Abstract for an Invited Paper
for the OSS12 Meeting of
The American Physical Society

Single-Molecule Spectroscopy and Imaging Studies of Protein Dynamics

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Enzymatic reactions and protein-protein interactions are traditionally studied at the ensemble level, despite significant static and dynamic inhomogeneities. Subtle conformational changes play a crucial role in protein functions, and these protein conformations are highly dynamic rather than being static. We applied AFM-enhanced single-molecule spectroscopy to study the mechanisms and dynamics of enzymatic reactions involved with kinase and lysozyme proteins. Enzymatic reaction turnovers and the associated structure changes of individual protein molecules were observed simultaneously in real-time by single-molecule FRET detections. Our single-molecule spectroscopy measurements of T4 lysozyme and HPPK enzymatic conformational dynamics have revealed time bunching effect and intermittent coherence in conformational state change dynamics involving in enzymatic reaction cycles. The coherent conformational state dynamics suggests that the enzymatic catalysis involves a multi-step conformational motion along the coordinates of substrate-enzyme complex formation and product releasing, presenting as an extreme dynamic behavior intrinsically related to the time bunching effect that we have reported previously. Our results of HPPK interaction with substrate support a multiple-conformational state model, being consistent with a complementary conformation selection and induced-fit enzymatic loop-gated conformational change mechanism in substrate-enzyme active complex formation. Our new approach is applicable to a wide range of single-molecule FRET measurements for protein conformational changes under enzymatic reactions.