Application of Computational Techniques in Drug Discovery

Speaker: Dr. Tarun Jain, Computational Aspects of Drug Discovery in Both Academia and Industry

Abstract: Predicting the binding affinities of candidate molecules to proteins is an essential step in structure-based drug design for discovering new drug leads. Available computational approaches are able to dock small molecules satisfactorily in the drug target but predicting accurate binding affinities still remains a major challenge in drug design. A multitude of methods at various levels of rigor and speed are available today for estimating binding affinities. A good agreement / correlation with the experiment on a diverse set of systems can only be achieved if the methodology integrates all the vital components involved in the thermodynamics of binding. First part of the talk shall focus on the research effort carried out towards the development of a fast and accurate empirical scoring function for predicting binding affinities of protein-ligand complexes.

Computational techniques have become an integral part of drug discovery process in a pharmaceutical industry. Various methodologies like, Molecular docking, Virtual screening (ligand-based + structure-based), Pharmacophore modeling, Scaffold-hopping etc. are being used regularly in drug discovery projects. These techniques can be used alone or in combination to generate rationale ideas to be tested out experimentally. Some practical case studies showing the effective use of these techniques in a drug discovery environment from hitidentification to lead optimization process will be presented in the second half of the talk.

Success of antibacterial drug discovery especially targeted towards gram-negative (GN) pathogens is hindered due to the lack of proper understanding of complex permeability obstacles posed by GN bacteria. These obstacles are interplay of presence of outer membrane, efficient efflux-pump system and orthogonal sieving properties of inner membrane. Physicchemical properties and their favorable range for GN permeability that are present in majority of the GN active compounds and absent from GN inactive compounds have been identified in this work. It is hypothesize that the presence of at least three such properties helps the compound to maintain high concentrations inside the bacterial cell by overcoming the GN permeability barrier. The third part of the talk shall present an analysis to identify physicchemical properties present in antibacterial agents which could influence their GN permeability