# Catalytic Strategies of Non-Heme Iron(II) and 2-Oxoglutarate-Dependent Enzymes

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## Abstract

Non-heme Fe(II) and 2-oxoglutarate (2OG)-dependent enzymes are remarkably versatile biological catalysts, capable of promoting a wide range of oxidative transformations of organic substrates using molecular oxygen under mild conditions. They play central roles in epigenetics, DNA repair, metabolism, and natural product biosynthesis, among others. Despite extensive experimental efforts, the molecular principles that govern their catalytic strategies, selectivity, and functional diversity remain incompletely understood.

In this talk, I will show how computational bioinorganic chemistry, combining molecular dynamics simulations with quantum mechanical and QM/MM modeling in rigorous correlation with experimental studies provides a detailed, physics-based view of catalysis in non-heme Fe(II)/2-oxoglutarate–dependent enzymes. Exploring a variety of Fe(II)/2OG enzymes, such as histone demethylases, DNA/RNA demethylases, halogenases, and the unique ethylene-forming enzyme (EFE), these computational studies reveal key aspects of the catalytic mechanism that are not accessible experimentally, predict new mechanistic pathways later confirmed experimentally, and guide new experiments.

Our work demonstrates that catalytic outcomes are not dictated solely by the metal center, but instead emerge from a subtle interplay between metal-center electronic structure and bonding, protein dynamics and electric fields, and interactions extending beyond the immediate active site. Through selected case studies from epigenetic regulation, DNA/RNA modifications, enzymatic ethylene formation, and small-molecule biosynthesis, I will illustrate how theory and experiment work together to identify key intermediates, rationalize selectivity, and predict new mechanistic features. These insights establish general principles for understanding metalloenzyme catalysis and for guiding the design of selective inhibitors and engineered metalloenzymes.

## Speaker Bio

*Christo Z. Christov* is a Professor of Chemistry at Michigan Technological University. He received his PhD in Theoretical Chemistry from the Bulgarian Academy of Sciences, Sofia, Bulgariaand RWTH-Aachen, Germany, and has held academic and research positions in the United States, the United Kingdom, and Spain, including visiting appointments at Stanford University, the University of Oxford, and the University of Barcelona.

His research focuses on Computational Bioinorganic Chemistry, with an emphasis on the catalytic mechanisms of non-heme Fe(II)/2-oxoglutarate-dependent enzymes involved in epigenetic regulation, DNA repair, ethylene formation, and halogenation, among others. Using physics-based methods, including quantum chemistry, molecular dynamics, and QM/MM approaches, his work is rigorously integrated with experiment. A central goal of his research is to predict reaction mechanisms, characterize the electronic and geometric structures of key reaction species, and elucidate the vital effects of second coordination sphere and long-range interactions on catalytic mechanisms, many of which have subsequently been confirmed experimentally and used to guide new experimental studies.

Prof. Christov has authored over 60 peer-reviewed publications and has received sustained funding from the NIH, NSF, EU-Marie Curie Actions, Fulbright, Bulgarian Science Council, NATO and DAAD. He currently serves on several editorial boards and regularly reviews for leading chemistry journals.