

Study on Different Types of Structure Based Properties in Keratin and Collagen Types of Fibrous Proteins

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Abstract— During the process of protein folding, amino acid residues along the primary sequence interact with each other in a cooperative manner to form the stable native structure. To understand the mechanism of protein folding and stability, the knowledge about inter-residue interactions in protein structures is very helpful. In this comparative study, we have systematically analyzed aminoacid composition and various structure based properties of molecular interactions in two different classes of Fibrous proteins, Keratin and Collagen. Aminoacid composition, long range order, surrounding hydrophobicity, long range interactions, medium range interactions, accessible surface area, ionic interactions and hydrophobic interactions are the parameters used in the study. Structural based properties of Keratin and Collagen were statistically analyzed. The results obtained in this work highlight the difference in different structure based properties like long range order, surrounding hydrophobicity, long range interaction ratio, and medium range interaction ratio, average number of residues within 8Å and accessible surface area of proteins, in Keratin and Collagen. Ionic interacting residues have higher value of surrounding hydrophobicity and higher value of neighbors within 8Å, compared to ionic noninteracting residues. Accessible surface area of polar residue was found to be greater than nonpolar residues. There is marked difference in structural based properties of buried and non buried residues. Buried residues have higher value of surrounding hydrophobicity and higher value of neighbors within 8Å, compared to non-buried residues. Hydrophobic interacting residues have higher value of surrounding hydrophobicity and higher value of neighbors within 8Å, compared to hydrophobic noninteracting residues. Long range interactions are more prominent in hydrophobic interactions than in ionic interactions.

Keywords— Surrounding hydrophobicity, long range order, ionic interaction, hydrophobic interactions, membrane proteins.

I. INTRODUCTION

Fibrous proteins are proteins with an elongated shape. Fibrous proteins provide structural support for cells and tissues¹. Fibrous proteins form long fibres that serve a structural role. Fibrous proteins are distinguished from globular proteins by their filamentous, elongated form. Also, fibrous proteins have low solubility in water compared with high solubility in water of globular proteins². Most of the Fibrous proteins play structural roles in animal cells and tissues, holding things together. Fibrous proteins have amino acid sequences that favour a particular kind of secondary structure which, in turn, confer particular mechanical properties on the proteins³.

Theoretical investigations were of great use to understand about Fibrous proteins. Several investigators have stressed the

importance of hydrogen bonds, electrostatic, hydrophobic and van der Waals interactions along with weak interactions. Amino acid residues along the polypeptide chain interact with each other in a cooperative manner to form the stable native structure, during the process of protein folding. To understand the mechanism of protein folding and stability, the knowledge about inter-residue interactions in protein structures is very helpful⁴. In the formation of stable secondary structures and a unique tertiary structure for a protein, interactions between amino acid residues of the protein and with the surrounding solvent molecules play an important role. These interactions are usually non covalent and include hydrogen bonds, ion pairs, van der Waals interactions, and hydrophobic interactions.

Long range order highlights the importance of long-range contacts, which are made by residues that are far in sequence and closer in the 3D structure. Surrounding hydrophobicity provides valuable information with regard to hydrophobic domains, nucleation sites, surface domains, loop sites and the spatial positions of residues in protein molecules. Medium range interactions and long range interactions are required to stabilize the conformation uniquely. Ionic and hydrophobic interactions are also needed for biological activity of proteins. Knowledge about the similarities and differences between structural based properties of Keratin and Collagen will help to understand about working mechanism of Keratin and Collagen.

An attempt was made to find the similarities and differences between structural based properties of Keratin and Collagen. Structure based properties used in this study are long range order, medium range interactions, long range interactions, surrounding hydrophobicity, average number of 8 Å neighbours, average accessible surface area of all residues, average accessible surface area of polar residues and average accessible surface area of non-polar residues, ionic interactions and hydrophobic interactions. Structure based properties of protein residues were calculated and from that structure based properties of protein chains were estimated.

Ionic non-interacting residues have lower value of surrounding hydrophobicity and lower value of neighbours within 8Å, compared to ionic interacting residues. Hydrophobic non-interacting residues have lower value of surrounding hydrophobicity and lower value of neighbours within 8Å, compared to hydrophobic interacting residues. Hence the environment, in which residues are present, has

great influence on ionic interactions and hydrophobic interactions.

II. MATERIALS AND METHODS

A. Data Set

To learn about Fibrous proteins we have collected data from Protein Data Bank, which were culled as non-redundant with sequence identities of 30%. Number of Fibrous proteins, with the sequence identity < 30% must be significant for statistical analysis of protein properties. Number of Fibrous proteins, with the sequence identity < 30% were significant in only two types of Fibrous proteins, Keratin and Collagen. Our final data set contains 8 protein chains from Keratin [3TNU:A, 3TNU:B, 3ZGH:A, 4F1Z:A, 4OX0:A, 4RMB:A, 4XIF:A, 5E3X:A] and 14 protein chains from Collagen [1AMX:A, 1AZZ:A, 1AZZ:C, 1DY2:A, 1O91:A, 1OLT:A, 1T61:A, 4AE2:A, 4IGI:A, 5CTD:C, 5JJD:A, 5JJD:B, 5KF4:A, 5NIR:A].

B. Computational Procedure

Clear description of Structure based properties like Medium range interactions, Long range interactions, Long range order, Surrounding hydrophobicity, number of 8Å⁰ neighbours and formulae needed to calculate them are available at the server at <http://www.iitm.ac.in/bioinfo/pdbparam/>⁵ which can be freely accessed. Procedure to calculate Ionic interactions and Hydrophobic interactions are also explained in the same web server.

1) *Medium and long-range interactions*: For a given residue, the surrounding residues within a sphere of 8 Å radii are analysed in terms of their sequence position. Residues within a window between three and four residues contribute to medium-range interactions and those more than four residues apart contribute to long-range interactions. Both medium range and long range interactions play an important role in the formation of protein structure.

2) *Number of 8Å contacts*: The contacts between amino acid residues in the crystal structure are computed with cutoffs of 8 Å using Ca. Number of residues within 8Å of a particular aminoacid residue gives number of 8Å contacts of that residue.

3) *Long-range order*: LRO is derived from long-range contacts (contacts between two residues that are close in space and far in the sequence) in the protein structure. It is defined as

$$LRO = \sum (n_{ij} / N)$$

$$n = 1 \text{ if } i - j > 12;$$

$$n = 0 \text{ otherwise}$$

where i and j are the two contacting residues within a distance of 8 Å, and N represents the total number of residues in the protein.

4) *Surrounding hydrophobicity*: The sum of hydrophobic indices assigned to the residues that appear within a distance of 8 Å from the central residue can be used to characterize the hydrophobic behaviour of each amino acid residue in the protein environment. It is defined as

$$H_p(i) = \sum_{j=0}^{20} n_{ij} * h_j$$

where n_{ij} is the total number of surrounding residues of type j around the ith residue of the protein, and h_j is the hydrophobicity index (kcal/mol) obtained from thermodynamic transfer experiments.

5) *Accessible surface area*: Accessible surface areas of all residues of proteins were calculated using PDB atomic coordinates and NACCESS program. From that average accessible surface areas of all residues of different proteins were calculated. Average accessible surface areas of polar residues of a protein was calculated by dividing total accessible surface areas of all polar residues of a protein by total number of polar residues of that protein. Similarly average accessible surface area of nonpolar residues of a protein was calculated by dividing total accessible surface areas of all nonpolar residues of a protein by total number of nonpolar residues of that protein.

6) *Ionic interactions*: Ionic interactions is contributed by ionic residue pairs Arginine(R), Lysine(K), Histidine(H): Aspartic Acid(D) Glutamic Acid(E) falling within a distance of 6Å.

7) *Hydrophobic interactions*: CB atoms of residues of Alanine(A), Valine(V), Leucine(L), Isoleucine(I), Methionine(M), Phenylalanine(F), Tryptophan(W), Proline(P) and Tyrosine(Y) show hydrophobic interactions when they fall within 5Å range.

8) *Hydrogen bond energy*: Using DSSP⁶ program, four hydrogen bond energies of a residue were calculated. Total hydrogen bond energy of a residue is the sum of all four hydrogen bond energy terms of a particular residue.

III. PRESENT STUDY

Aminoacid composition, Long range order, Surrounding hydrophobicity, Medium range interactions, Long range interactions, number of 8 Å neighbours, Accessible surface areas, Ionic interactions, Hydrophobic interactions were calculated using PDB atomic coordinate data files.

A. Computation of Amino Acid Composition

The amino acid composition for each protein has been computed using the number of amino acids of each type and the total number of residues. It is defined as:

$$Comp(i) = \sum_{j=0}^{20} n_i / N$$

where j stands for the 20 amino acid residues. n_i is the number of residues of each type and N is the total number of residues. The summation is through all the residues in the particular protein. We have repeated the calculation for all the proteins in all nine functional class types of Fibrous proteins. By calculating the average of aminoacid composition all proteins in a particular functional type of protein, average aminoacid composition of a particular functional type of protein was calculated.

TABLE I. Percentage of different groups of aminoacid residues in keratin and collagen.

Type of aminoacid	Keratin	Collagen
Acidic	14.094	11.075
Basic	14.38	11.891
Neutral and polar	28.844	25.745
Nonpolar and aromatic	7.716	8.436
Nonpolar and aliphatic	34.966	42.854

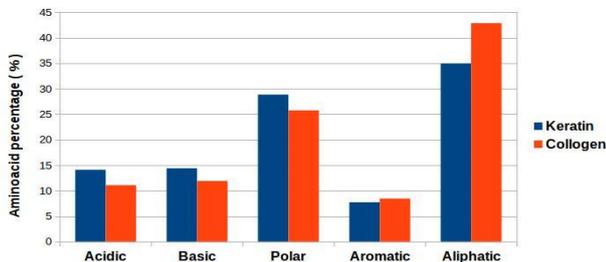


Fig. 1. Percentage of different groups of aminoacid residues in Keratin and Collagen.

From the above table and graph it is clear that the composition of Acidic, Basic and Polar groups of aminoacid residues is greater in Keratins, whereas composition of Aliphatic group of aminoacid residues is greater in Collagen type of fibrous protein.

B. Computation of Protein Properties

Using structure based properties of aminoacid residues, structure based properties of proteins were calculated using the following procedure.

- 1) Long range order of a protein (LRO) ⁷ = Sum of long range order of all aminoacid residues of that protein.
- 2) Ratio of total number of medium range interactions in a protein to total number of residues of a protein (MRR) = Total number of medium range interactions in a protein / Total number of residues of that protein.

3) Ratio of total number of long range interactions in a protein to total number of residues of a protein (LRR) = Total number of long range interactions in a protein / Total number of residues of that protein.

4) Surrounding hydrophobicity of a protein (Hp) = Average of surrounding hydrophobicity of all aminoacid residues of that protein.

5) Average value of accessible surface area of residues of a protein (ASA) = Sum of accessible surface area of all residues of a protein / Total number of residues of that protein.

6) Average value of accessible surface area of polar residues of a protein (ASAp) = Sum of accessible surface area of all polar residues of a protein / Total number of polar residues of that protein.

7) Average value of accessible surface area of nonpolar residues of a protein (ASAnp) = Sum of accessible surface area of all nonpolar residues of a protein / Total number of nonpolar residues of that protein.

8) Ratio of ionic interacting residues of a protein (RIR) = Total number of ionic interacting residues in a protein / Total number of (R,K,H,D,E) residues of that protein.

9) Ratio of hydrophobic interacting residues (RHR) = Total number of hydrophobic interacting residues in a protein / Total number of (A,V,L,I,M,F,W,P,Y) residues of that protein.

10) 8 Å contact number of a protein (n8År) = Average of 8 Å contact number of residues

Values of structure based properties of Fibrous proteins were tabulated and compared.

Correlation analysis method was also used to find the relation between different protein properties.

IV. RESULTS AND DISCUSSION

Average values of protein properties of Keratin and Collagen are tabulated below.

TABLE II. Average values of structure based properties of protein chains in fibrous proteins.

PROTEIN TYPE	LRO	MRR	LRR	Hp	n8AR	ASA	ASAp	ASAnp	RIR	RHR
Keratin (8)	1.099+/- 0.908	2.316+/- 1.338	2.659+/- 2.136	9.928+/- 1.008	11.047+/- 2.226	56.352+/- 16.215	71.038+/- 13.707	37.742+/- 19.354	0.544+/- 0.114	0.303+/- 0.229
Collagen (14)	1.681+/- 0.651	1.103+/- 0.480	4.183+/- 1.350	10.239+/- 1.314	12.422+/- 1.769	48.136+/- 10.903	63.882+/- 12.721	34.155+/- 14.156	0.464+/- 0.109	0.423+/- 0.141

Statistical significance of the data was analysed by calculating P value using ANOVA. For both cases P < 0.001, and highly statistical significant nature of the data was established.

For both types of proteins, average value of accessible surface area of residues of a protein (ASA) was found to be greater than average value of accessible surface area of nonpolar residues of a protein (ASAnp) and less than average value of accessible surface area of polar residues of a protein (ASAp). Above result explains the hydrophobic nature of nonpolar residues and hydrophilic nature of polar residues.

A. General Trend in Average Values of Protein Properties of Keratin and Collagen

Type of proteins having lower average value of LRO, have lower average value of LRR.

Type of proteins having lower LRR value have higher MRR value. This result shows the complementary nature of long range interactions and medium range interactions.

Keratins have low value of long range order (LRO) and lower value of ratio of total number of long range interactions in a protein to total number of residues in a protein (LRR). Whereas Collagens have lower value of ratio of total number of medium range interactions in a protein to total number of residues in a protein (MRR).

Type of proteins having higher average value of Hp, have higher average value of number of 8Å0 neighbours. So the regions of proteins having highest packing of atoms have highest surrounding hydrophobicity.

B. General Trend in Correlation between Average Values of Protein Properties

Correlation between values of long range order (LRO), ratio of total number of medium range interactions in a protein to total number of residues of that protein (MRR), ratio of total number of long range interactions in a protein to total number of residues of that protein (LRR), surrounding hydrophobicity (Hp), ratio of ionic interacting residues (RIR), ratio of hydrophobic interacting residues (RHR) of different types of proteins were found out.

For all types of proteins correlation between LRO and LRR was very high. LRO has high correlation with Hp and value of average number of 8A⁰ neighbours.

Significant negative correlation between MRR and LRO and between MRR and LRR was noticed. This shows that the long range interactions and medium range interactions are complimentary in nature.

LRR had very high correlation with value of average number of 8A⁰ neighbours. Significant correlation between LRR and Hp was noticed.

C. Relation between Surrounding Hydrophobicity and Other Protein Properties

For the complete set of 22 Fibrous proteins, belonging to Keratin and Collagen groups, linear regression equation connecting Surrounding hydrophobicity and other protein properties of protein chains was setup. Using linear regression equation, surrounding hydrophobicity values of 22 Fibrous proteins was predicted. Correlation between actual and predicted values of 22 Fibrous proteins were found out to be maximum (0.86), for the following regression equation

$$Hp = -1.7613 * LRO - 0.9592 * MRR + 2.2158 * n8AR - 6.4458$$

Graph connecting actual value of surrounding hydrophobicity calculated from PDB coordinates and predicted value of surrounding hydrophobicity is shown below

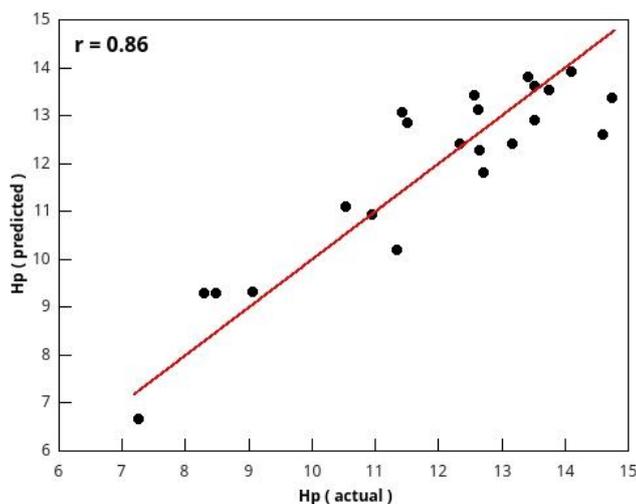


Fig 2. Actual value of surrounding hydrophobicity and predicted value of surrounding hydrophobicity in 22 Fibrous proteins.

Procedure used to calculate surrounding hydrophobicity Hp, medium range interactions, long range interactions and accessible surface area are different. Above regression equation shows the strong relation between them. This shows the relevance of above mentioned properties to learn about protein properties.

Percentage error in predicted value of surrounding hydrophobicity in Fibrous proteins was found to be less than 10 % in 19 Fibrous proteins out of 22 Fibrous proteins used for the analysis. Above result shows the relation between surrounding hydrophobicity, long range order, medium range interactions and 8 Å contact number of a protein.

D. Difference in Residue properties

Properties of residues such as percentage of nonzero LRO values, average LRO values, average number of medium range interacting residues, average number of long range interacting residues, average surrounding hydrophobicity and average number of 8A⁰ neighbours and accessible surface area of buried residues, which are having ASA less than 7, and non buried residues were compared.

Difference between properties of ionic interacting residues and ionic non-interacting residues were compared.

Similarly difference between properties of hydrophobic interacting residues and hydrophobic non-interacting residues were compared.

E. Comparison of Properties of Buried Resides and Nonburied Resides in Fibrous Proteins

An aminoacid residue is considered as buried residue if the accessible surface area of that residue is less than 7. Buried residues are positioned in the interior of protein. Hence the percentage of residues having nonzero long range order value was higher in buried residues than in non buried residues.

Average values of structure based properties of buried residues of both Keratin and Collagen types of Fibrous proteins were found out. Similarly average values of structure based properties of non buried residues of both Keratin and Collagen types of Fibrous proteins were found out. Difference between average values of structure based properties of buried residues and non buried residues of both Keratin and Collagen types of Fibrous proteins were found out. Values are tabulated. Average value of medium range interactions and long range interactions was higher in buried residues, which are positioned in the interior of protein than in non buried residues.

Average surrounding hydrophobicity values and number of 8A⁰ neighbours of buried residues which are positioned in the interior of protein were very high compared to average surrounding hydrophobicity values and number of 8A⁰ neighbours of non buried residues of proteins.

Accessible surface area of buried residues was less compared to non buried residues.

TABLE III. Difference between average values of structure based properties of buried residues and nonburied residues of fibrous proteins.

Protein type	Residue type	Total number of residues	Percentage of nonzero LRO values	Average MRR	Average LRR	Average Hp	Average 8A neighbours	Average ASA	Average ASAnp	Average ASAp
Keratin (8)	BURIED RESIDUES	522	63.793	2.01	5.967	16.693	12.977	1.685	1.108	0.577
	NONBURIED RESIDUES	1587	35.161	2.206	2.554	11.243	9.72	61.798	35.248	26.55
	DIFFERENCE		28.632	-0.196	3.413	5.45	3.257	-60.113	-34.14	-25.973
Collagen (14)	BURIED RESIDUES	622	62.379	1.167	6.989	17.08	13.145	1.596	0.947	0.649
	NONBURIED RESIDUES	1826	41.621	1.267	3.443	11.365	9.659	60.068	34.15	25.918
	DIFFERENCE		20.758	-0.1	3.546	5.715	3.486	-58.472	-33.203	-25.269

Above results showed that the atomic packing of aminoacid residues was high, in the interior of protein.

It is found that the percentage of buried residues is very high in both Keratin and Collagen compared to human membrane proteins⁸. Percentage of buried residues in Keratin is 24.75% and 25.4% of residues are buried in Collagen.

Average value of hydrogen bond energy of buried residues is greater than non buried residues.

F. Comparison of Properties of Ionic Interacting (R,K,H,D,E) Residues and Ionic Noninteracting (R,K,H,D,E) Residues of Fibrous Proteins

Average values of structure based properties of Ionic interacting (A,V,L,I,M,F,W,P,Y) residues of both Keratin and Collagen types of Fibrous proteins were found out. Similarly average values of structure based properties of Ionic

noninteracting (A,V,L,I,M,F,W,P,Y) residues of both Keratin and Collagen types of Fibrous proteins were found out. Difference between average values of structure based properties of Ionic interacting (A,V,L,I,M,F,W,P,Y) residues and Ionic noninteracting (A,V,L,I,M,F,W,P,Y) residues of both Keratin and Collagen types of Fibrous proteins were found out. Values are tabulated.

For all types of Fibrous proteins, percentage of nonzero LRO values was higher in Ionic interacting (R,K,H,D,E) residues compared to Ionic noninteracting (R,K,H,D,E) residues.

Average LRO value was higher in Ionic interacting (R,K,H,D,E) residues compared to noninteracting (R,K,H,D,E) residues.

TABLE IV. Difference between average values of structure based properties of ionic interacting and noninteracting residues of fibrous proteins.

Protein type	Residue type	Total number of residues	Percentage of nonzero LRO values	Average MRR	Average LRR	Average Hp	Average 8A neighbours	Average ASA	Average ASAnp	Average ASAp
Keratin (8)	IONIC INTERACTING	330	34.848	2.527	2.339	11.756	9.858	71.963	34.742	37.222
	IONIC NONINTERACTING	330	34.848	2.527	2.339	11.756	9.858	71.963	34.742	37.222
	DIFFERENCE		4.188	0.282	0.372	0.797	0.693	-20.667	-10.038	-10.627
Collagen (14)	IONIC INTERACTING	272	43.382	1.419	3.835	12.433	10.228	67.108	29.447	37.661
	IONIC NONINTERACTING	289	38.062	1.298	3.024	10.642	9.27	87.166	39.859	47.307
	DIFFERENCE		5.32	0.121	0.811	1.791	0.958	-20.058	-10.412	-9.646

Average surrounding hydrophobicity and number of 8A⁰ neighbours was higher in Ionic interacting (R,K,H,D,E) residues compared to noninteracting (R,K,H,D,E) residues.

Average value of MRI and LRI was higher in Ionic interacting (R,K,H,D,E) residues than in noninteracting (R,K,H,D,E) residues.

Average value of accessible surface area was lower in Ionic interacting (R,K,H,D,E) residues than in noninteracting (R,K,H,D,E) residues.

Average value of hydrogen bond energy of ionic interacting residues is greater than ionic non interacting residues.

Above results show that ionic interactions are favoured in regions where atomic packing of proteins is high.

G. Comparison of Properties of Hydrophobic interacting (A,V,L,I,M,F,W,P,Y) Residues and Hydrophobic Noninteracting (A,V,L,I,M,F,W,P,Y) Residues of Fibrous Proteins

Average values of structure based properties of Hydrophobic interacting (A,V,L,I,M,F,W,P,Y) residues of both Keratin and Collagen types of Fibrous proteins were found out. Similarly average values of structure based properties of Hydrophobic noninteracting (A,V,L,I,M,F,W,P,Y) residues of both Keratin and Collagen types of Fibrous proteins were found out.

Difference between average values of structure based properties of Hydrophobic interacting (A,V,L,I,M,F,W,P,Y) residues and Hydrophobic noninteracting

(A,V,L,I,M,F,W,P,Y) residues of both Keratin and Collagen types of Fibrous proteins were found out. Values are tabulated.

TABLE V. Difference between average values of structure based properties of hydrophobic interacting and noninteracting residues of fibrous proteins.

Protein type	Residue type	Total number of residues	Percentage of nonzero LRO values	Average MRR	Average LRR	Average Hp	Average 8A neighbours	Average ASA	Average ASAnp	Average ASAp
Keratin (8)	HYDROPHOBIC INTERACTING	330	34.848	2.527	2.339	11.756	9.858	71.963	34.742	37.222
	HYDROPHOBIC NONINTERACTING	330	34.848	2.527	2.339	11.756	9.858	71.963	34.742	37.222
	DIFFERENCE		4.188	0.282	0.372	0.797	0.693	-20.667	-10.038	-10.627
Collagen (14)	HYDROPHOBIC INTERACTING	272	43.382	1.419	3.835	12.433	10.228	67.108	29.447	37.661
	HYDROPHOBIC NONINTERACTING	289	38.062	1.298	3.024	10.642	9.27	87.166	39.859	47.307
	DIFFERENCE		5.32	0.121	0.811	1.791	0.958	-20.058	-10.412	-9.646

For all types of Fibrous proteins, percentage of nonzero LRO values was higher in Hydrophobic interacting (A,V,L,I,M,F,W,P,Y) residues compared to non interacting (A,V,L,I,M,F,W,P,Y) residues.

Average LRO value was higher in Hydrophobic interacting (A,V,L,I,M,F,W,P,Y) residues compared to non interacting (A,V,L,I,M,F,W,P,Y) residues.

Average LRI, surrounding hydrophobicity and number of 8A⁰ neighbours was higher in Hydrophobic interacting (A,V,L,I,M,F,W,P,Y) residues compared to non interacting (A,V,L,I,M,F,W,P,Y) residues.

Average MRI was lower in Hydrophobic interacting (A,V,L,I,M,F,W,P,Y) residues compared to non interacting (A,V,L,I,M,F,W,P,Y) residues.

Average value of hydrogen bond energy of hydrophobic interacting residues is greater than hydrophobic non interacting residues.

Above results show that the hydrophobic interactions are favoured in regions where atomic packing of proteins is high and the hydrophobic interacting residues prefer long range interactions at the expense of medium range interaction.

V. CONCLUSION

Structure based properties of different types of Fibrous proteins were found out and tabulated. Correlation between different, structure based properties were found out.

Average value of surrounding hydrophobicity values of buried residues, were higher than average value of surrounding hydrophobicity values of non buried residues. This shows the high hydrophobic nature of protein interior.

For both ionic and hydrophobic interactions, average value of Surrounding hydrophobicity values of interacting residues were greater than average value of surrounding hydrophobicity values of noninteracting residues for both Keratin and Collagen proteins. This shows that ionic and hydrophobic interactions are favoured in regions where atomic packing of proteins is high. Hydrophobic interacting residues prefer long range interactions compared to medium range interaction.

Average value of hydrogen bond energy of buried, ionic interacting and hydrophobic interacting residues are high.

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