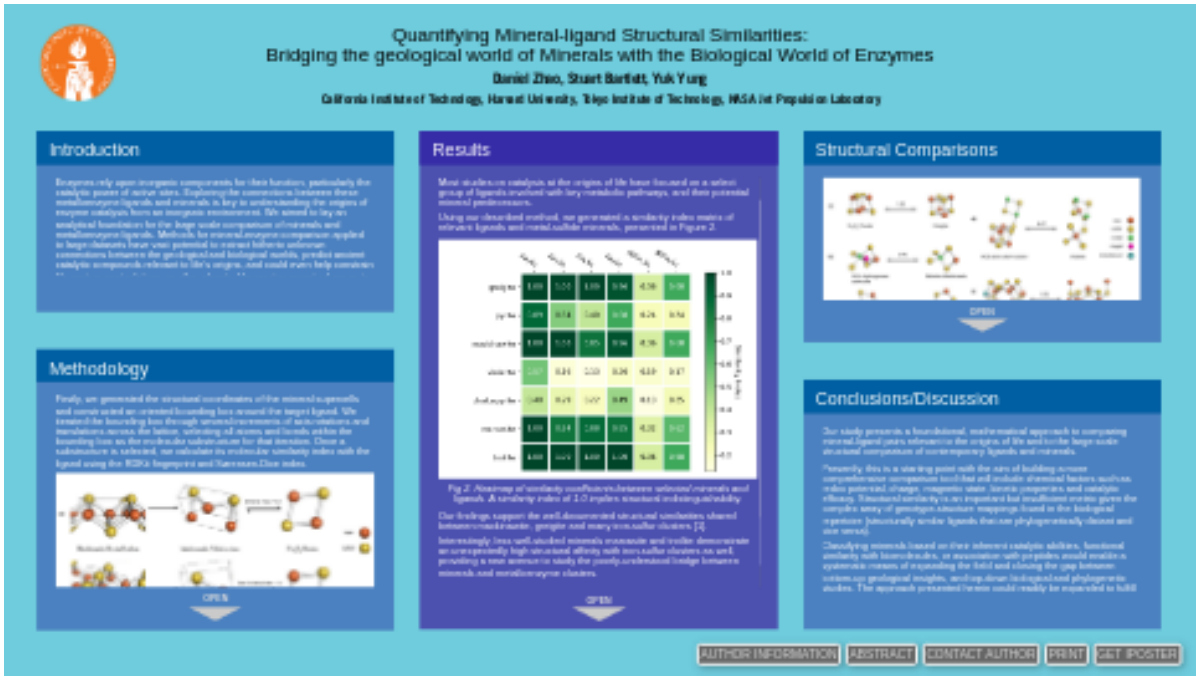
Quantifying Mineral-ligand Structural Similarities: Bridging the geological world of Minerals with the Biological World of Enzymes



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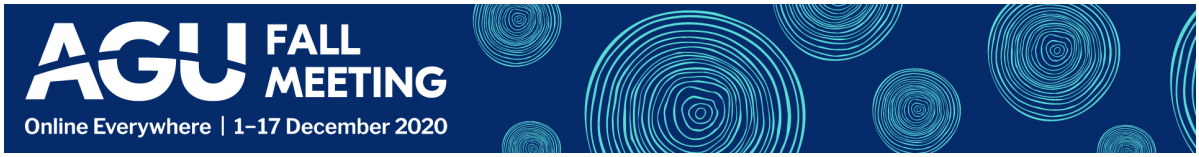

INTRODUCTION

Enzymes rely upon inorganic components for their function, particularly the catalytic power of active sites. Exploring the connections between these metalloenzyme ligands and minerals is key to understanding the origins of enzyme catalysis from an inorganic environment. We aimed to lay an analytical foundation for the large scale comparison of minerals and metalloenzyme ligands. Methods for mineral-enzyme comparison applied to large datasets have vast potential to extract hitherto unknown connections between the geological and biological worlds, predict ancient catalytic compounds relevant to life's origins, and could even help constrain life-environment relations on other planets. Harnessing recent advances in chemoinformatics, rational ligand design and big data, we present a mathematical method of detecting structually similar mineral-ligand pairs.

METHODOLOGY

Firstly, we generated the structural coordinates of the mineral supercells and constructed an oriented bounding box around the target ligand. We iterated the bounding box through several increments of axis rotations and translations across the lattice, selecting all atoms and bonds within the bounding box as the molecular substructure for that iteration. Once a substructure is selected, we calculate its molecular similarity index with the ligand using the RDKit fingerprint and Sørensen-Dice index.

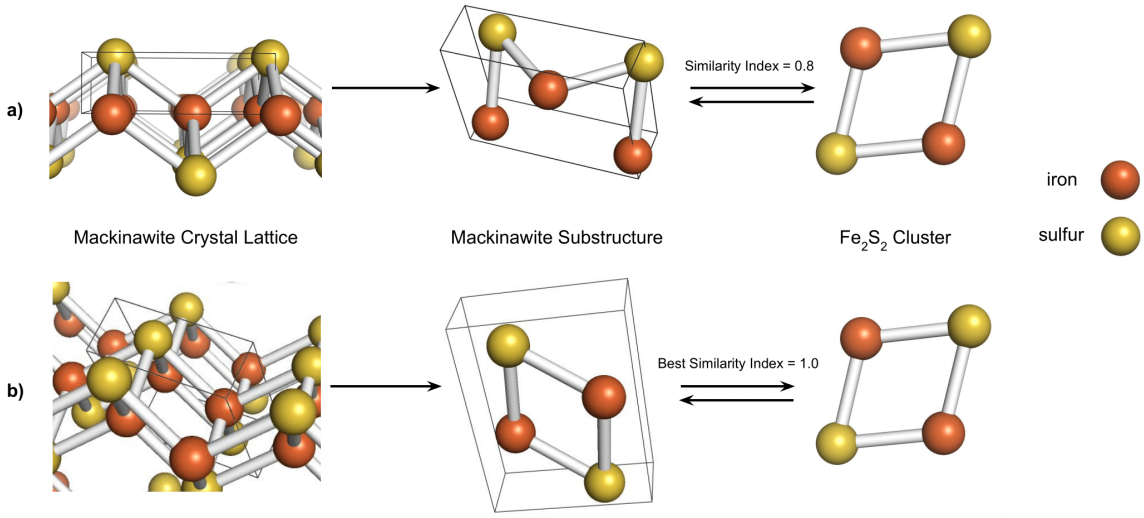

Fig 1. Example of substructure search in the crystal lattice of mackinawite, using the [Fe2S2] cluster as the target ligand.

Over several transformation iterations, the index with the largest value and its respective substructure is retained as the final similarity index.

RESULTS

Most studies on catalysis at the origins of life have focused on a select group of ligands involved with key metabolic pathways, and their potential mineral predecessors.

Using our described method, we generated a similarity index matrix of relevant ligands and metal-sulfide minerals, presented in Figure 2.

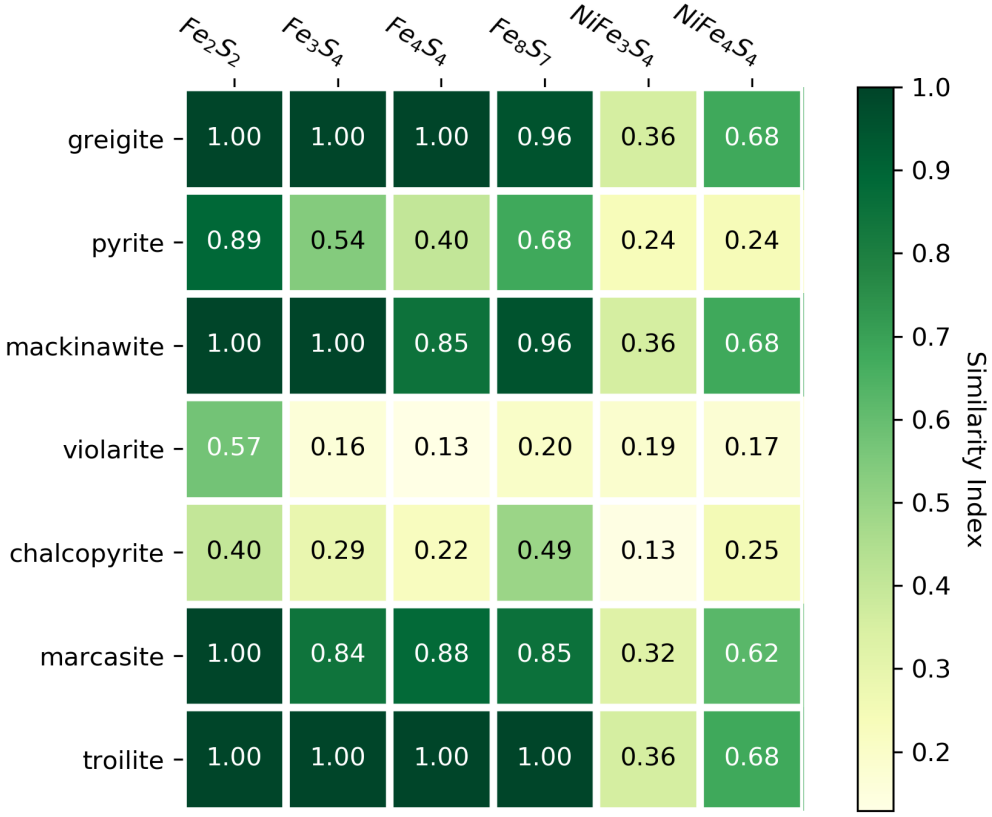

Fig 2. Heatmap of similarity coefficients between selected minerals and ligands. A similarity index of 1.0 implies structural indistinguishability.

Our findings support the well-documented structural similarities shared between mackinawite, greigite and many iron-sulfur clusters [1].

Interestingly, less well-studied minerals marcasite and troilite demonstrate an unexpectedly high structural affinity with iron-sulfur clusters as well, providing a new avenue to study the poorly-understood bridge between minerals and metalloenzyme clusters.

References

[1] Roldan, A.; Hollingsworth, N.; Roffey, A.; Islam, H.U.; Goodall, J.; Catlow, C.; Darr, J.; Bras, W.; Sankar, G.; Holt, K.; others. Bio-inspired CO2 conversion by iron sulfide catalysts under sustainable conditions. Chemical Communications 2015.

STRUCTURAL COMPARISONS

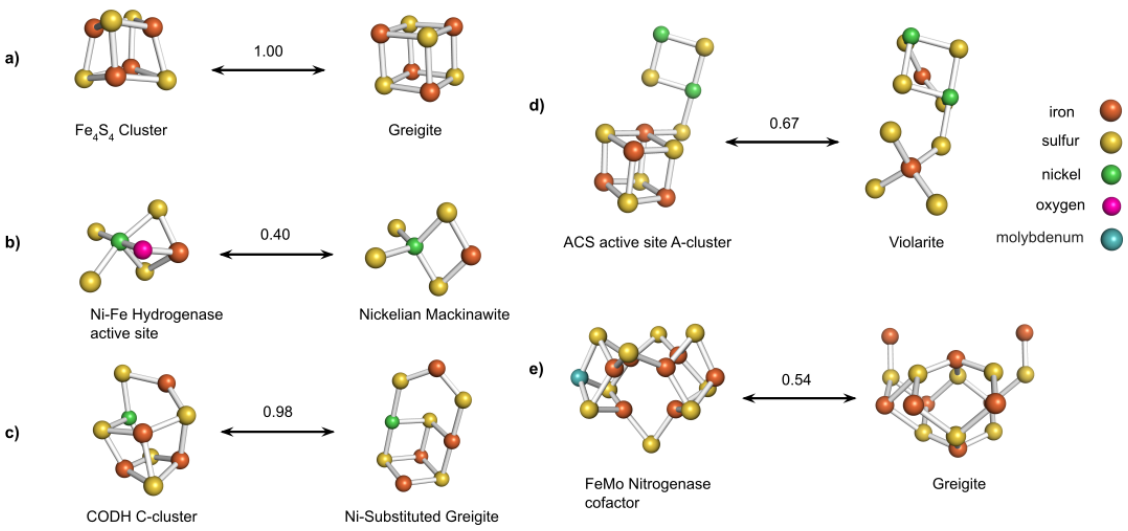

Fig 3. Structural comparisons using similarity index (number above arrows) of (a) [Fe4S4] and greigite, (b, c, d) nickel-containing ligands and minerals from Nitschke et al. [3], (e) [Fe7MoS9] nitrogenase cofactor and greigite [4]

References

[3] Nitschke, W.; McGlynn, S.E.; Milner-White, E.J.; Russell, M.J. On the antiquity of metalloenzymes and their substrates in bioenergetics. Biochimica et Biophysica Acta (BBA)-Bioenergetics 2013.

[4] Russell, M.J.; Hall, A.J. The onset and early evolution of life. MEMOIRS-GEOLOGICAL SOCIETY OF AMERICA 2006.

CONCLUSIONS/DISCUSSION

Our study presents a foundational, mathematical approach to comparing mineral-ligand pairs relevant to the origins of life and to the large scale structural comparison of contemporary ligands and minerals.

Presently, this is a starting point with the aim of building a more comprehensive comparison tool that will include chemical factors such as redox potential, charge, magnetic state, kinetic properties and catalytic efficacy. Structural similarity is an important but insufficient metric given the complex array of genotype-structure mappings found in the biological repertoire (structurally similar ligands that are phylogenetically distant and vice versa).

Classifying minerals based on their inherent catalytic abilities, functional similarity with biomolecules, or association with peptides would enable a systematic means of expanding the field and closing the gap between bottom-up geological insights, and top-down biological and phylogenetic studies. The approach presented herein could readily be expanded to fulfill this grand objective.

AUTHOR INFORMATION

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ABSTRACT

Metal compounds abundant in Early Earth are thought to play an important role in the origins of life. Certain iron-sulfur minerals, for example, are proposed to have served as primitive metalloenzyme cofactors for their ability to catalyze organic synthesis processes and facilitate electron transfer reactions. An inherent difficulty with studying the catalytic potential of many metal compounds is the wide range of data and parameters to consider when searching for individual minerals and ligands of interest. Detecting mineral-ligand pairs that are structurally analogous enables more relevant selections of data to study, since structural affinity is a key indicator of comparable catalytic function. However, current structure-oriented approaches tend to be subjective and localized, and do not quantify observations or compare them with other potential targets. Here, we present a mathematical approach that compares structural similarities between various minerals and ligands using molecular similarity metrics. We use an iterative substructure search in the crystal lattice, paired with benchmark structural similarity methods. This structural comparison may be considered as a first stage in a more advanced analysis tool that will include a range of chemical and physical factors when computing mineral-ligand similarity. This approach will seek relationships between the mineral and enzyme worlds, with applications to the origins of life, ecology, catalysis and astrobiology.