S N BOSE NATIONAL CENTRE
FOR BASIC SCIENCES
Block JD, Sector III, Salt Lake, Kolkata 700 106

DEPARTMENTAL SEMINAR
Chemical and Biological Sciences

21st December, 2022 11.30AM ONLINE / FERMION

SPEAKER

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TITLE OF THE TALK

Ligand (Un)binding Transition State Ensembles in soluble epoxide hydrolase: Expectation vs Reality!

ABSTRACT

The bound and unbound ensembles are often straightforward in the context of ligand (un)binding in a protein and provide little insight to the unbinding mechanism. The transition state (TS) ensemble, on the other hand, can provide us with critical insights of the (un)binding mechanism for a drug molecule inside a target protein. The molecular motions such as loop reorientation, ligand poses during (un)binding and the intermolecular ligand-protein interactions in the loosely bound to loosely unbound state (i.e., the whole TS ensemble) is key to decipher the mechanism of unbinding and the molecular determinants of the on- and off-rates. A substantial effort to characterize the TS can lead to designing of ligands with the optimal kinetics for a given protein target. The question, however, is when can a definition of the TS ensemble for one ligand provide information across a set of related ligands? Does the (un)binding mechanism involve an analogous TS ensemble for separate drug candidates for the same protein? To answer that, we carried out a series of simulations with the weighted ensemble algorithm, REVO, for a set of 7 proposed drug molecules unbinding from the soluble epoxide hydrolase (sEH) protein. All these molecules have stable interactions with sEH and are buried inside a channel in the core of the protein. The unbinding timescale of these drug candidates are on the order of minutes or more. We calculate the rate of unbinding for each of these molecules and compare with experimental measurements. We establish a general algorithm for comparing unbinding pathways of related ligands and determining their TS ensembles [1]. Finally, we quantitatively analyze the robustness of the ligand binding TS across the 7 ligands. The details of REVO and weighted ensemble based enhanced sampling methods will be discussed in detail as well.

1. Manuscript under preparation: S. Bose, S. D. Lotz, I. Deb, A. Dickson; Ligand (Un)binding Transition State Ensembles in sEH protein: From Concept to Reality.

HOST FACULTY

Dr. Suman Chakrabarty
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