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Local and Global Similarities of Molecules:

Electron Density Theorems, Computational Aspects, and Applications

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ABSTRACT

The local and global properties of molecular electron densities are interrelated by some of the fundamental theorems of molecular physics. These relations have significant consequences regarding the similarities between molecular properties and reactivities on various levels: in the comparisons of the roles of individual functional groups, and also on the level of spatial requirements and global shapes of molecules. The "Holographic Electron Density Theorem" [1] and the "Holographic Molecular Symmetry Theorem" [2] provide extensions of the celebrated Hohenberg-Kohn Theorem of density functional theory [3], and also provide new computational tools for assessing molecular similarity and other shape properties [4,5]. These new approaches, in combination with macromolecular quantum chemistry approaches [6,7] and various Electron Density Transform and Electron Density Averaging methods [8], represent a new computational chemistry toolbox. One of the aims of these methods is application for systematic, quantum chemistry approaches to QSAR in pharmaceutical drug discovery, toxicological risk assessment, and the study of olfactory activity of various molecular series.

The holographic approach to electron density similarities also provides a basis for treating host-guest interactions, macromolecular bonding, and the problem of molecular recognition within a unified framework. The high selectivity of some molecular recognition processes is justified by a theoretical result concerning the uniqueness of molecular recognition that is a direct consequence of locality principles and the holographic electron density property.

1. INTRODUCTION

Shape similarities of macromolecules can be viewed on various levels: on the macromolecular, large-scale level that in proteins corresponds to the tertiary (and quaternary) structure, on the level of intermediate size range, that in proteins corresponds to the interrelations between various subunits, such as individual amino acid components, or on the individual functional group level (in the extreme case, atomic level), where the actual chemical transformations of local bonds occur. The interrelations among these features may be rather complex, and the difficulties in the detailed interpretaion of the relations between macromolecular structure and function requires a proper accounting of these relations.

Whereas some of the fundamental theorems of quantum chemistry provide valuable guidelines, and the practical problems associated with the modeling of macromolecules are often computational, yet in some instances the fundamental, theoretical models commonly used are also insufficient to provide answers that could reflect reality with the required accuracy. Recent efforts to elucidate the theoretical background of macromolecular structure, however, are likely to provide new ideas and computational tools for the deatiled study of macromolecules.

The recently proven Holographic Electron Density Theorem [1] provides a link between local and global properties of molecules. This theorem, reflecting on a fundamental law of chemistry, states that within any, boundaryless molecular electron density cloud in a nondegenerate ground electronic state, any nonzero volume piece of the electron density cloud contains the complete information about the entire molecule. In more precise terms, any non-degenerate ground state electron density $\rho_D(\mathbf{r})$ within a nonzero volume local region D of the ordinary three-space E^3 fully determines the complete, boundaryless electron density $\rho(\mathbf{r})$ of the entire molecule, that in turn determines the molecular energy and all other molecular properties which follow from the molecular Hamiltonian H. The statement of the Holographic Electron Density Theorem is stronger than the celebrated Hohenberg-Kohn Theorem [3]. According to the Hohenberg-Kohn Theorem, the entire electron density determines the energy of the molecule; whereas according to the Holographic Electron Density Theorem the entire electron density is not required, and any small nonzero volume piece of the electron density is already sufficient to determine the energy (and other properties) of the molecule. In the actual proof it has been possible to solve the difficulties of the earlier small box to large box extension approach of Riess and Munch [9] that prevented the application of their extension approach to real, boundaryless quantum mechanical molecules. The actual proof of the Holographic Electron Density Theorem [1] has involved some of the results of density functional theory, a four-dimensional representation of the molecular electron density, and the Alexandrov compactification tool of differential topology.

The first method producing *ab initio* quality macromolecular electron densities was the Molecular ElectronDensity Loge, or MEDLA technique [10], based on a numerical electron density generation approach. The the first application of the general, additive, fuzzy electron density fragmentation (AFDF) principle [11] to a more versatile, non-numerical, *ab initio* quality quantum chemistry approach not restricted to electron densities was the Adjsutable Density Matrix Assembler, or ADMA method [6,12]. First, an electron density fragment data bank (storing only the fragment density matrices and basis set information) is generated, based on accurate, high quality *ab initio* quantum chemical calculations for small molecules, and the application of the electron density fragmentation principle. The corresponding "fuzzy" density fragments also account for the inter-fragment interactions

occurring within their molecular neighborhoods. These fuzzy fragment density matrices are combined according to an index assignment pattern based on the additivity principle[6,11,12]. This way, *ab initio* quality macromolecular density matrices can be constructed for large molecules, for any nuclear arrangement, using experimental or theoretically determined nuclear coordinates, or distorted arrangements assumed to occur along reaction paths or in protein folding processes. The ADMA approach is also suitable for ab intio quality computation of macromolecular forces [7]. Since the ADMA electron densities are equivalent to the ideal, infinite resolution MEDLA electron densities, the quality tests of MEDLA [13-15] provide a lower limit for the quality of ADMA results. The ADMA density matrix construction method, based on the additive, fuzzy density fragmentation principle is exact if a molecule is reconstructed from its fragments, and has been proven to be highly accurate, of *ab initio* quality, when constructing other molecules, faithfully reproducing the shapes of molecular electron densities, including those with hydrogen bonds, nonbonding interactions, conjugated and aromatic pi-electron distributions as calculated at the standard 6-31G** *ab initio* level. Note that these latter, important shape features are poorly described or simply ignored by conventional fused-sphere or "space-filling" representations.

The density distortion and density averaging methods [8] provie useful shortcust for approximate ADMA density generation, an option to be used when only a quick estimate of electron density is required.

In the present contribution a combination of local and global macromolecular shape analysis approaches is described that reflects the complexity as well as the varying levels of importance of various contributions to a similarity assessment of biologically important macromolecules. The local features are described by the shape group method and the associated topological shape matrices, reflecting the local curvature properties of the infinite set of isodensity contours of local functional groups within the macromolecule, whereas the large-scale features are described by the functional group polyhedron approach. The local shape information is combined with orientation information as represented by moment of inertia tensor information of local functional groups.

2. ORIENTATED RELATIVE CONVEXITY VERSION OF SHAPE GROUP METHOD AND RELATIVE ORIENTATION FOR FUZZY DENSITY FRAGMENS FOR FUNCTIONAL GROUPS

Consider a macromolecule M with a specified nuclear geometry K and a fuzzy electron density fragmentation scheme [6] that produces density fragments for the essential functional groups of the macromolecule.

The term “essential functional group” is used in the sense of ref. [16]; for a specific chemical process of the biomolecule, some functional groups do not seem to play any role, whereas some others appear essential. Those functional groups with a role in a given biochemical process will be referred to as Essential Functional Groups, EFGs, whereas all others will be regarded as Non-essential Functional Groups, NFGs. Naturally, for each biomolecule this distinction also depends on the biochemical process considered; functional groups which are essential in one biochemical process may play no role in some other

processes within the same biomolecule.

A fuzzy density fragment representing a given functional group within a molecule is defined in terms of the set of nuclei and the associated fuzzy eletron density contribution obtained within the AFDF decomposition scheme [11]. Using the fuzzy fragment's density matrix P^k, obtained by the AFDF docomposition [11], the additive fuzzy density "share" $\rho^k(\mathbf{r},K)$ of each molecular fragment (including each of the p essential functional groups) is defined as

$$\rho^k(\mathbf{r},K) = \sum_{i=1}^{n} \sum_{j=1}^{n} P^k_{ij}(\boldsymbol{\varphi}(K))\, \varphi_i(\mathbf{r},K)\, \varphi_j(\mathbf{r},K)\,, \quad k=1,2,...p, \qquad (1)$$

where $\varphi_i(\mathbf{r},K)$ are the AO basis functions.

These fuzzy electron density fragments have properties entirely analogous with the properties of electron densities of complete molecules, specifically, they do not have boundaries and the electron density values converge to zero with distance the same way as that of molecular electron densitties. Hence, the shape group approach of algebraic-topological shape characterization of molecules is also applicable to these functional group electron densities.

One of the special features we shall consider in the present study is orientational information. Since our interest is to obtain a shape representation of biological macromolecules incorporating both global and local shape information, where the latter refers to the essential functional groups, it is of some importance to specify both the mutual positioning and the mutual orientation of these essential functional group electron denities.

One family of orientational shape descriptors, within the framework of the shape group methodology, relies on the conept of oriented relative convexity [17]. The introduction of this concept was originally motivated by the need for shape description of molecular electron density clouds in external fields, such as the field represented by the cavity of an enzyme; however, the concept is applicable in general to any shape problem where specific directions in space have some distinguishable roles. Such is the case if the relative arrangements and the relative orientatins of molecular fragments, such as functional group electron densities are considered.

The simplest computational implementation of the oriented relative convexity approach, as applied within the algebraic-topological shape group technique can be obtained as follows. The ordinary shape group approach describes the detailed shape and curvature properties of molecular electron density contours in terms of relative curvatures as compared to local tangent planes (corresponding to zero reference curvature) and local tangent spheres (corresponding to reference curvatures of 1/r where r is the radius of the reference sphere). These comparisons lead to the algebraic-topological homology groups of truncated contour surfaces, describing relative convexities, and the concise Betti number representation of the essential information about these homology groups.

In terms of the patterns and topological invariants that various curvature domains of the electron density generate, the Shape Group Method is an algebraic-topological technique of shape characterization based on local geometrical curvature features, analyzed topologically. Each Molecular Isodensity Contour surface, MIDCO G(K,*a*) of the electron density, defined for a given nuclear configuration K of a molecule M, is a collection of all points **r** of the three-dimensional space where the electronic density $\rho(K,\mathbf{r})$ is equal to a given threshold value a,

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

In the Shape Group technique, each MIDCO is partitioned into domains based on a series local curvature thresholds *b*. For the entire electron density there are infinitely many MIDCOs but only a finite number of topologically distinct patterns for the entire range of density values *a* and chemically realistic curvature values *b*.

By removing all domains of a specific curvature classification, a new object is produced that typically shows a new set of topological properties. Such objects are easily characterized by topological tools, specifically, by the homology groups of algebraic topology, and homology groups of the truncated surface are, by definition, the shape groups of the original MIDCO surface G(K,a). It is important to note that there are only a finite number of shape groups for each molecule.

Variants of the shape group method have been used for the shape analysis of electron density functions, electrostatic potentials, spin densities, and nuclear potential functions. For shape similarity analysis, a concise numerical shape code is obtained by listing the ranks of the shape groups (their Betti numbers) for various *a* and *b* values. For each molecule M, this shape code is usually represented by a two-dimensional (*a*,*b*) parameter map, written either as a matrix or as a multidimensional vector, **v**(a,b,M). The maps of different molecules can be compared numerically, providing numerical measures for shape similarity and shape complementarity. These maps provide an example for the general principle: Geometrical Similarity can be treated as Topological Equivalence (GSTE principle).

In drug design and in toxicological risk assessment, the Shape Group methods serve as a tool for of Quantitative Shape Activity Relations, QshAR.

In case of oriended convexity, the actual curvature comparisons are specified in terms of oriented ellipsoids, instead of reference spheres, where the axes of the elipsoids correspond to some of the distinguished directions. Computationally, this approach is equivalent to carrying out an ordinary shape group analysis of the molecular shape within a distorted three-dimensional space, where three perpendicular coordinate axes of the space are scaled so that the original reference ellipsoids are converted to spheres. Then, the ordinary shape group analysis in this distorted space results in the same topological shape descriptors as the direct oriented relative convexity approach relying on oriented reference ellipsoids.

Since the orientational information in our case has the only role to describe the mutual orientations of the local fuzzy electron density clouds of the essential functional groups, it is sufficient to chose the axes of the local tensors of moments of inertia for each nuclear set of the essential functional groups as the specific directions for the axes of reference ellipsoids (in fact, for computational purposes, as the directions of the scaled coordinate axes of the distorted three-dimensional space). Note that electron densities are strongly influenced by the nuclear framework, and the electronic masses are small as compared to the nuclear masses, so this choice is reasonable for the specification of relative orientations.

The resulting shape information for each essential functional group is a shape matrix with elements the sets of Betti numbers, and the numerical information specifying the momont of inertia tensor for the corresponding nuclear set, defined with reference to an overall coordinate system, that in turn is defined by the moment of inertia tensor for the nuclear set of the whole marcomolecule.

3. SHAPE CODE FOR THE ESSENTIAL FUNCTIONAL GROUP (EFG) POLYHEDRON OF LARGE BIOMOLECULES

The Essential Functional Group (EFG) Polyhedron of a macromolecule M has been defined [16] as follows:

For a finite number p of the essential functional groups F_i of biomolecule M with a specified nuclear arrangement K, one selects a point **p**(i) within each local region corresponding to a functional group F_i. In the present case each point **p**(i) is chosen as the center of mass of the nuclei of the corresponding essential functional group F_i.

With respect to the given set of characteristic points **p**(i) of the essential functional groups of biomolecule M of nuclear arrangement K, the *bare EFG polyhedron* B(M,K) has been defined as the convex hull of point set {**p**(i)},

$$B(M,K) = < \{\mathbf{p}(i)\} >. \qquad (3)$$

For the case of a single essential functional group, p=1, the bare EFG polyhedron B(M,K) is a single point. For the case of two esential functional groups, p=2, the bare EFG polyhedron B(M,K) is a straight line segment. For three essential functional groups, p=3, the polyhedron B(M,K) is a triangle (with the exception of the case of three colinear points **p**(1), **p**(2), and **p**(3) when B(M,K) is again a straight line segment). Often, one considers a larger number of essential functional groups, p 4 and if not all these points **p**(i) are coplanar, then the bare EFG polyhedron B(M,K) is a convex polyhedron of positive volume. In order to avoid the need for repeated discussion of special low p cases, all these (possibly degenerate) polyhedra are referred to as bare EFG polyhedra, for all p values. Note that it is always possible to include formal "dummy" positions among the actual **p**(i) characteristic points. Consequently, in all the following discussions, we shall assume that the model involves p 4 non-coplanar essential functional groups, hence the formal bare EFG polyhedron B(M,K) is indeed, a polyhedron in the conventional sense.

If a characteristic point **p**(i) falls within the interior or on a face or edge of the convex bare EFG polyhedron B(M,K), then this point **p**(i) does not correspond to any vertex of B(M,K). For the given nuclear arrangement K of the biomolecule M, this characteristic point **p**(i) corresponds to a functional group F_i that is possibly, but not necessarily inaccessible by other molecules. The further this point **p**(i) falls from the surface of the bare EFG polyhedron B(M,K), the more likely that the functional group F_i is inaccessible. On the other hand, also note that if an essential functional group F_i corresponds to a vertex **p**(i) of the convex bare EFG polyhedron B(M,K), this does not mean that this functional group is necessarily accessible by other molecules. It is possible that a characteristic point **p**(i) is a vertex of B(M,K), and the corresponding functional group F_i may still be surrounded by electron density clouds of regions of the macromlecule M which do not belong to any of the essential functional groups. These parts of the electron density cloud may fall well on the outside of the bare EFG polyhedron B(M,K), consequently, it is possible that F_i is inaccessible to other molecules.

The moment of inertia tensor for the nuclei of macromolecule M provides a set of coordinate axes, with the center of mass of the nuclei at the origin of the coordinate axes, defining a global coordinate system for the entire macromolecule.

We assume that the order of essential functional groups is fixed, and if formally identical functional groups, for example, two carboxyl groups are among the essential

functional groups, then these are distinguished by some criteria, such as criteria based on local electron densities. (Note that according to the holographic electron density theorem no two carboxyl groups are truly identical unless they are related to one another by some strict symmetry).

With reference to the global coordinate system of macromolecule M, the coordinates of points **p**(i) and the vector coordinates of the local moment of inertia tensors **I**(i) of the individual essential functional groups F_i provide a numerical shape characterization of some of the essential large-scale features of the macromolecule M.

This characterization can be formulated in terms of a formal 12p-dimensional vector **b**(M,K) for each bare EFG polyhedron B(M,K),

$$\mathbf{b'}(M,K) = [p_1(1),p_2(1),p_3(1),p_1(2),\ldots p_1(i),p_2(i),p_3(i),\ldots p_3(p),I_{11}(1),I_{12}(1),$$

$$I_{13}(1),I_{21}(1),\ldots I_{32}(1),I_{33}(1),\ldots I_{11}(i),I_{12}(i),I_{13}(i),I_{21}(i),\ldots I_{32}(i),I_{33}(i)$$

$$,\ldots I_{33}(p)], \qquad (4)$$

where **b'**(M,K) denotes the transpose of vector **b'**(M,K). This vector **b**(M,K) is a numerical shape code for the large scale features of the distribution and local orientation of the essential functional groups.

4. A COMBINATION OF DISCRETE LOCAL AND CONTINUOUS LARGE-SCALE SHAPE CODES OF LARGE BIOMOLECULES

The essential functional groups are the actual chemical centers where the most important biochemial processes are focused, yet the global shape and orientational constraints of the assemblies ot the essential functional groups within a given large biomoleule also has a profound influence on the outcome of the biochemical process. For this reason, it appears useful to generate a shape description that accounts for both of these aspects within a single system, yet also provides the tools for identifying these components separately, that may aid the interpretation of shape correlations with biochemical activity. This aim provides the justification for the generation of a combined shape code for large biomolecules, incorporating detailed, local shape analysis of the electron density clouds in regions where the actual chemical processes are focussed, yet also providing a large-scale description of the interrelations and mutual arrangements as well as orientations of the functional groups.

The combined shape code is obtained by concatenating the two types shape descriptors, **b**(M,K) for the large-scale features and the detailed local shape descriptors **v**(a,b, F_i) for each of the p essential functional groups F_i, taken in the order defined for these groups. That is, the new, combined shape descriptor **w**(M,K, F_1,… F_i,… F_p) is defined as

$\mathbf{w}(M,K, F_1,\ldots F_i,\ldots F_p) =$

$$\mathbf{b}(M,K)\oplus\mathbf{v}(a,b,F_1)\oplus\mathbf{v}(a,b,F_2)\oplus \ldots \oplus \mathbf{v}(a,b,F_i)\oplus \ldots \oplus \mathbf{v}(a,b,F_p). \quad (5)$$

The first member $\mathbf{b}(M,K)$ in this concatenation $\mathbf{w}(M,K, F_1,\ldots F_i,\ldots F_p)$ is a list of real numbers, describing the relevant global features of macromolecule M by a continuous set of descriptors, whereas the remaining members of the concatenation are discrete shape codes $\mathbf{v}(a,b,F_i)$ for the individual essential functional groups F_i.

This special feature requires a special treatment when applying this tool for shape comparisons. Whereas for the continuous part the differences between numerical values provide a natural measure of dissimilarity, this is not the case for the discrete part, where a simple match-mismatch measure has been applied for shape comparisons. The percentage of the matches provided a similarity measure that has been shown to give very good correlations with some experimentally measured levels of biochemical activity, with most applications in toxicology.

By selecting a varying weighting scheme for the continuous and discrete components, depending on the required emphasis on local or large-scale features, the comparison of two or several $\mathbf{w}(M,K, F_1,\ldots F_i,\ldots F_p)$ descriptors may serve as a tool for macromolecular similarity analysis.

5. SUMMARY

The distribution, relative orientation, as well as the detailed local shape features of a set of the essential functional groups within a large biomolecule are encoded within a combined macromolecular shape code. This shape code, denoted by $\mathbf{w}(M,K, F_1,\ldots F_i,\ldots F_p)$ for a macromolecule M in nuclear configuration K and with essential functional groups $F_1,\ldots F_i,\ldots F_p$, is computed using

(i) the ADMA computational tools for local, fuzzy electron density contributions,
(ii) the algebraic-topological Shape Group method for local shape analysis of electron density clouds,
(iii) the EFG polyhedron approach for the description of some aspects of the large scale features
(iv) local moment of inertia tensors for the description of relative orientational aspects of the distribution of the essential funtional groups.

Whereas computational experience with the local shape analysis methodology has been very successful in toxicological risk assessment applications [18], further numerical tests are needed to develop an optimum scaling scheme for the relative weighting of the local and global contributions of the new macromolecular shape descriptor $\mathbf{w}(M,K, F_1,\ldots F_i,\ldots F_p)$.

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