Homology modelling

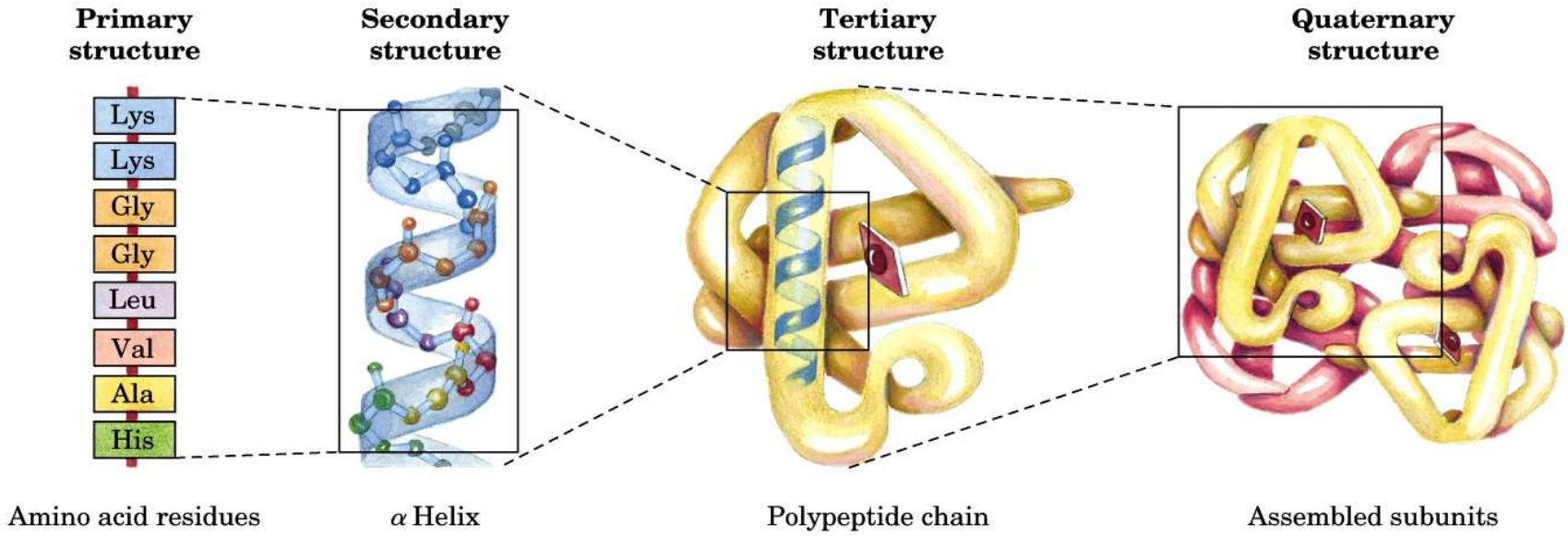
David Abia
dabia@cbm.csic.es

https://tinyurl.com/HMTH26

From Sequence to Structure

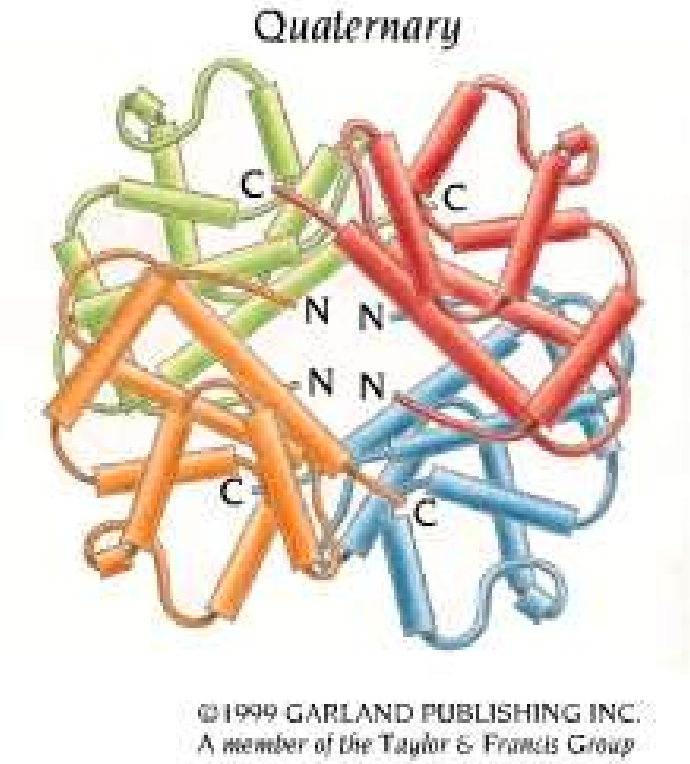
Protein structure is hierarchic:

- Primary – sequence of covalently attached amino acid
- Secondary – local 3D patterns (helices, sheets, loops)
- Tertiary – overall 3D fold
- Quaternary – two or more protein chains



Many Factors Influence Protein Folding

Protein



Proteins Assume the Lowest Energy Structure

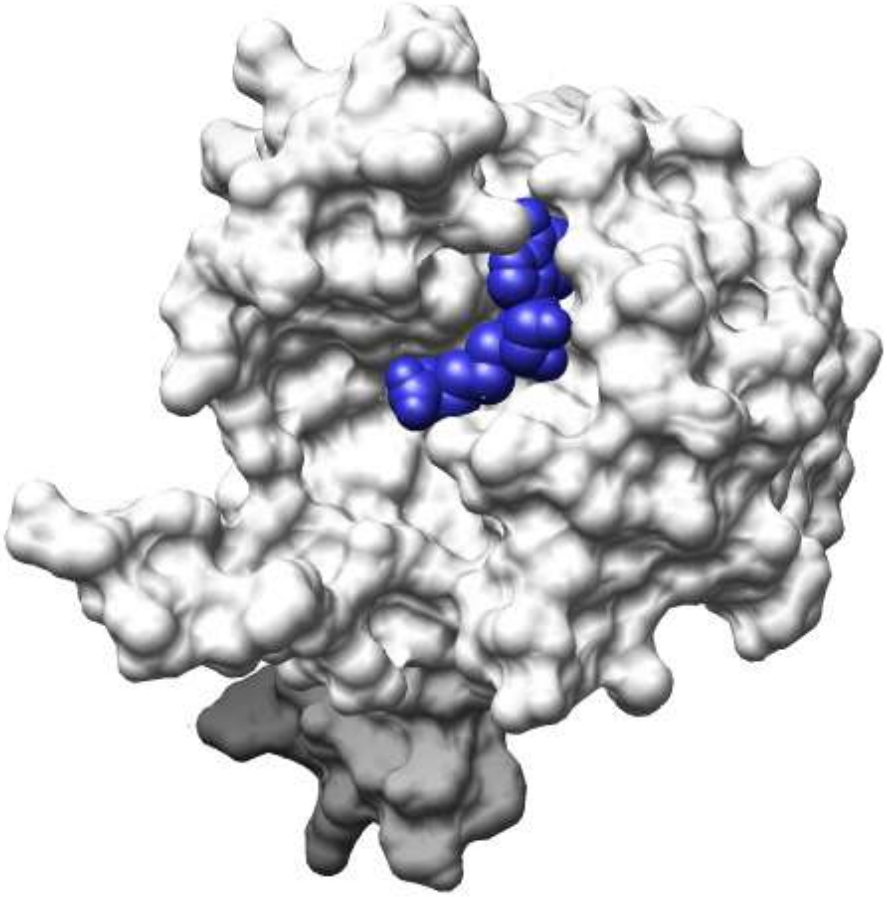
Factors that influence folding include:

1. **Hydrophobic Interactions** / collapse (particularly within the core)
2. **Hydrogen bonds** – lead to secondary structures
3. **Disulfide Bonds** (Cysteine residues)
4. **Salt Bridges** / Ionic Interactions (among charged residues)
5. **Multimeric interactions** with same type or other proteins

Protein 3D Structures

A protein's structure has a critical effect on its function:

1. Binding pockets

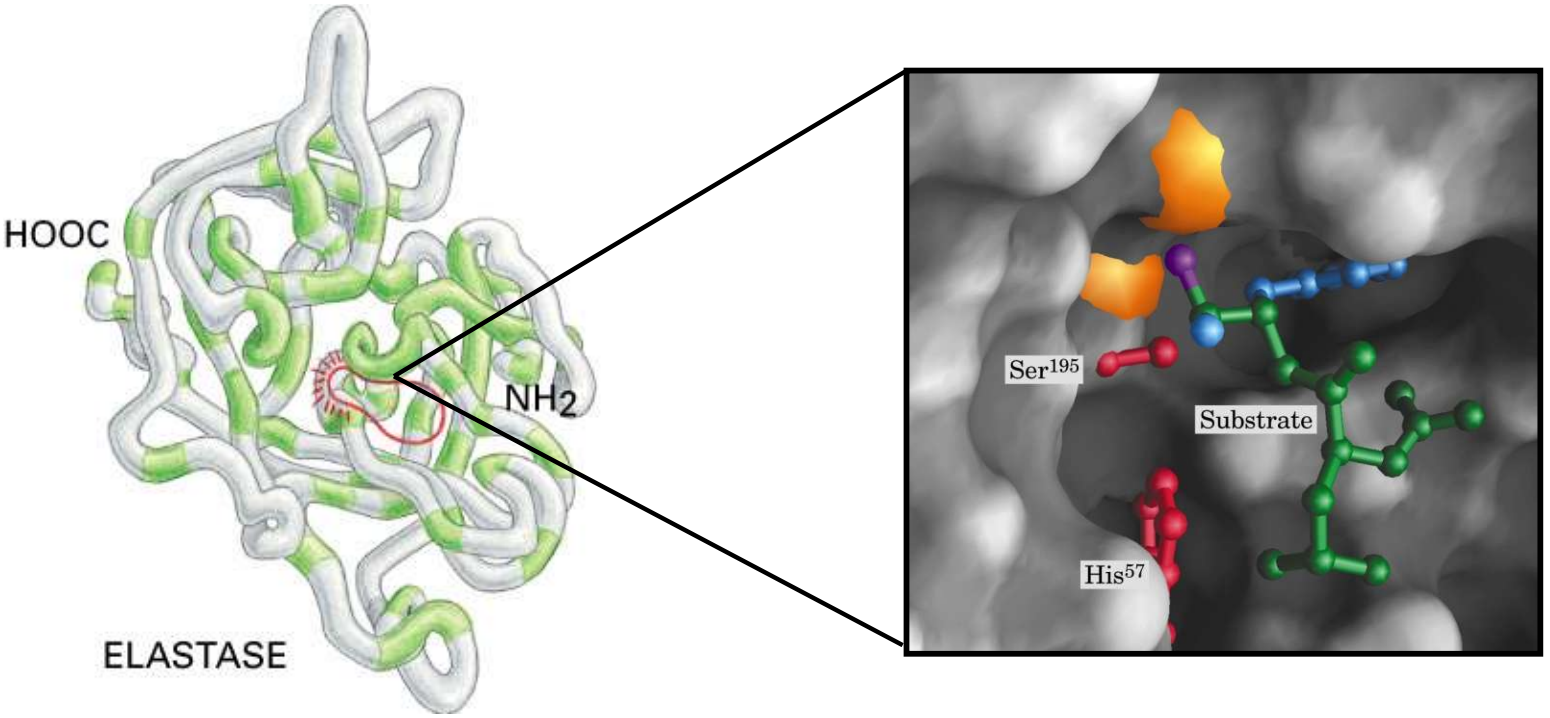


PDB ID 1nw7

Protein 3D Structures

A protein's structure has a critical effect on its function:

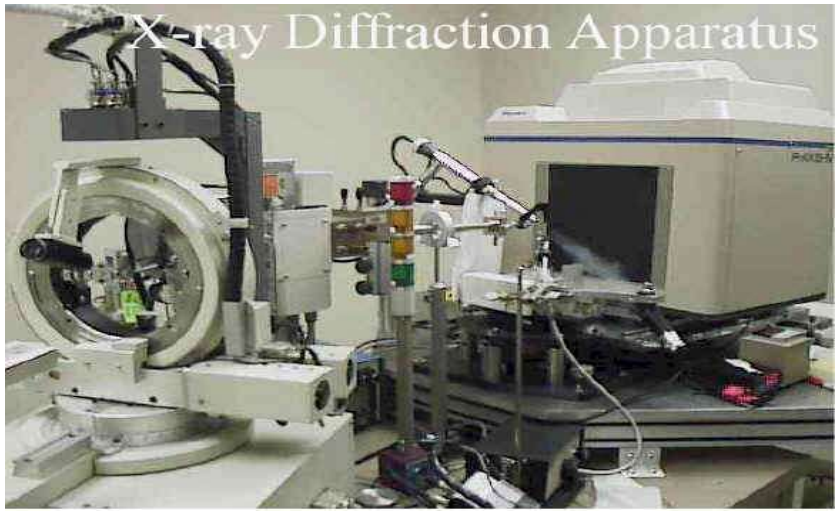
2. Areas of specific chemical\electrical properties

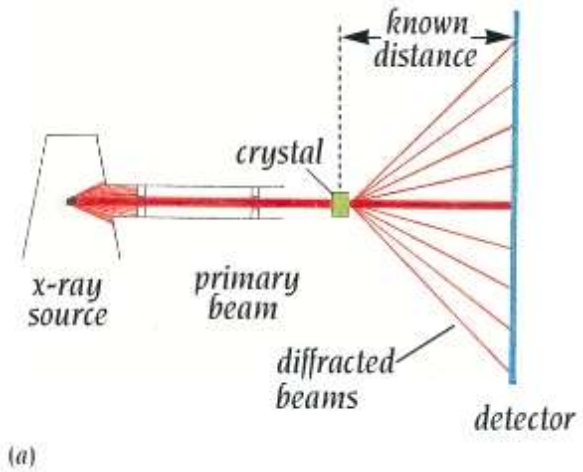


Experimental Methods of Structure Determination

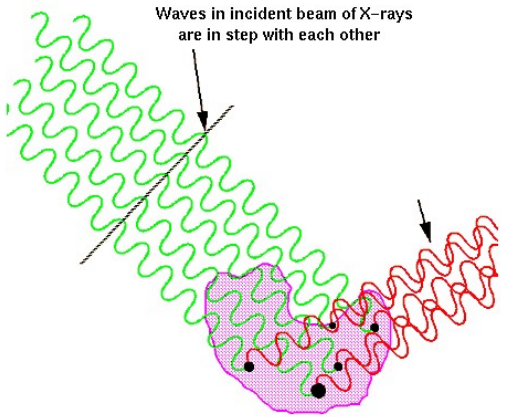
X-ray crystallography

High resolution structure determination



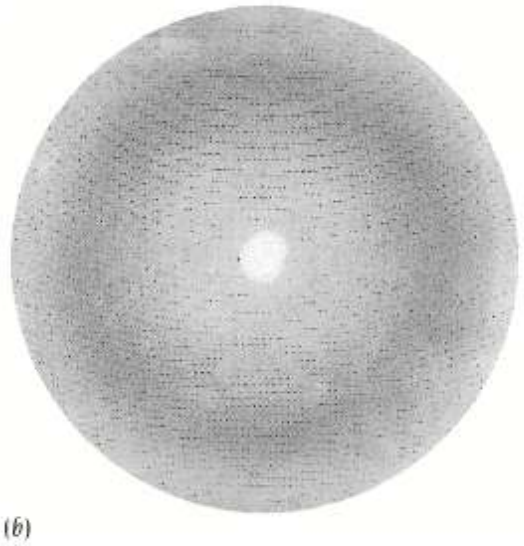


Scattering from the atoms in a molecule



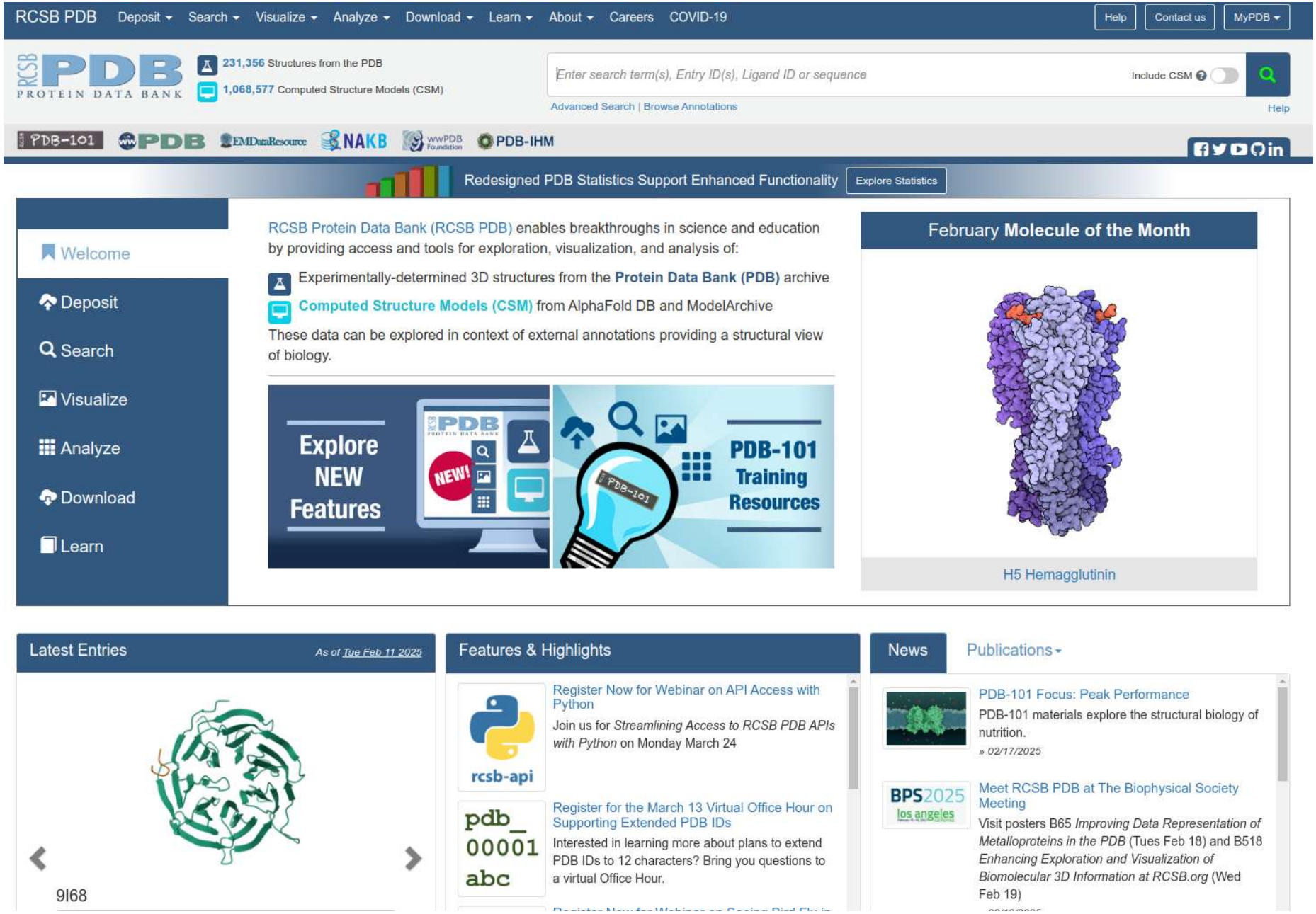
The scattered waves are all shown as having the same amplitude – in practice, the amplitude would vary in proportion to the number of electrons associated with the atom

ACT North 1997



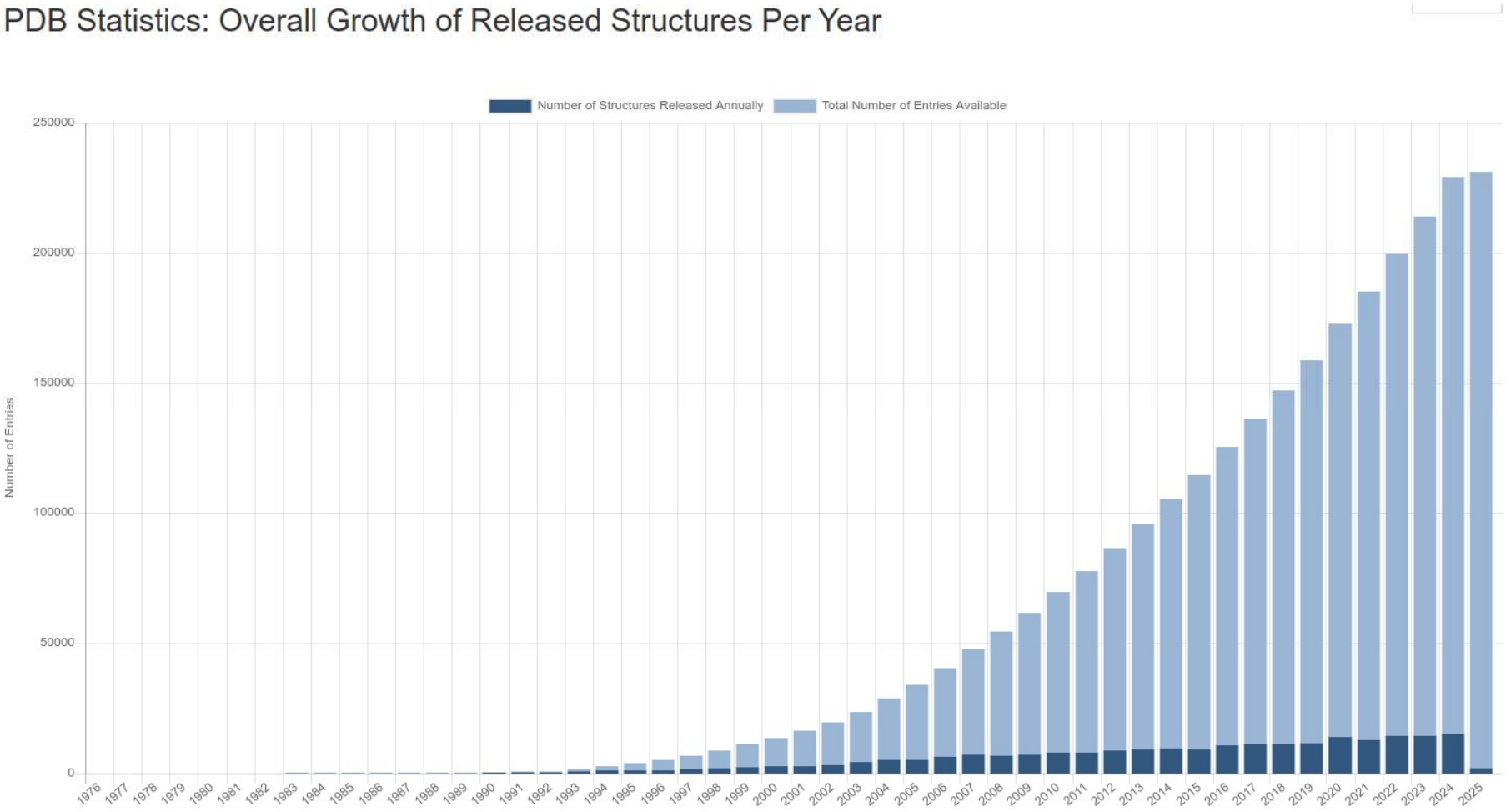
Database of Protein Structures

PDB – Protein Data Bank: https://www.rcsb.org/



Database of Protein Structures

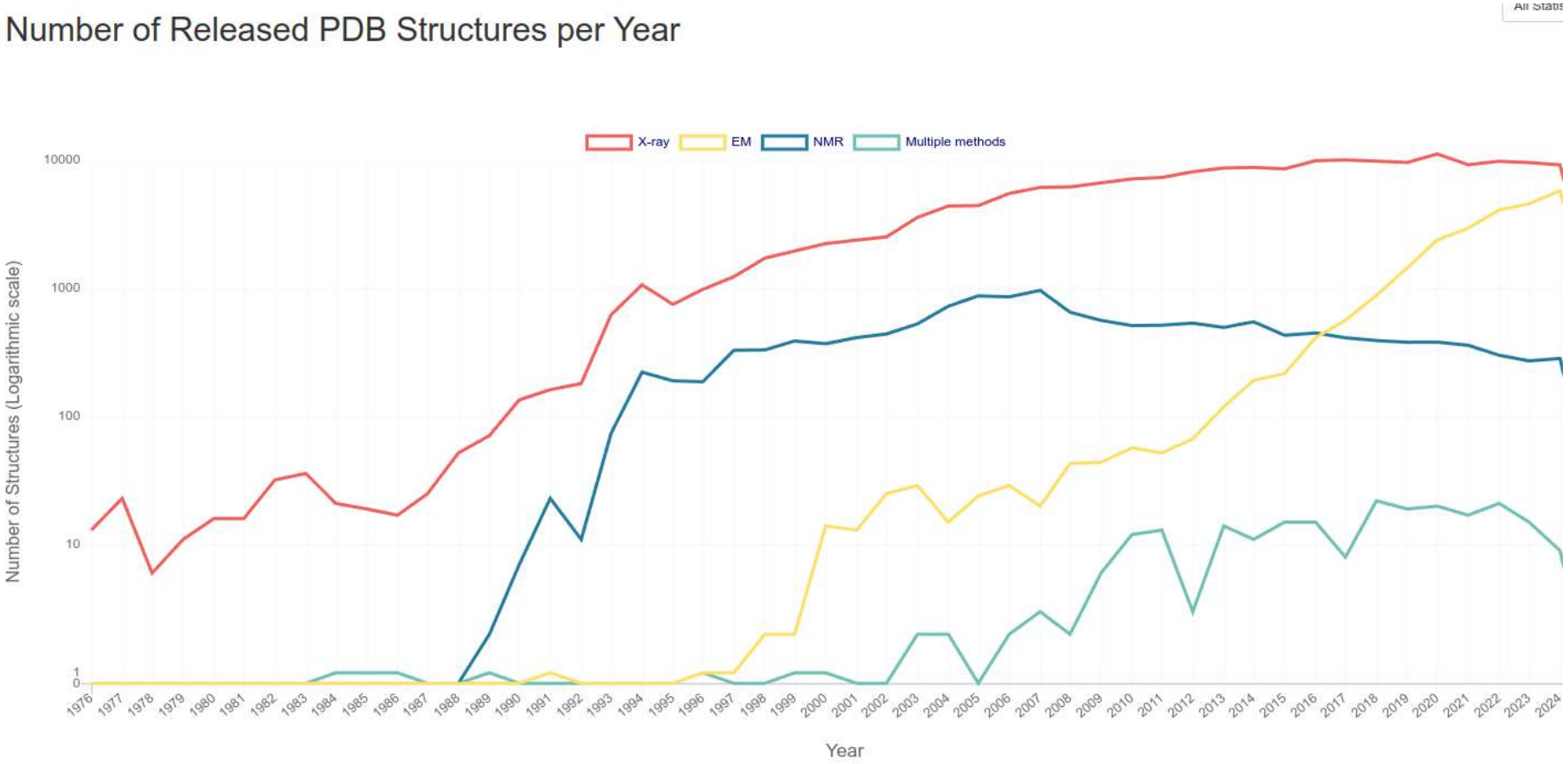
https://www.rcsb.org/stats/growth/growth-released-structures

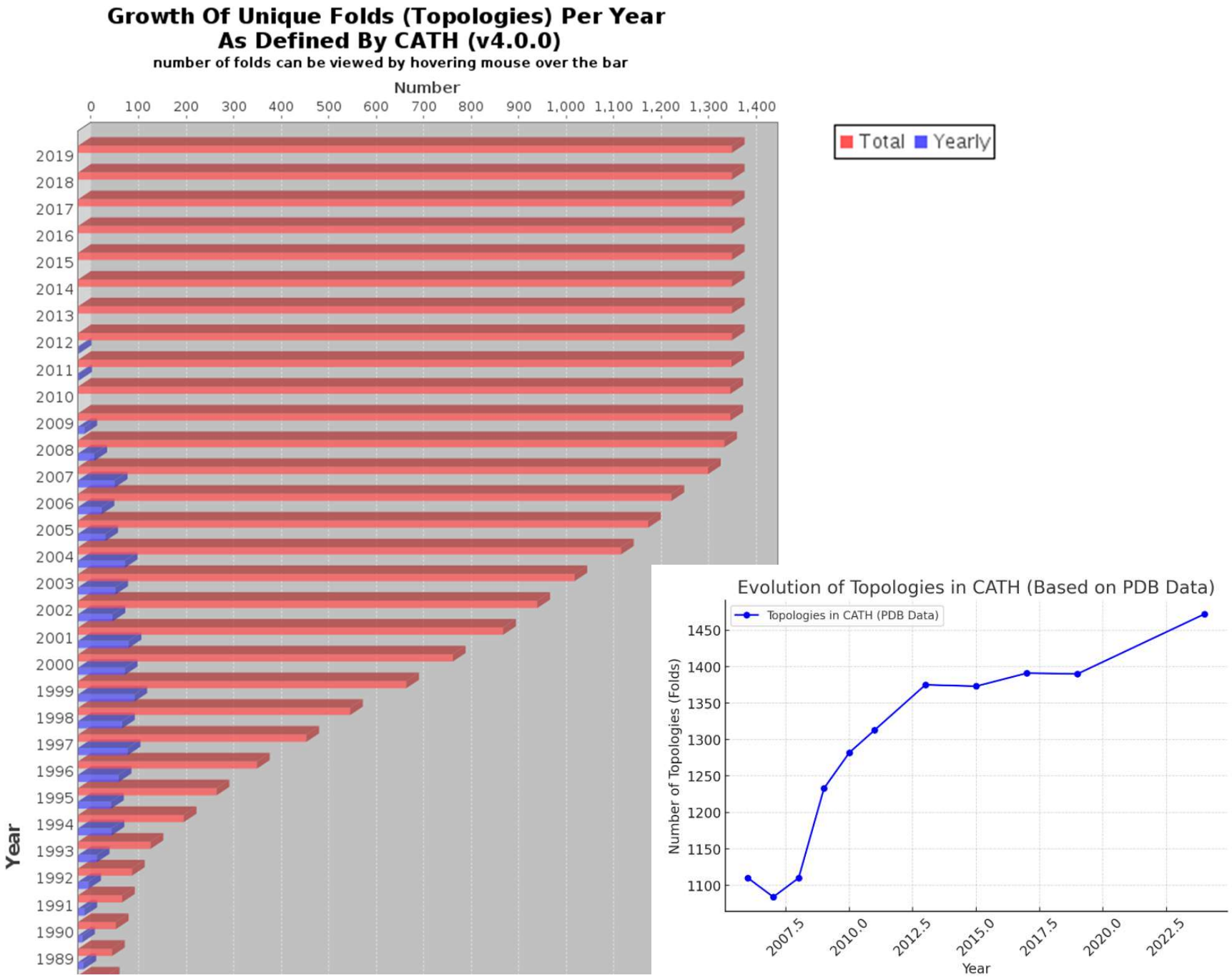


Even so, the number of solved structures greatly lags behind the rate of new genes being sequenced … Solution: Computational Structural Methods

Obtained structures per technique

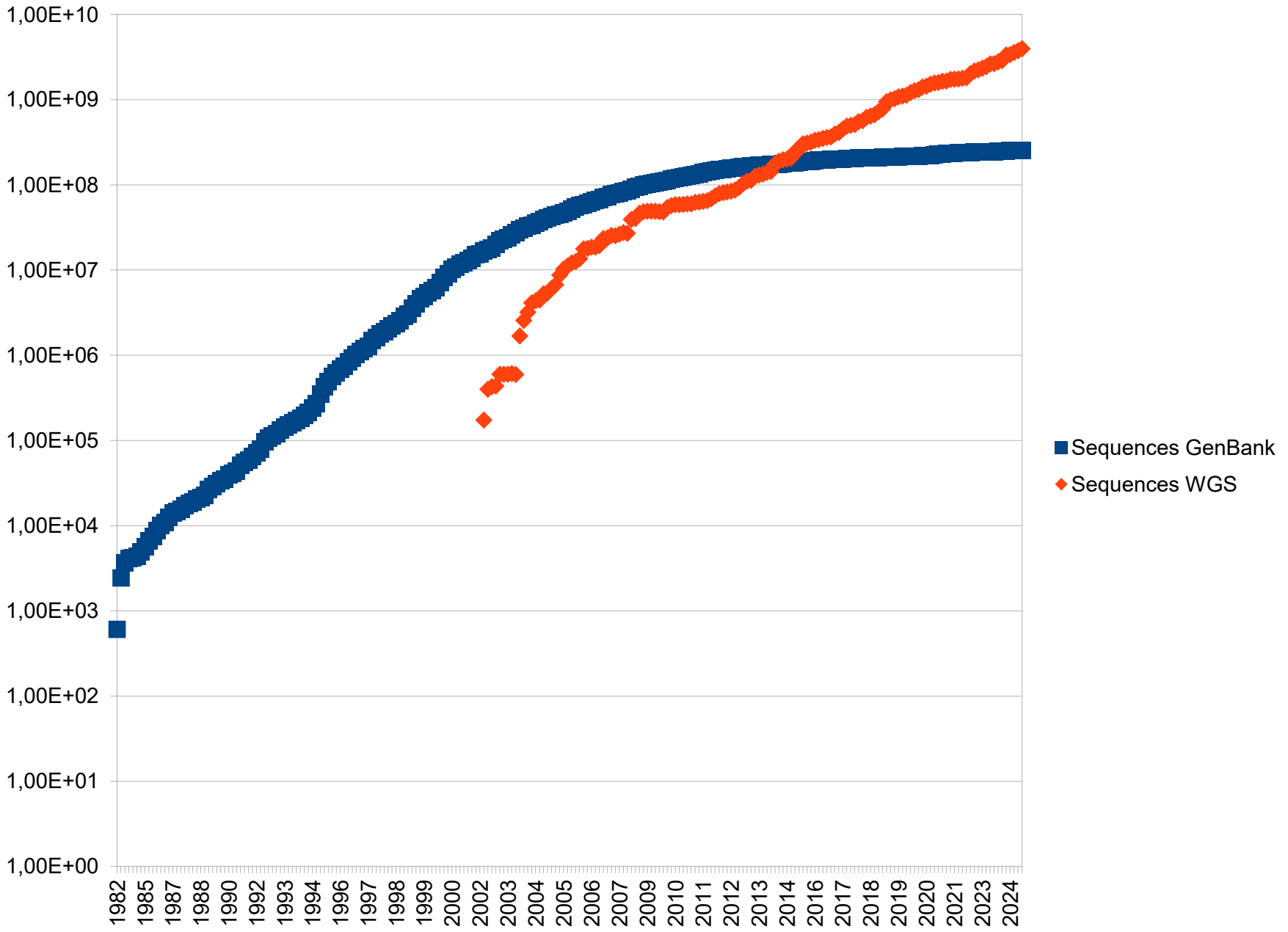
https://www.rcsb.org/stats/all-released-structures





http://www.rcsb.org/pdb/statistics/contentGrowthChart.do?content=fold-cath

GenBank Sequences



https://www.ncbi.nlm.nih.gov/genbank/statistics/

From Sequence to Structure

H1N1 NA

MNPNQKIITIGSVCMTIGMANLIL
QIGNIISIWISHSIQLGNQN
QIETCNQSVITYENNTWVNQTY
VNISNTNFAAGQSVVSVKLAGNSS
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RSPYRTLMS
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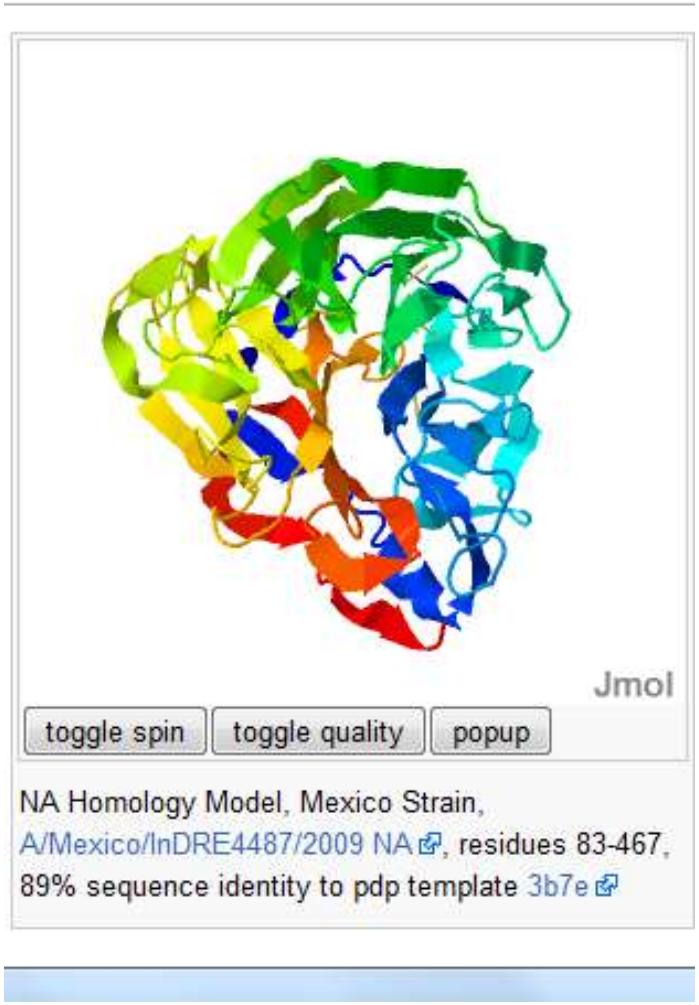
Computational Approach

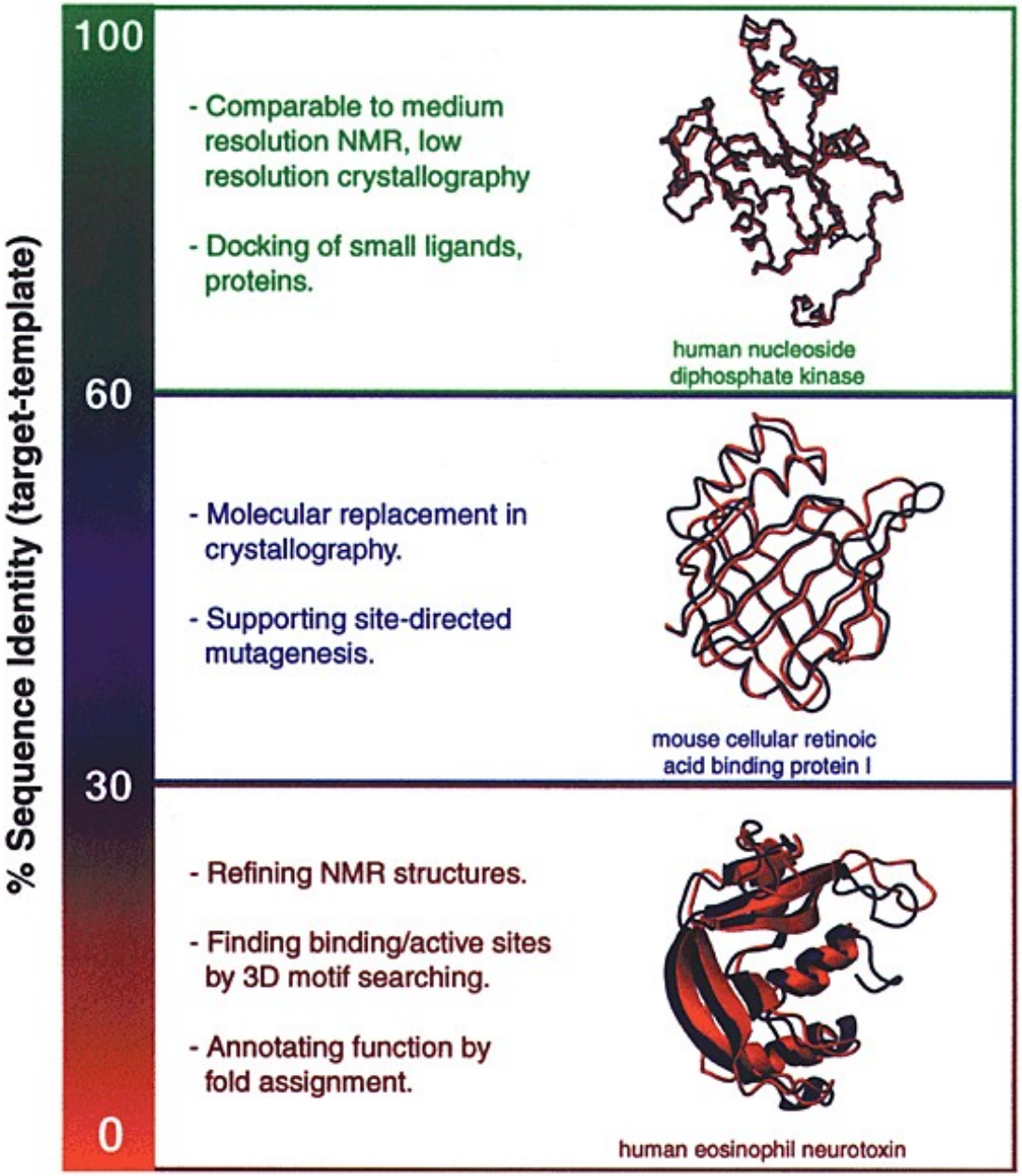


Comparative Modeling "Homology Modeling"

Steps include:

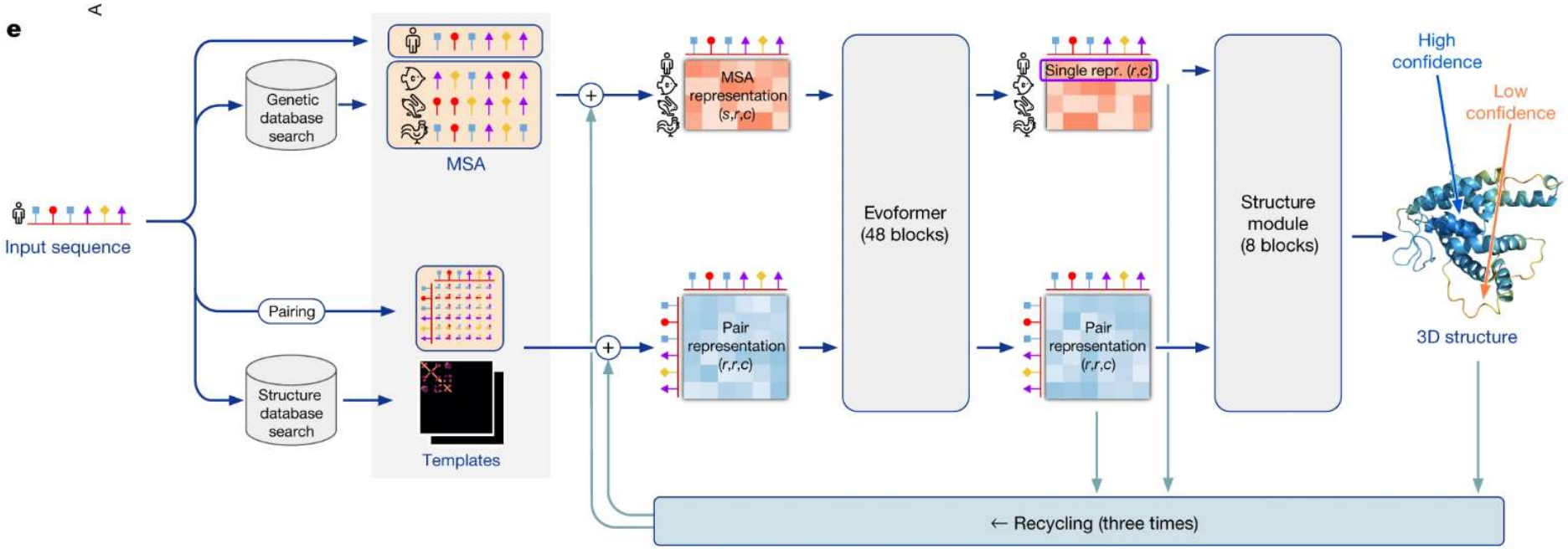
1. **Template recognition and initial alignment**
2. **Alignment Correction (Multiple Sequence Alignment can Help)**
3. **Backbone Generation (transfer coordinates from template)**
4. **Loop Modeling (loops hard to predict with insertions)**
5. **Side Chain Modeling (usually similar torsion angles at high sequenc ID)**
6. **Model Optimization (minor energy minimization steps or restrain some atom positions)**
7. **Model Validation (Higher ID more accurate usually, Calculate energy, or normality index (bond length, torsion angles))**
8. **Iteration (to refine)**

How Well Can We Do It?



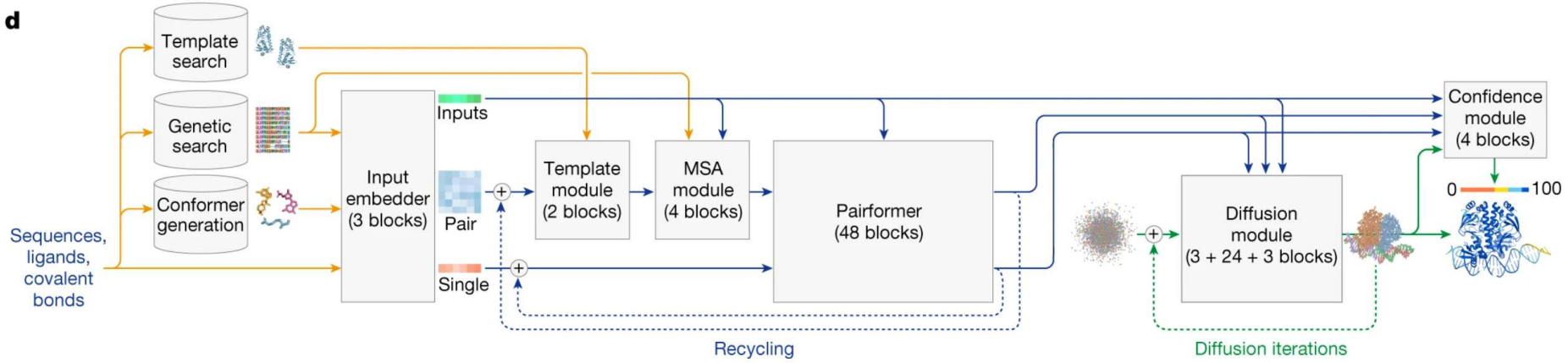
Sali, A. & Kuriyan, J. *Trends Biochem. Sci.* **22**, M20–M24 (1999)

Alphafold 2



Jumper, J., Evans, R., Pritzel, A. et al. Highly accurate protein structure prediction with AlphaFold. Nature 596, 583–589 (2021). https://doi.org/10.1038/s41586-021-03819-2

Alphafold 3



Abramson, J., Adler, J., Dunger, J. et al. Accurate structure prediction of biomolecular interactions with AlphaFold 3. Nature 630, 493–500 (2024). https://doi.org/10.1038/s41586-024-07487-w