A new perspective on Analysis of Helix-Helix Packing Preferences in Globular Proteins

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Introduction

For many years it had been believed that steric compatibility of helix interfacescould be the source of the observed preference for particular angles between neighbouring helices as emerging from statistical analysis of protein databanks. Several elegant models describing how side chains on helices can interdigitate without steric clashes were able to account quite reasonably for the observed distributions. However, it was later recognized [1,2] that the "bare" measured angle distribution should be corrected to avoid statistical bias. Disappointingly, the rescaled distributions dramatically lost their similarity with theoretical predictions casting many doubts on the validity of the geometrical assumptions and models. In this report we elucidate a few points concerning the proper choice of the random reference distribution. In particular we show the existence of crucial corrections induced by unavoidable uncertainties in determining whether two helices are in face-to-face contact or not and their relative orientations. By using this new rescaling, we show that "true" packing angle preferences are well described by regular packing models, thus proving that preferential angles between contacting helices do actually exist.

Materials and Methods

1. Databank and helix pair selection

We employed the same ensemble of 600 proteins considered by Chang et. al [3], which consisted of sequences varying in length from 44 to 1017, with low sequence homology and covering many different three-dimensional folds according to the Structural Classification of Proteins (SCOP). The structures were monomeric and determined using X-ray crystallography. We collected 4397 helices each with at least four consecutive residues classified as helical in the PDB files. The average number of residues of these helices was 11.5. Two helices were defined to be in close contact, if at least one inter-helical contact between C^{α} atoms was present, with a maximal threshold distance of 5.5 Å. Only helix pairs separated in sequence by at least 20 intervening residues were considered, to get rid of possible correlations induced by short loops. Finally, we kept only helix pairs whose axes were sufficiently straight. The resulting data set consisted of 627 closely packed helix pairs.

2. Helix axis reconstruction

The reconstruction of the helix axis from the coordinates of the C^{α} atoms of the corresponding residues is a critical step in the determination of packing angle preferences. Even though we eventually removed bent and

supercoiled helices from the data set, we adopted the procedure described by Walther *et al.* in ref. [4], in which a local axis is associated to every consecutive residue pair along the helix, since local distortions could as well occur for straight helices, due for instance to experimental uncertainties in the protein structure determination. The overall axis is thus a broken line consisting of short segments.

Conclusions

We show that the calculation of the probability distribution of interaxial angles between random finite helices which are in contact is not a trivial geometric problem, because of the approximations introduced to ensure face-to-face packing between contacting helices. Such approximations are unavoidable, due to the imperfect shape of natural occurring helices which do not have well defined axes and to experimental uncertainties in the determination of protein structures. Although analytical results can be found to estimate the correct reference distribution, the simplest way to obtain it consists in using numerical simulations. We have presented a re-analysis of the distribution of packing angles rescaled with our new reference distribution finding a remarkable agreement with the packing angles predicted by steric models [4].

Acknowledgements

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