Structural and Computational Enzymology: Bringing Computations and Experiments Together

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Enzymes, biological catalysts, are of great interest for biosciences, medicine, pharmacy and biotechnology (1). Historically, Enzymology started with determining the roles of enzymes in physiological processes, and passed along with identifying individual enzymes, their purification, characterization and exploration of the enzyme kinetics. The development of crystallography, NMR and spectroscopic methods such us UV absorption, fluorescence, circular dichroism, electron paramagnetic resonance, magnetic circular dichroism provided in-depth insight into understanding enzyme structure-function relationships such as substrate and cofactor binding, reaction mechanisms, inhibition, alosteric regulation, kinetic phenomena and mutation effects. (2-6). The aforementioned methods have provided invaluable contribution into the protein structure, active site geometry, and elucidated important electronic structure features of proteins (especially in the case of metalloenzymes). Further application of instrumental methods contributed for revealing conformational flexibility and time-dependent behaviour of proteins (dynamics) and their influence on the enzymatic functions.

In parallel to the accumulation of important experimental results, a new strategy and philosophy for analysis of chemical and biochemical processes emerged and became routinely applied nowadays - exploring and understanding the nature of molecular structures, interactions, reactivity and dynamics using computers (*in silico*). Enzyme structure and mechanisms became a central target for the computational methods and were intensively explored with a focus on different sides of enzyme structures, mechanisms, inhibition and

regulation (7-11). The exponential growth in computer power and the building of massive parallel supercomputers powerfully increased the applicability of the computational methods and the biological significance of their results. The recent development of graphical processor units is likely to provide the next level of increasing computer power and will help for getting even more thorough insights into biological processes.

Two main areas of computational methods have been developed: those based on the quantum mechanics (QM) (12) and those based on the classical mechanics, called molecular mechanics (MM) (13). The QM-based computational methods explicitly analyse the electronic structure (structure, energies, orbitals, vibrations etc.) and thus are used preferred for exploring the reaction mechanisms of enzymes. They are very computationally demanding and could be applied practically for up to several hundreds of atoms. The MM-based methods do not treat the electronic behaviour of the molecules explicitly. These methods are computationally very effective and require a set of parameters known as *force fields*. Therefore MM methods are very useful for studying conformational changes and determining the energies of large molecular systems such as solvated or membrane located enzymes, without going into electronic structural details. QM and MM methods can synergize into hybrid schemes such as combined Quantum Mechanical and Molecular Mechanical Methods (QM/MM) (14) which have been successfully applied to investigate a large number of enzyme reactions, correctly describing changes in the electronic structure (chemically relevant groups from the enzyme active site and the substrate) with QM method whilst calculating the structure, energy and interactions of the rest of the enzyme molecule at MM level (15,16).

Both strategies for investigation in the structural and mechanistic enzymology developed to some extent independently, however, over the last years a trend emerged for strengthening their integration. This combination not only brings together computational and experimental approaches on the same enzymatic issues, but also provides complementary insights into the investigated properties and has a powerful synergy effect.

The present thematic volume focuses on recent success in structural and mechanistic enzymology with main emphasis on explaining the enzyme structure-function relationships by both the experimental and computational approaches. The selected outstanding contributions demonstrate how the application of a variety of experimental techniques and

modelling methods helps for understanding of enzyme dynamics, mechanism, inhibition, and can be translated into drug design.

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