Structural bioinformatics

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

Leonid B. Pereyaslavets¹, Anna V. Glyakina¹,², Nikita V. Dovidchenko¹, Igor V. Sokolovskiy¹ and Oxana V. Galzitskaya¹*

¹Institute of Protein Research and ²Institute of Mathematical Problems of Biology, Russian Academy of Sciences, Pushchino, Moscow Region 142290, Russia

*To whom correspondence should be addressed.

Associate Editor: Anna Tramontano

Received on August 15, 2014; revised on October 10, 2014; accepted on November 3, 2014

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

Contact: ogalzit@vega.protres.ru

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 z-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:

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

One point is calculated in the beginning of the helix and the second in the end considering only the coordinates of \( C_{\alpha} \) atoms.
coefficients in equation are determined under condition that the
center mass of the helix calculated by using only $C_a$ 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 Å. 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 rota-
tion is clockwise. To determine this sign we consider three vectors:
$h_1$ and $h_2$ 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 deter-
mined as the sign of a scalar triple product $(h_1 \times d) \cdot h_2$. 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 cen-
ters 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 ser-
ver, 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 com-
plex) 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 neces-
sary to choose the corresponding three alpha helices. The server al-
ways 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

possible pairs of helices. The flowchart presented in Figure 1 illus-
trates the operation of the server.

4 Implementation

Our program was applied to the dataset of 332 three-helical do-
mains (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 essen-
tial difference in the distribution of interhelical angles between left-
and right-handed protein domains (see Fig. 2).

Acknowledgements

We are grateful to M.Yu. Lobanov for the assistance in some calculations. This
study was supported by the Russian Science Foundation grant No 14-14-00536,
and by the Russian Academy of Sciences (Molecular and Cell Biology program
grant 01201453567) to L.V.S.

Conflict of Interest: none declared.

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