Ligand Binding Free Energy Landscapes at the Tubulin Colchicine Site from Coarse-Grained Metadynamics

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Despite substantial progress in computational chemistry, reconciling the accuracy of all-atom molecular dynamics (AA-MD) with the efficiency required for high-throughput binding free energy predictions remains a central challenge in structure-based drug discovery. Recently, we proposed address this gap using coarse-grained funnel metadynamics (CG-FMD) [1] based on the Martini 3 force field [2,3]. This framework combines the computational efficiency of coarse-grained representations with enhanced sampling techniques capable of modelling full ligand binding and unbinding pathways, including access to deeply buried binding sites.

Results on model systems showed very good agreement with experimental references. Furthermore, thanks to the extensive sampling efficiently achievable with limited HPC resource allocation, the statistical uncertainty of CG-FMD estimations was much reduced compared to the AA-FMD counterpart. Indeed, we suggest that the improved sampling capabilities of CG simulations can partially compensate the simplified representation of the protein-ligand complex.

We will show preliminary results [4] of this methodology applied to the exploration of the tubulin αβ heterodimer, a complex multisite protein of strategic pharmaceutical relevance. In particular, we will highlight how CG-FMD has made it possible to obtain binding free energy predictions comparable to experimental reference for pharmaceutical scaffolds binding to the deeply buried colchicinoids site. Overall, we suggest that CG-FMD can become a valuable and efficient physics-based approach for the investigation of protein-ligand interaction on complex biosystems, with high scalability of system size.

References

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