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Objectives

Abstract: Enzymes exist as an ensemble of conformational states, whose populations can be shifted by substrate binding, allosteric interactions, but also by introducing mutations to their sequence. Tuning the populations of the enzyme conformational states through mutation enables evolution towards novel activity.[1] A common feature observed in many laboratory-evolved enzymes, is the introduction of remote mutations from the catalytic center, which often have a profound effect in the enzyme catalytic activity. [2] As it happens in allosterically regulated enzymes, distal mutations regulate the enzyme activity by stabilizing pre-existing catalytically important conformational states.

In this talk, our new computational tools based on inter-residue correlations from microsecond time-scale Molecular Dynamics (MD) simulations and enhanced sampling techniques are applied in Tryptophan synthase (TrpS) complex. TrpS is composed of TrpA and TrpB subunits, which allosterically activate each other and have no activity when isolated. [3,4] We show how distal mutations introduced in TrpS resuscitate the allosterically-driven conformational regulation and alter the populations and rates of exchange between multiple conformational states, which are essential for the multistep reaction pathway of the enzyme.[3] The exploration of the conformational landscape of TrpS is key for identifying conformationally-relevant amino acid residues of TrpB and TrpA distal from the active site.[4] We predict positions crucial for shifting the inefficient conformational ensemble of the isolated TrpB and TrpA to a productive ensemble through intra-subunit allosteric effects. The experimental validation of the new conformationally-driven TrpB and TrpA design demonstrates their superior stand-alone activity in the absence of binding partner, comparable to those enhancements obtained after multiple rounds of experimental laboratory evolution. Our work evidences that the current challenge of distal active site prediction for enhanced function in computational enzyme design can be ultimately addressed.

References:
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Short bio: Dr. Osuna is an ICREA research professor at the Universitat de Girona (UdG). Her research is based on the computational design of enzymes. This research line is funded by a European Research Council (ERC) –Starting Grant, Spanish MINECO project, and a Human Frontier Science Program – Program Grant. She has been awarded many prestigious grants: for her post-doc at the University of California, Los Angeles (UCLA) she was awarded a Marie Curie IOF fellowship, followed by Juan de la Cierva postdoctoral fellowship, later on Ramón y Cajal position, and the 2017 ICREA position. She has also been awarded many prestigious awards: Marcial Moreno award 2021 (RSEQ-Cat), Catalan National Research Award – Young Talent 2019 from Fundació Catalana de Recerca i Innovació (FCRi), Young Investigator Award by the company Lilly and Royal Spanish Society of Chemistry RSEQ (2019), the Young Investigator Award of EuCheMS Organic Division (2017), the Young Researcher award by the Royal Spanish Society of Chemistry (RSEQ 20116), and the Research award by the Fundación Princesa de Girona (FPdGi 2016-Science category).

Speakers

Speaker: Dr. Sílvia Osuna is an ICREA research professor at the Universitat de Girona (UdG)
Host: Victor Guallar, Electronic and Atomic Protein Modelling Group Manager, BSC
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