Shape-Focused Pharmacophore Modeling – Improving Docking Screening Efficiency

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MOLECULAR SYSTEMS BIOLOGY

INTRODUCTION

In structure-based drug discovery, flexible ligand molecular docking is a key virtual screening method. Although docking samples binding poses well, the default scoring typically fails to recognize active ligands from inactive ones. However, the docking yields can be massively improved using cavity shape-based rescoring. For the best docking boost, the cavity-filling models need to be trimmed via costly greedy search optimization. A novel shape-focused pharmacophore modeling method, O-LAP modeling, was tested for improving docking screening yield using human acetylcholinesterase as an example target.

METHODOLOGY

- Benchmark testing was done using the DUDE-Z set for human acetylcholinesterase
- Filling of the binding cavity with atomic content
  - PLANTS1.2: Flexible molecular docking of active small-molecule ligands
  - PANTHER: Negative image-based model
- O-LAP modeling (Fig. 1)
  - O-LAP: C++/Qt5-based software
  - Merges overlapping atoms using graph clustering with atom-type specific search radii
- Shape-focused pharmacophore filtering
  - ShaEP1.3.1: Shape/ESP similarity comparison or docking rescoring against the O-LAP model

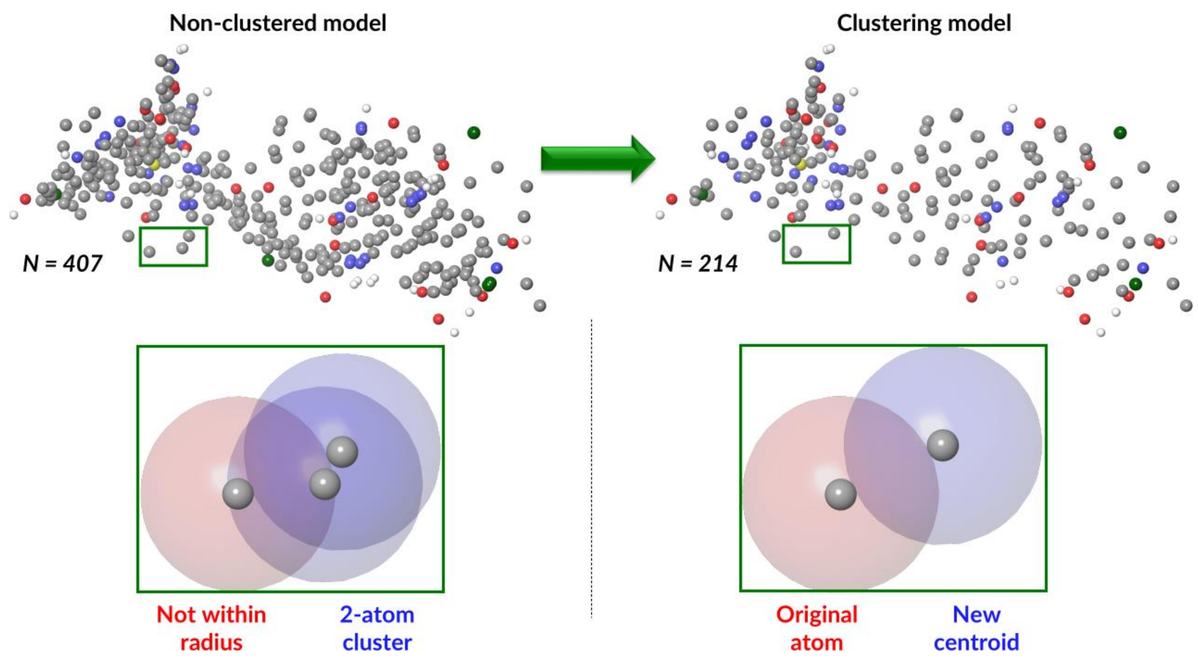

Figure 1. O-LAP modeling graph clustering principle. The non-clustered input was processed with O-LAP modeling. An example of how the new centroid within the same radius is shown with three carbons atoms (grey dots).

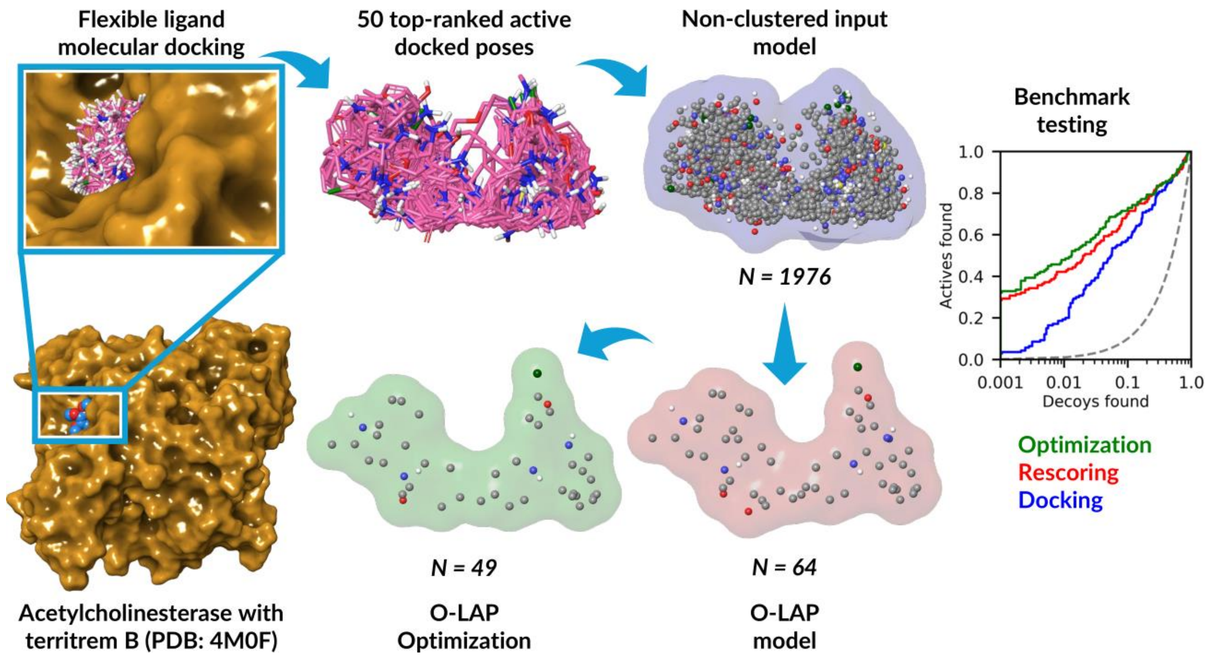

Figure 2. Docking scoring-based O-LAP modeling with the acetylcholinesterase (PDB: 4M0F).

RESULTS AND DISCUSSION

- O-LAP modeling is a hybrid ligand- and structure-based approach
- O-LAP modeling excels in flexible docking rescoring (Fig. 2), in rigid docking, and Hybrid NIB-ligand after optimization
- For the best docking boost O-LAP requires:
  - Carefully curated atomic input (e.g., top-ranked active docking poses)
  - Well-chosen graph clustering settings
  - Posteriori greedy search optimization

AVAILABLE IN GITHUB!

O-LAP

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