“Design and Evolution of Metalloenzymes through Multi-Scale Approaches”

Natural metalloenzymes are among the most proficient catalysts in terms of their activity, selectivity, and ability to operate at mild conditions. However, metalloenzymes are occasionally surprising in their selection of catalytic metals. Due to competing evolutionary pressures, many natural enzymes may not have evolved to be ideal catalysts, and can be improved for the isolated purpose of catalysis in vitro when the competing factors are removed. We approach these research questions from a multi-scale computational angle, utilizing our accurate and efficient hybrid dynamics method called quantum mechanics/discrete molecular mechanics (QM/DMD). QM/DMD has allowed us to answer many perplexing questions governing metal selectivity and activity in these enzymes. Additionally, QM/DMD has been shown to be an efficient design suite for novel metalloenzymes. Taking an existing scaffold of the Zn\(^{2+}\)-containing enzyme Carboxypeptidase A (CPA), that binds substrates with mild promiscuity, we completely redesigned the enzyme to bind a sequence-specific substrate in silico. Along with QM/DMD, our new method, Eris-QM/DMD, will be debuted. Eris-QM/DMD evaluates protein stability upon mutagenesis, a vital technique in the metalloenzyme design community. This arsenal of multi-scale tools allows us to push the boundary of biocatalyst design, where future works include manufacturing enzymes with catalytically potent, non-physiological metals.

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