

Theorems on Molecular Shape-Similarity Descriptors: External T-Plasters and Interior T-Aggregates

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Exterior T-plasters and interior T-aggregates, two new families of tools of molecular similarity analysis, provide shape comparisons between molecular bodies represented by electron density contours. Two theorems are proven, and some fundamental properties of T-plasters and T-aggregates are discussed, relevant to the shape-modifying effects of solvation layers and to the study of inner cavities filled with solvent molecules, such as water clusters in proteins.

INTRODUCTION

Quantum similarity measures originally introduced by Carbó provide a fundamental framework as well as practical means for a quantum mechanical description of similarity,^{1–11} involving, among other fields, pharmacological drug design. A very wide array of conceptual, theoretical, and computational methods has been applied to the problem of similarity of molecular bodies.^{12–24} In the present context, the shape group and related methods^{25–56} of molecular shape analysis represent the background for the introduction of shape comparisons in terms of two new types of objects derived from molecular electron densities: external T-plaster sets and interior T-aggregates.

Bond creation and bond breaking in chemical reactions as well as the shape changes in conformational processes are dominated by changes in the electronic density of molecules. The electronic density fully reflects the nuclear distribution, hence the electronic density and its changes account for all the relevant chemical information about the molecule. The shape analysis of the electronic density is of primary importance in molecular similarity analysis and in the interpretation of molecular properties.

For shape similarity analysis, the concepts of Density domain^{36,46,52} and Molecular Isodensity Contour (MIDCO) surface are of special importance. These descriptors are defined in terms of the electronic density $\rho(\mathbf{r})$. In SCF LCAO Hartree–Fock computational practice, an *ab initio* electronic density $\rho_A(\mathbf{r})$ of a molecule A of some fixed conformation K is usually computed by the relation

$$\rho_A(\mathbf{r}) = \sum_{i=1}^n \sum_{j=1}^n P_{ij} \varphi_i(\mathbf{r}) \varphi_j(\mathbf{r}) \quad (1)$$

given in terms of a basis set of atomic orbitals $\varphi_i(\mathbf{r})$ ($i = 1, 2, \dots, n$), where \mathbf{r} is the three-dimensional position vector variable and \mathbf{P} is the $(n \times n)$ -dimensional density matrix determined in the SCF *ab initio* calculation.

For the nuclear configuration K and some electron density threshold a , a density domain $DD(a, K)$ is the formal body^{36,46,52} enclosed by a molecular isodensity contour, MIDCO $G(a, K)$, defined as

$$DD(a, K) = \{\mathbf{r}: \rho(\mathbf{r}, K) \geq a\} \quad (2)$$

and

$$G(a, K) = \{\mathbf{r}: \rho(\mathbf{r}, K) = a\} \quad (3)$$

respectively. Note that in the usual mathematical terminology, the word “domain” is used with a different meaning.

Depending on the density threshold a and on the nuclear configuration K, a formal molecular body $DD(a, K)$ is either a single piece or it is composed from several disconnected pieces, the *maximum connected components* $DD_i(a, K)$ of $DD(a, K)$:

$$DD(a, K) = \bigcup_i DD_i(a, K) \quad (4)$$

The connectedness properties of density domains indicate that a given part of the molecule possesses a limited “autonomy” within the molecule. If for the given conformation K there exists a threshold a such that a connected density domain $DD_i(a, K)$ contains a subset of nuclei while the corresponding MIDCO $G_i(a, K)$ separates them from the rest of the nuclei of the molecule, then this subset of nuclei can be regarded as the *nuclear family* of a *functional group*. Using the connectedness properties of density domains, one can identify most of the important functional groups within molecules. Specifically, a maximum connected density domain component $DD_i(a, K)$, together with the collection of all nuclei within $DD_i(a, K)$, is regarded as a functional group of the molecule^{36,46,52} at the density threshold a .

The quantum chemical model of functional groups based on density domains is fully consistent with the general framework discussed earlier,⁴¹ where interrelations between families of functional groups are described by the algebraic structure of a lattice.

The MIDCOs, taken as the boundary surfaces of density domains, provide a detailed shape characterization of electron densities. One family of shape analysis techniques is based on the Shape Group Methods, that has been applied in similarity analysis within the pharmaceutical drug design context.^{31,50,51} The Shape Group Methods and related algebraic-topological computational techniques of similarity analysis^{25–56} have been reviewed recently.⁴⁴

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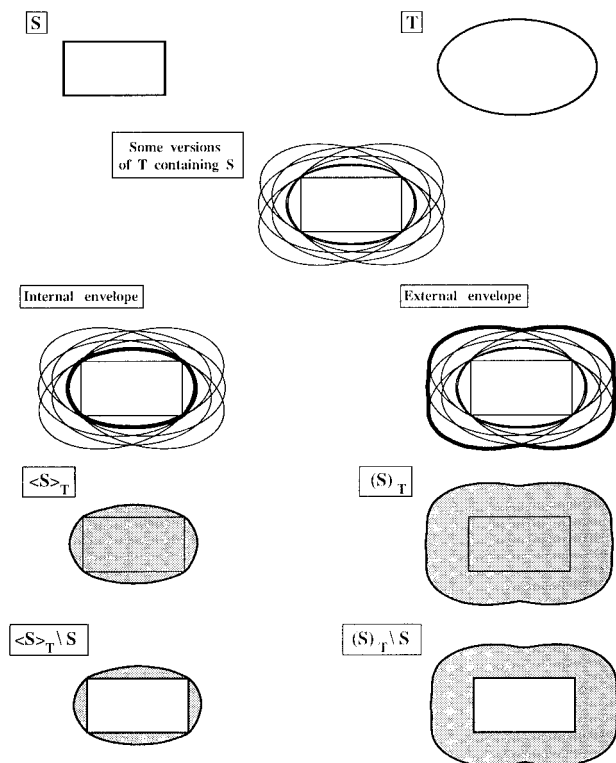


Figure 1. Illustration of the concept of T-hull $\langle S \rangle_T$ using the examples of a rectangle as set S and an ellipse as reference shape T . See text for detail.

Generalizations of convexity provide tools for shape analysis.⁵⁷ For both direct and indirect shape comparisons, for the representation of solvent contact surfaces, and for general similarity measures, an alternative technique, the T-hull method was proposed.⁵⁸

For a given reference object T , the ordinary T-hull $\langle S \rangle_T$ of an object S is defined⁵⁸ as the intersection of all rotated and translated versions of T which contain S . If a reference shape T is chosen, then other objects, S_1, S_2, \dots , can be compared to T and to one another by the method of T-hulls.⁵⁸ The T-hull is a generalization of the convex hull of objects according to a "bias" with respect to T . The introduction of T-hulls was motivated by an earlier generalization of convexity involving the α -hull of Edelsbrunner, Kirkpatrick, and Seidel.⁵⁷ The T-hull can be regarded as a generalization of the α -hull, hence a further generalization of convexity.

T-Hulls are designed for *relative* shape characterization of molecules, offering a family of tools for molecular shape and similarity analysis.^{40,44} Using local comparisons between the shapes of the actual object S and the reference object T and applying this method to molecules, the electron density T-hulls have been suggested for the analysis of various shape constraints in biomolecular complementarity and in solvent-solute interactions.⁵⁸⁻⁶⁰ Earlier applications of T-hulls include a new description of union surfaces in drug design and a geometrical-topological treatment of solvent accessible surfaces.⁵⁹

In 3D chemical shape analysis, T is usually chosen as a molecular density domain or the relative complement of a suitable molecular fragment. Usually, a version T_v of the reference object T is any set obtained from T by 3D translations and rotations.^{59,60} Alternatively, various constrained motions as well as additional freedoms can be considered.^{59,60}

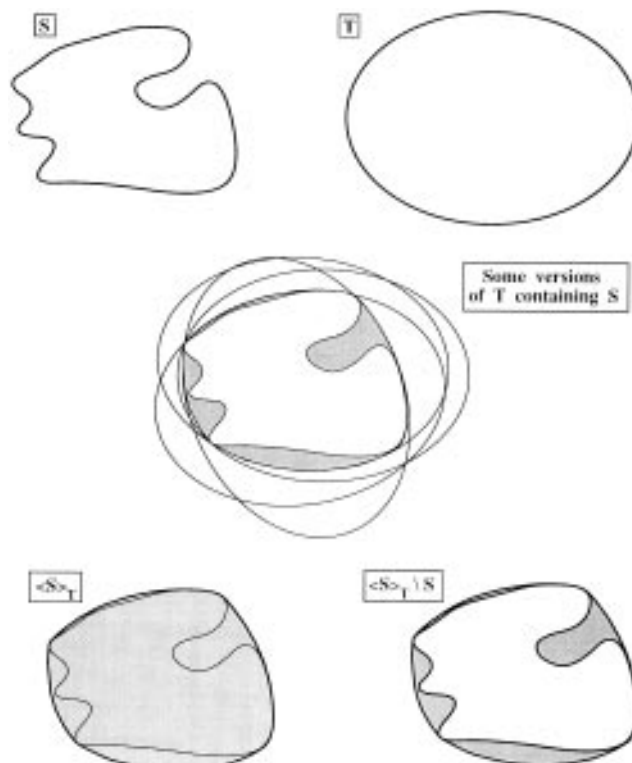


Figure 2. A more general example of a T-hull $\langle S \rangle_T$ of an irregular object S of no symmetry. See text for detail.

In Figure 1, the concept of T-hull is illustrated using the examples of simple geometrical objects, a rectangle as set S , and an ellipse as reference shape T . By taking the intersection of all translated and rotated versions of the ellipse which contain the rectangle S , one obtains the T-hull $\langle S \rangle_T$, with boundary the internal envelope also shown in the figure. In some applications, the "excess" of T-hull $\langle S \rangle_T$ beyond the original object S is of interest, denoted by $\langle S \rangle_T \setminus S$ in the figure.

Alternatively, one may take all versions T_v of the reference object T which participate in the generation of the T-hull $\langle S \rangle_T$ and generate the external envelope of the union of all these T_v versions. This union $\cup T_v$, denoted by $(S)_T$ in the figure, is called the T-coated S , whereas the "excess" of the T-coated S set $(S)_T$ beyond the original object S , denoted by $(S)_T \setminus S$ in the figure, is called the T-coat of S . These latter, "external" shape descriptors, with respect to a reference shape T and the T-hull $\langle S \rangle_T$, are discussed elsewhere.⁶¹

EXTERNAL T-PLASTERS AND INTERIOR T-AGGREGATES

In Figure 2 a more general example of a T-hull $\langle S \rangle_T$ is shown, where the object S is irregular, showing no symmetry; this object S better represents the general case of the vast majority of molecules with no symmetry. The following comments are equally valid for cases where the reference object T has no symmetry either. Group theory, however, still may play an important role.

In the typical cases, group theory can be used to describe the constraints (and extra freedoms) of the allowed versions of the reference object T . The allowed motions of T may form a group G of geometric transformations G , a subgroup of affine transformations, for example, rotations, translations,

reflections, and any combination of these. However, in some other cases, for example, if the family \mathbf{G} of allowed transformations is restricted to rotations within a limited angle interval, then group theoretical methods are not ideally suitable. In such cases, if one considers two rotations, each within the allowed range, the product of the two rotations, interpreted as one rotation performed after the other, may violate the constraints, hence may be excluded from the family of allowed transformations. In such cases, the family \mathbf{G} does not possess the closure property.

If the family \mathbf{G} of allowed transformations is specified, then two versions, T_v and $T_{v'}$, of reference object T are regarded \mathbf{G} -equivalent if both T_v and $T_{v'}$ are derived from the reference object T by an allowed transformation from the family \mathbf{G} . The notation $V(T, \mathbf{G})$ is used for the set of \mathbf{G} -equivalent versions T_v of T :

$$V(T, \mathbf{G}) = \{GT: G \in \mathbf{G}\} \quad (5)$$

With reference to an object S , the subset $V(T, \mathbf{G}, S)$ of $V(T, \mathbf{G})$ is defined as the set that contains all those versions T_v from $V(T, \mathbf{G})$ which contain set S :

$$V(T, \mathbf{G}, S) = \{T_v \in V(T, \mathbf{G}): S \subset T_v\} \quad (6)$$

The notation $I(V(T, \mathbf{G}, S))$ is used for the index set of all versions in set $V(T, \mathbf{G}, S)$:

$$I(V(T, \mathbf{G}, S)) = \{v: T_v \in V(T, \mathbf{G}, S)\} \quad (7)$$

If these notations are used, then the \mathbf{G} -constrained T-hull $\langle S \rangle_T$ of S can be written as

$$\langle S \rangle_T = \cap_{T_v \in V(T, \mathbf{G}, S)} T_v \quad (8)$$

or as the equivalent expression

$$\langle S \rangle_T = \cap_{v \in I(V(T, \mathbf{G}, S))} T_v \quad (9)$$

It is of some interest to decide whether a set B is or is not expressible as a \mathbf{G} -constrained T-hull of some set. In particular, if a set B happens to be a \mathbf{G} -constrained T-hull $\langle S \rangle_T$ of some set S , then some of the shape properties of B can be traced back to the shape properties of S and the reference object T . In this case, one can think of set B as the set obtained by using T as a tool to “plaster up” the set S .

Definition 1. A set B is called a T-plaster set if B is a T-hull $\langle S \rangle_T$ of some set S ,

$$B = \langle S \rangle_T \quad (10)$$

In this context, the T-hull $\langle S \rangle_T$ of a set S is the exterior T-plaster (or, simply, the T-plaster) of set S .

The example $\langle S \rangle_T$ shown in Figure 2 is, evidently, a plaster set, with respect to the reference shape of the ellipse T . The set $\langle S \rangle_T \setminus S$, shown as the shaded areas on the lower right hand side of the figure, can be regarded as the “plaster” added to the original object S .

For the study of solvent contact surfaces, it is advantageous to consider the relative complements of reference shapes. For simplicity, the notation $-T$ is used for the relative complement $E^3 \setminus T$, that is, for the object obtained by removing T from the full 3D space E^3 . In the example of Figure 3, set $-T$ symbolizes a solvent molecule, and the T-hull $\langle S \rangle_T$

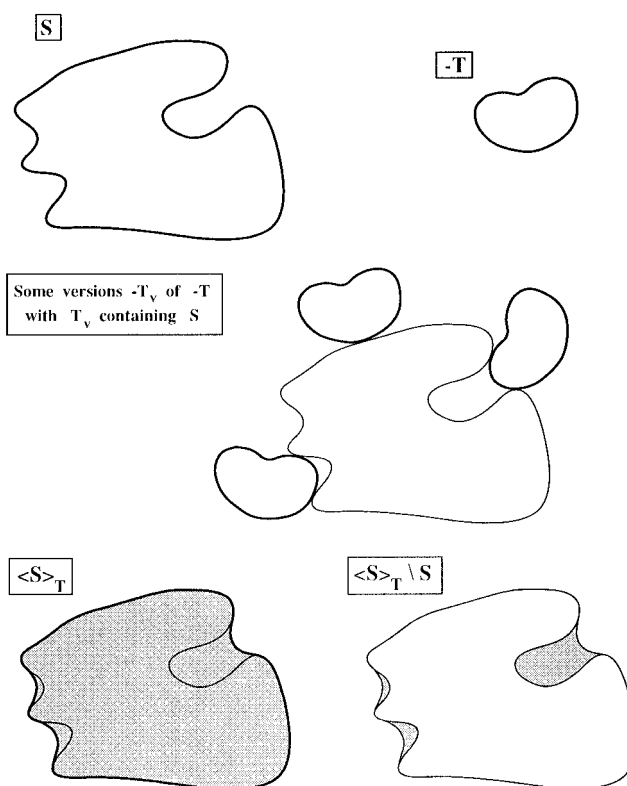


Figure 3. The use of the negative T-hull $\langle S \rangle_T$ with respect to a solvent molecule ($-T$) as a plaster set representing the solvent contact surface of a solute molecule S . See text for detail.

of a “solute molecule” S , obtained using the reference shape $T = E^2 \setminus (-T)$, is clearly a T-plaster set of S , representing the “solvent contact area” of S . The excess area $\langle S \rangle_T \setminus S$ is shown as the shaded domains on the lower right hand side of the figure.

If the reference set T is small enough when compared to S , then a similar operation can be carried out “from the inside” of a set S , by filling it up, as far as possible, by “aggregates” of various versions of the reference set T .

Definition 2. The interior T-aggregate $\rangle S \langle_T$ of a set S is the union of all $T_v \in V(T, \mathbf{G})$ versions of T contained in S :

$$\rangle S \langle_T = \cup_{v: T_v \in V(T, \mathbf{G}), T_v \subset S} T_v \quad (11)$$

If these versions of T are used to “plaster up” set S from the inside, then another construction, the interior T-plaster is obtained.

Definition 3. The interior T-plaster $\rangle \rangle S \langle \langle_T$ of a set S is the S -relative complement of the T-aggregate $\rangle S \langle_T$ of set S

$$\rangle \rangle S \langle \langle_T = S \setminus \rangle S \langle_T = S \setminus \cup_{v: T_v \in V(T, \mathbf{G}), T_v \subset S} T_v \quad (12)$$

An important property of T-plaster sets is proven below.

In the example of Figure 4, the same objects S and T of Figure 3 are used in different roles. Object S may represent the interior cavity of a protein, whereas object T (and *not* its relative complement $-T$) may represent a solvent molecule, possibly trapped within the cavity. The interior T-aggregate $\rangle S \langle_T$ and the interior T-plaster $\rangle \rangle S \langle \langle_T$ of set S are shown as the shaded areas in the figure.

Theorem 1. If sets A and B are T-plaster sets with respect to a reference set T , then their intersection $A \cap B$ is also a

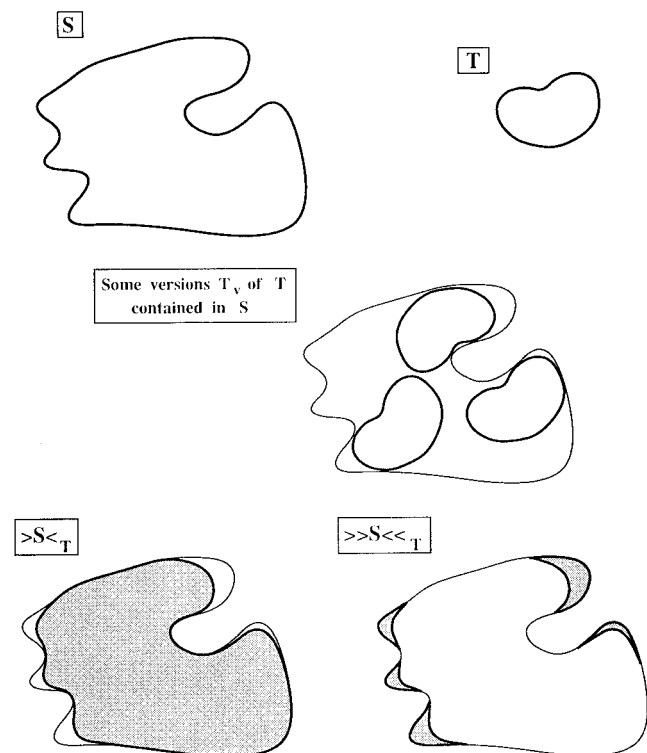


Figure 4. The interior T-aggregate $\rangle S \langle_T$, and the interior T-plaster $\rangle \rangle S \langle \langle_T$ of an interior cavity S of a macromolecule with solvent molecules T trapped within.

T-plaster set with respect to T . Furthermore, if $A = \langle S \rangle_T$ and $B = \langle S' \rangle_T$ then

$$\langle S \cap S' \rangle_T \subset A \cap B \quad (13)$$

Proof: For the two T-plaster sets A and B , there exist some sets S and S' such that $A = \langle S \rangle_T$ and $B = \langle S' \rangle_T$. We know that the T-hull of the T-hull is the T-hull,⁶⁰ hence

$$A = \langle S \rangle_T = \langle \langle S \rangle_T \rangle_T = \langle A \rangle_T = \bigcap_{v \in I(V(T,G,A))} T_v \quad (14)$$

and

$$B = \langle S' \rangle_T = \langle \langle S' \rangle_T \rangle_T = \langle B \rangle_T = \bigcap_{v \in I(V(T,G,B))} T_v \quad (15)$$

The first statement of the theorem is proven in two parts, (a) and (b).

(a) Since every set is contained in its own T-hull, the relation

$$A \cap B \subset \langle A \cap B \rangle_T \quad (16)$$

must hold.

(b) We are going to show that the relation

$$A \cap B \supset \langle A \cap B \rangle_T \quad (17)$$

also holds. Relations 14 and 15 imply that

$$\begin{aligned} A \cap B &= \bigcap_{v \in I(V(T,G,A))} T_v \cap \bigcap_{v' \in I(V(T,G,B))} T_{v'} = \\ &= \bigcap_{v'' \in I(V(T,G,A) \cup I(V(T,G,B)))} T_{v''} = \bigcap_{v''' \in I(V(T,G,A) \cup V(T,G,B))} T_{v'''} \end{aligned} \quad (18)$$

We also know that

$$V(T,G,A) \subset V(T,G,A \cap B) \quad (19)$$

and

$$V(T,G,B) \subset V(T,G,A \cap B) \quad (20)$$

consequently, the relations

$$V(T,G,A) \cup V(T,G,B) \subset V(T,G,A \cap B) \quad (21)$$

and

$$I(V(T,G,A)) \cup I(V(T,G,B)) \subset I(V(T,G,A \cap B)) \quad (22)$$

must also hold, that implies the reversed inclusion relation for the corresponding intersections:

$$\bigcap_{v''' \in I(V(T,G,A) \cup V(T,G,B))} T_{v'''} \supset \bigcap_{v'''' \in I(V(T,G,A \cap B))} T_{v''''} = \langle A \cap B \rangle_T \quad (23)$$

According to eq 18, the intersection for indices v''' is $A \cap B$, whereas the intersection for indices v'''' is, by definition, the T-hull of $A \cap B$. Consequently, the relation $A \cap B \supset \langle A \cap B \rangle_T$ holds, that proves part (b).

The first assertion of the theorem follows directly from results (a) and (b).

In order to prove the second assertion of the theorem, assume that $A = \langle S \rangle_T$ and $B = \langle S' \rangle_T$, then $S \subset A$ and $S' \subset B$, consequently,

$$S \cap S' \subset A \cap B \quad (24)$$

This is possible only if

$$\langle S \cap S' \rangle_T \subset \langle A \cap B \rangle_T \quad (25)$$

Since $A = \langle S \rangle_T$ and $B = \langle S' \rangle_T$, the first, proven assertion of the theorem implies that set $A \cap B$ is a T-plaster set, consequently, $\langle A \cap B \rangle_T = A \cap B$. Combining this with relation 25, the second assertion of the theorem follows:

$$\langle S \cap S' \rangle_T \subset A \cap B \quad (26)$$

Q.E.D.

One should point out that the relation $\langle S \cap S' \rangle_T \supset A \cap B$, the reverse of inclusion relation 26, does not necessarily hold.

A similar theorem holds for interior T-aggregates, where the roles of unions and intersections are interchanged. By analogy with the case of plaster sets, we shall use the notations

$$W(T,G,S) = \{T_v \in V(T,G): T_v \subset S\} \quad (27)$$

and

$$I(W(T,G,S)) = \{v: T_v \in W(T,G,S)\} \quad (28)$$

for the set of relevant allowed versions and for their index set, respectively.

Theorem 2. The union $A \cup B$ of any two interior T-aggregate sets A and B is also an interior T-aggregate set with respect to the same reference set T . Furthermore, if the two interior T-aggregates A and B can be expressed in the forms $A = \rangle S \langle_T$ and $B = \rangle S' \langle_T$ for some sets S and S' , then

$$\rangle S \cup S' \langle_T \supset A \cup B \quad (29)$$

Proof: For the two interior T-aggregates A and B there must exist some sets S and S' such that $A = \rangle S \langle_T$ and $B = \rangle S' \langle_T$.

$\rangle S'_T$. Since A is the union of all versions T_v which are contained in S, A itself is the union of all versions T_v which are contained in A. That is,

$$A = \rangle S_T = \rangle A_T = \cup_{v \in I(W(T,G,A))} T_v \quad (30)$$

The analogous relations must hold for T-aggregate B:

$$B = \rangle S'_T = \rangle B_T = \cup_{v \in I(W(T,G,B))} T_v \quad (31)$$

The first statement of the theorem is proven in two steps, (a) and (b).

(a) Since the interior T-aggregate of any set is contained in the set, the relation

$$A \cup B \supset \rangle A \cup B_T \quad (32)$$

must hold.

(b) We are going to show that the relation

$$A \cup B \subset \rangle A \cup B_T \quad (33)$$

also holds.

As implied by relations 30 and 31,

$$\begin{aligned} A \cup B &= \cup_{v \in I(W(T,G,A))} T_v \cup \cup_{v' \in I(W(T,G,B))} T_{v'} = \\ &\cup_{v'' \in I(W(T,G,A)) \cup I(W(T,G,B))} T_{v''} = \cup_{v''' \in I(W(T,G,A) \cup W(T,G,B))} T_{v'''} \end{aligned} \quad (34)$$

holds. However, we also know that

$$W(T,G,A) \subset W(T,G,A \cup B) \quad (35)$$

and

$$W(T,G,B) \subset W(T,G,A \cup B) \quad (36)$$

consequently, the relations

$$W(T,G,A) \cup W(T,G,B) \subset W(T,G,A \cup B) \quad (37)$$

and

$$I(W(T,G,A)) \cup I(W(T,G,B)) \subset I(W(T,G,A \cup B)) \quad (38)$$

also hold, implying that

$$\cup_{v''' \in I(W(T,G,A) \cup W(T,G,B))} T_{v'''} \subset \cup_{v'''' \in I(W(T,G,A \cup B))} T_{v''''} = \rangle A \cup B_T \quad (39)$$

According to eq 34, the union for indices v''' is $A \cup B$, whereas the union for indices v'''' is in fact the definition of the interior T-aggregate of $A \cup B$, implying that the relation $A \cup B \subset \rangle A \cup B_T$ must hold, proving part (b).

Combining the results of steps (a) and (b) proves the first assertion of the theorem.

In order to prove the second assertion of the theorem, first we note that if the two sets are represented as $A = \rangle S_T$ and $B = \rangle S'_T$, then $S \supset A$ and $S' \supset B$ must also hold, implying that

$$S \cup S' \supset A \cup B \quad (40)$$

Consequently, the inclusion relation

$$\rangle S \cup S'_T \supset \rangle A \cup B_T \quad (41)$$

holds. However, for the two interior T-aggregates A and

B, the first, proven assertion of the theorem implies that the set $A \cup B$ is also an interior T-aggregate set, consequently, $A \cup B = \rangle A \cup B_T$, hence relation 41 implies the second assertion of the theorem,

$$\rangle S \cup S'_T \supset A \cup B \quad (42)$$

Q.E.D.

One should point out that the reversed inclusion relation, $\rangle S \cup S'_T \subset A \cup B$, does not necessarily hold.

In some applications the T-coated S set

$$(S)_T = \cup_{T_v \in V(T,G,S)} T_v \quad (43)$$

and the T-coat $(S)_T \setminus S$ of set S, illustrated in Figure 1, are of importance. The analogous internal shape descriptor, the internal T-core

$$\rangle S_T = \cap_{v: T_v \in V(T,G), T_v \subset S} T_v \quad (44)$$

is the intersection of all versions of T contained in S, that provides a description of "crowdedness" within a cavity. Clearly, if two or more solvent molecules fit simultaneously within the cavity, then the internal T-core $\rangle S_T$ is the empty set. Some properties of T-coats and T-cores are described elsewhere.⁶¹

CLOSING COMMENTS

Although the exterior plaster and interior aggregate properties are far removed from ordinary convexity properties, it is remarkable that one of the fundamental properties of convex sets, namely, the fact that the intersection of convex sets is convex, is inherited in a generalized form by exterior plaster sets, and the counterpart relation also holds for interior aggregate sets. In future studies some additional analogies will be discussed.⁶¹

Besides their role as generalizations of convexity, T-hulls have been shown to provide novel tools for molecular shape analysis. In particular, T-hulls provide intuitively transparent representations of various shape constraints for solvent-solute interactions, for solvent accessible surfaces, for biomolecular shape-complementarity, and for union surfaces in drug design.⁵⁸⁻⁶⁰ Exterior plaster sets and interior aggregate sets represent a natural extension of the T-hull approach, suitable to study the shape-modifying role of solvation shells and the inner cavities of supramolecular structures filled with solvent molecules.

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