

Foreword

The enormous number of three-dimensional structures for proteins that emerged during the second half of the twentieth century – as of November, 2012, there are ca. 86,000 entries in the international Protein Data Base – led quite naturally to an intense focus on the relationship between protein structure and function. There was recognition that allosteric proteins could assume different shapes in the presence of allosteric regulators, and much work was dedicated to developing mathematical models for this behavior [1,2]. The classical studies on hemoglobin showed how the remote binding of small molecules could tune the affinity of molecular oxygen at the active site heme-iron center [3]. These protein motions were conceptualized as rigid body movements that linked the active and inactive protein states. The latter half of the twentieth century saw an increasing focus on the more general feature of protein dynamics. Once again, the binding of small gaseous molecules to heme proteins played an important role, with Frauenfelder and his co-workers demonstrating a photo-initiated, multi-exponential release of CO from myoglobin at low temperature [4]. The implication from these studies was that the inherent flexibility of proteins at room temperature had led to a family of low-temperature conformers with different inherent kinetic properties. Concomitant with experimental approaches, Karplus and co-workers developed methods for computer simulations of rapid protein motions (picosecond timescale) using Newton's equations of motion [5]. For many years, classical studies of enzyme function and the study of protein dynamics moved on largely parallel trajectories, occasionally intersecting but with considerable skepticism and reservation on both sides.

The last decade has seen a profound shift toward the recognition that the large size and inherent floppiness of proteins can manifest itself at every level of protein function. This type of motion goes beyond two state models for allostery, as well as the expected accommodation of a protein's shape to the binding of substrates and their conversion to products. The emerging models include a productive and causative role for protein motions at every level of function. This volume highlights some of the exciting directions that the field of protein dynamics has made in recent years. Here, the term "dynamics" refers to both equilibrium and non-equilibrium motions on all timescales. We have aimed at a balanced presentation of four

chapters on theory and an equal number on experimental approaches. This is a very active research area, and we apologize upfront to the many investigators who are not included in the present volume. Our hope was that the range of chapters chosen would highlight topics that may not always be considered in the same context.

From the experimental perspective, the role of protein dynamics in enzymatic bond-making and bond-cleavage events is addressed by Kohen and Cheatum. As has been discussed with increasing frequency in the literature, the enzymatic activation of C–H bonds opens up a special window for analyzing the role of heavy atom protein motions in catalysis [6]. Schulenberg and Hilvert address the very active area of intrinsically disordered proteins, and whether the properties of such enzymes can help us to understand the role of protein motions in native enzyme catalysis. The correlation of side chain entropy among protein side chains with function has increasingly attracted wide attention, and Wand and co-workers describe careful and insightful studies of this feature of calmodulin function according to an “entropy ruler.” Finally, Schrank, Wrabl, and Hilser talk about the role of a lid closure on the function of adenylate kinase, building upon multi-layered experimental data to generate a multi-state model for the progression of this enzyme from an open to a closed, catalytically active state.

From the theoretical perspective, the effects of macromolecular crowding on enzyme conformational dynamics and activity are discussed by Ma and Nussinov. Structured crowding, which refers to the highly organized cellular environment, could potentially enhance enzyme efficiency and specificity. Cui and coworkers discuss how atomistic and coarse-grained simulations can be used to elucidate the mechanism of activation transitions, which often precede the chemical steps in enzymes and are typically allosteric and multiscale in nature. In the simplest enzymes, such as adenylate kinase, the activation transition corresponds to the closure of the active site, but in biomolecular motors, such as myosin, it is more complex. Arora and Brooks focus on the enzyme dihydrofolate reductase (DHFR), which catalyzes the hydride transfer reaction required for the conversion of dihydrofolate to tetrahydrofolate. This enzyme has been studied extensively with a wide range of theoretical and experimental methods. The consensus is that equilibrium conformational motions of the protein and ligands impact catalysis in DHFR by generating configurations conducive to the hydride transfer reaction, but there is no evidence for dynamical coupling of protein vibrational modes to the breaking and forming of chemical bonds [7]. Schwartz proposes a more controversial perspective about the role of protein dynamics in enzyme catalysis. While he agrees with the above interpretation for DHFR, he also proposes that femtosecond to picosecond “promoting vibrations” of the protein can be directly coupled to the passage over the chemical barrier (i.e., to bond breaking/forming) and are catalytically relevant for other enzymes, such as lactate dehydrogenase and purine nucleoside phosphorylase. This aspect of catalysis contrasts with the more generally accepted model of equilibrium conformational sampling that has components of protein motions ranging from femtosecond to millisecond timescales.

As the reader will see, the included chapters are, at times, either complementary or divergent in their conclusions. We believe that this reflects the current vibrancy

of the field of protein dynamics. One of the goals of this community – hopefully achievable in the coming decades – will be to develop a level of understanding that allows us to replicate in the test tube the exquisite specificity and enormous catalytic rate accelerations of native proteins.

References

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