سمینار هفتگی ماده چگال نرم

Predicting Absolute Binding Affinity Using Streamlined Alchemical Free Energy Calculation

Abstract

The alchemical free energy perturbation (AFEP), a reliable approach, can predict ligand-protein binding affinities efficiently thanks to fictitious intermediate states. To achieve robust convergence, we implemented a double decoupling method using a recently introduced restraining potential limiting the ligand fluctuations to the bound state. In this approach known as Streamlined Alchemical Free Energy Perturbation (SAFEP), we take advantage of a particular restraint so-called “distance to bound coordinate” (DBC), leading to an accurate evaluation free of artificial bias. A new roto-translational restraint minimizing the root-mean-square deviation (RMSD) of ligand coordinates from a typical bound pose in the frame of reference is employed to reproduce the ligand binding affinity, which reduces the number of intermediate states and simulations used in the conventional double decoupling studies. Furthermore, the free energy estimation is well converged by sampling all relevant bound configurations in the phase space. In addition to empirically verifying the method using a standard benchmark system, we developed a remedy for the ligand symmetry issue integrating with the SAFEP method, which equates symmetric bound conformations to tighten the boundary condition of the restraint bias. The easy-to-use workflow in the SAFEF approach may open perspectives for the drug candidates’ optimizations in drug design with a more precise and cost-effective computer simulation technique.

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