Subject Name: Computational Structural Biology

Subject No: BT60007

Prerequisites: None

Objective: Functional units of a cell can be described as complex assemblies of several macromolecules. The fundamental building blocks for these complex assemblies are proteins and nucleic acids. Recent advancements in the field of structural genomics provide us the 3-dimensional repertoire of the cellular assemblies exemplified by nuclear pore complex, GroEl and so on, and help us to understand the molecular mechanism behind different cellular functions of these assemblies. However, the experimental methods to determine the structures of macromolecules and their assemblies have some limitations, and to overcome this, several computational methods have been developed. These methods have been widely used in the prediction of the structure of macromolecules such as protein, DNA and RNA, as well as they have been very successful in the prediction of the complexes involving them. They are also being used for de novo design of proteins with specific function. Computational Structural Biology not only help us to elucidate the structure of the large assemblies such as the ribosome complexes, chaperonin, and multienzyme complexes etc.; but also help us to understand the structural mechanism of their folding, function and assembly. Their stability, mode of assembly, biological function and target properties depend on the interactions between the component subunits. Study of these complex assemblies is not only important for their functional role in the cellular system but also they serve as major therapeutic targets in human healthcare

LTP- 3-0-0

Credit- 3

Content:

1. Fundamentals of biomolecular structure: Key concepts for the protein, DNA and RNA structures. Molecular interactions in tertiary structure, Fold space and evolution of the proteins. The quaternary structure of proteins and their association. Base-pair geometry in nucleic acids, conformation of the sugar phosphate backbone. DNA quadruplexes, RNA duplexes. Mismatched in bulged RNA. Structure and function of Ribosome. [5 lectures]

2. Computational aspects of macromolecular structure and assemblies: The structure of macromolecules and their file format. Introduction to computer programs to handle these files. Methodology for all atom contact analysis. Methods for structural comparison. Mapping protein fold space. The impact of structural genomics. [7 lectures]

3. Structure and function assignment of macromolecules: Computational methods for structural assignment of proteins and nucleic acids. Identification of structural domains. Folding of protein and nucleic acids. Flexibility

in macromolecules. Surface cleft and binding pockets. High throughput function prediction. Structure prediction and overview on CASP.

[7 lectures]

4. Structural annotation of Genomes: Availability of completed genomes. Methodologies available for identifying structural protein domains in genomes. Structural genome annotation resources.

[3 lectures]

5. Macromolecular interactions: Bonded and non-bonded interactions involved in folding and assembly of macromolecules. Analysis of intra and intermolecular interactions in the stability of macromolecules and their assembly. Prediction of protein-protein and protein-nucleic acids interactions. Overview on docking methods HADDOCK, ATTRACT, HEX, ligand design, and validating data sets. Search algorithms in docking and scoring functions. Binding site prediction and annotation. Overview on CAPRI.

[8 lectures]

6. Cellular machines: Overview on the structure of Ribosome, Proteasome, Nucleosome, Viral capsids. Computational tools for the structural analysis of the macromolecular interactions in these assemblies to understand their assembly pathways. [4 lectures]

7. Computational Structural Biology and Drug Discovery: Historical development. Modern drug discovery. Drug targets identification and assessment (ex. Kinases and other ATPases; Proteases). Protein flexibility and drug design. Protein-protein interaction *hot spots*. Towards personalized medicine.

[3 lectures]

8. Future challenges: Folding process for membrane proteins. Computational methods for the identification of membrane proteins and the prediction of their structures. The significance and impacts of protein disordered and conformational variants. [3 lectures]

Text books:

1. Proteins structures and molecular properties by T. E. Creighton.
2. Structural Bioinformatics by Jenny Gu and Philip E. Bourne
3. Bioinformatics and Functional Genomics by J. Pevsner
4. Protein-protein complexes; analysis, modeling and drug design. Edited by Martin Zacharias.

5. Computational Structural Biology: Methods and Applications by Torsten Schwede and Manuel C. Peitsch.
6. Molecular conformation and Biological interactions by P. Balaram and S. Ramaseshan.