

Protein Networks by Invariant Shape Coordinates and Deformation Indexes

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Abstract. The classification of proteins according to structural similarities is an increasingly relevant issue in biochemistry in the upcoming big data era. Proper choices of parameters, containing invariant structural information, could possibly induce convenient grouping of structures depending on structural motifs or also individual amino acid properties. Here, we give a summary of the theoretical background of parameter derivation from many-body hyperspherical coordinates and continue a previous work based on the use of shape parameters and deformation indexes. Such quantities are derived from "symmetric" hyperspherical coordinates and applied to a large set of protein structures each represented as a network of nodes corresponding to the amino acid residue centers of mass.

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

1 Introduction

The understanding of the biological function of proteins and the relationship with the structures of these complex molecules is mainly based upon their classification in families and, as far as it concerns the arrangement of atoms and residues, domains. A proper understanding of folding is also directly related to the knowledge of such aspects. Depending on the choice of parameters and on the schematic representation that is assigned to protein geometry (e.g. networks), different classifications can be induced and patterns can be revealed through application to large set of structures. Such parameters have to be preferably invariant and uniquely associated to a given molecular geometry by a simple and clear mathematical procedure applied to the corresponding atomic coordinate set. A first obvious use of a well grounded statistics of such parameters could be as a test for the realism and accuracy of the experimental measured and theoretically predicted structures. The increasing use computational approaches based upon deep learning are expected to further enhance the potential use of new parameters for the discovery of hidden patterns and regularities [1,2].

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The hyperspherical coordinates were originally adopted for quantum reactive scattering calculations, introducing convenient sets of invariant parameters. This approach can be extended to the general molecular dynamics of many-body systems, therefore directly applicable to large biomolecules. The fundamental feature of quantum hyperspherical dynamics are the hyperspherical functions which are used as wavefunction expansion basis set [3–5] for three and four-body collisions (see e.g. [6–11]). The specific form of such functions depends on the symmetry properties characterizing the set of angles adopted as coordinates, for which many choices are possible. Particularly, the Hamiltonian operator expressed in terms of the so called "symmetric" hyperspherical coordinates is a preferred choice since it is invariant with respect to all the possible product channels that characterize the given system. The clarity of the mathematical formulation and the computational efficiency is greatly improved if the same hyperspherical basis functions are combined as finite sums to represent the intermolecular and intramolecular interactions, see [12–39].

The hyperspherical coordinates are characterized by a partition of the degrees of freedom in terms of shape coordinates, ordinary rotation and kinematic rotation angles [8,40–44]. The kinetic energy associated to these different sets of degrees of freedom can be evaluated by classical mechanics as a function of hyperangular momenta. When applied to classical molecular dynamics simulations, the hyperspherical coordinates are not directly used in the integration of Hamilton's equations, since a procedure based on matrix transformations of the position vectors allows for the calculation of the energy contributions in the Hyperspherical Hamilton function as a function of time using Cartesian coordinates [8,41].

The key point for our work is that in the framework of hyperspherical coordinates the global shape of the system defined by the above mentioned shape coordinates is invariant under the action of both ordinary and kinematic rotations and so are the coordinates themselves [40,45–50]. Convenient shape parameters, to be used in classification studies of protein structures, can therefore be defined in terms of such hyperspherical degrees of freedom.

The paper is written according to the following scheme. In Sect. 2 the basic theory of hyperspherical coordinates, shape parameters and deformation indexes is outlined. Applications to a large set of protein structures is illustrated in Sect. 3. Sect. 4 draws conclusions and guesses perspectives.

2 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. The Jacobi vectors are a combinations of the position vectors of the N particles in the center of mass reference frame, denoted as $\mathbf{r}_\alpha$ [40]. The recipe to construct them is as follows: take the vector which connects particles 1 and 2, then a second connecting the center of mass of the particle pair to a third one, and so on. The procedure ends with the $(N-1)$th vector, which connects the center of mass of the first

$N-1$ particles to the Nth particle. The combination coefficients depends on the mass of the individual particles, see next Sect. 2.1 for more details. Being a generalization of spherical coordinates, the hyperspherical ones, applicable to the general N particle case, have an hyperradius ρ in place of the radius, defined as simply 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 the remaining $3N-4$ "hyperangles", mathematically defines the hyperspherical coordinates. The angular coordinates can be chosen in many alternative ways, but the one useful for us is that leading to the so called "symmetric" hyperspherical coordinates. The symmetric hyperspherical coordinates are obtained 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 Properties of the Hyperspherical Coordinates

The *singular value decomposition* [51] is a theorem for matrix decomposition that is valid for any 3 x N position matrix constructed starting from a given set of N vectors, by arranging them column-wise and is the mathematical tool for a general definition of such coordinates.

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 corresponding 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 contains, column-wise, the mass scaled vectors whose components are 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 generating rotations in the three-dimensional physical space. Also, an orthogonal matrix $K \in O(N)$ can act on the position matrix by right-multiplication, and rotates the coordinate frame in the so called *kinematic space* [7,41], $Z' = ZK$.

Allowed K matrices have, for example, 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, 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 always generate reduced matrices.

Many different linear combinations of the N Cartesian particle position vectors satisfying the Jacobi vector definition can be generated as a function of the particle masses [40,52]. Some of the different resulting vector sets resemble the asymptotic (reactive) channels of the system; remarkably, 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]:

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

We remark 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 parameters for molecular dynamics [40,54–57] and for the study of the minimum energy structures of N-particle systems.

It is worth to mention the special case $n = N - 1 = 3$, where 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 simple 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, and so one has $\xi_3 \leq 0$. This fact is directly connected to the mirror image and chirality sign of the system [45,58,59].

2.2 The Deformation Indexes

The singular values (ξ_1, ξ_2, ξ_3), are not only invariant under kinematic and ordinary rotations [60], they are also 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. These three parameters therefore account for the mass distribution with respect to the principal axis frame and are consequently referred to as shape coordinates. From Eq. 4 one obtains:

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

The relative values of the ξ's determine whether the system is an asymmetric, symmetric or 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 conveniently introduced as *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 Previous Sects. 2.1 and 2.2 gives an explicit procedure to uniquely associate to any molecular structures, expressed as a collection of atomic Cartesian coordinates, a set of values of the ξ's and of the deformation indexes.

In a previous work [61] we considered application to single protein structures for which the shape coordinates and the deformation indexes, as defined in the previous sections where calculated for three single amino acids (glycine, GLY, proline, PRO and alanine, ALA). In a another previous work a similar study was applied to Lennard-Jones clusters and chiral molecules [48,62]. To simplify the application of the above theory, we observe that there is actually no need to perform the complete singular value decomposition, since only the singular values are needed, so one can derive the following relation 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, 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. 2.1), this can be diagonalized by a numerical procedure or by the Cardano's formula for the third degree characteristic equation [40].

Here we extend the application of the hyperspherical method to a large set of structures from the Protein Data Bank [63]. For each structure the Cartesian coordinates have been extracted and used to build up the product matrix of Eq. 10 and to calculate the ξ values and the deformation indexes of Eqs. 8 and 9. We analyzed 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), for the large set of structures and also for the entire set of natural amino acids. In Fig. 1 the deformation indexes ξ_+ and ξ_- are represented in a 2-dimensional plot, accurately defining allowed index subspace for the three amino acid structures within proteins.

In Fig. 2 the values of the individual shape coordinates ξ_1, ξ_2 and ξ_3 are shown as two-dimensional plots, for the whole structure set for all natural amino acids. It is confirmed from previous figures that parameters and shape coordinates are not uniformly distributed but tend to be localized in a subset of the coordinate and parameter spaces. Being the set of structures considered here quite large (around 23000), we assume it to be potentially representative of all known proteins and the obtained plot to be an image of the "allowed" regions in the parameter space.

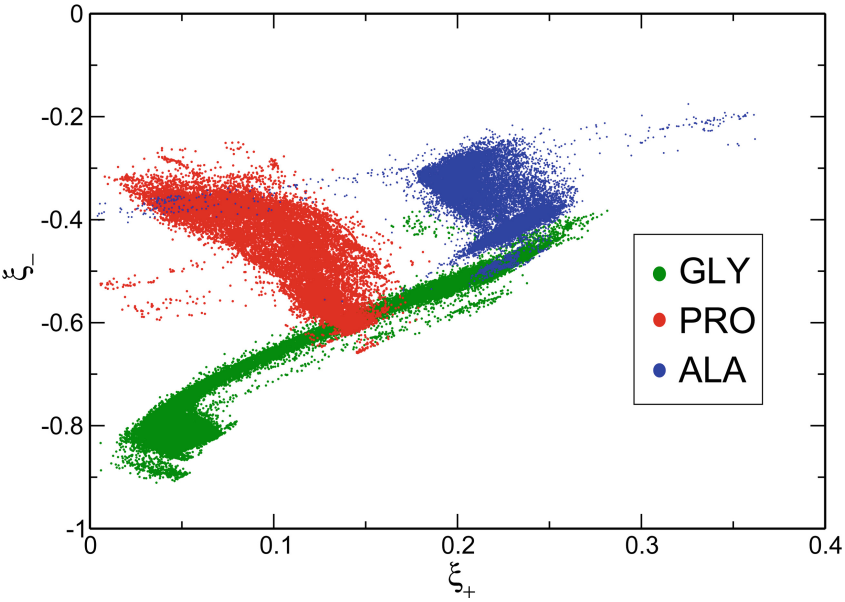

Fig. 1. Two-dimensional plot of the ξ_- and ξ_+ invariant deformation indexes, for the GLY, PRO and ALA amino acid configuration, as obtained from the large set of protein structures from the database [63]

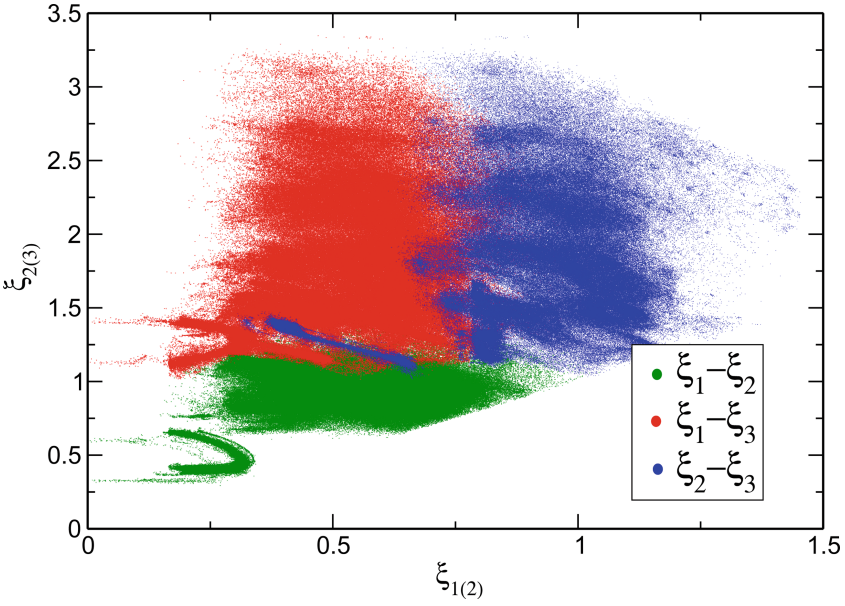

Fig. 2. Two-dimensional plots of the ξ_i, $i = 1, 2, 3$, invariant shape coordinates, for all the natural amino acids as occurring in the structure obtained from the database [63].

4 Conclusions

In this paper we analyzed a large set of protein structures using invariant structure parameters derived from hyperspherical coordinates. Using both shape coordinates and deformation indexes their distribution and the corresponding "allowed" regions in the parameter space have been obtained for three amino acids and for all the natural amino acids. This work is preluding to a systematic application of such parameters for the classification of protein molecular structures.

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