**Biological catalysts for H2 generation: challenges and opportunities of machine learning.**

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Hydrogen is hailed as green and sustainable energy career for the future.1 Over the last decade research on generation of H2 via water electrolysis (green H2) by hydrogen evolution reaction (HER), has taken center stage and scientists across diverse areas of computational biology, chemistry, material science and chemical engineering have been involved. Biological catalysts are the most attractive solution for HER, as they usually operate under mild conditions and do not produce carbon-containing byproducts. Hydrogenases (H2ases) promote reversible proton reduction to hydrogen in a variety of anoxic bacteria and algae displaying unparallel catalytic performances.2 However, the application of these sophisticated enzymes for scalable H2 production is a complex problem, lying at the interface between biology and chemistry. Therefore, a comprehensive understanding of H2ases stability and action mechanism is essential to maximize their potential applications, and to develop novel bioinspired artificial catalysts.

To this end, it is necessary to integrate diverse kinds of data, such as knowledge about H2ases catalytic sites, their reaction pathways and dynamic conformational changes occurring during catalysis. Automated methods, as Machine Learning (ML)-based algorithms, represent a valid strategy to accomplish this task. Indeed, the synergy between ML and computational modeling (CM) may allow the design and production of diverse HER catalysts and processes.

This PhD proposal aims at employing machine learning to comprehensively classify natural H2ases and their properties, with the final goal of developing artificial systems, able to promote the HER, *via* either electrochemical or light-driven catalysis. New bioinspired catalysts, based on small-molecule inorganic complexes housed within peptide scaffolds, will be developed and applied as innovative component for H2 generation. The integration of the expertise of the involved research groups in the field3-5 will allow to: a) develop small-artificial inorganic complexes as H2ase mimics; b) design peptide scaffolds to host these inorganic complexes. This makes the proposal original and innovative, as the known-how and experience in diverse and interconnected research topics of the joint groups will allow an iterative process of computational design, production of the catalysts and activity screening, for tuning the catalyst properties and selecting the best candidates for H2 generation.

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