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Predicting the structure of enzymes with metal cofactors: The example of [FeFe] hydrogenases

The advent of deep learning algorithms for protein folding opened a new era in the ability of predicting and optimizing the function of proteins once the sequence is known. The task is more intricate when cofactors like metal ions or small ligands are essential to functioning. In this case, the combined use of traditional simulation methods based on interatomic force fields and deep learning predictions is mandatory. We use the example of [FeFe] hydrogenases, enzymes of unicellular algae promising for biotechnology applications to illustrate this situation. [FeFe] hydrogenase is an iron–sulfur protein that catalyses the chemical reduction of protons dissolved in liquid water into molecular hydrogen as a gas. Hydrogen production efficiency and cell sensitivity to dioxygen are important parameters to optimize the industrial applications of biological hydrogen production. Both parameters are related to the organization of iron–sulfur clusters within protein domains. In this work, we propose possible three- dimensional structures of Chlorella vulgaris 211/11P [FeFe] hydrogenase, the sequence of which was extracted from the recently published genome of the given strain. Initial structural models are built using: (i) the deep learning algorithm AlphaFold; (ii) the homology modeling server SwissModel; (iii) a manual construction based on the best known bacterial crystal structure. Missing iron–sulfur clusters are included and microsecond-long molecular dynamics of initial structures embedded into the water solution environment were performed. Multiple- walkers metadynamics was also used to enhance the sampling of structures encompassing both functional and non-functional organizations of iron–sulfur clusters. The resulting structural model provided by deep learning is consistent with functional [FeFe] hydrogenase characterized by peculiar interactions between cofactors and the protein matrix.

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