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From sequence to 3D-model: An efficient use of homology modeling, molecular dynamics and ligand docking techniques to predict protein-carbohydrate complexes

Carlos Modenutti, Juan Blanco and **Marcelo Marti**
Universidad de Buenos Aires, Argentina

Proteins that bind carbohydrates are responsible for numerous important biological functions, such as signal transduction, cell adhesion, among many others. Despite the number of reported structures of protein-carbohydrates complexes (PCCs) is constantly increasing, achieving accurate predictions of the protein-carbohydrate interaction by means of structural homology models (SHM) and ligand-docking remains one of the biggest challenges in Glycobiology. This is mainly because the residues that form the carbohydrate binding site (CBS) can differ from its ideal binding rotamer in the SHM, which can thereafter significantly affect docking algorithm's performance. In addition, while generally available docking programs work reasonably well for most drug-like compounds, carbohydrates and carbohydrate-like molecules are often problematic, because force-fields and scoring functions are typically designed to reproduce structures of protein-drug complexes. In this work, we present an integrated approach that combines conformational-space sampling of SHM using molecular dynamics simulations (MD) and docking experiments. In order to obtain the most plausible binding structure of receptor and ligand, clustering analysis to identify different conformations was applied. Finally, water-site bias docking method (WSBDM, an Autodock based protocol) was performed to generate a diversity of structures. Energy-population parameters were used to rank each one of them. Here, we used human pulmonary surfactant-associated protein D (hSP-D) as a case study. The results show that this emerges as a promising tool to build reliable 3D-models, which can then be used for rational design or optimization of glycomimetic drugs.

Biography

Carlos Modenutti received his Bachelor of Science degree in Genetics from the National University of Misiones, Argentina in 2009. He then moved to Buenos Aires to join the working group of Dr. Silvia Hajos at Immunology Department, Faculty of Pharmacy and Biochemistry, University of Buenos Aires (UBA) for his PhD. He worked in close collaboration with Dr. Marcelo Marti at the Chemical Biology of Faculty of Exact and Natural Sciences of UBA. His PhD thesis focused on Hyaluronic Acid glycomimetic drug development. He continued his work in the Marti Lab as a Postdoc. His current work focuses on the development of bioinformatics tools for prediction of protein carbohydrate complex structures.

cpmode@gmail.com

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