A Journey from X-ray Crystallography to 3-Dimensional Protein Structures

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Abstract

Biological macromolecules such as proteins serve a very crucial function in all biological processes. Protein structure plays a key role in determining its function; therefore, one of the key areas of structural biology is inferring how proteins work by analyzing their three-dimensional structure. The availability of atomic resolution structure provides for a broader and more revolutionary understanding of protein function, as well as contributes to the unraveling of the inner workings of living cells. The need for an understanding of protein structures assists in determining their functionality and interactions with other macromolecules. The three-dimensional structure of proteins can be determined using X-ray crystallography and computational analysis. This project will allow to go through the training to determine the 3-D model structure of proteins from the information gathered from X-ray crystallography using CCP4i graphical interface suite. The structural analyses can further provide insights to target disease and play an important role in drug design and therapeutics.

Background

Proteins are an important class of biological macromolecules with one of the most complex and refined structures. Proteins are the most abundant organic molecule and constitutes the basis of structure and function of life. The biological function of a protein is determined by the arrangement of atoms in its three-dimensional structure. This could refer to how catalytic residues are arranged in an active site or how a protein interacts with other molecules. Determining the structure of a protein allows us to have a greater understanding of how it functions and to formulate theories about how to modify, control, or alter the structure. The three-dimensional structure of proteins are then submitted in protein data bank, an inventory resource that contains over 9,000 structures available from X-ray data (https://www.rcsb.org).

Matrix Metalloproteinases and Tissue Inhibitors

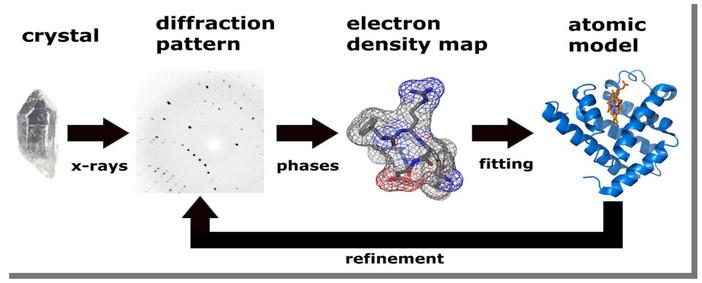
Matrix Metalloproteinase-10/TIMP-1 Structure

TIMP and MMP

Tissue inhibitors of metalloproteinases (TIMPs) are found in abundance in both the animal kingdom and human DNA. TIMPs were first identified as inhibitors of matrix metalloproteinases (MMPs), but their range of activities has now been expanded to encompass inhibition of other disintegrin-metalloproteinases, such as ADAMs and ADAMTSs. As a result, TIMPs are important regulators of metalloproteinases that destroy the extracellular matrix and shed cell surface molecules. MMP expression and activity are upregulated in almost all types of human cancer. Further understanding and development of these structures aid in the development of treatments.

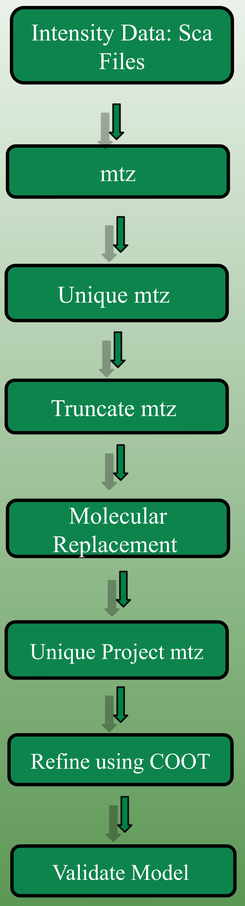
X-Ray Crystallography

The most utilized method for determining the structure of proteins and biological macromolecules is through x-ray crystallography. A high-concentration pure sample is crystallized, and the crystals are then subjected to an x-ray beam. The resulting diffraction patterns can then be examined to learn more about the crystal's packing symmetry and the size of the repeating units that makes up the crystal. This is determined by the diffraction spot pattern. The spots' brightness can be used to calculate "structure factors," which can subsequently be utilized to create an electron density map.



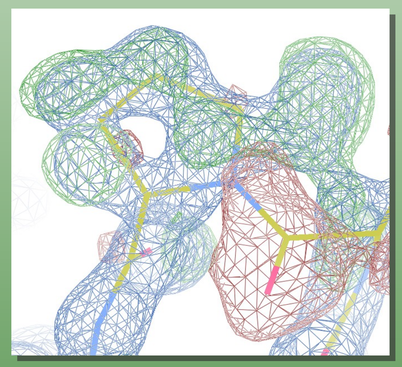
[2]The above illustrates the process from obtaining a crystal to the design of three-dimensional structure.

Method - CPP4i Graphical Interface



CCP4i (Collaborative Computational Project, Number 4) was established in 1979 among researchers in the United Kingdom for software developers to communicate and collaborate with regards to academic macromolecular crystallography. This suite consists of a collection of independent programs that interact via standard data files, rather than a single large program that performs all operations.

This suite is one universal platform to develop three-dimensional structures of proteins. This is a crucial step in refinement process in order to precisely alter the function.

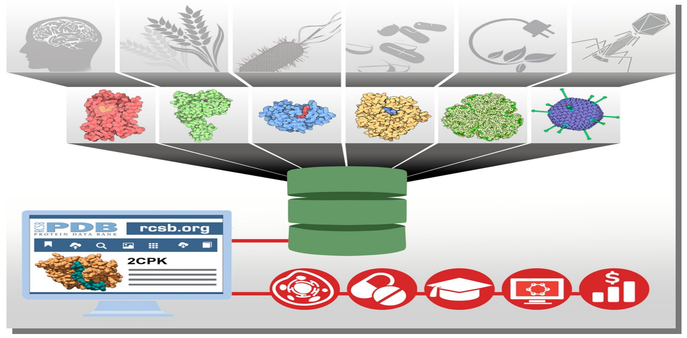


[4]The figure above shows the decoding journey from a protein crystal to three-dimensional structure model.

Conclusion/ Further Directions

Protein crystal structures are frequently utilized to deduce biology and structure-based medication development. Understanding the function of proteins allows for advancements in biomedicine, health and disease prevention, and agriculture. However, it is critical to first computationally design a precise and dependable protein model that provides confidence in the protein's interpretation. Knowing the three-dimensional structure allows for the proteins to be modified to preform a desired function. These complex macromolecules hold the key to modifying and altering their structures to change biological processes.

Future directions include learning different tools to solve 3D structure on CCP4 interface, including COOT, for refining the final model. Once the model is fully refined, we will move to the next step of validation by utilizing protein data bank platform.



[5]The image above illustrates the different areas protein structure contribute to further development.

References and Acknowledgments

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