**Protein Tertiary Structure Prediction**

**What is Tertiary Structure?**

Overall 3D folding of a single polypeptide chain.

* Stabilized by:
  + Disulfide bridges.
  + Hydrophobic interactions.
  + Ionic bonds.
  + Hydrogen bonds.
* Functional importance: enzyme active sites, receptor binding, protein–protein interactions.

**Analogy:**

* Primary structure = letters.
* Secondary = words (helix, sheet).
* Tertiary = complete sentence (meaningful function).

**Experimental vs Computational Methods**

1. **Experimental Approaches**
   * **X-ray crystallography** → very accurate, but time-consuming & costly.
   * **NMR spectroscopy** → good for small proteins.
   * **Cryo-EM** → works for large complexes, Nobel Prize 2017.
2. **Computational Approaches**
   * **Homology modeling** → predict structure using a similar known protein.
   * **Threading (Fold recognition)** → fit sequence into a library of known folds.
   * **Ab initio** → predict from scratch using physics-based rules (computationally heavy).

**Modern Advances in Structure Prediction**

* **SWISS-MODEL**: Online homology modeling tool.
* **I-TASSER**: Combines threading + ab initio methods.
* **AlphaFold (DeepMind)**: Revolutionized the field; predicts near-experimental accuracy using AI.
* Applications:
  + Drug discovery.
  + Understanding effects of mutations.
  + Protein engineering & synthetic biology.

**🧪 Lab Session: Predicting Protein 3D Structure**

**Objective:** Explore computational tools for tertiary structure prediction.

**Steps:**

1. Collect sequence of insulin protein (UniProt).
2. Use **SWISS-MODEL**:
   * Paste sequence → Generate 3D model.
   * Visualize model (helices, sheets, loops).
3. Compare predicted model with known PDB structure of insulin.
4. (Optional advanced) Explore **AlphaFold Protein Structure Database**.

Tasks**:**

* Students choose one protein sequence (enzyme, hormone, etc.).
* Predict structure online.
* Discuss: *What functional sites can you identify in your protein?*

**Quick Review Questions**

1. What is the difference between homology modeling, threading, and ab initio methods?
2. Why is AlphaFold considered a breakthrough in protein structure prediction?
3. How do experimental and computational methods complement each other?