Merging quantum mechanics and enzyme design through empirical valence bond simulations

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ABSTRACT: Enzymes have long served as useful tools in both industrial and academic settings. However, enzymes are best able to function in a narrow range of environmental conditions highly specific to the host organism, which is often quite different from the desired environments found in pharmaceutical synthesis, food processing, biofuel production, and textile manufacturing. With a desire to design enzymes with improved functionality in non-natural environments, modification of enzymes to better suit applications has been a major focus of research since the 1980s. In the initial stages this was mostly achieved through predicting mutations entirely from knowledge of the protein structure, in a process known as rational enzyme design. However, due to the complexity of structure-function relationships, mutations did not always modify enzyme function in desired ways, and directed evolution of enzymes by iteratively controlling their environment and selecting for desired traits grew in popularity. With the increases of computing power around the turn of the century, the ability to harness computers to aid in enzyme design allowed for the development of new tools to aid in modifying enzyme function. One such method is empirical valence bond (EVB) simulations. EVB is a hybrid quantum mechanical/molecular dynamics method inspired by Marcus theory of electron transfer, which uses the modelling of potential energy surfaces to calculate free energies for condensed-phase chemical reactions. In this talk I will discuss the use of EVB simulations in the design of a thermophilic chorismate mutase (CM). Chorismate mutase is an enzyme which converts chorismate to prephenate via a Claisen rearrangement, and is found in the biosynthetic pathways for aromatic amino acids in bacteria, fungi, and some plants. This enzyme class, due to the simplicity of the reaction, has been used extensively as a model system in computational benchmarking. By performing EVB simulations across a range of temperatures, we are able to uncover the enthalpic and entropic components making up the reaction free energy for CM, which we use in combination with dynamic information available from our simulations to predict areas of the enzyme which can best influence function in the desired way.

ALL ARE WELCOME!