POWERING COMPUTATIONAL ENZYME DESIGN WITH NATURAL EVOLUTIONARY INFORMATION

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Although computational enzyme design is of great importance, the advances utilizing physics-based approaches have been slow, and further progress is urgently needed. One promising direction is using machine learning, but such strategies have not been established as effective tools for predicting the catalytic power of enzymes. Here we show that the statistical energy inferred from homologous sequences with maximum entropy (MaxEnt) principle significantly correlates with enzyme catalysis and stability at the active site region and more distant region, respectively. This finding decodes enzyme architecture and offers a connection between enzyme evolution and the physical chemistry of enzyme catalysis, and deepens our understanding of the stability-activity trade-off hypothesis for enzyme. Overall, the strong correlations found here provide a powerful way of guiding enzyme design.

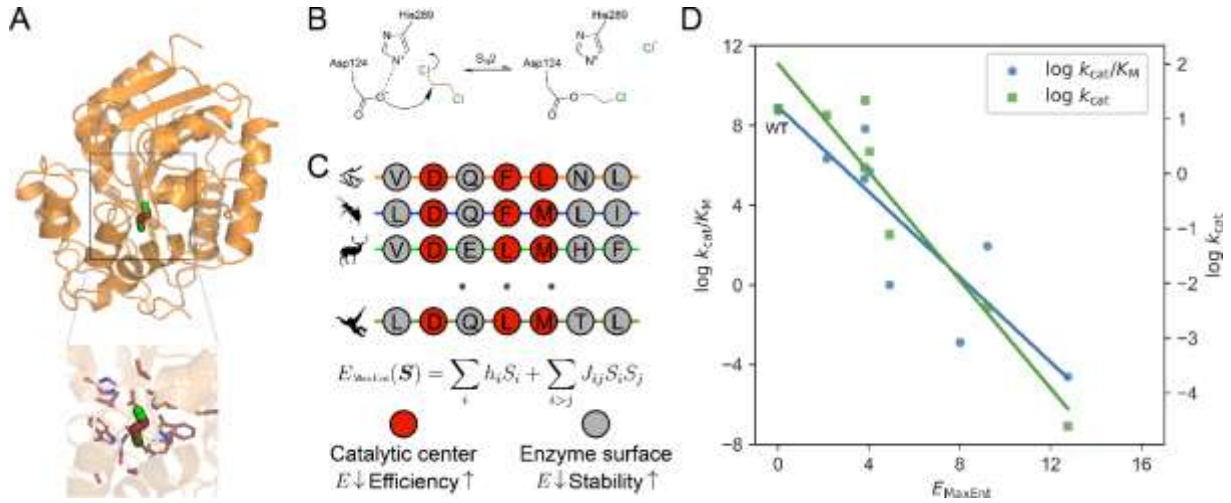

Figure 1. The maximum entropy model for enzyme sequences connects enzyme evolution and function. (A-B) Enzyme accelerates chemical reaction by lowering the activation energy using mainly the residues in the catalytic center. Haloalkane dehalogenase (PDB: 2dhc) is used as an example to illustrate enzyme catalysis and reaction mechanism. (A) The residues within a distance of 7.0 Å from the substrate are highlighted; (B) The scheme of the S_N2 step is illustrated using the substrate of 1,2-dichloroethane. (C) The MaxEnt model connects enzyme evolution to the physical chemistry of enzyme catalysis. A pair-wise MaxEnt model is learned from the MSA, and each protein sequence (S) is associated with statistical energy (E_{MaxEnt}) following the Boltzmann distribution. We found that decreasing the statistical energy significantly correlates with increasing enzyme efficiency and stability in the catalytic center and enzyme surface, respectively. (D) Performance of the MaxEnt model in predicting mutation effects on catalytic power.

Reference:
Enhancing computational enzyme design by a maximum entropy strategy. W.J. Xie, M. Asadi, A. Warshel, Proceedings of the National Academy of Sciences, 2022, 119, e2122355119