Fragment based modeling of protein-GAG complexes
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Glycosaminoglycans (GAGs) are linear anionic periodic polysaccharides. They bind to their protein targets in the extracellular matrix, and so participate in many cell-signaling processes. As such, they are very promising targets for the design of novel functional biomaterials for regenerative medicine.

**INTRODUCTION**

Glycosaminoglycans (GAG) rank worse than poses located at the protein–GAG complex. Chain-assembly is especially suited to select terminal fragments, which AD rank worse than poses located at the binding site of a central fragment.

Chain assembly for GAGs with different length (dp)

For each GAG we tested to assemble all sub-chains with dp6 to 7.

We could sample near-native (<5Å) dp5 chains for 12/13 complexes, and quasi-native (<5Å) for 6/13 complexes. Those ratios diminished to 6/11 for dp6, and 2/11 for dp7 chains.

**RESULTS**

Protein-GAG benchmark

<table>
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<th>Chain id</th>
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<td>heparin</td>
<td>dp6</td>
</tr>
<tr>
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<td>heparin</td>
<td>dp6</td>
</tr>
<tr>
<td>1f9p</td>
<td>FG3/FG1</td>
<td>heparin</td>
<td>dp6</td>
</tr>
<tr>
<td>1gsw</td>
<td>HEPXT1</td>
<td>heparin</td>
<td>dp6</td>
</tr>
<tr>
<td>1i5d</td>
<td>VCP</td>
<td>heparin</td>
<td>dp7</td>
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<td>1bc6</td>
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<td>heparin</td>
<td>dp6</td>
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<td>heparin</td>
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<tr>
<td>4e4n</td>
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<td>heparin</td>
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</tbody>
</table>

**METHODS**

Inputs

We chose 3mer as fragment length in order to conciliate binding specificity (enough contacts per frag.) and a low number of flexible bonds. GAG having a potentiality in [A-B], we dock two types of trimers : A-B-A and B-A-B.

Flexible Docking

- AutoDock3 ([Morris et al. 1998])
- All atoms representation, implicit solvent
- Grid centered on the COM of the bound ligand
- 1000 poses for each fragment type
- Rigid receptor (bound), fully flexible ligand

**CONCLUSION**

We developed a new method to model protein-bound GAGs with high accuracy, on a coarsely known binding site on the protein. The approach proved effective to select correct fragment poses at the surface of the protein, and to model GAG up to a degree of polymerisation dp7 with an accuracy of 3.0 Å RMSD, with more than 10% correct models.

Perspectives

- We considered the binding region as coarsely known. We will extend the method to cases where the binding region could not be predicted with sufficient confidence. We could either repeat the AD docking with a large number of grids, or use another docking engine for exhaustive sampling.
- For this second option, we will implement a saccharide coarse-grained representation in the ATTRACT docking program.
- We considered the protein as rigid. We intend to model also the protein flexibility, by representing parts of the surface in several conformations, that will have to match with neighbor conformations in the chain assembly.
- Finally, we will apply the method to the docking of intrinsically disordered proteins (IDPs).

**REFERENCES**


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