Role of Metastable Conformational States in Proteins: From Function to Drug Discovery

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Structural biology of proteins is dominated by a native structure-centric view. However, biomolecular functions are intimately connected to protein motion/dynamics and often low-lying metastable or "excited" conformational states play an important role.[1,2] For example, recent examples of "dynamic allostery" have established that a static structural view is not enough.[3] In this talk, we shall discuss several such examples based on large scale classical molecular dynamics (MD) simulations. We demonstrate that a "population shift" of highly coordinated hydrogen bonds and salt bridges might lead to the allosteric modulation in several proteins.[3,4] We shall also present our new ideas on identifying allosteric hotspots on protein surface to modulate therapeutically important protein-protein interactions (PPI) as a promising alternative strategy in computer aided discovery of allosteric inhibitors.[5]

References:

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