Protein Tetrahedral Networks by Invariant Shape Coordinates

Lombardi Andrea(✉), Noelia Faginas-Lago, and Leonardo Pacifici

Dipartimento di Chimica, Biologia e Biotecnologie, Università di Perugia, Perugia, Italy
{andrea.lombardi,noelia.faginaslago}@unipg.it
http://www.chm.unipg.it/gruppi?q=node/48

Abstract. Representations of large molecules, typically proteins or DNA, for classification purposes, are commonly obtained by molecular networks. These are usually made up by a set of specific atoms (e.g. C_α atoms in the amino acids) of the molecule plus a neighbourhood criterium, that establishes links between the centers, so building the network. The main objectve of such approaches is the discrimination of structures, the induction of grouping of them, depending on the basis of structural molecular properties. Here we propose applications of invariant shape coordinates as parameters for the construction of enhanced molecular networks for protein classification.

Keywords: Protein structure classification · Hyperspherical coordinates · Invariant shape coordinates

1 Introduction

Proteins are complex molecules, whose structures can hardly be put into clear relationships with the corresponding biological functions, unless a number of proper classification schemes, on the basis of conveniently chosen chemical and physical properties, are made available. The availability of large sets of geometries, continuously feeded by newly experimentally determined structures, allows to work on sufficiently large amounts of data to test new approaches to classification. Depending on the choice of parameters, the schematic representation adopted for the molecules (e.g. molecular networks) can be varied, and different classifications can be induced by application to large set of structures, revealing hidden patterns. Deep learning based methods, in particular, so helpful in unveiling patterns and regularities, could greatly benefit of alternative representations of the data structures used to feed neural networks [1,2].

A valid alternative for a set of suitable structural parameters for molecular networks, i.e. a mathematical object made up by a set of atoms or atom goups (nodes) with some closeness notion to establish links, is provided by hyperspherical coordinates, as traditionaly used in quantum reactive scattering calculations, or in their extention to the classical molecular dynamics of many-body systems

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2023
O. Gervasi et al. (Eds.): ICCSA 2023 Workshops, LNCS 14111, pp. 121–132, 2023.
https://doi.org/10.1007/978-3-031-37126-4_9

(more suited for application to large biomolecules). The fundamental feature of the quantum hyperspherical dynamics are the hyperspherical function basis sets [3–5] for three and four-atom collisions (see e.g [6–11]). Among the several variants of hyperspherical coordinates, the so called "symmetric" ones are characterized by invariance with respect to all the available product channels of a given system of atoms (as common in multi-channel processes). The same hyperspherical basis functions can be properly combined in finite sums to represent the intermolecular and intramolecular interactions. For theory and applications of the classical hyperspherical coordinates see Refs. [12,13,13–18,18–20,20–22,22–39].

The classical formulation of the hyperspherical coordinates introduces a partition of the degrees of freedom in terms of shape coordinates, ordinary rotation and kinematic rotation angles [8,40–44], for which the contributions to the kinetic energy can be calculated separately, as a function of time [8,41]. Moreover, the shape coordinates are such that to be invariant with respect to both types of rotations [40,45–50]. Using shape coordinates, invariant shape parameters can be defined, to be used for systematic classification of protein structures.

The paper is organized as follows. In Sect. 2 a definition of molecular networks is provided. In Sec 3 the theory of the hyperspherical coordinates, shape parameters and deformation indexes is succinctly resumed and alternative molecular networks, based on the local tetrahedral geometry of amino acids in proteins, are introduced. An example of application to representative protein structures is illustrated in Sect. 4. Sect. 5 draws conclusions and anticipates perspective applications.

2 Molecular Networks

In the context of the classification of proteins, it is possible to represent them schematically in the form of a graph. A graph is a network made up of vertices (or nodes) and edges (or links), an example of which is shown in Fig. 1, where, specifically, the vertices could represent amino acids and the links correspond to van der Waals type interactions or chemical bonds. Graphs of this type are called amino acid networks. The most common amino acid networks are the α carbon networks and the atomic distance networks. In such networks, for example, the nodes represent single C_α atoms, present in the various amino acid residues, or the atoms present in the various amino acids, except the hydrogen atoms. In both cases, two nodes are connected if the distance between them is less than a certain threshold value. In principle, network nodes can represent group of atoms, for example portions of each amino acid, and in these case the possibility of adding additional information to the node can be exploited to increase the informatio content of the network itself. In the next sections we will illustrate how a network of tetrahedral units can be constructed to represent a protein structure, by hypersherical shape coordinates.

3 Methodology

The $N-1$ Jacobi vectors $\mathbf{Q}_\alpha$, where $\alpha = 1, \cdots, N-1$, are the starting point to obtain the hyperspherical coordinates of a system of N particles. These vectors are combinations of the position vectors of the N particles of a system in the center of mass reference frame, which are denoted as $\mathbf{r}_\alpha$ [40] and are the starting point to generate hyperspherical coordinates by a bijective mapping in the Euclidean space. The combination coefficients are a function of the masses of the individual atoms, for details see next Sect. 3.1. As a generalization of spherical coordinates, the hyperspherical ones have an hyperradius ρ, modulus of a vector spanning the $3N-3$ dimensional configuration space, with Cartesian components equivalent to the Jacobi vector ones. The remaining $3N-4$ "hyperangles", mathematically define the hyperspherical coordinates. Many set of angles can be chosen, here we focus on the so called "symmetric" hyperspherical coordinates. These are obtained by a matrix transformation known as *singular value decomposition*, acting over a position matrix containing column-wise the Cartesian vectors of the particle in the system. A brief description is in the following section.

3.1 Properties of the Hyperspherical Coordinates

The *singular value decomposition* [51] is a theorem valid for any 3 x N position matrix constructed starting from a given set of N vectors, by arranging them column-wise.

Given $N \geq 2$ particles with masses $m_1, \cdots, m_N$ and radial position vectors in the center of mass reference frame, $\mathbf{r_1}, \cdots, \mathbf{r_N}$, a corrsponding set of mass *scaled* radii vectors, $\mathbf{q}_\alpha = (m_\alpha/M)^{1/2}\mathbf{r}_\alpha$ $(1 \leq \alpha \leq N)$, can be obtained, where $M = \sum_\alpha^N m_\alpha$ is the total mass of the system.
The $3 \times N$ position matrix is denoted by Z and its columns are the mass scaled vectors whose components denoted as q_{ij}:

$$Z = \begin{pmatrix} q_{1,1}\ q_{1,2} \cdots q_{1,N} \\ q_{2,1}\ q_{2,2} \cdots q_{2,N} \\ q_{3,1}\ q_{3,2} \cdots q_{3,N} \end{pmatrix}. \tag{1}$$

The orthogonal matrix R^t (transpose of a matrix $R \in O(3)$) can act on the position matrix Z by left-multiplication performing rotations in the three-dimensional physical space. Also, an orthogonal matrix $K \in O(N)$ can act on the position matrix by right-multiplication, again rotating the coordinate frame, but in the so called *kinematic space* [7,41], $Z' = ZK$.

Allowed K matrices have typically the following form:

$$K = \begin{pmatrix} k_{1,1} & k_{1,2} & \cdots & (m_1/M)^{1/2} \\ k_{2,1} & k_{2,2} & \cdots & (m_2/M)^{1/2} \\ \cdots & \cdots & \cdots & \cdots \\ k_{N,1} & k_{N,2} & \cdots & (m_N/M)^{1/2} \end{pmatrix} \tag{2}$$

such matrices applied to the Z matrix generate a subset of all the possible Cartesian frames. Note that the last column of such Z matrices are identically zero, as a consequence of the separation of the motion of the center of mass, therefore the number of degrees of freedom is reduced to $3N-3$. The matrix Z with one less column is called *reduced position matrix*.
The sets of (N-1) Jacobi and related vectors always generate reduced matrices.

The possible different linear combinations of the N Cartesian particle position vectors satisfying the Jacobi vector definition, all generated as a function of the particle masses [40,52] are such that some of them resemble the asymptotic (reactive) channels of the system; it is well known that properly defined kinematic rotations smoothly connect them.
The *singular value decomposition* applied to the $3 \times n$ position matrix Z (where $n = N$ or $n = N-1$) results in a product of three matrices:

$$Z = R \Xi K^t \tag{3}$$

where $R \in O(3)$ and $K \in O(n)$ are 3×3 and $3 \times n$ orthogonal matrices, respectively. The elements of the $3 \times n$ matrix Ξ are zeroes, with the possible exception of the three diagonal entries, $\Xi_{11} = \xi_1, \Xi_{22} = \xi_2, \Xi_{33} = \xi_3$, which are subjected to the inequality $\xi_1 \geq \xi_2 \geq \xi_3 \geq 0$.

The values ξ_i, $(i = 1, 2, 3)$ are called the *singular values* of the matrix Z and are uniquely determined, although the factors R and K in Eq. 3 are not. If $N \leq 3$ and Z is the full $3 \times N$ position matrix, then the smallest singular value ξ_3 is necessarily zero. The hyperradius and the ξ's are connected as follows [40,41]:

$$\xi_1^2 + \xi_2^2 + \xi_3^2 = \rho^2. \tag{4}$$

It has to be noted that the ξ's are invariant under both ordinary rotations in the three-dimensional physical space and kinematic rotations [7,8,41,53]. This invariance makes the ξ's appropriate as coordinates for molecular dynamics [40,54–57] and for the study of the minimum energy structures of N-particle systems.
In the special case $n = N - 1 = 3$, the matrix Z represents four particles or four center systems and the R and K matrices cannot be chosen to be *special orthogonal* ($R \in SO(3)$ and $K \in SO(n)$), but have to be just orthogonal matrices ($O(3)$). Accordingly, if the determinant of Z is lower than zero, its sign depends on the sign of the product of the ξ's, implying $\xi_3 \leq 0$. This fact is directly connected to the mirror image and chirality sign of the system [45,58,59].

3.2 Shape Coordinates and Tetrahedral Networks

The singular values (ξ_1, ξ_2, ξ_3) (shape coordinates), invariant under kinematic and ordinary rotations [60], can be put into relationship to the moments of inertia of the system:

$$\begin{aligned} \frac{I_1}{M} &= \xi_2^2 + \xi_3^2 \\ \frac{I_2}{M} &= \xi_1^2 + \xi_3^2 \\ \frac{I_3}{M} &= \xi_1^2 + \xi_2^2 \end{aligned} \tag{5}$$

where I_1, I_2 and I_3 are the moments of inertia in the principal axis reference frame. This clarifies why the ξs are referred to as shape coordinates: they contain information about the distribution of the masses with respect to the principal axis frame. From Eq. 4 one obtains:

$$I_1 + I_2 + I_3 = 2M\rho^2. \tag{6}$$

the square of the hypperadius of the hyperspherical coordinates. The values of the ξ's also determine whether the system is an asymmetric, symmetric or a spherical rotor. for spherical top configurations $\xi_1 = \xi_2 = \xi_3$, prolate and oblate tops one has $\xi_3 = \xi_2 < \xi_1$ and $\xi_1 = \xi_2 > \xi_3$ respectively.
As Cartesian variables, the three ξ's can be represented on a sphere, in terms of the hyperradius and two angles θ and ϕ, as follows [40]:

$$\begin{aligned} \xi_1 &= \rho \sin\theta \cos\phi \\ \xi_2 &= \rho \sin\theta \sin\phi \\ \xi_2 &= \rho \cos\theta \end{aligned} \tag{7}$$

As anticipated in previous section, the special case of a four-atom (or four-center) system is symmetric and the three ξs can be tought of as representative of the shape of a tetrahedron. Accordingly, a complex protein structure can be represented as a set of tetrahedral units, taking as the four centers the atoms surrounding the alpha carbon atoms of each amino acid unit. To each tetrahedron is associated a triple of ξs, accounting for its volume (product $\xi_1\xi_2\xi_3$) and surface area $\sum_{i<j} \xi_i\xi_j$).

4 Tetrahedral Networks for Protein Structures

In previous works [43,48,61,62] we considered applications to protein structures for which the shape coordinates and derived the deformation indexes, properly defined, where calculated single amino acids (GLY, PRO, ALA) or globally for all the amino acids.

Here, given certain molecular structures, namely the sets of Cartesian coordinates defining its geometry, the procedure illustrated in previous Sects. 3.1

and 3.2 provides a recipe to build up a tetrahedral molecular network, by identifying the C_α atoms and the surrounding four centers defining deformed tetrahedra. To each of such tetrahedra a triple of ξs can be associated.

To obtain numerically the ξ values we use the following relationship coming from Eq. 3:

$$ZZ^t = R\Xi\Xi^t R^t \tag{8}$$

where the product $\Xi\Xi^t$ is a 3×3 square diagonal matrix, whose entries are the squares of the ξ's. The diagonal entries are just the eigenvalues of the product matrix ZZ^t, obtained from the position matrix. Once the ZZ^t matrix is built from the Cartesian components of the mass scaled atomic position vectors (see Sect. 3.1), this can be diagonalized by a numerical procedure or analitically through the Cardano's formula applied to the third degree characteristic equation [40].

As and example of application we consider here two different proteins, whose structures are available from the Protein Data Bank [63] and are shown in Fig. 2. They have different secondary structures, one being made up by β-sheets only, the other characterized by prevalent α-helix motifs. For each structure the Cartesian coordinates have been extracted, the coordinates of the four atoms surrounding the C_α atoms of each amino acid have been identified and used to build up the product matrix of Eq. 8, so calculating the values of the ξs. The shape coordinates account for the local structure of the tetrahedra in the network, as they occur in the protein chain (also repeatedly). In particular we consider the products $\xi_1\xi_2\xi_3$ and $\sum_{i<j}^{3} \xi_i\xi_j$, as obtained from the network, representative of the tetrahedron volume and surface area, respectively. In Fig. 3 the two above quan-

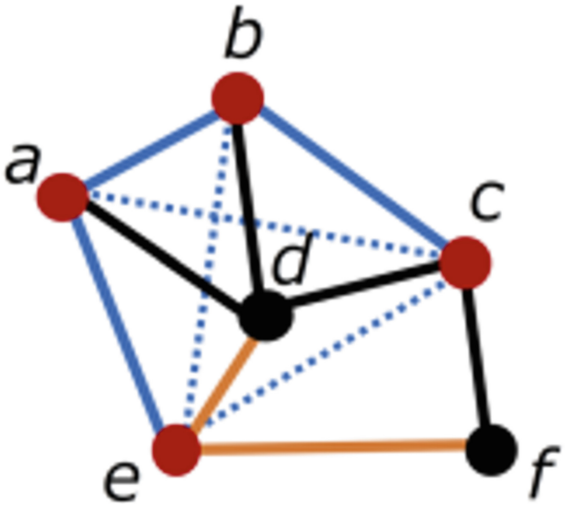


Fig. 1. Representation of a molecular network, the vertices represent atoms and the link connection between them, as established by a measurable neighbourhood notion.



Fig. 2. Schematic representation of the two proteins 2A00 and 2A0A (Protein Data Bank classification name). The 2A0A structure accounts for a β-protein, since in β-sheets prevail, while 2A00 is mixed with a strong α-helix presence.

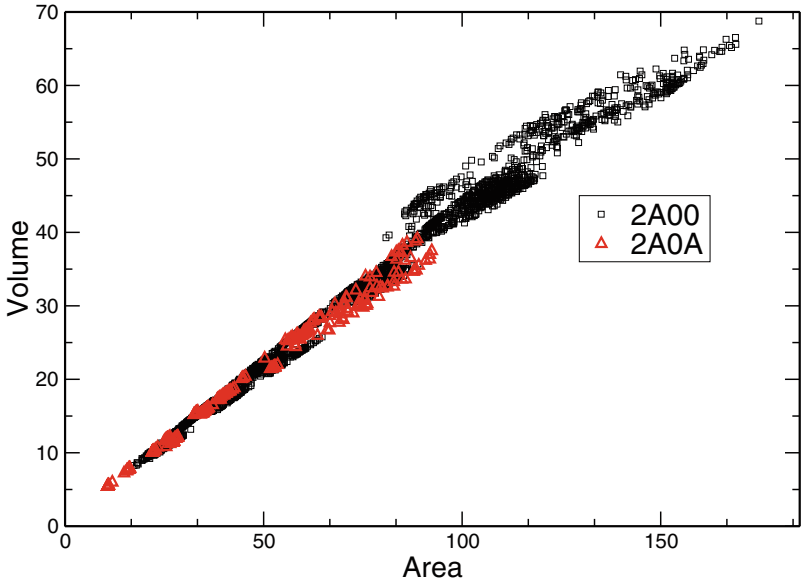


Fig. 3. Two-dimensional plot of the shape coordinate volume and area for the 2A0A and 2A00 protein structure obtained from the database [63]

tities are represented in a 2-dimensional plot. It can be seen that the shape coordinate volume/area plots, as expected, show apparently a linear correlation, but the range of the two quantities differ for the two proteins, probably due to their different secondary structures. Further analysis of such behaviour is beyond the scope of present work. However, this is a preliminary indication of the suitability of shape coordinates to identify structural properties.

5 Conclusions

In this paper we considered the possibility of building tetrahedral networks to represent proteins, by using invariant structure parameters derived from hyperspherical coordinates. The definition of tetrahedral network was given and a recipe to build provided. A preliminar application to selected protein molecular structures has been presented.

Acknowledgments. Thanks are due to the Dipartimento di Chimica, Biologia e Biotecnologie dell'Università di Perugia (FRB, Fondo per la Ricerca di Base 2019 and 2020). A. L. and N. F. L. acknowledge financial support from Fondazione Cassa di Risparmio di Perugia, n.# 19839.2020.0513. A.L. thanks the OU Supercomputing Center for Education & Research (OSCER) at the University of Oklahoma, and the Italian GARR for allocated computing time.

References

1. Perri, D., Simonetti, M., Lombardi, A., Faginas-Lago, N., Gervasi, O.: Binary classification of proteins by a machine learning approach. In: Gervasi, O., et al. (eds.) ICCSA 2020. LNCS, vol. 12255, pp. 549–558. Springer, Cham (2020). https://doi.org/10.1007/978-3-030-58820-5_41
2. Perri, D., Simonetti, M., Lombardi, A., Faginas-Lago, N., Gervasi, O.: A new method for binary classification of proteins with machine learning. In: Gervasi, O., et al. (eds.) ICCSA 2021. LNCS, vol. 12958, pp. 388–397. Springer, Cham (2021). https://doi.org/10.1007/978-3-030-87016-4_29
3. Zhao, B., Guo, H.: State-to-state quantum reactive scattering in four-atom systems. WIREs Comput Mol Sci **7**, e1301 (2017)
4. Skouteris, D., Castillo, J., Manolopoulos, D.E.: ABC: a quantum reactive scattering program. Comput. Phys. Comm. **133**, 128–135 (2000)
5. Lepetit, B., Launay, J.M.: Quantum-mechanical study of the reaction $He+H_2^+ \rightarrow HeH^+ + H$ with hyperspherical coordinates. J. Chem. Phys. **95**, 5159–5168 (1991)
6. Aquilanti, V., Beddoni, A., Cavalli, S., Lombardi, A., Littlejohn, R.: Collective hyperspherical coordinates for polyatomic molecules and clusters. Mol. Phys. **98**(21), 1763–1770 (2000)
7. Aquilanti, V., Beddoni, A., Lombardi, A., Littlejohn, R.: Hyperspherical harmonics for polyatomic systems: basis set for kinematic rotations. Int. J. Quantum Chem. **89**(4), 277–291 (2002)
8. Aquilanti, V., Lombardi, A., Littlejohn, R.: Hyperspherical harmonics for polyatomic systems: basis set for collective motions. Theoret. Chem. Acc. **111**(2–6), 400–406 (2004)
9. Kuppermann, A.: Quantum reaction dynamics and hyperspherical harmonics. Isr. J. Chem. **43**, 229 (2003)
10. De Fazio, D., Cavalli, S., Aquilanti, V.: Benchmark quantum mechanical calculations of vibrationally resolved cross sections and rate constants on ab initio potential energy surfaces for the F + HD reaction: comparisons with experiments. J. Phys. Chem. A **120**, 5288–5299 (2016)
11. Aquilanti, V., Cavalli, S.: The quantum-mechanical hamiltonian for tetraatomic systems insymmetric hyperspherical coordinates. **93**, 801–809 (1997)

12. Barreto, P.R.P., Vilela, A.F.A., Lombardi, A., Maciel, G.S., Palazzetti, F., Aquilanti, V.: The hydrogen peroxide-rare gas systems: quantum chemical calculations and hyperspherical harmonic representation of the potential energy surface for atom-floppy molecule interactions. J. Phys. Chemis. A **111**(49), 12754–12762 (2007)
13. Lombardi, A., Laganà, A., Pirani, F., Palazzetti, F., Lago, N.F.: Carbon oxides in gas flows and earth and planetary atmospheres: state-to-state simulations of energy transfer and dissociation reactions. In: Murgante, B., et al. (eds.) ICCSA 2013. LNCS, vol. 7972, pp. 17–31. Springer, Heidelberg (2013). https://doi.org/10.1007/978-3-642-39643-4_2
14. Lago, N.F., Albertí, M., Laganà, A., Lombardi, A.: Water $(H_2O)_m$ or benzene $(C_6H_6)_n$ aggregates to solvate the K^+. In: Murgante, B., et al. (eds.) ICCSA 2013. LNCS, vol. 7971, pp. 1–15. Springer, Heidelberg (2013). https://doi.org/10.1007/978-3-642-39637-3_1
15. Faginas-Lago, N., Albertí, M., Costantini, A., Laganá, A., Lombardi, A., Pacifici, L.: An innovative synergistic grid approach to the computational study of protein aggregation mechanisms. J. Mol. Model. **20**(7), 2226 (2014)
16. Faginas-Lago, N., Yeni, D., Huarte, F., Alcamì, M., Martin, F.: Adsorption of hydrogen molecules on carbon nanotubes using quantum chemistry and molecular dynamics. J. Phys. Chem. A **120**, 6451–6458 (2016)
17. Faginas-Lago, N., Lombardi, A., Albertí, M., Grossi, G.: Accurate analytic intermolecular potential for the simulation of Na^+ and K^+ ion hydration in liquid water. J. Mol. Liq. **204**, 192–197 (2015)
18. Albertí, M., Faginas Lago, N.: Competitive solvation of K^+ by C_6H_6 and H_2O in the K^+-$(C_6h_6)_n$-$(H_2O)_m$ (n = 1–4; m = 1–6) aggregates. Eur. Phys. J. D **67**, 73 (2013)
19. Albertí, M., Faginas Lago, N.: Ion size influence on the Ar solvation shells of M^+-C_6F_6 clusters (m = Na, K, Rb, Cs). J. Phys. Chem. A **116**, 3094–3102 (2012)
20. Albertí, M., Faginas Lago, N., Pirani, F.: Ar solvation shells in K^+-HFBz: From cluster rearrangement to solvation dynamics. J. Phys. Chem. A **115**, 10871–10879 (2011)
21. Lago, N.F., Albertí, M., Laganà, A., Lombardi, A., Pacifici, L., Costantini, A.: The molecular stirrer catalytic effect in methane ice formation. In: Murgante, B., et al. (eds.) ICCSA 2014. LNCS, vol. 8579, pp. 585–600. Springer, Cham (2014). https://doi.org/10.1007/978-3-319-09144-0_40
22. Faginas-Lago, N., Huarte Larrañaga, F., Albertí, M.: On the suitability of the ILJ function to match different formulations of the electrostatic potential for water-water interactions. Eur. Phys. J. D **55**(1), 75 (2009)
23. Bartolomei, M., Pirani, F., Laganà, A., Lombardi, A.: A full dimensional grid empowered simulation of the CO_2+ CO_2 processes. J. Comp. Chem. **33**, 1806 (2012)
24. Lombardi, A., Lago, N.F., Laganà, A., Pirani, F., Falcinelli, S.: A bond-bond portable approach to intermolecular interactions: simulations for n-methylacetamide and carbon dioxide dimers. In: Murgante, B., et al. (eds.) ICCSA 2012. LNCS, vol. 7333, pp. 387–400. Springer, Heidelberg (2012). https://doi.org/10.1007/978-3-642-31125-3_30
25. Albertí, M., Faginas-Lago, N., Laganà, A., Pirani, F.: A portable intermolecular potential for molecular dynamics studies of NMA-NMA and NMA-H_2O aggregates. Phys. Chem. Chem. Phys. **13**(18), 8422–8432 (2011)
26. Albertí, M., Faginas-Lago, N., Pirani, F.: Benzene water interaction: From gaseous dimers to solvated aggregates. Chem. Phys. **399**, 232 (2012)

27. Falcinelli, S., et al.: Modeling the intermolecular interactions and characterization of the dynamics of collisional autoionization processes. In: Murgante, B., et al. (eds.) ICCSA 2013. LNCS, vol. 7971, pp. 69–83. Springer, Heidelberg (2013). https://doi.org/10.1007/978-3-642-39637-3_6
28. Lombardi, A., Faginas-Lago, N., Pacifici, L., Costantini, A.: Modeling of energy transfer from vibrationally excited CO_2 molecules: Cross sections and probabilities for kinetic modeling of atmospheres, flows, and plasmas. J. Phys. Chem. A **117**(45), 11430–11440 (2013)
29. Lombardi, A., Pirani, F., Laganà, A., Bartolomei, M.: Energy transfer dynamics and kinetics of elementary processes (promoted) by gas-phase CO_2-N_2 collisions: Selectivity control by the anisotropy of the interaction. J. Comp. Chem. **37**, 1463–1475 (2016)
30. Pacifici, L., Verdicchio, M., Faginas-Lago, N., Lombardi, A., Costantini, A.: A high-level ab initio study of the n2 + n2 reaction channel. J. Comput. Chem. **34**(31), 2668–2676 (2013)
31. Lombardi, A., Faginas-Lago, N., Pacifici, L., Grossi, G.: Energy transfer upon collision of selectively excited CO_2 molecules: State-to-state cross sections and probabilities for modeling of atmospheres and gaseous flows. J. Chem. Phys. **143**, 034307 (2015)
32. Celiberto, R., Armenise, I., Cacciatore, M., Capitelli, M., Esposito, F., Gamallo, P., Janev, R., Lagana, A., Laporta, V., Laricchiuta, A., et al.: Atomic and molecular data for spacecraft re-entry plasmas. Plasma Sources Sci. Technol. **25**(3), 033004 (2016)
33. Faginas-Lago, N., Lombardi, A., Albertí, M.: Aqueous n-methylacetamide: New analytic potentials and a molecular dynamics study. J. Mol. Liq. **224**, 792–800 (2016)
34. Palazzetti, F., Munusamy, E., Lombardi, A., Grossi, G., Aquilanti, V.: Spherical and hyperspherical representation of potential energy surfaces for intermolecular interactions. Int. J. Quantum Chem. **111**(2), 318–332 (2011)
35. Lombardi, A., Palazzetti, F.: A comparison of interatomic potentials for rare gas nanoaggregates. J. Mol. Struct. (Thoechem) **852**(1–3), 22–29 (2008)
36. Barreto, P.R., Albernaz, A.F., Palazzetti, F., Lombardi, A., Grossi, G., Aquilanti, V.: Hyperspherical representation of potential energy surfaces: intermolecular interactions in tetra-atomic and penta-atomic systems. Phys. Scr. **84**(2), 028111 (2011)
37. Barreto, P.R., et al.: Potential energy surfaces for interactions of H_2O with H_2, N_2 and O_2: a hyperspherical harmonics representation, and a minimal model for the H_2O-rare-gas-atom systems. Comput. Theor. Chem. **990**, 53–61 (2012)
38. Lombardi, A., Pirani, F., Bartolomei, M., Coletti, C., Laganà, A.: A full dimensional potential energy function and the calculation of the state-specific properties of the CO+ N_2 inelastic processes within an Open Molecular Science Cloud perspective. Front. Chem. **7**, 309 (2019)
39. Faginas Lago, N., Lombardi, A., Vekeman, J., Rosi, M., et al.: Molecular dynamics of CH_4/N_2 mixtures on a flexible graphene layer: adsorption and selectivity case study. Front. Chem. **7**, 386 (2019)
40. Aquilanti, V., Lombardi, A., Yurtsever, E.: Global view of classical clusters: the hyperspherical approach to structure and dynamics. Phys. Chem. Chem. Phys. **4**(20), 5040–5051 (2002)
41. Sevryuk, M.B., Lombardi, A., Aquilanti, V.: Hyperangular momenta and energy partitions in multidimensional many-particle classical mechanics: The invariance approach to cluster dynamics. Phys. Rev. A **72**(3), 033201 (2005)

42. Castro Palacio, J., Velazquez Abad, L., Lombardi, A., Aquilanti, V., Rubayo Soneira, J.: Normal and hyperspherical mode analysis of NO-doped Kr crystals upon Rydberg excitation of the impurity. J. Chem. Phys. **126**(17), 174701 (2007)
43. Lombardi, A., Palazzetti, F., Aquilanti, V.: Molecular dynamics of chiral molecules in hyperspherical coordinates. In: Misra, S., et al. (eds.) ICCSA 2019. LNCS, vol. 11624, pp. 413–427. Springer, Cham (2019). https://doi.org/10.1007/978-3-030-24311-1_30
44. Lombardi, A., Palazzetti, F., Sevryuk, M.B.: Hyperspherical coordinates and energy partitions for reactive processes and clusters. AIP Conf. Proceed. **2186**, 030014 (2019). AIP Publishing LLC (2019)
45. Lombardi, A., Palazzetti, F.: Chirality in molecular collision dynamics. J. Phys.: Condens. Matter **30**(6), 063003 (2018)
46. Lombardi, A., Palazzetti, F., Peroncelli, L., Grossi, G., Aquilanti, V., Sevryuk, M.: Few-body quantum and many-body classical hyperspherical approaches to reactions and to cluster dynamics. Theoret. Chem. Acc. **117**(5–6), 709–721 (2007)
47. Aquilanti, V., Grossi, G., Lombardi, A., Maciel, G.S., Palazzetti, F.: Aligned molecular collisions and a stereodynamical mechanism for selective chirality. Rend. Fis. Acc. Lincei **22**, 125–135 (2011)
48. Lombardi, A., Faginas-Lago, N., Aquilanti, V.: The invariance approach to structure and dynamics: classical hyperspherical coordinates. In: Misra, S., et al. (eds.) ICCSA 2019. LNCS, vol. 11624, pp. 428–438. Springer, Cham (2019). https://doi.org/10.1007/978-3-030-24311-1_31
49. Caglioti, C., Dos Santos, R.F., Lombardi, A., Palazzetti, F., Aquilanti, V.: Screens Displaying Structural Properties of Aminoacids in Polypeptide Chains: Alanine as a Case Study. In: Misra, S., et al. (eds.) ICCSA 2019. LNCS, vol. 11624, pp. 439–449. Springer, Cham (2019). https://doi.org/10.1007/978-3-030-24311-1_32
50. Caglioti, C., Ferreira, R.d.S., Palazzetti, F., Lombardi, A., Aquilanti, V.: Screen representation of structural properties of alanine in polypeptide chains. AIP Conf. Proceed. **2186**, 030015 (2019). AIP Publishing LLC (2019)
51. Horn, R.A., Johnson, C.R.: Matrix Analysis, 2nd edn. University Press, Cambridge (1990)
52. Gatti, F., Lung, C.: Vector parametrization of the n-atom problem in quantum mechanics. i. jacobi vectors. J. Chem. Phys. **108**, 8804–8820 (1998)
53. Aquilanti, V., Lombardi, A., Sevryuk, M.B.: Phase-space invariants for aggregates of particles: hyperangular momenta and partitions of the classical kinetic energy. J. Chem. Phys. **121**, 5579 (2004)
54. Aquilanti, V., Carmona Novillo, E., Garcia, E., Lombardi, A., Sevryuk, M.B., Yurtsever, E.: Invariant energy partitions in chemical reactions and cluster dynamics simulations. Comput. Mat. Sci. **35**, 187–191 (2006)
55. Aquilanti, V., Lombardi, A., Sevryuk, M.B., Yurtsever, E.: Phase-space invariants as indicators of the critical behavior of nanoaggregates. Phys. Rev. Lett. **93**, 113402 (2004)
56. Calvo, F., Gadea, X., Lombardi, A., Aquilanti, V.: Isomerization dynamics and thermodynamics of ionic argon clusters. J. Chem. Phys. **125**, 114307 (2006)
57. Lombardi, A., Aquilanti, V., Yurtsever, E., Sevryuk, M.B.: Specific heats of clusters near a phase transition: Energy partitions among internal modes. Chem. Phys. Lett. **30**, 424–428 (2006)
58. Lombardi, A., Maciel, G.S., Palazzetti, F., Grossi, G., Aquilanti, V.: Alignment and chirality in gaseous flows. J. Vacuum Soc. Japan **53**(11), 645–653 (2010)
59. Palazzetti, F., et al.: Aligned molecules: chirality discrimination in photodissociation and in molecular dynamics. Rendiconti Lincei **24**(3), 299–308 (2013)

60. Littlejohn, R.G., Mitchell, A., Aquilanti, V.: Quantum dynamics of kinematic invariants in tetra-and polyatomic systems. Phys. Chem. Chem. Phys. **1**, 1259–1264 (1999)
61. Lombardi, A.: Symmetry and deformations of cluster and biomolecules by invariant shape coordinates. AIP Conf. Proceed. **2343**, 020004 (2021). AIP Publishing LLC (2021)
62. Andrea, L., Faginas-Lago, N., Pacifici, L.: Protein networks by invariant shape coordinates and deformation indexes. In Gervasi, O., Murgante, B., Misra, S., Rocha, A.M.A.C., Garau, C., eds.: Computational Science and Its Applications - ICCSA 2022 Workshops. ICCSA 2022. Lecture Notes in Computer Science, vol. 13382, pp. 348–359. Springer, Cham (2022). https://doi.org/10.1007/978-3-031-10592-0_26
63. Berman, H., et al.: The protein data bank. Nucleic Acid Res. **28**, 235–242 (2000)