An algorithm for the calculation of volume and surface of unions of spheres. Application for solvation shells

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***Abstract*— A simple algorithm for the calculation of the volume and surface area of a union of spheres of different radii is presented. It is based on the ideas published in *S.Sastry et al, Phys.Rev.E, v.56, pp.5524-5532, 1997* [1], where they computed volume and surface of interatomic voids in simple liquids. They proposed to work with the intersection of Delaunay simplexes and the corresponding Voronoi polyhedra. Analytical formulas for volume and surface area were derived for the atoms occupying this region. This could be achieved without explicit calculation of multiple intersections of the overlapping atoms. We have implemented such ideas for the calculation of the occupied volume and its surface inside the polyhedra defined by power Voronoi diagram. This allows calculating the required values for spheres with different radii. Simple analytical formulas are also valid in this case. We applied our algorithm to the calculation of the solvation shell volume for complex solute molecules in molecular dynamics models of solutions. A comparison of our program with the available implementation of the certified algorithm for unions of spheres by F.Cazals et al. (*ACM Trans. Math. Soft. 38 (1), 2011*) [2] shows coincidence of the results.**

Index terms*— Power Voronoi diagram, solvation shell, solvent accessible surface, union of balls.

I. INTRODUCTION

Volume and surface of a union of overlapping spheres is of interest for many applications. One of the best known is the calculation of volume and surface of molecules in chemistry and molecular biology [3, 4]. Any molecule can be approximated as an aggregate of spherical atoms with given van der Waals radii. These spheres overlap because chemical bonds between neighbor atoms are shorter than the sum of the radii. Another problem is the calculation of volume and surface of voids between atoms. In this case the union of the surrounding atoms determines the empty space between them [1,5]. An important field of research is the investigation of solvation shells in solutions. Of particular interest is the so called solvent accessible surface (SAS). The area of this surface and the enclosed volume are calculated for the union of spheres, which are centered on the atoms of the solute molecule and have radii given by the sum of the atomic van der Waals radius and the radius of the solvent molecule. Traditionally, the solvation shell is similarly constructed, but the outer surface lies at some additional distance radius R, representing the width of the shell [6-8].

The problems discussed can be solved by different methods. There are approaches which are based on Monte Carlo or lattice methods [9-11]. Others utilize analytical calculations [12-17]. A recently rather popular method used inclusion-exclusion formulae combined with Delaunay simplexes to reduce the complexity of calculating the intersections of overlapping spheres [18-20]. Some of the approaches do not compute the intersections of spheres at all, in particular [1,2].

Sastry et al. calculated the volume of voids in simple (monatomic) liquids [1]. Such voids can be represented by Delaunay simplexes. It leads to the problem of finding the empty (or occupied) volume inside Delaunay simplexes. They suggest to involve Voronoi polyhedra, and examine the intersection of each simplex with the Voronoi polyhedra of its *constituent* atoms, i.e. which define the vertices of the simplex. A property of such an intersection is that it "belongs" to the Voronoi polyhedron of this atom only. This means that, if the intersection contains a free volume, i.e. which is not covered by the atom, then this volume is not covered by any other atom too. Thus, finding an empty volume in this intersection, we can attribute it to one definite atom. This intersection has a rather complicated shape, therefore it was proposed to divide it into six triangular pyramids (subsimplexes) [1]. Explicit formulas for the occupied volume can be derived for each of these pyramids. Seemingly, a simple summation over these pyramids gives the desired volume. However, as it was noted, the subsimplexes can be overlapping in some cases. This occurs because the center of the Delaunay simplex (the common Voronoi vertex) lies sometimes outside the simplex interior. A rule of signs has been proposed to avoid this problem. Some of the subsimplexes were marked by a negative sign, thus the contribution of overlapping subsimplexes can be compensated and the total value becomes correct.

Another complexity of working with simplexes is related with the fact that *extraneous* atoms, i.e. atoms which are not the vertices of the simplex, can intrude into the simplex. The occupied volume of the simplex, calculated without considering the extraneous atoms will be underestimated. However, the occupied volume of the neighboring simplex,

978-0-7695-4483-0/11 $26.00 © 2011 IEEE
DOI 10.1109/ISVD.2011.30

where this atom is belonging to, will be overestimated by the same amount. As a result, the total occupied volume of a cluster of Delaunay simplexes, which represent a void, will be calculated correctly [1]. On the other hand, the extraneous atoms present a serious problem for the calculation of the occupied volume, if we like to calculate it for single Delaunay simplexes.

If Delaunay simplexes *per se* are not important for the study, then the ideas proposed in [1] can be realized in a different way. It is possible to calculate the occupied volume inside a Voronoi region without using Delaunay simplexes explicitly. From the definition of a Voronoi region follows, that the interior points cannot be covered by other atoms, if they are not covered by the central one. Thus, if we want to calculate the occupied volume inside a Voronoi region, we can deal with the sole atom, which is related to this polyhedron. Of course, other atoms can intrude partly into a given Voronoi region, but in this case their volumes are covered by the central atom, Fig. 1 and Fig. 2.

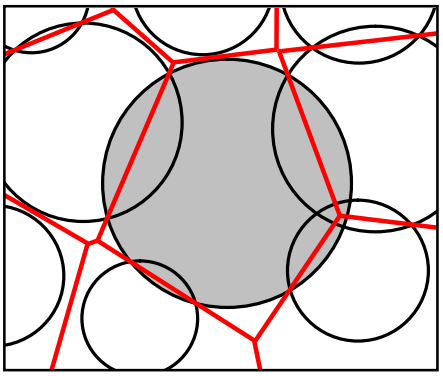

Figure 1. Two-dimensional illustration of the power Voronoi diagram of a union of disks. To find the occupied volume inside a given polyhedron, we just need to consider only its central atom (shaded disk). Nearby atoms extending into this polyhedron do not contribute to this volume, because they are covered by the central atom.

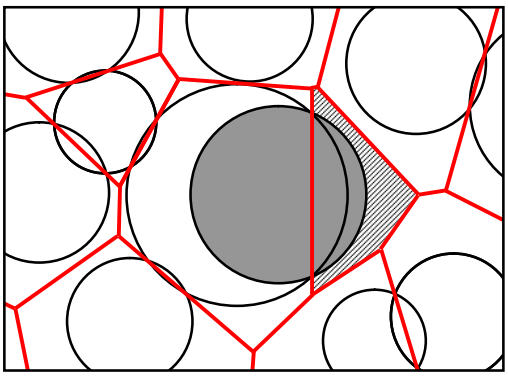

Figure 2. Illustration of a situation, when the center of an atom lies outside of its power Voronoi polyhedron (shaded). The free volume inside this polyhedron is also not accessible for other atoms.

When we are dealing with atoms (spheres) of different radii, we have to use either Voronoi S-cells, where the distance to an atom is measured to the nearest point on its surface (additively weighted Voronoi cells) [21,22], or power Voronoi polyhedra, where the distance to an atom is "the power" of a given point, i.e. its distance, measured along the tangent line [23,24]. In principle, both types of the Voronoi diagram can be used for the given problem. However the last one is preferable. The explicit formulas for the computation of the occupied volume can be easily obtained, because the power Voronoi cells have plane faces.

Note, both for ordinary Voronoi diagrams, defined for a system of atomic centers, and for additively weighted Voronoi diagrams, the center of an atom is always located inside its Voronoi cell. However, for power Voronoi diagrams it is possible that the center can be outside its cell [23-24], see Fig. 2. This fact is not very significant to the concept of the algorithm, but should be taken into account at the implementation, see below.

The idea to use power Voronoi diagrams for the given problem, was successfully implemented in [2]. However, these authors calculate the occupied volume and the surface by a method, which differs from the one discussed here.

This paper presents our solution of the problem of union of spheres. Our algorithm uses simple analytical formulas for the calculations and can be easily implemented. Testing of the algorithm shows that it is fast and robust.

II. Main Topics of the Algorithm

A. *Partitioning of a polyhedron into triangular pyramids*

To calculate the occupied volume inside a power Voronoi polyhedron, we divide it into elementary triangular pyramids, Fig. 3. The common vertex of all these pyramids is the center of the atom of this polyhedron (point A). The bases of the pyramids lie on the faces of the polyhedron. The first vertex on the base (point B) is the point of intersection of the perpendicular from point A to the plane of a given face. The second vertex of the base (point E) is defined by the intersection of the perpendicular from point B to one of the edges of the face (or to its continuation). The third vertex of the base (point V) is one of the two polyhedron vertices which lie on the edge, used to construct point E. One can easily ascertain that these elementary pyramids are exactly Sastry's subsimplexes [1]. The only difference: instead of Delaunay simplexes we really use here simplexes which are dual to the power Voronoi tessellation.

Each vertex V of a polyhedron is the common vertex of six elementary pyramids. Each face contains two such pyramids, and three faces of the polyhedron are incident to a given vertex. The total number of pyramids inside a polyhedron can differ. It depends on the number of vertices of the polyhedron. Note that the Delaunay simplexes are divided always into the same number of subsimplexes [1]. This is because a simplex has only four vertices.

Fig. 4 illustrates the partitioning of the Voronoi polygon into the required pyramids (triangles in this case). One of the triangles (ABV) is shaded. The base of the triangle is defined by points B and V. The first one is the projection of point A to a given edge of the polygon. The point V is one of the vertices lying on this edge. Each vertex of the polygon

belongs to two triangles. Note, in this example the triangles do not intersect with each other and do not extend beyond the polygon. Thus the total occupied volume inside the polygon can be calculated as a simple summation of the occupied volume of each triangle. This situation is typical for physical atomic systems, unfortunately it does not cover all possibilities (see below).

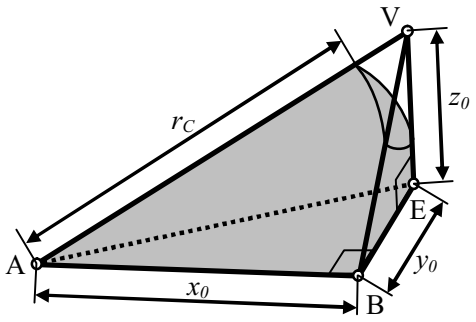

Figure 3. An elementary triangular pyramid of the partitioning of a polyhedron. Vertex *A* is the center of the atom of this given polyhedron. Point *B* is the foot of the perpendicular from point *A* to the plane of one of the faces. Point *E* is the foot of the perpendicular from point *B* to one of the edges (or its continuation) of this face. Point *V* is one of the vertices of the polyhedron at this edge.

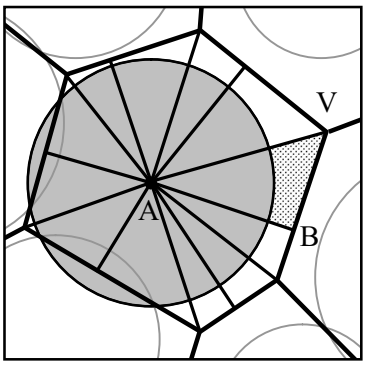

Figure 4. Partitioning of a polygon into the elementary triangles. Common vertex of all triangles is the center of the atom of this polygon (point *A*). The edge *AB* of the triangle is a perpendicular from *A* to one of the polygon edges. The triangle edge *BV* connects point *B* with one of the vertices (point *V*), lying on a given polygon edge.

B. Formulas for occupied volume and surface area inside the elementary triangular pyramid

By construction, the triangular pyramids have one right dihedral angle (between faces *ABE* and *BEV*, Fig. 3), and additionally two right angles between edges *AB* and *BE*, and also *BE* and *EV*. As it was mentioned, our pyramids are similar to the subsimplexes used in [1]. Thus it is not surprising that the formulas for the occupied volume and its surface area inside our pyramids are identical to the formulas given in [1], in spite that they used ordinary Voronoi cells and atoms of the same radius.

In this paper we keep the basic notation used in [1], but write these formulas in a shorter way. Let us denote the lengths of the edges of a triangular pyramid as x_0, y_0, z_0, then $r_E = \sqrt{x_0^2 + y_0^2}$; and $r_V = \sqrt{x_0^2 + y_0^2 + z_0^2}$, see Fig. 3. The occupied volume and the area of the spherical surface section in the pyramid depends on which edges of the pyramid are intersected by the surface of the sphere (atom) with radius r_C. The following cases are possible:

I: $r_C \le x_0$

$$V_C = \frac{r_C^3}{6}\left(2\theta - \frac{\pi}{2} - a_1\right) \tag{A3}$$

$$S_C = \frac{r_C^2}{2}\left(2\theta - \frac{\pi}{2} - a_1\right) \tag{A4}$$

II: $x_0 < r_C \le r_E$

$$V_C = \frac{\theta}{2}\left(r_C^2 x_0 - \frac{x_0^3}{3}\right) - \frac{r_C^3}{6}\left(\frac{\pi}{2} + a_1\right) \tag{A5}$$

$$S_C = \theta x_0 r_C - \frac{r_C^2}{2}\left(\frac{\pi}{2} + a_1\right) \tag{A6}$$

III: $r_E < r_C \le r_V$

$$V_C = \left(\frac{r_C^2 x_0}{2} - \frac{x_0^3}{6}\right)\left(\theta - \frac{\pi}{2} + a_2\right) + \frac{r_C^3}{6}(a_3 - a_1) + \frac{x_0 y_0}{6}\sqrt{r_C^2 - r_E^2} \tag{A7}$$

$$S_C = x_0 r_C\left(\theta - \frac{\pi}{2} + a_2\right) + \frac{r_C^2}{2}(a_3 - a_1) \tag{A8}$$

IV: $r_C \ge r_V$

$$V_C = \frac{x_0 y_0 z_0}{6} \tag{A9}$$

$$S_C = 0 \tag{A10}$$

Here we use the notations:

$\theta = \arctan(z_0 / y_0)$, $x_2 = r_C x_0 / r_E$, $y_2 = r_C y_0 / r_E$,

$a_1 = \arcsin\left[\frac{\left(z_0^2 x_0^2 - y_0^2 r_V^2\right)}{r_E^2\left(y_0^2 + z_0^2\right)}\right]$, $a_2 = \arcsin\left[\frac{y_0}{\sqrt{r_C^2 - x_0^2}}\right]$,

$a_3 = \arcsin\left(\frac{x_2^2 - y_2^2 - x_0^2}{r_C^2 - x_0^2}\right)$. Note that the formula for the area (A8) in [1] contained an error, which we have corrected here.

C. *Rule of signs for summation of the pyramids.*

Fig. 5 demonstrates a situation where the base of a perpendicular (point B_{12}) is located outside the polygon border (outside the edge V_1V_2). This point defines two triangles: $AB_{12}V_1$ and $AB_{12}V_2$. The first one is completely covered by the second one and is partly overlapped by the triangle $AB_{51}V_1$. This means that the sum of the occupied atomic volumes over all triangles will include the occupied volume inside triangle $AB_{12}V_1$ three times. In order to calculate the total volume correctly, we propose to use the contribution of this triangle with a minus sign. In this case, the sum volume will be correct. The determination of the triangle's sign depends on the position of point B with respect to the vertices of the polygon edge. It is considered positive (with a plus sign) if point B belongs to a given polygon edge, i.e. positioned between its vertices. If point B lies on the continuation of the edge, there are two possibilities. The first one is realized for the triangle $AB_{12}V_2$. In this case both point B_{12} and the edge V_1V_2 are located on the same side relative to the used vertex V_2 and the contribution of the triangle is considered positive. The second possibility is implemented in the triangle $AB_{12}V_1$: point B_{12} and the edge V_1V_2 are located on the opposite sides of the used vertex V_1. In this case the contribution of the triangle will be recorded with a minus sign. Formally the triangles can be characterized by a factor S_B, which is equal to 1 or −1.

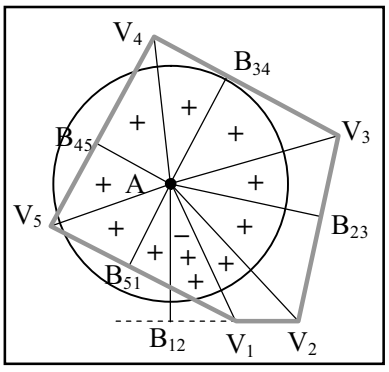

Figure 5. Partitioning of the polygon into triangles, when the foot of the perpendicular from point A to a given polygon edge lies outside of the polygon (point B_{12}). In this case the triangle $AB_{12}V_1$ overlaps with neighboring triangles $AB_{12}V_2$ and $AB_{51}V_1$. In the summation over the triangles, the volume of the atom inside the triangle $AB_{12}V_1$ is counted three times. Taking into account the negative contribution of triangle $AB_{12}V_1$ gives us the correct result.

A power polyhedron that does not contain the center of its atom (see Fig. 2) can also be divided into triangular pyramids according to our rules. However, in this case some pyramids are also overlapping. It is easy to formulate for this case the rule of signs by using an additional factor S_A. If the center of the atom and its polyhedron lie on the same side relative to the plane of the face, on which the perpendicular is dropped, then $S_A = 1$, otherwise $S_A = -1$. Fig. 6 illustrates this situation. The center of the atom (point A) is located outside of its polyhedron. For triangles $AB_{12}V_1$ and $AB_{12}V_2$ the factor $S_A = -1$, because the point A and the polyhedron lie on opposite sides of the edge V_1V_2. For all other triangles $S_A = 1$. In the summation of the occupied volumes of all triangles, the volume located outside the polyhedron is counted twice, since the triangles $AB_{12}V_1$ and $AB_{12}V_2$ intersect in this area with all the others. However, the opposite signs of the volumes will lead to zero contribution outside the polyhedron.

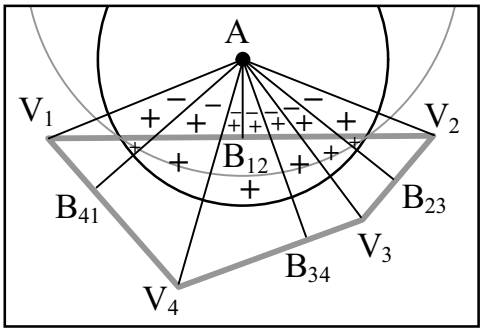

Figure 6. Partition of the polygon into triangles when the center of atom A lies outside its polygon. Occupied volume of the triangles $AB_{12}V_1$ and $AB_{12}V_2$ intersects with the occupied volume of the other triangles. The first triangle pair is used with minus sign and all the rest with plus sign. Summation over all triangles yields the occupied volume only inside the polyhedron.

In general, the factor S_A should be introduced for all polyhedra, including those in which the center of the atom is inside the polyhedron. In this case $S_A = 1$ for each pyramid, which corresponds to the rule proposed above. Note that S_B and S_A are used as multipliers, i.e. when both factors are negative the final sign of such triangle will be positive.

In the three-dimensional case (for a three-dimensional pyramid) the rule of signs is complemented by one more factor S_E, because now we have to take into account the position of point E, Fig. 3. The rules for point E are similar to those considered in Fig. 5 for point B in the two-dimensional case. Thus if point E lies on the edge of the polyhedron, then $S_E = 1$. If point E lies on the continuation of the edge on the same side as the edge according to vertex V, then $S_E = 1$, otherwise $S_E = -1$. The sign for the summation of the occupied volume or its surface area is determined as the product of all factors: $S_A \cdot S_B \cdot S_E$.

III. Implementation of the Algorithm

In the first step, the power Voronoi diagram should be calculated for the studied union of spheres (atoms). This is a

routine procedure, all theoretical aspects of this diagram have been treated in the last century, see in particular [22-25], and there are many available programs for its calculation.

It is important for our algorithm that each sphere of the studied union should have a completely constructed power Voronoi polyhedron. This can be met for molecules inside a solution, which are surrounded by solvent atoms. However if we work with an isolated molecule, extra atoms should be added in the surroundings to avoid "unclosed" Voronoi cells for atoms at the surface of the molecule. The extra atoms should have zero radii to avoid any contribution to the occupied volume, and should be used for the calculation of the power Voronoi diagram of the studied union, Fig. 7. There is only one condition for the surrounding points. They should not produce degenerated configurations. Note that the computer models of atomic and molecular systems contain usually no degeneracy. However, it can be introduced by artificially added atoms if an inappropriate procedure is used to create them. All other conditions like the number of the additional points, or their distance from the molecule, are not very important.

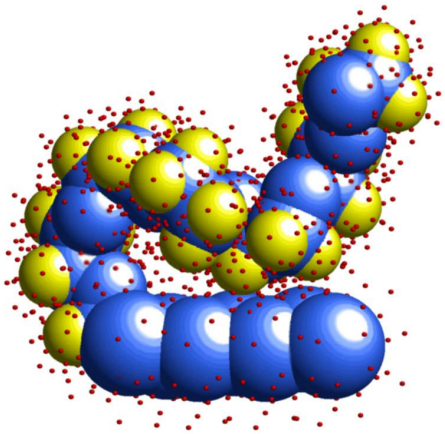

Figure 7. An example of a composite system while working with an individual molecule. It is surrounded by artificial atoms (points). A complete power Voronoi polyhedron must exist for each atom of the molecule (blue and yellow spheres) taking into consideration the added points.

Next, each sphere of the union should be treated, to find the occupied volume and surface inside its power Voronoi polyhedron. This procedure consists of the following steps:

1. Each polyhedron is divided into elementary triangular pyramids (like to *ABEV*, Fig. 2), as discussed above.
2. For each pyramid, volume and surface area of the atom within this pyramid are calculated according to the formulas A3-A10.
3. For each pyramid a "sign" is calculated as the product of three factors $S_A \cdot S_B \cdot S_E$ following the rule of signs:
   a. If the vertex A of the triangular pyramid and the polyhedron are located on one side of the base of the pyramid (a plane containing the point B), then $S_A = 1$. Otherwise $S_A = -1$.
   b. If point B at the base of the pyramid and the corresponding face of the polyhedron are located on one side of the line containing the polyhedron edge, selected to construct point E, then $S_B = 1$. Otherwise, $S_B = -1$.
   c. If point E and the polyhedron edge, selected to construct point E, are located on the same side of point V (vertex of the polyhedron chosen as a vertex of the pyramid) then $S_E = 1$. Otherwise, $S_E = -1$.
4. The occupied volume and surface inside the polyhedron are calculated as a sum over all the pyramids, in accordance with their signs.

Finally, the total occupied volume and surface for the union of spheres is calculated as a sum of the corresponding values over all its polyhedra.

IV. PROGRAM TESTING

For the testing of our algorithm we compared our software with two available programs used for analytic computation of the union of spheres. The first program (VORLUME) is an implementation of a recently published algorithm, based on power Voronoi diagrams and the Gauss' divergence theorem for volume calculations [2]. The second program (ALPHAVOL) [26] uses an inclusion-exclusion formula and the alpha-shape approach to avoid the computation of multiple intersections of spheres [18-19]. Different complex molecules were tested. Tables 1 and 2 collect the results of our testing of two models from the Protein Data Bank: a molecule of an antigen-antibody complex with 2731 atoms (PDB code 1vfb), and an E. coli ribosome subunit of 90983 atoms (code 1vow). These molecules were used to compare with the results from [2], where the solvent accessible surface areas and their volumes were calculated. All hydrogen atoms and the bound water molecules were discarded. The van der Waals radii of all heavy atoms were taken from [27] and expanded by the radius of the solvent molecule 1.4 Å. All three programs returned the same results for these models with an accuracy which is higher than it is needed for biological applications, see Tables I and II.

TABLE I. RESULTS FOR PDB FILE 1VFB (ANTIGEN-ANTIBODY COMPLEX, 2731 ATOMS)

Program	Total volume, Å^3	Total area, Å^2	Time[a], s
our code	64101.949	15259.481	0.90
Vorlume	$64101.949 \pm 4.5\times10^{-07}$	$15259.481 \pm 3.3\times10^{-07}$	0.96
alphavol	64101.949	-	0.14

a. Timings are reported for computations on one core of an Intel® Xeon® CPU X5482 @ 3.2GHz

TABLE II. RESULTS FOR PDB FILE 1VOW (E. COLI RIBOSOME SUBUNIT, 90983 ATOMS)

Program	Total volume, Å^3	Total area, Å^2	Time, s
our code	2136605.87	528693.40	32.6
Vorlume	2136605.86 ± 0.01	528693.40 ± 0.01	39.5
alphavol	2136605.87	-	8.0

Our code and the program VORLUME demonstrated practically the same operating speed, whereas ALPHAVOL is appreciably faster. However, we also found the program ALPHAVOL to be not robust. The calculations failed for approximately 10% of our investigated structures. Thus we did not use it for the following test with a molecular dynamics model of an aqueous solution of a C8E6 molecule (hexaethylene glycol monooctyl ether) consisting of 54 atomic units (this molecule is shown in Fig. 7).

7000 independent instantaneous configurations of the molecule were taken from a molecular dynamics trajectory. For each configuration the radii of atoms were expanded by a value R, ranging from 0 to 20 Å with steps of 0.1 Å. The volumes of the unions of these spheres were computed by our code and the VORLUME program. The molecular dynamics configurations that we used represent a set of very different conformations of the molecule, which can be stretched as well as entangled. Using different values of radii R we change the overlapping of the spheres of our union. Thus this calculation performs testing of the programs over 1.4×10^6 unions of 54 spheres of different morphology and radii. It turned out, that the results of the two programs on this dataset coincided with absolute accuracy better than 6×10^{-6} Å^3 which corresponded to the precision of storage format for the values.

Note, in this paper we used our in-house program for calculations of the power Voronoi diagrams.

V. APPLICATION FOR SOLVATION SHELL ANALYSIS

Let us illustrate the application of our algorithm by the example of computation of the *apparent* volume of a solute molecule in a molecular dynamics model of a solution. In our article [8] we investigated the so called Aβ42 polypeptide in aqueous solution. The apparent volume depends on the influence of the solute on the surrounding water. This analysis gives information about protein conformations in water.

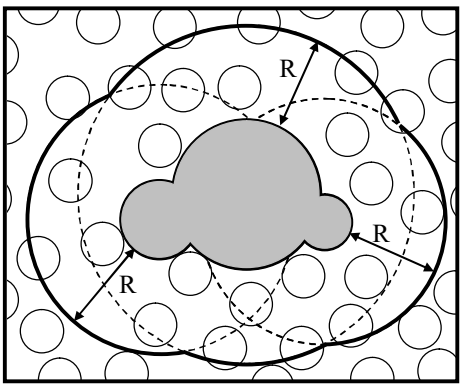

Figure 8. Illustration of a shell around a solute molecule. The outer border is the surface of the union of spheres which are centered on the atoms of the solute molecule (dark), with radii exceeding their van der Waals values by a given value R.

The calculation of the apparent volume is not a trivial task. This volume is strongly fluctuating from one molecular dynamics configuration to another. Thus we should make averaging over a large number of configurations. This requires fast and robust calculations. The most time-consuming part of the work is the calculation of the volume inside the surface located at a given distance R from the solute molecule, Fig. 8. Obviously, this volume can be found as the volume of the union of spheres.

We calculated this volume for sequential values of R from 0 to 1.2 nm with a step of ΔR=0.02 nm. The apparent volume of the dissolved molecule is then calculated as the difference between this volume and the volume, which would be occupied in pure water by the water molecules which are found within the surface of this union of spheres.

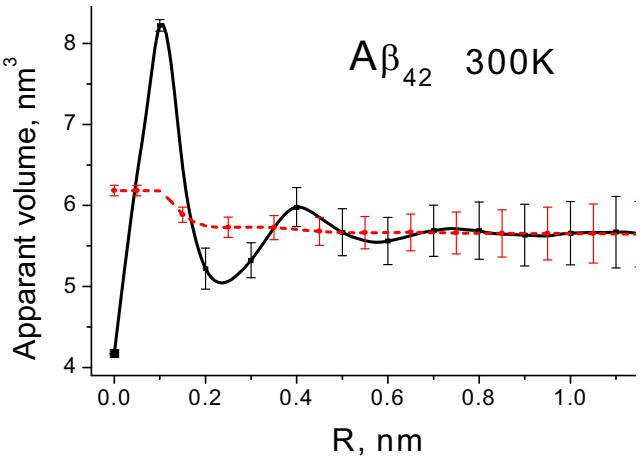

Figure 9. Profile of the apparent volume of an Aβ42 molecule in aqueous solution . Curve 1 (black solid) was calculated using the proposed algorithm for the union of spheres. Curve 2 (red dashed) was calculated by another method using the volume of Voronoi cells [8].

Fig. 9 (black line) illustrates the calculation of the apparent volume as a function of the outer distance R for our molecule in solution at temperature 300K. The value of the apparent volume to be compared with experiments corresponds to the asymptotic value of this function, i.e. where this function does not change with R. Deviations of the function from the asymptotic value for smaller R reflect just the structure of water itself, and do not relate to the experimentally obtained apparent volume. The other curve in Fig. 9 shows the profile of the apparent volume calculated by a different method, without the discussed calculation of volumes inside shells, see [8]. The different behavior for small R reflects differences of the methods. It is worth to be noted that both curves have the same asymptote. This means that the proposed algorithm for the calculation of the union of spheres gives a correct physical result, and is a good tool for applications.

VI. CONCLUSIONS

In this paper we propose an algorithm for the computation of volume and surface of union of spheres of different radii. It employs ideas of paper [1], where the elementary triangle pyramids (subsimplexes) were used for

the calculation of the occupied volume inside Delaunay simplexes for the investigation of voids between atoms in simple liquids. The use of such pyramids enables to get explicit formulas for the calculation of volume and surface of voids. We extended this approach to the problem of union of spheres, using similar triangle pyramids and power Voronoi diagrams. In this way we avoid the problem of calculating multiple overlapping of spheres and get simple formulas for the implementation of the algorithm.

Testing of the algorithm shows that it is competitive with the certified one [2], concerning speed and robustness. The formulas proposed give the possibility to use it for different applications. In this paper we demonstrate the calculation of the apparent volume of polypeptides in water in molecular dynamics models of aqueous solutions.

ACKNOWLEDGMENT

Financial support from Alexander von Humboldt Foundation and from RFFI grant 08-03-00140 is gratefully acknowledged.

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