

Generalized chirality and symmetry deficiency

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Some of the elementary properties of molecular electron densities are studied from the perspectives of generalizations of symmetry, symmetry deficiency, and in particular, chirality. A simple, information-theoretical proof of the Hohenberg–Kohn theorem is discussed, and the information contents of local and global molecular electron densities are compared using a formulation of quantum chemistry on a compact manifold. One result, the “holographic electron density theorem”, involving a compactification step combined with analytic continuation, gives a tool for comparing local and global symmetry properties. The compact manifold quantum chemistry approach leads to a precise statement on the role of local molecular regions in determining global properties of complete, boundaryless molecules, resulting in constraints on their symmetry, chirality, and other types of symmetry deficiencies. A special similarity measure, the SLT measure, is used for generalized density domain comparisons, suitable in general for the comparison of semilattices with a tree structure.

1. Introduction

The study of electron density provides a very broad foundation for diverse branches of theoretical chemistry [1–77]. As it is established by the Hohenberg–Kohn theorem [22] of density functional theory, the electronic energy as well as other nondegenerate ground state molecular properties are fully determined by the ground state electronic density $\rho(\mathbf{r})$ of the molecule. This theorem, and the associated developments of various branches of density functional theory, have provided the foundations for some of the approaches of molecular quantum mechanics [1,5–8,16,23–30,41,57–61,63,64,67,68,70,77]. One area of particular interest is the relation between local and global properties of electron densities, including their local and global symmetry and more general shape properties. A topological model of local, fuzzy regions of electron densities, called density domains [41] builds density functional models based on local electron densities computed using conventional, molecular orbital methodology [17–21,31,55,56,62,65,66,69]. One important area of study is the shape analysis of molecular electron densities [3,32–34,36,40,42,43,45–49,54,72–76,78] that is linked to some of the fundamental quantum mechanical properties of electron distributions [4,9–15,71].

In more precise terms, the theorem of Hohenberg and Kohn [22] describes the relations between the nondegenerate ground state electron density $\rho(\mathbf{r})$,

$$\rho(\mathbf{r}) = n \sum_{s_1} \cdots \sum_{s_n} \int \cdots \int |\Psi(\mathbf{r}, s_1, \mathbf{r}_2, s_2, \dots, \mathbf{r}_n, s_n)|^2 d^2\mathbf{r}_2 \cdots d^3\mathbf{r}_n, \quad (1)$$

of a system of n electrons in a local spin-independent external potential V , and the corresponding Hamiltonian H , where in equation (1), the electron density is given in a spin-averaged form.

Here we shall focus on the special case of molecular Hamiltonians H . In terms of the usual kinetic energy operator T ,

$$T = -(1/2) \sum_{i=1}^n \Delta_i, \quad (2)$$

the electron–electron repulsion operator V_{ee} ,

$$V_{ee} = \sum_{i=1}^{n-1} \sum_{j=i+1}^n (|\mathbf{r}_i - \mathbf{r}_j|)^{-1}, \quad (3)$$

and external potential $V(\mathbf{r})$,

$$V(\mathbf{r}) = \sum_{i=1}^n V(\mathbf{r}_i), \quad (4)$$

this Hamiltonian H is given as

$$H = \sum_{i=1}^n V(\mathbf{r}_i) + T + V_{ee}, \quad (5)$$

where $V(\mathbf{r}_i)$ is the electron–nuclear attraction operator for the interaction of the set of nuclei with the i th electron of the molecule.

According to the Hohenberg–Kohn theorem, a nondegenerate ground state electron density $\rho(\mathbf{r})$ determines H within an additive constant, consequently, $\rho(\mathbf{r})$ determines all ground state and all excited state properties of the system described by the Hamiltonian H .

An elegant proof of the Hohenberg–Kohn theorem is provided by the generalized and concise “constrained search” proof as described by Levy [26–29]. Here we shall consider an alternative treatment, a simple, information-theoretical approach that leads to the statement of the Hohenberg–Kohn theorem.

The conditions for the Hohenberg–Kohn theorem are rather simple, since the theorem is based on two pieces of information:

- (i) the electronic density as a three-dimensional function given in some form;
- (ii) the additional knowledge that it is a nondegenerate ground state electron density of the system under consideration. (The treatment is equally applicable to any

physical system built from nuclei and electrons, however, here we are concerned with molecules.)

Based on this information, and on some elementary assumptions on molecules, the following statements can be made:

1. A molecule contains only a set of nuclei and an electron density cloud.
2. Since there is no other material present to encode information, all information concerning the static properties of the molecule must be contained in the nuclear and electron distributions.
3. The location and atomic numbers of the nuclei are fully determined by the nondegenerate ground state electron density $\rho_0(\mathbf{r})$ of the molecule.
4. Consequently, the nondegenerate ground state electron density $\rho_0(\mathbf{r})$ contains all information concerning all static properties of the molecule, including its ground state energy, and any other molecular properties.

The last statement, statement 4, is equivalent to the statement of the Hohenberg–Kohn theorem for molecules.

In fact, among the various molecular properties, the external potential $V(\mathbf{r})$ is also determined by the nondegenerate ground state electron density $\rho_0(\mathbf{r})$. Since the ground state electron density $\rho_0(\mathbf{r})$ determines the molecular Hamiltonian

$$H = \sum V(\mathbf{r}_i) + T + V_{ee},$$

consequently, excited state information is also implied by the nondegenerate ground state electron density.

2. Local and global electron density information

In the simple, information-theoretical justification of the Hohenberg–Kohn theorem described in the introduction, an important assumption was made. The molecule was considered localized or at least identifiable in the following sense: the molecule is distinguishable from the rest of the universe, although a molecular electron density has no boundary, and in an asymptotic sense, it converges exponentially to zero with distance from the molecular center of mass. The problem of localization of electron density and local information plays an important role in the relations between a subsystem and the complete system, as well as in the role of local symmetries and symmetry deficiencies concerning the global symmetry properties of the complete, boundaryless molecules.

One important assumption in the first application of the Hohenberg–Kohn theorem to a subsystem [64] was necessary for using analytic continuation of the subsystem electron density, extending it to a complete system assumed to be confined to a finite, bounded region of the ordinary three-dimensional space. The assumption of boundedness, although a very reasonable approximation for most practical purposes, is not

strictly valid within a rigorous quantum mechanical model. In a strict sense, molecular electron densities are boundaryless, fuzzy objects, fulfilling various corollaries of the Heisenberg uncertainty relation. This fact must be taken into account when analyzing relations between subsystems and a complete system.

We shall outline the original argument for bounded systems, followed by a brief discussion of a compactification method used earlier for potential surface studies [35], and a four-dimensional electron density model [38,39,79]. Next, an outline of the four-dimensional “holographic electron density theorem” [53] will be given, where the compactification technique is applied to the four-dimensional electron density representation allowing one to use analyticity arguments for complete, boundaryless molecular electron densities no longer confined to any finite, bounded region of the ordinary three-dimensional space.

These tools provide precise statements on the relations between local and global electron density descriptions, leading to new symmetry constraints discussed in the following section, where we are concerned with a special adaptation of the “holographic electron density theorem” to the problems of generalized chirality and symmetry deficiency.

The original argument of [64] was based on the following information and plausible assumptions: the spin-free, n -electron, nonrelativistic Born–Oppenheimer Hamiltonian H of equation (5) is a Hermitian operator, bounded from below. Operator H has a discrete energy spectrum below some energy.

The physical region of the system is an arbitrary, simply connected region g in the ordinary 3-space R^3 , $R^3 \supset g$, where the restriction that g is bounded will be required only at a later stage of the discussion. However, as follows from elementary quantum mechanical considerations, for a precise model, the domain g should be taken as the entire 3-space R^3 .

If G denotes the n -fold direct sum of the arbitrary, simply connected region g in the ordinary 3-space R^3 , $R^3 \supset g$, then we assume that the Hamiltonian H of the physical system belongs to an elliptic differential equation of coefficients analytic almost everywhere within its domain G , $R^{3n} \supset G$, and the (zero-measure) set of points of nonanalyticities leaves the rest G_0 of the domain G connected.

Consider two Hamiltonians, H_1 and H_2 ,

$$H_1 = V_1(\mathbf{r}) + T + V_{ee} \quad (6)$$

and

$$H_2 = V_2(\mathbf{r}) + T + V_{ee}, \quad (7)$$

and assume nondegenerate, variationally determined ground states. Furthermore, assume that the corresponding normalized ground state eigenfunctions Ψ_1 and Ψ_2 are related to each other by

$$\Psi_1 = \alpha\Psi_2, \quad (8)$$

where α , $|\alpha| = 1$, is a complex phase factor. Then, from

$$H_1\Psi_1 = E_1\Psi_1 \quad (9)$$

and

$$H_2\Psi_1 = E_2\Psi_1, \quad (10)$$

the relation

$$[V_1(\mathbf{r}) - V_2(\mathbf{r})]\Psi_1 = [E_1 - E_2]\Psi_1 \quad (11)$$

follows. The coefficients of the elliptic Hamiltonians H_1 and H_2 are analytic in G_0 of G , implying that the wavefunction Ψ_1 must also be analytic in G_0 . Consequently,

$$\Psi_1 \neq 0, \quad (12)$$

except on a set of measure zero. This is possible only if

$$V_1(\mathbf{r}) - V_2(\mathbf{r}) = E_1 - E_2 = \beta, \quad (13)$$

with β a real constant.

On the other hand, if the only difference between the two Hamiltonians, H_1 and H_2 , is an additive real constant β in their external potentials,

$$V_1(\mathbf{r}) = V_2(\mathbf{r}) + \beta, \quad (14)$$

then H_1 and H_2 must have the same spectrum. Nondegeneracy of the lowest eigenvalues implies that for some complex factor α , $|\alpha| = 1$, the two ground state eigenfunctions Ψ_1 and Ψ_2 are related by

$$\Psi_1 = \alpha\Psi_2. \quad (15)$$

Evidently, there are strong connections between the similarities of the external potentials and the similarities of the nondegenerate ground state wavefunctions.

Significant differences in the two external potentials $V_1(\mathbf{r})$ and $V_2(\mathbf{r})$, and significant differences in the corresponding nondegenerate ground state electron densities $\rho_1(\mathbf{r})$ and $\rho_2(\mathbf{r})$ also imply one another. This can be verified as follows.

If the two external potentials differ by more than a simple additive constant β , that is, if

$$V_1(\mathbf{r}) \neq V_2(\mathbf{r}) + \beta \quad (16)$$

for any real constant β , then $\Psi_1 \neq \alpha\Psi_2$ follows, since equation (8) implies equation (13). According to the variational theorem for nondegenerate ground states,

$$E_1 = \langle \Psi_1 | H_1 | \Psi_1 \rangle < \langle \Psi_2 | H_1 | \Psi_2 \rangle = E_2 + \langle \Psi_2 | V_1(\mathbf{r}) - V_2(\mathbf{r}) | \Psi_2 \rangle, \quad (17)$$

or expressed for electron density,

$$E_1 < E_2 + \int_g \rho_2(\mathbf{r}) [V_1(\mathbf{r}) - V_2(\mathbf{r})] d^3\mathbf{r}. \quad (18)$$

By changing roles, one also obtains

$$E_2 < E_1 + \int_g \rho_1(\mathbf{r}) [V_2(\mathbf{r}) - V_1(\mathbf{r})] d^3\mathbf{r}, \quad (19)$$

and comparison of strict inequalities (18) and (19) gives

$$0 < \int_g [\rho_2(\mathbf{r}) - \rho_1(\mathbf{r})] [V_1(\mathbf{r}) - V_2(\mathbf{r})] d^3\mathbf{r}, \quad (20)$$

that is possible only if $\rho_1(\mathbf{r}) \neq \rho_2(\mathbf{r})$.

On the other hand, if $\Psi_1 = \alpha\Psi_2$ for some complex factor α , $|\alpha| = 1$, then $\rho_1(\mathbf{r}) = \rho_2(\mathbf{r})$ follows. Consequently, $\rho_1(\mathbf{r}) \neq \rho_2(\mathbf{r})$ implies $\Psi_1 \neq \alpha\Psi_2$, but then $V_1(\mathbf{r}) \neq V_2(\mathbf{r}) + \beta$, for any real constant β .

Indeed, significant differences in the external potentials imply significant differences in the nondegenerate ground state electron densities, and *vice versa*.

Some of the results described above would not hold if the wavefunctions Ψ_1 and Ψ_2 could become zero on a subset of non-zero measure.

These statements on the connections between external potentials, nondegenerate ground state wavefunctions and the corresponding electron densities are equivalent to the conclusions of the original Hohenberg–Kohn theorem, implying, in fact, that the nondegenerate ground state electron density $\rho(\mathbf{r})$ uniquely determines the ground state energy E , the corresponding wavefunction Ψ up to a complex phase factor, and consequently, also the expectation values of all spin-free observables.

If one assumes that the entire physical system is confined to a finite, bounded region g of the space, then a direct application of analytic continuation of a subsystem electronic density provides a unique determination of the electronic density of the entire system. Following the treatment of [64], this can be demonstrated as follows.

Select an arbitrary subset d of non-zero volume within the finite and bounded physical region g of the ordinary 3-space R^3 , where the entire physical system, for example, the entire molecule is assumed to be contained within domain g :

$$R^3 \supset g \supset d. \quad (21)$$

According to these assumption, the complete electron density $\rho_g(\mathbf{r})$ is given by the equation

$$\rho_g(\mathbf{r}) = n \sum_{s_1} \cdots \sum_{s_n} \int_g \cdots \int_g |\Psi(\mathbf{r}, s_1, \mathbf{r}_2, s_2, \dots, \mathbf{r}_n, s_n)|^2 d^3\mathbf{r}_2 \cdots d^3\mathbf{r}_n, \quad (22)$$

where the $n-1$ integrations are carried out over the finite domain g , and the summations are for the n spin variables.

The wavefunction $\Psi(\mathbf{r}, s_1, \mathbf{r}_2, s_2, \dots, \mathbf{r}_n, s_n)$, as well as the associated n -electron density

$$\rho_g(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n) = n \sum_{s_1} \cdots \sum_{s_n} |\Psi(\mathbf{r}_1, s_1, \mathbf{r}_2, s_2, \dots, \mathbf{r}_n, s_n)|^2, \quad (23)$$

are almost everywhere analytic in G , with the exception of a set of singular points including the Coulomb singularities of coincident nucleus–electron and electron–electron locations. These points of singularities form a set Y of measure zero in G , where none of the $(3n - 3)$ -dimensional subspaces of G is cut into two disjoint parts with non-analytic common boundary by the set Y .

Almost everywhere analyticity implies that the function $\rho_g(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n)$ is integrable in G , hence it is necessarily integrable on the subset $(\mathbf{r}_2, \dots, \mathbf{r}_n)$ of its $n - 1$ variables, that gives the electron density $\rho_g(\mathbf{r})$ within the finite domain g of the physical system:

$$\rho_g(\mathbf{r}) = n \int_g \cdots \int_g \rho_g(\mathbf{r}, \mathbf{r}_2, \dots, \mathbf{r}_n) d^3\mathbf{r}_2 \cdots d^3\mathbf{r}_n. \quad (24)$$

The electronic density function $\rho_g(\mathbf{r})$ of equation (24) is obtained by integrating according to the $n - 1$ variables $\mathbf{r}_2, \dots, \mathbf{r}_n$ over a finite, $(3n - 3)$ -dimensional domain G^{3n-3} that is the $(n - 1)$ -fold direct sum of the finite, 3-dimensional domain g . The almost everywhere analyticity of $\rho_g(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n)$ in terms of the variables $\mathbf{r} = \mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n$ also implies that the electronic density function $\rho_g(\mathbf{r})$ of equation (24), where the \mathbf{r} is the variable not involved in the integration, is also almost everywhere analytic over the three-dimensional domain g .

These properties are sufficient conditions for the application of the theorem of analytic continuation to a subsystem of the electronic density. Consequently, if $\rho_d(\mathbf{r})$ is the subsystem electron density function over any non-zero volume subset d of the finite and bounded physical domain g , $g \supset d$, then $\rho_g(\mathbf{r})$ over the entire finite and bounded domain g is uniquely determined by $\rho_d(\mathbf{r})$.

One may restate this result in terms of direct comparisons of subsystem densities. Subject to the condition of boundedness of domain g , if over a subdomain d the restrictions $\rho_d^a(\mathbf{r})$ and $\rho_d^b(\mathbf{r})$ of electron densities $\rho_g^a(\mathbf{r})$ and $\rho_g^b(\mathbf{r})$, respectively, agree for every point \mathbf{r} of d ,

$$\rho_d^a(\mathbf{r}) = \rho_d^b(\mathbf{r}), \quad (25)$$

then

$$\rho_g^a(\mathbf{r}) = \rho_g^b(\mathbf{r}) \quad (26)$$

necessarily follows for every point \mathbf{r} of g .

Although an analogous statement appears plausible for the case of boundaryless electron densities, not confined to a finite, bounded region of the space, and such a general property is, in fact, the natural expectation, nevertheless, the above proof is valid only for the case of the finite, bounded model.

Unfortunately, in rigorous quantum mechanics the localizability of a molecular system within any finite domain of the three-dimensional space is not strictly valid, and for the relations between a complete, boundaryless molecular electron density and its subsystems one needs a different approach. Such an approach is provided by a compactification procedure applied to a four-dimensional representation of the mole-

cular electron densities, establishing the result that the electron density of any finite subsystem of non-zero volume determines the electron density of the rest of a complete, boundaryless system. The general result is the “holographic electron density theorem” [53] that will be reviewed briefly, providing the basis for the special adaptation of this theorem to some of the problems of generalized symmetry deficiency in the next section.

Since the essential step in this approach is the compactification of the space where the quantum chemical system has been originally described, the treatment may be regarded as a formulation of quantum chemistry on a compact manifold. One advantage of this approach is the replacement of one continuum with another where some problems which in the ordinary case cannot be treated easily now can be confined to local ranges of a compact manifold, or in the extreme case, to single points. Establishing convergence properties at individual points, and the use of sets of measure zero are much easier in the latter case.

The Alexandrov one-point compactification of Euclidean spaces E^n is a technique that provides a one-to-one mapping between the points of the Euclidean space E^n and the points of a punctured sphere S^n of the same dimension n , followed by the completion of the sphere S^n by adding a single point, usually taken as the formal “north pole” \mathbf{n} of the sphere (for an illustration, see, for example, the compactification applied to a nuclear configuration space in the study of potential energy hypersurfaces [35]). A four-dimensional representation of molecular electron densities [38,39,79] has been applied to molecular shape analysis, and this representation is also advantageous in our present problem.

The unique extension property of the electron density of a subdomain to the electron density of the complete system, for example, to the complete, boundaryless electron density of a molecule, is analogous to a property of holographic plates. Any fragment of a holographic plate contains the complete information about the entire recorded image; similarly, the electron density of any subsystem of non-zero volume can be extended uniquely to the electron density of the entire molecule, hence, it also contains the complete information about the entire, boundaryless molecule. This analogy is reflected in the name of the “holographic electron density theorem” and in the terminology of “holographic electron density maps”. Whereas the proof of this theorem is based on a four-dimensional representation of the electron density of the system, the conclusions apply to the ordinary, three-dimensional density functions.

In a four-dimensional Euclidean space E^4 the molecular electron density $\rho(\mathbf{r})$ is represented as a hypersurface [38,39,79] defined “over” the ordinary three-dimensional space E^3 that is a subspace of E^4 . That is, the first three dimensions correspond to the position within the ordinary three-dimensional space E^3 , and the fourth dimension corresponds to the function values of the molecular electron density $\rho(\mathbf{r})$.

Each point \mathbf{Y} of the hypersurface representing the electron density in this four-dimensional space E^4 is characterized by four coordinates, r_x, r_y, r_z and $\rho(\mathbf{r})$, where r_x, r_y and r_z are the three components of the position vector \mathbf{r} in E^3 where the

electron density of the system is evaluated. These four quantities are the components of a four-dimensional column vector representing point \mathbf{Y} :

$$\mathbf{Y} = [r_x, r_y, r_z, \rho(\mathbf{r})]^\dagger, \quad (27)$$

where the symbol \dagger stands for “transpose”.

If the four-dimensional version of the Alexandrov compactification is applied to the space E^3 , then the points of space E^3 are mapped to a 3-sphere S^3 by a one-to-one assignment of points \mathbf{r} of E^3 to the points \mathbf{r}' of the sphere S^3 . In the three-dimensional Euclidean space E^3 the origin may be taken as the center of mass of the molecule, and the “north pole” \mathbf{n} of the 3-sphere S^3 corresponds to infinite distance from this origin specified within E^3 .

The assignment

$$\rho'(\mathbf{r}') = \rho(\mathbf{r}) \quad (28)$$

and

$$\rho'(\mathbf{n}) = 0 \quad (29)$$

re-defines the electron density function on the sphere S^3 .

The distance $p = |\mathbf{r}|$ of any point \mathbf{r} of space E^3 from the origin \mathbf{o} is related to the polar angle θ of decline from the vertical axis on the sphere S^3 by

$$p = 2 \cot(\theta/2), \quad (30)$$

hence the exponential asymptotic convergence of $\rho(\mathbf{r})$ to zero as p approaches infinity behaves as the following limit on the sphere S^3 :

$$\lim_{\mathbf{r}' \rightarrow \mathbf{n}} \rho'(\mathbf{r}') = \lim_{\theta \rightarrow 0} \exp[-2 \cot(\theta/2)]. \quad (31)$$

The exponential function is analytic everywhere and the $\cot(x)$ function is analytic in the open interval $0 < |x| < \pi$. Consequently, with the exception of $\theta = 0$ and $\theta = \pi$, the function $\exp[-2 \cot(\theta/2)]$ is analytic on the sphere S^3 , since it is a composition of analytic functions. One finds that $\exp[-2 \cot(\theta/2)]$ is analytic almost everywhere on the sphere S^3 .

Since $\cot(\theta/2) \rightarrow \infty$ as $\theta \rightarrow 0$,

$$\lim_{\theta \rightarrow 0} \exp[-2 \cot(\theta/2)] = 0. \quad (32)$$

By repeated differentiation of the function $\exp[-2 \cot(\theta/2)]$ one finds that near the north pole \mathbf{n} as $\theta \rightarrow 0$ the dominant term that controls the convergence of the k th derivative behaves as

$$\sin^{-2k}(\theta/2) \exp[-2 \cot(\theta/2)]. \quad (33)$$

Then, repeated application of l'Hospital's rule gives the result that all derivatives of the function $\exp[-2 \cot(\theta/2)]$ converge to zero as $\theta \rightarrow 0$,

$$\lim_{\theta \rightarrow 0} \frac{d^k \exp[-2 \cot(\theta/2)]}{d\theta^k} = 0. \quad (34)$$

Consequently, the four-dimensional electron density $\rho'(\mathbf{r}')$ on the sphere S^3 converges smoothly (infinitely differentially) to zero at the north pole \mathbf{n} , hence $\rho'(\mathbf{r}')$ can be extended continuously and infinitely differentially to the complete sphere S^3 . The almost everywhere analyticity of the electron density $\rho(\mathbf{r})$ at any specified point \mathbf{r} of the ordinary Euclidean space E^3 is a property inherited by $\rho'(\mathbf{r}')$ on the sphere S^3 everywhere except at the north pole \mathbf{n} . The almost everywhere analyticity of $\exp[-2 \cot(\theta/2)]$ on the sphere, combined with the condition of infinitely smooth convergence to zero at \mathbf{n} , adds only a single additional point \mathbf{n} of nonanalyticity, consequently, the four-dimensional electron density $\rho'(\mathbf{r}')$ is almost everywhere analytic when extended to the entire sphere S^3 .

The conditions of the general theorem of analytic continuation are fulfilled by the almost everywhere analytic four-dimensional electron density $\rho'(\mathbf{r}')$ on the closed and bounded sphere S^3 , consequently, the nondegenerate ground state electron density $\rho'_d(\mathbf{r}')$ over any subdomain d of non-zero volume uniquely determines the complete electron density $\rho'(\mathbf{r}')$ over the entire sphere S^3 , except for a possible subset of measure zero.

This result outlined above has been stated as the

Holographic electron density theorem ([53]). If $\rho'_d(\mathbf{r}')$ denotes the nondegenerate ground state electron density over a subset d of three-dimensional sphere S^3 , $S^3 \supset d$, where d has non-zero volume, then the ground state electron density $\rho'(\mathbf{r}')$ over the entire sphere S^3 is uniquely determined by the local ground state electron density $\rho'_d(\mathbf{r}')$ over the subdomain d .

The statement of this theorem can be rephrased as follows:

If the restrictions $\rho'_d{}^a(\mathbf{r}')$ and $\rho'_d{}^b(\mathbf{r}')$ of two, complete densities $\rho'^a(\mathbf{r}')$ and $\rho'^b(\mathbf{r}')$, respectively, agree at every point \mathbf{r}' of a non-zero volume subdomain d ,

$$\rho'_d{}^a(\mathbf{r}') = \rho'_d{}^b(\mathbf{r}'), \quad (35)$$

then the complete, boundaryless electron densities also must agree for every point \mathbf{r}' of S^3 ,

$$\rho'^a(\mathbf{r}') = \rho'^b(\mathbf{r}'), \quad (36)$$

except for a possible subset of measure zero.

An important consequence follows from the Hohenberg–Kohn theorem. Since the ground state density $\rho'_d(\mathbf{r}')$ of the subsystem determines the complete, boundaryless nondegenerate ground state electron density $\rho'(\mathbf{r}')$ of the entire system, and in turn, as implied by the Hohenberg–Kohn theorem, $\rho'(\mathbf{r}')$ determines the ground state energy E

and the ground state wavefunction Ψ , consequently, the ground state energy E and the ground state wavefunction Ψ are uniquely determined by the electron density $\rho'_d(\mathbf{r}')$ of any non-zero volume subsystem d .

3. Relations between local and global symmetries, chirality properties, and other symmetry deficiencies of molecular electron densities

Some interesting applications of the holographic electron density theorem are formal proofs of some plausible and some less plausible relations between local and global symmetries of molecular electron densities.

We shall use the following notations: if the holographic electron density theorem applies to a subsystem $\rho_d(\mathbf{r})$ and the corresponding complete system $\rho(\mathbf{r})$, that is, if the extension of the subsystem $\rho_d(\mathbf{r})$ to the complete system $\rho(\mathbf{r})$ is unique, then we write

$$\text{EXT } \rho_d(\mathbf{r}) = \rho(\mathbf{r}). \quad (37)$$

Consider the electron density $\rho_D(\mathbf{r})$ of a subsystem D of a complete, boundaryless, nondegenerate ground state electron density $\rho(\mathbf{r})$ of a molecule. In some of the applications to molecular shape analysis [3,32–34,36,40,43,45,47,48] it is advantageous, but not necessary, to choose D as a density domain [41], denoted by $DD_i(K, a)$, and defined as the i th maximum connected component of the a -cut $DD(K, a)$ of the complete molecular electron density $\rho(\mathbf{r}) = \rho(K, \mathbf{r})$, where in the notation the nuclear configuration K and the density threshold a are specified:

$$DD(K, a) = \{\mathbf{r}: \rho(K, \mathbf{r}) \geq a\}. \quad (38)$$

The term “density domain” is also used for the set $DD(K, a)$, with the understanding that $DD(K, a)$ may be the union of several, disconnected pieces $DD_i(K, a)$. Such density domains [41] are related to *molecular isodensity contours*, MIDCOs $G(K, a)$, defined as

$$G(K, a) = \{\mathbf{r}: \rho(K, \mathbf{r}) = a\}, \quad (39)$$

where the MIDCO $G(K, a)$ can be regarded as the boundary surface of the density domain $DD(K, a)$.

Density domains and MIDCOs play important roles in molecular shape analysis and in the study of quantum chemical functional groups [47]. A quantum chemical functional group was defined as an additive fuzzy electron density fragment (AFDF fragment [45,47,48]) associated with a family f_i of nuclei where there exists a MIDCO $G(K, a)$ of some density threshold a that separates the nuclear family f_i from the rest of the nuclei of the molecule [47]. By analogy with the existence of isodensity contours separating the nuclei of two molecules placed at some distance, say, 10 Å between their nearest nuclei, where these molecules evidently maintain their separate identity, the limited autonomy and separate identity of functional groups within molecules is reflected in the definition of quantum chemical functional groups [47].

The first result we prove between relations of local and global symmetries is rather plausible:

Local symmetry extension theorem. Take a complete, boundaryless, nondegenerate ground state electron density $\rho(\mathbf{r})$ of a molecule and the local electron density $\rho_D(\mathbf{r})$ of an arbitrary non-zero volume subsystem D of this molecule. If the local electron density $\rho_D(\mathbf{r})$ of the subsystem D has a symmetry element R , then the entire electron density $\rho(\mathbf{r})$ must have this symmetry element R .

Proof. Denote the symmetry operator that corresponds to the symmetry element R by \mathbf{R} . We know that

$$\mathbf{R}\rho_D(\mathbf{r}) = \rho_D(\mathbf{r}). \quad (40)$$

However, the holographic electron density theorem applies, implying that the extension of $\rho_D(\mathbf{r})$ into $\rho(\mathbf{r})$ is unique, that is,

$$\text{EXT } \rho_D(\mathbf{r}) = \rho(\mathbf{r}). \quad (41)$$

By applying the symmetry operator \mathbf{R} , a linear operator, to the entire space, the holographic electron density theorem must apply to the resulting pair of densities $\mathbf{R}\rho_D(\mathbf{r})$ and $\mathbf{R}\rho(\mathbf{r})$ as well. Consequently, the extension of the local density $\mathbf{R}\rho_D(\mathbf{r})$ into $\mathbf{R}\rho(\mathbf{r})$ must also be unique, that is,

$$\text{EXT } \mathbf{R}\rho_D(\mathbf{r}) = \mathbf{R}\rho(\mathbf{r}). \quad (42)$$

However, using equation (40), the left-hand side of equation (42) becomes

$$\text{EXT } \rho_D(\mathbf{r}) = \mathbf{R}\rho(\mathbf{r}), \quad (43)$$

and comparing this to equation (41) one obtains

$$\rho(\mathbf{r}) = \mathbf{R}\rho(\mathbf{r}). \quad (44)$$

Consequently, the complete electron density $\rho(\mathbf{r})$ must also possess the symmetry element R . \square

The next result, a simple consequence of the local symmetry extension theorem, is somewhat reminiscent to the ‘‘catchment region symmetry theorem’’ describing some symmetry relations on potential energy hypersurfaces [37]. We recall that a catchment region is the collection of all those nuclear configurations which relax (by an ideal, infinitely slow, vibrationless relaxation) to the same critical point of the potential energy hypersurface. That theorem established that in any catchment region the critical point nuclear configuration must have the highest symmetry [37]. In the next theorem, the role of arbitrary points of the catchment region is played by the local electron densities of arbitrary, non-zero volume subsystems, whereas the role of the critical point configuration is played by the complete electron density.

We shall use the group–subgroup terminology in the following sense: each group is regarded as one of its own subgroups. Similarly, for simplicity in phrasing statements, we regard the complete system as one of its own subsystems.

Global density symmetry accumulation theorem. Consider a complete, boundaryless, nondegenerate ground state electron density $\rho(\mathbf{r})$ of a molecule and the local electron density $\rho_D(\mathbf{r})$ of an arbitrary non-zero volume subsystem D of this molecule.

- (i) The symmetry group $g[\rho_D(\mathbf{r})]$ of the local electron density $\rho_D(\mathbf{r})$ of the subsystem D must be a subgroup of the symmetry group $g[\rho(\mathbf{r})]$ of the complete electron density $\rho(\mathbf{r})$:

$$g[\rho(\mathbf{r})] \supset g[\rho_D(\mathbf{r})]. \quad (45)$$

- (ii) Among the electron densities of all non-zero volume subsystems D of the complete system, the complete electron density $\rho(\mathbf{r})$ must have the highest symmetry.

Proof. For each non-zero volume subsystem D , the local symmetry extension theorem applies to every symmetry element R of the subsystem electron density $\rho_D(\mathbf{r})$. Consequently, if $g[\rho_D(\mathbf{r})]$ is the symmetry group of the corresponding symmetry operators \mathbf{R} of the subsystem electron density $\rho_D(\mathbf{r})$, then this group $g[\rho_D(\mathbf{r})]$ must be a subgroup of the symmetry group $g[\rho(\mathbf{r})]$ of the complete electron density $\rho(\mathbf{r})$. This applies to every subsystem D , that proves (i).

Statement (ii) is a direct consequence of statement (i). \square

Relations between symmetry deficiencies, for example, between chiralities of local subsystem electron densities and global electron densities can also be derived from the holographic electron density theorem.

Stated in simple terms, if a complete system has a certain symmetry deficiency, then all non-zero volume subsystems must also have it.

Subsystem symmetry deficiency theorem. If a complete, boundaryless, nondegenerate ground state electron density $\rho(\mathbf{r})$ of a molecule is deficient in a symmetry element R , then the local electron density $\rho_D(\mathbf{r})$ of every non-zero volume subsystem D of this molecule must also be deficient in this symmetry element R .

Proof. If the complete electron density $\rho(\mathbf{r})$ of the molecule does not possess a symmetry element R , then none of the local electron densities $\rho_D(\mathbf{r})$ of its non-zero volume subsystems D can have this symmetry element R , since if any one of the local densities $\rho_D(\mathbf{r})$ would possess R , then the local symmetry extension theorem would imply that $\rho(\mathbf{r})$ also has R , a contradiction. \square

Corollary. If a complete, boundaryless, nondegenerate ground state electron density $\rho(\mathbf{r})$ of a molecule is chiral, then the local electron density $\rho_D(\mathbf{r})$ of every non-zero volume subsystem D of this molecule must also be chiral.

Evidently, if the local electron density $\rho_D(\mathbf{r})$ of any of the non-zero volume subsystems D of this molecule would be achiral, then this local electron density would possess a symmetry element of either a reflection plane σ or an improper rotation of type S_{2k} that, by the local symmetry extension theorem would imply that $\rho(\mathbf{r})$ also has this symmetry element, hence $\rho(\mathbf{r})$ is also achiral, a contradiction.

4. Holographic properties of the range of “low density glue” bonding of electron densities in macromolecules

Some of the earlier limitations of macromolecular quantum chemistry have been overcome by the spectacular advances in computer technology and by advances in quantum chemical computational methodologies [50,52]. In this regard, the recent introduction of the macromolecular Adjustable Density Matrix Assembler (ADMA) method [42,44–46,48,49] has led to new methodologies for the computation of *ab initio* quality macromolecular electron densities and of similar quality macromolecular forces [49].

These new methods provided motivation for the study of electron density ranges that were not accessible to *ab initio* quality quantum chemistry investigations by earlier methods. Among these ranges are some of the low density moieties of folded macromolecules, such as proteins [51,52].

In most small molecules the low electron density ranges are primarily found on the peripheries of the molecule, and these ranges do not contribute much to the bonding within the molecule. However, in folded macromolecules, for example, in proteins, the low density ranges within the interior of the nuclear framework have significant role in determining the shape and folding pattern of the macromolecule. Since these contributions to chemical bonding are not localized and have less prominent directional properties than the more familiar formal chemical bonds between atom pairs, in an earlier study they were compared to macroscopic “bonding” by some low viscosity “glue”. Motivated by this analogy, the term “low density glue” (LDG) bonding was used when referring to some of the quantum chemical properties of these regions of macromolecular electron densities [52].

The importance of macromolecular quantum chemistry methods, such as the ADMA approach in the study of LDG bonding is underlined by the fact that the low density regions of macromolecular electron distributions are not well described experimentally. Most experimental methods, such as X-ray crystallography, provide very limited information concerning the low density ranges and focus on the high density regions, primarily near the nuclear neighborhoods. The ADMA approach provides more information concerning the shape of the LDG regions. These regions are of importance in the study of local shape features of electron densities in enzyme–substrate interactions, in protein folding processes, and in the assessment of local chemical reactivities within a multifunctional macromolecule.

If a local subsystem is chosen within a low density region, then the shape features of the subdomain are usually more sensitive to interactions with other molecular

regions than the shape features of subsystems in the high density regions. In fact, the high density nuclear neighborhoods show a high degree of shape stability when the local surroundings change [2]. By contrast, the MIDCOs $G(K, a)$ of low a thresholds may undergo large local deformations, even topologically significant changes as a consequence of minor conformational changes. This difference is due to the higher degree of polarizability of the LDG domains. Consequently, in a topological sense, the LDG range is a sensitive diagnostic tool for assessing some of the subtle aspects of conformational changes and their effects on local interactions. In particular, the loss of local symmetries is often manifested in topological changes in the shapes of LDG MIDCOs $G(K, a)$. By virtue of the holographic property of non-degenerate, ground state densities, a local topological change of an LDG MIDCOs $G(K, a)$ can be used as a manifestation of a change of the global symmetry of the molecule.

5. A topological shape characterization of density domains using semilattice tree (SLT) codes and the detection of symmetry deficiency

A topological description of some of the essential features of LDG MIDCOs $G(K, a)$ is a tool that is applicable to the detection of local and global symmetry changes. However, such a topological description is not necessarily restricted to the LDG range of molecules, and here we shall describe a technique that is generally applicable to molecular electron densities.

In general, the topological patterns of MIDCOs $G(K, a)$ of a series of density domains $DD(K, a)$ can be used for similarity analysis. Consider a finite series of monotonically increasing electron density thresholds,

$$a_1, a_2, \dots, a_k, \dots, a_t, \quad (46)$$

and the corresponding family of density domains

$$DD(K, a_1), DD(K, a_2), \dots, DD(K, a_k), \dots, DD(K, a_t) \quad (47)$$

of a molecule of conformation K .

The topological pattern generated by these density domains can be characterized by a simple numerical code, called the semilattice tree code, or SLT code.

In figure 1, we shall illustrate this code by a two-dimensional example, that may be regarded as the pattern of a two-dimensional cross-section of a family of three-dimensional density domains. The three-dimensional, and in general, any of the finite n -dimensional cases are entirely analogous. Each contour of this pattern is labeled with the serial number k of the corresponding density threshold a_k .

The pattern itself is characterized by a semilattice that has the topological structure of a tree. If there are m contour lines, the tree has $m + 1$ vertices. Note that $t \leq m$. A vertex of the tree labeled with the number 0 corresponds to zero-density, a contour at infinity, that is equivalent to the north pole \mathbf{n} of the 3-sphere S^3 of the compact

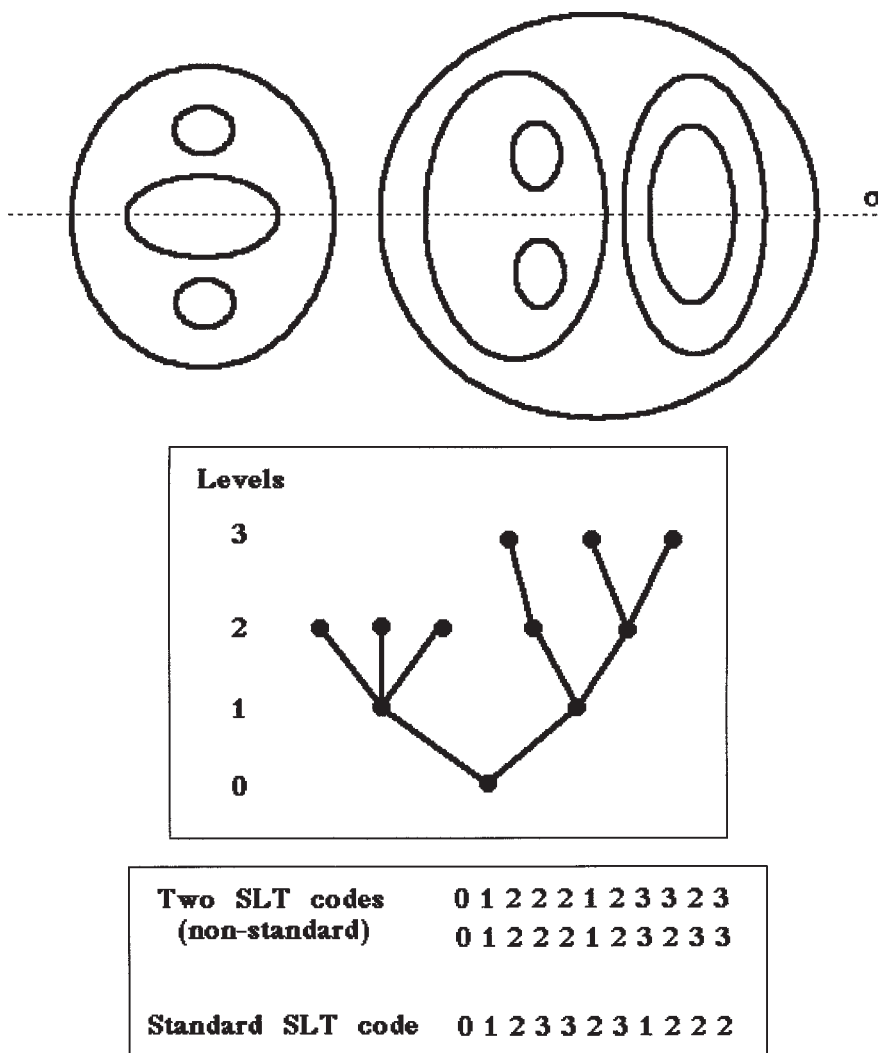


Figure 1. Example of a planar topological pattern of density domains, the corresponding lower semilattice tree, and some of the valid SLT numerical codes, including the lexicographically dominant standard SLT code. The pattern involves four density thresholds, including the formal threshold of 0 that corresponds to level 0 of the semilattice. The topological pattern is shown in a geometrical representation exhibiting the maximum symmetry for the pattern, indicated by the dashed reflection line σ .

manifold representation of quantum chemical electron densities. If a contour of label k contains a contour of label $k + 1$ then the former contour is the parent contour of the latter, and the corresponding vertices of the graph are connected by an edge.

The resulting graph with the natural ordering for the vertex labels as the partial order is a lower semilattice. This semilattice can be characterized by a numerical code, the SLT code, that can be determined by the following three simple rules:

- (i) start the numerical sequence with label 0;
- (ii) immediately after writing the label k of a contour, write the label $k + 1$ of a contour contained within, if such contour exists;
- (iii) if no contour is contained in the contour of label just written down, then go back in the sequence already written down, find the label of the first contour that contains another contour not yet recorded, and write to the end of the current sequence the label of this unrecorded contour.

The process ends if no more contour is left to be recorded.

The code obtained by this process is sufficient to reproduce the lower semilattice tree, however, it is not unique, that hinders its use in pattern comparisons.

In order to obtain a unique SLT code, one can use permutations of “finished subsequences”. A finished subsequence of the code is a subsequence that starts at some label k , and contains all subsequent numbers in the sequence up to but not including the next label of the same value k , if there is one. Any permutation of any number of finished subsequences starting with the same value k and having the same parent contour of index $k - 1$, corresponds to the same lower semilattice tree. Furthermore, each valid SLT code of a given lower semilattice tree can be obtained from any other valid SLT code by such permutations of finished subsequences. These permutations are referred to as allowed permutations.

Since the family of all valid SLT codes can be ordered lexicographically, a unique, standardized lower semilattice tree code can be obtained by carrying out all allowed permutations of finished subsequences and determining the code that has the greatest numerical value, that is, the dominant code in the lexicographic order.

The example shown schematically in figure 1 corresponds to a pattern of density domains involving four density thresholds (including the formal threshold of 0, corresponding to level 0 of the semilattice). One may also regard this example as a pattern of level sets, such as those of geographical terrains or potential surfaces of chemical reactions. For these four levels, there are ten contour lines. The lower semilattice tree corresponding to this pattern has eleven vertices. This tree and three of the valid SLT codes are also shown. The second code can be obtained from the first one by swapping the two finished subsequences 233 and 23. The code of highest numerical value, that is, the dominant SLT code in the lexicographic order of all valid SLT codes is the third code shown. By swapping the finished subsequences 1222 and 123323 of the first code shown, one obtains the standard SLT code.

A topological pattern of an object, and a representative numerical code of this pattern such as the SLT code can be used to characterize symmetry deficiency of the original object. Take the geometrical representation of the topological pattern that admits the highest symmetry if this symmetry is unique, or the set of geometrical representations if there is more than one maximal symmetry that can be realized geometrically. These symmetries are the topological symmetries of the pattern. Any higher symmetry, or in general, any symmetry that is not realizable by any geometrical representation of the topological pattern corresponds to a symmetry deficiency of the

topological pattern. This implies that the physical object represented topologically by the pattern also must have these symmetry deficiencies. Note, however, that the actual geometry of the physical object may lack some or all of those symmetries which are not excluded by the topological pattern.

The actual geometrical representation of the topological pattern shown in figure 1 is one that admits the maximum possible planar symmetry for this topological pattern, as indicated by the dashed reflection line σ in the figure. Note that the topological symmetry element σ is a property for all geometrical representations of this pattern which are topologically equivalent to the one shown, that is, no distortion of the pattern that preserves its topology can lead to the loss of this topological symmetry element, neither can any such distortion lead to the gain of any other, nontrivial symmetry element.

6. Summary

A framework where the interrelations between the local electron density of a subsystem and the global electron density of the complete system are described without any truncation of the space is used for the study of local and global symmetry properties of molecules. Such a description is made possible by applying a compactification technique to a four-dimensional representation of molecular electron densities that avoids the difficulties of an earlier, finite and bounded model. Several theorems interrelating the local and global symmetries and symmetry deficiencies of molecular electron densities are proven, and the special role of low density ranges in macromolecular bonding of folded structures (the "low density glue", LDG bonding) is discussed. A topological code, suitable for the detection of some of the symmetry deficiencies is introduced.

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References

- [1] J. Andzelm and E. Wimmer, *J. Chem. Phys.* 96 (1992) 1280.
- [2] G.A. Arteca, N.D. Grant and P.G. Mezey, *J. Comput. Chem.* 12 (1991) 1198.
- [3] G.A. Arteca and P.G. Mezey, *Chem. Phys.* 161 (1992) 1.
- [4] R.F.W. Bader and T.T. Nguyen-Dang, *Adv. Quantum Chem.* 14 (1981) 63.
- [5] A. Becke, *J. Chem. Phys.* 84 (1986) 4524.
- [6] A. Becke, *Phys. Rev. A* 33 (1986) 2786.
- [7] A. Becke, *J. Chem. Phys.* 88 (1988) 1053.
- [8] A. Becke, *Phys. Rev. A* 38 (1988) 3098.
- [9] J. Cioslowski, *J. Phys. Chem.* 94 (1990) 5496.
- [10] J. Cioslowski and E.D. Fleischmann, *J. Chem. Phys.* 94 (1991) 3730.
- [11] J. Cioslowski and S.T. Mixon, *Can. J. Chem.* 70 (1992) 443.

- [12] J. Cioslowski, S.T. Mixon and W.D. Edwards, *J. Am. Chem. Soc.* 113 (1991) 1083.
- [13] J. Cioslowski, S.T. Mixon and E.D. Fleischmann, *J. Am. Chem. Soc.* 113 (1991) 4751.
- [14] J. Cioslowski, P.B. O'Connor and E.D. Fleischmann, *J. Am. Chem. Soc.* 113 (1991) 1086.
- [15] K. Collard and G.G. Hall, *Int. J. Quantum Chem.* 12 (1977) 623.
- [16] Ph. Coppens and M.B. Hall, eds., *Electron Distributions and the Chemical Bond* (Plenum Press, New York, 1982).
- [17] V. Fock, *Z. Physik* 61 (1930) 126.
- [18] M.J. Frisch, M. Head-Gordon, G.W. Trucks, J.B. Foresman, H.B. Schlegel, K. Raghavachari, M.A. Robb, J.S. Binkely, C. Gonzalez, D.J. DeFrees, D.J. Fox, R.A. Whiteside, R. Seeger, C.G. Melius, J. Baker, R.L. Martin, L.R. Kahn, J.J.P. Stewart, S. Topiol and J.A. Pople, *Gaussian 92*, Gaussian Inc., Pittsburgh, PA (1992).
- [19] G.G. Hall, *Proc. Roy. Soc. London Ser. A* 205 (1951) 541.
- [20] D.R. Hartree, *Proc. Cambridge Phil. Soc.* 24 (1928) 111, 426.
- [21] D.R. Hartree, *Proc. Cambridge Phil. Soc.* 25 (1929) 225, 310.
- [22] P. Hohenberg and W. Kohn, *Phys. Rev. B* 136 (1964) 864.
- [23] W. Kohn and L.J. Sham, *Phys. Rev. A* 140 (1965) 1133.
- [24] E.S. Kryachko and E.V. Ludena, *Density Functional Theory of Many-Electron Systems* (Kluwer, Dordrecht, 1989).
- [25] J.K. Labanowski and J. Andzelm, eds., *Density Functional Methods in Chemistry* (Springer, New York, 1991).
- [26] M. Levy, *Bull. Amer. Phys. Soc.* 24 (1979) 626.
- [27] M. Levy, *Proc. Natl. Acad. Sci. USA* 76 (1979) 6062.
- [28] M. Levy, *Phys. Rev. A* 26 (1982) 1200.
- [29] M. Levy, *Adv. Quantum Chem.* 21 (1990) 69.
- [30] E.V. Ludena, *J. Chem. Phys.* 79 (1983) 6174.
- [31] R. McWeeny and B.T. Sutcliffe, *Methods of Molecular Quantum Mechanics* (Academic Press, New York, 1969).
- [32] P.G. Mezey, *Int. J. Quantum Chem. Quantum Biol. Symp.* 12 (1986) 113.
- [33] P.G. Mezey, *Int. J. Quantum Chem. Quantum Biol. Symp.* 14 (1987) 127.
- [34] P.G. Mezey, *J. Comput. Chem.* 8 (1987) 462.
- [35] P.G. Mezey, *Potential Energy Hypersurfaces* (Elsevier, Amsterdam, 1987).
- [36] P.G. Mezey, *J. Math. Chem.* 2 (1988) 325.
- [37] P.G. Mezey, *J. Am. Chem. Soc.* 112 (1990) 3791.
- [38] P.G. Mezey, Three-dimensional topological aspects of molecular similarity, in: *Concepts and Applications of Molecular Similarity*, eds. M.A. Johnson and G.M. Maggiora (Wiley, New York, 1990).
- [39] P.G. Mezey, Topological quantum chemistry, in: *Reports in Molecular Theory*, eds. H. Weinstein and G. Náray-Szabó (CRC Press, Boca Raton, 1990).
- [40] P.G. Mezey, *Shape in Chemistry: An Introduction to Molecular Shape and Topology* (VCH Publishers, New York, 1993).
- [41] P.G. Mezey, Density domain bonding topology and molecular similarity measures, in: *Molecular Similarity*, ed. K. Sen, Topics in Current Chemistry, Vol. 173 (Springer, Heidelberg, 1995).
- [42] P.G. Mezey, *J. Math. Chem.* 18 (1995) 141.
- [43] P.G. Mezey, Methods of molecular shape-similarity analysis and topological shape design, in: *Molecular Similarity in Drug Design*, ed. P.M. Dean (Chapman & Hall-Blackie Publishers, Glasgow, 1995).
- [44] P.G. Mezey, Program ADMA 95, Mathematical Chemistry Research Unit, University of Saskatchewan, Saskatoon, SK, Canada (1995).
- [45] P.G. Mezey, *Structural Chem.* 6 (1995) 261.
- [46] P.G. Mezey, *Adv. Molec. Similarity* 1 (1996) 89.
- [47] P.G. Mezey, *Adv. Quantum Chem.* 27 (1996) 163.

- [48] P.G. Mezey, Local shape analysis of macromolecular electron densities, in: *Computational Chemistry: Reviews and Current Trends*, Vol. 1, ed. J. Leszczynski (World Scientific Publ., Singapore, 1996).
- [49] P.G. Mezey, *Int. J. Quantum Chem.* 63 (1997) 39.
- [50] P.G. Mezey, *Int. Rev. Phys. Chem.* 16 (1997) 361.
- [51] P.G. Mezey, *Pharmaceut. News* 4 (1997) 29.
- [52] P.G. Mezey, Chemical bonding in proteins and other macromolecules, in: *Pauling's Legacy: Modern Theory of Chemical Bonding*, eds. Z. Maksic and W.J. Orville-Thomas (Elsevier, Amsterdam, 1998).
- [53] P.G. Mezey, *Molec. Phys.*, to be published (1998).
- [54] P.G. Mezey, Z. Zimpel, P. Warburton, P.D. Walker, D.G. Irvine, D.G. Dixon and B. Greenberg, *J. Chem. Inf. Comput. Sci.* 36 (1996) 602.
- [55] R.S. Mulliken, *J. Chem. Phys.* 23 (1955) 1833, 1841, 2338, 2343.
- [56] R.S. Mulliken, *J. Chem. Phys.* 36 (1962) 3428.
- [57] I. Pápai, A. Goursot, A. St.-Amant and D.R. Salahub, *Theoret. Chim. Acta* 84 (1992) 217.
- [58] R.G. Parr, *Proc. Natl. Acad. Sci. USA* 72 (1975) 763.
- [59] R.G. Parr, *J. Phys. Chem.* 92 (1988) 3060.
- [60] R.G. Parr and W. Yang, *Density Functional Theory of Atoms and Molecules* (Clarendon Press, Oxford, 1989).
- [61] J.P. Perdew, *Phys. Rev. B* 33 (1986) 8822.
- [62] F.L. Pilar, *Elementary Quantum Chemistry* (McGraw-Hill, New York, 1968).
- [63] P. Politzer, *J. Chem. Phys.* 86 (1987) 1072.
- [64] J. Riess and W. Münch, *Theoret. Chim. Acta* 58 (1981) 295.
- [65] C.C. Roothaan, *Rev. Mod. Phys.* 23 (1951) 69.
- [66] C.C. Roothaan, *Rev. Mod. Phys.* 32 (1960) 179.
- [67] D.R. Salahub, *Adv. Chem. Phys.* 69 (1987) 447.
- [68] J.M. Seminario and P. Politzer, *Int. J. Quantum Chem. Symp.* 26 (1992) 497.
- [69] A. Szabo and N.S. Ostlund, *Modern Quantum Chemistry: Introduction to Advanced Electronic Structure Theory* (MacMillan, New York, 1982).
- [70] A. Tachibana, *Int. J. Quantum Chem.* 34 (1988) 309.
- [71] Y. Tal, R.F.W. Bader, T.T. Nguyen-Dang, M. Ojha and S.G. Anderson, *J. Chem. Phys.* 74 (1981) 5162.
- [72] P.D. Walker and P.G. Mezey, *J. Am. Chem. Soc.* 115 (1993) 12 423.
- [73] P.D. Walker and P.G. Mezey, *Can. J. Chem.* 72 (1994) 2531.
- [74] P.D. Walker and P.G. Mezey, *J. Am. Chem. Soc.* 116 (1994) 12 022.
- [75] P.D. Walker and P.G. Mezey, *J. Comput. Chem.* 16 (1995) 1238.
- [76] P.D. Walker and P.G. Mezey, *J. Math. Chem.* 17 (1995) 203.
- [77] T. Ziegler, *Chem. Rev.* 91 (1991) 651.
- [78] Z. Zimpel and P.G. Mezey, *Int. J. Quantum Chem.* 59 (1996) 379.
- [79] Z. Zimpel and P.G. Mezey, *Int. J. Quantum Chem.* 64 (1997) 669.