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Decomposition of a protein solution into Voronoi shells and Delaunay layers

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***Abstract*— A simple formalism is proposed for a quantitative analysis of interatomic voids inside and outside of a molecule in solution. It can be applied for the interpretation of volumetric data, obtained in studies of protein folding in water. The method is based on the Voronoi-Delaunay tessellation of molecular-dynamic models of solutions. It is suggested to select successive *Voronoi shells*, starting from the interface between the solute molecule and the solvent, and continuing to the outside (into the solvent) as well as into the inner of the molecule. Similarly, successive *Delaunay layers*, consisting of Delaunay simplexes, can also be calculated. Geometrical properties of the selected shells and layers are discussed. The behavior of inner and outer voids is discussed by the example of a molecular-dynamic model of an aqueous solution of the polypeptide hIAPP.**

***Index terms*—Voronoi diagram, solvation shell, molecular dynamics of solutions, Voronoi cells, Delaunay simplexes.**

I. INTRODUCTION

The investigation of biological molecules in aqueous solution is an important problem of molecular biology. In particular, it is important to understand the mechanism of protein folding in water at different temperatures and pressures. Volumetric experiments are used for this study. The change of the volume of the solution, induced by the addition of a protein molecule is measured [1]. The influence of temperature and pressure induces changes of the volumetric properties, both inside the solute molecule, at its boundary, and also in the surrounding water. The knowledge of these contributions to the volume of the solution helps to validate propositions about the occurring conformational changes. However, using only experimental data, it is very difficult to separate these contributions. Computer simulations help to solve this problem.

Models of the solutions are generated usually by molecular dynamic simulations, see for example [2]. The next step is the analysis of the models: detection and characterization of interatomic voids and local densities. There are very different approaches used for the analysis of voids in atomic and molecular systems. Some of them were developed for the investigation of the empty space between the atoms in liquids and glasses [3-5], granular matters and colloids [6,7], polymers and membranes [8,9]. Others are specialized to study cavities and pockets in large biological molecules [10-12]. Solvation shells [13,14] and the boundary region between proteins are also studied [15,16]. Consecutive shells, consisting of Voronoi cells, were used for the analysis of the density of hydration shells around polypeptides in [17]. However, we are not aware of articles, where the voids both inside and in the surroundings of a solute molecule were analyzed. Such investigations should be made by a single-stage method for all regions of the solution. Fortunately, there is no necessity to develop a new method for such a work. At present, there is no doubt, that the most suitable and general method for the selection and analysis of voids and the local density in molecular system is an approach, which is based on Voronoi diagrams (the Voronoi -Delaunay method) [18,19].

In this work, we present a simple technique for the decomposition of the Voronoi-Delaunay tessellation into shells (layers) related with the solute. It allows to characterize voids (local density) both inside and outside the solute molecule.

II. VORONOI-DELAUNAY TESSELLATION OF A SOLUTION

Fig.1 shows a two-dimensional illustration of a solution model and its Voronoi-Delaunay tessellation.

Remember, the size of the atoms should be taken into account, if one studies interatomic voids [3,20,21]. This means that the Voronoi tessellation should be calculated allowing for the surface of the atoms. Thus we should deal with S-tessellation [22,23] (additively weighted [18]), instead of the ordinary Voronoi tessellation (related with the atomic centers). In this case we make a correct assignment of the empty space to a given atom, i.e. we include all points of space, which are closer to the *surface* of a given atom, than to the surfaces of all other atoms of the system. A simpler variant, which considers the atomic surfaces, is the well-known *power* or *radical* tessellation [18,21,24]. In this case the assignment of the empty space to individual atoms is not quite physical, but it is easier to implement. The known complexities of the S-tessellation (theoretically possible disconnectivity of the tessellation and overlapping of Delaunay simplexes in some cases [19,23,25] do not arise for our molecular systems, where the size difference of the atoms is rather small (usually less than a factor of 2). In addition, these peculiarities of the S-tessellation can be easily taken in to account at the calculation of the tessellation.

The molecules of the solvent (usually water molecules) are considered as uniform spheres, as it is usually done in structure analyses of computer models of water and water solutions. Note, the specific features of the interaction

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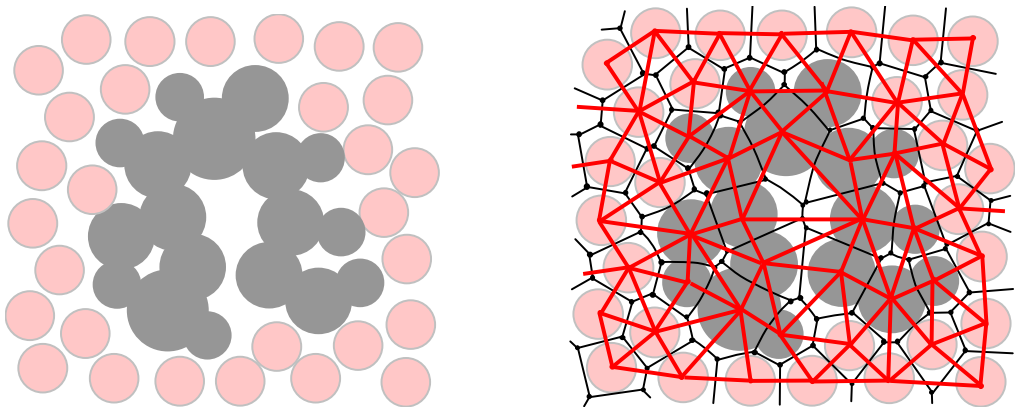

Figure 1. Left: 2D illustration of a solution. Atoms of the solute molecule are shown by dark disks. Atoms of the solvent are pink (light). Right: Voronoi-Delaunay tessellation of the model. Thin (black) lines show Voronoi cells, thick (red) lines show Delaunay simplexes.

between water molecules (hydrogen bonds) are essential in the stage of the molecular dynamics simulation.

The Voronoi-Delaunay tessellation is calculated for every configuration of the studied model. All atoms (both of the solute and solvent) are considered as a single system in this stage. The calculation of the tessellation is straightforward now. Algorithms for the calculation of the S-tessellation were described in the literature, see e.g. [23]. Programs for the calculation of the power tessellation (as for ordinary Voronoi-Delaunay tessellations) are available in standard geometrical libraries.

For the processing of the tessellation, it is convenient to use the Delaunay network. The sites of this network are the atoms of the system, and the bonds connect adjacent atoms. Remember, adjacency on the Delaunay network means, that the Voronoi cells of a given pair of atoms have a common face, Fig.1. For the following applications it is convenient to establish, which atoms determine the vertexes of the Delaunay simplexes. In this stage of the work, we will differentiate between the atoms of the solute and the solvent.

III. VORONOI SHELLS

Knowing the adjacency of the atoms (Delaunay network), one can begin the selection of the Voronoi shells around the solute molecule.

A. Selection of the boundary Voronoi shells

Go over all atoms of the solute molecule and find the atoms, which are adjacent to at least one atom of the solvent. Record the numbers of these atoms.

Thus we establish the atoms of the solute molecule, which are in direct contact with the solvent, and simultaneously, the atoms of the solvent which are in contact with the solute. The former represent the boundary atoms of the solute, and the latter define the nearest solvation shell. Let us assign indexes 0 and 1 to these atoms, and call these groups of atoms (and their Voronoi cells) as 0-*th* and 1-*st Voronoi shells*, see Fig.2. Let us denote the number of atoms in the shells as N_0 and N_1.

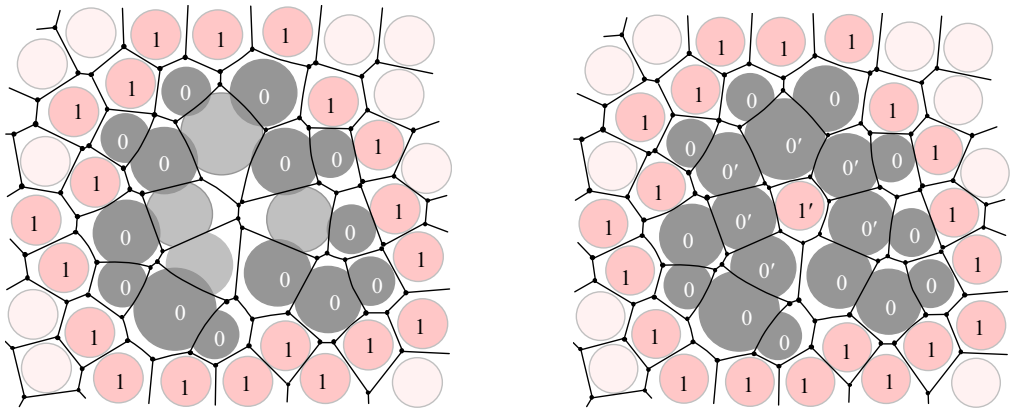

Figure 2. Illustration of the 1-st and the 0-th Voronoi shells. All atoms with index 1 have at least one atom of the solute as a neighbor. All atoms with index 0 have at least one atom of the solvent as a neighbor. If there are no solvent atoms inside the solute, both Voronoi shells are simply connected (left). The existence of solvent atoms inside the solute results in a not simple connectivity of the shells. See shells 1 and 1′ (right).

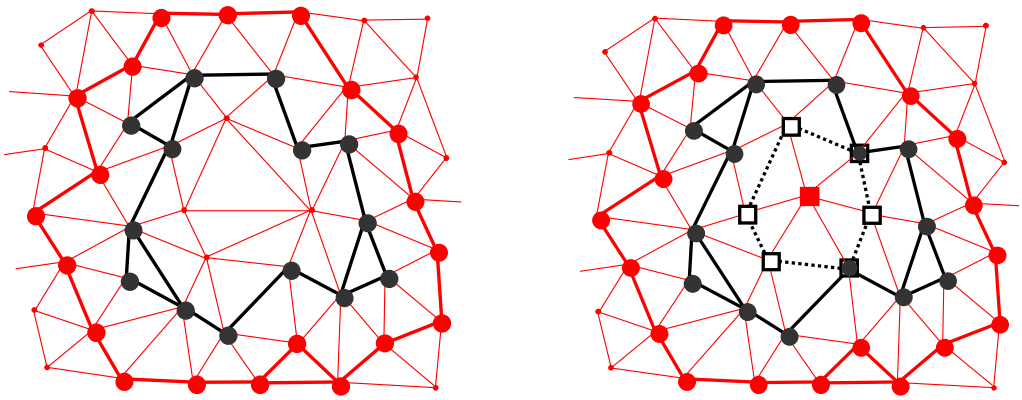

Figure 3. The 1-st (red) and the 0-th (black) Voronoi shells are presented as clusters on the Delaunay network for the models shown in Fig.2. Selected atoms are shown by large points and squares.

The volume of the shells (V_0 and V_1) can be calculated as the sum of the volumes of the Voronoi cells in a given shell.

Usually both of these shells are simply connected, Fig.2a. However, if some atoms are inside the solute (this means, that the set of solvent atoms is not simply connected on the Delaunay network), the 1-st shell is also not simply connected. The existence of water molecules inside the solute protein molecule has a special interest in biology. Our technique can be used to find such molecules in computer models. Simply, one should make a standard analysis of the clusters on the Delaunay network. If the selected (colored) sites (the atoms with index 1) represent a simply connected cluster, then water inside the solute is absent.

Fig.3 demonstrates our Voronoi shells as clusters on the Delaunay network. In the first case they are simple connected (Fig.3a). If there is a water molecule inside the solute (Fig. 3b), there is a more complicated situation.

Note, it is obvious, that when the solute molecule is simply connected on the Delaunay network, then the 0-th Voronoi shell is also simply connected.

B. Calculation of subsequent Voronoi shells

The 2-*nd Voronoi shell* is defined by the solvent atoms which are neighbors of the 1-st shell (adjacent to atoms with index 1). Let us assign index 2 to these atoms. Obviously, none of these atoms are in contact with atoms of the solute, else it could be assigned to the 1-st shell.

Similarly, we can select outer neighbors of the 2-nd shell. They define the 3-*rd Voronoi shell* and get index 3. To continue further, all subsequent Voronoi shells can be selected, and called the 4-th, 5-th, ... k-th ... and so, up to the maximum, that is permitted by the model.

From a mathematical point of view, the Voronoi shells correspond to the consecutive topological neighbors on the Delaunay network, see for example [26] and references there. However, the selection of the neighbors usually begins from a single (central) site (Voronoi cell). In our case we start from the boundary atoms of the solute molecule. If the 1-st Voronoi shell is simply connected, all subsequent shells are also simply connected. However, the shape of the Voronoi shells can be very different and is determined by the morphology of the solute molecule. Protein molecules have usually a globular shape. In this case the 0-th, 1-st and other Voronoi shells (understood as unions of the Voronoi cells with equal index) are isomorphic to spherical layers. However, in the case of a torus-like molecule, containing a ring of atoms, solvent molecules can be located in the interior of this ring. In this case the first Voronoi shells will also be tori.

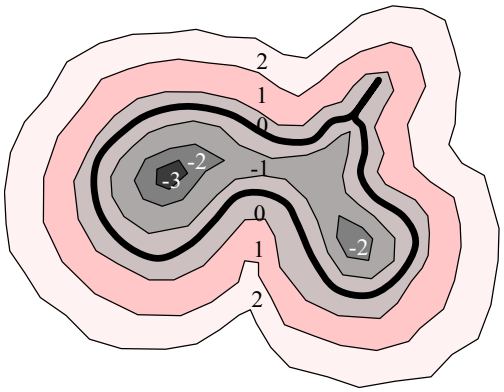

Figure 4. 2D illustration of Voronoi shells outside and inside a big solute molecule. Atoms are not shown. The location of the boundary atoms (with index 0) are marked symbolically by the bold curve. The digits show the numbers of the shells. The inner shells have negative numbers. They may be not simply connected.

Note, the Voronoi shells do not contain "through holes", i.e. going from the (k-1)-th to the (k+1)-th shell, one will be obligated to traverse the k-th shell. This is an obvious consequence of the Voronoi shell definition. Indeed, the k-th Voronoi shell is an obligatory "intercalation" between these shells: it is derived from the (k-1)-th, and generates the (k+1)-th one.

Let us consider now the Voronoi shells, which are constructed, when proceeding from the 0-th shell into the interior of the molecule. All internal neighbors of the 0-th shell represent the *-1-st (minus first) Voronoi shell*, Fig.4.

The atoms of this shell have index -1. None of these atoms contact the solvent, else it would belong to the 0-th shell. Similarly, one can select inner neighbors of the -1-st shell. They represent *the -2-nd (minus second)* Voronoi shell, and its atoms get the index -2. By continuing this, one can determine all subsequent "negative" shells, until all atoms of the molecule are covered. These shells can have a more complicate topology than the outer ones. In particular, they can be not simply connected, in spite of a simply connected 0-th shell, Fig.4.

Thus, we decomposed the solution into shells in relation to the surface of the solute molecule. This decomposition is unambiguous: no atom (Voronoi cell) is unconsidered, and none are taken into account twice.

For each Voronoi shell different characteristics can be calculated, e.g.: the number of atoms N_k ; the volume V_k, defined as the sum of the volumes of all Voronoi cells of the shell, the mean volume of the Voronoi cell $v_k = V_k / N_k$, the inner and outer surface areas S_{k-1} and S_k, which are calculated as the sum of the area of the boundary Voronoi faces. Since the outer surface of a given shell is the inner one for the following shell, it is sufficient to speak of intermediate surfaces $S_{k-1,k}$. One can propose also other characteristics of the Voronoi shells, e.g. the empty volume, and so on.

Every configuration of the solution is characterized by a sets of numbers, in particular:
the numbers of atoms in the Voronoi shells

$$\dots N_{-2}, N_{-1}, N_0, N_1, N_2 \dots,$$

the shell volume values

$$\dots V_{-2}, V_{-1}, V_0, V_1, V_2, \dots,$$

the areas of the intermediate surfaces

$$\dots S_{-2,-1}, S_{-1,0}, S_{0,1}, S_{1,2}, S_{2,3} \dots\dots,$$

and so on.

IV. DELAUNAY LAYERS

A. *Selection of the first (boundary) Delaunay layer*

We can classify the Delaunay simplexes by the atomic indexes defined over Voronoi shells. Let us define thus the index I of a given Delaunay simplex as the sum of the atomic indexes at its vertexes:

$$I = i_1+i_2+i_3+i_4 \qquad \text{(A1)}$$

Remember, the Delaunay simplex is formed by "mutually close" atoms, all of them are first topological neighbors. This means that the difference between the atomic indexes i in (A1) cannot be greater than 1.

Atoms of the 0-th and 1-st Voronoi shells can form the following simplex indexes:

$I = 0$ (all simplex vertexes are located on the solute molecule: 0+0+0+0);
$I = 1$ (three vertexes on the solute and one on solvent: 0+0+0+1);
$I = 2$ (correspondingly: 0+0+1+1);
$I = 3$ (correspondingly: 0+1+1+1);
$I = 4$ (all vertexes are on solvent molecules: 1+1+1+1).

We will call the union of Delaunay simplexes with the same index I as *Delaunay sub-layer I*. The sub-layers 0 and 4 are produced by atoms of the same Voronoi shells. They are result of "wrinkles" of the Voronoi shells, and do not play a principal role in our analysis. Moreover they can be absent in some models. We will discuss such sub-layers in more details below. More important are the sub-layers, whose vertexes are both on the 0-th and 1-st Voronoi shells (I=1,2,3). The union of these simplexes represents a shell (layer) between the atoms of solute and solvent. We call this shell the *1-st Delaunay layer*.

Fig.5 shows a two-dimensional illustration of these Delaunay constructions. In a plane a Delaunay simplex has three vertexes, thus there are only four different simplex indexes: I=0, (0+0+0); I=1, (1+0+0); I=2, (1+1+0) and I=3 (1+1+1), and the first Delaunay layer is presented by two sub-layers, (I= 1 and 2).
[1]

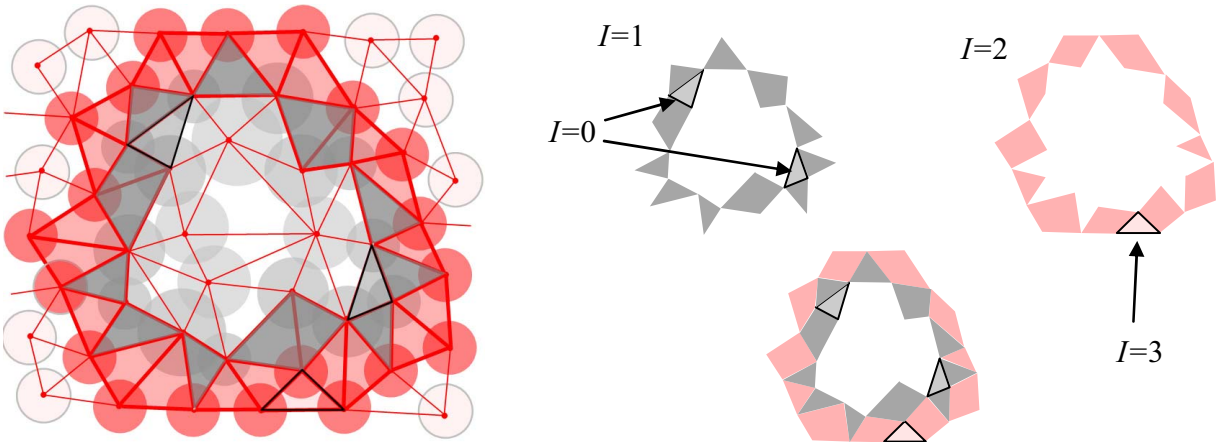

Figure 5. 2D-illustration of the first Delaunay layer for the model shown in Fig.2a. Separate Delaunay sub-layers and their unions are shown at the right.

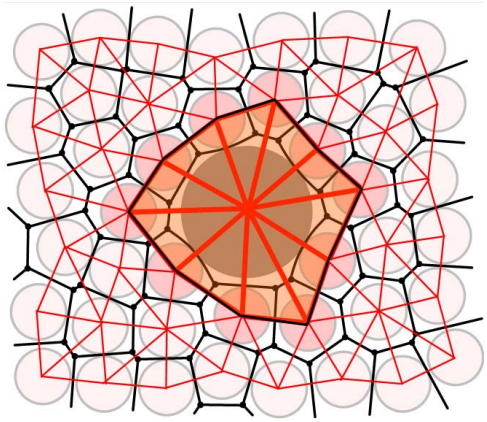

Figure 6. Illustration of the first Delaunay layer of a one-atomic solute. It consists of Delaunay simplexes with one index only: I=2, (0+1+1).

It is significant that the union of Delaunay simplexes, the vertexes of which are both on the solute and solvent represent a solid shell, i.e. at no point its width is equal to zero. For separate sub-layers this is not true. The thickness of a sub-layer degenerates into a point at the common vertexes, see Fig.5. (In 3D a zero width can also be along a common edge).

The first Delaunay layer characterizes the void space between the atoms of the solute and solvent. This important feature of the Delaunay layer is also valid, if some sub-layers are absent, see for example the one-atomic solute, Fig.6.

B. Calculation of the subsequent Delaunay layers

Let us consider Delaunay simplexes between the (k-1)-th and k-th Voronoi shells. They produce the indexes:

$I = 4k\text{-}4$, (k-1+k-1+k-1+k-1);
$I = 4k\text{-}3$, (k-1+k-1+k-1+k);
$I = 4k\text{-}2$, (k-1+k-1+k+k);
$I = 4k\text{-}1$, (k-1+k+k+k);
$I = 4k$, (k+k+k+k).

The simplexes with indexes 4k-3, 4k-2 and 4k-1, whose vertexes are positioned on atoms of both Voronoi shells, represent a solid shell between the atoms, and define the *K-th Delaunay layer*. In this case K=k. The simplexes with index I=4k-4 had been obtained already in the calculation of the previous, (K-1)-th Delaunay layer, and the index I=4k will appear once more in the calculation of the next (K+1)-th Delaunay layer. For the sake of definiteness, we will assign sub-layer 4k to the K-th Delaunay layer. In this case all Delaunay simplexes will be assigned to the Delaunay layers unambiguously.

We can also select Delaunay simplexes inside the solute molecule. They manifest the inner Delaunay layers.

The 0-th and -1-st Voronoi shells define simplex indexes:

$I = 0$, (0+0+0+0);
$I = -1$, (-1+0+0+0);
$I = -2$, (-1-1+0+0);
$I = -3$, (-1-1-1+0);
$I = -4$, (-1-1-1-1).

The union of sub-layers -1,-2,-3 represents the *0-th Delaunay layer*. We should also add sub-layer 0 to this layer, and sub-layer -4 will be assigned to the *-1-st Delaunay layer*. If there is a -2-nd Voronoi shell, then one can define the -1-st Delaunay layer, which consist of sub-layers -4, -5, -6, -7. Sub-layer -8 will be related to the next "negative" Delaunay layer (-2-nd). We can continue this procedure until all Voronoi shells inside the solute molecule are covered.

Thus, Delaunay layers are defined unambiguously by the Voronoi shells and represent an additional method for the decomposition of the Voronoi-Delaunay tessellation of the solution both inside and outside the solute.

Every Delaunay layer can be characterized, for example, by a volume D_K, calculated as the sum of its Delaunay simplex volumes. For physical applications it can also be interesting to know the empty volume E_K of the layers. In this case one sums the empty volumes of the simplexes (without the volume occupied by the atoms).

Every configuration of the solution can be characterized by sets of Delaunay layer parameters, in particular, by the volumes:

$$\ldots\ D_{-2},\ D_{-1},\ D_0,\ D_1,\ D_2,\ \ldots,$$

and/or the empty volumes:

$$\ldots\ E_{-2},\ E_{-1},\ E_0,\ E_1,\ E_2,\ \ldots$$

and so on.

V. Examination of an Aqueous Solution of the Polypeptide hIAPP

Molecular-dynamic models of a single amyloidogenic polypeptide molecule (hIAPP) (Fig.7) in aqueous solution had been generated in [27], and had been used for the calculation of volumetric characteristics in [17]. The solute molecule contains 462 heavy atoms (i.e. without hydrogen atoms) and is surrounded by 10843 water molecules. Production runs of 200 to 500 ns each were performed for 11 different temperatures from 250 to 450 K.

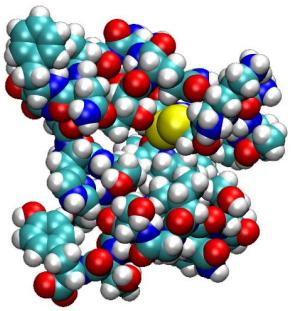

Figure 7. A configuration of the hIAPP molecule in aqueous solution. Water molecules are not shown.

For the analysis, 1000 independent configurations, equally spaced over the last 200 ns (every 200 ps) of the equilibrated production runs, were used for averaging.

These models can be decomposed properly into five consecutive Voronoi shells: k = -1, 0, 1, 2, 3. Shell -2 appears not in every configuration, therefore we do not analyze it specially. We calculated also the 4-th and 5-th Voronoi shells. However the linear dimension of these shells exceeds half of the model box in some configurations. An analysis of these shells could be problematic, because of the periodic boundary conditions used for our models. Although, as we found, all distant shells (beginning from the 2-nd) behave similarly, and are in accordance with bulk water.

Fig.8 demonstrates the temperature dependence of the volumes for the Voronoi shells with numbers -1, 0, 1 and 2. The total Voronoi volume of the molecule is also shown in the central diagram of Fig .8. In our approach it is calculated as the sum of the volumes of all inner Voronoi shells: -2, -1 and 0. It represents the *intrinsic volume* of hIAPP [1,17,28], i.e. the volume "assigned" to a solute molecule in solution. It includes the van der Waals volume of the molecule as well as the volume of voids assigned to the molecule: all voids inside the molecule plus a part of the surrounding empty space.

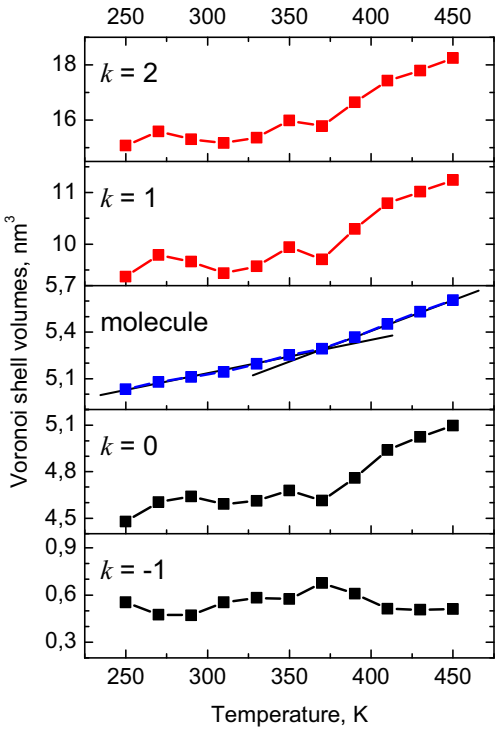

Figure 8. Voronoi shell volumes as a function of temperature. From bottom to top: the shells with the numbers from -1 to 2. In the center (blue): the total Voronoi volume of the hIAPP molecule (intrinsic volume).

The volumetric calculations performed in [17] gave exactly the same behavior for the intrinsic volume of hIAPP. The increase of this volume with temperature is natural, however the growth rate (slope of the curve) is larger at temperatures higher than 350K, see Fig.8 (and also Fig.16 in [17]). The previous analysis cannot explain this change of the thermal expansion coefficient. Our present decomposition into selected Voronoi shells helps to clarify the situation.

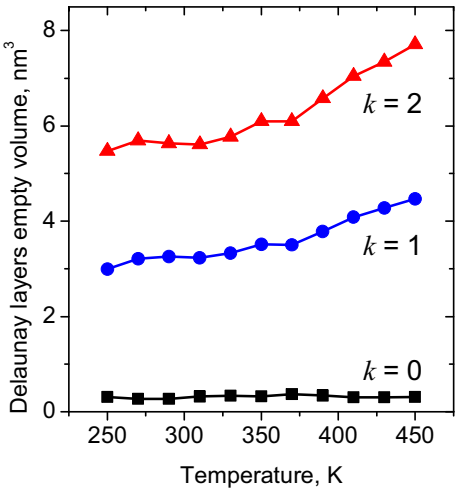

Figure 9. Empty volume of the *Delaunay* layers in aqueous solution of hIAPP as function of temperature. From bottom to top: the layers from K=0 to K=2.

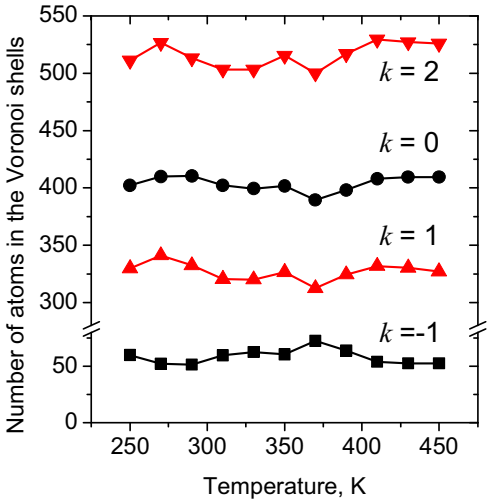

Figure 10. The number of atoms in the Voronoi shells. From bottom to top: the shells from k=-1 to k=2.

The following considerations can lead to an explanation of the observed temperature behavior of the intrinsic volume of hIAPP in aqueous solution. First, one could imagine, that some structural changes occur inside the molecule at higher

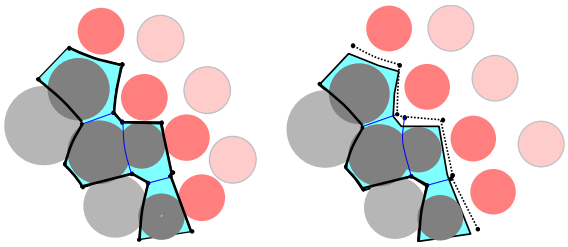

Figure 11. Left: a fragment of the boundary area between molecule and solvent (from Fig.2). The 0-th Voronoi shell is marked and colored (light blue). Right: the same part of the boundary area but with the lower density of the surrounding water. Dotted line shows the new border between molecule and solvent. One can see, the volume of the shell is increased in comparison with the previous situation.

temperature, which result in an additional increase of the interatomic voids. In our analysis, the -1-st Voronoi shell and the 0-th Delaunay layer belong to the molecular interior. However, there is no increase of the volume of these shells after 350K, see Fig.8 and Fig.9. Instead, one can see an increase of the volumes of the 0-th Voronoi shell and the 1-st Delaunay layer, which are at the border of the molecule. Therefore it could be reasonable to assume, an onset of "unfolding" of the hIAPP molecule causes this behavior. Indeed, if the molecule is (on average) more unfolded at higher temperature, it will have more atoms in contact with the solvent. As the boundary atoms involve some volume from outside, an increase of the number of these atoms should result in increase of the intrinsic volume of the molecule. However, as one can see in Fig. 10, the numbers of atoms in the Voronoi shells have no tendency to increase with temperature.

This means that the additional increase of the intrinsic volume cannot be explained by conformational changes (as the unfolding of the molecule). We calculated the gyration radius of the molecule and indeed, the fraction of "elongated" configurations increases slightly with temperature. However, this is not the reason for the change of the intrinsic volume: when calculating the correlation coefficient between gyration radius and intrinsic volume, we found that it is negligible. Its value is less than 0.01 at 350K and decreases at higher temperatures.

Based on these considerations, we suppose that the origin of the additional increase of the intrinsic volume of hIAPP at high temperature is the density decrease of the surrounding water. Indeed, the water density changes faster above 350K than at lower temperatures. This can be seen for the 1-st and 2-nd Voronoi shell in Fig. 8. The next shells (k=3,4,5) demonstrate a very similar increase for the same temperatures (not shown here). Fig.11 illustrates that the decrease of the water density results in an increased volume, assigned to the boundary atoms, and consequently to an increase of the intrinsic volume of the solute molecule. A stronger change of the water density results in a stronger increment of the volume in the 0-th Voronoi shell.

In molecular biology, the contribution to the intrinsic volume, arising from increasing thermal motions at higher temperatures, leading to a change of the density, is called *thermal volume* [1,28]. Thus we can say that the increase of the thermal expansion coefficient of hIAPP in water at 350K is mainly related with an additional change of the thermal volume of the molecule, but not with conformational changes of the molecule itself.

VI. Conclusion

A simple method for the construction of shells around a solute molecule for the analysis of molecular-dynamic models of solutions is proposed. In the first stage, the Voronoi -Delaunay tessellation is calculated for the total ensemble of atoms of the solution. After that, consecutive *Voronoi shells* are defined, starting from the border between molecule and solvent, proceeding to the outside (into the solvent), as well as into the interior of the solute molecule. The shells are numbered by k = ... -2, -1, 0, 1, 2, 3, ... The 0-th Voronoi shell corresponds to the atoms of the solute, which are adjacent to the solvent, and the 1-st one is defined by the solvent atoms which are nearest neighbors of the solute molecule. Positive numbers belongs to the shells outside the solute (in the solvent), negative numbers refer to shells inside the solute molecule. (It is assumed, that the solute molecule can be large). Each atom gets an index equal to the number of the Voronoi shell to which it belongs. These indexes are used to identify Delaunay simplexes, and to define *Delaunay layers* which characterize the void space between the atoms of neighboring Voronoi shells (also both outside and inside the solute molecule).

Note the proposed decomposition on the Voronoi shells and Delaunay layers can be performed very fast. In particular, it needs negligible computational time as compared with calculation of the Voronoi-Delaunay tessellation if the data structure are represented as described in [23].

The temperature behavior of the Voronoi shells and Delaunay layers was investigated, using a molecular-dynamic model for an aqueous solution of an amyloidogenic polypeptide (hIAPP). The non-trivial change of the thermal expansion coefficient was discussed. Our analysis suggests that this is the result of the influence of the surrounding water, but not of a conformational modification of the solute molecule itself. Specifically, one can say, that the *thermal volume*, which is located in the boundary layer between solute and solvent, produces an additional increase of the intrinsic volume of hIAPP with temperature. The situation can be different for other molecules. In particular, modification of internal voids and molecular morphology can also play a role. The presented method is a formalized instrument for such investigations.

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References

[1] T. V. Chalikian, "Volumetric properties of proteins". Annu. Rev. Biophys. Biomol. Struct. vol. 32, 2003, pp. 207–235.

[2] D. van der Spoel, E. Lindahl, B. Hess, G. Groenhof, A.E. Mark, H.J.C. Berendsen, “GROMACS: Fast, Flexible, and Free”, J. Comp. Chem. vol. 26, 2005, p. 1701.

[3] N.N. Medvedev, “Computational porosimetry“, in book Voronoi's Impact on Modern Science, Institute of Math National Acad. of Sciences of Ukraine, Kiev, Eds. P.Engel, H.Syta,1998. pp.165-175.

[4] S. Sastry, T. M. Truskett, P. G. Debenedetti, S. Torquato, and F. H. Stillinger, “Free Volume in the Hard-Sphere Liquid”, Molecular Physics, vol. 95, 1998, p. 289.

[5] G. Malavasi, M. C. Menziani, A.Pedone, U.Segre, “Void size distribution in MD-modelled silica glass structures”, Journal of Non-Crystalline Solids, vol 352, 2006, pp. 285–296.

[6] S. Rémond, J. L. Gallias, A. Mizrahi, “Characterization of voids in spherical particle systems by Delaunay empty spheres”, Granular Matter, vol.10, 2008, pp. 329–334.

[7] M. D. Haw, “Void structure and cage fluctuations in simulations of concentrated suspensions”, Soft Matter, vol. 2, 2006, pp. 950–956.

[8] B.J. Sung, A. Yethiraj, ‘Structure of void space in polymer solutions”, Phys. Rev. E vol. 81, 2010, 031801.

[9] M. G. Alinchenko, A. V. Anikeenko, N. N. Medvedev and V. P. Voloshin, M. Mezei, P. Jedlovszky, “Morphology of voids in molecular systems. A Voronoi-Delaunay analysis of a simulated DMPC membrane,” J. Phys. Chem. B, vol. 108 (49), 2004, 19056–19067.

[10] H. Edelsbrunner, M. Facello, J. Liang, “On the definition and construction of pockets in macromolecules”, Discr Appl Math, vol.88, 1998, pp. 83-102.

[11] J. Liang J, H. Edelsbrunner, P. Fu, P. Sudhakar, S. Subramaniam, “Analytical shape computation of macromolecules: II. Inaccessible cavities in proteins”, Proteins: Struct. Func. Genet., vol. 33, 1998, pp. 18-29.

[12] D. Kim, C.-H. Cho, Y. Cho, J.Ryu, J. Bhak, D.-S.Kim, “Pocket extraction on proteins via the Voronoi diagram of spheres”, Journal of Molecular Graphics and Modelling, vol. 26 (7), 2008, pp. 1104-1112.

[13] T.M. Raschke, M. Levitt, “Nonpolar solutes enhance water structure within hydration shells while reducing interactions between them”, PNAS, vol. 102 (19), 2005, pp. 6777–6782.

[14] C. Schröder, T. Rudas, S. Boresch, O. Steinhausera, “Simulation studies of the protein-water interface. I.Properties at the molecular resolution” J. Chem. Phys, vol. 124, 2006, 234907.

[15] B. Bouvier, R. Grünberg, M. Nilges, F. Cazals, “Shelling the Voronoi interface of protein-protein complexes predicts residue activity and conservation”, Proteins: Structure, Function, and Bioinformatics, vol. 76(3), 2008, pp. 677 – 692.

[16] G.Neumayr, T.Rudas, O. Steinhausera, „Global and local Voronoi analysis of solvation shells of proteins” J. Chem. Phys. vol. 133, 2010, 084108.

[17] V.P. Voloshin, N.N. Medvedev, M.N. Andrews, R.R. Burri, R. Winter, A. Geiger, “Volumetric Properties of Hydrated Peptides: Voronoi-Delaunay Analysis of Molecular Simulation Runs”, J. Phys. Chem. B, vol. 115 (48), 2011, pp 14217–14228.

[18] A. Okabe, B. Boots, K. Sugihara, S. Chiu, Spatial tessellations - concepts and applications of Voronoi diagrams, New York: John Wiley & Sons, 2000.

[19] Medvedev, N.N. “Voronoi-Delaunay method for non-crystalline structures. SB of Russian Academy of Science, Novosibirsk (2000) (in Russian)

[20] F. M. Richards, “Calculation of molecular volumes and areas for structures of known geometry,” Methods in Enzymology, vol. 115, 1985, pp. 440–464.

[21] B. J. Gellatly, J. L. Finney, “Calculation of protein volumes: an alternative to the Voronoi procedure,” J. Mol. Biol., vol. 161, 1982, pp. 305-322.

[22] S.V.Anishchik, N.N.Medvedev, “Three-dimensional Apollonian packing as a model for dense granular systems”, Phys.Rev.Lett., vol. 75(23), 1995, pp.4314-4317.

[23] N.N. Medvedev, V.P. Voloshin, V.A. Luchnikov, and M.L. Gavrilova, “An algorithm for three-dimensional Voronoi S-network”, J. Comput. Chem. vol. 27, 2006, pp. 1676–1692.

[24] F. Aurenhammer, “Power diagrams: properties, algorithms and applications,” SIAM J Comput, vol. 16, 1987, pp. 78–96.

[25] D.-S. Kim, Y. Cho, K. Sugihara, “Quasi-worlds and Quasi-operators on Quasi-triangulations”, Computer-Aided Design, vol. 42(10), 2010, pp. 874-888.

[26] T. Aste, K.Y. Szeto, and W.Y. Tam, “Statistical properties and shell analysis in random cellular structures”, Phys.Rev.E, vol. 54 (5), 1996, pp. 5482-5492.

[27] M. N. Andrews, and R. Winter, "Comparing the Structural Properties of Human and Rat Islet Amyloid Polypeptide by MD Computer Simulations", Biophys. Chem. vol. 156, 2011, pp. 43-50.

[28] L. Mitra, N. Smolin, R Ravindra, C. Royer, R Winter. “Pressure perturbation calorimetric study of the solvation properties and the thermal unfolding of proteins in solution - experiment and theoretical interpretation”, Phys.Chem. Chem. Phys. vol. 8, 2006, pp. 1249–1265.