

Mathematical problems of nuclear configuration averaging

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The concept of the average of a family of related nuclear configurations, for example, the average of those configurations which are slightly distorted versions of a given stable conformer of a molecule, has a role as both interpretative tool and also as a reference configuration in practical, computational use. However, depending on the actual coordinates used along which the average is defined, the average of nuclear configurations is not necessarily a physically viable arrangement, a fact that has to be taken into account when generating the corresponding electron density averages. Some of the associated mathematical and computational problems are described and the validity of a macroscopically motivated approach to conformation averaging is discussed.

KEY WORDS: conformational deformations, small amplitude vibrations, shape similarity, shape complementarity, active conformation, conformation averaging, union surfaces, electron density averaging

1. Introduction

The concept of nuclear configuration is quantum-mechanical, implying that models involving precise nuclear positions are necessarily approximate and are only convenient, classically motivated tools for the description of nuclear arrangements. Nevertheless, nuclei have much greater masses than electrons, hence exhibit stronger particle-like properties than electrons in a molecule, consequently, it is often useful to model molecules with a formal geometrical nuclear arrangement in mind [1]. However, these nuclear arrangements are subject to a quantum mechanical uncertainty, consequently, topological techniques are more suitable for their description than classical, geometrical tools. A differential topological and algebraic topological approach has served as the basis of a detailed description of nuclear configuration spaces of polyatomic molecules and the associated potential energy hypersurfaces [2–85]. One important constraint that is not universally appreciated is the fact that even within a semiclassical, geometrical model, the nuclear configuration space restricted to the $3N - 6$ internal coordinates of a poly-

atomic molecule (in fact, of the entire stoichiometric family of molecules to which the actual polyatomic molecule belongs) is not a vector space, and cannot even be converted into one without loss of information [50]. Hence, geometrical tools are somewhat restricted even without invoking quantum mechanical uncertainty and the realization for the need of topology.

Of course, it is also well recognized that even within a semiclassical model, the nuclei of a polyatomic molecule are in continuous motion, and in fact, the zero point vibrational motion implies that we are dealing with a distribution of nuclear arrangements and not with any fixed nuclear configuration. In this context, some form of average nuclear configuration appears as a useful concept.

In this contribution some of the quantum mechanical and mathematical problems associated with nuclear configuration averaging are discussed, placing earlier studies [82,85] on the subject in a broader and more general perspective. In particular, with the introduction of combinatorial quantum chemistry approaches [86], involving electron density fragment data libraries or fragment density matrix libraries, containing many variants corresponding to slightly distorted nuclear configurations and slightly distorted fragment surroundings, the need for nuclear configuration averaging has acquired additional significance.

2. Averaging according to Cartesian or internal coordinates

Consider first two slightly distorted conformers of a nonlinear molecule *A*, where in the two conformers the internal coordinates are nearly the same, allowing a formal superposition of the two structures where the largest deviation in any of the corresponding Cartesian coordinates is less than 0.1 Å. By carrying out a direct averaging of all pairs of Cartesian nuclear coordinates, the resulting conformation will be rather reasonable, showing a deviation of any nuclear coordinate from that in either of the two molecules less than 0.05 Å.

Rotate now either of the two conformations by 180° according to any axis. An averaging of the corresponding pairs of Cartesian coordinates will lead to a chemically impossible arrangement for all but some nearly linear molecules, where all nuclei are crowded into a tube along the rotation axis, having a square base with edge length of 0.1 Å.

Clearly, the mutual arrangements of the two conformers is of major importance for averaging, and if the deviations in the molecular shapes are small, then it is reasonable to carry out averaging of the optimally superimposed arrangements. Such optimum superpositions can be obtained by least square fitting, or by other, more efficient methods in special cases.

Let us consider now a pair of L and D amino acids. In any mutual arrangement of the two molecules, even in the case of an optimum superposition, a direct averaging of the Cartesian coordinates of the nuclei of these two nuclear configurations would lead to chemically impossible results.

Instead of Cartesian coordinates, an averaging procedure can be associated with internal coordinates. If a chemically reasonable conformational change interconnects the two conformers for which an average internal configuration is required, then it is reasonable to consider those internal coordinates along which the dominant components of the configuration change occurs. For example, if the two configurations are two rotamers derived from one another by a 60° rotation of a methyl group, then a direct Cartesian coordinate averaging would produce the correct dihedral angles but much too short C–H distances. However, an averaging along the rotational internal coordinate would lead to a reasonable structure that belongs to a 30° internal rotation of the methyl group (relative to either of the two conformers), with chemically reasonable C–H distances.

In such instances, averaging along internal coordinates is advantageous.

3. Energy considerations

The involvement of chemically unreasonable nuclear arrangements appears as a fundamental problem associated with some approaches to nuclear configuration averaging. One possibility to overcome these difficulties is based on energy considerations. In general, low energy conformations are likely to occur, whereas many high energy conformations are unlikely; high energy appears as a practical criterion for excluding highly unreasonable nuclear arrangements. Energy in most instances determines the degree of accessibility of a given nuclear arrangement, hence it is reasonable to apply energy conditions to facilitate the choice of rearrangement paths in the nuclear configuration space, along which the averaging is to be performed.

3.1. Single catchment region

In the simplest case, we shall make the assumption that the two configurations A and B to be averaged are similar enough that they belong to the same catchment region of a minimum of the potential energy hypersurface [50]. In such case it is reasonable to consider the internal coordinates defined by the quadratic form of the Hessian matrix at the energy minimum, that is, the eigenvectors of the Hessian which are the actual normal coordinates for the vibrations of the minimum energy conformation. Within this local coordinate system of the manifold describing the complete nuclear configuration space, the distance between the two configurations A and B is well defined, furthermore, there is a unique shortest line interconnecting A and B . An interpolation between A and B along this line can then be used for averaging. A simple internal coordinate averaging with reference to the given minimum energy conformation K of the catchment region can be obtained by

$$C_{\text{av},K} = 0.5A_K + 0.5B_K, \quad (1)$$

where vectors $C_{\text{av},K}$, A_K , and B_K , are representing the two original and the new average nuclear configurations expressed in terms of the normal coordinates of energy minimum K .

If a weighted average is required, for example, by emphasizing energy, a weighting different from the value 0.5 can be used. In the case of energy weighting, emphasizing the greater importance of lower energies,

$$C_{av,K,E} = \frac{E_B}{E_A + E_B} A_K + \frac{E_A}{E_A + E_B} B_K \quad (2)$$

can be used, where E_A and E_B are the respective energies for nuclear configurations A and B , and the $C_{av,K,E}$ notation refers to averaging using energy weighting with reference to the internal coordinates corresponding to the normal coordinates of the local energy minimum K .

Usually, in both the unweighted and energy weighted cases, such an averaging procedure results in an averaged nuclear arrangement that belongs to the same catchment region of energy minimum K . However, if the shortest path between the two configurations, A and B , taken within the nuclear configuration space M using the local metric defined by the local coordinate system of the given catchment region leads to configurations not falling within the catchment region, then it is possible that average configuration so obtained also falls within a different catchment region, with a different local coordinate system. Whereas the average is a valid concept even in such unusual cases, nevertheless, such a case may be taken as an indication that the actual average configuration has lesser physical significance with respect to the configurations A and B .

3.2. Two neighbor catchment regions

In a somewhat more complicated case that may often arise, the two nuclear configurations A and B to be averaged belong to two neighbor catchment regions of the potential energy hypersurface [50].

In such a case, the manifold model of the potential energy hypersurface specifies two, usually rather different internal coordinate systems, one for each of the two critical points (usually energy minima) of the two catchment regions. The differentiable manifold model assumes some overlap between the local coordinate systems, but this overlap is not required to extent over the entire neighbor catchment region. Consequently, if coordinates are required for averaging, then either one of the two local coordinate system can be taken as dominant, or one may rely on the underlying metric d of the reduced nuclear configuration space M , a metric space, but not a vector space, and a space usually without a global coordinate system.

If extension of one local coordinate system, say that of nuclear configuration A , to be applied to the nuclear configuration B in the other catchment region is practical (for example, if the configuration B does not lie too far from the boundary of the catchment region of configuration A), then the methods applied for the single catchment region problem, discussed in the previous section, are applicable.

If, however, this is not feasible, then one may rely on the global metric $d(A, B)$ of the reduced nuclear configuration space M . Since the two catchment regions are neighbors, there must exist a transition structure nuclear configuration T that lies on the

common boundary of the two catchment regions. Note that in special cases there might exist more than one such transition structure nuclear arrangement; in such a case that T_i transition structure is selected for which the sum of its distances from the structure A and structure B is minimum, where these distances are measured by the global metric of the reduced nuclear configuration space M :

$$d(T_i, A) + d(T_i, B) = \text{minimum.} \quad (3)$$

Whereas for the selection of appropriate transition structure T_i the global metric d of the nuclear configuration space M is the natural tool, nevertheless, this metric is cumbersome for the actual averaging process, since it is independent from any local internal coordinate choice. Consequently, the actual interpolation will rely on a path from conformation A , through the transition structure T_i , to the conformation B . This path $p(A, B)$ has two segments, a segment $p(A, T_i)$ from A to T_i that is linear in the local metric of the catchment region of conformer A , and a second segment $p(T_i, B)$ from T_i to the conformation B , that is linear in the local metric of the catchment region of conformer B . Using the terminology of homotopy theory of algebraic topology, the complete path $p(A, B)$ is the product of the two segment paths, $p(A, T_i)$ and $p(T_i, B)$,

$$p(A, B) = p(A, T_i)p(T_i, B), \quad (4)$$

where the parametrizations of $p(A, T_i)$ and $p(T_i, B)$ are given by the arc length as measured by the local metrics in each of the two catchment regions, respectively, and the parametrization for $p(A, B)$ preserves proportionality of the locally measured arc lengths.

With these constraints, the parameter u of path $p(A, B) = p(A, B, u)$ can be chosen so that

$$0 \leq u \leq 1, \quad (5)$$

where $u = 0$ corresponds to the beginning, and $u = 1$ corresponds to the endpoint of the path:

$$p(A, B, 0) = A \quad (6)$$

and

$$p(A, B, 1) = B. \quad (7)$$

Note that nonlinear relations between overlapping local coordinate systems within a differentiable manifold may occur, hence the two segments may appear nonlinear when described in terms of the coordinate system of the other catchment region.

The fully parametrized path from A to B fulfills the natural expectation for energy that the involvement of the transition structure is likely to ensure that the path does not visit very high energy, hence unreasonably distorted conformations. In the possession of this path, in complete analogy with the single catchment region case, the direct, un-

weighted average of the two nuclear configurations A and B is taken as the point along the path with parameter value

$$u = 0.5, \quad (8)$$

that is,

$$C_{av,A,B} = p(A, B, 0.5). \quad (9)$$

If, on the other hand, an energy-dependent weighting is required, then

$$C_{av,A,B,E} = p\left(A, B, \frac{E_A}{E_A + E_B}\right), \quad (10)$$

where the

$$u = \frac{E_A}{E_A + E_B} \quad (11)$$

parameter choice provides the required energy weighting, placing greater emphasis on the structure that is of lower energy.

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References

- [1] P.G. Mezey, Optimization and analysis of energy hypersurfaces, in: *Computational Theoretical Organic Chemistry* (Reidel, New York, 1981) pp. 101–128.
- [2] P.G. Mezey, Catchment region partitioning of energy hypersurfaces, I, *Theor. Chim. Acta* 58 (1981) 309–330.
- [3] P.G. Mezey, The isoelectronic and isoprotonic energy hypersurface and the topology of the nuclear charge space, *Internat. J. Quantum Chem. Symp.* 15 (1981) 279–285.
- [4] P.G. Mezey, Manifold theory of multidimensional potential surfaces, *Internat. J. Quantum Chem., Quant. Biol. Symp.* 8 (1981) 185–196.
- [5] P.G. Mezey, Critical level topology of energy hypersurfaces, *Theor. Chim. Acta* 60 (1981) 97–110.
- [6] P.G. Mezey, Lower and upper bounds for the number of critical points on energy hypersurfaces, *Chem. Phys. Letters* 82 (1981) 100–104; 86 (1982) 562.
- [7] P.G. Mezey, The symmetry of electronic energy level sets and total energy relations in the abstract nuclear charge space, *Mol. Phys.* 47 (1982) 121–126.
- [8] P.G. Mezey, Topology of energy hypersurfaces, *Theor. Chim. Acta* 62 (1982) 133–161.
- [9] P.G. Mezey, Level set topologies and convexity relations for Hamiltonians with linear parameters, *Chem. Phys. Letters* 87 (1982) 277–279.
- [10] P.G. Mezey, Level set topology of the nuclear charge space and the electronic energy functional, *Internat. J. Quantum Chem.* 22 (1982) 101–114.
- [11] P.G. Mezey, Quantum chemical reaction networks, reaction graphs and structure of potential energy hypersurfaces, *Theor. Chim. Acta* 60 (1982) 409–428.

- [12] P.G. Mezey, Reaction topology: manifold theory of potential surfaces and quantum chemical synthesis design, in: *Chemical Applications of Topology and Graph Theory*, ed. R.B. King (Elsevier, Amsterdam, 1983) pp. 75–98.
- [13] P.G. Mezey, An approach to conformation analysis on multidimensional potential surfaces, *Internat. J. Quantum Chem., Quant. Biol. Symp.* 10 (1983) 153–160.
- [14] P.G. Mezey, Inequalities and homotopy relations in reaction topology, *Internat. J. Quantum Chem., Quant. Chem. Symp.* 17 (1983) 453–460.
- [15] P.G. Mezey, The differentiable manifold model of quantum chemical reaction networks, *Internat. J. Quantum Chem., Quant. Chem. Symp.* 17 (1983) 137–152.
- [16] P.G. Mezey, Classification schemes of nuclear geometries and the concept of chemical structure. Metric spaces of chemical structure sets over potential energy hypersurfaces, *J. Chem. Phys.* 78 (1983) 6182–6186.
- [17] P.G. Mezey, A molecular geometry invariant property of energy level set boundaries in Z-space, *Internat. J. Quantum Chem.* 24 (1983) 523–526.
- [18] P.G. Mezey, The topology of energy hypersurfaces. II. Reaction topology in Euclidean spaces, *Theor. Chim. Acta* 63 (1983) 9–33.
- [19] P.G. Mezey, Molecular structure and reaction mechanism: a topological approach to quantum chemistry, *J. Mol. Struct. Theochem* 103 (1983) 81–99 (volume dedicated to Nobel Laureate Prof. K. Fukui).
- [20] P.G. Mezey, Reaction topology of excited state potential energy hypersurfaces, *Canad. J. Chem.* 61 (1983) 956–961 (volume dedicated to Prof. H. Gunning).
- [21] P.G. Mezey, The topological model of non-rigid molecules and reaction mechanisms, in: *Symmetries and Properties of Non-Rigid Molecules: A Comprehensive Survey*, eds. J. Maruani and J. Serre (Elsevier, Amsterdam, 1983) pp. 335–353.
- [22] P.G. Mezey, Topology of doublet potential surfaces, *Bull. Soc. Chim. Belg.* 92 (1983) 555.
- [23] P.G. Mezey, A general formulation of the “quantum chemical Le Chatelier principle”, *Internat. J. Quant. Chem.* 25 (1984) 853–861.
- [24] P.G. Mezey, The hyperspherical coordinate representation of potential surfaces of large molecules, *Internat. J. Quantum Chem., Quant. Biol. Symp.* 11 (1984) 267–272.
- [25] P.G. Mezey, The algebraic structure of quantum-chemical reaction mechanisms, *Internat. J. Quantum Chem. Symp.* 18 (1984) 77–85.
- [26] P.G. Mezey, Network relations on potential surfaces as aids to computer-based quantum chemical synthesis planning, *Internat. J. Quantum Chem. Symp.* 18 (1984) 675–681.
- [27] P.G. Mezey, The metric properties of the reduced nuclear configuration space, *Internat. J. Quantum Chem.* 26 (1984) 983–985.
- [28] P.G. Mezey, Constraints on electronic energy hypersurfaces of higher multiplicities, *J. Chem. Phys.* 80 (1984) 5055–5057.
- [29] P.G. Mezey, Simple lower and upper bounds for isomerization energies, *Canad. J. Chem.* 62 (1984) 1356–1357.
- [30] P.G. Mezey, The reaction polyhedron and group theory of reaction mechanisms, *Internat. J. Quantum Chem., Quant. Chem. Symp.* 19 (1985) 93–105.
- [31] P.G. Mezey, A simple relation between nuclear charges and potential surfaces, *J. Amer. Chem. Soc.* 107 (1985) 3100–3105.
- [32] P.G. Mezey, New global constraints on electronic energy hypersurfaces, *Internat. J. Quantum Chem.* 29 (1986) 85–99.
- [33] P.G. Mezey, Cluster topology and bounds for the electronic energy, *Surface Science* 156 (1985) 597–604.
- [34] P.G. Mezey, A comparison of two group theoretical models of reaction mechanisms on potential surfaces, *Internat. J. Quantum Chem.* 28 (1985) 387–398.
- [35] P.G. Mezey, Group theory of constrained reaction mechanisms, *Canad. J. Chem.* 63 (1985) 1972–1975 (volume dedicated to Prof. C. Sandorfy).

- [36] P.G. Mezey, Catchment regions as “molecular loges” on potential energy hypersurfaces, *J. Mol. Structure, Theochem* 123 (1985) 171–177 (volume dedicated to Prof. R. Daudel).
- [37] P.G. Mezey, Topological model of reaction mechanisms, in: *Structure and Dynamics of Molecular Systems*, Vol. I., eds. R. Daudel, J.-P. Korb, J.-P. Lemaistre and J. Maruani (Reidel, Dordrecht, 1985) pp. 57–70.
- [38] P.G. Mezey, Topological theory of molecular conformations, in: *Structure and Dynamics of Molecular Systems*, Vol. I., eds. R. Daudel, J.-P. Korb, J.-P. Lemaistre and J. Maruani (Reidel, Dordrecht, 1985) pp. 41–56.
- [39] P.G. Mezey, The topology of energy hypersurfaces. III. The fundamental group of reaction mechanisms on potential energy hypersurfaces, *Theor. Chim. Acta* 67 (1985) 43–61.
- [40] P.G. Mezey, The topology of energy hypersurfaces. IV. Generator sets for the fundamental group of reaction mechanism and the complete set of reaction paths, *Theor. Chim. Acta* 67 (1985) 91–113.
- [41] P.G. Mezey, The topology of energy hypersurfaces. V. Potential defying chemical species: a global analysis of vibrational stabilization and destabilization on potential energy hypersurfaces, *Theor. Chim. Acta* 67 (1985) 115–136.
- [42] P.G. Mezey, Reaction topology, in: *Applied Quantum Chemistry, Proceedings of the Hawaii 1985 Nobel Laureate Symposium on Applied Quantum Chemistry*, eds. V.H. Smith, Jr., H.F. Schaefer III and K. Morokuma, (Reidel, Dordrecht, 1986) pp. 53–74.
- [43] P.G. Mezey, Nuclear charges and molecular total energies: a rule on nested reaction globes, *Internat. J. Quantum Chem.* 29 (1986) 333–343.
- [44] P.G. Mezey, Differential and algebraic topology of chemical potential surfaces, in: *Mathematics and Computational Concepts in Chemistry*, ed. N. Trinajstić (Ellis Horwood, Chichester, UK, 1986) chapter 19, pp. 208–221.
- [45] P.G. Mezey, Theory of reaction mechanisms and molecular design, *J. Mol. Struct. Theochem* 138 (1986) 13–21.
- [46] P.G. Mezey, Reflection properties of reaction paths in the reduced nuclear configuration space, *Internat. J. Quantum Chem. Symp.* 21 (1987) 191–198.
- [47] G.A. Arteca and P.G. Mezey, A method for the characterization of molecular conformations, *Internat. J. Quantum Chem., Quant. Biol. Symp.* 14 (1987) 133–147.
- [48] R.K. Gosavi, O.P. Strausz, F. Bernardi, A. Kapur and P.G. Mezey, A molecular orbital study of triplet state $[\text{Be}\bullet\text{C}_2\text{H}_4]$ exciplexes and their reaction hypersurfaces, *J. Phys. Chem.* 91 (1987) 283–288.
- [49] P.G. Mezey, Global analysis and group theory of reaction mechanisms, *J. Mol. Struct. Theochem* 149 (1987) 57–66 (volume dedicated to Nobel Laureate Prof. G. Herzberg).
- [50] P.G. Mezey, *Potential Energy Hypersurfaces* (Elsevier, Amsterdam, 1987).
- [51] P.G. Mezey, Symmetry and periodicity of potential surfaces: a test for multicenter interactions, *Theor. Chim. Acta* 73 (1988) 221–228.
- [52] F. Harary and P.G. Mezey, Embedding and characterization of quantum chemical reaction graphs on two-dimensional orientable surfaces, *Discrete Appl. Math.* 19 (1988) 205–214.
- [53] G.A. Arteca and P.G. Mezey, Shape description of conformationally flexible molecules: application to two-dimensional conformational problems, *Internat. J. Quantum Chem., Quant. Biol. Symp.* 15 (1988) 33–54.
- [54] G.A. Arteca and P.G. Mezey, Validity of the Hammond postulate and constraints on general one-dimensional barriers, *J. Comput. Chem.* 9 (1988) 728–744.
- [55] P.G. Mezey, From geometrical molecules to topological molecules: a quantum mechanical view, in: *Molecules in Physics, Chemistry and Biology*, Vol. II, ed. J. Maruani (Reidel, Dordrecht, 1988) chapter 2, pp. 61–81.
- [56] P.G. Mezey, Reaction topology and quantum chemical molecular design on potential energy surfaces, in: *New Theoretical Concepts for Understanding Organic Reactions*, eds. J. Bertran and I.G. Csizmadia, Nato ASI Series (Kluwer Academic, Dordrecht, 1989) pp. 55–76.
- [57] P.G. Mezey and H. Flakus, Rotation-independent conjugation of sulfur-nitrogen bonds, *J. Mol. Struct. Theochem* 186 (1989) 117–129.

- [58] G.A. Arteca and P.G. Mezey, Molecular similarity and molecular shape changes along reaction paths: a topological analysis and consequences on the Hammond postulate, *J. Phys. Chem.* 93 (1989) 4746–4751.
- [59] P.G. Mezey, Molecular point symmetry and the phase of the electronic wavefunction; Tools for the prediction of critical points of potential energy surfaces, *Internat. J. Quantum Chem.* 38 (1990) 699–711.
- [60] P.G. Mezey, Point symmetry groups of all distorted configurations of a molecule form a lattice, *J. Math. Chem.* 4 (1990) 377–381.
- [61] G.A. Arteca and P.G. Mezey, A quantitative approach to structural similarity from molecular topology of reaction paths, *Internat. J. Quantum Chem. Symp.* 24 (1990) 1–13.
- [62] G.A. Arteca, G.A. Heal and P.G. Mezey, Comparison of potential energy maps and molecular shape invariance maps for two-dimensional conformational problems, *Theor. Chim. Acta* 76 (1990) 377–390.
- [63] G.A. Arteca and P.G. Mezey, Analysis of molecular shape changes along reaction paths, *Internat. J. Quantum Chem.* 38 (1990) 713–726.
- [64] P.G. Mezey, Non-visual molecular shape analysis: shape changes in electronic excitations and chemical reactions, in: *Computational Advances in Organic Chemistry (Molecular Structure and Reactivity)*, eds. C. Ogretir and I.G. Csizmadia, Nato ASI Series (Kluwer Academic, Dordrecht, 1991) pp. 261–288.
- [65] G.A. Arteca and P.G. Mezey, Energy and shape analysis along reaction paths of chemical reactions. The case of hydrogen–deuterium exchange, *J. Mol. Structure Theochem* 230 (1991) 323–338.
- [66] X. Luo, G.A. Arteca and P.G. Mezey, Shape analysis along reaction paths of ring opening reactions, *Internat. J. Quantum Chem. Symp.* 25 (1991) 335–345.
- [67] G.A. Arteca and P.G. Mezey, Configurational dependence of molecular shape, *J. Math. Chem* 10 (1992) 329–371.
- [68] X. Luo and P.G. Mezey, A global characterization and similarity analysis of two-dimensional potential energy surfaces, *Internat. J. Quantum Chem.* 41 (1992) 557–579.
- [69] G.A. Arteca and P.G. Mezey, Similarities between the effects of configurational changes and applied electric fields on the shape of electron densities, *J. Mol. Struct. Theochem* 256 (1992) 125–134 (special volume on “Electrostatics in Molecules”, eds. G. Naray-Szabo and W.J. Orville Thomas).
- [70] X. Luo, G.A. Arteca and P.G. Mezey, Shape similarity and shape stability along reaction paths. The case of the PPO \rightarrow OPP isomerization, *Internat. J. Quantum Chem.* 42 (1992) 459–474.
- [71] P.G. Mezey, On the allowed symmetries of all distorted forms of conformers, molecules, and transition structures, *Canad. J. Chem.* 70 (1992) 343–347 (special issue dedicated to Prof. S. Huzinaga).
- [72] P.G. Mezey, Dynamic shape analysis of biomolecules using topological shape codes, in: *The Role of Computational Models and Theories in Biotechnology*, ed. J. Bertran (Kluwer Academic, Dordrecht, 1992) pp. 83–104.
- [73] J.-E. Dubois and P.G. Mezey, Relations among functional groups within a stoichiometry: a nuclear configuration space approach, *Internat. J. Quantum Chem.* 43 (1992) 647–658.
- [74] P.G. Mezey and J. Maruani, The fundamental syntopy of quasi-symmetric systems: geometric criteria and the underlying syntopy of a nuclear configuration space, *Internat. J. Quantum Chem.* 45 (1993) 177–187.
- [75] P.G. Mezey, Dynamic shape analysis of molecules in restricted domains of a configuration space, *J. Math. Chem.* 13 (1993) 59–70.
- [76] P.G. Mezey, New rules on potential surface topology and critical point search, *J. Math. Chem.* 14 (1993) 79–90.
- [77] P.G. Mezey, Discrete representations of three-dimensional molecular bodies and their shape changes in chemical reactions, in: *Graph Theoretical Approaches to Chemical Reactivity*, eds. D. Bonchev and O. Mekenyan (Kluwer Academic, Dordrecht, The Netherlands, 1994) pp. 181–208.
- [78] P.G. Mezey, From reaction path to reaction mechanism: fundamental groups and symmetry rules, in: *Reaction Path in Chemistry*, ed. D. Heidrich (Kluwer Academic, Dordrecht, 1995) pp. 11–38.

- [79] P.D. Walker, P.G. Mezey, G.M. Maggiora, M.A. Johnson and J.D. Petke, Application of the shape group method to conformational processes: shape and conjugation changes in the conformers of 2-phenyl pyrimidine, *J. Comput. Chem.* 16 (1995) 1474–1482.
- [80] P.G. Mezey, Two symmetry constraints on the identity and deformations of chemical species, *J. Phys. Chem.* 99 (1995) 4947–4954.
- [81] P.G. Mezey, Molecular similarity measures of conformational changes and electron density deformations, *Advances in Molecular Similarity* 1 (1996) 89–120.
- [82] P.G. Mezey, Averaged electron densities for averaged conformations, *J. Comput. Chem.* 19 (1998) 1337–1344.
- [83] P.G. Mezey, The topology of catchment regions of potential energy hypersurfaces, *Theor. Chem. Acc.* 102 (1999) 279–284.
- [84] P.G. Mezey, K. Fukui and S. Arimoto, A treatment of small deformations of polyhedral shapes of functional group distributions in biomolecules, *Internat. J. Quant. Chem.* 76 (2000) 756–761.
- [85] P.G. Mezey, Distributions and averages of molecular conformations, *Comput. Chem.* 25 (2001) 69–75.
- [86] P.G. Mezey, Computational aspects of combinatorial quantum chemistry, *J. Comput. Methods Sci. Engrg. (JCMSE)*, in press.
- [87] P.G. Mezey, Molecular informatics and topology in chemistry, in: *Topology in Chemistry*, eds. R.B. King and D.H. Rouvray (Ellis Horwood, UK) in press.