UNIVERSITÄT DUISBURG ESSEN

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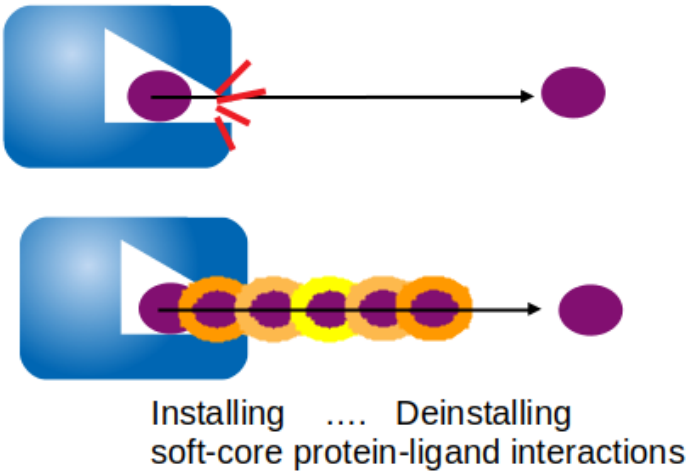
Improving potential of mean force and nonequilibrium pulling simulations by simultaneous alchemical modifications

Dr. Maria Reif

TU München



Absolute ligand-protein binding free energies are commonly calculated with either a physical-pathway free-energy calculation method such as umbrella sampling or alchemical free-energy calculations (double decoupling). We present an approach combining alchemical modifications and a physical-pathway method, where the latter is e.g. stratified umbrella sampling or nonequilibrium pulling. Along the physical unbinding pathway, an alchemical transformation of ligand-protein interactions is installed and de-installed. As an example system, we study a mutant of T4 lysozyme with a benzene ligand. The binding pocket is occluded, which may pose problems in standard physical-pathway free-energy calculations. Installation and de-installation of soft-core interactions concurrent with physical ligand unbinding allows successful potential of mean force calculations and nonequilibrium pulling simulations. The latter turned out to be remarkably compute-efficient. We conclude that physical ligand unbinding combined with simultaneous alchemical modifications proves useful for the calculation of binding free energies to occluded pockets, where sampling problems associated with steric clashes and conformational rearrangement can be reduced.