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Mechanistic pathways of recognition of a solvent-inaccessible cavity of protein by a ligand JAGANNATH MONDAL, SUBHENDU PANDIT, BHUPENDRA DANDEKAR, PRAMODH VALLURUPALLI, TIFR Center for Interdisciplinary Sciences — One of the puzzling questions in the realm of protein-ligand recognition is how a solvent-inaccessible hydrophobic cavity of a protein gets recognized by a ligand. We address the topic by simulating, for the first time, the complete binding process of benzene from aqueous media to the well-known buried cavity of L99A T4 Lysozyme at an atomistic resolution. Our multiple unbiased microsecond-long trajectories, which were completely blind to the location of target binding site, are able to unequivocally identify the kinetic pathways along which benzene molecule meanders across the solvent and protein and ultimately spontaneously recognizes the deeply buried cavity of L99A T4 Lysozyme at an accurate precision. Our simulation, combined with analysis based on markov state model and free energy calculation, reveals that there are more than one distinct ligand binding pathways. Intriguingly, each of the identified pathways involves the transient opening of a channel of the protein prior to ligand binding. The work will also decipher rich mechanistic details on unbinding kinetics of the ligand as obtained from enhanced sampling techniques.

Jagannath Mondal
TIFR Center for Interdisciplinary Sciences

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