

Structural bioinformatics

What handedness and angles between helices has the studied three-helical protein domain?

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Abstract

Summary: We have created a new server FoldHandedness. Using this server it is possible: (i) to define the regions of helices from two issues (from the PDB file and using the last version of the DSSP program), (ii) to determine the handedness for any chosen three helices and (iii) to calculate the angle and sign between the chosen pairs of the helices for large proteins and complexes of proteins with DNA or RNA.

Availability and implementation: The FoldHandedness server is available for users at <http://bioinfo.protres.ru/foldhandedness>

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1 Introduction

Recently, the role of a mirror image conformation as a subtle effect in protein folding has been considered (Kachlishvili *et al.*, 2014). The understanding of chirality both in protein structures and amyloid suprastructures is an important issue in molecular biology now (Rubin *et al.*, 2008). Chiral amino acids form chiral helices that self-assemble into structural domains. The left-handed beta helix was a dogma during 20 years (Jenkins *et al.*, 1998). It should be noted that the left-handed beta helix has a more regular structure than the right-handed helix, and the first may be implicated in the formation of amyloid aggregates, for example, the prion protein (Choi *et al.*, 2009). We are the first who have demonstrated that folding optimization depends not only on the secondary structure but also on the handedness of α -helices. Left-handed three-helical domains have the fastest folding rates in comparison with right-handed three-helical domains among eight proteins with known experimental folding rates (Glyakina *et al.*, 2013). When studying the mechanical properties of these eight domains, under stretching at a constant speed and at a constant force on the atomic level, it has been demonstrated using molecular dynamics simulations that the right-handed three-helix domains are more resistant mechanically than the left-handed domains (Glyakina *et al.*, 2014). We explained this fact by that the right-handed domains have a larger number of contacts per

residue than the left-handed domains. Moreover, from our analysis we have revealed that bacterial three-helix proteins have some advantages in packing over eukaryotic right-handed three-helix proteins, which should result in faster folding (Galzitskaya *et al.*, 2014). Identification of protein handedness raises the question how to determine this value. For some domains this value is not evident. Here, we present a server able to calculate this value, the packing angle and the sign between all helices for any large protein consisting of alpha helices. For prediction of handedness the user should choose a 3D structure using a standard 4-symbol PDB code or use a home PDB file from MD simulations and choose three helices from the same chain.

2 Algorithm

The determination of regions of helices is taken from the PDB file containing the description of the secondary structure or from the DSSP program (Kabsch *et al.*, 1983). The user should choose three helices from the same chain. The axes of the helices are defined as a vector connecting two points:

$$C_{i,axis} = \frac{1.275 \cdot C_{\alpha,i-1} + 0.45 \cdot C_{\alpha,i} + 1.275 \cdot C_{\alpha,i+1}}{3}$$

One point is calculated in the beginning of the helix and the second in the end considering only the coordinates of C_{α} atoms. The

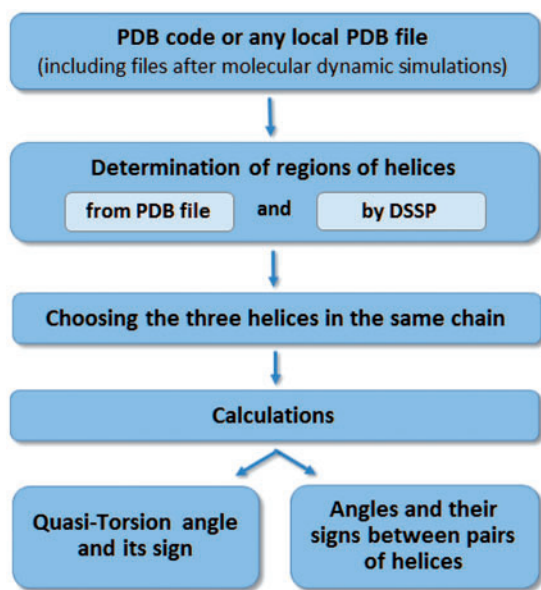


Fig. 1. Scheme for server processing

coefficients in equation are determined under condition that the center mass of the helix calculated by using only C_{α} atoms coincides with the origin of coordinates and axis Z coincides with the axes of the helix. The deflection from the center does not exceed 0.02 \AA . It is much smaller than the deviations from ideality in the PDB.

We determine the sign of an angle as suggested in the paper (Chothia *et al.*, 1981): the angle is positive if the near helix is rotated anti-clockwise relative to the far helix, and it is negative if the rotation is clockwise. To determine this sign we consider three vectors: b_1 and b_2 are the two helix axis vectors, and d is the vector of the closest approach in the direction of helix 2 to helix 1. Vector d is determined as in Chothia *et al.* (1981). The sign of the angle is determined as the sign of a scalar triple product $(b_1 \times d) \cdot b_2$. In the case of three-helical domain we will consider vector d from the second helix to the first helix, from the third helix to the second one and from the third helix to the first one.

We used five points to define the domain handedness: three centers of helices and two midpoints between corresponding edges of helices (see description on the server). The first two helical centers and the midpoint between their edges represent an imaginary plane. With the third helical center added to the plane these four points form a torsion angle. Positive and negative signs of this torsion angle correspond to right- and left-handed proteins. We defined the Quasi-Torsion angle as an average of forth-propagating and back-propagating torsion angles, if they have the same sign.

3 The FoldHandedness server

The FoldHandedness web-server is available at <http://bioinfo.protres.ru/foldhandedness/>. To calculate handedness with this server, one should specify the corresponding PDB entry (in the standard 4-symbol format, for example, PDB entry 3mba). For a protein in which more than one chain (or in the case of a protein–RNA complex) is presented in the PDB file to be used, one should also specify which chain should be used. If the studied protein is large it is necessary to choose the corresponding three alpha helices. The server always defines the regions of helices from two issues: from the PDB file and using the last version of the DSSP program. In addition, there is a possibility to calculate the angle and sign between three

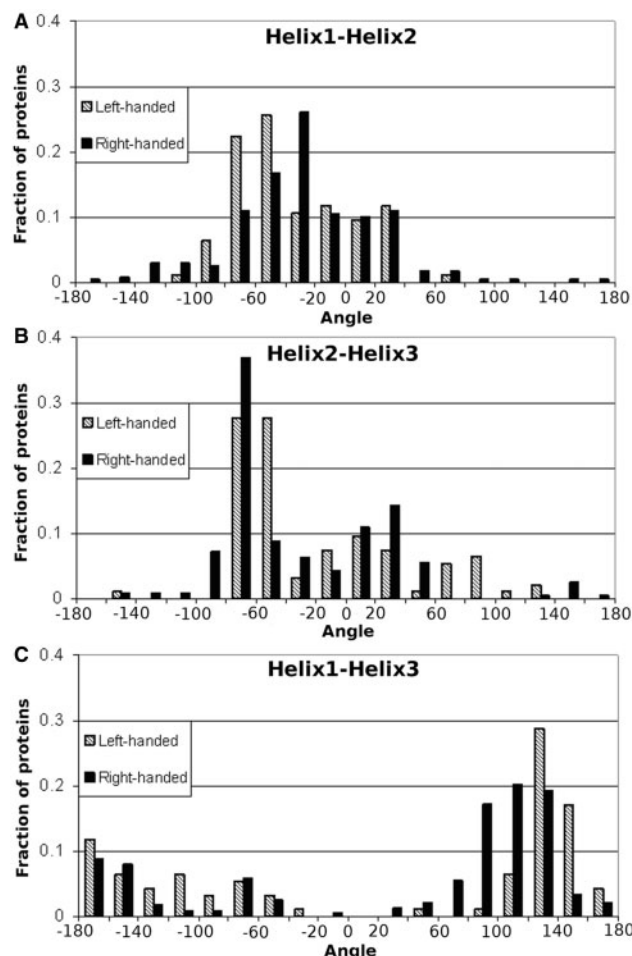


Fig. 2. Distribution of interhelical angles for 94 left-handed and 238 right-handed three-helical protein domains

possible pairs of helices. The flowchart presented in Figure 1 illustrates the operation of the server.

4 Implementation

Our program was applied to the dataset of 332 three-helical domains (Glyakina *et al.*, 2013) obtained from the SCOP database (Andreeva *et al.*, 2008). Two distributions of Quasi-Torsion angles for the left- and right-handed proteins have been obtained (see Fig. 2b in Glyakina *et al.*, 2013). At the same time there is no essential difference in the distribution of interhelical angles between left- and right-handed protein domains (see Fig. 2).

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Conflict of Interest: none declared.

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