Abstract

Biomolecular recognition, including the binding of small molecules, peptides, carbohydrates, and proteins to their target receptors, is fundamental in biological processes such as immune responses, cellular signalling, and catalysis. Uncovering the physical mechanisms of biomolecular recognition and characterising the critical biomolecular interactions is vital to understanding their functions. Furthermore, these processes are implicated in developing various human diseases and serve as potential drug targets. One way to get a deeper understanding of these interactions at the atomic level is by deploying computational tools. Computational methods are constantly advancing to model biomolecular recognition and predict binding thermodynamics thanks to the increasing accessibility to the power of supercomputers. They are not only complementary to experiments but also recognised as powerful tools capable of providing experimentally inaccessible insights.

This PhD Thesis aimed to characterise biologically active systems consisting of proteins, carbohydrates, and ions using theoretical approaches. The molecular systems chosen as the research objects were glycosaminoglycans (GAGs), linear anionic periodic polysaccharides with metal ions, cyclodextrin (CD) with anionic surfactants, and bovine serum albumin (BSA) with small molecules. In the first part of the Thesis, I focused on investigating the role of ions in carbohydrate-containing systems. The initial goal was to understand the calcium ion (Ca^{2+}) role in annexin-Ca^{2+}-heparin (HP) and HP-Ca^{2+} systems at the atomic level. To do this, I: a) examined how the most commonly deployed standard molecular modelling tools are sensitive and accurate to investigate the protein-ion-GAG systems, and b) rigorously characterised how different Ca^{2+} parameters affect HP's structural and dynamic properties in the simulation. Next, β-CD systems with some alkyl sulfates (SXS) were analyzed (where X=8,10 and 12 denote the number of carbon atoms in the alkyl chain of the sulfate). In this study, I: a) investigated how the alkyl chain length affects the CD-SXS interactions; b) proposed a potential molecular mechanism for the entrance of the ion into the CD cavity; and c) determined how the initial SXS orientation influences the formed inclusion complex. I also reviewed and summarised four aspects of the currently deployed theoretical approaches for investigating protein-GAG complexes, including molecular docking, free binding energy calculations, modelling ion impacts, and addressing the phenomena of multipose binding of GAGs to proteins.

The second part of the Thesis was dedicated to the BSA-containing systems and the BSA interactions with small molecules, including ions. Firstly, I deployed computational techniques

to monitor the influence of pH and temperature on the interactions in the BSA-sodium dodecyl sulfate (SDS) complex and localised potential binding sites and poses. Then, I localised two binding sites in the BSA-$[B(Ph)_4]^-$ complex. Finally, I applied the umbrella sampling (US) protocol to investigate the free energy profile of divanillate (DVT) and divanillin (DVN) orientation change in terms of the dihedral angle between the planes defined by the aromatic moieties of DVT/DVN on the BSA/HSA surfaces or in the absence of the protein.

The results of my PhD research contributed to a better understanding role of ions in biologically active systems, and an attempt to develop novel protocols to model these systems more efficiently was undertaken. Moreover, the limitations of computational methods are discussed in detail, and potential solutions to overcome those challenges are proposed.