Machine learning model for the prediction of redox potential of Iron-Sulfur clusters.

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Abstract:

Iron-Sulfur (Fe-S) clusters play a critical role as electron transfers in many energy-related metalloenzymes such as hydrogenases, CO dehydrogenases, formate dehydrogenases and nitrogenases, which drive energy-transforming reactions by storing energy in chemical bonds. Understanding Fe-S clusters is, therefore, essential for developing new sustainable strategies for energy storage and transformation.

A key property of these clusters is their redox potential (RP), which significantly influences enzyme reactivity. However, measuring RP poses significant challenges. Current in silico methods have great computational costs and often yield poor accuracy. Machine learning (ML) offers a promising approach to correlate a protein's 3D structure with its properties, including the RP of its clusters.

In this work we developed a ML model to predict the RP of single and binuclear Fe-S clusters. Our training dataset included small proteins with only one Fe-S cluster such as rubredoxins, ferredoxins, Rieske proteins and MitoNEETs, with a range of potentials from -460 mV up to +390 mV. The model performs with a mean absolute error of 37.24 mV (SD ± 5 mV), significantly outperforming more sophisticated computational methods, which typically exceed 170 mV in error[1].

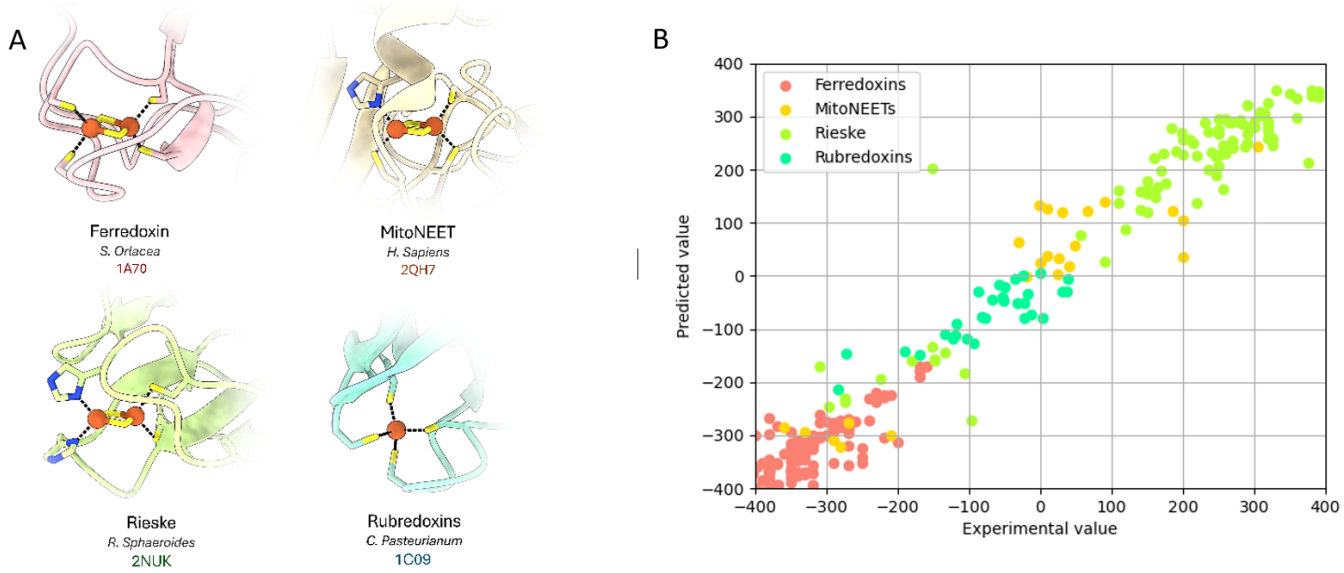

Figure 1 ***A*** *Structure and ligands of Fe-S clusters in different protein types.* ***B*** *Predicted RP VS experimentally measured RP. The Spearman's correlation coefficient between the predicted and the experimentally measured RP is 0.94±0.02.*

[1] *Benchmark Study of Redox Potential Calculations for Iron–Sulfur Clusters in Proteins.* Sonia Jafari, Yakini A. Tavares Santos, Justin Bergmann, Mehdi Irani, and Ulf Ryde. Inorganic Chemistry 2022 61 (16), 5991-6007. DOI: 10.1021/acs.inorgchem.1c03422