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THE MANY DIFFERENT ROLES OF MOLECULAR DYNAMICS IN DRUG DISCOVERY

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Molecular dynamics (MD) samples the potential energy surface of molecular entities thereby providing information on their dynamics. Based on the ergodic hypothesis, time averages obtained from MD trajectories are equivalent to ensemble averages. Since free energy is an ensemble property rather than a single molecule property, it follows that MD simulations could also provide reliable (within the approximation of the force field) estimates of ligand-protein binding free energies, taking into account both enthalpic and entropic contributions as well as solvent effects. This is in marked contrast to the over-simplified scoring functions used for docking. On the other hand, MD simulations require significantly larger computational resources and moreover, are notoriously slow to converge on complex potential energy surfaces necessitating the development of so-called enhanced sampling methods.

This seminar 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.