Classical Molecular Docking Procedures in the Context of Enzyme Engineering

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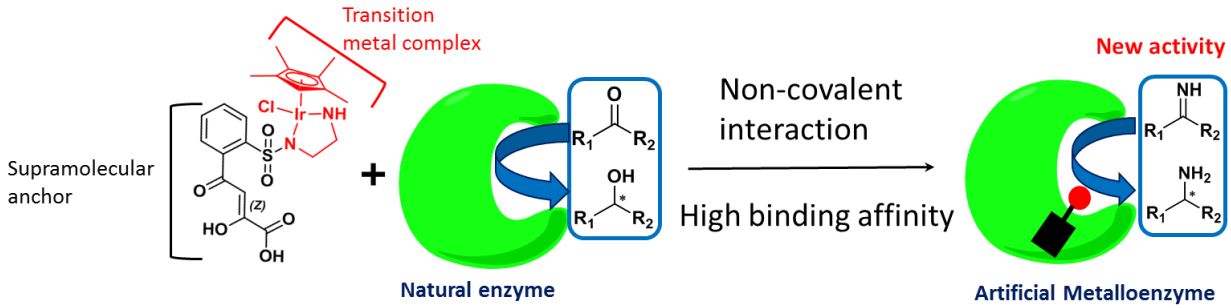
Molecular docking procedures are widely used in computer aided molecular design approaches as a central part of the computational chemist's toolbox. Particularly in the pharmaceutical industries it fills a prominent role in drug design and virtual screening for the optimisation of lead structures within drug discovery, often combined with methods of higher accuracy to predict ligand-target complexes and to estimate the binding affinities. These rational design techniques appear as a time and experimental resource saver in the drug discovery process.[1]
In those examples, the focus often lies more on binding affinity prediction over the accurate determination of orientation and direction of ligand structures positioning inside enzyme active sites. However, the correct representation of docking poses is more important when these methods are applied to engineering of new functional enzymes.

We will present examples where we have used docking procedures to support projects aiming to design and engineer enzymes with improved or altered functionality. The focus will be on an approach to design artificial metalloenzymes (Figure). In these hybrid catalysts, a synthetic metal complex is incorporated within a host enzyme, allowing non-natural synthesis of building blocks in a natural environment.[2]



In this approach, we aim to incorporate the catalyst by supramolecular anchoring. At first, docking calculations have been used in the design of metal anchors where strong binding affinities with the enzyme scaffold are explored by mimicking natural cofactors. A ranking score have thus been created to choose the best metal complexes based on their affinity for the enzyme and their optimal position/orientation for an efficient catalytic activity. From the selected structures, a short synthesis path has been designed to allow the quick construction of a metal complexes library.

[1] I. A. Guedes, C. S. de Magalhaes, L. E. Dardenne, *Biophys. Rev.* **2014**, *6*, 75–87.
[2] J. F. H. P.Dydio, H.M. Key, A. Nazarenko, J.Y.-E. Tha, V. Seyedkazemi, D.S. Clark, *Science* **2016**, *354*, 104–106.