Can Coarse-Grained Simulations Reach Chemical Accuracy? Revisiting the Sampling–Accuracy Trade-off

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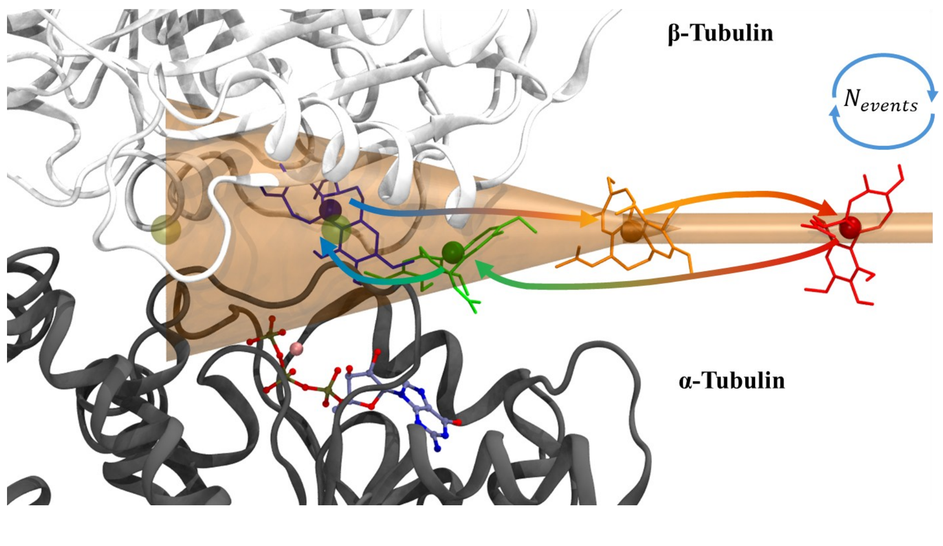


Introduction

Accurate computation of protein-ligand binding affinities has long been an area of active interest in computational chemistry[1], as it can guide the drug design process.

Funnel MetaDynamics[2,3,4] (FMD) allows the ligand freedom of exploration while inside the binding pocket, whereas restricts its roto-translation to a narrow cylindric section toward the solvent bulk (**Fig.1**). This results in the **efficient sampling** of several binding events in one replica. In this project, FMD has been applied to the elucidate the binding of several chemical scaffolds to proteins of increasing size (from 130 residues to the 860 residues of αβ-tubulin, **Fig.2**) **both at AA and CG resolution**.

Figure 1. Restraining potential applied to the ligand's center of mass. The conical section of the funnel enables exploration of the colchicinoids' binding site, while the cylindrical section prevents ligand dispersion into the solvent bulk.

Simulation Efficiency

The improved efficiency of CG-FMD compared to AA-FMD has been determined by computing the **average** number of **binding events** observed in **1μs** at both resolutions. Interestingly, CG-FMD can capture **50%** more binding events (**Fig.3**). Furthermore, if we compare the rate at which new binding events are observed (as a function of the simulation wall-time), CG-FMD can offer an improvement of **25 times** compared to AA-FMD, with the additional advantage of requiring less hardware.

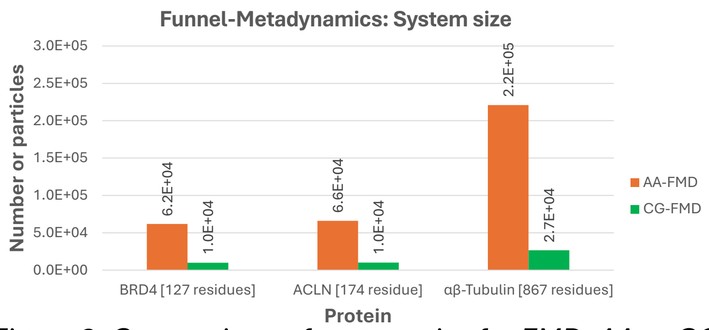


Figure 2. Comparison of system size for FMD: AA vs CG.

Simulation type	CPU-allocation	GPU-type	Performance	#Binding Events/ 1μs-simulation	Walltime 1μs-simulation	Rate of acquisition [Events/h]
AA-FMD	8cores-Intel Xeon Platinum 8358@2.60GHz	NVIDIA Ampere A100 64GB	190ns/day	15.0	**126.3 h**	0.1
CG-FMD	8cores-AMD EPYC 7763@2.45 GHz	***none***	3600ns/day	22.8	**6.7 h**	3.4

Figure 3. Hardware requirements and rate of binding event collection: AA-FMD vs CG-FMD; Data from the Colchicine-Colchicalin system.

KEY-takeaways

- CG-FMD **scales well** with system's size (**Fig.2**).
- CG-FMD is **25x more efficient** than AA-FMD.

Free Energy landscapes at the colchicinoids' site

Preliminary FMD simulations have been performed with a simple set of **geometric descriptors** (limited *a-priori* bias), namely pocket-ligand *distance* and *angle* between two residues and the ligand. Interestingly, both AA–FMD and CG-FMD **free energy surfaces** (FES) suggest a complex mechanism for the binding of compounds to the colchicinoids sites, with a first minimum in a solvent-exposed **vestibular** region, followed by complete penetration to the more **buried** region of the pocket (**Fig. 4**).

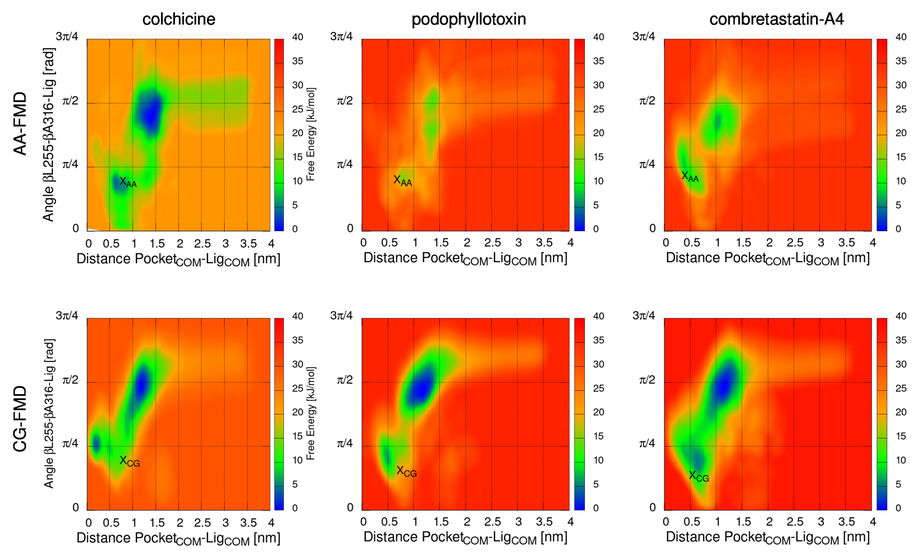


Figure 4. FES obtained from FMD simulations of the three compounds investigated binding to the colchicinoids site. First row shows results from AA-FMD, while second row highlights results from CG-FMD performed with the Olives CG-Protein model. "X" marks the projections of the crystallographic pose in the CV-space.

Binding Free Energy estimations

Binding free energies have been estimated from the FMD simulations after correction for the presence of the funnel restraint[2,3]. **Fig.5** shows that **CG-FMD** yields affinity predictions **comparable** to **AA-FMD**, although some systematic **underestimation** compared to experimental references is present. Interestingly, we note that the **protein's flexibility** plays a key role in CG results. Indeed, changing from a rigid Elastic Network to more flexible Olives or goMartini CG-models can improve the free energy estimation.

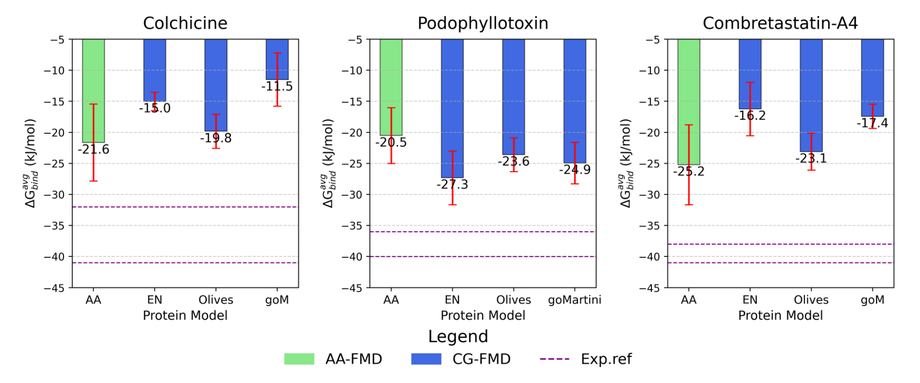


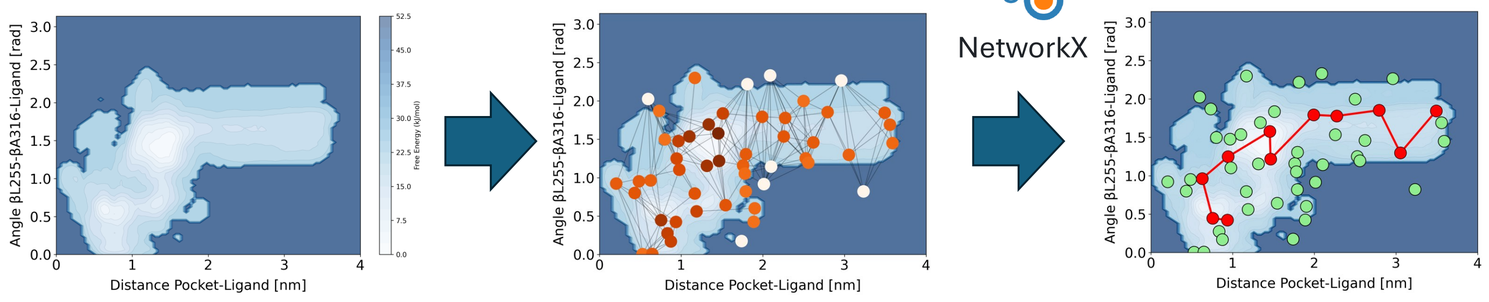
Figure 5. Binding free energy estimations from FMD simulations at AA and CG resolution. Red error-bar is the standard error of the mean over a dataset of ten replicas. Purple dashed lines indicate the upper and lower affinity value reported in literature for each compound.

From CG-exploration to *physics-based* path-CV

Exploratory CGFMD & Preliminary FES

Waypoints definition

Optimal path



Recovery of atomistic detail

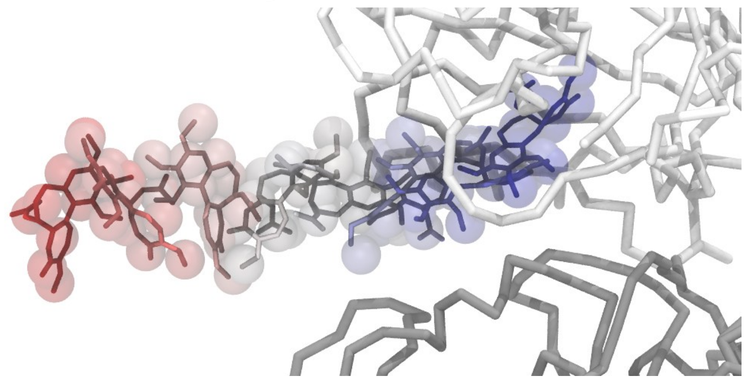


Figure 6. Colchicine poses from a physics-based path CV. Red pose represents a fully solvated state, while blue pose is fully inserted in the crystallographic site.

Outstanding questions

- Can we increase the sampling while limiting computational cost?
- Can we obtain converged 1-D FE profiles, quantifying the activation barrier?
- Can we improve the overall ΔG_{bind} estimation?

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References

1. Limongelli, V., *Wiley Interdisciplinary Reviews Computational Molecular Science*, 2020, **10**

2. Limongelli, V. B., *et al. PNAS*, 2013, **110**, 6358-6363.

3. Raniolo, S., & Limongelli, V., *Nature Protocols*, 2020,**15**, 2837-2866.

4. Grazzi, A., *et al*. JCTC,2026, **22**, 1164–1176.