COMPUTATIONAL BIOLOGY AT CENTRE FOR CELLULAR & MOLECULAR BIOLOGY, HYDERABAD, INDIA

Theoretical approaches are increasingly used in modern biology to model and describe structure and function of biological molecules (e.g., DNA and Protein) and to uncover information contained in the genome and protein sequences to study evolutionary processes. Several groups in CCMB are involved in computational modelling of such phenomena, along with generating data to test or supplement their models. Here are short descriptions of work in the areas of Genome Analysis, Structural Biology, and Molecular Modelling from six different groups and projects highlighting the computational aspects.

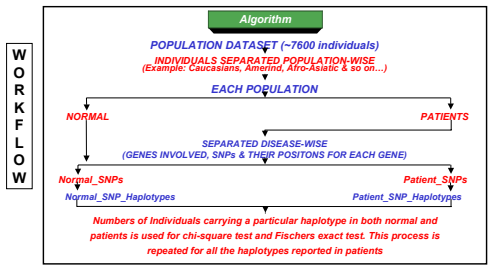
Genome Analysis (Dr. Shrish Tiwari, shrish@ccmb.res.in)

Objectives

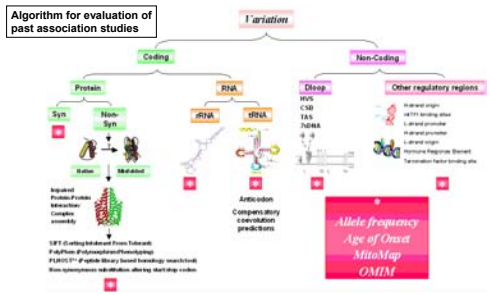
Introduction

With personal genomics round the corner, studying the variation in the human genome gains importance due its potential in personalised medicine. Single nucleotide polymorphisms (SNPs) are a major source of this variation. Our group has focused on exploring the possibility of using SNPs as diagnostic markers.

We started by analysing past association studies involving SNPs, since they have not been consistent, to uncover the reasons behind the inconsistencies. We developed a tool for scoring SNPs for their deleterious effects and prioritise only harmful SNPs for genotyping. We also analysed synonymous changes, since some of them could be harmful. These analyses have resulted in the development of several tools and databases.

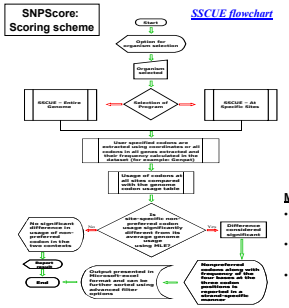


Algorithm for evaluation of past association studies



SNPScore: Scoring scheme

SSCUE flowchart



Algorithm for synonymous codon usage

The codon changes are classified as

Codon change	Genome Average	Site-specific
Synonymous Non-synonymous	Preferred	Preferred
	Preferred	Non-Preferred
	Non-Preferred	Non-Preferred
	Non-Preferred	Preferred

Major results

- Avoid SNPs in CpG dinucleotides for association studies
- Rare codons preferentially used for hydrophobic amino acids
- Allele frequency differences not enough to associate SNPs to disease phenotypes

Computational Analysis of Non-Coding DNA (Dr. Rakesh Mishra, mishra@ccmb.res.in)

Background: Importance and motivation

Other than the coding sequences which constitutes only < 2% of the human genomes, function of much of the genomic DNA remains to be understood. Why complex genome have increasing proportion of non coding DNA in general and repetitive DNA in particular is not understood.

Major results

We have identified ultra conserved regions in the context of Hox genes, particularly HoxD locus. Function of such identified regions needs to be studied. We also did pattern search in the context of intergenic regions flanked by differentially expressed genes to predict potential chromatin domain boundary elements. The evolution of complex organisms is associated with increase in the number of regulatory elements and the trans acting factors associated with them. One of such regulatory module is Polycomb regulatory system which is involved in the maintenance of differential expression of genes. Like the expansion of cis regulatory elements higher organisms show expansion of PcG system. We have analyzed the members of this group in the context of their evolution and identified new motifs in these proteins that enable us to address the mechanism of evolution of complexity.

Focus and objectives

We use bioinformatics approach to analyze the non coding part of genome to understand their possible function.

We look for the conservation, pattern of small motifs and context as criteria to analyze the function of non coding DNA. We also use transcription from non coding region as criteria for functional analysis

Publications:

- Ch Sabarinadh, S Subramanian, A Tripathi ,and R K Mishra, *(*2004) *BMC Genomics* 5(1), 75.
- M K Basu and R K Mishra, (2004) *In: Recent Advances in Biotechnology, Shree Publishers, New Delhi*, pp. 21-41.
- S Subramanian, R K Mishra and L Singh, (2003) *Bioinformatics* 19, 681-685.
- S Subramanian, R K Mishra and L Singh, (2003) *Genome Biology* 4, R13.
- S Subramanian, V M Madgula, R George, R K. Mishra, M W Pandit, C S Kumar and L Singh, (2003) *Bioinformatics* 19, 549-552.

Structural Biology (Dr. R. Sankaranarayanan, sankar@ccmb.res.in)

Background: The underlying principle of the function of a macromolecule is its structure. Our laboratory aims at exploring the structure-function relationship of biomolecules by combining experimentally obtained structural information using X-ray crystallography with other biophysical and biochemical data to understand various cellular processes.

1. Translational accuracy: *Exploring the structural basis of amino acid recognition in Class II tRNA Synthetases*

Aminoacyl-tRNA synthetases (aaRSs) establish the rules of genetic code by attaching the correct amino acid to the cognate tRNA. Our major goal is to understand how similar amino acid substrates are recognized with a high accuracy during translation. Defective aaRSs form proteins with incorrect sequences causing misfolding and consequent neurodegeneration. Our structural work provides insight into the mechanism of editing domain and the structural basis of its defect. We determined the structure of editing domain from *Pyrococcus abyssi,* an archael threonyl-tRNA synthase(ThrRS) which showed structural and functional homology to D-amino acid deacylases(DTDs) of eubacteria & eukaryotes. The study allowed us to propose a post-transfer editing mechanism. To understand the structural basis of editing mechanism we determined the crystal structure of editing domain from *Pyrococcus abyssi* (Pab-NTD) in complex with substrate analogs. The study identified an 'enantioselectivity sieve' for discriminating chiral molecules, used by nature (a) for L-Ser removal in archael ThrRSs and b) for incorrect D-amino acid removal from tRNA in DTDs.

2. Structural basis for enhanced thermostability: *Exploring the structural basis for thermostability of Bacillus subtilis Lipase (in collaboration with Dr. N. Madhusudana Rao,CCMB)*

Protein thermostability is a key factor in biotechnology industry where enzymes can catalyze chemical reactions at high temperatures. A triple mutant of *B. subtilis* lipase (LipA) was obtained by directed evolution approaches with ~300-fold increased thermostability compared to the wild-type. Structural information was used to combine mutants for obtaining a minimalist solution for enhancing thermostability. To gain insights into the structural basis of observed enhancement in thermostability and to improve it further we crystallized and solved the structure of a double & triple mutant of LipA. High-resolution crystal structures show subtle changes, which include stacking of tyrosines, peptide plane flipping and a better anchoring of the terminus, that challenge rational design and explain the structural basis for enhanced thermostability. The approach offers an efficient and minimalist solution for the enhancement of a desired property of a protein.

3. Structural Biology of *Mycobacterium tuberculosis*: *Structure-function studies on Polyketide Synthases(PKS) and Fatty Acid Synthases(FAS) from Mycobacterium tuberculosis (in collaboration with Dr. Rajesh Gokhale, NII, New Delhi)*

M.tb has a complex lipid composition and constitutes 50% of the dry cell weight. *M.tb* genome sequence revealed a battery of PKS & FAS genes. PKSs in conjunction with FASs generate unusual lipids that constitute the complex cell wall of mycobacteria and serve as virulence factors. We are looking at the structure-function relationship of these proteins. PKS18, a type III PKS displays remarkable substrate specificity for incorporating C2–C26 acyl-CoA units. We determined the structure of PKS18 which led us to identify a 20Å long 'novel tunnel' in the molecule and provided a clear structural basis for PKS18 function. *M.tb* genome also hosts a large family of fadD genes classified as fatty acyl-AMP ligase (FAAL) and fatty acyl-CoA ligase (FACL). FAAL mutants are deficient in important lipid metabolites. FadD28 is a FAAL-specific protein involved in the biosynthesis of a virulent lipid pthiocerol dimycocerosate. To develop FadD proteins as anti-tuber drug targets, we determined the crystal structure of N-ter domain of FadD28 protein which reveals crucial residues involved in enzymatic activity and the determinants of substrate specificity at the fatty-acid binding pocket. Furthur analysis of the FAAL structure from *M.tb* is being explored for rational design of anti-tuberculosis agents. At present, several of the PKS and FAS from *M. tb* are expressed and we are in the process of crystallizing and determining their structures to understand their function.

4. Plant Virulence Factors: *Structure-function analysis of virulence factors of Xanthomonas oryzae pv. oryzae, bacterial leaf blight pathogen of rice (in collaboration with Dr. Ramesh V. Sonti, CCMB)*

Xanthomonas oryzae pv. oryzae (Xoo) causes bacterial leaf blight, a serious disease of rice. LipA, a secretory virulence factor of Xoo, is implicated in degradation of rice cell walls and concomitant elicitation of innate immune responses such as callose deposition and programmed cell death. To understand the structural basis of LipA function, we solved the structure of LipA and its complex with β-octyl glucoside. High-resolution structural characterization of LipA reveals a ligand-binding domain, a unique functional attachment in the realm of well-studied hydrolase scaffold, with a distinct glucose recognition pocket. Structural and functional analysis of the sugar-binding site shows its essentiality for LipA to induce innate immune responses and to promote pathogenesis on rice. Conservation of the module in LipA across xanthomonads emphasizes its significance in this group of plant pathogenic bacteria and provides a remarkable example of the evolution of new functions around existing scaffolds in the context of pathogens.

5. Calcium Binding Proteins: *Structure-function studies on Calcium binding proteins (in collaboration with the group of Dr. Yogendra Sharma, CCMB)*

The project deals with understanding structural, metal binding & functional aspects of calcium binding proteins like neuronal calcium sensors and βγ-crystallins. Neuronal calcium sensors are a group of conventional EF-hand calcium binding proteins & play sensory roles in various Ca^{2+} dependent cellular functions. βγ-crystallin superfamily comprises of proteins involved in rendering the eye lens transparent and helps microbes counter stressful conditions. We found the domain to have calcium binding properties. To understand the effect of large scale sequence variation in βγ-crystallins we have solved the structures of βγ-crystallin domain of AIM1 from *Homo sapiens* and nitrollin, a βγ-crystallin from soil bacterium *Nitrosospira multiformis*. The study provides a holistic understanding of the calcium-binding properties of βγ-crystallins.

Achievements/Awards:

1)Wellcome Trust Senior Research Fellowship
2) Swarna Jayanti Award
3) Ranbaxi Science Scholarship Award (Medical Sciences)

Collaboration:

1) Dr. Rajesh S Gokhale's Group, National Institute of Immunology, New Delhi, India

CCMB Collaborations:

Dr. Yogendra Sharma, Dr. Ramesh V Sonti, Dr. N Madhusudana Rao

Publications:

- Aravind P, Suman SK, Mishra A, Sharma Y & Sankaranarayanan R (2008) *J. Mol. Biol.* (In Press).
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- Rao MR, Kumari G, Balasundaram D, Sankaranarayanan R & Mahalingam S (2006) *J. Mol. Biol.* 364, 637.
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- Acharya P, Rajakumara E, Sankaranarayanan R & Rao NM (2004) *J. Mol. Biol.* 341, 1271-1281.
- Sankaranarayanan R, Saxena P, Marathe U, Gokhale RS, Shanmugam VM & Rukmini R (2004) *Nature Struct. Mol. Biol.* 11, 894-900.
- Rukmini R, Shanmugam VM, Saxena P, Gokhale RS & Sankaranarayanan R (2004) *Acta Cryst.* D60, 749-751.
- Rajakumara E, Acharya P, Ahmad S, Shanmugam VM, Rao NM & Sankaranarayanan R (2004) *Acta Cryst.* D60, 160-162.
- Chatterjee S, Sankaranarayanan R & Sonti RV (2003) *Molecular Plant-Microbe Interactions* 16, 973-982.

Protein Structure-Function Bioinformatics (Dr. K. Guruprasad, guru@ccmb.res.in)

Background: Importance and motivation

In our group, we examine features in protein sequences and their relatedness to conformations in proteins of known three-dimensional structures. The knowledge derived from such analysis is useful for developing computational tools for protein structure prediction, modeling and design. The gap between proteins of known sequences inferred from genome projects and those of known three-dimensional structures obtained from central repository – the Protein Data Bank, is ever widening. Although, comparative protein modeling is useful to generate reliable models for a large number of proteins of known sequence of unknown structure, 'rules' derived for well-characterized structural motifs may provide an alternate route to predicting protein fold. This is particularly useful in situations where related proteins share less than 15% or so sequence identities ('twilight zone') that are not easily detected by heuristic methods, yet the proteins share a similar fold. This provides the necessary motivation for our work.

Focus and objectives

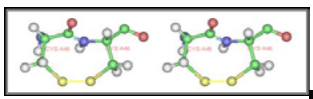
We analyze protein sequences and their corresponding conformations. Our objective is to develop novel methods for recognizing fold at the level of structural motifs.

Schematic organization of the program

We select a dataset of non-redundant protein sequences and structures for analysis of structural motifs and develop the required computer applications for this purpose.

Major results

We developed a database called PSSARD (1,2) that is useful to make flexible queries relating 'user-defined' peptide/protein sequences and to obtain the corresponding main-chain secondary structure conformations or vice-versa in proteins of known three-dimensional structures. We have developed a database HETATM (3) for analyzing the distribution of heteroatom groups in proteins of known three-dimensional structures, such as, metal ions, prosthetic groups, etc., and a simple program to identify their environment in protein structure. We have analyzed the intra-chain disulfide-bridges in proteins of known three-dimensional structure and have classified them on the basis of disulfide connectivity patterns and protein superfamily (4). This database is useful to recognize proteins with a common superfamily and disulfide connectivity pattern that may be useful for predicting proteins of unknown structure characterized by the known disulfide bond connectivity. Further, we have examined the conformations corresponding to intra-chain disulfide bridged peptides in protein structure (5) and observed certain unexpected juxtaposed half-cystines as disulfide bridged partners (6). We analyzed the statistically significant turn-type amino acid preferences for beta and gamma turns in enlarged representative datasets (7). We showed a number of instances where proline is observed at the third position in isolated beta-turn that was hitherto unexpected (8). We analyzed how simple structural motifs, such as, beta-turns and gamma-turns in protein structure are associated as multiple turns (9), continuous turns (10) or as combi nations of turns (11). This led to the development of a database of structural motifs in proteins (10) and we are continuing to work on this project at different hierarchical levels of domain architecture to infer sequence/structure relatedness.



Stereo-view of "Ring of 8-atoms" formed by juxtaposed half-cystines involved in a disulfide bridge in protein structure (6).

We have demonstrated based on large non-redundant dataset analysis and using the residue-coupled model that the prediction of known beta-turns and gamma-turns from their amino acid sequence is around 67% and 57%, respectively (12,13). We have analyzed the structural diversity associated with the beta-propeller architecture in protein structures (14) and developed a novel method to detect the beta-propeller architecture in an automated manner from proteins of known three-dimensional structures (15). We have proposed a three-dimensional model corresponding to the dimer of C-terminal domain of human αA and αB eye-lens crystallins (16) that identifies the positions of amino acid residues in the three-dimensional structure known to be important for oligomerization, chaperone activity and implicated in cataract. We recently identified a characteristic Glu/Arg side-chain constellation at the dimer interface of antiparallel coiled-coil in chorismate mutase from Thermus thermophilus HB8 (communicated).

Schematic representation of the secondary structure overlay corresponding to the dimer models of human alphaA -crystallin (dark) and human alphaB-crystallin (light). The N- and C-terminal ends for monomer 1 in the dimer are labeled as N1 and C1, respectively. The beta6 strand from monomer 2 extends the beta-sheet in monomer 1 by making an anti-parallel strand with beta2 strand in monomer 1 (16).

Publications:

1. *Int J Biol Macromol.* (2005) Sep;36(4), 259-62.
2. *Int J Biol Macromol.* (2007) Jun 1;41(1), 109-13.
3. *Int J Biol Macromol.* (2005) Oct 30;37(1-2) ,35-41.
4. *Int J Biol Macromol.* (2006) May 30;38(3-5), 174-9.
5. *Protein and Peptide Letters* (2008) 15(2), 160-87.
6. *Protein and Peptide Letters* (2006) 13(6), 577-9.
7. *J Biosci.* (2000) Jun;25(2), 143-56.
8. *Current Science.* (2000) Oct;79(7), 992-994.
9. *J Pept Res.* (2000) Oct;56(4), 250-63.
10. *J Pept Res.* (2001) Apr;57(4), 292-300.
11. *J Pept Res.* (2003) Oct;62(4), 167-74.
12. *J Pept Res.* (2003) Apr;61(4), 159-62.
13. *J Pept Res.* (2003) May;61(5), 243-51.
14. *Int J Biol Macromol.* (2004) Apr;34(1-2), 55-61.
15. *Int J Biol Macromol.* (2005) Aug;36(3), 176-83.
16. *Int J Biol Macromol.* (2003) Nov;33(1-3), 107-12.

Algorithms

A novel method for detecting beta-propeller architecture in proteins of known 3 dimensional structure.

Future plan and perspective

We intend to engage and develop methods where necessary in predicting protein fold from sequence, predicting protein function in the cellular context, protein interactions, protein design and to study protein dynamics.

Computational Analysis in Human Evolutionary Studies (Dr. K Thangaraj, thangs@ccmb.res.in)

India is well known for its cultural, linguistic and genetic diversity. This group has been carrying out research to establish the origin and affinities of anthropologically well-defined populations, inhabited in India, using uniparentally inherited Y chromosome and mitochondrial DNA markers. Mutations exist in the Y chromosome and the mtDNA defined different haplogroups of human, which would help in establishing genetic relationship among the populations of India. So far, they have analysed over 14,000 samples from 300 ethnic populations of India.

In order to analyse and interpret the huge data, they use suitable computational tools from bioinformatics and phylogenetic analysis. Large numbers of phylogenetic tools are now freely available in the web. Some of the popularly used software for the phylogenetic analysis are; CLUSTAL, PHYLIP, MEGA, ARLEQUINE, BATWING, NETWORK, STRUCTURE, ANCESTRY, etc. These software helps in revealing the genetic diversity, affinity, AMOVA, selection and level of admixture.

In addition to this they also calculate the effective male population size by analyzing highly evolving short tandem repeats (STR) within same SNP marker lineage of the ancestral migrating population. The most significant finding using the phylogenetic tools are - Origin of the "Negrito" tribes of Andaman Islands about 65,000 years before present, and origin of 25bp deletion in the MyBPC3 gene in the Indian subcontinent about 33,000 years before present.

Publications:

- Thangaraj et al (2005) *Science* 308, 996.
- Dhandapany et al (2008) *Nature Genetics* (in press).

Molecular Modeling and Computational Biology (Dr. R. Nagaraj, nraj@ccmb.res.in)

This group is working on peptide/protein conformation and membrane biochemistry employing various experimental and theoretical techniques. They study the conformational and structural aspects of the peptides by theoretical methods using Molecular modeling, Homology modeling, Simulated Annealing, Docking and Sequence Analysis techniques. The present work highlights some of these aspects in brief, for detail information one can refer to the publications.

Background importance and motivation

The de novo design of proteins has recently emerged as a powerful tool in the engineering of new materials. It is now possible to design and synthesize relatively small peptides with defined structure and function from already existing large proteins. This group is working mainly on sequencing, synthesis and designing of novel antibacterial and anti-microbial peptides through various experimental techniques. Despite intensive effort in peptide and protein design very few molecules with intrinsically stable secondary structure have been reported so far. The rapid increase of publicly available sequences and protein structure has made available a huge amount of information for any protein. It is of tremendous interest for the drug designers and other related pharmaceutical industries to engineer these host defense peptides, having activities as well as short lengths at the same time for potential therapeutic use. Computational analysis of the molecular function of these proteins is therefore crucial in order to interpret the data fruitfully and carry out further experiments. Large-scale computational analyses optimize, the selection of antibacterial, anti-microbial and anti-fungal peptides, which in turn enable the development of drug targets for therapeutic intervention. Techniques of Molecular Modeling, Homology Modeling and Docking methods and database searches along with sequence analysis become very useful in understanding these mechanisms.

Focus and Objective

Techniques of Molecular Modeling, Homology Modeling and Docking methods become very useful in understanding the structural aspects of peptides. Large-scale computational analyses optimize, the selection of anti bacterial, anti-microbial and anti-fungal peptides, which in turn enable the development of drug targets for therapeutic intervention. The rapid increase of publicly available sequences and protein structure have made available a huge amount of information for any protein that made possible the designing and synthesizing relatively small peptides with defined structure and function. It is of interest for the drug designers and pharmaceutical industries to engineer these host defense peptides, having activities as well as short length.

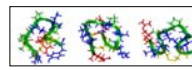
I. Consequences of Introducing a Disulphide Bond into an Antibacterial and Hemolytic Peptide -Molecular Modeling study

Molecular modeling studies conducted to understand the conformation of these peptides.

PKLLKTFLSKWIG Antibacterial & Hemolytic
CKLLKTFLSKWIC Linear Antibacterial activity Helical by CD
CKLLKTFLSKWIC Cyclic Hemolytic activity Distorted helix by CD

II. Tigerinins, Novel Antimicrobial Peptides from Indian Frog *Rana tigerina* – Molecular Modeling study--Novel peptides were extracted from Indian Frog's skin that showed antibacterial activity

FCTMIPIPRCY - am – Tigerinin 1
RVCFAIPLPICH - am – Tigerinin 2
RVCYAIPLPICY -am – Tigerinin 3



III. Molecular Modeling Studies of the Analogs of Bovine Neutrophil Beta Defensins (BNBD-2)

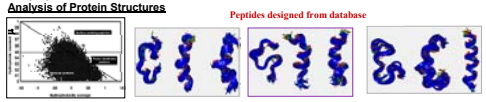
BNBD-2 is an antibacterial peptide containing 6 conserved cysteines forming 3 disulphide bonds the conformational aspects of the analog sequence in linear as well as cyclic forms and correlate the variations if any to the functions were studied using molecular modeling.

RCP$_1$GRTRQIGTIFP$_2$GRIKCRSW PEPT1
RCP$_1$ GRTRQIGTIFP$_2$ GRIKCRSW PEPT2
RCP$_1$ GRTRQP$_2$GTIFP$_3$ GRIKCRSW PEPT3
RCP$_1$ GRTRQP$_2$GTIFP$_3$GRIKCRSW PEPT4
RCP$_1$GRTRQIGTIFGP$_2$RIKCRSW PEPT5

Linear
Cyclic
PEPT1 PEPT2 PEPT3 PEPT4

IV. Amphipathic α-Helices in Proteins: Results from Analysis of Protein Structures

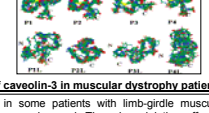
Peptides designed from database



V. Single Disulfide and Linear Analogues of Bovine β-Defensin-2: Introducing the β-Hairpin Nucleating Sequence D-Pro-Giv

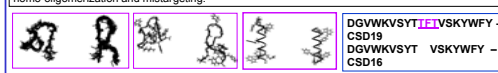
VRNHVTC$_1$RINRGFC$_2$VPIRC$_2$PGRTRQIGTC$_1$FGPRIKC$_2$C$_2$RSW (positions of disulfide bonds are C1-C5, C2-C4, and C3-C6)

RCP$_1$ GRTRQI GTIF G PRIKCCRSW -Nat
RCP$_0$ GRTRQI GTIF P$_0$ GRIKC RSW -P1
RCP$_1$ GRTRQI GTIF P$_1$ GRIKC RSW - P2
RCP$_2$ GRTRQP$_0$ GTIF P$_2$ GRIKC RSW - P3
RCP$_1$ GRTRQP$_1$ GTIF P$_1$ GRIKC RSW - P4



VI. Conformational studies on deleting a tripeptide of caveolin-3 in muscular dystrophy patients

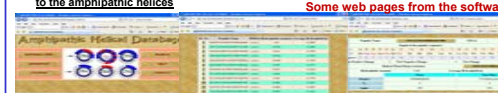
There have been reports of mutations in caveolin-3 in some patients with limb-girdle muscular dystrophy, deletion of three amino acids in the region was observed. The micro deletion affected homo-oligomerization and mistargeting.



DGVWKVSYTETVSKYWFY - CSD19
DGVWKVSYT VSKYWFY – CSD16

VII. Amphipathic Helices identified from PDB. Various Facets of The Distribution of Polar and Apolar Residues: Development of a database driven dynamic website having data related to the amphipathic helices

Some web pages from the software



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