SAMLE OF THE ABSTRACT

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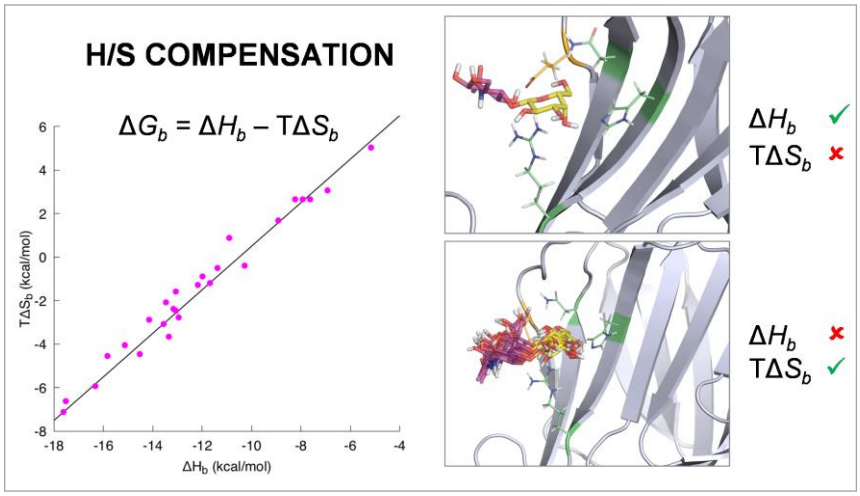
Grant Title: Addressing Enthalpy-Entropy Compensation in Carbohydrates Binding by Computation

Molecular recognition is central to biology, governing host-guest interactions, cell signaling and communication. Modern medicine is largely based on interfering molecular recognition by designing molecules able bind to specific proteins involved in precise signaling pathways. Drug design aims to generate high affinity and specific ligands to bind such protein targets. Despite the vast efforts dedicated both by industry and academia, the computer-aided structure-based design of ligands remains exceedingly challenging. The main reasons for this lack of success are well-known. First, binding free energy of binding is calculated as a small difference between large numbers derived from the different interactions between the protein, ligand, ions, and solvent molecules. Second, such energy terms –particularly entropy– are strongly dependent on a constellation of (insufficiently explored) molecular conformations. Third, the enthalpy-entropy compensation problem is ubiquitous to molecular recognition and arises when flexible and highly polar biomolecules, particularly carbohydrates, are recognized by biological receptors such as glycosidases and lectins. A very effective enthalpy-driven binding in which many attractive interactions between the host and the guest are established in the bound state, is virtually always accompanied with a large entropic penalty due to the loss of conformational freedom and unfavorable solvation balance from the unbound state.



In this project, we have used state-of-the-art computer modelling techniques including quantum mechanics (DFT), microsecond molecular dynamics (μs-MD) and free energy calculations (MM/PBSA, US) to decipher the structural and dynamic determinants of carbohydrate recognition by lectins, particularly the interplay between enthalpy and entropy. Human galectins Gal-3 (monomer), Gal-1 and Gal-7 (homodimer) and Gal-4 and Gal-8 (peptide linked heterodimer), as well as C-type lectin receptor DC-SIGN and their interactions with A and B blood-group antigens and fluorinated carbohydrates, have been investigated. Additionally, an atomistic computer model for the interaction between N-linked glycans in the receptor binding domain of the SARS-CoV-2 spike protein and human lectins, has been developed. This work, together with other studies, has resulted in several joint publications with experimental groups. Additionally, we have written a computational perspective on molecular recognition by galectins, and an open access review of different computational approaches to tackle enthalpy-entropy compensation in biomolecular recognition.