Study of ligand binding to HIF-2α through Path-Metadynamics

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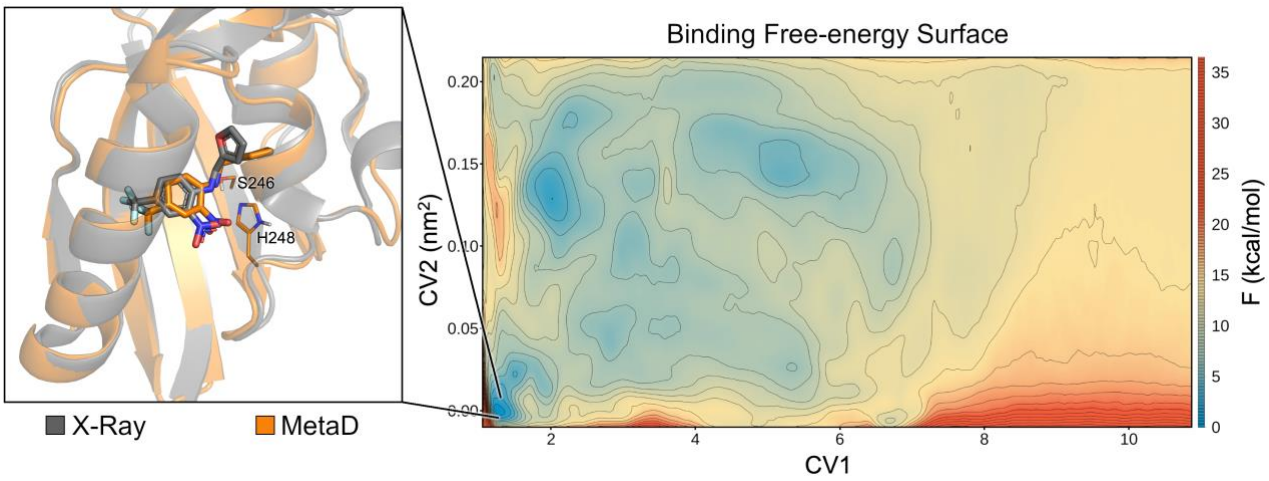
Several methods based on enhanced-sampling molecular dynamics have been proposed for studying ligand binding processes[1]. Herein we developed a protocol that combines the advantages of steered Molecular Dynamics[2] (SMD) and Metadynamics[3]. In SMD a moving restraint bias is applied to the system to pull it along a selected variable. [2]. In Metadynamics simulations, a history-dependent bias potential is applied to a small number of suitably-chosen collective variables (CVs) to discourage the system from revisiting already sampled configurations. Since the choice of CVs is a crucial aspect to obtain an accurate free-energy calculation, Branduardi et al.[4] developed the Path Collective Variable (PCVs) method, which allows exploration of complex multidimensional processes along a predefined pathway described by a single CV.
In this work we propose a combined use of SMD and Metadynamics for the investigation of ligand binding processes. SMD was used to compare the forces required to achieve ligand unbinding through different pathways and identify the preferred one. The employment of Metadynamics with PCVs was used to explore the binding processes along the pathway defined on the basis of SMD. We applied our approach to study the binding of two known inhibitors of the Hypoxia Inducible Factor 2α (HIF-2α), a pharmaceutically relevant system widely recognized as a target for cancer therapy[5].The buried nature of the binding cavity of this protein makes simulation of the process a challenging task. Our approach allowed identification of the preferred entrance pathway for each ligand, highlighted the features of the bound- and the intermediate- states in the free-energy surface, and provided a binding-affinity scale in agreement with experimental data.[6] Therefore, it seems to be a suitable tool for elucidating ligand binding processes of similar complex systems.



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