Exploring Multi-conformational Modeling and Flexibility of Molecular Recognition Features In Improving Drug Docking

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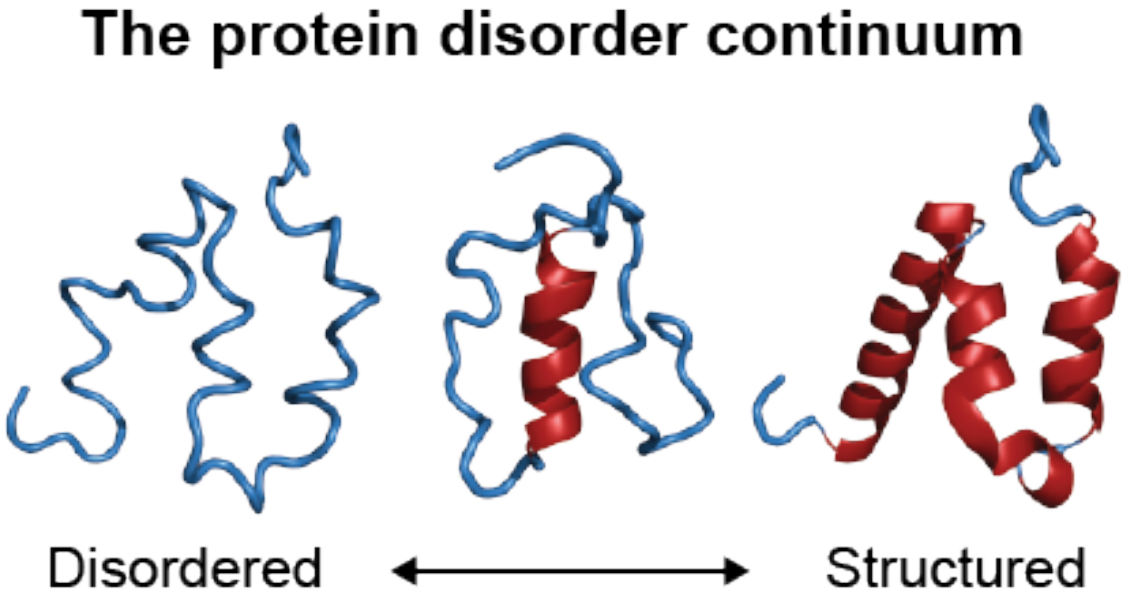
- They lack a fixed tertiary, or 3-D structure.
- IDPs are potential drug targets and are now closely studied.

Example Picture



Molecular Recognition Features (MoRFs)

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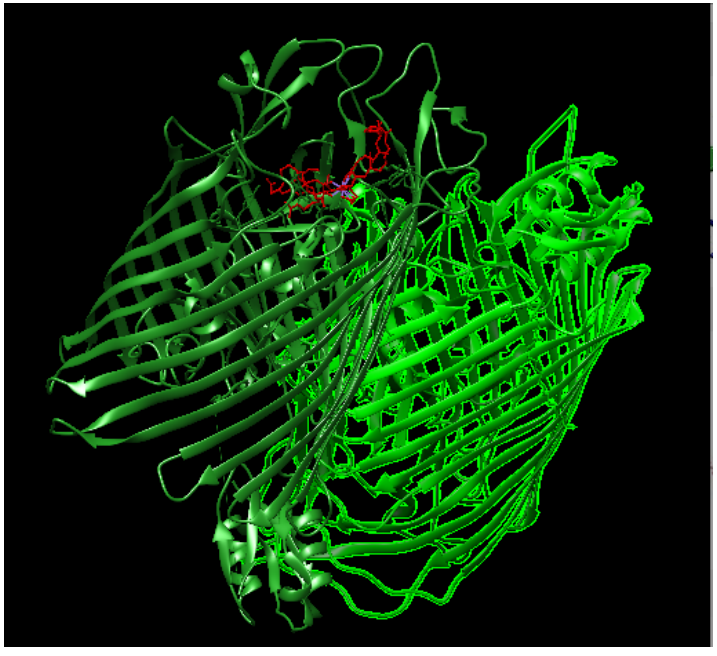

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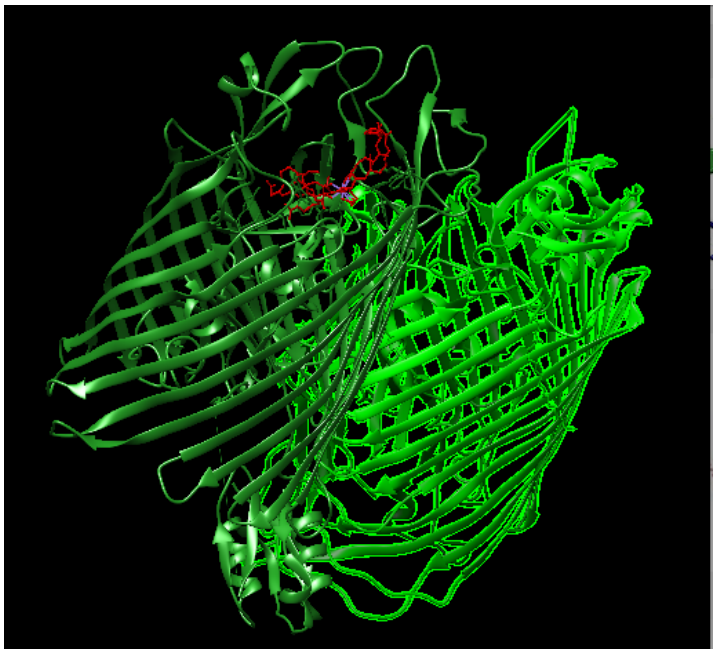

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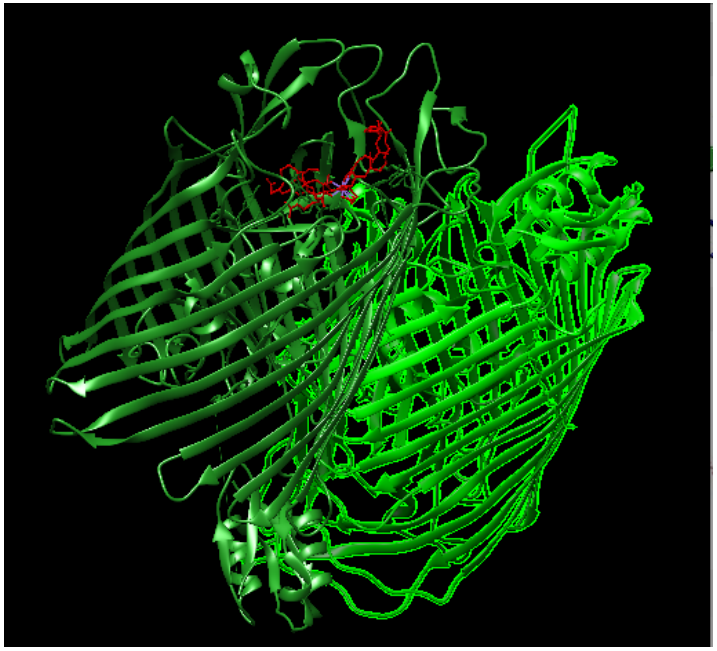
- They are usually defined to be between 10-70 residues long.



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- What are different paradigms within which we can analyze binding affinities of flexible regions?
- How can these results be applied to finding new drugs for diseases such as cancer?

Data Collection and Processing

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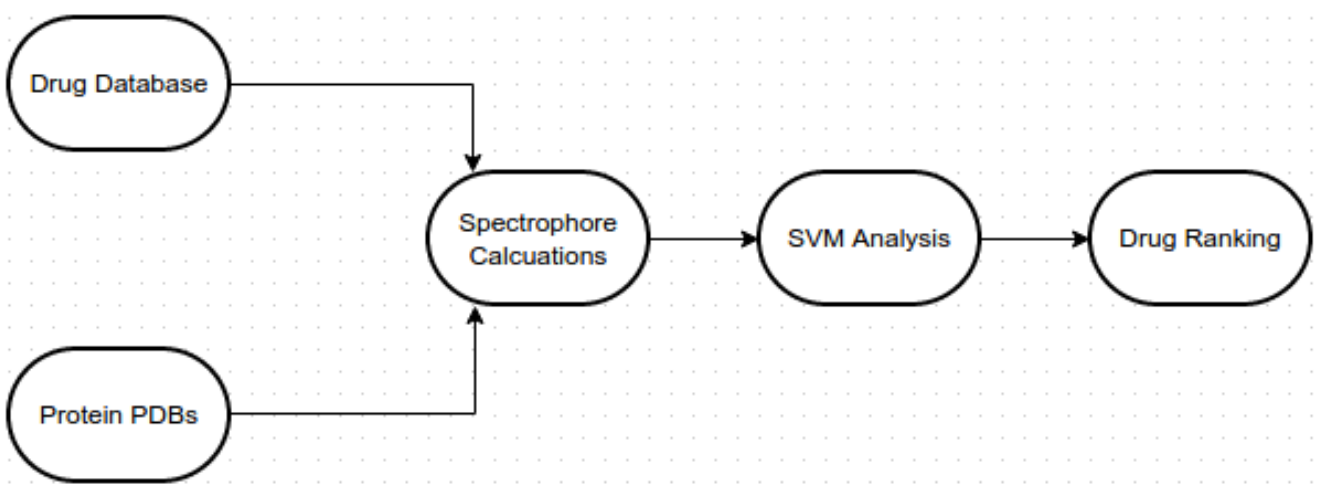
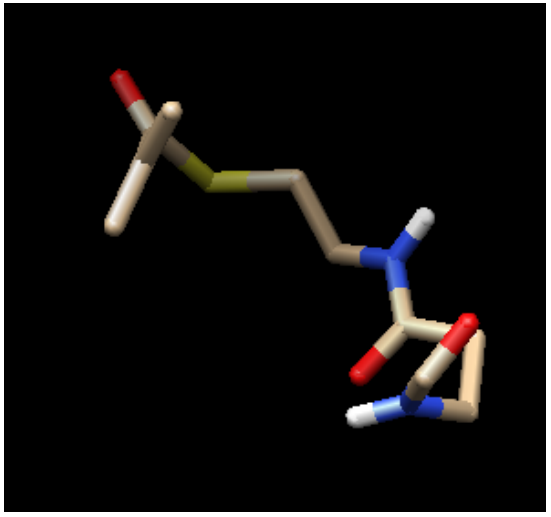
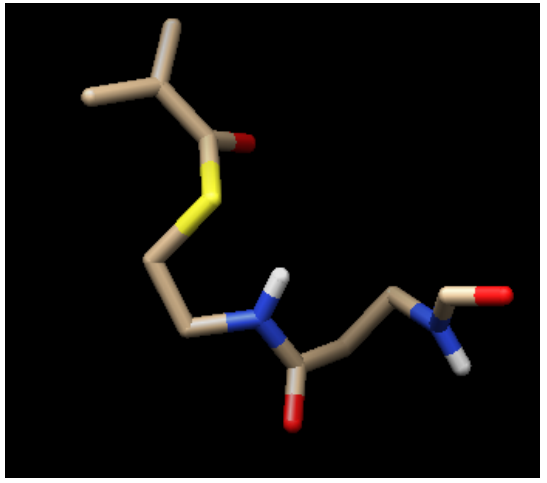
- From the Protein Data Bank, proteins were gathered related to major pathogens.
- The MoRF segments were isolated from the PDB files, and ran through the pipeline to find drugs that might bind with the MoRFs.



Simulation of Flexibility

- TraDES was used to generate 200 conformations of each protein analyzed.





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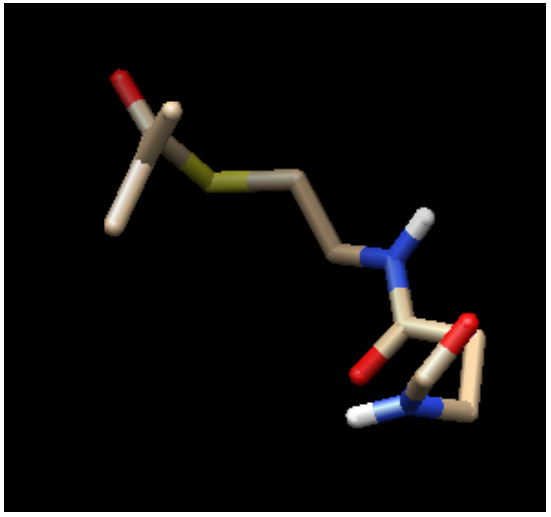

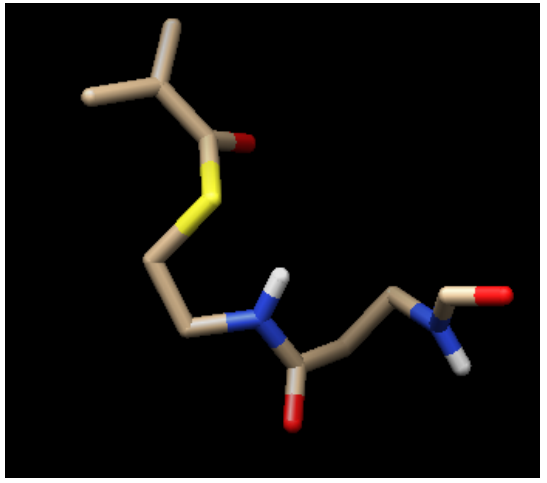

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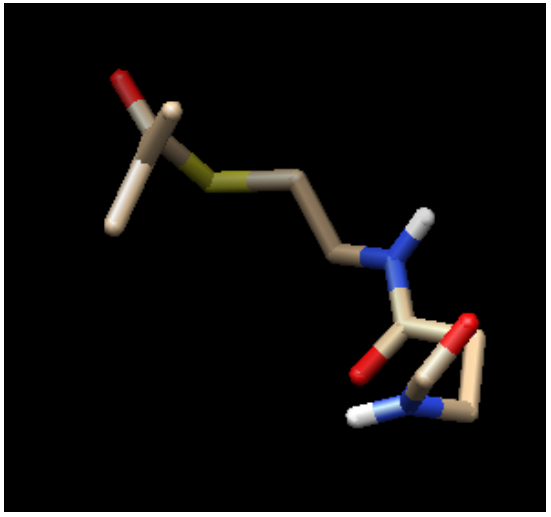
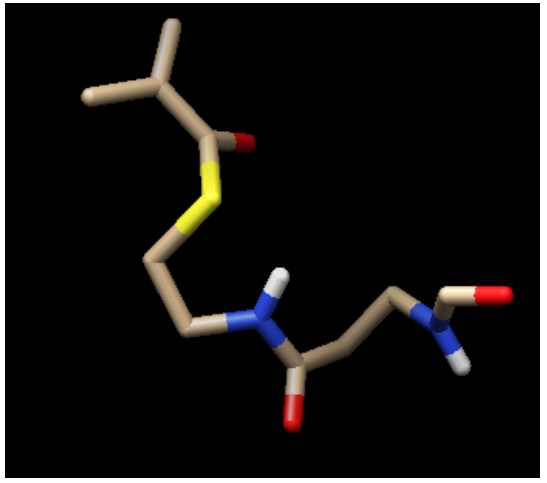
- (two pictures of different conformations side by side)





Drug Results

Based on the process used, six drugs have been found to address *Pseudomas Aeruginosa* (which affects airways and can cause blood infections)

PubchemID	Prob-SSB
46507215	0.926
46506020	0.929
46508185	0.926
45406770	0.926
45406528	0.926
46507414	0.928

Comparison of Methods

- Using a matched pairs test between all MoRFs analyzed and the top score from their conformations, I obtain a p-value of 0.02.

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- At the $\alpha = 0.05$ level, this is significant, and shows an improvement in docking score.

Alternative Method of Flexible Docking

- A program was written in order to dock multiple pieces of the MoRF with the drug individually.

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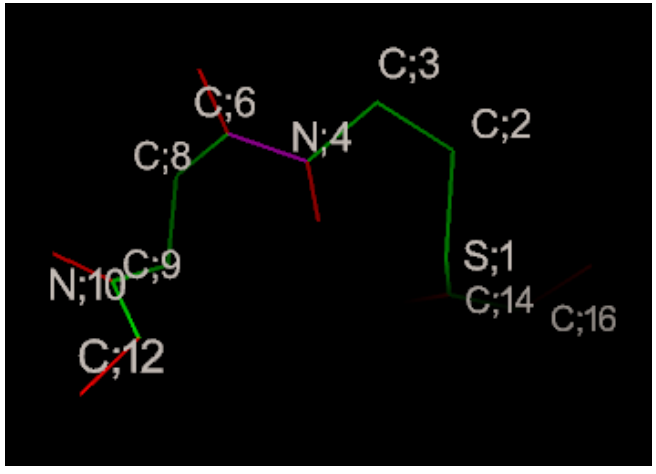
- This is possible because of the difference in size between the MoRF (or protein) and the drug.

Analysis of Method Runtime

- All bonds which can rotate are kept rotatable, and if the sections are divided correctly only one will bind to the drug.
- Further work must be done in automating this process.



Conclusion

The property of flexibility for MoRFs was utilized to improve docking score by generating a large number of conformations, and binding them with the appropriate drugs. Additionally, a new method of docking with flexible proteins was developed to reduce docking runtime significantly.

Acknowledgements

I would like to thank the following people for their essential role in allowing this project to succeed:

- Dr. Gil Alterovitz
- Anvita Gupta
- MIT PRIMES
- Parents!