



Designability landscape reveals sequence features that define axial helix rotation in four-helical homo-oligomeric antiparallel coiled-coil structures



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ABSTRACT

Coiled coils are widespread protein domains comprising α -helices wound around each other in a regular fashion. Owing to their regularity, coiled-coil structures can be fully described by parametric equations. This in turn makes them an excellent model for studying sequence–structure relationships in proteins. Here, we used computational design to identify sequence features that determine the degree of helix axial rotation in four-helical homo-oligomeric antiparallel coiled coils. We designed 135,000 artificial sequences for a repertoire of backbone models representing all theoretically possible axial rotation states. Analysis of the designed sequences revealed features that precisely define the rotation of the helices. Based on these features we implemented a bioinformatic tool, which given a coiled-coil sequence, predicts the rotation of the helices in its structure. Moreover, we showed that another structural parameter, helix axial shift, is coupled to helix axial rotation and that dependence between these two parameters narrows the number of possible axial rotation states.

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1. Introduction

Coiled-coil domains are simple protein structural motifs, consisting of two or more α -helices that are wound around each other and may run in the same (parallel) or in opposite (antiparallel) directions (Lupas and Gruber, 2005). Coiled coils are characterized by a specific interaction mode termed knobs-into-holes (Crick, 1953, 1952), in which a residue from one helix (knob) packs into a cavity formed by side-chains of the facing helix (hole). The knobs-into-holes packing requires that the involved side-chains occupy periodically equivalent positions along the helix interface. This is not possible with an undistorted helix, which have 3.6 residues per turn, where the position of side-chains in their surface drifts continuously. For this reason in coiled coils the number of residues per turn is effectively (with respect to the bundle axis) reduced to 3.5 by bending the helices, and thus allowing the posi-

tion of side-chains to repeat after two helical turns (7 residues). Positions of these seven-residue sequence repeats, referred to as heptad repeats, are labeled *a–g*: the core-forming positions (*a* and *d*) are usually occupied by hydrophobic residues, whereas the remaining, solvent-exposed positions (*b*, *c*, *e*, *f*, and *g*) are dominated by hydrophilic residues (Fig. 2). The regularity of heptad repeat allows a relatively easy prediction of coiled coils in sequences (Gruber et al., 2006).

The canonical *a–d* hydrophobic core can be extended by global axial rotation of all helices by about 26° (Fig. 1) (Dunin-Horkawicz and Lupas, 2010a; Lupas and Gruber, 2005). The rotation shifts the relative position of residues and leads to the transformation of knobs-into-holes packing into a variant called knobs-to-knobs (Fig. 2). In contrast to knobs-into-holes packing, in which the hydrophobic core is formed by two positions (*a* and *d*), knobs-to-knobs uses three. When viewed from the N-terminus of the helix, a clockwise rotation brings position *g* of the heptad into the core whereas the counter-clockwise rotation will do so with the position *e*. The positions of an extended hydrophobic core can assume two distinct geometries: an *x* layer, if the side-chains point towards the center of the coiled-coil bundle, or a *da* layer, if the two side-chains point side-ways, enclosing a central cavity (note that *x* and *da* represent structural nomenclature and *da* should not be

Abbreviation: SVR, support vector regression.

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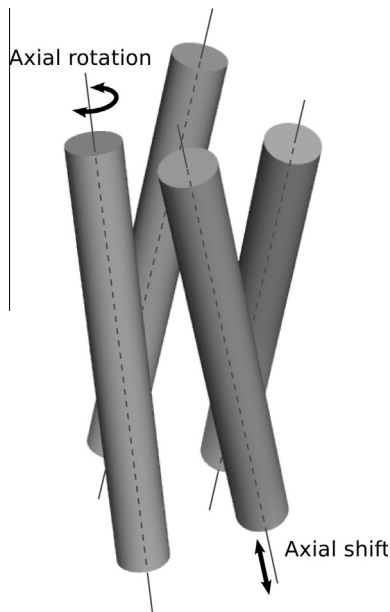


Fig. 1. Helix axial rotation and helix axial shift in four-helical antiparallel coiled coils. A schematic representation of a four-helical homo-oligomeric antiparallel coiled-coil bundle is shown. The two basic motions investigated in this study, helix axial rotation and helix axial shift, are indicated with arrows.

confused with positions *d* and *a* of a heptad). In the *a-d-g* core, positions *g* and *a* form the *da* layer and position *d* forms the *x* layer. Similarly, in the *a-d-e* core, positions *d* and *e* assume *da* geometry and position *a* forms the *x* layer (Fig. 2). The knobs-to-knobs packing is almost invariably observed in coiled coils where the helices are arranged in antiparallel fashion. This is because the *x* and *da* layers alternate along the helices and, therefore, the geometrically most favorable packing is achieved when the two pairs of diagonally opposite helices run in an inverse direction and the *x* layers in one pair are combined with *da* layers in the other (Lupas and Gruber, 2005).

The regular nature of coiled coils, resulting from the presence of a repeating heptad pattern, allows us to readily describe their structures by parametric equations (Lupas and Gruber, 2005). The structural parameterization allows for the detection of coiled-coil motifs in structures (Walshaw and Woolfson, 2001), quantification of the properties of coiled-coil structures solved

experimentally (Dunin-Horkawicz and Lupas, 2010a; Grigoryan and Degrado, 2011; Strelkov and Burkhard, 2003) and the generation of models for coiled coils with predefined properties (Grigoryan and Degrado, 2011; Offer et al., 2002). The parametrization-based tools together with a wealth of available coiled-coil structural data (Testa et al., 2009) provides an opportunity to perform global analyses focusing on the individual parameters of coiled-coil structures (Grigoryan and Degrado, 2011). It must be emphasized that the local structural parameters of many experimentally-determined coiled coils deviate from those expected from the parametrization. In a previous study, we implemented a method that measures such local deviations (Dunin-Horkawicz and Lupas, 2010a) and by employing this method we showed that coiled coils rarely assume an ideal *x-da* packing in which helices are rotated by $+26^\circ$ or -26° and residues in positions *x* point directly towards the bundle axis. Instead, a continuum of axial rotational states was observed, implying that *x-da* packing does not correspond to two well-defined structural states.

It is intuitive that the presence of small hydrophobic residues in either *e* or *g* position triggers formation of *a-d-e* or *a-d-g* packing, respectively. For example, Lac repressor tetramerization domain (PDB code: 1lbi) has natively two alanines in position *e* and adopts *a-d-e* packing. Also in tyrosine hydroxylase tetramerization domain (PDB: 1toh, 2toh, and 2xsn) *a-d-e* packing appears to be induced by the presence of alanine in one of the *e* positions. Similarly, mutating a single glutamate of GCN4-pLI in position *e* to cysteine (PDB: 2ccn) yielded *a-d-e* packing. Although all of these structures adopt *a-d-e* packing, they differ substantially in terms of axial helix rotation. In the first two structures helices are rotated by -16° , while in the last one they are rotated by only -6° . This raises the question what sequence features determine the degree of axial helix rotation. Some answers can be derived from the analyses of HAMP domain; a four-helix coiled coil involved in modulation of signal transduction by chemoreceptors and histidine kinases (Dunin-Horkawicz and Lupas, 2010b). Its structure does not assume a single axial rotation state, but it alternates between knobs-into-holes and knobs-to-knobs packing. It must be however emphasized that the HAMP domain, in contrast to the aforementioned examples, is a parallel coiled coil and thus its *x-da* layers have a very unusual architecture comprising both *e* and *g* positions (Hulko et al., 2006). Bioinformatics analyses of HAMP domains demonstrated that, as expected, heptad positions *e* and *g* forming the knobs-to-knobs core tend to be small and hydrophobic (Dunin-Horkawicz and Lupas, 2010b). However, structural studies of HAMP domain variants revealed that side-chain size of a single

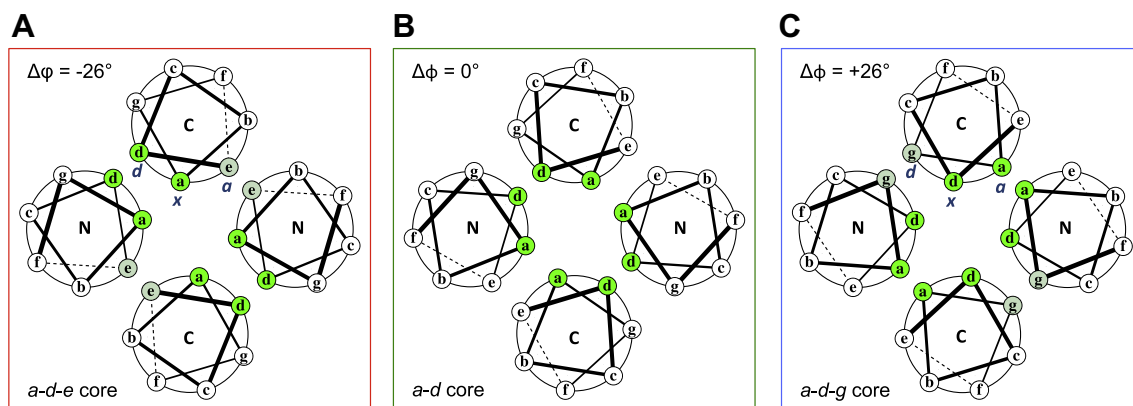


Fig. 2. Helix axial rotation in four-helical antiparallel coiled coils. Helical wheel-diagrams depict (A) *a-d-e*, (B) *a-d*, and (C) *a-d-g* hydrophobic cores in an antiparallel four-helix coiled coil starting with heptad position *f*. Canonical hydrophobic core positions *a* and *d* are shown in green, whereas positions co-opted to the core (*e* or *g*) in *x-da* packing are shown in light green. A transition between *x-da* packing and knobs-into-holes packing requires rotation of the helices in the same direction, thus, in antiparallel coiled coils the adjacent helices appear to be rotated in opposite direction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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