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Advancing the Prediction of Binding Events in Highly Flexible, Allosteric and Multidomain Proteins

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Accurately predicting ligand-protein interactions remains a cornerstone of rational drug discovery [1,2]. Traditional docking methods often struggle to capture the dynamic conformational landscapes of such proteins, especially when only apo (unbound) structures are available [1]. In this work, I will introduce our recent protocol gEDES (generalized Ensemble Docking with Enhanced sampling of pocket Shape) [2,3], a computational method designed to generate holo-like conformations from apo protein structures. gEDES employs enhanced sampling techniques to explore the conformational space of proteins, focusing on the dynamic reshaping of binding pockets and sub-pockets that are critical for ligand binding. This approach enables the modeling of induced-fit effects and allosteric transitions without prior knowledge of the bound state. We applied gEDES to adenylate kinase, a prototypical allosteric enzyme with significant domain movements upon ligand binding. Our results demonstrate that gEDES accurately reproduces holo-like conformations, facilitating precise docking of substrates, inhibitors, and non-competent analogs. Compared to state-of-the-art deep learning methods such as NeuralPLexer [4], which utilizes multiscale generative diffusion models for protein-ligand complex prediction, gEDES exhibits superior sensitivity to subtle chemical variations in ligands, leading to more accurate binding pose predictions [2]. When benchmarked against the DUD-E (Directory of Useful Decoys, Enhanced) database, a comprehensive resource for evaluating docking and virtual screening performance, gEDES was able to generate druggable conformations for more than 80% of the targets. gEDES will be made available to the through a user-friendly web server to make gEDES accessible to the broader scientific community, facilitating the generation of holo-like structures and the setup of simulations for diverse protein targets.

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