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Chemical dynamical ensembles as compass to navigate the mutational landscape in enzyme engineering

Enzymes are the key molecular machinery that enables chemical transformations on the timescale of life. Throughout evolution, enzymes have developed specific substrate scope, stereospecificity and catalytic proficiency. In recent years, routines to improve enzyme stability through amino acid substitutions have become commonplace. However, it is still more challenging to manipulate the catalytic scope of enzymes using computational methods without extensive trial and error.

In our research group, we have stablished a new metrics by analysis of enzyme conformational ensembles to explore the impact of remote mutations on enzyme function, including stability, connectivity to the active site, and overall enzyme dynamics1,2 (Figure 1). Additionally, we have developed SmarTSzyme,3 a python-based software tool that analyses quantum mechanics/molecular mechanics (QM/MM) trajectories of the reaction at the active site, to compare key interactions in both substrate and transition-state enzyme complexes. With SmarTSzyme, a shortlist of positions for protein engineering can be obtained, to speed up the identification of novel biocatalysts with improved efficiency for the studied chemical transformation.

Figure 1. (A) Metrics to evaluate the impact of remote mutations in enzyme function. (B) SmarTSzyme, a new tool to the selection of key amino acids to manipulate catalysis.

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