Geometry for Modeling Biomolecules

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Space filling diagrams are geometric models of molecular conformations in three-dimensional space. Each atom is a location is space and a quantitative expression of influence on the immediate surrounding. This paper surveys the basic types of space filling diagrams with a focus on the dual alpha shape. Properties of those diagrams that relate to questions of connectivity, size, shape and symmetry, and metamorphosis are discussed.

1 Introduction

The concept of a molecule seems to be an essential and stable ingredient in scientific studies of microscopic events. Still, people's understanding and image of what molecules are has changed with time. Even today the question whether there are atoms can still be asked, Bader [3]. We rephrase and ask whether it is *useful* to postulate the existence of atoms, and if yes, what model of an atom is most productive. This is the utilitarian viewpoint which is adopted in this paper, but the question is directed towards molecules. Since even the utilitarian goal is rather ambitious, we claim without justification that some of the most useful models are geometric. We then go ahead and survey a class of geometric models known as space filling diagrams.

Geometry in biology. There is in fact a large body of evidence in favor of the thesis that geometry plays an important role in life on the microscopic level. One of the most striking insights generated by decades of research is that geometric shape decides how biomolecules function. We quote Rose [39]: "What role a protein takes in the grand biological opera depends on exactly one thing: its shape. For a protein molecule, function follows form." It thus seems imperative to design and fabricate refined tools that permit focussed probes into the geometry of this opera. It is likely that such tools will find use in the design of drugs, in the classification of molecular components, in simulating docking and folding processes, etc.

Purpose and scope. The goal of this paper is a biased survey of space filling diagrams used to model large molecules. The bias follows the author's background and is directed towards topological, geometric, and algorithmic properties of these models. Even within this narrow scope, the reader will find a bias towards the author's own work, for which the author apologizes.

The methods used and discussed in this paper come primarily from combinatorial disciplines within topology, geometry, and algorithms. Among the many textbooks in these areas we recommend the following: the short monograph by Alexandrov [2] for an easy and intuitive introduction to topology, the text by Guillemin and Pollack [24] for an introduction to differential ideas in topology, the two-volume handbook edited by Gruber and Wills [23] for a broad coverage of discrete geometry, and the text by Cormen, Leiserson and Rivest [9] for a comprehensive introduction to combinatorial algorithms.

Outline. Section 2 describes four types of space filling diagrams. Section 3 introduces the alpha shape, which is dual to these diagrams. Section 4 focuses on holes in molecules. Section 5 studies formulas for measuring the geometric size of a molecule. Section 6 considers questions of shape and symmetry. Section 7 discusses the phenomena of change under growth and motion. Section 8 concludes the paper.

2 Space Filling Models

The step from molecule to geometric shape is facilitated by space filling diagrams. This section introduces four types: the Van der Waals model, the solvent accessible model, the molecular surface model, and the molecular skin model.

Van der Waals model. A molecule is a collection of atoms. Each atom, A_i, is specified by its type and a location in space: $z_i \in R^3$. The Van der Waals radius maps A_i to a positive real r_i that is the same for all atoms of the same type. The *Van der Waals* model of the molecule is a union of balls:

$$\mathsf{VW} \;=\; \{x \in R^3 \mid \exists i : \|x - z_i\| \leq r_i\},$$

see Figure 1. The Van der Waals radius is assigned

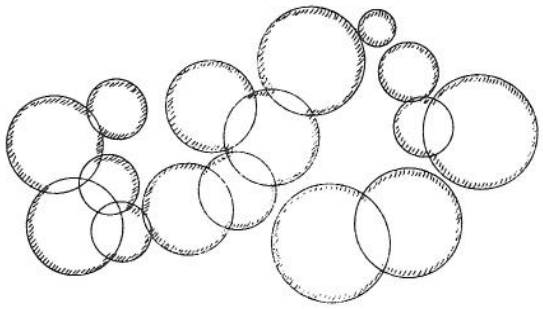

Figure 1: *Van der Waals model: each disk represents an atom specified by its center and radius.*

so atoms in non-binding position do not overlap, see Creighton [10]. Since overlap depends on two atoms and not on one, we can imagine a certain amount of ambiguity in the assignment of radii and it seems indeed common that different research schools in molecular biology use slightly different maps.

Solvent accessible model. Interaction between the Van der Waals model and a solvent represented as an omnipresent sphere of radius ϱ is studied by increasing the radius of every atom ball by ϱ. A solvent sphere is disjoint from VW iff its center lies outside the *solvent accessible* model define by Lee and Richards [30, 38] as the union of enlarged balls:

$$\mathsf{SA} \;=\; \{x \in R^3 \mid \exists i : \|x - z_i\| \leq r_i + \varrho\},$$

see Figure 2. The overlap free positions of the solvent

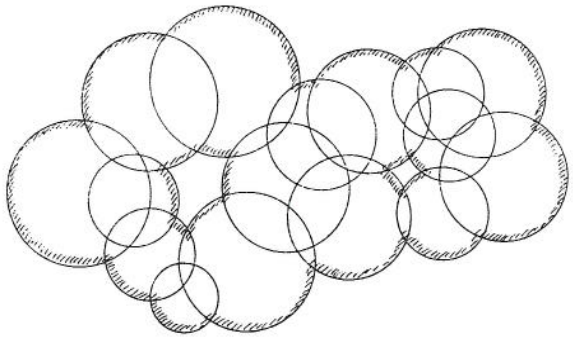

Figure 2: *Solvent accessible model: the radius of each disk in Figure 1 is increased by a constant, which is the radius of the solvent.*

are exactly the centers in the complement of SA. It follow that a solvent particle can move between locations $x, y \in R^3$ without touching VW iff x and y belong to the same component of the complement of SA.

Molecular surface model. A model that resembles in size the Van der Waals and in connectivity the solvent accessible model is the *molecular surface* model. It consists of all points $x \in R^3$ that lie outside all solvent spheres disjoint from VW:

$$\mathsf{MS} \;=\; \{x \in R^3 \mid \forall y \notin \mathsf{SA} : \|x - y\| > \varrho\},$$

see Figure 3. According to Michael Connolly, the molecular surface model was originally introduced by Greer and Richards. The first computer program for constructing its surface is due to Connolly [7]. The surface is generated by a sphere of radius ϱ rolling about VW. The envelope of this motion is a surface that bounds MS. It consists of sphere and torus patches connected in a tangent continuous manner. Because of

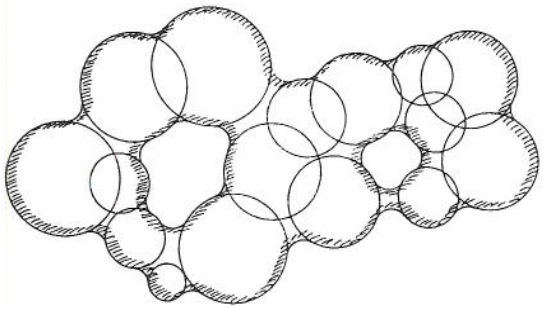

Figure 3: *Molecular surface model: a circle representing the solvent rolls about the Van der Waals model.*

occasional self-intersections, this surface is in general different from the boundary of MS. Two consequences are that the boundary is not everywhere tangent continuous, and that MS and SA do not necessarily have the same homotopy type.

Molecular skin model. Think of the torus patches of MS as blending surfaces that connect neighboring spheres in VW. A similar but different blending effect is achieved by shrinking an infinite family of spheres. The family, F, is obtained by increasing each radius by a factor $\sqrt{2}$ and adding combinations of 2, 3, and 4 balls. The *molecular skin* model is the union of the family after shrinking the radius of every ball by a factor $\frac{\sqrt{2}}{2}$:

$$\mathsf{SK} \quad = \quad \{x \in R^3 \mid \exists (z,r) \in F : \|x - z\| \leq \frac{\sqrt{2} \cdot r}{2}\}.$$

Details of this construction including a precise specification of F can be found in section 6. The surface of SK consists of sphere and hyperboloid patches that meet in a tangent continuous manner. Similar to MS, the molecular skin model is not homotopy equivalent to SA, but it is homotopy equivalent to the union of atom balls whose radii are increased by a factor of $\sqrt{2}$. A property unique to SK is a symmetry between inside and outside useful in studies of complementarity.

3 Dual Models

The space filling models have a common dual counterpart. To construct it we introduce the Voronoi diagram that decomposes the union of balls into convex pieces. This union could either be a Van der Waals or a solvent accessible model. The overlap between the pieces defines what we call the dual complex.

Voronoi cells. The *weighted distance* of a point $x \in R^3$ from A_i is $\pi_i(x) = \|x - z_i\|^2 - r_i^2$. For $r_i = 0$ this is the same as the square of the Euclidean distance. Weighted distance is defined for any real so possibly also negative square radius. The corresponding extension from real to imaginary radii and balls is useful in sections 6 and 7 when we talk about the complement and metamorphosis of a molecule. The *Voronoi cell* of A_i is the region of points whose weighted distance to A_i is at least as small as to any other ball:

$$V_i \quad = \quad \{x \in R^3 \mid \forall j : \pi_i(x) \leq \pi_j(x)\},$$

see Figure 4. Each Voronoi cell is an intersection of

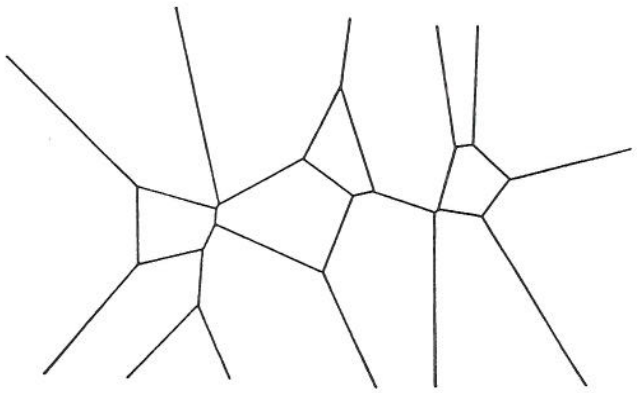

Figure 4: *Voronoi cells: each atom generates a convex polyhedron.*

closed half-spaces and therefore a convex polyhedron. Any two cells overlap at most along some piece of their boundary, and together the collection of cells covers the entire R^3. To simplify the exposition we assume throughout this paper that the balls are in non-degenerate position. With this assumption the common intersection of $k + 1 \geq 1$ Voronoi cells is either

empty or a common $(3-k)$-dimensional face. For $k \geq 4$ the common intersection is always empty.

The cells are named after the Russian mathematician Voronoi who studied the geometry of numbers [40]. The terminology in the literature is not entirely uniform and Voronoi cells are also known as power cells, Dirichlet cells, Thiessen polygons, etc.

Delaunay complex. The Delaunay complex is a collection of simplices that records the overlap pattern among Voronoi cells. Specifically, the complex contains the convex hull of $k+1$ ball centers iff the corresponding $k+1$ Voronoi cells have a non-empty common intersection. To develop the necessary mathematical notation let B be a subset of $k+1$ atoms and define $z_B = \{z_i \mid A_i \in B\}$ and $V_B = \{V_i \mid A_i \in B\}$. The *Delaunay complex* is

$$\mathcal{D} \;=\; \{\sigma = \operatorname{conv} z_B \mid \bigcap V_B \neq \emptyset\},$$

see Figure 5, where $\operatorname{conv} z_B$ denotes the convex hull of the points in z_B. The non-degenerate position assumption implies that the points in z_B are affinely independent and their convex hull is a simplex of dimension $\operatorname{card} B - 1$.

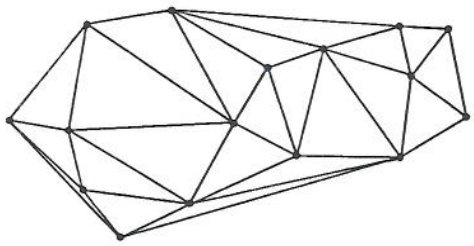

Figure 5: *Delaunay complex: Voronoi cells are represented by vertices and the pairwise and triplewise overlap among cells is represented by edges and triangles.*

The complex is named after the Russian mathematician Delaunay, also Delone, who defines the complex as the collection of cells that satisfy the empty sphere property [11]. For a set of points the condition is expressed in terms of spheres passing through points. The generalization to a set of balls is expressed in terms of spheres that are *orthogonal* to balls, which means the square distance between their centers equals the sum of square radii.

Fact 1 *$\sigma = \operatorname{conv} z_B$ belongs to $\mathcal{D}$ iff there is a ball orthogonal to all $A_i \in B$ and further than orthogonal from all other balls.*

Dobkin and Laszlo [13] design a data structure for storing a 3-dimensional Delaunay complex and Facello [21] describes the implementation of an incremental algorithm for constructing it.

Alpha shape. In order to apply duality to molecules it is necessary to restrict the construction of simplices to the portions of Voronoi cells covered by the atom balls. This leads to the definition of alpha complexes and alpha shapes. Observe first that the Voronoi cells decompose the union of balls into convex regions: $V_i \cap \mathsf{VW} = V_i \cap A_i$. The *dual* or *alpha complex* records the overlap pattern among these regions:

$$\mathcal{K} \;=\; \{\sigma = \operatorname{conv} z_B \mid \bigcap V_B \cap \bigcap B \neq \emptyset\},$$

see Figure 6. The dual complex is a subcomplex of the Delaunay complex: $\mathcal{K} \subseteq \mathcal{D}$. The *alpha shape* is the union of simplices in $\mathcal{K}$. It is often convenient to ignore

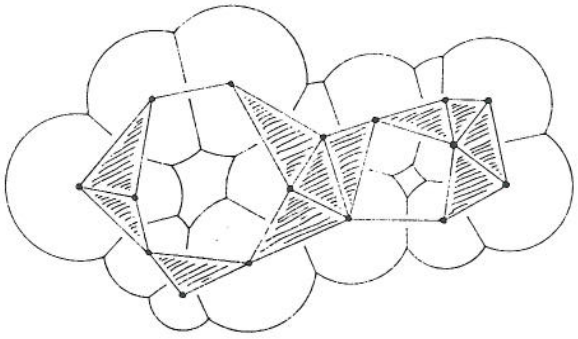

Figure 6: *Dual or alpha complex: it contains the subset of simplices in $\mathcal{D}$ that record overlap among Voronoi cells that reach into the union of balls.*

the difference between alpha shape and alpha complex, but sometimes it is essential to remember that the former is a polyhedron and thus a subset of space while the latter is a complex and therefore a combinatorial structure.

Alpha shapes have been introduced for points in the plane by Edelsbrunner, Kirkpatrick and Seidel [19]. They have been generalized to points in three dimensions by Edelsbrunner and Mücke [20] and to balls in general dimensions by Edelsbrunner [14]. The alpha is a parameter that expresses growth of balls. When we talk about a fixed set of balls this parameter is irrelevant, but it will be used in section 7 where simultaneous growth of atom balls is discussed.

Duality. As a first application we mention the use of the alpha shape in constructing the dual union of balls. Consider for example the Van der Waals model: $\mathsf{VW} = \bigcup_i A_i$. The boundary of VW consists of sphere patches that meet along circular arcs and corner points. We call these k-patches, for $k = 2, 1, 0$. The direct construction of the patches is made difficult by numerical inaccuracies resulting from the use of floating-point computation. A more robust strategy is to first compute the alpha complex and to use the dual correspondence for all decisions on patch overlap. This idea has been implemented by Akkiraju and Edelsbrunner [1] who construct a triangulation of the surface. Another fast algorithm for constructing the surface, but not a triangulation, is described in Halperin and Overmars [25].

The particular dual correspondence useful in this context relates the boundary of VW with the boundary of the alpha shape, see Figure 6. To express the correspondence let B be a set of $k+1$ balls and define S_B as the set of spheres bounding the balls in B.

Fact 2 *The intersection of the spheres, $\bigcap S_B$, contains a $(2-k)$-patch of the boundary of* VW *iff the simplex $\sigma = \operatorname{conv} z_B$ belongs to the boundary of the alpha shape. Furthermore, a patch is face of another patch iff the corresponding simplex of the latter is a face of the corresponding simplex of the former patch.*

4 Connectivity

A topologically interesting aspect of molecules is their connectivity. It is fairly common for biomolecules to have tunnels and voids. A tunnel is a hole through the molecule that is accessible from the outside whereas a void is a hole that is completely surrounded by atoms. Classifying and counting holes is one of the major topics in topology. A particularly useful formalism is that of homology groups and Betti numbers, see e.g. Munkres [33]. Curiously, the type of holes that is most important in the study of biomolecules is not a hole in the topological sense at all. These holes are cavities or depressions through which biomolecules interact. They are called hollows in the philosophical treatment of holes by Casati and Varzi [5] and pockets in this paper.

Voids and dual simplex sets. A *void* of a shape $M \subseteq R^3$ is a bounded component of the complement, $R^3 - M$. For example, the solvent accessible model $M = \mathsf{SA}$ in Figure 2 has two voids, and so does the corresponding alpha shape in Figure 6. That this is not a coincidence follows from a general result implied by the nerve theorem first proved by Leray [31].

Fact 3 *A union of balls and the corresponding alpha shape are homotopy equivalent.*

In a nutshell this means that the two are connected the same way: they have the same type, number, and arrangement of holes. The correspondence between the two shapes can be made geometrically more specific, see Figure 6.

Fact 4 *A union of balls contains the corresponding alpha shape, and each void of the alpha shape contains the corresponding void of the union of balls.*

A void of the alpha shape is covered by a collection of simplices that belong to $\mathcal{D}$ but not to $\mathcal{K}$. We call this the *dual simplex set* of the void. Each dual simplex set is open at the boundary. Applications of these sets will be discussed in section 5.

Pockets. Cavities that are not voids are more difficult to define because it is not immediately clear where

they should start and what criterion can be used to differentiate shallow depressions from ones that should be taken seriously. Connolly [8] sought to visualize such cavities indirectly through highlighting the skeleton of the complement. Kuntz [27] identifies a region of the complement as a cavity if a sphere can get stuck there.

We follow the approach of Edelsbrunner, Facello and Liang [18] who use an acyclic relation of the tetrahedra in the Delaunay complex to define pockets. Specifically, let the *orthosphere* of a tetrahedron $\sigma = \operatorname{conv} z_B$ be the unique sphere orthogonal to all four balls in B. Two tetrahedra form a pair in the relation, $\sigma \preceq \tau$, if they share a common triangle and the center of the orthosphere of σ lies on τ's side of the triangle. Similarly, we set $\sigma \preceq \infty$ if one of the triangles of σ belongs to the convex hull and the center of the orthosphere lies on the other side of that triangle. Take all tetrahedra in $\mathcal{D} - \mathcal{K}$, arrange them in groups defined by shared descendents, and remove the group containing ∞. For each remaining group add the faces that do not belong to $\mathcal{K}$ and combine two groups if they share at least one triangle. The result is what we call the *dual simplex sets* of pockets. A *pocket* is the part of space outside the ball union covered by simplices in its dual simplex set. In the end, the notion of pocket is very similar to Kuntz's ideas about cavities.

The dual simplex set of a pocket is typically partially open and partially closed. Define the *mouth* as a component of boundary simplices. Each mouth describes a connection between the pocket and the space outside the molecule. A void is a pocket without mouth. Figure 7 shows a large pocket formed by the HIV-1 protease molecule. Pockets of one molecule naturally interact with protrusions of another. It is desirable to define a protrusion in a symmetric manner, such as the pocket of the complement. This is indeed possible once we understand that the structure of the complement can also be expressed in terms of finite sets of balls, see section 6.

Computing and counting holes. The three types of topological holes of a molecule are counted by Betti numbers, which are the ranks of the three possibly non-trivial homology groups. Definitions of these concepts are technically fairly involved and can be found in every text on algebraic topology. Intuitively, the Betti number β_0 counts the components, β_1 counts the independent tunnels, and β_2 counts the voids. Traditional algorithms, such as the matrix manipulation method described in Munkres [33], are impractical for the size of complexes that arise as duals of biomolecules. An algorithm that is efficient in R^3 is developed by Delfinado and Edelsbrunner [12]. It computes all three Betti numbers using a filter of the Delaunay complex. This is a linear ordering of the simplices so every prefix is a subcomplex, and the alpha complex is one such prefix. The simplices following the alpha complex in the filter form the dual simplex sets of all voids and of the outside of the molecule.

The filter can be extended to also represent the relation over the tetrahedra needed to define dual simplex sets of pockets. The Betti number algorithm can then be extended and compute pockets by collecting simplices of $\mathcal{D}-\mathcal{K}$ in groups as determined by the relation, see Edelsbrunner, Facello and Liang [18].

5 Geometric Size

There is a connection between the topological complex representation of a molecule and its geometric size. We restrict the discussion to the volume of a union of balls and a void, but similar formulas also exist for surface area and length of arcs.

Inclusion-exclusion. This combinatorial principle expresses the volume of a union of balls as an alternating sum of volumes of common intersections:

$$\operatorname{vol} \bigcup A = \sum_{B \subseteq A} (-1)^{\operatorname{card} B - 1} \operatorname{vol} \bigcap B.$$

The number of terms is exponential in the number of balls, and the volume of $\bigcap B$ is progressively more difficult to evaluate as the cardinality of B increases. Kratky [26] observed that most of the terms in the inclusion-exclusion formula are redundant, and this includes the non-zero terms many of which cancel. Specifically, he considered the common intersection of a finite collection of disks and proves that there is an

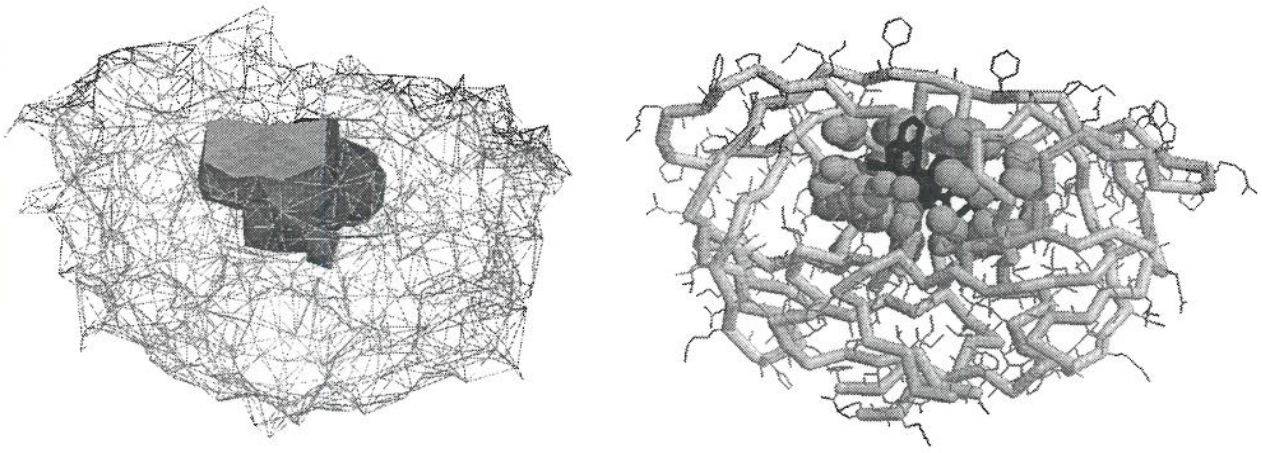

Figure 7: *HIV-1 protease: dual simplex set inside alpha shape to the left, and pocket indicated by balls defining the wall of the pocket to the right.*

exact inclusion-exclusion formula that contains only terms for sets B of cardinality 1, 2 and 3. Scheraga and collaborators use the generalization of Kratky's result to balls in R^3 in their software for volume computation [36].

Truncated formulas. A weakness of Kratky's result is that it does not specify which terms of the basic inclusion-exclusion formula are redundant. For example, the formula that simply takes all terms for sets B of cardinality 1, 2, 3 is not correct. Naiman and Wynn [34] observe that the formula that has a term for each Delaunay simplex is exact. Even this formula contains redundant information, and the smallest inclusion-exclusion formula that gives the exact volume contains a term for each simplex in the alpha complex.

Fact 5 *The volume of a union of balls is*

$$\mathrm{vol} \bigcup A = \sum_{\sigma \in \mathcal{K}} (-1)^{\mathrm{card}\, B - 1} \mathrm{vol} \bigcap B,$$

where B is the set of balls so that $\sigma = \mathrm{conv}\, z_B$.

This result is due to Edelsbrunner [14] who proves it by integration over Euler characteristics. All intersections of $k+1$ balls that correspond to k-simplices in $\mathcal{K}$ have the same combinatorial type, see Figure 8. For this

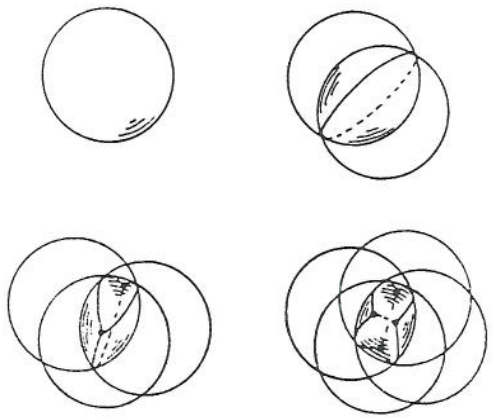

Figure 8: *The common intersection of 1, 2, 3, 4 spherical balls.*

reason the formula in Fact 5 is significantly easier to implement than that over simplices in $\mathcal{D}$.

The proof in [14] reveals a relationship between the union of balls in R^3 and a convex polyhedron in R^4.

More generally, one can consider the union of intersections of balls, which corresponds to a possibly non-convex polyhedron in R^4. Edelsbrunner [15] shows that the volume can be computed with a truncated inclusion-exclusion formula derived from the boundary complex of that polyhedron.

Angle-weight formulas. The volume of a void can be computed using Fact 5 if we first fill the void with balls and then subtract from the total volume the volume of the original molecule. This seems roundabout and indeed there is a direct formula based on the dual simplex set. For a tetrahedron σ and a face τ define the *angle*, $\varphi_{\tau,\sigma}$, equal to $\frac{1}{2}$ if τ is a triangle, equal to the dihedral angle at τ if it is an edge, and equal to the solid angle at τ if it is a vertex. The volume is the total volume of the dual simplex set minus its intersection with the ball union.

Fact 6 *The volume of void V with dual set of tetrahedra T is*

$$\begin{aligned}\operatorname{vol} V &= \sum_{\sigma\in T} \operatorname{vol}\sigma \\ &\quad + \sum_{\sigma\in T}\sum_{\sigma\supseteq\tau\in\mathcal{K}} (-1)^{\operatorname{card} B}\cdot\varphi_{\tau,\sigma}\cdot\operatorname{vol}\bigcap B,\end{aligned}$$

where B is such that $\tau = \operatorname{conv} z_B$.

The dimension of any simplex τ in the above formula is at most 2. The terms are therefore restricted to intersections of at most 3 spheres.

Experimental results. The alpha shapes software includes the implementation of inclusion-exclusion formulas for volume and surface area and has been publically available for many year at `ftp.ncsa.uiuc.edu`. Its functionality with a focus on geometric size is described in Edelsbrunner, Facello, Fu and Liang [17]. Peters, Fauck and Frömmel use the software to automatically identify ligand binding sites near the boundary of proteins [37].

The more recent facility to identify and compute pockets is used by Liang and McGee to estimate hydration change due to osmotic stress [32]. Edelsbrunner, Liang and Woodward [29] use the software and extensions of the inclusion-exclusion formulas to pockets for the purpose of gathering statistical data about average sizes of pockets and mouths and computing correlation to the size of ligands, etc. For general binding sites they observe a remarkable variety in size, and for the HIV-1 protease molecule they measure a surprisingly large range of sizes for a flexible pocket that adjusts to the binding ligand.

6 Shape and Symmetry

Questions of complementarity are common in biology, and Blaney and Dixon [4] study the problem of molecular docking where complementarity assumes a concrete geometric meaning. An interesting special case arises when one type of molecule forms aggregates where the molecule docks with a copy of itself. To do this the molecule must be locally self-complementary. This section studies the molecular skin model, which provides a means to realize perfect complementarity.

Body and skin. Given a finite set of atom balls, A_i, the skin is obtained as the envelope of an infinite family, F. We generate this family through addition and scaling. A ball is the preimage of the weighted distance function $\pi_i : R^3 \to R$: $A_i = {\pi_i}^{-1}(-\infty, 0]$. Addition and multiplication with a scalar are well defined and give rise to the vector space of functions. We borrow the vector space for the balls and define

$$\sum \gamma_i \cdot A_i \;=\; \pi^{-1}(-\infty, 0],$$

where $\pi(x) = \sum \gamma_i \cdot \pi_i(x)$. In this vector space we define the convex hull of the A_i as the set of combinations $\sum \gamma_i \cdot A_i$ with $\sum \gamma_i = 1$ and $\gamma_i \geq 0$ for every i, as usual. For each ball (z, r) in the convex hull, the infinite family F contains the ball $(z, \frac{\sqrt{2}r}{2})$, which is a shrunken copy that shares the same center. The *body* is the union of balls in F, and the *skin* is the envelope, see Figure 9. The only difference between the body and the molecular skin model in section 2 is that the latter first grows the balls to compensate for the shrinking effect inherent in the construction. The definition of body and skin is due to Edelsbrunner [16]. Some of the important properties are:

Fact 7 *The body and the union of the A_i are homotopy equivalent.*

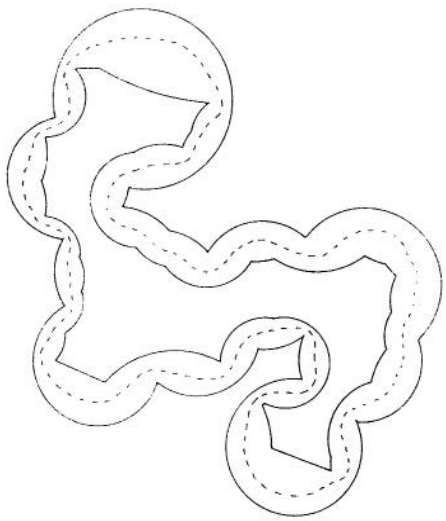

Figure 9: *From outside in: boundaries of the union, the body, and the complement of the union of orthogonal disks.*

Together with Fact 3 this implies that the body is homotopy equivalent to the alpha shape.

Fact 8 *The skin consists solely of sphere and hyperboloid patches, and in the non-degenerate case it is everywhere tangent continuous.*

The exception to tangent continuity happens when two of the atom balls touch and the point where they touch lies on the boundary of the union. In this case the hyperboloid that blends between the two spheres degenerates to a double-cone and tangent continuity is violated at the apex of that double-cone.

Complementarity. We use a fundamental symmetry between Voronoi and Delaunay complexes to represent the complement of a molecule by another finite set of balls. The idea is similar to the computer program DOCK by Kuntz and collaborators where a pocket is filled with balls to get a positive imprint [28]. We replace the heuristic filling process by a canonical construction.

Recall that each tetrahedron $\sigma \in \mathcal{D}$ corresponds to a vertex shared by four Voronoi cells. Let $B_j = (y_j, q_j)$ be the ball whose center, y_j, is that Voronoi vertex and whose square radius, q_j^2, is the weighted distance of y_j from any one of the four balls that generate the four Voronoi cells. By construction, B_j is orthogonal to the four balls and further than orthogonal from all other A_i. To complete the construction we add an infinitely large ball (a half-space) with center at the infinite end of every unbounded Voronoi edge. An example is shown in Figure 9 where the innermost curve is the boundary of the union of the B_j. The new set of balls has some possibly surprising properties.

Fact 9 *The complement of the interior of the* $\bigcup_j B_j$ *is contained in and homotopy equivalent to* $\bigcup_i A_i$.

This implies that the A_i and B_j together cover the entire R^3.

Fact 10 *The skin of the* B_j *is the same as the skin of the* A_i. *The bodies of the two sets are complementary and intersect in the common skin.*

Protrusions. One of the applications of the set of balls B_j is that it facilitates the definition and construction of protrusions. Recall the definition of a pocket in section 4 and think of a pocket as a protrusion of the complement. Symmetrically, we can think of a protrusion as a pocket of the complement.

Consider the Delaunay complex of the B_j, which is the same as the set of Voronoi cells of the A_i together with their faces. The dual complex of the B_j is a subcomplex of that Delaunay complex. Define a relation over the cells, as in section 4, and group the cells and their faces outside the dual complex to form dual cell sets of pockets. One difficulty with this approach is the asymmetry with respect to ∞, which is part of the old but not of the new relation. We can either manually pick cells and remove the groups that contain them, or we can construct another set of balls C_k from the non-imaginary B_j, the same way as the B_j are derived from the A_i. Because we select only non-imaginary balls, the set of C_k is not equal to the set of A_i, but their union and body are the same. The cell generated by the largest of the C_k would be the best candidate to play the role of ∞ in the construction of protrusions.

While the Delaunay complex of the A_i is simplicial, if we assume non-degenerate position, the Delaunay

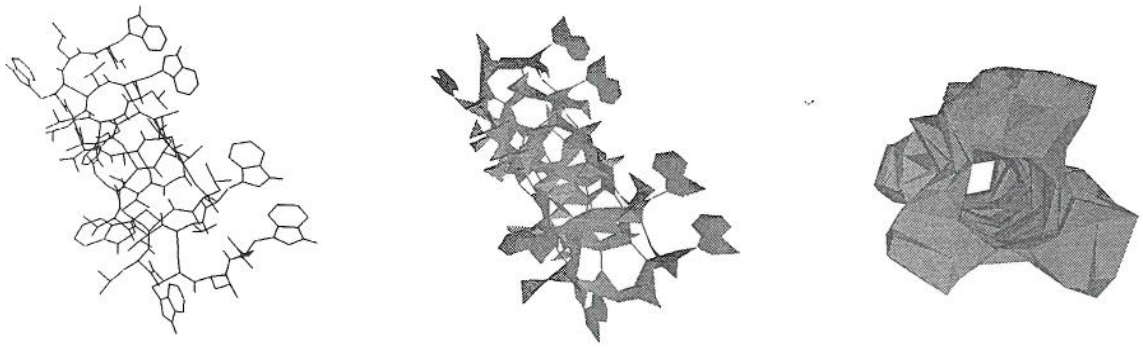

Figure 10: *Three alpha shapes of the Gramicidin A molecule. The parameter α grows from left to right.*

complex of the B_j is simple. This is because it is not defined by input data but rather by balls derived from the input data.

7 Metamorphosis

The assumption of static molecules with fixed atoms is convenient but certainly not realistic and therefore of limited use.

Growth. A simple form of change is growth, but even in this framework there is more freedom than can be controlled. Alpha shapes are designed to control simultaneous growth with only one parameter: α^2. Similar to the square radii, α^2 can be negative in which case α is imaginary. For a given $\alpha^2 \in R$ we define

$$A_i(\alpha) \quad = \quad (z_i, \sqrt{r_i^2 + \alpha^2}).$$

For vanishing α we have the original balls, and for vanishing r_i we have all balls of the same radius, α. The *α-complex*, $\mathcal{K}_\alpha$, is the dual complex of the union of the $A_i(\alpha)$. An example is shown in Figure 10.

In this framework smaller balls grow faster than larger ones and as α grows all balls converge to radius α. The ramification of the quadratic growth formula is computational efficiency. The weighted distance of $x \in R^3$ from $A_i(\alpha)$ is

$$\|x - z_i\|^2 - r_i^2 + \alpha^2 \quad = \quad \pi_i(x) + \alpha^2.$$

In words, the ordering of the balls by weighted distance of x does not change with changing α. It follows that the Voronoi cells remain unchanged and so does the Delaunay complex. The only thing that changes with growing α is that $\mathcal{K}_\alpha$ contains more and more simplices of $\mathcal{D}$ until, for large enough α, we have $\mathcal{K}_\alpha = \mathcal{D}$. An interesting application that still needs to be explored is the use of the hierarchy of α-complexes in algorithmic approaches to shape matching as it occurs in the simulation of docking processes.

The difference between the Van der Waals and the solvent accessible models of the A_i can generally not be bridged by quadratic growth. In this case we observe linear growth defined by

$$A_i(\alpha) \quad = \quad (z_i, r_i + \alpha).$$

A computationally reasonable efficient approach to representing this one-parametric family constructs the Delaunay complex for the $A_i(0) = A_i$ and adopts the complex through edge and triangle flips as α changes continuously. Details are described by Facello [22].

Motion. A molecular shape represented by a space filling diagram deforms if the atom balls move about. Possibly the geometrically cleanest deformations are observed when the molecular skin model is used. It remains tangent continuous at all times except at points in time and space where it changes topology. The

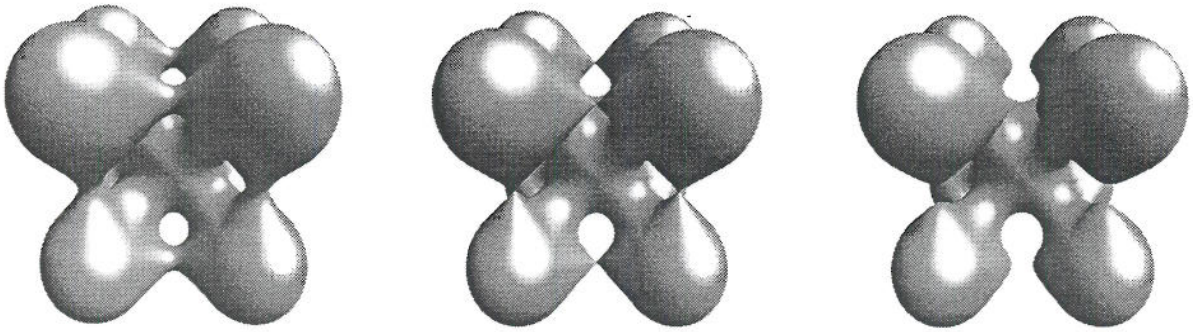

Figure 11: *Three skins of the same nine balls that go through a small amount of shrinking.*

breaking of a connection is locally realized by a hyperboloid of one sheet that gets narrower, becomes a double cone, and flips over to a hyperboloid of two sheets, see Figure 11. The creation of a tunnel goes through the same sequence backwards and with inside and outside exchanged.

A possible application of general motion is, for example, the visualization of the folding process. The driving force of the motion could be a molecular dynamics software, such as the one created by Schulten and collaborators [35]. The numerical simulation produces snap shots of the computed motion that need to be connected by small interpolating homotopies. A full implementation of such a system could be used to efficiently and accurately track any size and topology change during the motion. This information can be fed back into the software that computes the motion for the next time step.

Space of shapes. The ability to canonically deform shapes opens up the possibility to construct spaces of shapes. This idea is pursued by Cheng, Edelsbrunner, Fu and Lam who use a single parameter to control the deformation from one shape to another [6]. To sketch the particulars of the method, let the two shapes be the skins of two sets of balls, X and Z. At time $t \in [0,1]$ the set of moving balls is

$$Y(t) \quad = \quad \{(1-t) \cdot X_i + t \cdot Z_j \mid X_i \in X, Z_j \in Z\}.$$

Even far apart balls X_i and Z_j are matched, but due to the vector space of balls their combination is usually redundant as it shrinks away on its trip from X_i to Z_j. The time parameter defines a 1-dimensional space of shapes. Members of this space can be combined with a third shape, etc. With $k+1$ shapes, each the skin of a set of balls, we get a k-dimensional space of shapes. Any shape in this space is indexed by its barycentric coordinates that specify the fractions in which the given shapes contribute to the mixing of shapes.

It would be interesting to test this idea of shape indexing in the construction of databases for small drug compounds. To get the method off the ground we need, in addition to the synthesis algorithm outlined above, and analysis algorithm that finds for a given skin the best approximation within the space.

8 Conclusion

The author's personal interest in molecular biology is based on the strong connection to geometry and topology. He is still amazed, in fact, of the extent in which biological questions influenced his thinking about problems in quite a few seemingly unrelated areas.

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