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Fuzzy Electron Density Fragments in Macromolecular Quantum Chemistry, Combinatorial Quantum Chemistry, Functional Group Analysis, and Shape−Activity Relations

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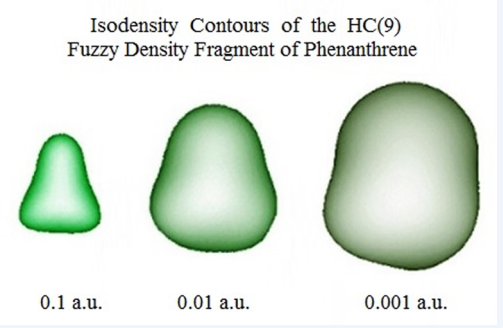
CONSPECTUS: Just as complete molecules have no boundaries and have "fuzzy" electron density clouds approaching zero density exponentially at large distances from the nearest nucleus, a physically justified choice for electron density fragments exhibits similar behavior. Whereas fuzzy electron densities, just as any fuzzy object, such as a thicker cloud on a foggy day, do not lend themselves to easy visualization, one may partially overcome this by using isocontours. Whereas a faithful representation of the complete fuzzy density would need infinitely many such isocontours, nevertheless, by choosing a selected few, one can still obtain a limited pictorial representation. Clearly, such images are of limited value, and one better relies on more complete mathematical representations, using, for example, density matrices of fuzzy fragment densities. A fuzzy density fragmentation can be obtained in an exactly additive way, using the output from any of the common quantum chemical computational techniques, such as Hartree−Fock, MP2, and various density functional approaches.



Such "fuzzy" electron density fragments properly represented have proven to be useful in a rather wide range of applications, for example, (a) using them as additive building blocks leading to efficient linear scaling macromolecular quantum chemistry computational techniques, (b) the study of quantum chemical functional groups, (c) using approximate fuzzy fragment information as allowed by the holographic electron density theorem, (d) the study of correlations between local shape and activity, including through-bond and through-space components of interactions between parts of molecules and relations between local molecular shape and substituent effects, (e) using them as tools of density matrix extrapolation in conformational changes, (f) physically valid averaging and statistical distribution of several local electron densities of common stoichiometry, useful in electron density databank mining, for example, in medicinal drug design, and (g) tools for combinatorial quantum chemistry approaches using fuzzy fragment databanks and rapid construction of a large number of approximate electron densities for large sets of related molecules, relevant in theoretical molecular and nanostructure design.

INTRODUCTION

A classically motivated "cutting" of an electron density cloud into pieces by sharp boundaries generates fragments, which are fundamentally different from the complete molecules. For example, at the cut, there is a surface with discontinuous electron density, and the natural, exponential decay of the density in real molecules as the distance increases from the nearest nucleus is drastically violated. Besides, such sharp boundaries are inherently non-quantum-mechanical: the uncertainty relation does not favor sharp features, let alone such a discontinuity. If one attempts to combine such fragments from different molecules to form a model for a larger system, a perfect match is strictly impossible, and between such fragments either zero density regions (100% local error) or an approximate doubling of density occurs.

It is more advantageous to obtain a fragmentation that results in fragments following an approximately exponential decay with distance, similarly to complete molecules. This implies a fuzzy fragmentation approach. If such fuzzy fragments are used to reunite the complete molecule, they will interpenetrate one another, just like smaller clouds interpenetrate each other if some wind unites them. A large electron density cloud can be taken apart by pulling out several smaller clouds from it, where none of these smaller fuzzy clouds has a boundary, and when they are united again, each, having approximately exponential decay, will have some, possibly small but nonzero, contribution to any of the locations within the large cloud. Although this interpenetration might appear as a complicating aspect, in fact, this approach also allows exact additivity of the fuzzy fragment clouds; that is, when they are united, the original cloud of the complete fuzzy electron density of the original molecule is exactly reproduced. If fuzzy fragments from different molecules are combined, the fuzziness ensures that the errors can never be

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even close to those of fragments with boundaries; in fact, the errors can be reduced below any positive limit.

By a suitable choice of the fragmentation method, each fuzzy fragment density can be treated the same way as the complete molecular electron densities.

After a brief review of the additive fuzzy density fragmentation (AFDF) methods, several of the wide-ranging applications of such fuzzy electron density fragments will be outlined.

ADDITIVE FUZZY DENSITY FRAGMENTATION (AFDF) METHODS

A forerunner of all quantum chemistry fragmentation approaches is the linear combination of atomic orbitals (LCAO) approach of Mulliken,[1−4] where the molecular wave function is built from linear combinations of atomic orbitals. Both the AO and the MO functions are "fuzzy", they do not have boundaries. A point r in space does not belong exclusively to any of the atomic orbitals. Point r belongs to various degrees to each of the AOs; hence, each AO is a fuzzy set as defined by Zadeh.[5,6] Mulliken's approach is also an early application of "local Hamiltonians" (atomic Hamiltonians), followed by a combination of local solutions (AOs), and "readjustment" by determination of the linear coefficients in the Hartree−Fock method.

Using density matrices,[7−14] one can implement a similar "fuzzy set" approach. An early summary is given in the context of quantum chemical functional groups.[15] The additive fuzzy density fragmentation (AFDF) method has roots in Mulliken's population analysis. The Mulliken−Mezey fragmentation[15] is the simplest within Hartree−Fock but is applicable to other quantum chemistry methodologies. For a molecule M of nuclear configuration K and AO basis functions $\varphi_i(\mathbf{r},\mathrm{K})$ (i = 1, 2, ..., n), and $n \times n$ dimensional density matrix $\mathbf{P}(\boldsymbol{\varphi}(\mathrm{K}))$, the electronic density $\rho(\mathbf{r},\mathrm{K})$ is

$$\rho(\mathbf{r},\mathrm{K}) = \sum_{i=1}^{n}\sum_{j=1}^{n} P_{ij}(\varphi(\mathrm{K}))\varphi_i(\mathbf{r},\mathrm{K})\varphi_j(\mathbf{r},\mathrm{K}) \tag{1}$$

The "anchor" points of the fragments are the nuclei. The set of nuclei of the molecule M are classified into m mutually exclusive families

$$f_1, f_2, ..., f_k, ..., f_m \tag{2}$$

A membership function $m_k(i)$ is defined:

$$m_k(i) = \begin{cases} 1 & \text{if } \varphi_i(\mathbf{r},\mathrm{K}) \text{ is centered on one of the nuclei of set } f_k \\ 0 & \text{otherwise} \end{cases} \tag{3}$$

The Mulliken−Mezey fuzzy fragmentation defines the fragment density matrix as

$$P_{ij}^{k}(\boldsymbol{\varphi}(\mathrm{K})) = [m_k(i)w_{ij} + m_k(j)w_{ji}]P_{ij}(\boldsymbol{\varphi}(\mathrm{K})) \tag{4}$$

where the w_{ij} and w_{ji} weighting factors fulfill

$$w_{ij} + w_{ji} = 1, \quad w_{ij}, w_{ji} > 0 \tag{5}$$

leading to exact fragment additivity. The choice of $w_{ij} = w_{ji} = 0.5$ has been used in most applications, as the population analysis scheme of Mulliken without integration.

These fragment density matrices $\mathbf{P}^k(\boldsymbol{\varphi}(\mathrm{K}))$ are additive, generating exactly the original density matrix:

$$\mathbf{P}(\boldsymbol{\varphi}(\mathrm{K})) = \sum_{k=1}^{m} \mathbf{P}^k(\boldsymbol{\varphi}(\mathrm{K})) \tag{6}$$

With the fragment density matrix elements $P_{ij}^k(\boldsymbol{\varphi}(\mathrm{K}))$, the kth additive fuzzy density fragment is

$$\rho^k(\mathbf{r},\mathrm{K}) = \sum_{i=1}^{n}\sum_{j=1}^{n} P_{ij}^k(\boldsymbol{\varphi}(\mathrm{K}))\varphi_i(\mathbf{r},\mathrm{K})\varphi_j(\mathbf{r},\mathrm{K}),$$

$$k = 1, 2, ...m \tag{7}$$

The fuzzy density fragments $\rho^k(\mathbf{r},\mathrm{K})$ are also exactly additive:

$$\rho(\mathbf{r},\mathrm{K}) = \sum_{k=1}^{m} \rho^k(\mathbf{r},\mathrm{K}) \tag{8}$$

The fuzzy density fragments are analogous to complete molecules; hence all tools of molecular electron density analysis are applicable to them.

FUZZY ELECTRON DENSITY FRAGMENTS IN EFFICIENT LINEAR SCALING MACROMOLECULAR QUANTUM CHEMISTRY COMPUTATIONAL TECHNIQUES

An important special application of these fuzzy fragments is in linear scaling macromolecular quantum chemistry methods.[16−35] For a macromolecule M, the nuclear families, eq 2, are chosen, and for each nuclear family f_k a smaller, artificial "parent molecule" M_k is constructed. In each M_k, the family f_k has the same local arrangement and surroundings within some d distance as in the macromolecule M; often, several additional nuclear families $f_{k'}$, surrounding f_k are included. By calculation of the density and performance of a fuzzy density fragmentation for each M_k, the central fuzzy density fragment $\rho^k(\mathbf{r},\mathrm{K})$ will include "half" of the interactions with all other fuzzy density fragments M_k within the distance d. If this is carried out for each nuclear family f_k of M, the fuzzy fragments

$$\rho^1(\mathbf{r},\mathrm{K}), \rho^2(\mathbf{r},\mathrm{K}), ..., \rho^k(\mathbf{r},\mathrm{K}), ..., \rho^m(\mathbf{r},\mathrm{K}) \tag{9}$$

are obtained. These turn out to be excellent approximations to the "true" fuzzy fragments one could obtain from the macromolecule M directly, since all interactions are reproduced for each fragment within a distance d; hence the accuracy is dependent only on d, the size of the parent molecules. Due to the rapid decay of electron density with distance, a 6 Å choice for d already provides excellent part-per-million accuracy, when fuzzy fragment HF is compared with traditional HF energy for the protein crambin,[25] and the accuracy can be further improved using larger d, and the error can be reduced well below 1 kcal/mol using larger d size parameter.[25]

By simply adding these fuzzy fragment densities, to locations determined by their nuclear families, we obtain the total electron density $\rho(\mathbf{r},\mathrm{K})$ of the macromolecule M. Also, by combining the fragment density matrices from each parent molecule, an excellent approximation to the macromolecular density matrix can be obtained, which allows the calculation of a whole range of macromolecular properties.

For a given d, the process scales linearly with the macromolecular size, proportionally with the number of nuclear families (the number of parent molecules).

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The two main macromolecular AFDF methods are the numerical electron density assembler MEDLA[16−20] (molecular electron density "loge" assembler, or molecular electron density "lego" assembler) based on numerically stored electron densities and the more efficient density matrix approach ADMA[21−35] (adjustable density matrix assembler), both with a large number of *ab initio* quality applications to proteins, including bovine insulin,[18] HIV-1 protease,[19] hemoglobin,[27] and other large systems,[17] well over 1000 atoms.

The ADMA density matrix approach[21] is also suitable for macromolecular similarity studies[20] and for the computation of macromolecular forces.[22] Some methodological developments[26−29] have contributed to the recognition that in the crystallographic structure refinement process the replacement of spherical Gaussian density representations with actual fuzzy density fragments evidently provides better accuracy.[30] Another application, the use of precomputed fuzzy fragments in a "combinatorial quantum chemistry" approach for the quick generation of a large number of approximate macromolecular densities has also been advocated.[31−34]

Whereas there are limitations on fragment transferability, adjustability, and additivity,[35] as set by the Hohenberg−Kohn theorem[36,37] and by its extension, the holographic electron density theorem,[38−40] still, it is possible to obtain better than 1 kcal/mol accuracy by the linear scaling fuzzy fragment approach for proteins relative to traditional and expensive nonfragment quantum chemistry methods.[25]

QUANTUM CHEMICAL FUNCTIONAL GROUPS DEFINED BY FUZZY ELECTRON DENSITY FRAGMENTS

The approach uses some analogies with a pair of interacting molecules, relying on molecular isodensity contour surfaces, MIDCOs, defined for threshold value a as

$$G(a, \mathrm{K}) = \{r: \rho(\mathbf{r}, \mathrm{K}) = a\} \quad (11)$$

If the interaction of the two molecules is weak, there must exist some MIDCO for each that surrounds all the nuclei of one molecule but none of the nuclei of the other molecule, indicating that some "autonomy" of each molecule is preserved. If the interaction becomes stronger, a major rearrangement of the electron density may occur, and after that the condition of separating isodensity contours may no longer hold.

The same principle can be applied for various parts of a single molecule. If some subset of nuclei is separated by some isodensity contour from the other nuclei, one may regard this subset of nuclei and an associated fuzzy fragment of the electron density cloud to possess some "limited autonomy" within the molecule, a condition that typically holds for most functional groups. The presence of a separating isodensity contour is taken as a condition for the presence of a "quantum chemical functional group".[15,32]

The fuzzy fragment approach allows the direct study of functional groups, and their shape comparisons often reveal important trends.[15,32]

APPLICATIONS OF THE HOLOGRAPHIC ELECTRON DENSITY THEOREM TO FUZZY FRAGMENTS AND PROPERTY PREDICTION

The fundamental theorem of density functional theory, the Hohenberg−Kohn theorem,[36] states that the ground state energy E, and the ground state wave function Ψ (hence, essentially all ground state properties of the molecule) are uniquely determined by the nondegenerate ground state electron density $\rho(\mathbf{r},\mathrm{K})$. Riess and Munch derived an important local version of this theorem valid for artificial, bounded, and finite Coulomb systems, although, as they have correctly emphasized, it was not applicable for real molecules, which cannot have boundaries.[37] Relying on both of these results, a statement stronger than the Hohenberg−Kohn theorem was proven using a four-dimensional transformation and compactification technique, leading to the holographic electron density theorem,[38] "Any nonzero volume piece $\rho_d(\mathbf{r},\mathrm{K})$ of the nondegenerate ground state electron density fully determines the ground state electron density $\rho(\mathbf{r},\mathrm{K})$ of the entire, boundaryless molecular system."

The holographic electron density theorem has important role in local shape analysis,[38] in drug design,[23,39] in toxicological risk assessment,[39] and in the prediction of "latent properties", for example, excited state properties not exhibited in the ground electronic ground state,[39,40] and in a wide range of additional applications by various authors.[41−74,75−86]

An extension of the fragment principle is the so-called universal molecule[84,86] model that is an "anti-quantized" abstract structure where all variables are considered continuous. Some of these variables take physically valid values only by quantization, for example, becoming integers, such as a formally continuous nuclear charge variable. In the universal molecule model a (physically impossible) continuous transformation between the molecules of CO and N_2 yields, among other results, upper bounds for some energy expectation values.[86]

THE STUDY OF CORRELATIONS BETWEEN LOCAL SHAPE AND ACTIVITY

Using fuzzy fragments, we can study the correlations between local shape and activity, including biochemical activities, important in pharmaceutical applications.[23,39,87−91] The molecular electron density shape analysis methods[92−97] originally developed for complete molecules are fully applicable to fuzzy fragments, useful in pharmaceutical drug design.[95]

Interactions within Molecules: Through-Bond and Through-Space Effects

The local shape analysis of molecular fragments provides a unique way to study of the relative roles of through-bond and through-space components of interactions within molecules, where the through-bond components appear to dominate in most, but not all, situations.[87]

A special case involves a systematic deviation from perfect periodicity in some polymers, which can be analyzed in terms of local features.[90]

Relations between Local Shape and Substituent Effects

Numerical shape similarity measures provide quantitative relations between local molecular shape variations and the type and strength of various substituent effects, confirming some of the expected experimental trends but also pointing out some novel aspects.[88]

INTERPOLATION, EXTRAPOLATION, PHYSICALLY VALID AVERAGING AND STATISTICAL DISTRIBUTION OF LOCAL ELECTRON DENSITIES

Comparisons of electron densities for changed nuclear arrangements, for example, along reaction paths or conformational domains on potential surfaces, often reveal important

trends.[98−102] Yet, a direct averaging of electron densities of molecules with the same nuclei but with differing nuclear locations leads to false maxima; hence a transformation to a common nuclear framework is needed.

By suitable interpolation or extrapolation methods, the electron densities can be transformed to a common nuclear framework. Among density transformation methods,[103−112] the approach based on Löwdin's symmetric orthogonalization,[103,104] also used by Massa, Huang, and Karle[105,106] for crystallography applications, is the most versatile. The Löwdin−inverse Löwdin (LIL) transformation, involving density matrix pre- and postmultiplication by the 1/2 power of the overlap matrix in one conformation and repeating this procedure with the −1/2 power of the overlap matrix at a different conformation, achieves a good, approximate density matrix extrapolation. The level of fulfillment of the idempotency condition for approximate density matrices, for example, an ADMA macromolecular density matrix, is not affected by LIL; hence, an efficient conformational search can be implemented even for macromolecules.[112]

Each electron density can be transformed to a common nuclear geometry, and then their average can be obtained by simply superposing them; the nuclear locations now exactly agree. Similarly, higher statistical moments, such as standard deviation, skewness, or kurtosis can be obtained, and by "data-mining" in large electron density databanks, important trends can be deduced, useful in pharmaceutical molecule design.

■ COMBINATORIAL QUANTUM CHEMISTRY APPROACHES IN THEORETICAL MOLECULE AND NANOSTRUCTURE DESIGN

The fuzzy fragment methods have both computational and interpretative advantages compared with alternative macromolecular linear scaling methods.[113,114] Local properties are often studied by orbital localization approaches;[115,116] however, fuzzy fragments can also be used to combine local properties. By generating and storing many fragment density matrices for various stoichiometries and nuclear arrangements, a combinatorial quantum chemistry approach can rapidly produce models for many molecules, analogously to synthetic combinatorial approaches, as invented by Furka[117−120] and further developed by Darvas and co-workers.[121,122]

■ CONCLUDING REMARKS

The fuzzy electron density fragment approach has provided input to both fundamental, theoretical analysis of molecules, such as local shape interpretation and the holographic properties of electron densities, and practical, computational methods and applications in areas such as macromolecular computations, pharmaceutical drug design, the interpretation of substituent effects, and the study of through-bond, through-space interactions.

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Notes

The authors declare no competing financial interest.

Biography

Paul G. Mezey is the Canada Research Chair in Scientific Modelling and Simulation at the Memorial University of Newfoundland, St. John's, Canada, and the Editor in Chief of the *Journal of Mathematical Chemistry* (Springer). Until 2003, before accepting his present position, he was Professor of Chemistry and Director of Mathematical Chemistry Research Unit, affiliated with the Department of Chemistry and Department of Mathematics, University of Saskatchewan, Canada. He is a member of the European Academy of Sciences, Arts, and Humanities, Paris, France, as well as the Hungarian Academy of Sciences. He has served as Vice President of WATOC, the World Association of Theoretical Organic Chemists, and as the Secretary General of the UNESCO/ICSU organization CODATA (Committee for Data in Science and Technology), Paris, France. He is an author or coauthor of over 400 scientific publications and several books.

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