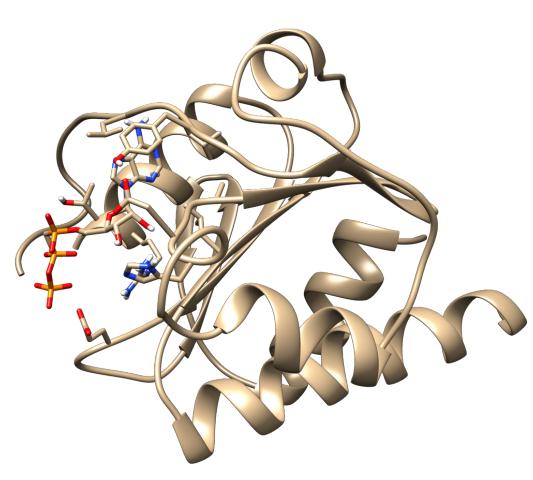
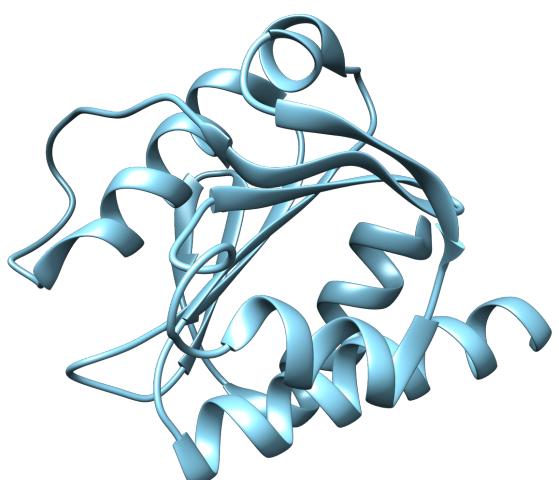


# Prediction Of Conformational Changes using Existing sTructures (POCCETs)

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## 1. Apo and Holo Proteins

- Apo proteins:- no ligand bound
- Holo proteins:- have a bound ligand



## 4. Dataset filtration

- Common Uniprot IDs, with atleast one apo and one holo.
- Filtered out NMR structures.
- Resolution cutoff 3.5 Å.
- Ligands between 100-1000 Da.
- Dataset of 798 protein pairs.

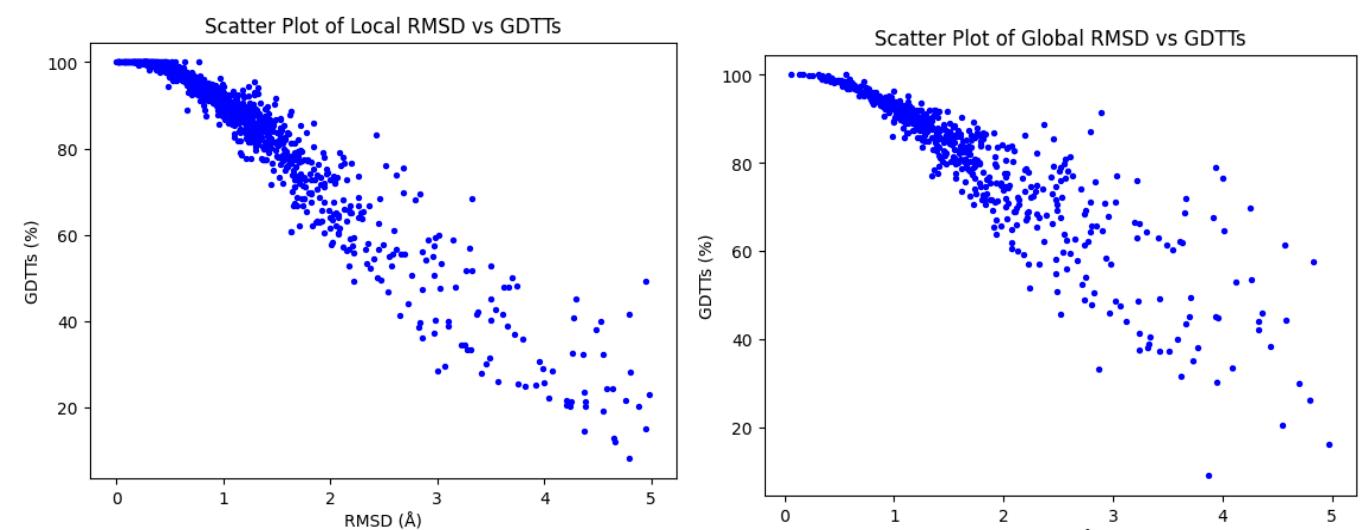
## 6. Structural Overlap and GDTSs

- Structural Overlap (SO)- percentage of aligned atoms within structural overlap distance cutoff (SODC).
- If m out of n atoms in SODC, then SO is  $(m/n) * 100$ .
- 3 cutoffs i.e. 1 Å, 2 Å and 3.5 Å and calculate a Global Distance Test Total Score (GDTSs).

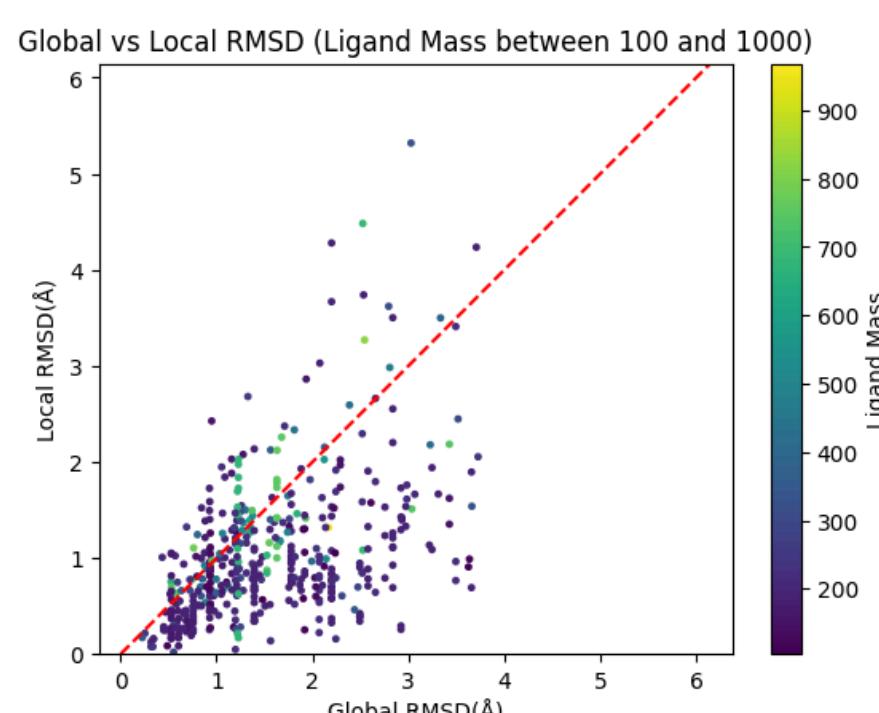
$$GDTSs = \frac{1}{3} \sum_{i \in \{1\text{\AA}, 2\text{\AA}, 3.5\text{\AA}\}} SO_i$$

- Also done for binding pockets in ligand vicinity.

## 7. Ligands cause conformational changes at the binding sites of proteins



- Structural overlap varies inversely with the RMSD.
- More atoms are outside the SODC, therefore RMSD should increase.



- Points above the red dotted line represent binding pockets where the ligand binding is a major factor contributing to change in local environment
- Cases of further interest.

## 2. Aim of the Project

- Studying and analysing the local extent of change due to ligand binding.

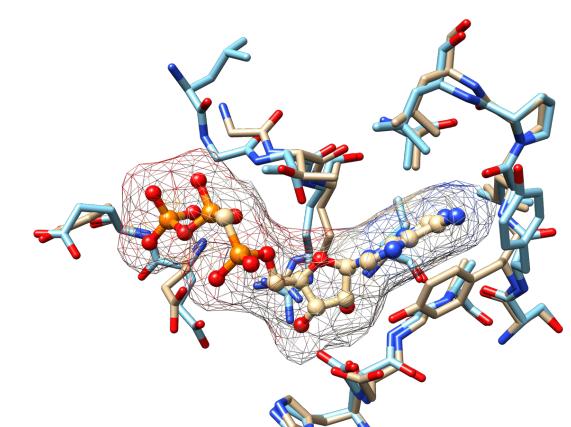
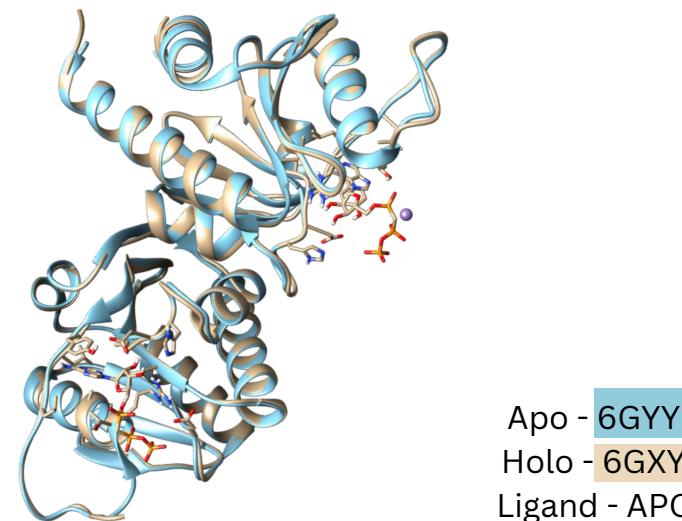
## 3. 3D Least Square Algorithm

- Translation matrix T and Rotation matrix R to minimise Root Mean Square Deviation.
- Requires atom-atom correspondences.
- Feed in matrix X and Y and we get transformed Y.

$$RMSD = \sqrt{\frac{1}{n} \sum_{i=1}^n \| \mathbf{X}_i - (\mathbf{Y}_i \mathbf{R} + \mathbf{T}) \|^2}$$

## 5. Aligning the proteins and binding pockets

- Pairwise match the common Uniprot ID chains.
- Set of common residues from both files and Least Square Algorithm applied.
- 5 Å binding pocket in holo protein to compare local change.
- 5300 binding pockets, 1300 in common chains.

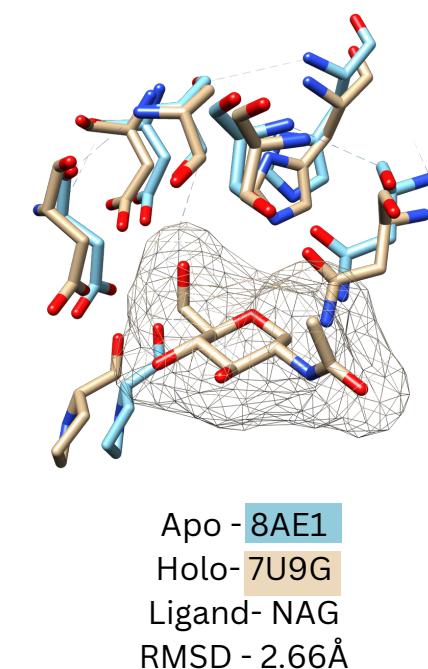
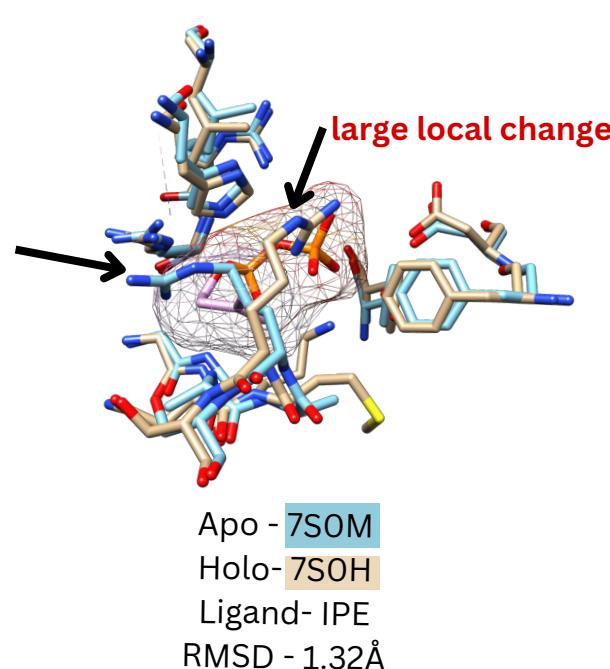


Ligand - APC

Global Alignment

Local Alignment

## 8. Significant changes in binding pockets



- Observe the large changes that occur in the vicinity of the ligand.
- In one case, one residue specifically undergoes a large change .
- In the other case there is considerable change for most of the residues in the binding pocket

## 9. Future work

- Analyse residue and ligand specific changes
- Training models to predict binding pockets.
- Run Molecular Dynamic Simulations to see if these holo structures can be predicted.

## 10. Acknowledgements

- COSPI lab members
- IISER Pune