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New applications of non-conventional nonempirical methodologies for the analysis of catalytic and inhibitory properties of biomolecules

Chemistry has become an integral part of industry ever since the potential of chemical reactions was discovered. As a result, researchers continue to look for more efficient methods to obtain products in less time and at lower costs. Catalysts, substances that greatly accelerate chemical reactions by reducing the activation energy barrier, have proven to be ideal tools for achieving these goals. They allow reagents to react under milder conditions, such as lower temperatures and pressures, while enhancing efficiency and minimizing environmental impact.

Enzymes, the most effective catalysts found in nature, have evolved within living organisms to accelerate specific reactions. Despite extensive research efforts, attempts to theoretically design enzymes capable of catalyzing other reactions for industrial or environmental purposes have been largely unsuccessful. The experimental development of such enzymes through laboratory directed evolution is a costly process and often leads to mutations whose underlying mechanisms remain poorly understood.

In this project, we will utilize various computational methods developed in our laboratory to decipher the molecular basis of the way the most efficient enzymes work. By focusing on the physical nature of interactions in the enzyme active sites, we will explore the possible relationship between the covalent binding of the reaction transition state (the transient species occurring along the reaction path) and the extremely high enzymatic activity. Another important topic we plan to investigate involves the cytosine deamination reaction which might be associated with frequently mutating sites in DNA.

The key element of our methodology is the concept of a catalytic field, which involves determining the charge distribution of an ideal catalyst. This is achieved by performing quantum chemical calculations of the molecular electrostatic potentials of the transition state and substrates. By employing a bottom-up approach, we can analyze and construct a catalytic environment without relying on numerous arbitrary assumptions that are often necessary in conventional top-down methods, which involve considering the entire enzyme complex composed of thousands of atoms. Herein, we aim to investigate other applications of catalytic fields in analyzing certain enzyme characteristics that are not yet fully understood.

Enzyme inhibition, which refers to the process of reducing or preventing the activity of an enzyme, often occurs through the binding of a ligand molecule (an inhibitor) to the active site of the enzyme. Scoring protein-ligand interactions is crucial in the field of drug discovery and design and involves assessing the strength and quality of the binding between the protein and ligand. Computational methods, such as molecular docking, are commonly used to predict and evaluate these interactions. By calculating a scoring function, researchers can estimate the binding affinity and predict the most favorable binding mode between the protein and ligand. The commonly used empirical scoring functions suffer from the lack of generality and the system-dependent performance. The nonempirical scoring model developed in our group has already been demonstrated to outperform a variety of empirical scoring functions. Herein, we will apply this model to rank the docked poses generated by docking programs to assess its ability to predict the optimal protein-ligand binding.

Overall, the results of our computational efforts are important for the fields of enzyme and drug design. Establishing the contribution of covalent transition state binding to enzyme catalytic activity associated with insight into the catalytic mechanisms of the most efficient enzymes will aid the protocols of de novo enzyme design by highlighting the enzyme features that cannot be overlooked in the design process. Identifying the DNA sequence that elevates the mutation risk due to cytosine deamination will greatly enhance our understanding of genetic mutations. Finally, validating the performance of our nonempirical model for screening the docked ligand poses will significantly improve the quality of docking results.