Protein Resiliency to the Effects of Drugs

Tess Thackray, Max Ismailov, Piper Wolters, Zak Domingo, Lucy Innes, Matthew Alleria Rowan

Computer Science Department, Western Washington University

Introduction

Abstract: The biological and chemical interactions between a protein and a ligand (drug) can provide insights about the efficacy of a drug. To study how a protein might be resilient to the effects of a drug, we generate, in silico, all possible mutants with single amino acid substitutions for many protein ligand complexes. We use our custom rMutant-2 software to mutate every amino acid on the protein, and another custom program to reattach the ligand after the mutation is complete. Using Kinari software, we perform rigidity analysis on the mutated protein to determine the number of atoms in each cluster and their frequency to then infer effects of the mutations on protein structure and function. Through rigidity analysis, we can determine the resilience of the mutated protein to the drug in order to further understand the effects of the drug on that protein.

Motivation

- The potential to further validate our software used to assess the impact of drugs
- Supplement experiments done in the wet lab, which can be time and cost prohibitive.
- Narrow down which protein-ligand complexes are valuable enough to warrant a time and resource-intensive wet lab experiment
- Assisting with a long term project that will likely result in a useful tool for future research

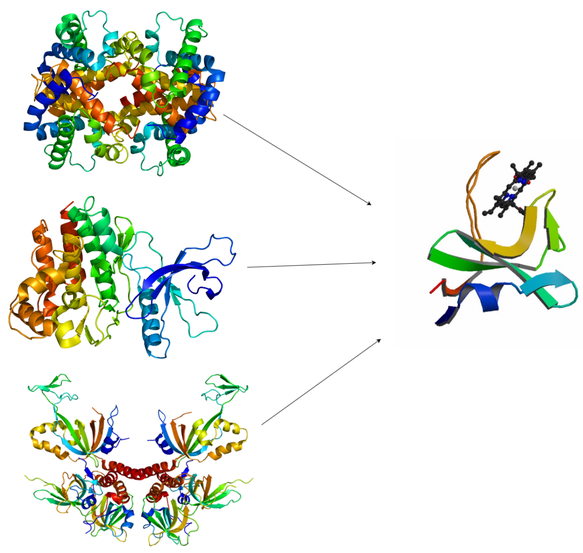


Figure 1: Decision to ultimately focus on 6NZX.

Methods

- *Search Criteria:*
  - Drug specific ligand attached
  - 50-300 residues in length
  - Single chain proteins
  - Proper file format for proper computation

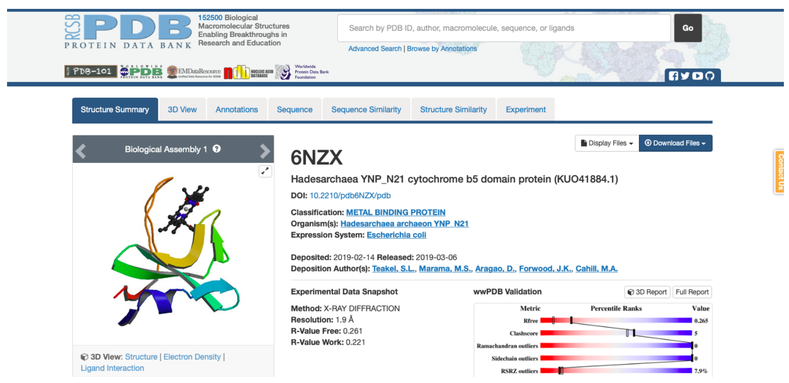


Figure 2: Hadesarchaea Cytochrome b5 Domain Protein

- *Generate:*
  - rMutant -> performs all of the possible mutations of a given protein and performs energy minimization for each protein if necessary
  - New Software -> Removes ligand during mutation and reattaches ligand after
  - Kinari -> outputs rigidity analysis metrics for each mutation

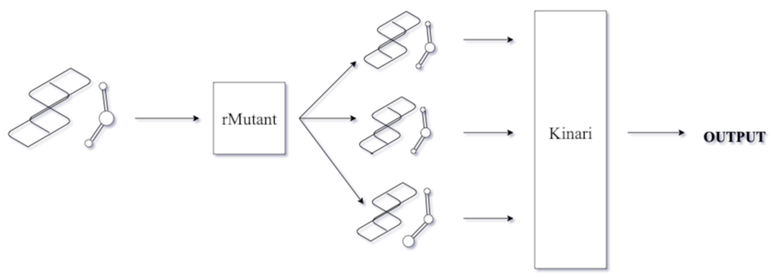
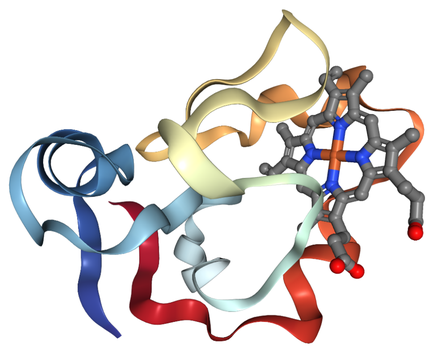


Figure 3: Data Generating Methodology

- *Visualize:*
  - Create visualizations to display mutation metrics
  - Attempt to find correlations between protein resiliency and the given data



Results

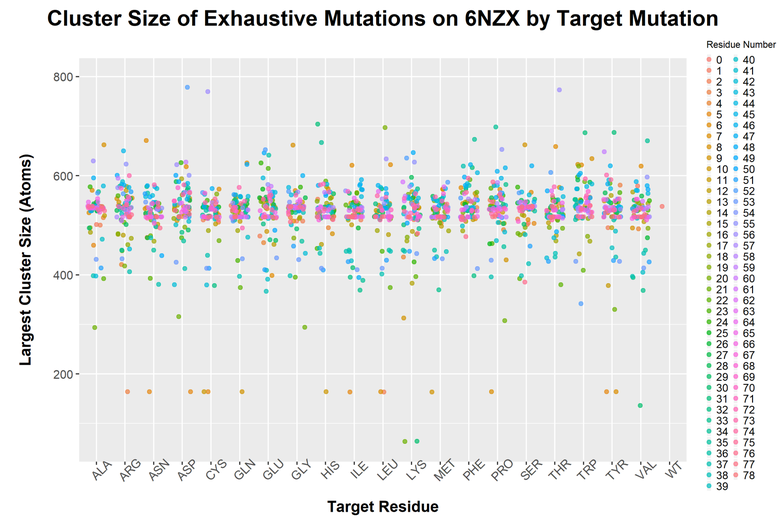


Figure 4: The relationship between target residue and largest cluster size with an emphasis on residue location for 6NZX

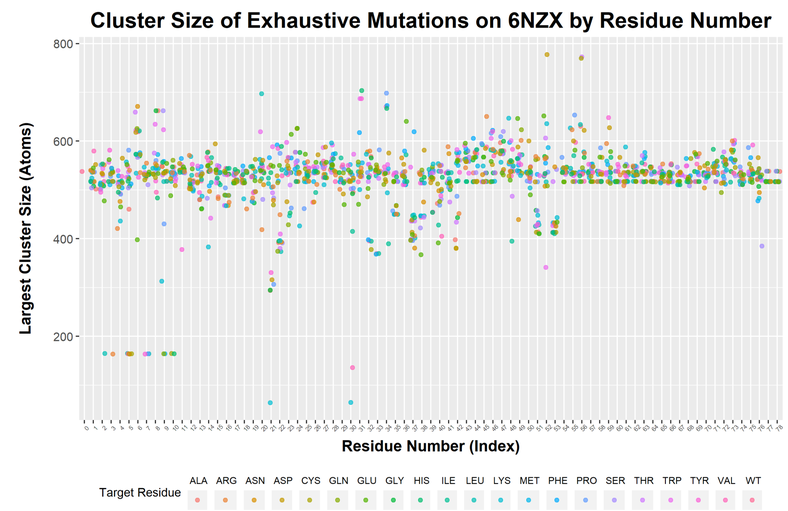


Figure 5: The relationship between residue location and largest cluster size, with an emphasis on readability of target residue for 6NZX

Discussion

- Mutations that occur at an earlier residue number result in a larger variability of cluster size
- Residues 1-24: show trend of lowest largest cluster size
- Residues 25-50: show trend of just below average largest cluster size
- Residues 50-78: show trend of average largest cluster size

Location	Target	Property	Original	Property
52	Asp	Hydrophilic	Leu	Hydrophobic
56	Cys	Hydrophilic	Ile	Hydrophobic
56	Thr	Hydrophilic	Ile	Hydrophobic

- Residues 52 and 56 may be more significant in the protein chain than others, implying a potential change in the protein structure and function.
- There is potential for other, less unique outliers to also be important for the structure.

References

- KINARI-Mutagen: Filip Jagodzinski, Jeanne Hardy, and Ileana Streinu. Using Rigidity Analysis to Probe Mutation-Induced Structural Changes in Proteins, Journal of Bioinformatics and Computational Biology, Vol. 10, No. 3, 2012.
- Katie Hursh, Filip Jagodzinski. "ProMuteHT 2.0 : A High Throughput Compute Pipeline for Generating Protein Mutants in silico"

Acknowledgements

- Dylan Carpenter: special thanks for your programming, ideas, and advising throughout the project