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Editorial

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Emerging Concepts about the Role of Protein Motion in Enzyme Catalysis

The Special Issue of *Accounts of Chemical Research* on Protein Motion in Catalysis addresses one of the most active and compelling areas of investigation regarding protein function: the relationship of motions within a protein to catalytic rate enhancement, allosteric control, and thermal adaptation. There is growing acceptance that our ability to understand and predict protein function must go beyond the static views obtained from traditional X-ray crystallography and incorporate both local and global protein conformational landscapes that can involve large segments of a protein and take place on time scales from femtosecond to millisecond. The fields of computation and experimentation, which at times have appeared in conflict, are increasingly providing synergistic pictures of protein behavior.

The most direct properties that can be studied are for the ground state protein alone or in complex with substrate or modulator ligands. The emerging importance of Markov state models and the computation or measurement of side chain entropy is facilitating the evaluation of interconverting ground state structures and the relative importance of surface versus buried protein motions. Advances in NMR have provided the ability to detect low population protein substates, as do room temperature Ringer X-ray studies. Monitoring the progression of the enzyme−substrate complexes toward the activated complex introduces additional challenges for achieving sufficient spatial and temporal resolution of functionally linked protein motions. A wide range of studies has supported the concept of modulation of reaction barrier width and height, as well as active site electrostatics, through protein motions. What is particularly exciting is that this concept, which originally emerged from the properties of room temperature electron and most recently hydrogen tunneling, has become apparent in many different classes of enzyme reactions.

Advances in methodology are critical to the growth within this field of inquiry. Well-established computational approaches that include mixed quantum mechanical/molecular mechanical (QM/MM) approaches, empirical valence bond (EVB) potentials, molecular dynamics free energy simulations, and transition path sampling methods are being expanded to address challenges such as sampling for much longer (i.e., microsecond) time scales and incorporating a growing number of atoms in the region treated quantum mechanically. The experimental toolkit has also gained traction, with the availability of techniques that can be monitored and evaluated as a function of perturbations that alter catalytic efficiency. In the picosecond to nanosecond time regime, changes to vibrational frequencies can be observed through the selective modification of amino acid side chains or the use of bound substrates with vibrational frequencies that lie outside of the protein envelope. Time-resolved fluorescence measurements continue to provide important insight into local motions that control the lifetime and emission wavelengths for appropriately placed chromophores. On the much longer time scale, seconds to hours, hydrogen−deuterium exchange is a well-validated tool to evaluate changes in local protein unfolding and its dependence on perturbations to the protein or environment. One critically needed time scale lies within the microsecond to millisecond regime, which is the one most generally implicated for the real time interconversion among multiple protein substates. Future methodological developments within this time regime will be a boon to the field of protein dynamics.

Unraveling the mysteries of protein motions and conformational sampling is also relevant to protein design efforts. Attempts at rational protein design have often focused on the structural aspects of ligand binding and enzyme catalysis. The recent discoveries and insights summarized in this special issue suggest that protein motion and conformational sampling should also be taken into account in protein design strategies. Thus, these concepts could have broad implications for drug design and for the design of more effective catalysts for biomedical and technological purposes.

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