From Monte Carlo methods to drug discovery

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Molecular mechanics (MM) simulations have become crucial to understand biophysical and biochemical processes. In these simulations, an accurate generation of the ensemble is essential to ensure valid estimations of the system properties. Traditionally, Molecular dynamics (MD) have become the main algorithm to explore the conformational space in molecular systems. In contrast, as MD is expensive computationally speaking, different Monte Carlo (MC) approaches have been developed to speed up the conformational sampling producing equivalent ensembles. This talk will be focused on the description of two MC algorithms (PELE[1,2] and MCPRO[3]) which have been successfully applied to study the protein-ligand binding process.

PELE is a heuristic algorithm that combines a MC stochastic approach with structural prediction techniques for fast mapping of molecular biophysics. It is capable of accurately reproducing long time scale processes in only a few hours of CPU. It has been used to study ligand migration, protein/NA conformational sampling and ligand binding process. Recently, PELE has been successfully applied to estimates absolute binding free energies through Markov State Models.[4] On the other hand, MCPRO performs statistical mechanics simulations in NPT and NVT ensembles performing small and localized MC perturbations. MCPRO is mostly applied for estimation of relative and absolute binding free energies using free energy perturbation theory.

The talk will cover different examples were both algorithms have been successfully applied showing the main capabilities.

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