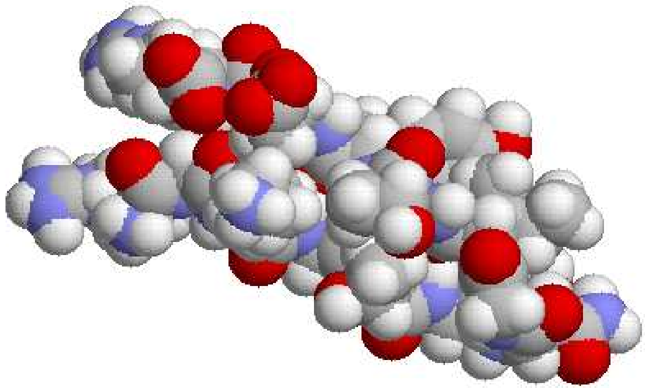


Figure 1: The 14-residue peptide rg-kwty-ng-itye-gr

Nonlinear Poisson-Boltzmann equation for electrostatic potential $u$:

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

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

The existence of cavities should be taken into account when solving different problems connected to the molecular properties.

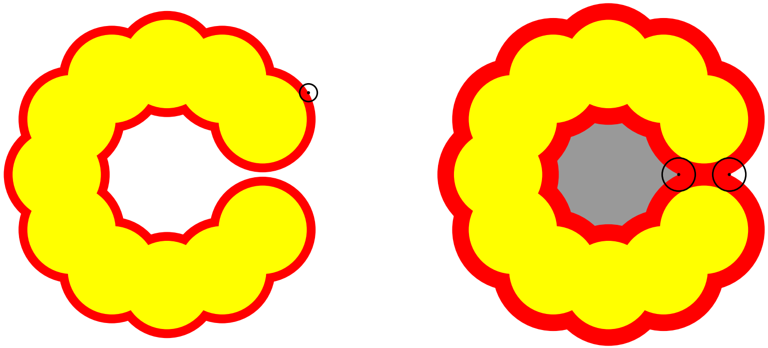


Figure 2: A molecule (yellow) without (left) and with (right) a cavity

Different positions of a point:[1]

1. The point is outside of the molecule's envelope (inside solvent accessible volume) — white color.
2. The point is inside of some molecule's atom — yellow color.
3. The point is outside a molecule, but inside its neighborhood of size equal to the solvent radius — red color.
4. The point is inside a molecule's cavity — gray color.

[1] The cavity existence depends on the probe spheres radius.

# 2D inspiration of triangulation

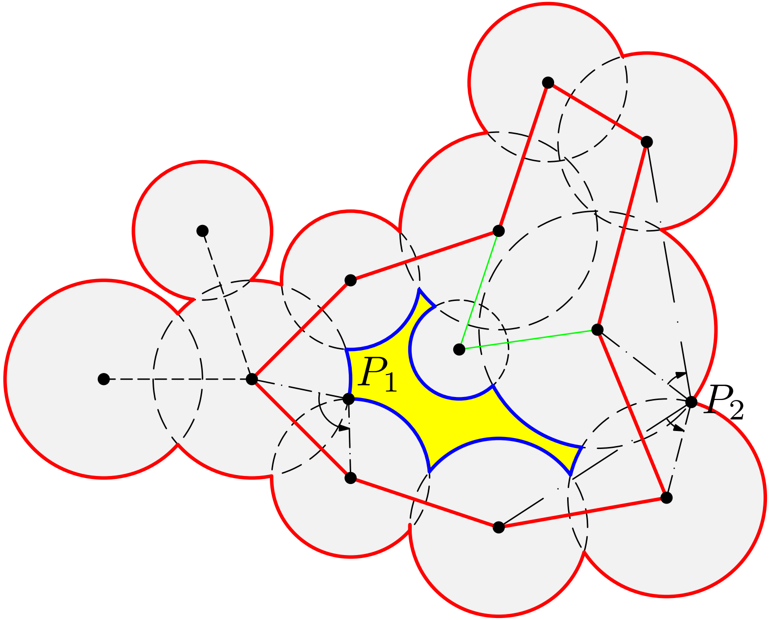



Figure 3: 2D analogy for triangulation

The sum of oriented angles for an internal point $P_1$ is equal $2\pi$ rad (in 3D $4\pi$ steradian), for an external point $P_2$ it is equal 0.

Let $\mathcal{M} = \bigcup_{i=1}^{N} \mathcal{S}_i$ be a finite union of spheres in $E_3$ — $\mathcal{M}$ is a molecule's model, in which atoms are represented by spheres.

**Definition 1** *The triangle $\Delta C_1C_2C_3$ of centres of spheres of $\mathcal{M}$ is a* wall triangle *in $\mathcal{M}$ if and only if the intersection $\delta\mathcal{S}_1 \cap \delta\mathcal{S}_2 \cap \delta\mathcal{S}_3$ of the surfaces of the spheres consists just of one or two points, and at least one of them is external, it does not lie in Int $\mathcal{M}$.*

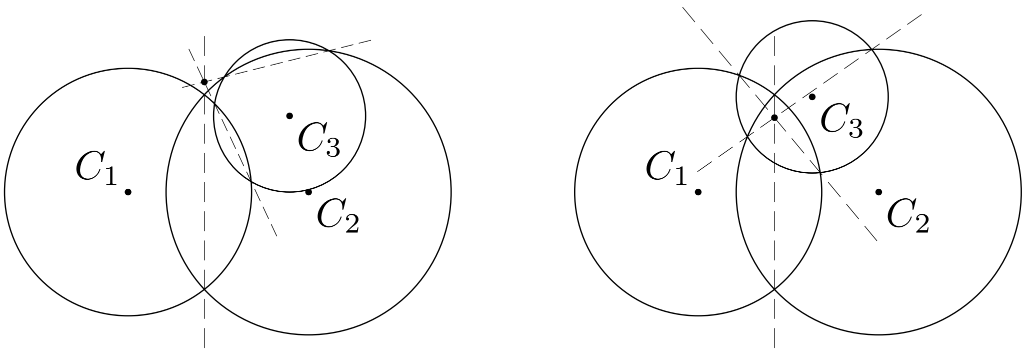



Figure 4: Nonwall and wall triangles

**Definition 2** *A* cavities enveloping triangulation $\Delta\mathcal{M}$ *(briefly* envelope triangulation*) of a finite system of spheres $\mathcal{M}$ is either an empty set or it is such a set of* wall triangles *in $\mathcal{M}$ with coincident orientation that*

*(i) $\Delta\mathcal{M}$ forms a family of polyhedral $\mathcal{P}_i$ with wall triangles at post of faces oriented inward such that Int $\mathcal{P}_i \cap$ Int $\mathcal{P}_j = \emptyset$, for all $i \neq j$,*

*(ii) any cavity point lies inside of some of these polyhedrons,*

*(iii) if a point from $E_3 - \mathcal{M}$ is not included in any cavity of $\mathcal{M}$, it lies outside of the triangulation $\Delta\mathcal{M}$.*

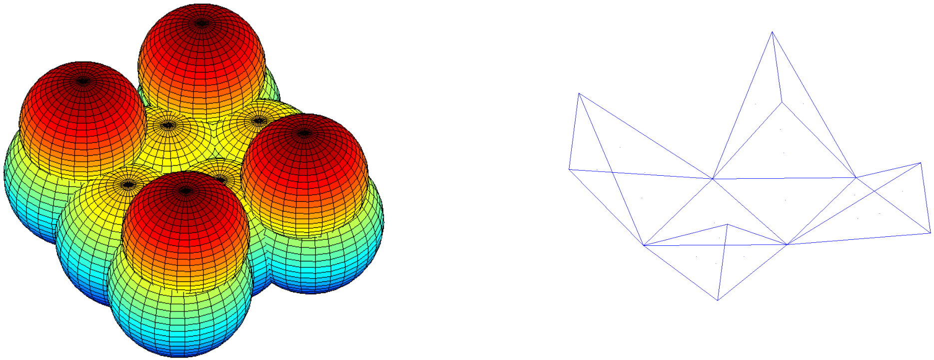


Figure 5: Cavity triangulation

Back

Close

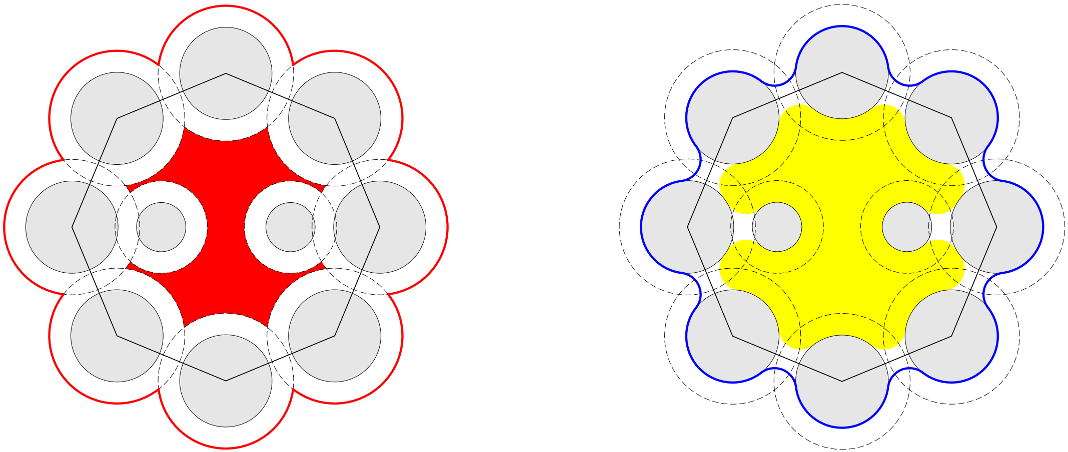


Figure 6: Two different definitions of the cavity volume. The molecule's atoms are lightgray. Red area in the left picture represents the volume of the part of the space, where the center of "water atom" can be put. The yellow right cavity volume [3] is the "volume of the water" included inside the molecule. Molecular surface [3] is blue. The definitions are equivalent if the probe radius $r_p = 0$.

- The solvent accessible surface introduced by Lee and Richards [1], and Chothia [2], is traced out by the probe sphere center as the sphere rolls over the molecular surface of the protein.
- The solvent-excluded or inaccessible volume is the volume contained within the solvent accessible surface.

# Numerical result

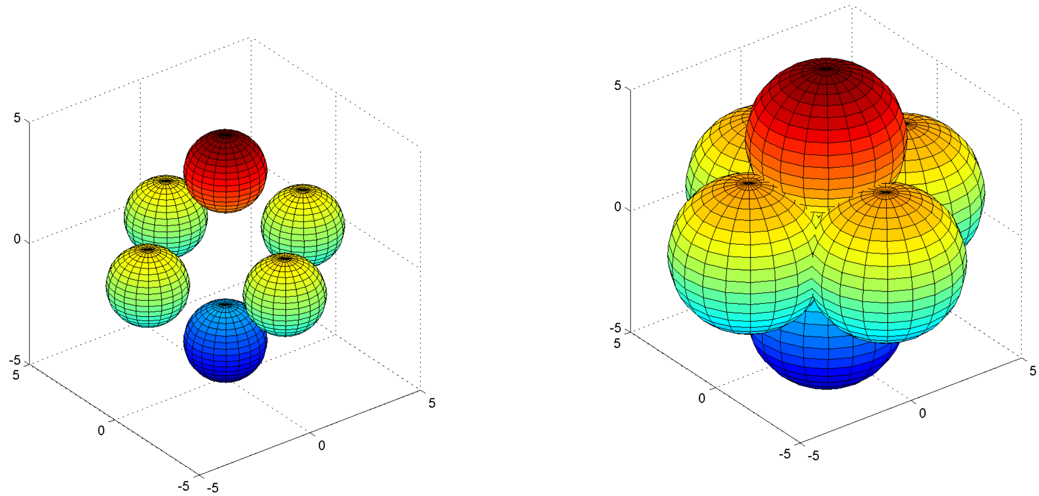


Figure 7: 6 atoms from file `jan6.pdb` – $r_a = 1.501$, $r_w = 1.401$

```
ATOM      1  O   MET    41       3.500   0.000   0.000  2.00  2.04           O
ATOM      2  O   MET    41       0.000   3.500   0.000  2.00  2.04           O
ATOM      3  O   MET    41       0.000   0.000   3.500  2.00  2.04           O
ATOM      4  O   MET    41      -3.500   0.000   0.000  2.00  2.04           O
ATOM      5  O   MET    41       0.000  -3.500   0.000  2.00  2.04           O
ATOM      6  O   MET    41       0.000   0.000  -3.500  2.00  2.04           O
```

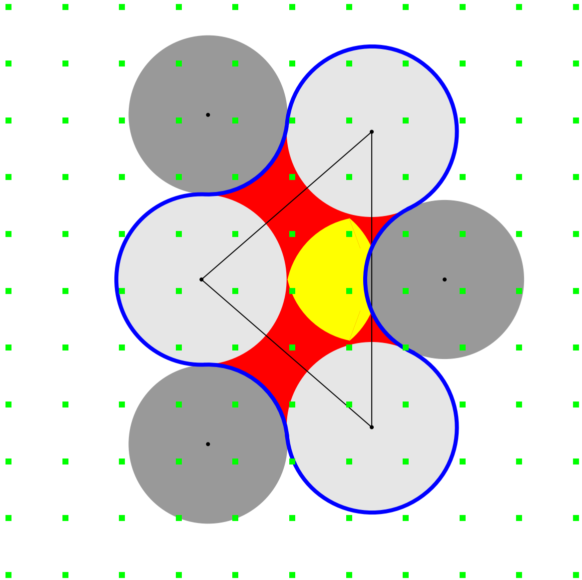
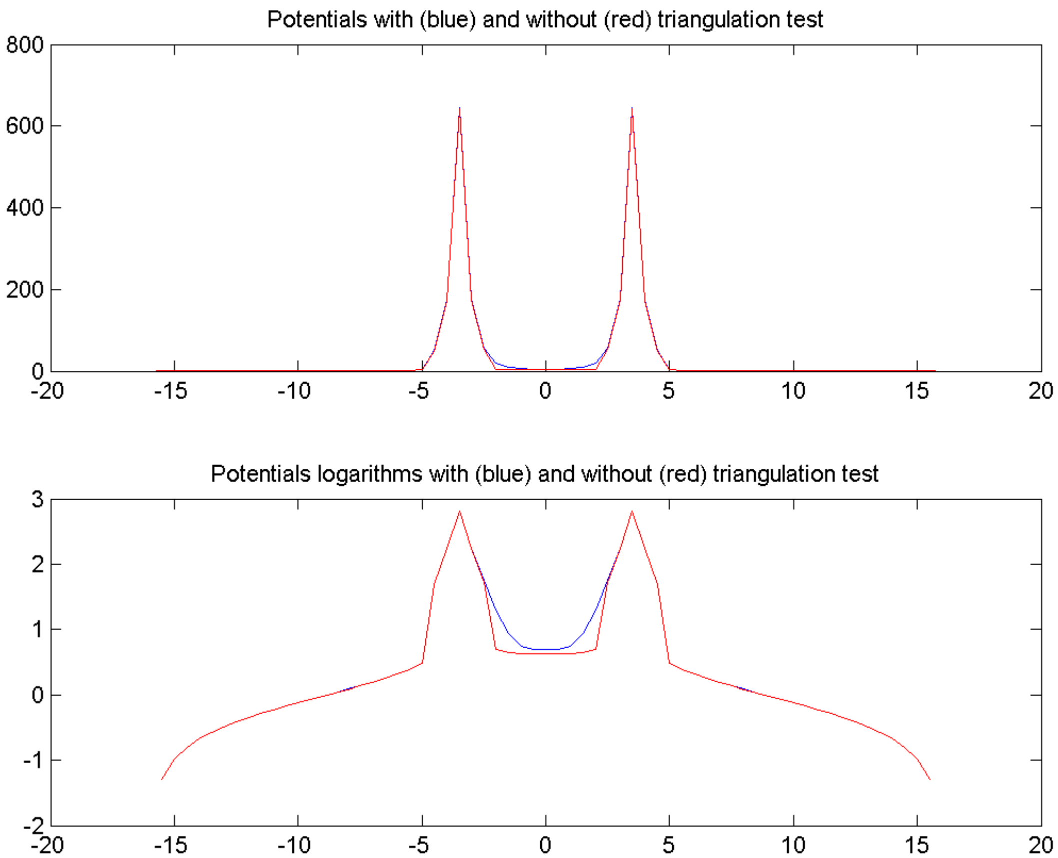
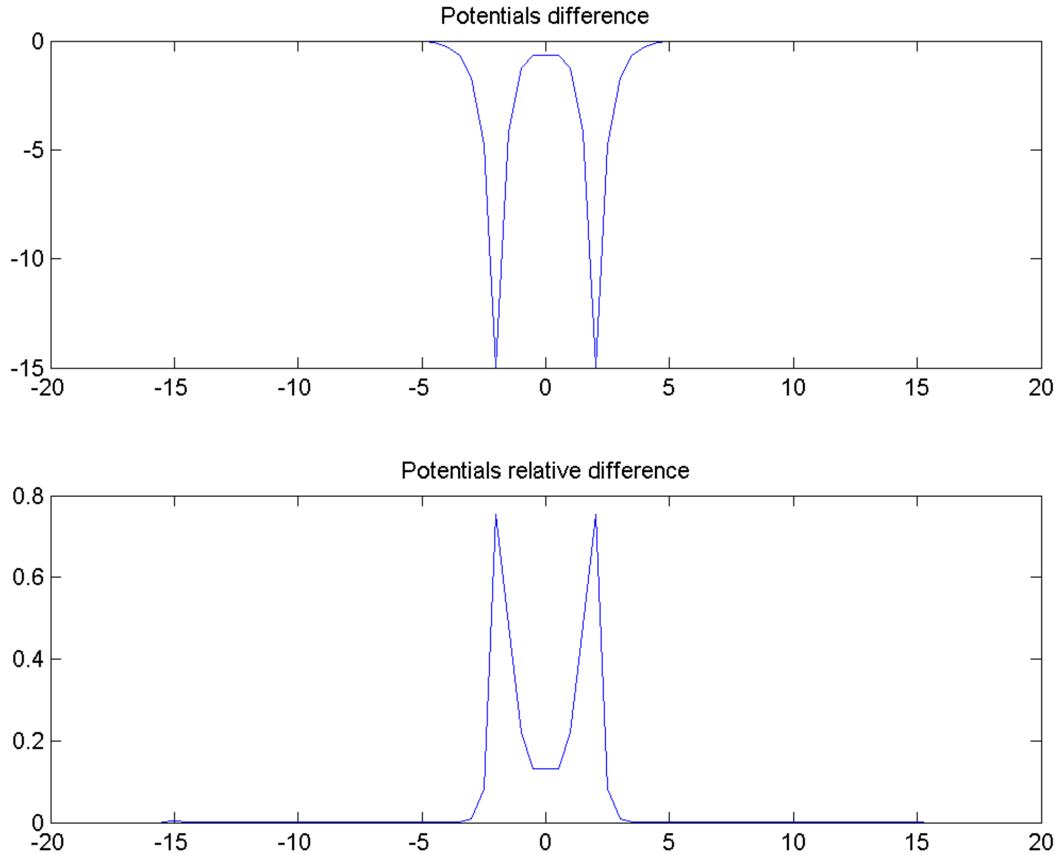


Figure 8: Space inside of the molecular surface: molecule (gray), between two molecula (red), between three molecula, inside a cavity (yellow)

Number of internal points ($h = 0.5$ Å, total number of grid points is $65 \times 65 \times 65 = 274625$):

```
nxi:  660 32 0 200
nyi:  660 32 0 200
nzi:  660 32 0 200
```


Potentials with (blue) and without (red) triangulation test
800
600
400
200
0
-20
-15
-10
-5
0
5
10
15
20
Potentials logarithms with (blue) and without (red) triangulation test
3
2
1
0
-1
-2
-20
-15
-10
-5
0
5
10
15
20


Potentials difference
0
-5
-10
-15
-20
-15
-10
-5
0
5
10
15
20
Potentials relative difference
0.8
0.6
0.4
0.2
0
-20
-15
-10
-5
0
5
10
15
20

Back
Close

# Conclusions

**Pro:** The cavity triangulation construction and its usage for the triangulation test may lead to more realistic values of the electrostatic potential and corresponding energies (we suppose, that the DelPhi program doesn't include such a test).

**Contra:** Our algorithm and program is nowadays not very efficient, the calculation time with the triangulation test included is sufficient larger than the time without the test.

# References

[1] B. Lee and F. M. Richards: *The interpretation of protein structures: Estimation of static accessibility,* J. Mol. Biol. 55, 379–400 (1971).

[2] C. Chothia: *Hydrophobic bonding and accessible surface area in proteins,* Nature 248, 338–339 (1974).

[3] M. L. Connolly: *Molecular surface guide* (2006).

[4] A. A. Rashin, M. Iofin, and B. Honig: *Internal cavities and buried waters in globular proteins*, Biochemistry, v. 25, 3619–3625 (1986).

[5] M. K. Gilson, K. Sharp, and B. Honig: *Calculating the Electrostatic Potential of Molecules in Solution: Method and error assessment,* J. Comp. Chem. 9, 327–335 (1987).

[6] K. A. Sharp, A. Nicholls, B. Honig: *DelPhi: A macromolecular electrostatics software package,* Copyright Dept. of Biochemistry and Molecular Biophysics, Columbia University, New York; 1990.

[7] J. Liang, H. Edelsbrunner, P. Fu, P. V. Sudhakar, and S. Subramaniam: *Analytical shape computation of macromolecules: I. Molecular area and volume through alpha shape*, Proteins: Structure, Function, and Genetics 33, 1–17 (1998).

[8] J. Liang, H. Edelsbrunner, P. Fu, P. V. Sudhakar, and S. Subramaniam: *Analytical shape computation of macromolecules: II. Inaccessible cavities in proteins*, Proteins: Structure, Function, and Genetics 33, 18–29 (1998).

[9] M. F. Sanner, A. J. Olson, and J.-C. Spehner: *REDUCED SURFACE: an efficient way to compute molecular surfaces*, Biopolymers 38, (3), 305–320 (1996).

[10] J. Buša, Sh. Hayryan, Ch.-K. Hu, J. Skřivánek, and M.-Ch. Wu: *Enveloping triangulation method for detecting internal cavities in proteins and algorithm for computing their surface areas and volumes*, Journal of Computational Chemistry , 30, 3, 346–357 (2009).

WWW pages:

[11] `http://mathworld.wolfram.com/SphericalTriangle.html` (October 31, 2008)

[12] `http://mathworld.wolfram.com/SphericalTrigonometry.html` (October 31, 2008)

[13] `http://www.shef.ac.uk/~phys/people/vdhillon/Teaching/` The Course of Spherical Geometry (October 31, 2008)

Thank You for the attention!

Danke für die Aufmerksamkeit!

Bedankt voor jullie aandacht!

Спасибо за внимание!

あなたの注意をありがとう Shaji, shai!

Shnorhakalutjun ushadrutjan hamar!

Merci! Grazie!

Xiè xie!

Ďakujem Vám za pozornosť!

# The surface area of a spherical triangle

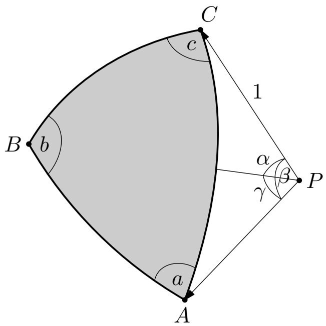



Figure 9: The surface area of the spherical triangle

A spherical angle is the surface area of the unit sphere's triangle:

$$\sigma(\Delta ABC) = A + B + C - \pi, \tag{1}$$

where the arc lengths $\alpha = \angle BPC$, $\beta$, $\gamma$ (angular lengths) and vertex angles $A$, $B$, and $C$ of the triangle in Figure 9 are related by the following cosine formula

$$\cos\alpha = \cos\beta\,\cos\gamma + \sin\beta\,\sin\gamma\cos A \tag{2}$$

and its next two permutations by variables (see, e. g., [11, 12, 13]).

# Cavity index of a point

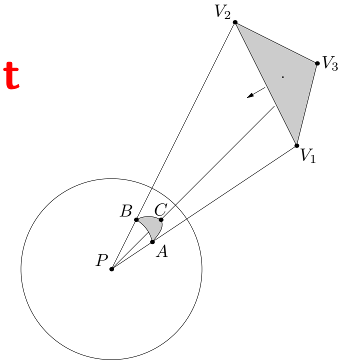



Figure 10: Cavity indexing

**Definition 3** *Let $P$ be a point of $E_3$ not belonging to the cavity triangulation $\Delta\mathcal{M}$. The index of $P$ with respect to the cavity triangulation $\Delta\mathcal{M}$ is the number*

$$\chi_P(\Delta\mathcal{M}) = \frac{1}{4\pi}\sum_{\delta\in\Delta\mathcal{M}} \sigma_P(\delta).$$

**Proposition 1** *An envelope triangulation $\Delta\mathcal{M}$ contains the point $P$ (different from vertices of triangulation) inside itself if and only if*

$$\chi_P(\Delta\mathcal{M}) = 1.$$

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

$$\|X - C_i\| < r_i \text{ for some ball } \mathcal{B}_i \tag{1}$$

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

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

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 (a), the point $X$ is inside of both cones (with the scalar product of vectors on the left side) and outside of the torus

$$(X - C_i)\cdot(C_j - C_i) > \frac{\|C_j - C_i\|^2 + (r_i + r_s)^2 - (r_j + r_s)^2}{2(r_i + r_s)}\|X - C_i\|$$

$$(X - C_j)\cdot(C_i - C_j) > \frac{\|C_i - C_j\|^2 + (r_j + r_s)^2 - (r_i + r_s)^2}{2(r_j + r_s)}\|X - C_j\| \qquad (2)$$

$$\|X - D_{ij}\|^2 + R_{ij}^2 > 2R_{ij}\mathrm{dist}\left(X, \overleftrightarrow{C_iC_j}\right) + r_s^2$$

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 $\overleftrightarrow{C_iC_j}$ of the torus is

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

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

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 $X$ less than $2r_s$. So, it satisfies inequalities

$$\|X - C_m\| < r_m + 2r_s \text{ for each } m \in \{i,\ j,\ k\}. \tag{b}$$

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

$$\|X - E\| > s$$
$$\alpha_m \geq 0 \text{ and } \sum_{m=1}^{3} \alpha_m \leq 1 \tag{3}$$

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 (b) and $E_{ijk}$ or $E'_{ijk}$ in role $E$.