A Generalized Optimization Framework for Carbohydrate Materials

Implemented with Vina-Carb for the Design of Novel hGAL-1 Inhibitors

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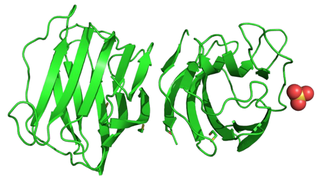
Introduction

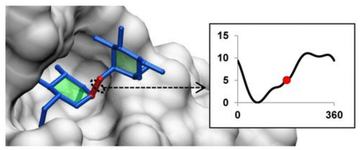
Designing new molecules by combining well-defined chemical structures such as monosaccharides, amino acids, synthetic monomers and functional groups is an excellent way to sample a synthetically accessible domain within a near infinite chemical design space. Here, we have developed an evolutionary algorithm-based framework to design new small molecules by combining monosaccharides and functional group substituents. As a test case, the framework was employed in the design of disaccharide inhibitors targeting the human Galectin-1 (hGAL-1) protein. The novel molecules suggested by our framework share several properties with the natural binding ligand suggesting that our algorithm/fitness function model reflects ground truth structure-activity relationships of hGAL-1

hGAL-1 Protein

- Human body carbohydrate binding protein
- Excess concentrations of this protein are associated with the progression of
  - Inflammatory disease
  - Cancer



Vina-Carb



- Modified Autodock Vina docking scoring function to incorporate Chi energy penalties in glycosidic torsions
- Improved the accuracy of carbohydrate docking

MM/GBSA Binding Free Energy

- Calculates the binding free energy between two chemical entities through the Generalized Borne implicit solvent model

$$\Delta G_{GB} = -\left(\frac{1}{\varepsilon_{in}} - \frac{1}{\varepsilon_{sol}}\right)\sum_{i,j}\frac{q_i q_j}{f_{GB}}$$

- Protein-Ligand Complex solvated and minimized in explicit water before performing calculations

$$f_{GB} = \sqrt{r_{ij}^{\,2} + a_{ij}^{\,2} exp\left(\frac{r_{ij}^{\,2}}{4a_{ij}^{\,2}}\right)}$$

Objectives

1. Design an adaptable software framework for the optimization of carbohydrate molecules and glycomaterials.
2. Apply our framework in order to design disaccharide inhibitors for hGAL-1.

Research Questions

1. Can this framework generate substituted glycans with desired target properties?
2. Does Vina-Carb provide an advantage over AutoDock Vina in the context of free energy optimization?

Optimization Framework

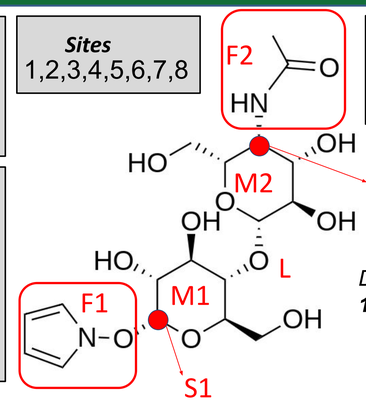
Monosaccharides
aDGlc bDGlc
aDMan bDMan
aDGal bDGal

Sites
1,2,3,4,5,6,7,8

Glyco. Link
(1->2) (1->3)
(1->4) (1->6)

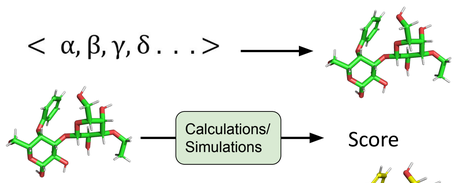
Substituents
Benzene , Ethyl, CF3, Methyl, CHF2, Nitro, Phosphate, Pyrrole, Sulfate

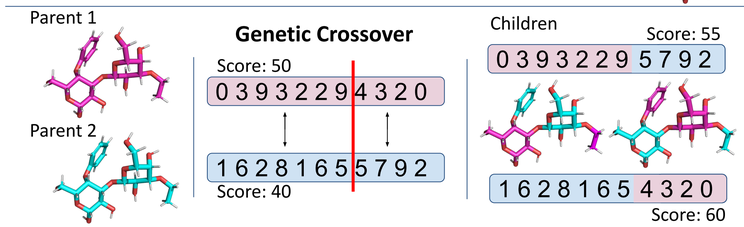
Deoxy Groups:
Cl, F, NAc, Amino,



Design Space: ***1.8M*** *Compounds*

1. **Build:**
   input: a design vector
   outputs: 3d structure
2. **Objective Function** f :
   input: a 3d Structure
   output: Score
3. **Optimizer:**
   implements *Build* and *Score* to optimize design vector



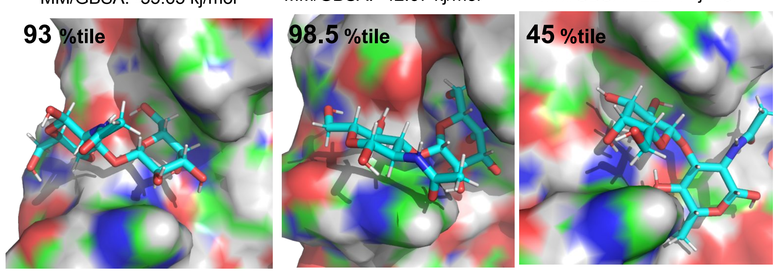


Validation

Crystal Structure
MM/GBSA: -35.65 kj/mol

Re-docked: Vina Carb
MM/GBSA: -42.67 kj/mol

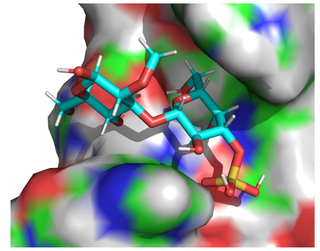
Re-docked: Autodock Vina
MM/GBSA: -22.14 kj/mol

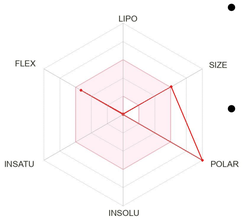


Results

Optimal Solution

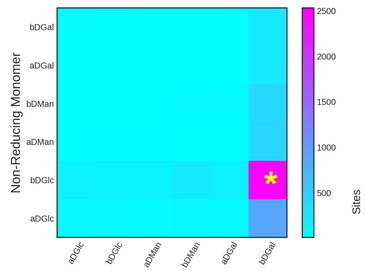
Rank **1**/6400: **bDGal-(1->3)-bDGlc** C3-sulfate C2-Methyl
MMGBSA -64.2 kJ/mol



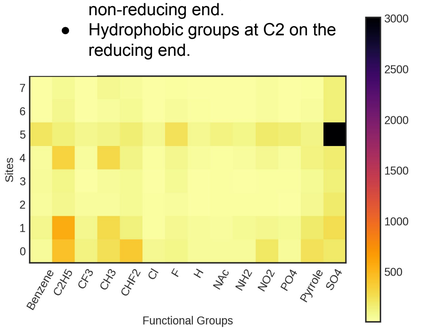


- Optimization to favor polar and electronegative groups.
- However these charged ligands are often unspecific and are not absorbed well by the body.
- Therefore the challenge is to develop molecules which maintain druggability and bind specifically to our target.

Optimization Convergence



Algorithm converges towards
- Polar and ionic groups at C3 on non-reducing end.
- Hydrophobic groups at C2 on the reducing end.



Algorithm converges towards
- Reducing bDGal
- Non-Reducing bDGlc
- (1->3) Glycosidic Linkage

Conclusions

The software framework introduced in this work facilitates the design of carbohydrate materials through the optimization of computationally predicted properties. We plan to expand the scope of this framework through the exploration of materials design problems.

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Deshmukh Group
Computational Design of Hybrid Materials (CDHM)

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