Computational Approaches for Enzyme Redesign

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Keywords: Biocatalysis, cheminformatics, quantum-chemical modelling

Background / Introduction:

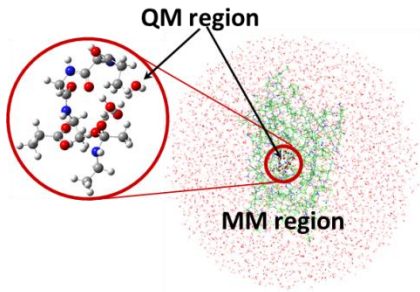
Our MACiE database holds 350 stepwise enzyme reaction mechanisms in both human- and computer-readable formats. MACiE combines extensive coverage of the universe of enzyme reactions with a very detailed stepwise description of the mechanism of each one, including every chemical bond made or broken.[1] The mechanisms are chosen to cover the full diversity of chemical reactions catalysed by enzymes and comprise 85% of the third level chemistry-defining Enzyme Commission (EC) numbers for which PDB structures exist.

The detailed information held in MACiE provides a powerful resource for enzyme design, aimed at opening up natural reactions to new industrially or environmentally important substrates, and at improving catalytic efficiency. With the current understanding of enzymes, it is possible to improve the catalytic power of an artificial enzyme and to control their biological and physicochemical properties while designing or redesigning the protein.[2] *De novo* designed proteins are novel with respect to structure and catalysis, whereas in redesign the natural protein is mimicked with improved catalysis.

A Computational Approach to Biocatalyst Design:

The goal of the project is twofold: firstly, to develop and apply cheminformatics tools that can tap into the diversity and coverage of MACiE to identify suitable template reactions as starting points for re-engineering; and secondly, to substantiate these predictions through state-of-the-art quantum-mechanical/molecular-mechanical (QM/MM) modelling.

Figure 1: Schematic QM/MM setup: the active site is described quantum-mechanically, the remaining enzyme (green) and solvent (red) in a more approximate way



QM/MM methods allow detailed mechanistic studies through calculation of reaction pathways, where the reactive centre (including the bonds that are being broken or formed) is described at an appropriately high QM level, while the effects of the protein and solvent environment are incorporated in a more approximate way (see Figure 1). Such methods are part of the developments that were awarded 2013 Nobel Prize in Chemistry, and we have already used them to unravel catalytic mechanisms in proteins.[3] After computationally confirming the established mechanism in the wild types, *in silico* modelling of possible mutants identified by our data mining in MACiE will be conducted. The resulting activation barriers of the rate-limiting steps will be the key findings, from which it can be predicted if and by how much these mutants should be more active than the wild types. Thus, subsequent engineering of such mutants can concentrate on the most promising targets.

References

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