CHAPTER 6

BIOPHYSICS

Doctoral Theses

01.   BANDANA KUMARI
        Bioinformatics Analysis of the Protein Sequence : Structure, Function Relationships.
        Supervisor : Dr. Manish Kumar
        <u>Th 24197</u>

Abstract
(Verified)

In a majority of proteins, a small region or sometimes entire protein may lack a well-defined structure or have repeats of similar amino acids. The unstructured regions of proteins are called as intrinsically disordered regions (IDRs) and repeat regions are called as low complexity region (LCR). Palmitoylation is a post-translational modification (PTM) often associated with the disordered regions of proteins. Experimental identification of palmitoylated amino acid is quite expensive and time consuming, hence despite of being an extremely important PTM, only limited number of palmitoylation sites have been identified. Hence we have developed two machine-learning based *in silico* methods for prediction of palmitoylation sites. The common palmitoylation prediction i.e. on cysteine can be predicted by PalmPred while rare palmitoylation i.e. on glycine and serine palmitoylation prediction method was called as *RARE*Palm for investigation and characterization before putting them for experimental verification. We also used association rule mining approach for detecting palmitoylation motif with help of statistically overrepresented amino acids near the palmitoylation sites. LCRs occupy nearly 15% of total proteome. But there is contrasting hypothesis about their structural and functional properties. Commonly LCRs are considered as surface-exposed disordered regions which act as neutral spacrs between protein domains. Our analysis revealed that LCRs may not always be highly accessible disordered region but may have secondary structures (mostly helix). Investigation about functional involvement of LCRs composed of single amino acid and those containing amino acids of similar functional groups showed both types are associated to nucleus, membrane enclosed lumen and non-membrane bounded organelle. They perform molecular functions specifically nucleotide and metal binding, transcription, transport and cell cycle. LCRs containing non-polar amino acids showed other functions also, such as signaling and innate immune response. Overall, LCRs containing honmopolymers or repeats of same functional groups have similar functional importance.

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1. Introduction 2. Review of literature 3. Prediction of cysteine palmitoylation 4. Prediction of rare palmitoylation events in proteins 5. Identifiying residues that determine palmitoylation using association rule minig 6. Correlation between structural and amino acid preferences in low complexity and disordered regions of proteins 7. Comparative functional analysis of proteins containing amyloidogenic low complexity regions 8. Summary & future prospects. Bibliography. Annexure.

02.   SRIVASTAVA (Abhishikha)
Computational Analysis of Beta – lactamase Mediate Antibiotic Resistance in Microbial Pathogens.
Supervisor: Dr. Manish Kumar and
TH 24198

Abstract
(Verified)

β-lactam antibiotics are among the most widely used antibiotics to cure bacterial infection sowing to their high efficiency, low cost and minimum side effects. However, enzymatic hydrolysis by bacterial β-lactamases is increasingly compromising their efficiency. β-lactamase enzymes encompass a large and diverse group of bacterial enzymes, which can be classified on the basis of primary structure-Ambler classification or on the basis of their functional characteristics-Bush classification. Ambler schema classifies β-lactamases into four classes, A, B, C, and D. Class A, C, and D are serine β-lactamases while class B is zinc containing metallo-β-lactamases. To reduce β-lactamase mediated resistance newer generation β-lactam antibiotics were discovered, which are more effective than their predecessors but have exerted a strong selection pressure resulting in the evolution of newer variants of β-lactamases, denoted as extended spectrum β-lactamases (ESBLs). The propagation of resistance in bacteria towards β-lactam antibiotics become a serious challenge and cannot be addressed until we gain a fair understanding of their sequence, structure and functional relationship. This thesis presents a comprehensive investigation of β-lactamase with some main finding including a comprehensive centralized database of β-lactamase, Support Vector Machine based prediction method for multiclass prediction and classification of β-lactamase, application of identifying zinc metal binding sites in metallo-β-lactamase and comparative functional and evolutionary studies to decipher the evolution of β-lactamase. Taken altogether, this dissertation provides comprehensive and centralized database, various prediction methods for multiclass classification of β-lactamase and also evolutionary pattern that influence the evolution of β-lactamase. We anticipate that study may help to extend the life of current antibiotics and also provides a clue towards the discovery of novel therapeutic drug targets.

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