Assessing Protein-Ligand Binding Accessibility Using Motion Planning and Energy Metrics

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Motivation

Problem Statement
- Protein shape and functionality changes when the protein interacts with drug molecules known as ligands
- Ligands bind to a specific region of the protein known as the binding site
- We use motion planning algorithms to assess the **accessibility** of the tunnels to the binding site
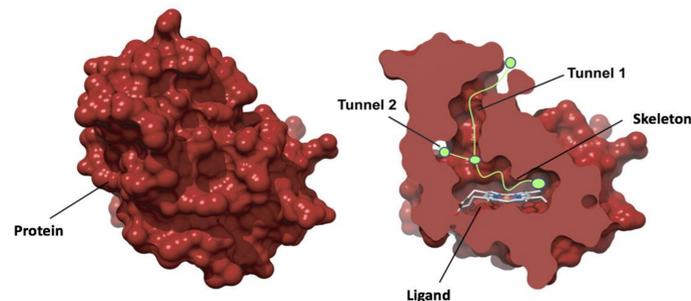
Objective
- **Bias** towards exploring favorable tunnels of low energy for accuracy and efficiency
- Evaluate and gain more insight on meaningful tunnels

## Guided Motion Planning
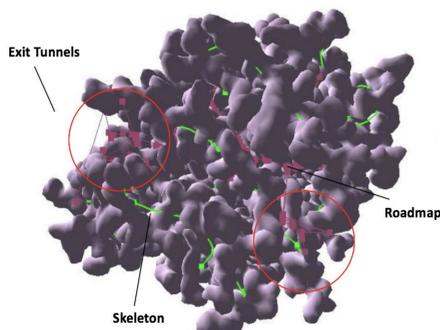
Algorithm 1 Basic Guided Planning
Require: Environment E, goal config. G
1: $SK \leftarrow \text{GetSkeleton}(E)$
2: $G \leftarrow \text{root}$
3: **while** !(found exit tunnels) **do**
4:    $R \leftarrow \text{SelectRegion}()$
5:    $\{S\} \leftarrow \text{Sample}(R)$
6:    **for all** sample $\in \{S\}$ **do**
7:       $\text{ConnectClosest}(\text{sample}, G)$
8:    **end for**
9: **end while**

- Motion planning can simplify a complex geometric problem like navigating a binding site within a hard environment like a protein
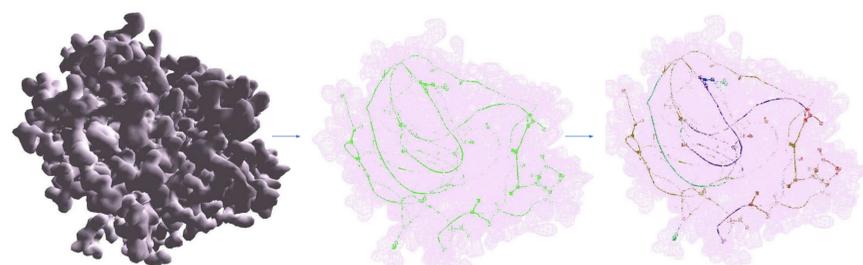
Method

Energy Annotation
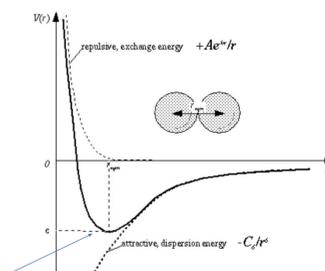
- The Van der Waals function shows the attraction between two non-bonded atoms
- We predict ligands will arrange and move themselves where the **energy is the lowest** and is the most stable

- Our strategy calculates energy values for each region of the protein
- Builds a skeleton with annotated energy values

Energy Visualization Tool

a) Protein structure   b) Protein and skeleton   c) Skeleton with Annotations

- Added a feature to Parasol Lab's MP visualization tool that colors the skeleton with energy annotations

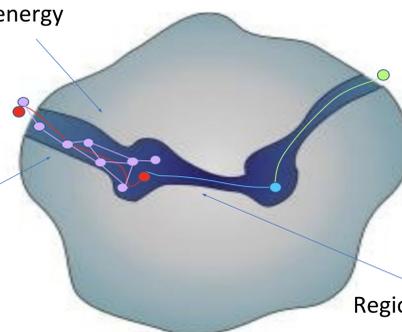### Biased Guided Motion Planning

Algorithm 2 Selecting Region with Energy Bias
0: **procedure** SELECTREGIONUSINGENERGY(Skeleton SK)
1:    **for all** node $\in SK$ **do**
2:       regions $\leftarrow SK.\text{annotation.energy}$
3:    **end for**
4:    **return** $\min_e(\text{regions})$

Region of low energy

Strategy plans towards regions with lower energy

Region of high energy

Experiments

Set-Up
- Comparison between biasing with energy and non-biasing (topological analysis)
- Protein environment is the same in all runs (fbw)
- 10 seeds were randomly generated, and the metrics (e.g. runtime, nodes, etc.) were averaged for both planning strategies

a) Selecting region with topology   b) Selecting region with energy (my implementation)

	Runtime	Nodes	Edges	Tunnels found
Selecting with Topology	169	644	2765	12
Selecting with Energy	123	497	2761	12

Discussion
- Energy biasing strategy on average created smaller roadmaps with more connectivity
- It was able to find the same number of tunnels in less time

Conclusion

- By biasing our motion planning strategy with energy, energetically favorable regions will be explored first
- Creates a more accurate and informed model of the accessibility tunnels, with less extraneous testing
- In the future, the biasing strategy can include a combination of biometrics for more accuracy

Acknowledgements