DOCKING LONG GLYCOSAMIGLYCANS WITH ADVANCED SAMPLING MOLECULAR DYNAMICS-BASED APPROACHES

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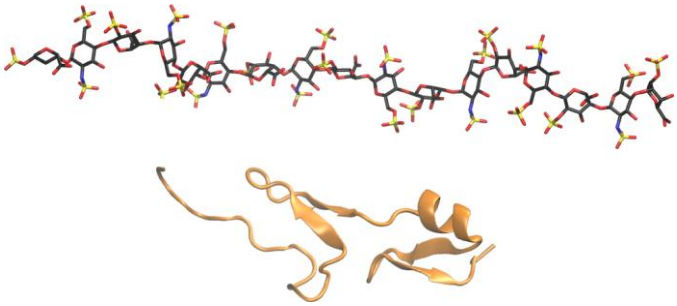
Due to their unique intrinsic properties, glycosaminoglycans (GAGs), long anionic periodic polysaccharides, are challenging molecules to analyze experimentally. Consequently, computational methods are particularly promising for uncovering the structural and dynamic principles underlying the biologically relevant interactions of these molecules with their protein targets. Conventional molecular docking approaches, which predict the structures of protein-ligand complexes, encounter substantial difficulties when applied to long GAG ligands because of their flexibility and high number of degrees of freedom. To address these challenges, we have developed and successfully applied the Repulsive Scaling - Replica Exchange Molecular Dynamics (RS-REMD) approach to dock GAGs up to 50-mers in length. Currently, RS-REMD is the only efficient method for docking long GAGs that does not require prior knowledge of the GAG binding region, incorporates explicit solvent, which is a key for modeling protein-GAG interactions, and its performance is independent of GAG length within a protein-GAG complex. The application of this method enables the modeling of large tertiary complexes involving multiple proteins and a long GAG chains, thereby advancing the fundamental understanding of the biochemical processes mediated by GAGs.



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