Tata Institute of Fundamental Research
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Internal Webinar

Understanding bio-molecular recognition of various biological systems : From proteins to membranes

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Molecules in solution are kinetically active. They collide and interact with their neighbor molecules man times and get dispersed in most cases because the products formed by these interactions are short-lived, weak, and energetically unfavorable. But, when the featured surface of one molecule is complementary to those of its neighbor/partner i.e, when the generated attractive forces between the molecule and its partner outweigh the repulsive forces and the entropic costs of being together then long-lived, stronger, and energetically favourable interactions are established leading to the formation of stable complexes. These specific complexes have significant biological significance. Molecular recognition refers to the process of such binding or aggregation between the molecules such as protein-ligand binding, interactions between receptors and enzymes, macro-molecular assembly, etc. These molecular interactions directly or indirectly affect biological micro-molecular processes such as cell division, movement of a cell, adhesion, and signalling between cells, cell death, cell immunity, propagation of cancer cells to name a few. Hence understanding the forces and mechanisms that drive the formation of complexes will yield many insights and allows rational design of molecules that interact in desired ways. Despite the dedicated research over the decades, the underlying molecular interactions leading to stable complexes such as interactions and conformational dynamics involving protein folding, drug molecules and small peptides binding with their respective target proteins, protein oligomerization, poration through ion channels, electro-chemical exchange of molecular reactions, etc, have been hard to capture because of their fast kinetics involved and low time-scales of the interactions in solution. With the emergence of molecular mechanical forcefields which incorporate potentials arising due to atomistic parameters such as charge, bonds, angles, dihedrals, and non-bonded interactions with their neighboring atoms.

Hence in this discussion, I will start by showing the heterogeneity among carbohydrate force-fields for an amylose dodecamer. Out of 4 commercially available force-fields, we observe GLYCAM06 and CHARMM show good agreement with experimental observations. Using GLYCAM06, parameters for LacNAc a bi-saccharide are were obtained, which helped us in observing successful binding of LacNAc and Galectin-3 protein. Next, I will discuss about how small length peptides made up of 10 β-amino-acids disrupt a bacterial mimic bi-layer to cause water poration through it. Drug resistance is a common phenomenon where a target protein decreases its binding affinity with a drug molecule by mutating a single or multiple amino-acid residues. One such know mutation is gate-keeper mutation of T338M residues in Src-kinase protein. Here, I discuss about a computational work-flow where we design and characterise a set of kinase inhibitors which are derived from second-generation kinase inhibitor RL-45. These derived inhibitors show increased binding affinity with wild-type and mutated Src kinase.

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