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Introduction

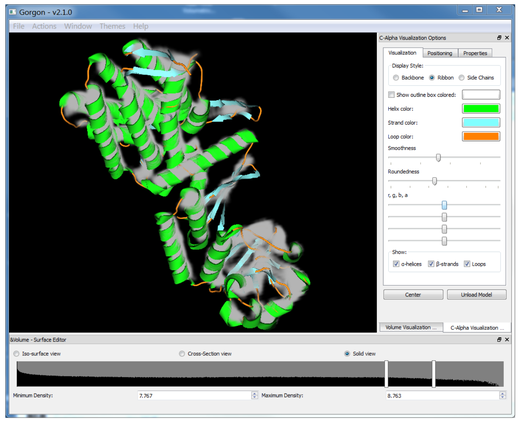
Macromolecular assemblies drive nearly all cellular events. The assemblies' structures, which consist of tens to hundreds of interlocking proteins, are critical to understanding how biological systems work[1]. Our work addresses the computing challenges of generating structural models of macromolecular assemblies from Cryo-EM density maps.

Purpose

Develop geometric algorithms for modeling protein structures from Cryo-EM density maps of macromolecular assemblies by implementing geometric algorithms in Gorgon, a molecular modeling software.

Gorgon

Gorgon is an interactive molecular modeling system collaboratively developed between Washington University and Baylor College of medicine. It is geared towards cryo-EM structures of macromolecular complexes.



Gorgon displaying fitted structures overlaid on top of a protein density map, with visualization options on the right and bottom panels

Algorithms

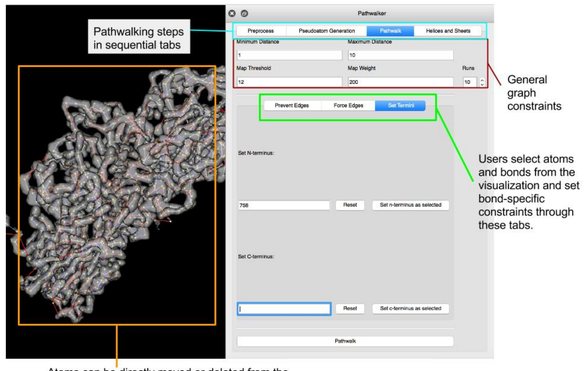
Pathwalking

Pathwalking traces the primary backbone of a protein[2]:

1. Pseudo-atom generation: Use k-means clustering to generate vertices at locations that likely make up a protein's backbone.
2. Pathwalking step: Fit a model through the pseudo-atoms such that every atom is connected to two others and deviation from the expected bond distance is minimized. Analogous to the Traveling Salesman Problem (Shortest path visiting each node).

Pathwalking in Gorgon

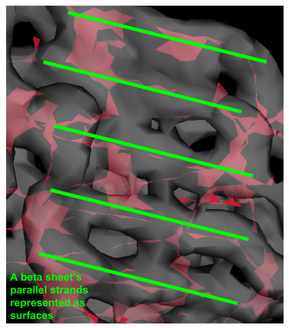
Our user interface for Pathwalking allows the user to set constraints and manipulate the predicted model both before and after Pathwalking:



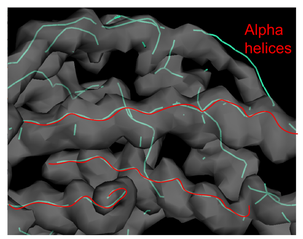
Extremal Curve Skeletonization

This technique identifies locally maximums:

- Points with density values that are local maxima on a single axis are parts of max surfaces. These may be part of beta sheets.
- Maximums on two axes are part of max curves. These may be part of alpha helices.



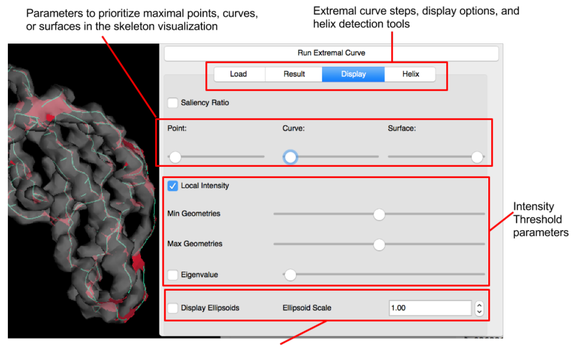
Beta sheets on the max surfaces of Extremal Curve Skeleton of vp6 rotavirus density map



Alpha helices on max curves of Extremal Curve Skeleton of vp6 rotavirus density map

Skeletonization in Gorgon

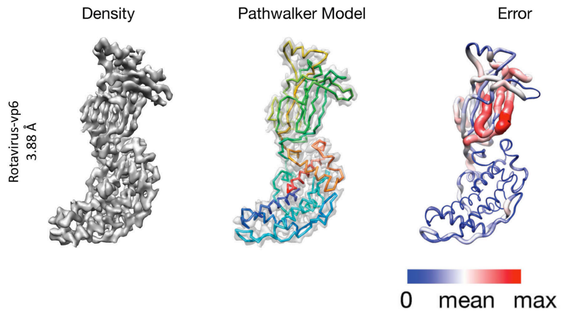
Gorgon's interface for the algorithm has parameters for pruning based upon intensity measures and geometry characteristics:



Results

Pathwalking

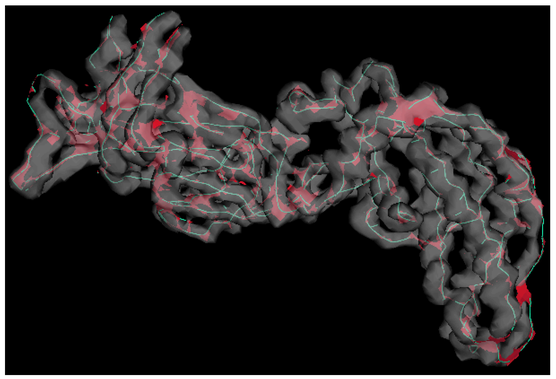
Shown below are sample results for Pathwalking on a density map of rotavirus vp6. In the right figure, thin and blue ribbons correspond to no error, white and medium-thickness ribbons correspond to average error, and red and thick ribbons correspond to maximum error.



As evidenced by the significant presence of thin blue ribbons, Pathwalking produces topologically correct models of protein backbones on both simulated and authentic density maps without user intervention.

Extremal Curve Skeletonization

Extremal Curve Skeletonization was performed for the same rotavirus vp6 density map.



Pruned max curves and surfaces of Extremal Curve Skeleton

Extremal Curve Skeletonization provides a detailed description of the map's density profile. Both alpha helices and beta sheets can be identified when carefully observing the max curves and surfaces.

Evaluation

- At lower resolutions (> 5 Å), Pathwalking provides a clearer picture of the protein backbone.
- At higher resolutions (<4 Å, the shapes of secondary structures are more distinguishable in max curves and surfaces produced by skeletonization than in protein backbones generated with Pathwalking.

Next Steps

Our results suggest that resolution-aware algorithms would optimize both the speed and accuracy of the modeling process. We will create algorithms that will detect the resolution of the input density map, then reap the benefits of both Pathwalking and Extremal curve skeletonization. Skeletonization would first identify secondary structure structures. These structures will be used as anchors to find the rest of the protein structure using Pathwalking.

References

1. Sali A. and Chiu W. 2012. Macromolecular Assemblies Highlighted.
2. Baker et al. 2012. Gorgon and pathwalking: Macromolecular modeling tools for subnanometer resolution density maps.

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