Towards automated exploration of enzymatic reactions

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Mapping out a reaction mechanism involves optimizing the reactants and products, finding the transition state and following the reaction path connecting them. Enzymes, however, consist of several thousand atoms, and about one order of magnitude more electrons, a system size that is not easily tractable. Modelling enzymatic pathways is challenging because of the complexity of the system. The numerous degrees of freedom in an enzymatic system, out of which many can be relevant for the reaction and its energetic profile, at least indirectly, render the notion of "the reaction mechanism" naïve. Instead many reaction pathways are conceivable, which might be different conceptually such as a dissociative vs. an associative pathway. One approach to overcome previous difficulties is to use transition network approach to sample conformational transitions in proteins, to explore enzymatic reaction pathways [1].

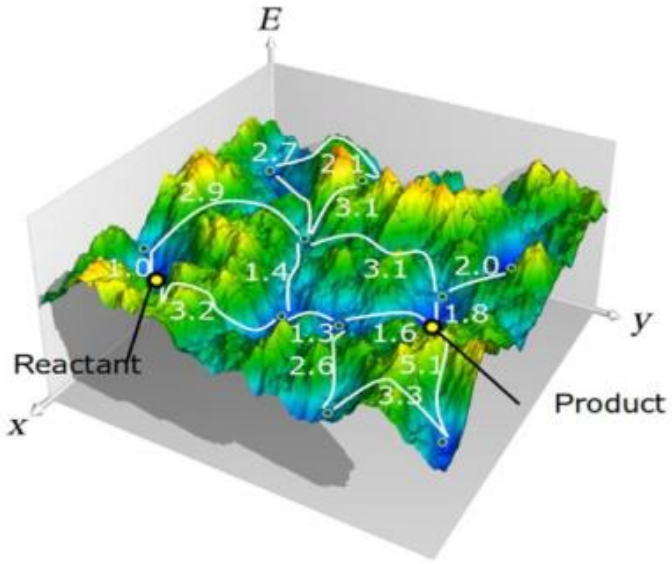

Figure: Schematic energy landscape with "valleys" (blue) and "mountains" (yellow/orange). Yellow points mark end states and green dots are intermediate states. White connections with transition barriers indicate a variety of possible pathways. Figure is taken from [1]

Carboxypeptidase A (CPA) an exopeptidase secreted by the pancreas which catalyzes the elimination of the C-terminal amino acid via hydrolysis, with a preference toward residues with hydrophobic side chains [2]. CPA occupies a special place in enzymology as the third enzyme whose three dimensional structure was determined with hight resolution by X-ray diffraction. Despite the abundance of structural information, however, there are still controversies concerning its catalytic mechanism.

[1] P. Imhof, A networks approach to modelling enzymatic reactions, *Computational approaches for Studying Enzyme Mechanism Part B*, 578, **2016**, 249-271.
[2] B. L. Vallee, A. Galdes, D. S. Auld, J. F Riordan, *Wiley*, *New-york*, **1983**,
[3] F. Noe, D. Krachtus, J. C. Smith, S. Fischer, *Journal of Chemical Theory and Computation*, **2006**, 2, 840-857