On the Role of Molecular Modeling in Building Artificial Metaloenzymes

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Merging synthetic compounds with biological entities is a concept increasingly explored to expand the scope of enzymatic reactions. One of the most proficient strategies consists in the integration of organometallic scaffolds into biological frameworks (i.e., protein, DNA or peptides).

Despite the major successes of several groups in developing efficient biometallic hybrids, the prediction and analysis of their molecular behavior still represents a complex exercise. The lack of evolutionary pressure generally leads to a first generation of molecules with relatively low stability and difficult structural characterization. Moreover, the identification of the best complementarities amongst biological receptor, organometallic cofactors and substrates implies a major combinatorial space that challenges biochemical and chemical intuitions.

Virtually, molecular modeling could be of the best allies in this field since computational methodologies can deal with processes related to molecular recognition andcatalytic mechanisms. However, the modeling of artificial metaloenzymes stands out of the scope of standard approaches and novel methodologies are needed.

In the recent years, our group designed, tested and applied a series of computational strategies in the field of artificial bioinorganics. From protein-ligand dockings to multi-scale approaches, our work allowed to better understand the molecular mechanism of artificial metaloenzymes, provided information on how they mechanistically diverge from natural ones and gave some hints on how we could computationally guide the design of new candidates. In this talk, I will briefly present the underpinning concepts of our strategies and the most important results obtained so far both from pure computational works and in collaboration with experimentalists.

Muñoz Robles, V. et al. ACS Catal. Just Accepted Manuscript ***DOI:*** *10.1021/acscatal.5b00010*