REGIONAL CENTRE FOR BIOTECHNOLOGY

Seminar series

Protein Glycosylation: From Force Field Development to Applications

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Abstract

Glycosylation is a ubiquitous post-translational modification of proteins that involves the covalent attachment of carbohydrates to the side chains of either asparagine (N-linked) or serine/threonine (O-linked). It is found to play key roles in cell signaling, molecular recognition and immunity. Close to 50% of all proteins have potential glycosylation sites. However, only 6% of protein crystal structures contain carbohydrate linked structures. In the absence of crystallographic structural information molecular dynamics (MD) simulations can be used to provide atomic-level-of-detail properties such as structure, dynamics, and thermodynamics.

The development of the CHARMM all-atom additive force field parameters for O-linkages and N-linkages that enable MD simulations of glycoproteins will be presented. The importance of experimental data in the development and validation of the force field, specifically the use of NMR J coupling constants, will be highlighted. The successful parameter development led to the recognition of conformational flexibility associated with glycosidic linkages requiring the use of enhanced conformational sampling to describe them. To this end a Hamiltonian Replica Exchange (HREX) enhanced conformational sampling protocol was developed. Application of the HREX methodology allowed for rationalization of the differences between Ser and Thr O-linkages which stemmed from the solvent structure around the linkages. The parameters and HREX methodology were also applied to develop a structure-activity relationship (SAR) for antiproliferative factor (APF), a glycosylated nonapeptide involved in interstitial cystitis. Together the developed parameters and enhanced sampling protocol should enable the study of glycoprotein structures that will improve our understanding of carbohydrate-protein interactions, the role of these common post-translational modifications in biology and be of utility for the development of novel therapeutic agents including antibiotics and vaccines.