Conformational heterogeneity in the evolution of enzyme function

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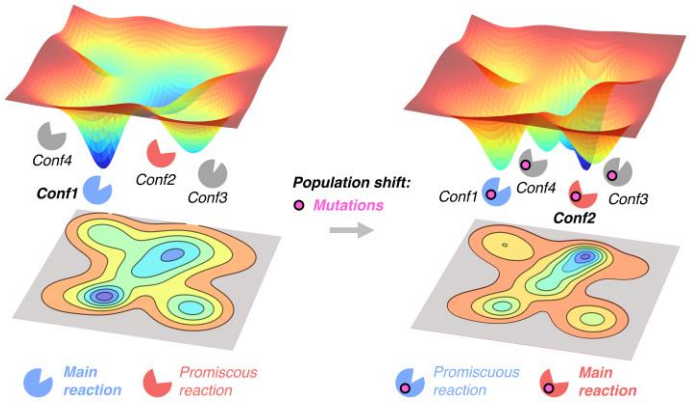
Enzymes exist as an ensemble of conformations important for their function. By introducing mutations to the enzyme sequence, the populations of the different conformational states can be gradually tuned for allowing novel function. In this talk, the population shift induced by distal and active site mutations introduced along a series of laboratory-evolved enzymes[1-4] is presented. Microsecond time-scale Molecular Dynamics (MD) simulations in combination with correlation-based analysis, Markov State Models (MSM), and enhanced sampling techniques are applied to elucidate the changes in the conformational landscape of laboratory evolved variants. Dramatic changes in the conformational dynamics of active site loops involved in substrate entrance and product release are revealed, which provide a rationalization for the enhancement in catalytic activity of the new evolved variants.[4] Most importantly, our new tools based on inter-residue correlations observed along the microsecond-scale MD simulations provides a strategy to identify the amino acid positions that influence the dynamic properties of laboratory-evolved enzymes.[1] Our method is therefore able to rationalize, but most importantly to predict which residues situated far away from the active site can have a large impact on the enzyme catalytic activity.[1]



References:

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(4) Maria-Solano, M. A.; Serrano-Hervás, E.; Romero-Rivera, A.; Iglesias-Fernández, J.; Osuna, S., **2018** submitted for publication.