Combining advanced sampling and free energy simulation to study biomolecular recognition and DNA repair

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Understanding the dynamics and stability of biomolecules and biomolecular complexes is of critical importance to better understand its biological function. For many applications currently accessible time scales of molecular dynamics simulations are too short to sufficiently sample relevant conformational states. We employ advanced sampling molecular dynamics (MD) simulations based on Hamiltonian replica exchange (H-REMD) to study the dynamics and free energy changes of proteins and nucleic acids during structure formation and binding processes. DNA damage can alter the fine structure and flexibility of DNA which can influence the recognition by repair enzymes. We have systematically investigated the altered fine structure of damaged DNA and the free energy changes of helical and global deformations allowing to better understand the mechanism of conformational changes associated with the repair process. In a second part combinations of advanced sampling techniques and alchemical transformations will be discussed that allow a rapid estimation of free energy changes associated with chemical modifications of a receptor-ligand complex.