COMPUTATIONAL DESIGN OF EFFICIENT ENZYMES THROUGH COEVOLUTION AND CORRELATION-MEDIATED ALLOSTERIC NETWORKS

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Enzymes exist as an ensemble of conformational states, whose populations can be altered through substrate binding, allosteric interactions, post-translational modifications, and even by introducing mutations into their sequence. In many enzymatic systems, full catalytic potential is only retained when in the presence of binding partners, either from additional proteins to generate heterocomplexes or from the formation of homo-oligomers.[1] Despite progresses and recent advances in generative models for protein design,[2] designing efficient enzymes and predicting oligomeric assemblies presenting a tight communication for enhancing a specific catalytic function remains challenging. Such tightly intertwined enzymatic assemblies modulate the conformational heterogeneity of the systems and allow the adoption of the multiple catalytically relevant conformational states needed for catalysis.[3]

In this talk, we will explore our developed computational pipelines that integrate AlphaFold2 with quantum mechanics and molecular dynamics simulations to guide enzyme design and foster protein assembly, thereby enabling the cooperative interactions and conformational transitions crucial for enhanced catalytic performance. [3-5] We will also discuss how our approach, which combines coevolutionary analysis and correlation-mediated allosteric networks, can be used to redesign enzymes and modify protein–protein interfaces for improved catalytic activity.[3, 5] Over the years, our work with diverse enzyme systems has generated strong evidence that rational design strategies can effectively yield active enzyme variants.[5] Moreover, we demonstrate that the current challenge of predicting distal active sites to enhance functionality in computational enzyme design can ultimately be met. [3]

References:

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