COMPUTATIONAL CHARACTERIZATION OF BIOCATALYTIC REACTIVE INTERMEDIATES FOR THE DISCOVERY AND DESIGN OF NEW ENZYMATIC ACTIVITIES

Dr. Marc García Borrás

Institut De Química Computacional I Catàlisi
Universidad de Girona

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C/ Pedro Cerbuna, 12. Zaragoza 50009. Spain

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Resumen:

Enzymes catalyze complicated chemical reactions in a highly specific, efficient, and selective manner. Many enzymes require cofactors, that usually participate in biocatalytic cycles that involve the formation of organometallic, ionic or radical reactive intermediate species. These reactive intermediates can then evolve through divergent reaction pathways, being a source for enzymatic promiscuity and thus serving as starting points for the design of new enzyme-catalyzed reactions. The accurate characterization of enzymatic “fleeting” reactive intermediates has been proved to be experimentally very challenging due to limitations of structural and spectroscopic techniques, while computational methods have been shown to be an important alternative in describing those intermediate species at the atomic level precision.[1],[2] Our research program aims to develop and apply new multiscale computational protocols to study, characterize and rationally improve the formation and stabilization of reactive intermediates generated in enzyme active sites that are involved in key catalytic cycle steps.

Herein, we will present recent successful cases where the combination of different multiscale computational techniques, including small truncated models, molecular dynamics (MD) simulations and QM/MM calculations, allowed us to unveil the molecular basis for enzymatic catalysis of natural and laboratory evolved enzymes that involve the formation of key reactive intermediates using iron-based cofactors. Our computational studies provide atomistic descriptions and basic knowledge about how natural and laboratory engineered enzymes can catalyze such reactions. This information is finally used for computationally-guide rational protein engineering toward new reactivities and selectivities not observed in Nature.

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Bio:

Dr. Marc Garcia-Borràs obtained his PhD with academic honors at the University of Girona (2012-2015, Cum Laude, Extraordinary PhD Award), under the supervision of Prof. Miquel Solà and Dr. Josep M. Luis. He worked on the computational study of the structure and reactivity of endohedral (metallo-)fullerenes.

After a short (6 months) postdoc stay in the group of Prof.. Sílvia Osuna (UdG, Spain), he joined the group of Prof. K. N. Houk at UCLA (USA) as a postdoc for 3 years (Jan. 2016 – Jan. 2019) to work on the computational modelling and design of new (metallo-)enzyme catalyzed reactions. For his work at the Houk lab, he was awarded the “2018 UCLA Department of Chemistry and Biochemistry Postdoctoral Research Award”.

In February 2019 he returned to Spain as a Juan de la Cierva -Incorporación (JdC-I) research fellow to start his independent research program on computational biocatalysis at the University of Girona. In January 2020 he obtained a Beatriu the Pinós MSCA-COFUND grant, and he is currently a PI of two Spanish national projects (Spanish State Research Agency (AEI), 3 years projects) to work on the study and characterization of reactive intermediates for the discovery and design of new biocatalytic activities.

In September 2020 he was approved as a new independent Principal Investigator at the Institute of Computational Chemistry and Catalysis (IQCC, University of Girona), where he heads a research group formed by three PhD students and one postdoc.

In 2022 he obtained a Ramón y Cajal (RyC, tenure-track) contract form the Spanish State Research Agency (AEI) to become assistant professor at the University of Girona.
Sus líneas de investigación se centran en el estudio computacional de reacciones catalíticas en fase homogénea, especialmente aquellas mediadas por luz. Además, participa en proyectos de descubrimiento de energías sostenibles y de fotoprotección, así como en numerosas colaboraciones internacionales con grupos experimentales de primer nivel. Ha publicado más de 50 artículos científicos, incluyendo prestigiosas revistas como Science (2), JACS (3), ACIE (11) o Nat. Commun. (1), siendo autor principal en 10 de ellos, así como 2 patentes. Actualmente, disfruta de un proyecto nacional de transición ecológica y codirige a cuatro estudiantes de doctorado junto al Prof. Diego Sampedro. Además, su labor investigadora ha sido reconocida por numerosos premios, destacando el premio RSEQ al mejor investigador postdoctoral, el premio Sus-Chem Investiga, el Thieme Chemistry Journal award y varios premios en divulgación científica.