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Advancing Computational Modeling of Protein-Carbohydrate Interactions using Water Sites Biased Docking

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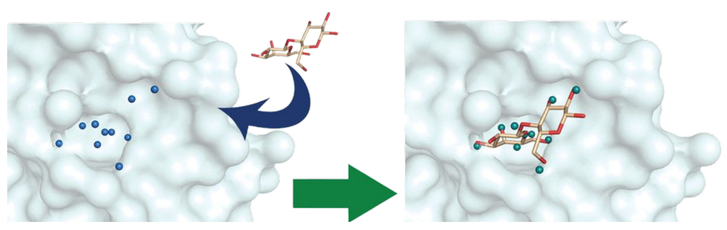
INTRODUCTION

Molecular docking is a widely used computational method for modeling ligand-receptor interactions, primarily focusing on small rigid drug-like molecules. However, its application to flexible carbohydrate molecules often leads to suboptimal performance due to their hydrophilic nature, low affinity, and ligand conformational flexibility (1, 2). To address this, our study aims to develop a precise method capable of predicting both oligosaccharide conformations and relative binding energies to their receptors. To improve the conventional method (CADM, from *Conventional Autodock Docking Method*), it was proposed to use information derived from the solvent structure at the ligand binding site to modify the scoring function of several docking programs (**WSBDM, for Water Sites Biased Docking Method**) (2, 3, 4, 10). This was possible due to the recently developed ***Autodock Vina Site*** program, which allows the application of user-defined biases to the scoring function.



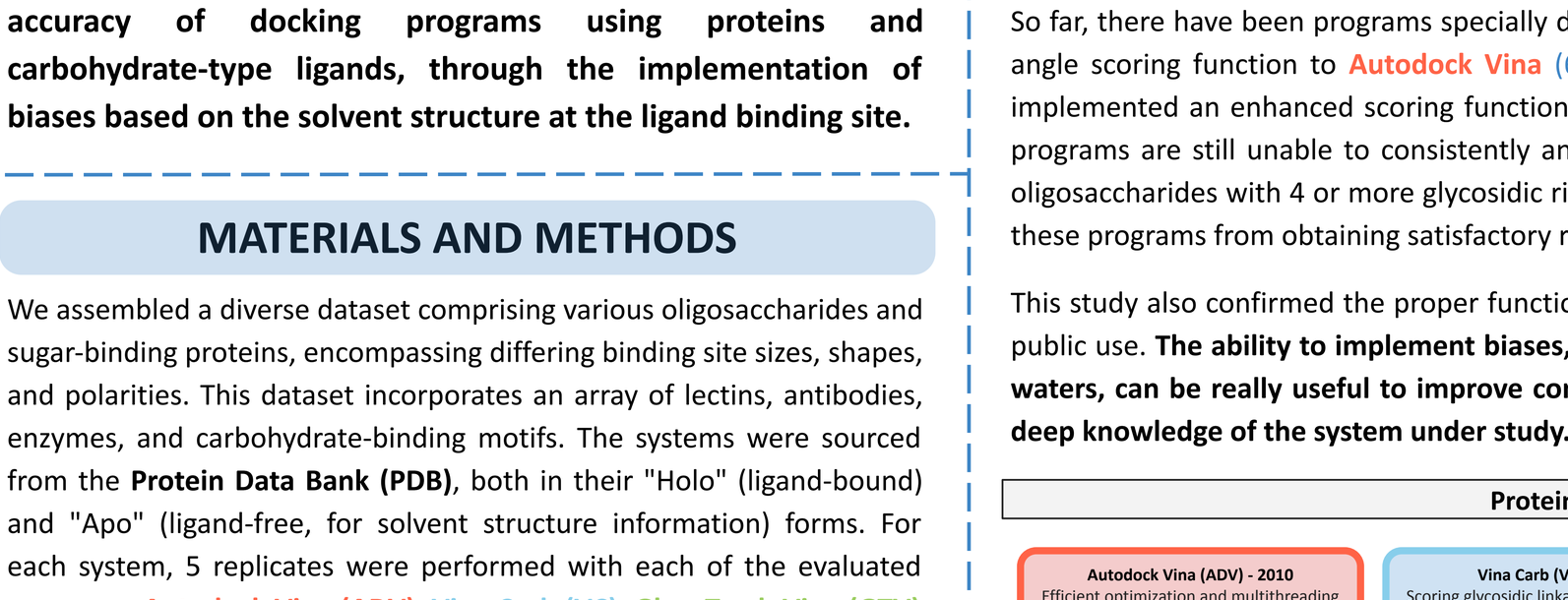
(3)

The ultimate goal is to **significantly increase the precision and accuracy of docking programs using proteins and carbohydrate-type ligands, through the implementation of biases based on the solvent structure at the ligand binding site.**

MATERIALS AND METHODS

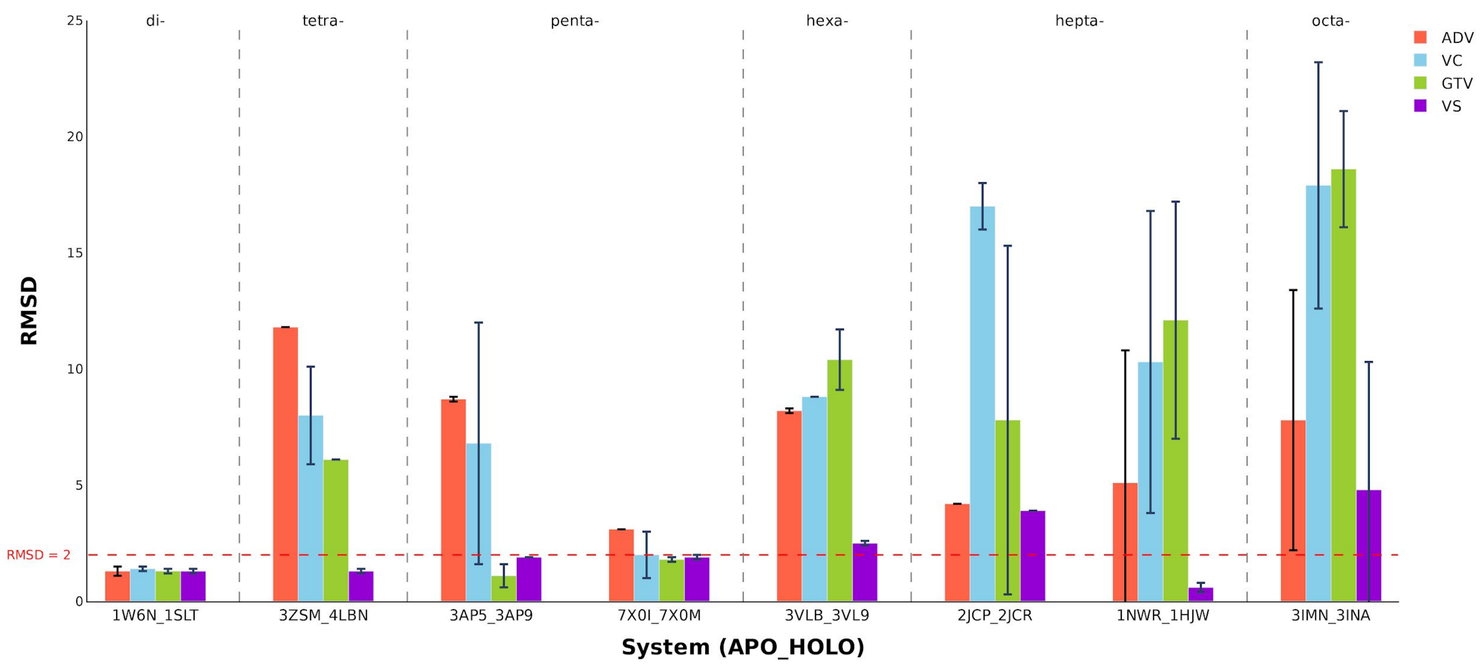
We assembled a diverse dataset comprising various oligosaccharides and sugar-binding proteins, encompassing differing binding site sizes, shapes, and polarities. This dataset incorporates an array of lectins, antibodies, enzymes, and carbohydrate-binding motifs. The systems were sourced from the **Protein Data Bank (PDB)**, both in their "Holo" (ligand-bound) and "Apo" (ligand-free, for solvent structure information) forms. For each system, 5 replicates were performed with each of the evaluated programs: **Autodock Vina (ADV)**, **Vina Carb (VC)**, **GlycoTorch Vina (GTV)** and **Vina Site (VS)**. The protocol parameters were set according to the bibliography for each program. The performance of the programs was evaluated using *Root Mean Square Deviation* (RMSD).

Re-docking using crystallographic structures (*model: human Galectin-3*)



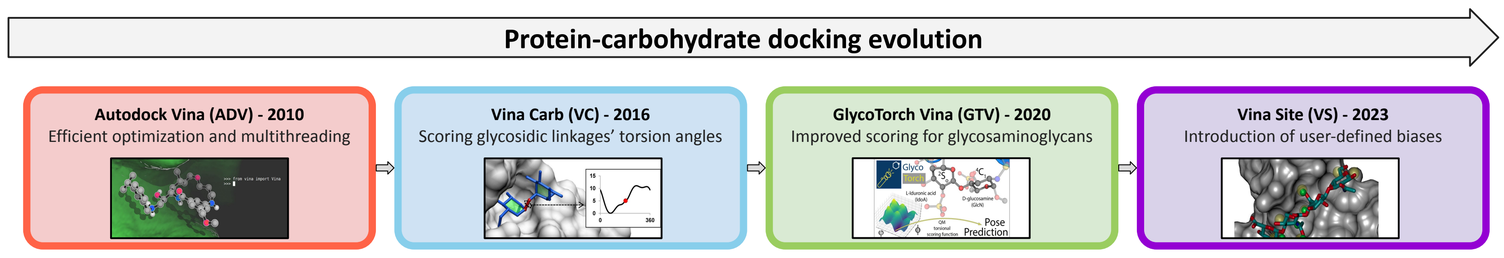
RESULTS

The Water Sites Biased Docking Method (WSBDM) exhibited significant enhancement in precision and accuracy across the analyzed programs for the studied systems. By incorporating solvent structure data from the receptor's ligand binding site, our method yielded predictions closer to experimental observations. Most notably, substantial improvements were evident in systems involving large ligands, where other programs tend to underperform.



So far, there have been programs specially designed to work with carbohydrates. Vina Carb introduced a dihedral angle scoring function to Autodock Vina (6, 7, 8), significantly improving results. Years later, GlycoTorch Vina implemented an enhanced scoring function specific to glycosaminoglycans (9). Although results improved, these programs are still unable to consistently and reliably produce results for systems with large ligands, specifically oligosaccharides with 4 or more glycosidic rings. The vast number of possibilities for these types of ligands hinders these programs from obtaining satisfactory results (1, 7, 9).

This study also confirmed the proper functionality of the new program, Vina Site, which will soon be available for public use. **The ability to implement biases, although in this case was used with the criterion of crystallographic waters, can be really useful to improve computational predictions based on different criteria coming from the deep knowledge of the system under study.**



CONCLUSIONS

Proteins and carbohydrates are two of the main types of biomolecules in living organisms, and their interaction plays a fundamental role in a wide variety of biological processes. The interaction between these molecules can regulate protein activity and function, influence membrane structure, and participate in cellular signaling, among other vital processes (5). **WSBDM, using the new program Vina Site, not only enhances the comprehension of protein-carbohydrate interactions but also improves the reliability, quality, and reproducibility of computational predictions. Its utilization promises a more nuanced understanding of molecular-level protein-ligand interactions, significantly impacting the field of glycobiology**. Furthermore, it holds potential for improving carbohydrate docking predictions in homology-based models when crystal structures are unavailable, which nowadays is essential for understanding key biological processes and for the development of glycomimetic drugs.

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