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Learning from Natural Evolution to Reprogram Enzyme Catalysis

Abstract: Rationally reprogramming enzyme catalysis requires adequate knowledge of vast enzyme mutations, which is extremely challenging. This barrier may be overcome by understanding how nature produces enzymes. To this end, we distilled evolutionary information from natural enzyme homologs using a generative machine-learning model and established a connection between enzyme evolution and enzyme catalysis. Our findings indicate that nature applies various evolutionary pressures to different enzyme regions to enhance biocatalysis. Besides, the evolution-catalysis relationships offer a rational enzyme engineering approach, and the success rate in improving enzyme catalytic power is ~50% in a recent experimental collaboration. Along these lines, we demonstrated that natural evolutionary information could explain the directed evolution of *de novo* enzymes with natural protein scaffolds; we provided new insights into designing selective covalent inhibitors by analyzing kinase sequences. Overall, our studies show that the availability of natural protein sequences is promising to advance enzymology and enable rational enzyme engineering.

Bio: Wenjun Xie is a postdoctoral associate in Dr. Arie Warshel's group at USC studying computational enzymology. Meanwhile, he stays in Boston working with Dr. Chris Sander at Harvard Medical School on bioinformatics. He received both his BS in chemistry&mathematics and PhD in physical chemistry from Peking University. After graduation, he joined Dr. Bin Zhang's lab at MIT as a postdoctoral associate before his current appointment. Dr. Xie's research focuses on decoding the principles behind natural evolution through computation and has provided the first effective method for predicting mutation effects on enzyme catalysis. His ultimate research goal is to achieve rational enzyme engineering.

