Using UOBPRM to Study Ligand Binding

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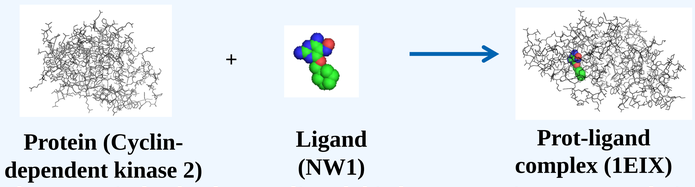
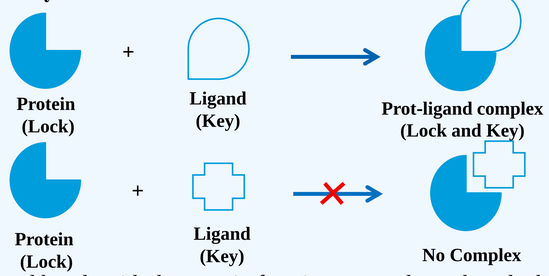
Motivation



- In pharmaceuticals, the drug, or ligand, binds to a protein to cause a desired effect.
- Screening drug candidates is costly.
- Performing part of the screening computationally cuts cost.

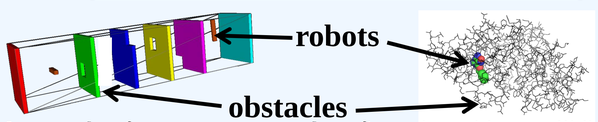
Ligand Binding

- **"Lock and Key" Model**



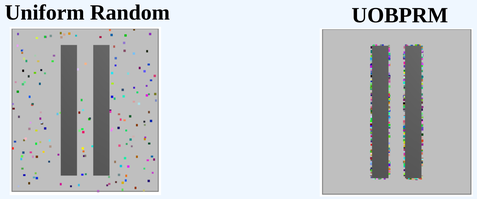
- Here, a ligand bonds with the protein forming a complex, a.k.a. docking.
- The specific area in the protein to which the ligand binds is the binding pocket or ligand binding site or active site.
- Different ligands may bind to one protein and vice versa.
- Binding affinity is a measure of the strength of the protein-ligand bonding.
- Factors affect affinity. For example,
  - a higher bond energy,
  - a greater ability to reach and remain in the active site, and
  - a longer time spent by the ligand in the active site, all contribute to higher affinity.

Motion Planning and UOBPRM



- Move a robot from a start to a goal configuration without colliding with any obstacles in the environment.
- Probabilistic Roadmaps (PRMs) are sampling techniques that generate configurations randomly.
- **Uniform Obstacle-Based Probabilistic Roadmap (UOBPRM)** is a *novel* approach to help generate robot configurations uniformly distributed around obstacles.

Uniform Random **UOBPRM**



UOBPRM distribution around the obstacles is close to uniform.

Method

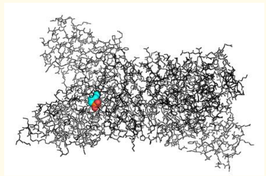
Algorithm

Input: A protein, *P*, and a ligand, *L*.
Output: A rank, *r*, to represent the binding affinity between protein, *P* , and ligand, *L*.

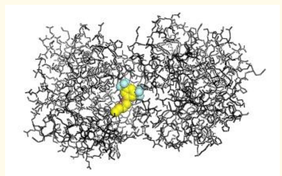
1. Generate UOBPRM samples for *L*.
2. For each ligand sample, calculate distance between the center of mass of the ligand and the center of mass of the protein.
3. Find the minimum among all the distances.
4. Calculate the distance between the center of mass of the ligand and the center of mass of the protein in the native state.
5. Return the affinity rank, *r*, with respect to the absolute difference between the minimum distance and the native state distance.

Results

- We show 5 protein-ligand pairs with experimentally-determined binding affinities published in the literature.



2EGH



3W6H

Sample Representations of Two of the Five Protein-Ligand Complexes Studied

- In our work, we made the assumption that if the binding affinity is higher, it is likely that the ligand is bound deeper in the protein.

- **Set 1: One Ligand with Multiple Proteins**

			Our Simulation		Published
Ligand (CID)	Protein	Affinity (IC_{50})	Abs. Δ Dist (Å)	Rank	Rank
162204	2EGH	58 nM	0.2342	1	1
	4OOE	2390 nM	2.6459	2	2

Affinity High ↓ Low

- **Set 2: One Protein with Multiple Ligands**

			Our Simulation		Published
Protein	Ligand (CID)	Affinity (K_i)	Abs. Δ Dist (Å)	Rank	Rank
3W6H	768	$5 * 10^{-4}$ nM	0.0695	1	1
	24530	$12 * 10^{-4}$ nM	0.5548	2	2
	19366655	$200 * 10^{-4}$ nM	1.2712	3	3

Affinity High ↓ Low

- **Our results match the published results.**

Discussion & Conclusions

- We proposed to use UOBPRM to study a computational biology problem, i.e. ligand binding.
- UOBPRM can generate potential ligand samples to bind the protein.
- We measure the distance as our affinity metric.
- We showed 5 protein-ligand pairs with known binding affinities determined experimentally.
- Our ranking of approximated binding affinity matches the ranking from published binding affinities.
- We used a coarse-grain method to approximate the protein and the ligand.
- We approximate the protein as a rigid body which may cause us to lose the true binding site.
- In reality, proteins can change conformation when the ligand binds.
- In the future, we hope to give the protein more flexibility.
- We also hope to measure binding affinity with other metrics such as
  - energy,
  - rigidity, and
  - compactness.

Acknowledgments

- Dr. Nancy Amato, my faculty mentor, for the opportunity to participate in this summer research program, for guidance, and for financial and other support.
- Dr. Shawna Thomas, post-doc, for her oversight.
- Hsin-Yi (Cindy) Yeh, my Ph.D. graduate student mentor, for her guidance, supervision, and support.
- Computing Research Association (CRA) and Coalition to Diversify Computing (CDC) for funding this Distributed Research Experiences for Undergraduates (DREU) experience.

References

1. Ligand .sdf files from Protein Data Bank (PDB) converted into .pdb using CADD Group Chemoinformatics Tools and User Services (CACTUS). http://cactus.nci.nih.gov/translate/
2. 1E1X, 2EGH, and 3W6H protein and ligand images processed using Pymol. http://www.pymol.org
3. M. Teodoro, G. Phillips, Jr., and L. Kavraki. Molecular Docking: A Problem With Thousands of Degrees of Freedom. In *Proc. IEEE Int. Conf. Rob. Autom. (ICRA)*, pages 960-965, 2001.
4. H.-Y. Yeh, S. Thomas, D. Eppstein, and N. Amato. UOBPRM: A Uniformly Distributed Obstacle-Based PRM. In *Proc. IEEE Int. Conf. Intel. Rob. Syst. (IROS)*, pages 2655-2662, 2012.