Correlations of Amino Acids with Secondary Structure Types: Connection with Amino Acid Structure

Saša Malkov,1 Miodrag V. Živković,1 Miloš V. Beljanski,2 Snežana D. Zaric3*

1 Department of Mathematics, University of Belgrade, Belgrade, Serbia and Montenegro
2 Institute of General and Physical Chemistry, Belgrade, Serbia and Montenegro
3 Department of Chemistry, University of Belgrade, Belgrade, Serbia and Montenegro, szaric@chem.bg.ac.yu

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The correlations of primary and secondary structures were analyzed using proteins with known structure from Protein Databank. The correlation values of amino acid type and the eight secondary structure types at distant position were calculated for distances between -25 and 25. Shapes of the diagrams indicate that amino acids polarity and capability for hydrogen bonding have influence on the secondary structure at some distances. Clear preference of most of the amino acids towards certain secondary structure type classifies amino acids into four groups: α-helix admirers, strand admirers, turn and bend admirers and the others. Group four consists of His and Cis, the amino acids that do not show clear preference for any secondary structure. Amino acids from a group have similar physicochemical properties, and the same structural characteristics. The results suggest that amino acid preference for secondary structure type is based on the structural characteristics at Cβ and Cγ atoms of amino acid. α-helix admirers do not have polar heteroatoms on Cβ and Cγ atoms, nor branching or aromatic group on Cβ atom. Amino acids that have aromatic groups or branching on Cβ atom are strand admirers. Turn and bend admirers have polar heteroatom on Cβ or Cγ atoms or do not have Cβ atom at all. Our results indicate that polarity and capability for hydrogen bonding have influence on the secondary structure at some distance, and that amino acid preference for secondary structure is caused by structural properties at Cβ or Cγ atoms.

Key words: proteins, amino acid, protein secondary structure, statistical correlation.

Introduction

The prediction of protein structure from its sequence is fundamental problem and its solution is goal of all protein folding theories. There are many methods that consider protein folding (1-15) and many of them use some information about the protein secondary structure (1, 3, 8-16).

The principle that secondary structures of proteins are determined by their amino acid sequence is a basis of the protein secondary structure prediction methods. It is known for long time that different amino acids have distinct propensities for the adoption of helical, strand, and random coil conformation (17, 18-23). There are many secondary structure prediction algorithms that are based on these propensities (24). Correlation of amino acid and secondary structure is also important for de novo protein design.

Furthermore, amino acids propensities are position dependent. It is known that amino acids show distinct position-dependent helix-forming propensities near the ends of α-helices (25). It also was shown that the amino acids have very strong position-dependent propensities throughout the length of a helix. These propensities are connected to amino acids hydrophobicity (26, 27). In β-strands alternating hydrophobic/polar patterns are very frequent (28).

Although individual amino acids show intrinsic propensities towards certain secondary structure type (18-23), these preferences are modulated by the sequence segments within which they reside (29-31). Moreover, any amino acid in the protein could have influence on secondary structure type at certain position. It is practically impossible to consider the influence of the complete amino acid sequence (R1, R2, ... Rn) on the secondary structure type Sj at the fixed position j. It is therefore necessary to limit the analysis to a local segment of the amino acid sequence. Local structural information is often contained in local parts of sequences (32, 33). It is estimated that local information contains roughly 65% of the secondary structure information (34). There are also approaches that consider non-local interactions in the sequence (35-38).

In order to check influence of local segment on the secondary structure type Sj it is natural to consider the symmetrical window in the amino acid sequence centered at position j. The width of the window has to be chosen in the way that: (i) the influence of the rest of the sequence on
Statistical approach to the protein secondary structure prediction is usually based on amino acids propensities to be part of different types of secondary structures (18). The propensity of the amino acid \( A \) towards the secondary structure \( S \) is the quotient of probability (relative frequency) of \( A \) inside \( S \) and the overall probability of \( A \),
\[
P_{A|S} = \frac{P(A|S)}{P(A)} = \frac{n_{A,S}}{n_S} / \frac{n_A}{n},
\]
where \( n_{A,S} \), \( n_S \), \( n_A \), and \( n \) are the numbers of occurrences of \( A \) as parts of \( S \), occurrences of \( S \), occurrences of \( A \), and the sample size, respectively (40).

More advanced information content is based on propensities and defined by
\[
I(S,A) = \log(P_{A|S}) - \log(P_{A,S}) = \log \left( \frac{n_{A,S}}{n_S} \right) - \log \left( \frac{n_{A,S}}{n_{A,S}} \right).
\]
(41). Here \( \neg S \) denotes the appearance of "non \( S \)" secondary structure.

Correlations of amino acids with secondary structure types are used to predict protein structure, but they are also important for understanding the forces that stabilize protein structures. Increasing number of proteins with known structure, makes the correlations more reliable and better represents the interactions in proteins. Noncovalent interactions play important role in stabilizing tertiary structures of proteins and there are many types of noncovalent interactions that should be considered. The analysis of data from Protein Data Bank (PDB) (42) enabled to elucidate different kind of noncovalent interactions in proteins (43, 44). It was found out that new type of cation-π interactions, interactions of ligands coordinated to a metal with aromatic groups of amino acid residues, play role in stabilizing structure of proteins (43).

In this paper we describe the influence of amino acids on secondary structure types. Secondary structure types are \( \alpha \)-helix (H), isolated \( \beta \)-bridge (B), extended strand (E), 3-helix (G), 5-helix (I), hydrogen bonded turn (T), and bend (S) (45). All other structural elements, not belonging to these secondary structure types, are considered coil and denoted by C. Here we consider all eight secondary structure types, including coils.

**Method**

Secondary structure types are assigned by DSSP (45). They are denoted using letters: H for \( \alpha \)-helix, B for isolated \( \beta \)-bridge, E for extended strand, G for 3-helix, I for 5-helix, T for hydrogen bonded turn and S for bend. All other structural elements, not belonging to these secondary structure types, are considered coil and denoted by C. Here we consider all eight secondary structure types, including coils.

**Computational Model**

Consider a set \( P \) of \( n \) protein chains. Primary structures of these protein chains are described by sequences \( a_1, ..., a_n \). If \( \text{len}(i) \) denotes the length of the sequence \( a_i \), then residues of the sequence \( a_i \) are \( a_{i,1}, ..., a_{i,\text{len}(i)} \), \( 1 \leq i \leq n \). The corresponding assigned secondary structures are described by sequences \( b_1, ..., b_n \), where \( b_i \) is a sequence \( b_{i,1}, ..., b_{i,\text{len}(i)} \), \( 1 \leq i \leq n \).

If \( A \) is a logical expression, then the indicator variable \( I(A) \) is defined by:
\[
I(A) = \begin{cases} 
1, & A = \text{true} \\
0, & A = \text{false} 
\end{cases}
\]

Let \( X_j(s) = I(b_j = s) \) and \( Y_p(p) = I(a_{ij} = p) \) denote binary random variables corresponding to events that the secondary structure type assigned to residue \( a_{ij} \) is \( s \), and that \( a_{ij} \) is the amino acid \( p \), respectively. Consider the window in the sequence \( i \), centered at the position \( j \). Let
\[
Z_{ij}(s, p, \tau) = X_j(s) - Y_{ij}(p)
\]
denote the random variable corresponding to the joint event that the secondary structure type assigned to \( a_{ij} \) (amino acid in the center of the window) is \( s \) and that \( a_{ij} \) is the amino acid \( p \). Let \( S(\tau) \) denote the set of valid pairs \((i,j)\):
\[
S(\tau) = \{(i,j) | 1 \leq j, j + \tau \leq \text{len}(i)\}
\]

Let \( T(\tau) \) denote the size of \( S(\tau) \).

Let us now introduce some notation. \( NPS(s, p, \tau) \) - the number of times the amino acid \( p \) occurs at distance \( \tau \) from the position \( j \), where the secondary structure type is \( s \).
\[
NPS(s, p, \tau) = \sum_{j} Z_j(s, p, \tau) ;
\]
\[
NP(p, \tau) - \text{the number of occurrences of amino acid } p \text{ at positions } j+\tau \text{ such that the position } j \text{ is inside the same chain, for all secondary structure types } s:
\]
\[
NP(p, \tau) = \sum_{s} NPS(s, p, \tau) ;
\]
\[
NS(s, \tau) - \text{the number of times the secondary structure type } s \text{ is assigned at the position } j, \text{ such that the position } j+\tau \text{ is inside the same chain:}
\]
\[
NS(s, \tau) = \sum_{p} NPS(p, s, \tau) .
\]

The total count of valid sample pairs at distance \( \tau \) is
\[
T(\tau) = \sum_{p,s} NPS(s, p, \tau) . \quad (2)
\]

The correlation coefficient of random variables \( X \) and \( Y \) is defined by
\[
\rho(X,Y) = \frac{\text{Cov}(X,Y)}{\sqrt{\text{Var}(X) \cdot \text{Var}(Y)}} .
\]
(see (48), for example). If both variables are binary, then
\[
\rho(X,Y) = \frac{XY - X \cdot Y}{\sqrt{(X-\bar{X})(Y-\bar{Y})}} .
\]

The correlation coefficient is always in the range \([-1, 1]\). It is 0 if \( X \) and \( Y \) are independent. The correlation coefficient is 1 or -1 if and only if the random variables are linearly dependent.

Consider the correlation of random variables \( X_k \) and \( Y_{ik} \),
\[
\rho(X_k(Y_{ik}),Y_{aj}) = \frac{Z_k(s, p, \tau) - X_k(s) Y_{aj}(p)}{\sqrt{X_k(s)(1-X_k(s))Y_{aj}(p)(1-Y_{aj}(p))}} ,
\]
where \( k = j+\tau \) and \( Z_k(s, p, \tau) \) is defined by Equation 1. Assuming that distributions of \( X_k \) and \( Y_{aj} \) depend on \( p, s \) and \( \tau \) only (i.e. they are independent on the sequence choice and the absolute position inside the sequence), we estimate the correlation coefficients at offset \( \tau \) by
\[
\rho(p, s, \tau) = \frac{Z(s, p, \tau) - X(s, \tau) Y(p, \tau)}{\sqrt{X(s, \tau)(1-X(s, \tau))Y(p, \tau)(1-Y(p, \tau))}} .
\]

The estimates of means of \( X \), \( Y \) and \( Z \) are
\[
\bar{X}(s, \tau) = NS(s, \tau)/T(\tau) ,
\]
\[
\bar{Y}(p, \tau) = NP(p, \tau)/T(\tau) ,
\]
\[
\bar{Z}(s, p, \tau) = NPS(s, p, \tau)/T(\tau) .
\]

Hence the correlation coefficient estimate is
\[
\rho(p, s, \tau) = \frac{NPS(s, p, \tau)T(\tau) - NP(p, \tau)NS(s, \tau)}{\sqrt{NP(p, \tau)T(\tau) - NP(p, \tau)NS(s, \tau)(T(\tau) - NS(s, \tau))}} \quad (3)
\]

The value of \( \rho(p, s, \tau) \) is positive (negative, zero) if the pair \((p, s)\) occurs more (less, equally) frequently at the distance \( \tau \) than it would occur if \( p \) and \( s \) were independent at the distance \( \tau \).

In order to evaluate the significance of the correlation coefficient, we compute the statistics \( t_\tau \)
\[
t_\tau = \rho \sqrt{\frac{n-2}{1-\rho^2}} ,
\]
where \( n = T(\tau) \). Under assumption that the correlation coefficient is 0, the distribution of the statistics \( t_\tau \) is \( t \)-distribution with \( n-2 \) degrees of freedom (see (48) for example).

If the sample size \( n \) is large, then \( t \)-distribution is approximated by the normal distribution \( N(0,1) \). Let the null hypothesis be that \( X \) and \( Y \) are independent, i.e. that there is no dependence of the secondary structure type \( s \) and amino acid \( p \) at distance \( \tau \). The null hypothesis is considered false if it implies that the probability to obtain correlation coefficient estimate with absolute value greater than calculated is less than 0.001. If the null hypothesis is true, using the normal distribution approximation we obtain that the probability of the event "\( |t_\tau| \) is greater than \( t_{lim} \)" is 0.05 for \( t_{lim} = 1.96 \). Hence, the correlation coefficient is significant, and we consider \( X \) and \( Y \) are dependent if \( |t_\tau| \geq 1.96 \). If we denote the corresponding value of the correlation coefficient by \( \rho_{lim} \), then the correlation coefficient is significant if
\[
|\rho| \geq \rho_{lim} = \frac{t_{lim}}{\sqrt{t_{lim}^2 + n - 2}} = \frac{1.96}{\sqrt{3.84 + n}} \quad (4).
\]

Data Sets

As a source of protein data we used Protein Data Bank (PDB), release #103 from January 2003, containing 18482 proteins (42). The secondary structures assignment is performed by the program DSSP (45). There are many families of proteins that are overrepresented in PDB. The full set of protein sequences is filtered to eliminate redundant data - we used the PDBSELECT list of nonredundant protein chains (49), with the threshold 25%. The resulting set contains 1737 sequences with 282,329 amino acid residues. The sample size ranges from 244,329 (for \( |\tau| = 25 \)) to 282,329 (for \( \tau = 0 \)). The corresponding values of \( \rho_{lim} \) are 0.0040 (for \( |\tau| = 25 \)) and 0.0037 (for \( \tau = 0 \)).

Results and Discussion

The values of correlation of amino acids with secondary structure types are computed for the PDBSELECT subset of protein sequences using Equation 3. The 8160 correlation values are calculated (8 types of secondary structures, 20 amino acids and 51 offsets). Based on correlation values amino acids are classified in four groups according to their preferences to participate in secondary
structures (Table I). The groups are: α-helix admirers, strand admirers, turn and bend admirers, and the fourth group consists of amino acids that do not show preference for any of secondary structure types. The correlation values are represented in Figures 1-4. Every Figure contains diagrams for one group of amino acids; there are separate diagrams for every amino acid. Diagrams consist of eight graphs, representing the correlation of the amino acid and eight secondary structure types. The diagrams show that almost every amino acid prefers one secondary structure type, since it has much higher correlation values for one secondary structure than for others (Figures 1-3).

Table I - Values of correlation coefficients of amino acids and secondary structure types at same position, and elements of amino acids structure. The table contains correlation values calculated using Formula 3, for distance τ = 0, and multiplied by 10,000. To emphasize the most important correlations, significant positive correlation coefficients (ρ > 0.015) are presented in bold and significant negative correlation coefficients (ρ < -0.015) are presented in italic. Three rightmost columns contain information on structural properties of amino acids. If an amino acid has branching on Cβ or aromatic Cγ atom, the appropriate cell is marked. Otherwise it is empty. If there is a polar heteroatom on Cβ or Cγ, the chemical symbol for the atom is presented in the last column.

(a) There is a nonpolar sulfur atom on Cγ atom in Met.

| Amino Acids And Secondary Structure Types At Same Position | Propensities Of Amino Acids |

Correlation values represented in Figures 1-4 characterize the behavior of different amino acids. In Table I the correlation values for the secondary structure type at the position of amino acid are presented. These numbers correspond to the values from diagrams at the position with τ =0. Amino acids in Table I are classified according to their preference to participate in specific secondary structures. Amino acids in each group are ordered by the correlation values. Our results are in some extent in agreement with calculated propensities of amino acids by Chou and Fasman (17), but there are also substantial differences, as it will be discussed for each group.

α-helix admirers. The amino acids from the first group in Table I (Ala, Leu, Glu, Gln, Arg, Met and Lys) are helix admirers, showing preference to build α-helices. Because of the high level of their correlations with α-helices, three of them (Ala, Leu, Glu) could be further classified as strong helix admirers. The previous findings, (17, 50) that Glu, Ala and Leu are found most frequently in helical regions, are in agreement with our results. However, Chou and Fasman finding that His and Val are also very frequent differs from our results, where both of these amino acids show negative correlation with α-helix.
The amino acids from this group show similar behavior with respect to other secondary structures, but there are also differences in their behavior. Amino acids Ala, Glu, Gln, Arg and Lys dislike strands and coils. At the contrary, Leu is a unique amino acid in this group that tends to build strands. It prefers short strands but obstructs both longer strands and coils. Met is relatively neutral to appearance in strands, 3-helices and coils. Ala, Leu and Met obstruct the formation of turns and bends. Glu supports the formation of short 3-helices.

**Strand admirers.** The amino acids from the second group (Val, Ile, Tyr, Phe, Thr and Trp) prefer strands. Thr is unique among strand admirers and among all amino acids because it has almost the same correlation value with strands and with coils. Based on the correlation value for coils, it could be also classified as turn and bend admirer. Still, because of large negative correlation value for turns, we put it among strand admirers. However, it differs from other members of the group, what is obvious from Figure 2.

Results of Chou and Fasman (17) that Val and Ile prefer strands, and results of Gibrat et al. (50) that Val, Ile, Tyr and Trp prefer strands are in agreement with our results. Interestingly, in these previous results Met (17) and Cis (17, 50) were among the strongest β-sheet formers, while our data show that Met has slightly negative and Cis only a small positive correlation.

Though helix admirer, Leu is also positively correlated with strands, as already mentioned.
Figure 2. Correlations of strand admirers with secondary structure types. See Figure 1. for detailed description. Correlations for each of strand admirers are presented in a separate diagram: (a) Valine, (b) Isoleucine, (c) Tyrosine, (d) Phenylalanine, (e) Threonine and (f) Tryptophan.
Most of the strand admirers are weakly correlated with \( \alpha \)-helices. \( Val \) obstructs \( \alpha \)-helices while \( Thr \) strongly obstructs \( \alpha \)-helices. All strand admirers obstruct the formation of turns and bends, except \( Thr \), that supports the formation of bends. As it was mentioned, \( Thr \) is also unique among strand admirers because it supports the formation of coils. \( Thr \) and \( Tyr \) are positively correlated with \( \beta \)-bridges. \( Val \) and \( Ile \) obstruct while \( Trp \) supports the formation of 3-helices.

**Turn and bend admirers.** The amino acids from the third group (Gly, Asn, Pro, Asp and Ser) show preference to build bends or turns or coils. This is good agreement with results of Chou and Fasman who found that Pro, Gly, Asn and Ser are the most frequent coil residues (17) and with Gibrat et al. (50), who added Asp to the set.

Turn and bend admirers, Gly, Asn, Pro, Asp and Ser, have quite large positive correlation values for bends, turns, 3-helices and coils. Only Gly has negative value for 3-helices, Asn very small value for 3-helices, and Ser for turns. All amino acids in this group occur rarely in \( \alpha \)-helices and strands. Gly has very high tendency to build turns and appears very often at their end. Pro tends to initiate turns. Pro tends to appear in terminating parts of bends and coils. Pro, Asp and Ser support the formation of 3-helices.
Cys and His. The remaining two amino acids Cys and His are relatively weakly correlated with all secondary structure types. The correlation values suggest statistical significance, but compared to other amino acids these values are substantially lower. They do not show clear preference to build any secondary structure and do not show large negative correlation values for any of secondary structure types. With small correlation coefficients Cys tends to build strands, while His has negative correlation with α-helices. It is interesting that results of Chou and Fasman show large preference of His towards α-helices, and preference of Cys towards β-sheet structures (17).

Influence Of Amino Acids Properties

Polarity and size of amino acids. Amino acids tendencies to take part in certain secondary structure can be connected with physicochemical properties of amino acids. It is known that in strands there are predominantly hydrophobic amino acids (17).

It was recently shown that propensities of amino acids for certain position in helix depend on physicochemical properties (27). Polar and nonpolar amino acids show different phase distribution – they usually appear at different positions in helices. Long polar (Glu, Gln, Arg, Lys) and short polar (Asn, Asp, Ser) amino acids have the same phase distribution. Hydrophobic aromatic (Phe, Tyr, Trp) and hydrophobic aliphatic (Leu, Met, Val, Ile) have the same phase distribution that is opposite to phase distribution of polar amino acids (27). Only five amino acids fail to follow this pattern, Gly, Ala, Thr, Pro, and His. Gly and Ala have very small side chains; Thr has also small side chain and has intermediate polarity. Pro occurs very rarely in α-helices. His do not cluster either with polar or nonpolar because of its pKa that is near neutral pH (27).

Classification of amino acids as long polar (Glu, Gln, Arg, Lys), short polar (Asn, Asp, Ser), hydrophobic aromatic (Phe, Tyr, Trp), and hydrophobic aliphatic (Leu, Met, Val, Ile) could be connected with our results. All long polar amino acids are α-helix admirers, all aromatic are strand admirers, while all short polar are turn and bends admirers. However, aliphatic amino acids do not belong to one group of admirers (Figures 1-4, Table I), some of them are among α-helix admirers, and some of them are strand admirers. Looking at the structures of aliphatic amino acids it can be noticed that amino acids with branch at Cβ atom are among strand admirers (Val and Ile), while amino acids without branching on Cβ atom are α-helix admirers ( Ala, Leu, Met). Some more general rules connecting structural properties of amino acids with our classification can be noticed, and we will discuss them later.

As in the case of position in α-helices (27) Thr, Gly and Pro are exceptions. However, Ala is not an exception, because it is α-helix admirer, like Leu and Met.

Hence, there is connection of polarity and size of amino acids with our groups (Table I).

All strand admirers are hydrophobic, with exception of Thr that is slightly polar. The tendency of nonpolar amino acids for strand structures is known for long time (17, 50). It is also supported by the fact that all polar amino acids, that belong to α-helix admirers and turn and bend admirers, have negative correlation with strand structures, while hydrophobic Leu has positive correlation. This is in agreement with the finding that proteins with increased hidrophobicity are less stable against misfolding (51).

Among α-helix admirers there are hydrophobic and long polar amino acids. The tendency of α-helix for hydrophobic amino acid is also supported by the fact that hydrophobic aromatic amino acids have positive (Phe, Trp), or slightly negative (Tyr) correlation with α-helices, while all short polar amino acids show negative correlation.

All turn and bend admirers are small polar amino acids as well as Gly and Pro. The tendency of small polar amino acids to build turns, bends, and coils is also in agreement with positive correlation of Thr (that is classified as strand admirer) with bends and coils (Table I). Gly and Pro are only exceptions in this group, since they are not polar.

Structural properties of amino acids. Groups of amino acids given in Figures 1-4 and in Table I are formed based on our results about preference of amino acid to be part of certain secondary structure. However, we realized that amino acids that are in the same group have the same structural properties. This means that certain amino acids structural properties are attuned to certain secondary structure types.

Figure 3. Correlations of turn and bend admirers with secondary structure types. See Figure 1. for detailed description. Correlations for each of turn and bend admirers are presented in a separate diagram: (a) Glycine, (b) Asparagine, (c) Proline, (d) Aspartic acid and (e) Serine.
The only exception is Met with sulfur on Cγ atom. Met is probably among α-helix admirers because sulfur in this case does not bring polarity. Hence, we can say that there are nonpolar heteroatoms on Cγ atom, and classify Met as α-helix admirer. There could be polar groups, or polar heteroatoms in structures of α-helix admirers, but further than Cγ atom.

All aromatic and all amino acids with branching on Cß atom are strand admirers. Thr has branching on Cß atom and it is among strand admirers, although it is polar amino acid and the rest are nonpolar.

All turn and bend admirers have polar heteroatoms on Cß or Cγ atoms. Pro is also among turn and bend admirers with its unusual structure. However, it also has polar heteroatom, N, on Cß.

The example of Thr is extremely interesting. It has branching on Cß, and also polar heteroatom on Cß. Hence it has structural properties of both strand admirers and turn and bend admirers. At the same time Thr indeed has almost the same correlation coefficient for strands and coils. This shows clearly that structural properties are connected very closely with the type of secondary structure forming by certain amino acid.

His and Cis, showing no preference for any of secondary structures, also do have structures quite different than all other amino acids. His has polar heteroatom on Cß and at the same time that polar atom is part of the aromatic ring. Cis has not very polar SH group on Cß atom, hence it differs from turn and bend admirers. Another difference is the fact that SH groups can make disulfide bridges, making this amino acid quite different from the others, and explaining why it do not belong to any of previous groups.

Based on these observations, it seem that tendency of amino acid to take part in certain secondary structure type is not defined by polarity or hidrophobicity of amino acid (although there is some connection), but that the crucial property of amino acid is the structure on Cß or Cγ atoms – branching and polar heteroatoms. In other words it seems that the part of the amino acid that is close to the backbone determines the type of secondary structure.

Amino Acids And Secondary Structure Types At Distant Positions

Diagrams in Figures 1-4 show correlation of amino acid and the secondary structure at the offset τ varying from –25 to 25. It is seen that the range of the offset τ values, for which the correlation coefficients are significant (Equation 4), varies for different amino acids, and different secondary structures. If we take 0.004 (see Method/Data Sets) as the threshold correlation value, then the average range with significant correlations is [-9, 10]. In some cases, significant correlation values are obtained for τ beyond that range. For example, the amino acids that are helix admirers often have significant correlations with secondary structure positioned separated by 10-12 amino acids. In papers (39, 47, 50) a smaller range [-8,8] is considered to be significant. We assume that larger data set and different computational model provide a wider range of significant values.

Figure 4. Correlations of other amino acids with secondary structure types. See Figure 1. for detailed description. Correlations for Cysteine (a) and Histidine (b) are presented in separate diagrams.
**Propensities Of Amino Acids**

**α-helix admirers.** These amino acids support the appearance of α-helices in the vicinity, but there are differences in their appearance in different parts of helices. That is in agreement with previous results showing that certain amino acids have preference to be in the beginning or end of α-helix (27, 17, 47).

While Ala induces α-helices in its vicinity almost equally in both directions, the other amino acids from this group have asymmetrical distribution of the α-helices support. The asymmetry of Glu's correlation is not large. The correlation distribution for amino acids Leu, Arg, Met, and Lys with α-helices is shifted towards positive values of τ, with the largest shift for Lys. At the contrary, the correlation for Glu is very strongly shifted towards negative values of τ. That leads to the conclusion that Ala and Gln are evenly distributed in, while Leu, Arg, Met and Lys tend to be closer to the end of helices. Glu tends to be very close to the beginning of α-helices, agreeing very well with (27).

Amino acids Ala, Glu, Gln, Arg dislike strands and coils. All α-helix admirers, except Lys, obstruct the formation of strands in their neighborhood. Lys obstructs the formation of strands in its and preceding positions, but strongly supports their formation in subsequent positions, which can be explained by its higher α-helix propensity at the helix end. As mentioned before, Leu is a unique amino acid in this group that tends to build strands, however, it is interesting that Leu has strong negative correlation with strands at distance 5-6 in both directions. Met is relatively neutral to appearance in strands, but it has negative correlation with strands in its neighborhood.

Lys supports turns formation in its immediate neighborhood. Met obstructs the formation of coils in the preceding positions. Glu strongly supports the formation of coils in the preceding positions.

**Strand admirers.** It is interesting that most of amino acids from the strand admirers group (Val, Ile, Tyr, Phe, Thr and Trp), do not have positive correlation with strands at the distance. Amino acids Ile, Phe have quite negative correlation with strands at distance of 4 to 8, while Val, and Trp have less pronounced but still negative correlation at the same distance. Trp has stronger negative correlation for negative values of τ. It is interesting that Val again has positive correlation with strands at distances larger than 8 positions. Tyr is relatively neutral to strands in its vicinity. Thr differs from other members of the group, having positive, but small correlation with strands for all τ values.

Many of strand admirers have negative correlation with distant α-helix structures. Thr and Val have negative correlation with α-helices for positive values of τ. Ile shows small positive correlation for almost all positive values of τ. There is also uniform small negative correlation between Tyr and α-helices for both positive and negative values of τ.

Most of strand admirers have positive correlation with distant turns. Thr is an exception: it supports the formation of turns in the preceding, but has negative correlation with them in the subsequent positions.

All strand admirers, except Thr, obstruct the formation of bends. Thr weakly supports the formation of bends, mostly in positions between -2 and 5.

Thr, Tyr, Phe and Ile are positively correlated with β-bridges. Val, Ile and Thr obstruct the formation of 3-helices, while Phe and Tyr support them at both its and immediately preceding positions.

Thr supports the formation of coils at its and precedent positions. Ile, Val, Tyr and Phe obstruct coils. Val tends to support coils in its vicinity.

**Turn and bend admirers.** The amino acids from the third group (Gly, Asn, Pro, Asp and Ser), turn and bend admirers, are frequent in the vicinity of strands, but have negative correlation with α-helices in their vicinity, except Asp for τ < 0. It supports α-helices in the subsequent positions. Most of them have positive correlation with bends, turns and coils in their close vicinity, but often asymmetrically.

Asp supports coils at it’s and the preceding positions (τ ≥ 0). Gly tends to build turns and appears very often at their end. It supports the formation of coils at the subsequent position (τ = -1). Pro tends to initiate turns and to support turns in its vicinity, but it strongly obstructs the formation of turns at τ = +1. Pro tends to appear in terminating parts of bends and coils. Asp and Ser support the formation of 3-helices.

**Cys and His.** As it was mentioned the remaining two amino acids Cys and His are relatively weakly correlated with secondary structures, and it is also the case for their vicinity. With low correlation value Cys has negative correlation with strands for τ values below -4 and above +5, while His has small negative correlation with α-helices for τ between -3 and 1.

As discussed above, the amino acids belonging to the same group tend to express similar behavior in respect to certain secondary structure type, not only to the one they admire, but also to the others. It is interesting to compare the diagrams to those of Robson and Suzuki (47). There are substantial similarities for most of amino acids (Ala, Leu, Glu, Lys, Val, Ile, Gly, Asn, Pro, Asp and Ser), but there are substantial differences also (Gln, Arg, Phe, Trp and His).

**Influence Of Amino Acids Properties**

It is interesting to connect shape of the diagrams with structural properties of amino acids. The large asymmetry for α-helices is observed for Glu and Asp that have carboxyl groups. Arg and Lys, amino acids with amino groups, also have asymmetric diagrams for α-helices and strands. Hence, polarity and charge of amino acids, as well as possibility to be hydrogen bond acceptor or donor, is connected with the similar influence of amino acids on the distant secondary structure. Diagrams for Ser and Thr show asymmetry and similar behavior of these two amino acids in respect to α-helix and strand structures. It is again
connected with their similar structure, OH group on Cβ atom.

The asymmetry is the most pronounced for α-helix structures. Obviously it is connected with hydrogen bonds that exist in α-helices.

From the data presented in Figures 1-4 and in Table I it seems that polarity, charge and capability for hydrogen bonding have more influence on the distant secondary structure, while structural properties of Cβ or Cγ atoms have influence on the secondary structure at the position of amino acid (τ near zero). Hence, atoms close to the backbone define secondary structure at the position of amino acid, while hydrogen bonding and other noncovalent interactions between amino acids have influence on distance.

Conclusions

The calculated correlations of amino acids with secondary structure types enable to determine amino acid tendency to participate in certain secondary structure type. Results confirm that there is a significant dependence of secondary structure type on amino acid, not only on the corresponding position, but also on amino acids in nearby positions. It confirms that the secondary structure prediction should equally consider preceding and subsequent amino acids. In most cases, the type of the secondary structure depends on 9 preceding and 10 subsequent amino acids.

Results show that most of amino acids have clear preference to participate in certain secondary structure type. Based on it amino acids are classified in four groups: α-helix admirers, strand admirers, turn and bend admirers and the others that do not show preference for any secondary structure. The amino acids from the same group often show similar behavior to certain secondary structure type, not only to the one they admire, but also to the others.

Analyzing physicochemical and structural properties of amino acids show that amino acids from the same group have similar physicochemical and the same structural characteristics. Nonpolar aliphatic without branching on Cβ atom and long polar amino acids are α-helix admirers. Strand admirers are aromatic and aliphatic amino acids with branching on Cβ atom, while turn and bend admirers are small polar amino acids. The common structural properties of α-helix admirers are: no polar atoms on Cβ and Cγ atoms, no branching on Cβ, and aliphatic (sp³) Cγ atom. All amino acids that have aromatic groups or branching on Cβ atom are strand admirers. All turn and bend admirers have polar heteroatom on Cβ or Cγ atoms, or do not have Cβ atom. Hence, based only on structure amino acid can be classified to certain group.

Diagrams that show correlation of amino acid with secondary structure at neighboring positions, for offset τ values from -25 to 25, reveal that the distance range of significant correlation is usually between -9 and 10. Shape of the diagrams is connected to structural properties of amino acids. The largest asymmetry is observed for polar amino acids, and amino acids that can make hydrogen bonds. These results indicate that polarity and capability for hydrogen bonding have influence on the secondary structure at some distance. However, polarity and hydrogen bonding do not have crucial influence on preference for certain secondary structure type. Our results suggest that amino acid preference for secondary structure is caused by structural properties of Cβ or Cγ atoms.

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