[L12] Molecular Dynamics Simulations: Theory and Applications in Drug Design

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Molecular dynamic (MD) simulations have evolved in recent years to contribute to many aspects of contemporary drug design. The increased usage and popularity of this technique once considered largely the domain of dedicated experts, results from several reasons including the constant and rapid increase in computational power (including the introduction of GPUs), the development of new methods for better sampling of the potential energy surface (PES), and the introduction of multiple, freely available MD packages, some with accompanying GUIs.

MD simulations can sample the PESs of molecular entities of different sizes ranging from small molecules to e.g., large membrane proteins embedded in their physiological environment. The resulting trajectories could be analyzed in multiple ways to provide a wealth of information on structure, dynamics, energetic, and other molecular properties. Of a particular relevance to drug discovery is the ability of MD simulations to provide reliable (within the approximation of the force field and solvent models used) estimates of ligand-protein binding free energies. This is in contrast to the over-simplified scoring functions used in molecular docking. On the other hand, MD simulations require significantly larger computational resources and moreover, are slow to converge necessitating the development of enhanced sampling methods.

This lecture will present the basic theoretical and practical background of standard MD simulations as well as some of the enhanced sampling methods. Next, methods for calculating binding free energies from MD simulations will be discussed. Finally, examples will be provided describing the ability of MD simulations to: (1) unveil binding sites not apparent from crystal structures; (2) calculate ligand-protein binding free energies; (3) study protein stability; (4) calculate free energy differences between protein conformations and (5) refine protein structures based on experimentally derived constraints.