Detection of Cryptic Pockets for Drug Discovery

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Detecting cryptic pockets holds great promise in uncovering hidden ligand binding sites within static apo structures of a target protein, thus presenting novel therapeutic opportunities. Furthermore, these allosteric cryptic pockets can prove invaluable in the development of target-selective ligands, especially in cases where the known orthosteric binding sites exhibit high conservation. In this context, we introduce a recently devised approach that utilizes weighted ensemble molecular dynamics simulations[1], incorporating inherent normal modes as progress coordinates, to explore cryptic pockets. To demonstrate the effectiveness of our approach, we applied it to investigate the onco-target KRAS and its crystal structures, specifically focusing on the G12D isoform. Through all-atomic simulations, both with and without various co-solvents such as xenon, ethanol, and benzene, we performed an in-depth analysis of the resulting trajectories using three distinct methods, aiming to identify potential binding pockets.

Bibliography :

[1] Russo, J. D. et al. J Chem Theory Comput 18 (**2022)**, 638-649.