Minireview

Complementary packing of α-helices in proteins

Alexander V. Efimov*

Institute of Protein Research, Russian Academy of Sciences, 142292 Pushchino, Moscow Region, Russia

Received 18 October 1999

Edited by Vladimir Skulachev

Abstract The packing of α-helices in proteins is restricted by both the principle of close packing and the chemical nature of side chains. As a result, (1) α-helical surfaces forming the interface should be complementary to each other, (2) hydrophobic stripes of the α-helices should fit together like pieces of a jigsaw puzzle, and (3) buried polar side chains (if there are any) should be arranged in a complementary fashion.

Key words: Complementarity; Helix packing; Hydrophobic stripe; Packing angle; Protein structure

1. Introduction

The α-helix is one of the main secondary structural elements of proteins. Analysis of observed helix-helix associations shows that α-helices pack in one of three characteristic arrangements, aligned parallel or anti-parallel, orthogonal, or slanted. A reason for such packing preferences is that in proteins α-helices pack closely and, therefore, their assemblies are subject to strong packing constraints dictating their mutual orientations. Side chains of the interacting α-helices should fit together in a complementary fashion, without holes or misfits. Several models for the packing of α-helices have been developed and are mostly devoted to surface complementarities upon packing [1–6]. The chemical nature of amino acid residues was not considered in most of these models. However, mutual arrangements of α-helices also depend on the distribution of hydrophobic and polar side chains on the surfaces as their hydrophobic faces should be pointed to the protein hydrophobic core or to each other and polar faces to the solvent. Amphipathic α-helices having continuous hydrophobic stripes on their surfaces can be packed in a face-to-face (apolar) or side-by-side (polar) manner [7–9]. Hydrophobic stripes of the closely packed α-helices are shown to fit together in a complementary fashion like pieces of a jigsaw puzzle.

This paper presents a survey of these models as well as some examples of complementary packing of α-helices from known proteins.

2. Models for the packing of α-helices based on geometric constraints

The first detailed model for the helix-to-helix packing was proposed by Crick in 1953 [1]. In this model a side chain from one α-helix (knob) packs into a space surrounded by four side chains of the opposite α-helix (hole) and vice versa. This model gives two preferred orientations of the closely packed α-helices, $\Omega = 20°$ and $\Omega = -70°$ (Ω denotes the torsion angle between the helix axes). This 'knobs-into-holes' model for helix packing continues to be relevant, especially for coiled coils.

According to the 'ridges-into-grooves' model developed by Chothia et al. [2,3], α-helices pack with the ridges on one α-helix packing into the grooves of the other and vice versa. The ridges and grooves are formed by residues whose separation in the amino acid sequence is four, three or one. According to this model, there are three basic packing classes with characteristic packing angles of −105°, −52° and +23°. The model was shown to be in good agreement with the experimentally observed helix-to-helix packings.

Richmond and Richards [4] also suggested three possible classes of helix-to-helix packings and concluded that the packing angle is inversely correlated with the size of the residue at the centre of the interface, the distance between the helix axes and the number of residues forming contacts across the interface. Reddy and Blundell [10] found that the inter-helix distance is correlated with the volume of residues in the packing interface and used this correlation to predict inter-helix distances of structurally equivalent helices in homologous proteins. Murzin and Finkelstein [5] concluded that the geometries of the α-helices packed around a central core can be described by polyhedrons. They attempted to explain the general assembly of α-helices into the core by arranging them in polyhedral shells. Recently, the lattice superposition model that treats the packing problem on the basis of individual side chains as the smallest packing unit has been developed [6]. In this work, the helix-to-helix packing is considered from a purely mathematical perspective and only three solutions for the perfect superposition of α-helical lattices have been demonstrated. The application of the model suggests that the packing of amino acid residues is best described by the 'knobs-into-holes' scheme rather than by a 'ridges-into-grooves' one.

3. Face-to-face and side-by-side packings of amphipathic α-helices

In proteins, the packing of α-helices is restricted by both the principle of close packing and the chemical nature of the side chains. As a rule, α-helices are amphipathic and pack so that their hydrophobic faces are buried in a hydrophobic core and polar side chains are accessible to the solvent [11–13]. There are two main ways that amphipathic α-helices pack against each other [7–9]. In the first case, two α-helices are

*Fax: (7) (095) 924 04 93.
E-mail: efimov@protres.ru

PII: S0014-5793(99)01507-0

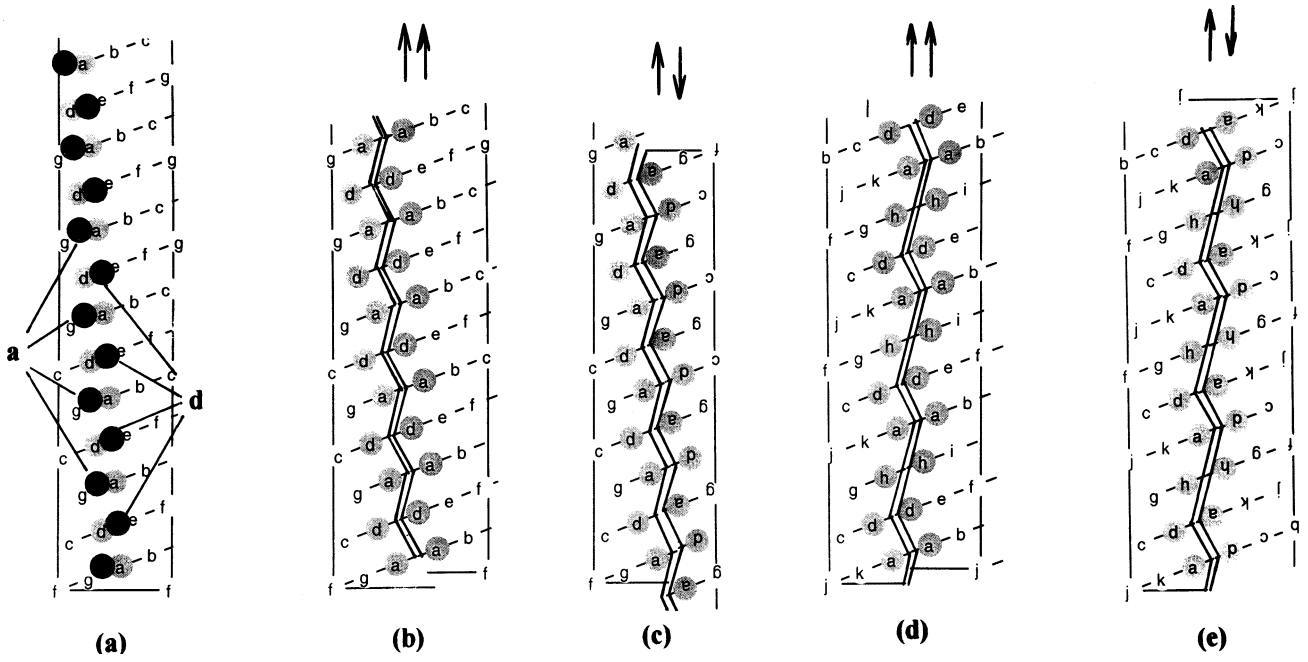

Fig. 1. Examples of complementary packings of amphipathic α-helices shown with α-helical net layouts. a: Parallel face-to-face packing of two α-helices having minimal hydrophobic stripes produced by heptad repeats. The 'bottom' α-helix is shown as the α-helical net layout (shaded circles are hydrophobic residues). For clarity, only the hydrophobic residues of the 'upper' α-helix (solid circles) are shown. b, c: Parallel and anti-parallel side-by-side packings of α-helices with hydrophobic stripes formed by heptad repeats. d, e: Parallel and anti-parallel packings of α-helices having hydrophobic stripes produced by 11-residue repeats.

packed so that their hydrophobic side chains form a double layer in the packing interface. Here, hydrophobic stripes of the α-helices interact in a face-to-face manner and hence this is referred to as a face-to-face packing of α-helices (initially called apolar packing [7,8]). In the case of a side-by-side packing of α-helices, their hydrophobic stripes associate in a side-by-side manner and form a common hydrophobic surface of the bihelical structure while the opposite surface is predominantly formed by polar side chains (this was initially called polar packing [7,8]).

To simplify a more detailed description of these packings, let us consider α-helices having a minimal number of hydrophobic side chains. A stereochemical analysis showed that there should be at least one hydrophobic residue per turn of the α-helix and side chains of these residues should be arranged so as to form a continuous hydrophobic stripe on one side of the α-helix. Such minimal hydrophobic stripes can be of three types, those formed by hydrophobic residues in positions 1-4-8-11-15-18-..., 1-4-8-12-15-19-23-..., and 1-5-9-13-..., respectively [14,15]. The sequence encoding the first type of stripe shows a heptad repeat in the chemical nature of side chains similar to that in coiled coils [16–18]. The seven positions of repeats are conventionally referred to as positions a–g, where a and d are hydrophobic. The sequence encoding the second type of stripe is characterised by an undecatad repeat and the 11 residues are denoted a–k, where a, d and h are hydrophobic. The sequence producing the third type of stripe may be represented as four-residue repeats.

Fig. 1a represents interactions between α-helices packed in a face-to-face manner. In this packing, both the α-helices have minimal hydrophobic stripes produced by heptad repeats. The packing of side chains in the interface obeys the normal 'knobs-into-holes' scheme similar to that described for coiled coils [1,16]. Such packing of α-helices occurs in known two-stranded coiled coils, for example, in the dimer formed by the Asn16Aba mutant of the GCN4 leucine-zipper peptide [19], in the linker domain of human topoisomerase I [20] and in the hepatitis delta antigen [21].

Fig. 1b–e shows some variants of parallel and anti-parallel side-by-side packings of α-helices having hydrophobic stripes produced by heptad and undecatad repeats. There is an exquisite complementarity between the hydrophobic stripes of the α-helices that fit together like pieces of a jigsaw puzzle. It is noteworthy that the best fitting takes place when both α-

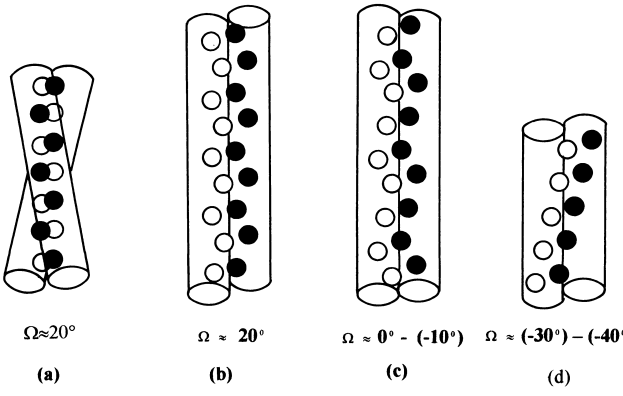

Fig. 2. Schematic presentation of complementary packings of α-helices and the corresponding packing angles *Ω*. α-Helices are shown as cylinders. Hydrophobic residues forming the minimal hydrophobic stripes are shown by solid and open circles. In each case, parallel and anti-parallel orientations of α-helices may occur. a, b: Face-to-face and side-by-side packings of α-helices having hydrophobic stripes produced by heptad repeats, respectively. c: Side-by-side packing of α-helices with hydrophobic stripes formed by 11-residue repeats. d: Side-by-side packing of α-helices with hydrophobic stripes formed by four-residue repeats.

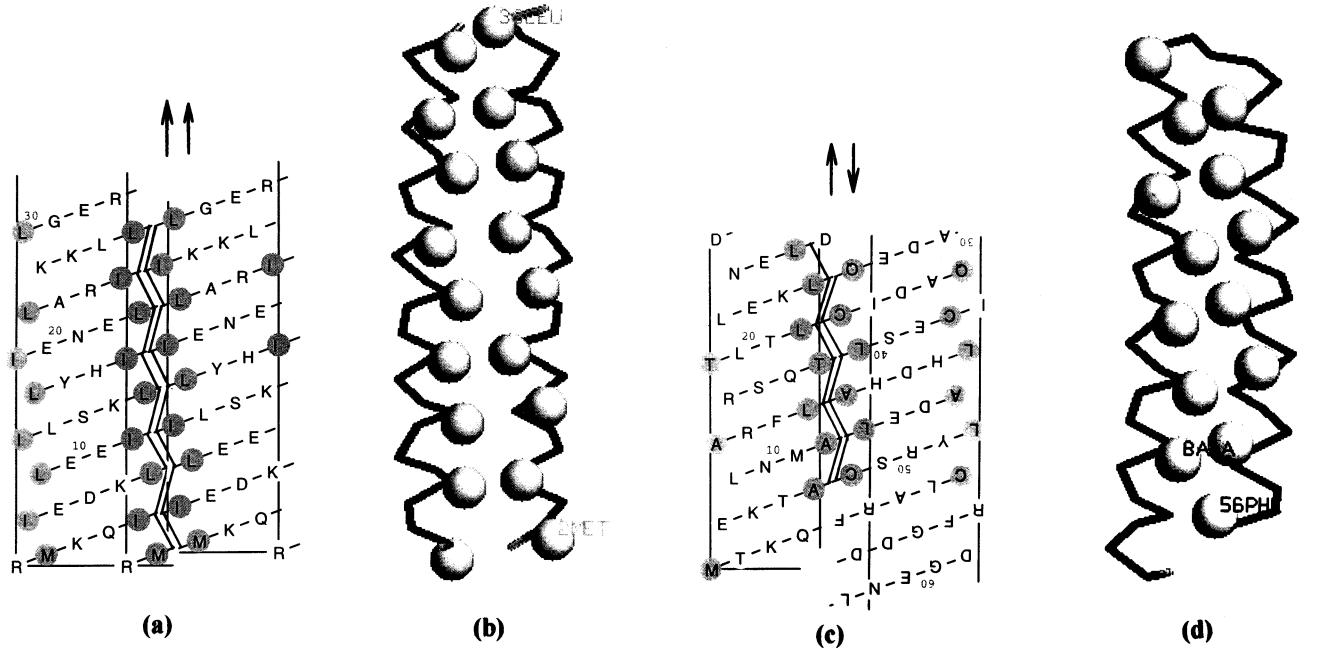

Fig. 3. Examples of α-helices packed in a side-by-side manner from known protein structures. a, b: Two adjacent α-helices in the tetramer formed by the GCN4 Zip mutant pLI [23] (PDB code 1GCL) drawn with the α-helical nets and the program RasMol [24]. c, d: Anti-parallel packing of α-helices in the α-α-hairpin of ROP [25] (PDB code 1ROP) is shown similar to that in a and b. Shaded circles in a and c and grey balls in b and d show residues forming minimal hydrophobic stripes of the α-helices.

helices have hydrophobic stripes of the same type, for example, both stripes produced by heptad repeats (Fig. 1b,c) or both stripes formed by 11-residue repeats (Fig. 1d,e). In the bihelical structures shown in Fig. 1b,c, the packing of side chains in the interfaces obeys the 'knobs-into-holes' model although the interface in each case is formed by a different set of side chains and differs from that of α-helices packed in the face-to-face manner (Fig. 1a). The packing of side chains in the interfaces of the bihelical structures represented in Fig. 1d,e does not obey the 'knobs-into-holes' scheme, although the hydrophobic stripes fit together in a complementary fashion. A more detailed analysis of these and other variants of side-by-side packings of α-helices is described elsewhere [9].

There is a relationship between the packing angle Ω and the geometry of minimal hydrophobic stripes of closely packed α-helices [9,14,15]. If both α-helices have the minimal hydrophobic stripes formed by heptad repeats, they should be packed at $\Omega \approx 20°$. This angle is observed in the face-to-face and side-by-side packings (Fig. 2a,b). Long and regular α-helices with minimal hydrophobic stripes produced by 11-residue repeats pack closely at a small negative packing angle similar to that in the right-handed coiled coil [22]. In globular proteins, relatively short α-helices having such stripes can be packed at Ω values from about 0 to -10–$15°$ (Fig. 1c). If both α-helices have minimal hydrophobic stripes formed by residues in positions 1-5-9-13-..., they are packed at $\Omega \approx -40°$ (Fig. 2d).

Examples of parallel and anti-parallel side-by-side packings of α-helices from known proteins are presented in Fig. 3 (for some other examples, see [8,9]). In both cases, the α-helices have minimal hydrophobic stripes produced by heptad repeats. The main features of these structures are in good agreement with the modelled structures presented in Figs. 1 and 2.

Note that a pair of α-helices packed in a side-by-side manner has a large hydrophobic surface on one side. To bury the hydrophobic surface, these α-helices take part in the formation of higher-order structures, for example three-, four- or five-stranded coiled coils. In contrast, parallel and anti-parallel two-stranded coiled coils are formed by α-helices packed in a face-to-face manner.

4. Complementary arrangement of buried polar side chains

Although hydrophobic side chains are usually found in the interior of proteins and polar side chains on the exterior, many known proteins contain some buried charged or polar chemical groups [26,27]. In general, when polar or charged groups are buried, they have partners to form hydrogen or salt bonds and therefore are said to be 'compensated'. A rearrangement of secondary structural elements to obtain alternative packing of the elements results in a buried polar side chain packing against hydrophobic residues and, due to the large penalty for burying 'uncompensated' polar groups, this may drastically destabilise the alternative structures. Thus, complementary buried polar interactions may play an important role in the specificity of α-helix packing. For example, in the GCN4 leucine zipper and its Asn16Lys mutant, the buried asparagine or lysine selectively favours the parallel dimeric coiled coil [28]. A single buried polar interaction can specify either a parallel or an anti-parallel helix orientation in a two-stranded coiled coil [29]. A stereochemical analysis shows that buried polar interactions can prevent shifting of α-helices relative to each other and discriminate between the face-to-face and side-by-side packings of α-helices [9].

Acknowledgements: I thank Dr. E.V. Brazhnikov for his help in drawing the figures. This work was supported in part by the Russian Foundation for Basic Research (Grant 98-04-48252).

References

[1] Crick, F.H.C. (1953) Acta Crystallogr. 6, 689–697.
[2] Chothia, C., Levitt, M. and Richardson, D. (1977) Proc. Natl. Acad. Sci. USA 74, 4130–4134.
[3] Chothia, C., Levitt, M. and Richardson, D. (1981) J. Mol. Biol. 145, 215–250.
[4] Richmond, T.J. and Richards, F.M. (1978) J. Mol. Biol. 119, 537–555.
[5] Murzin, A.G. and Finkelstein, A.V. (1988) J. Mol. Biol. 204, 749–769.
[6] Walther, D., Eisenhaber, F. and Argos, P. (1996) J. Mol. Biol. 255, 536–553.
[7] Efimov, A.V. (1977) Dokl. Akad. Nauk. SSSR 235, 699–702.
[8] Efimov, A.V. (1979) J. Mol. Biol. 134, 23–40.
[9] Efimov, A.V. (1999) J. Mol. Biol. (submitted).
[10] Reddy, B.V.B. and Blundell, T.L. (1993) J. Mol. Biol. 233, 464–479.
[11] Perutz, M.F., Kendrew, J.C. and Watson, H.C. (1965) J. Mol. Biol. 13, 669–678.
[12] Schiffer, M. and Edmundson, A.B. (1967) Biophys. J. 7, 121–135.
[13] Lim, V.I. (1974) J. Mol. Biol. 88, 857–872.
[14] Efimov, A.V. (1982) Mol. Biol. (Moscow) 16, 271–281.
[15] Efimov, A.V. (1993) Prog. Biophys. Mol. Biol. 60, 201–239.
[16] McLachlan, A.D. and Stewart, M. (1975) J. Mol. Biol. 98, 293–304.
[17] Cohen, C. and Parry, D.A.D. (1994) Science 263, 488–489.
[18] Lupas, A. (1996) Trends Biochem. Sci. 21, 375–382.
[19] Gonzalez Jr., L., Brown, R.A., Richardson, D. and Alber, T. (1996) Nature Struct. Biol. 3, 1002–1010.
[20] Stewart, L., Redinbo, M.R., Qiu, X., Hol, W.G.J. and Champoux, J.J. (1998) Science 279, 1534–1541.
[21] Zuccola, H.J., Rozzelle, J.E., Lemon, S.M., Erickson, B.W. and Hogle, J.M. (1998) Structure 6, 821–830.
[22] Harbury, P.B., Plecs, J.J., Tidor, B., Alber, T. and Kim, P.S. (1998) Science 282, 1462–1467.
[23] Harbury, P.B., Zhang, T., Kim, P.S. and Alber, T. (1993) Science 262, 1401–1407.
[24] Sayle, R. and Milner-White, J. (1995) Trends Biochem. Sci. 20, 374–376.
[25] Castagnoli, L., Scarpa, M., Kokkinidis, M., Banner, D.W., Tsernoglou, D. and Cesareni, G. (1989) EMBO J. 8, 621–629.
[26] Barlow, D.J. and Thornton, J.M. (1983) J. Mol. Biol. 168, 867–885.
[27] Rashin, A.A. and Honig, B. (1984) J. Mol. Biol. 173, 515–521.
[28] Gonzalez Jr., L., Woolfson, D.N. and Alber, T. (1996) Nature Struct. Biol. 3, 1011–1018.
[29] Oakley, M.G. and Kim, P.S. (1998) Biochemistry 37, 12603–12610.