

Classification of Biomolecules by Invariant Shape Coordinates and Deformation Indexes

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Abstract. In this paper we consider to approach the issue of the classification of protein structures by assigning them, in a unique way, sets of invariant parameters. To such purpose we suggest the use of shape parameters and deformation indexes derived from "symmetric" hyperspherical coordinates, as introduced by us in previous works. We give a resume of the theoretical background of coordinate and parameter derivation, followed by an application of the method to some representative protein structures.

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

1 Introduction

The classification of structures of proteins is a longstanding issue, mainly motivated by the need for comparison and recognition of them in connection to folding process. The use of appropriate invariant parameters, uniquely associated to a given molecular geometry, can in principle induce a kind of structure classification, leading to emergence of patterns and regularities. A comprehensive statistics of such parameters could also be a test for the quality of the experimental measured and theoretically predicted structures. The recent increased use of computational approaches based on machine learning and neural networks, oriented to the search for hidden patterns and regularities, further motivates renewed efforts in such direction [1].

Convenient sets of invariant parameters can be derived from the hyperspherical approach to molecular dynamics, traditionally adopted for quantum reactive scattering calculations. Quantum hyperspherical dynamics relies on the definition of sets of hyperspherical functions [2–4] for three and four-body collisions (see e.g. [5–10]), which in turn depend in the symmetry properties of the particular angular coordinate set adopted. The Hamiltonian in so called "symmetric" hyperspherical coordinates is invariant with respect to the possible product

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arrangements, as in multi-channel processes, and for such reason is largely preferable with respect to other approaches. The same hyperspherical basis functions, due to their symmetry properties, can be combined in finite sums to represent the intermolecular and intramolecular interactions [11–38].

In spite of the original application to few-atom systems, hyperspherical coordinates can be derived for any number of atoms and used for molecular dynamics simulations of large molecules based on classical mechanics (see e.g. [39]).

Unlike Cartesian coordinates, the hyperspherical ones partition the degrees of freedom into shape coordinates, ordinary rotations and kinematic rotations angles [7,40–44]. A kinetic energy term corresponds to each such variable sets and can be evaluated in the classical mechanics framework as a function of hyperangular momenta. The hyperspherical Hamilton function, is remisicent of the quantum hyperspherical Hamiltonian operator (differing for some purely quantum extra-terms). Integration of Hamilton's equations in Cartesian coordinates can be still retained with hyperspherical coordinates since a procedure based on matrix transformations of the set of position vectors has been developed, which allows for the evaluation of the energy terms appearing in the Hyperspherical Hamilton function as a function of time [7,41].

The global shape of the system in the three-dimensional physical space is invariant under the action of both ordinary and kinematic rotations. As a consequence shape coordinates must be themselves invariant with respect to both kinds of rotations, as shown in previous works [40,45–50].

Exactly for such invariance property of shape hyperspherical coordinates, we consider them suitable as shape parameters for the classification of local structures of biomolecules.

The paper is organized as follows. In Sect. 2 the basic theory of hyperspherical coordinates and the derivation of shape coordinates and deformation indexes are reported. Applications to two examples of protein structures is illustrated in Sect. 3. Section 4 contains conclusions and perspectives.

2 Methodology

The hyperspherical coordinates are defined, for an N-particle system, starting from the corresponding set of $N-1$ Jacobi vectors $\mathbf{Q}_\alpha$, where $\alpha = 1, \cdots, N-1$. These can be obtained as a combinations of the position vectors of the N particles in the center of mass reference frame, denoted as $\mathbf{r}_\alpha$ [40]. In practice, the construction of Jacobi vectors proceeds as follows: take the vector which connects particles 1 and 2, then the one connecting the center of mass of the pair to the third particle, and so on, up to the $(N-1)$th vector, which connects the center of mass of the first $N-1$ particles to the Nth particle. The coefficients of the combination depends on the particle masses, see Sect. 2.1 for details. The generalization of the radius coordinate of the spherical system to the N particle case leads to the hyperradius ρ, which is the modulus of a vector of dimension $3N-3$, spanning the configuration space of the system. The Cartesian components of the hyperradial vector are just the Jacobi vector components. The

transformation linking the Jacobi vector components with the hyperradius and $3N-4$ "hyperangles", defines the hyperspherical coordinates. There are in principle many alternative choices for the a angular variables, the one leading to the so called "symmetric" hyperspherical representation is the most convenient for us. The symmetric hyperspherical coordinates are generated by a matrix transformation known as *singular value decomposition*, applied to the position matrix containing column-wise the Cartesian vector of the particle system. The details of such transformation are described in the following section.

2.1 Hyperspherical Coordinates for Many Particle Systems

The *singular value decomposition* [51] is a matrix decomposition theorem that can be applied to any given set of N vectors arranged column-wise to form a 3 x N position matrix, and it is precisely the tool allowing for a general definition of hyperspherical coordinates.

Let us suppose we have a collection of $N \geq 2$ particles with masses $m_1, \cdots, m_N$ and positions identified by a set of radii vectors in the center of mass reference frame, $\mathbf{r_1}, \cdots, \mathbf{r_N}$. Mass *scaled* radii vectors, $\mathbf{q}_\alpha = (m_\alpha/M)^{1/2}\mathbf{r}_\alpha$ $(1 \leq \alpha \leq N)$, can be simply obtained, with $M = \sum_\alpha^N m_\alpha$ is the total mass of the system.

The $3 \times N$ position matrix is denoted by Z and contains, column-wise, the components of the mass scaled vectors:

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

The action of an orthogonal matrix R^t (transpose of a matrix $R \in O(3)$) on the position matrix Z by left-multiplication generates rotations in the three-dimensional physical space. An orthogonal matrix $K \in O(N)$ acting in the position matrix by right-multiplication, instead rotates the coordinate frame in the so called *kinematic space* [6,41], $Z' = ZK$.

Some of the allowed K matrices have the following form:

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

and its application to the Z matrix generates a subset of all the possible Cartesian frames. The last column of such Z matrices are identically zero, due to the separation of center of mass motion, so 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 invariably generate reduced matrices.

The Jacobi vectors can be generated in many different ways, as linear combinations of the N Cartesian particle position vectors, and always the coefficients of the combination are function of the particle masses [52,53]. The different vector sets are close to the different particle coupling schemes, the asymptotic (reactive) channels of the system; properly defined kinematic rotations smoothly connect them.

The *singular value decomposition* when applied to the $3 \times n$ position matrix Z (where $n = N$ or $n = N - 1$) gives 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 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 singular values are connected to the hyperradius as follows [40,41]:

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

The ξ's are invariant under both ordinary rotations in the three-dimensional physical space and kinematic rotations [6,7,41,54]. The invariance makes the ξ useful set of parameters for molecular dynamics [40,55–58] and in 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 two matrices R and K cannot be chosen to be *special orthogonal* ($R \in SO(3)$ and $K \in SO(n)$), but have to be orthogonal matrices ($O(3)$). In this case it can be seen that if the determinant of Z is lower than zero, its sign depends on the sign of the product of the ξ's, and so one has $\xi_3 \leq 0$. This fact is directly connected to the mirror image and chirality sign of the system [45,59,60].

2.2 Invariant Deformation Indexes

The singular values (ξ_1, ξ_2, ξ_3), besides being invariant under kinematic and ordinary rotations [61], are related 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. Consequently, they can be thought of as representative of the mass

distribution with respect to the principal axis frame and will be referred to as shape coordinates. From Eq. 4 one obtains:

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

The values of the ξ's determine whether the system is an asymmetric, symmetric or a spherical rotor. Spherical top configurations are those for which $\xi_1 = \xi_2 = \xi_3$, prolate tops those for which $\xi_3 = \xi_2 < \xi_1$, while oblate tops occur when $\xi_1 = \xi_2 > \xi_3$.

The ξ's can be represented in terms of the hyperradius and two angles θ and ϕ as follows:

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

Parameters measuring the deviation from the spherical top shapes, can be introduced by two following *deformation indexes* [40]:

$$\xi_+ = \frac{\xi_2^2 - \xi_3^2}{\rho^2}, \;\; \xi_+ \geq 0 \tag{8}$$

which is zero for prolate top configurations, and

$$\xi_- = \frac{\xi_2^2 - \xi_1^2}{\rho^2}, \;\; \xi_- \leq 0 \tag{9}$$

which is zero for oblate top configurations. By definition, when both indexes are zero, one has a spherical rotor.

3 Invariant and Deformation Index Distribution for Protein Structures

Given a certain molecular structure, the procedure illustrated in Sects. 2.1 and 2.2 allows to uniquely assign to that a set of values of the ξ's and deformation indexes. These can be used for the classification of global structures of large molecular systems, looking for patterns and regularities.

As an example of application, we consider a plot of protein structures in the shape coordinate space and in the subspace of deformation indexes, as defined in the previous sections. In a previous work, a similar study was applied to Lennard-Jones clusters and chiral molecules [43,48]. The calculation of the indexes requires the values of the invariant ξ's for each protein structure. There is no need to perform the complete singular value decomposition, since it can be seen that following relation comes from Eq. 3:

$$ZZ^t = R\Xi\Xi^t R^t \tag{10}$$

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, which can be obtained from the position matrix. Using the Cartesian components of the mass scaled atomic position vectors (see Sect. 2.1), one has to calculate the ZZ^t matrix and diagonalize by a numerical procedure or by resorting to Cardano's formula for the third degree characteristic equation [40].

Here we analyze 3 protein structures randomly chosen from the Protein Data Bank [62], these are identified as 1A0N, 1A03 and 1A23 in the database. The extracted Cartesian coordinates are the starting point to build up the product matrix of Eq. 10 and generate the ξ values and the deformation indexes of Eqs. 8 and 9 for each structure. In this case, we analysed separately the ξ's and the deformation indexes for three representative amino acids, Glycine (GLY), Proline (PRO) and Alanine (ALA), considering their local structures as they occur in the protein chain (also repeatedly), as resulting from the [62] database. In Figs. 1 and 2, the deformation indexes ξ_+ and ξ_- are represented in a 2-dimensional plot for the 1A0N and 1A23 structures respectively, defining the average index subspace to which the amino acid structure belongs. The allowed deformation values draw a clear shaped region in the index space for the three target amino acids.

In Fig. 3 the values of the individual shape coordinates ξ_1, ξ_2 are shown as they distribute in two-dimensional plots, for the three amino acids above, as obtained from the structure 1A03. It can be seen from the above figures

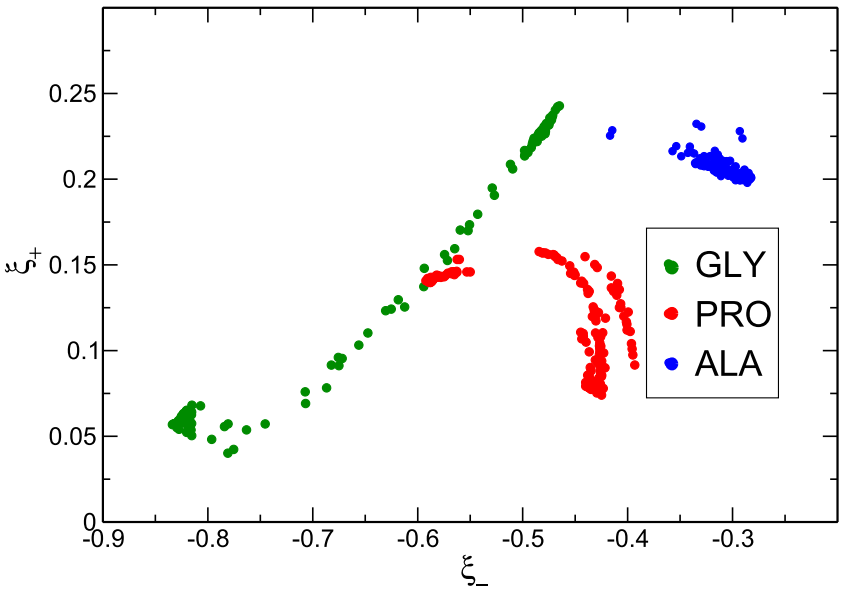

Fig. 1. Two-dimensional plot of the ξ_+ and ξ_+ invariant deformation indexes, for the GLY, PRO and ALA amino acid configuration, as obtained from the protein structure identified as 1a0n in the database [62]

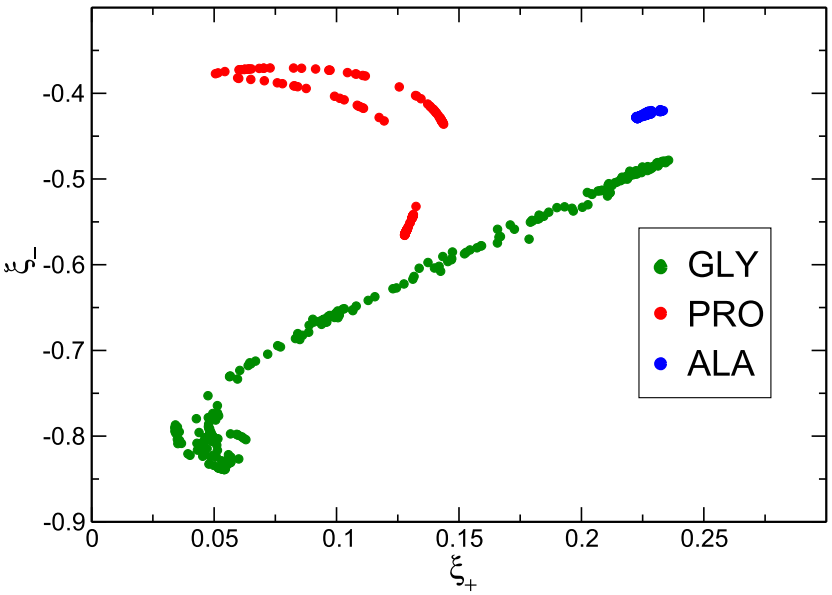

Fig. 2. Two-dimensional plot of the ξ_+ and ξ_+ invariant deformation indexes, for the GLY, PRO and ALA amino acid configuration, as obtained from the protein structure identified as 1a23 in the database [62]

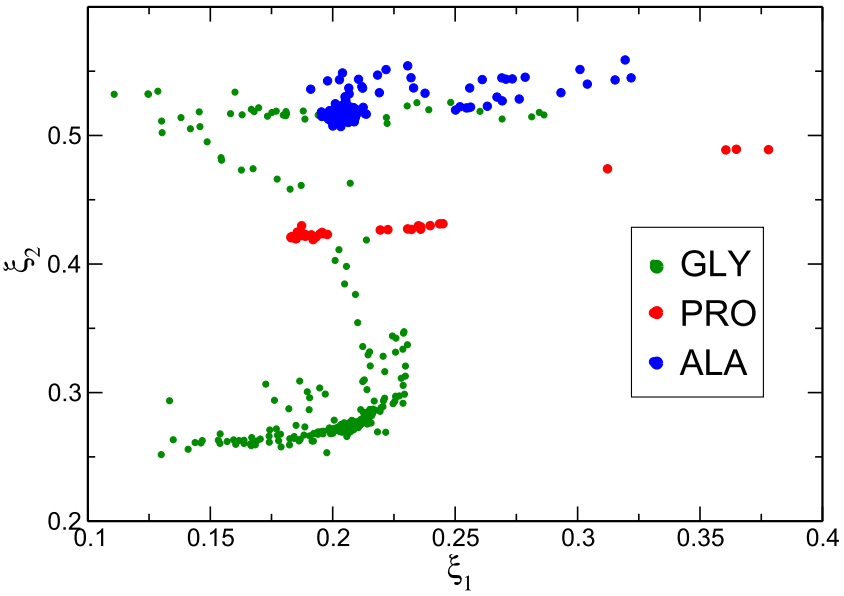

Fig. 3. Two-dimensional plots of the ξ_i, $i = 1, 2, 3$ invariant shape coordinates, for the GLY, PRO and ALA amino acid configurations as occurring in the structure identified as 1A03 in the database [62].

that parameters and shape coordinates are not uniformly distributed but tend to localize in a subset of the coordinate and parameter spaces. Assuming that the set of structure so far analysed could be considered as representative of all proteins, could be indeed an image of the "allowed" regions in the parameter space for the aforementioned three amino acids, a sort of footprint characteristic of such units in the protein chains. Confirmation and extension to other amino acid residues and to structural motifs will require systematic application to a large set of protein structures from the database.

4 Conclusions

In this paper we suggested the possible application of invariant structure parameters derived from hyperspherical coordinates to the classification problem for protein molecular structures. The parameters are three shape coordinates, and we have shown that can be assigned to any structure uniquely. They can be properly combined to generate deformation indexes. As an example, a set of protein structures has been analysed, limited to just three amino acids, using both shape coordinates and deformation indexes, determining their distribution and the corresponding "allowed" regions in the parameter space. Further steps will be the application to larger numbers of structures and to all the basic amino acids present in the protein chains, as well as extension to other biomolecules such as DNA.

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