

STRUCTURAL AND COMPUTATIONAL BIOLOGY

Students' learning outcomes

After studying this chapter, students will be able to:

1. [B-12-L-01] Define structural biology.
2. [B-12-L-02] Explain that structure determination of biomolecules is important.
3. [B-12-L-03] Describe how X-ray crystallography works.
4. [B-12-L-04] Outline the online databases where biomolecule structures are available.
5. [B-12-L-05] Describe computational Biology.
6. [B-12-L-06] Define Sequence Homology.
7. [B-12-L-07] Define Structural Homology.

As you learned in biotechnology chapter, that it is an emerging and ever growing branch of biology. It has many subfields including genetic engineering, synthetic biology, structural biology, computational biology, bioinformatics and many others. Here we will learn about structural and computational biology.

12.1 STRUCTURAL BIOLOGY

The study of the 3D structure and organization of biological molecules, such as proteins, nucleic acids (DNA/RNA), lipids, and carbohydrates, to understand their function, interactions, and role in biological processes is known as structural biology.

The emphasis of structural biology includes determining molecular structure, understanding molecular function and macromolecular complex formations. The techniques used are X-ray crystallography, Nuclear Magnetic Resonance (NMR) spectroscopy, Cryo Electron Microscopy (Cryo-EM), molecular dynamics simulations, bioinformatics and computational modelling.

The aims of structural biology are explaining biological mechanisms, developing new treatments, designing novel biomolecules and understanding disease mechanisms.

The advances in structural biology are applied in drug discovery and development, vaccine design, enzyme engineering, cancer research and neurological disorder studies.

12.2 THE IMPORTANCE OF STRUCTURAL DETERMINATION OF BIOMOLECULES

Determining the three-dimensional (3D) structure of biomolecules, such as proteins, DNA, and RNA, is crucial for understanding how they function in our bodies. This information is essential for understanding biological processes, developing life-saving treatments, and advancing biotechnology. Continued research in this field will unlock new discoveries, improving human health and quality of life.

- a. **Understanding Function and Mechanism:** The structure of a biomolecule reveals its function. Imagine a key and a lock - the structure of the key determines how it fits into the lock. Similarly, the structure of a biomolecule determines how it interacts with other molecules. Knowing the structure helps us understand how biomolecules perform specific tasks, such as enzyme catalysis or protein-protein recognition.
- b. **Designing Life-Saving Treatments:** Accurate structural information enables the design of targeted therapies. By knowing the shape and chemical properties of a biomolecule, researchers can create drugs that specifically bind to and inhibit or activate it. This has led to breakthroughs in treating diseases like cancer, HIV, and Alzheimer's.
- c. **Understanding Disease Mechanisms:** Structural biology helps us comprehend disease mechanisms. By studying the structure of disease-associated biomolecules, we can identify vulnerabilities to target with treatments. For example, understanding the structure of the influenza virus has informed vaccine development.
- d. **Advancing Biotechnology:** Structural biology drives innovation in biotechnology. Knowing biomolecular structures enables the design of novel enzymes, biosensors, and biomaterials. This has led to advancements in biofuels, agriculture, and biomedical devices.
- e. **Enabling Personalized Medicine:** Structural biology informs personalized medicine. By understanding individual variations in biomolecular structures, researchers can develop tailored treatments. This approach has shown promise in *cancer treatment and genetic disorders*.

12.3 X-RAY CRYSTALLOGRAPHY

X-ray crystallography is a powerful tool for determining the three-dimensional (3D) structure of biomolecules, such as proteins, DNA, and RNA. X-ray crystallography has revolutionized our understanding of biomolecular structure and function, enabling breakthroughs in medicine, biotechnology, and materials science. This technique uses X-rays to scatter off electrons in a crystallized biomolecule, producing a diffraction pattern that reveals the molecule's atomic structure. It has following steps:

Step 1: Crystallization

The process begins with crystallizing the biomolecule. This involves dissolving the molecule in a solution and slowly cooling or evaporating the solvent to form a crystal lattice. The crystal must be high-quality, with uniform orientation and minimal defects.

Step 2: X-Ray Diffraction

The crystal is then exposed to a beam of X-rays, which scatter off the electrons in the biomolecule. This scattering produces a diffraction pattern, consisting of intense spots or reflections. The diffraction pattern is captured on a detector, such as a CCD camera.

Step 3: Data Collection and Processing

The diffraction data are collected and processed using specialized software. The data are indexed, integrated, and scaled to produce a set of reflection intensities. These intensities represent the amplitude of the scattered X-rays. The reflection intensities are used to reconstruct the 3D electron density map of the biomolecule. This is achieved through mathematical techniques. The electron density map reveals the arrangement of atoms within the molecule.

Step 4: Model Building and Refinement

A molecular model is built into the electron density map, using software. The final result is a precise 3D structure of the biomolecule, revealing its atomic arrangement, bond lengths, and angles. This information is essential for understanding biological mechanisms, designing drugs, and engineering biomolecules.

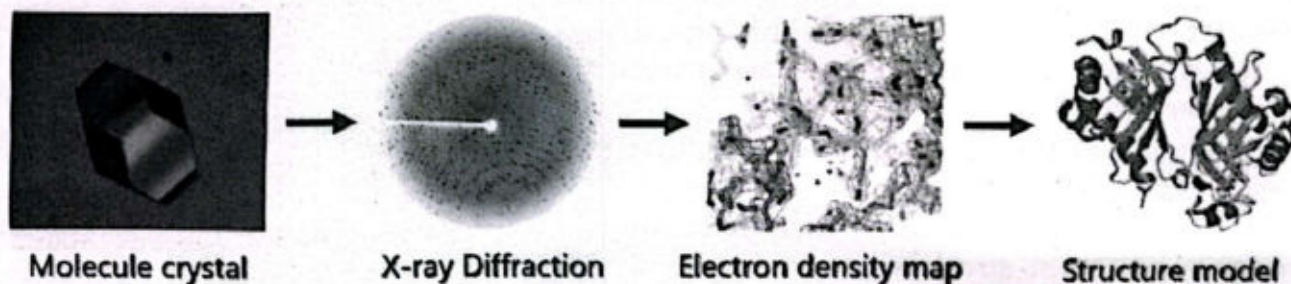


Fig. 12.1: X-ray crystallography

12.4 ONLINE DATABASE FOR BIOMOLECULE STRUCTURES THE PROTEIN DATA BANK (PDB)

The Protein Data Bank (PDB) is a freely accessible online database (www.wwpdb.org) that stores and provides three-dimensional (3D) structural information of biomolecules, including proteins,

nucleic acids, lipids, and carbohydrates. Established in 1971, the PDB is managed by the Worldwide Protein Data Bank (wwPDB) consortium, comprising leading research institutions and organizations. The database has grown exponentially, now containing over 180,000 biomolecule structures.

The PDB contains 3D atomic coordinates for biomolecules, structural information, experimental and functional data. The PDB serves as a cornerstone for biomolecular research, providing essential structural information to advance our understanding of biological processes and develop innovative treatments.

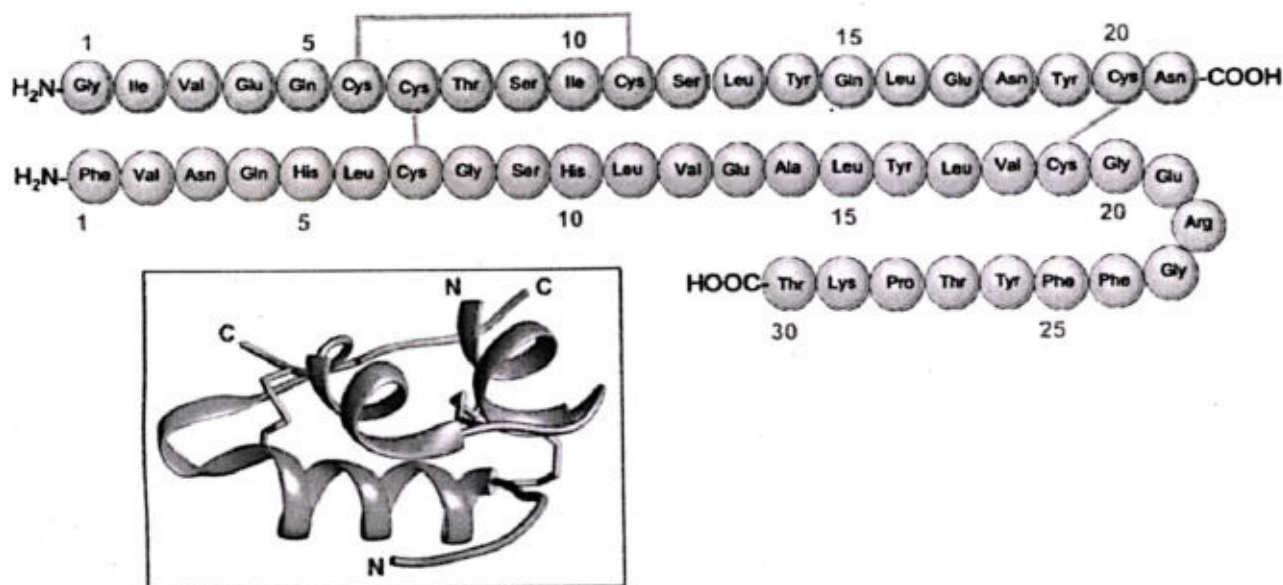


Fig. 12.2: Insulin structure details on PDB

12.5 COMPUTATIONAL BIOLOGY

Computational biology is an interdisciplinary field that combines computer science, mathematics, and biology to analyse and model biological systems. This field utilizes computational tools and methods to understand complex biological processes, interpret large datasets, and make predictions.

Computational biology is applied in personalized treatments based on individual genetic profiles, understanding gene regulation and function, modelling protein 3D structures, rapid analysis of large data, understanding of complex biological systems and disease mechanisms, phylogenetic and synthetic biology.

Tools and methods used in computational biology are algorithms, machine learning, database management and programming languages.

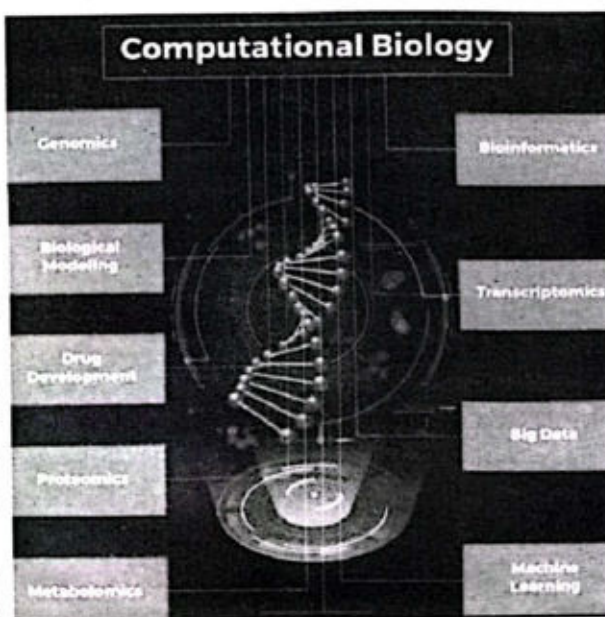


Fig. 12.3: Key areas of computational biology

By integrating computer science and biology, computational biology continues to advance our understanding of life and improve human health.

12.6 COMPUTATIONAL EVOLUTIONARY BIOLOGY

Computational evolutionary biology uses computational methods and algorithms to study evolution, particularly by analysing large data sets of genomics, transcriptomics and other related biological information.

Homology is the similarity of the structure, physiology, or development of different species of organisms based upon their descent from a common evolutionary ancestor. Here we will discuss sequence and structure homology.

12.7 SEQUENCE HOMOLOGY

Sequence homology is the study of similarities and relationships between biological sequences, such as DNA, RNA, or protein sequences. This concept is fundamental to understanding evolutionary relationships, functional conservation, and genetic diversity.

Sequence homology is the presence of shared sequences or structural features between two or more biological molecules, indicating a common ancestral origin.

Sequence homology provides a powerful tool for understanding the intricate relationships between biological sequences, shedding light on the complex history of life on Earth.

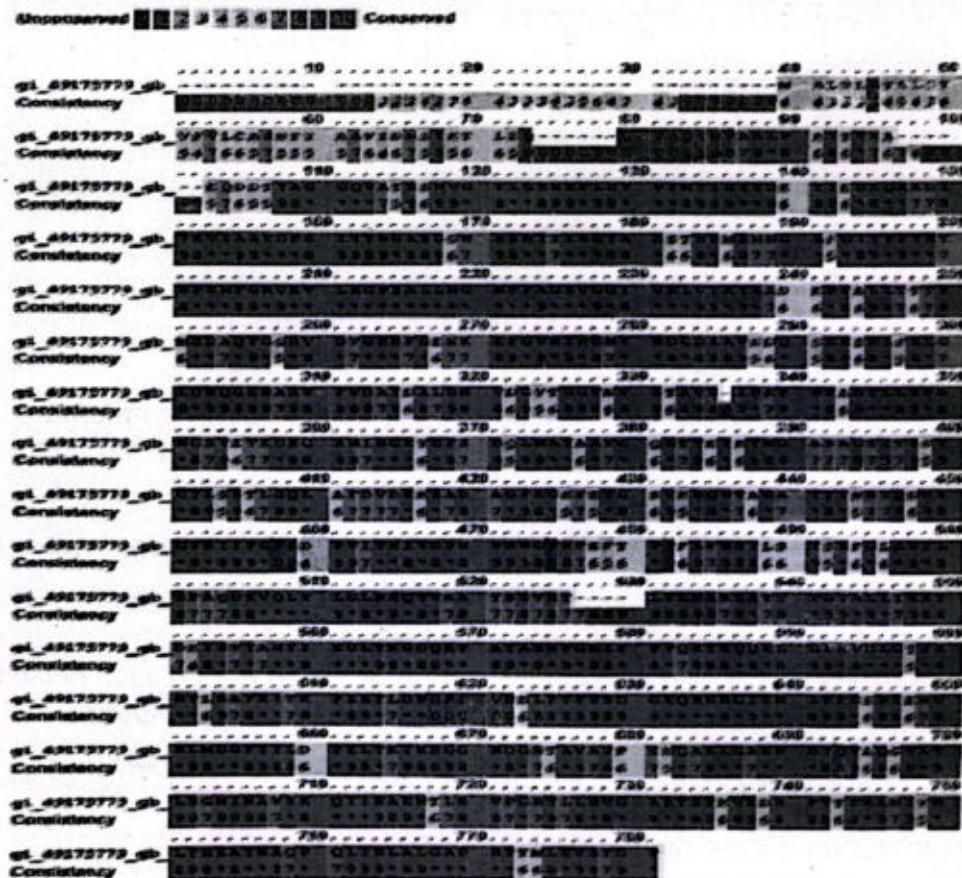


Fig. 12.4: BauA sequence homology shown in 25 samples. BauA is a protective antigen found in mice that is why its sequence is conserved in most samples.

12.8 STRUCTURAL HOMOMOLOGY

Structural homology refers to similarities in three-dimensional (3D) structures among biological molecules, such as proteins, RNA, or DNA. This concept reveals shared architectural features, indicating evolutionary relationships or functional conservation.

Structural homology is the presence of similar 3D structures or substructures between two or more biological molecules, suggesting a common ancestral origin or functional analogy.

Structural homology provides valuable insights into the shared architectural features of biological molecules, illuminating the complex relationships between structure, function, and evolution.

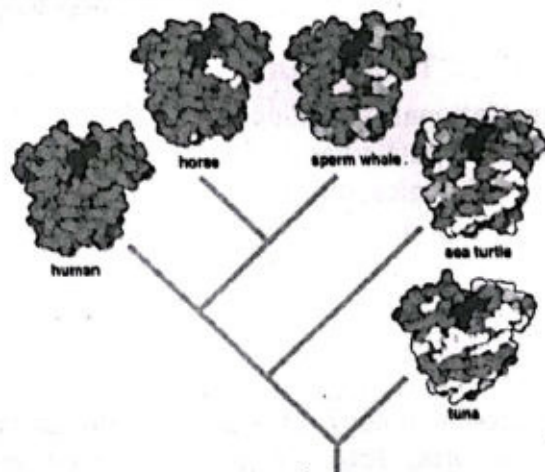


Fig. 12.5: Structural homology of Myoglobin molecule in different mammals

EXERCISE

Section I: Multiple Choice Questions

Select the correct answer:

- The function of protein is very much dependent on its:
 - size
 - number of amino acids
 - 3D structure
 - types of amino acids
- Structure of biomolecules can be very helpful to understand the:
 - spread of diseases
 - mechanism of diseases
 - cause of diseases
 - symptoms of diseases
- Lock and key model is applicable to:
 - active site of enzyme and substrate
 - hormones and their receptors
 - antigens recognized by antibodies
 - all of above
- Targeted therapies can be more effective against:
 - bacterial infections
 - viral infections
 - metabolic diseases
 - syndromes
- There are more than 200 types of cancers. Proper treatment of a specific cancer requires personalized medicines because each cancer has a:
 - different name
 - different effect on each person
 - specific cell surface marker
 - different set of symptoms
- X-ray crystallography cannot be done on liquid or gaseous sample because:
 - 3D electron maps are formed on solids
 - X-ray diffraction is done on crystals
 - solutions on evaporation form solids
 - gases on slow cooling can form liquids

7. As a Pakistani student you can access the Protein Data Bank:
- by using VPN
 - after paying require fee
 - freely via internet
 - if you get reference letter from concerned department
8. The rRNA sequence of all organisms has homology. It shows that all organisms:
- use ribosomes for protein
 - have same size of ribosomes
 - have evolved from common ancestor
 - have same types of ribosomes
9. Structural homology of myoglobin in different mammals is helpful for these organisms as:
- it gives their meat red colour
 - similar shapes are related with similar functions
 - myoglobin can replace haemoglobin function when required
 - different mammals eat each other so they can use it in their bodies
10. The Protein Data Bank provide information about:
- all molecules
 - all proteins
 - all enzymes
 - all biomolecules

Section II: Short Answer Questions

- How is the structure of molecule is related with its function?
- How does structural biology give hope to cancer treatment research?
- If you want to study the structure of pepsin enzyme, what will you do?
- Which fields of science are related to computational biology?
- Define structural biology, X-ray crystallography, computational biology, PDB, sequence homology and structural homology.

Section III: Extensive Answer Questions

- Why is it necessary to determine the structure of biomolecules?
- Describe the steps of X-ray crystallography.
- Differentiate between sequence and structural homology.