Challenges in modeling protein-glycosaminoglycan systems

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Glycosaminoglycans (GAGs), long unbranched negatively charged periodic polysaccharides are present in extracellular matrix and lysosomes where they play a vital role in diverse biological processes such as adhesion, anticoagulation or signalling cascades. Due to their predominantly electrostatic interactions with respective protein targets, GAGs can mediate biological functions of various proteins including chemokines, growth factors and collagen. It is reported that GAGs are also involved in several enzymatic reactions including cathepsins and their immature precursors – procathepsins.

Due to high cost of reagents and devices used in experiments as well as timescale needed to analyse protein-GAG systems, theoretical approaches are often used to aid *in vitro* and *in vivo* studies which allowes us to characterize studied systems at molecular level. Nevertheless, modeling protein-GAG complexes still represent substantial challenge in computational approaches. Features that make modeling GAG containing systems challenging are: *i)* extensive conformational space of GAGs in terms of their glycosidic linkages and monosaccharide rings; *ii)* GAGs highly charged nature; *iii)* GAGs preference to bind at solvent-exposed and spatially close but sequentially not necessarily successive positively charged amino acid patches made up of long and, therefore, flexible lysine or arginine residues; *iv)* the multipose binding observed in several protein-GAG complexes; *v)* highly variable sulfation pattern of GAGs known as “sulfation code” defining its structural properties, molecular recognition and functional activity; *vi)* the possibility of a protein-GAG complex formation, in which GAG orientation is 180° rotated in reference to experimental structure of the complex. In such case, the rotated GAG interacts with exactly the same aminoacid residues as in the X-ray structure, but its direction in reference to its reducing/non-reducing is opposite.

In our studies, we proposed methodology that could address these challenges. We performed long, microsecond scale Molecular Dynamics (MD) of Fibroblast Growth Factor-1-heparin (FGF-1-HP) in order to characterize the impact of glycosidic linkage conformations and ring puckers on the stability of the complex represented as the calculated binding free energies, hydrogen bonds between the ligand and receptor as well as native/non-native contacts. In the present study, we would like to explain how the orientation of a GAG on a protein surface may affect the stability of a complex. In order to do that we performed 1μs MD simulation of FGF-1-HP complex. In our analysis, the HP of different length of the chain (dp2 and dp4 which were modeled as well as dp6 present in X-ray structure; dp stands for degree of polymerisation) was bound in parallel and antiparallel orientation on the protein surface in the binding site corresponding to X-ray structure (pdb ID: 2AXM) of FGF-1-HP dp6 complex (Figure 1).

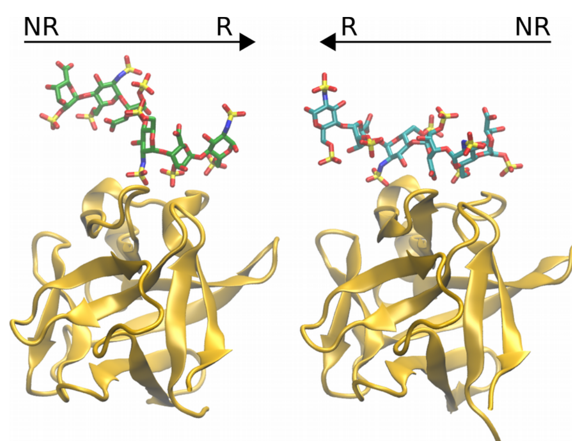

Figure 1: The structure of FGF-1 complex with HP dp6 in different orientations on the protein surface.