

# Evolutionary History of Bioessential Elements Can Guide the Search for Life in the Universe

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Our understanding of life in the universe comes from one sample, life on Earth. Current and next-generation space missions will target exoplanets as well as planets and moons in our own solar system with the primary goal of detecting, interpreting and characterizing indications of possible biological activity. Thus, understanding life's fundamental characteristics is increasingly critical for detecting and interpreting potential biological signatures elsewhere in the universe. Astrobiologists have outlined the essential roles of carbon and water for life, but we have yet to decipher the rules governing the evolution of how living organisms use bioessential elements. Does the suite of life's essential chemical elements on Earth constitute only one possible evolutionary outcome? Are some elements so essential for biological functions that evolution will select for them despite low availability? How would this play out on other

worlds that have different relative element abundances? When we look for life in the universe, or the conditions that could give rise to life, we must learn how to recognize it in extremely different chemical and environmental conditions from those on Earth. We argue that by exposing self-organizing biotic chemistries to different combinations of abiotic materials, and by mapping the evolutionary history of metalloenzyme biochemistry onto geological availabilities of metals, alternative element choices that are very different from life's present-day molecular structure might result. A greater understanding of the paleomolecular evolutionary history of life on Earth will create a predictive capacity for detecting and assessing life's existence on worlds where alternate evolutionary paths might have been taken.

## Introduction

Life-as-we-know-it relies on a suite of biologically essential elements. These primarily include carbon, hydrogen, oxygen, nitrogen, phosphorus, and sulfur – together referred to as CHNOPS – as well as several trace elements that are required for catalysis, structural elements, and cellular signaling. Though scientists have learned a tremendous amount in the past 50 years about *how* these elements are used in biochemistry, there remains deep uncertainty about *why* evolution selected for these elements. An open question is to what degree two key factors influenced the natural selection of elements over Earth history: each element's chemical characteristics, or

function within a biological context, and availability, which varies across environments and over time.

Redox-sensitive transition metals provide an avenue toward investigating this interplay because their environmental availabilities are well-documented to have shifted as a function of progressive Earth atmospheric oxygenation.<sup>[1–6]</sup> Notably, many of these metals are critical cofactors for the metalloenzymes that serve as prime molecular intermediaries between biological and geological chemical reservoirs.<sup>[7]</sup> The role of metals in modern biochemistry has been used to infer how metals may have contributed to biological and prebiotic processes early in Earth history. For example, the notion that metals played a vital role in the emergence of life from prebiotic systems is now broadly held.<sup>[8–13]</sup> The potential impact of secular changes in environmental metal availabilities on their natural selection over geologic timescales has been an area of significant interest.<sup>[3,4,6,7,14–21]</sup> Minimal abundances of particular metals are certainly necessary for their use in biological and prebiotic processes. And yet, the requirement of certain metals for critical biochemical functions may result in their continued selection despite large-scale changes in environmental abundance. Furthermore, the contingency of evolution may slot metals into performing particular biochemical roles even when other metals are similarly capable of complementing these processes.<sup>[22]</sup>

Understanding why life selects for certain elements is needed to guide the search for life because our ability to gauge the potential of life's existence elsewhere in the universe is inevitably rooted in predictions regarding the chemical demands of possible alien biochemistries.<sup>[14,23–28]</sup> Within the next decade, the search for life on other worlds will require difficult decisions about Mars sample selection, Solar System mission

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destinations, and exoplanet observational priorities.<sup>[26,27,29–31]</sup> Even in the most fortunate circumstance, we will still face the challenge of interpreting potential signs of life and filtering false positives.<sup>[25,32,33]</sup> These decisions and interpretations will be guided by knowledge of how the physicochemical characteristics of various planetary environments determine their habitability, how they shape the emergence and evolution of life, and how they affect our ability to detect of life.

Because there is only one known example of an inhabited planet, predictions regarding the habitability of alien planets must be informed by our knowledge of how life's chemical requirements evolved on Earth. However, the pathway taken by Earth life to its present-day state of element utilization represents only one evolutionary possibility. Other outcomes may have been possible over the coevolutionary trajectory of life on Earth. It is important to understand the *could-have-been* pathways if we are to assess whether life could have evolved – or will evolve in the future – given other planetary environments with very different elemental abundances from the past or present-day Earth. If we are to be able to recognize life or its required preconditions, it is necessary to generate a predictive capacity – a theory of planet-life coevolution – that incorporates the rules governing the natural selection of the elements. The first step in constructing such a theory is to determine the path of element selection during the evolution of life on Earth, understand why it took that path, and consider the factors that might have produced alternative outcomes.

The natural selection of elements operates at the intersection between the geochemical abundances of elements through time and across planetary bodies and the biological processes that use these elements. The role of the elements in biogeochemical cycling – both as substrates within these cycles

as well as the catalysts that drive them – must be understood within the framework of an evolving planetary geochemistry. This knowledge would help to potentially predict whether biology has largely shaped the bulk chemistry of another planet, and vice versa. Several unanswered questions that could benefit from a synthesis of early life biochemistry, biogeochemistry, and metallochemistry include:

- What were the abundances and sources of biologically important elements on early Earth?
- What were the elemental requirements of prebiotic synthesis? Of key biological processes, including transcription, translation, and biogeochemical cycling on early Earth?
- Are there alternatives to the elements used in modern biological processes?
- Are some elements so essential for biological functions that evolution will select for them despite low availability, or does the coevolutionary history of life and the Earth environment reveal other possibilities?
- What different trajectories might planetary coevolution take given different biological elemental requirements and environmental availabilities?
- How large a deviation from Earth's elemental abundances and distributions is needed to push evolution in novel and unpredictable directions?

These questions can be approached by using the ancient Earth as a natural laboratory for discovering the rules governing life's elemental requirements. A significant challenge lies in the interpretation of historical records of life that might elucidate the relationship between function and availability in the natural selection of elements. The interpretation of ancient Earth biosignatures, including microfossils, preserved biomolecules, and isotopic compositions, within the context of the metabolic



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processes responsible for major biogeochemical cycles rely on comparisons with those of modern taxa.<sup>[34–39]</sup> However, it is not clear to what degree modern biological processes can serve as proxies for their counterparts in deep time, given the significant biogeochemical changes that have occurred over Earth history. Solving this problem will require an integration of life and Earth sciences to experimentally test synthetic and reconstructed ancient biological systems<sup>[40–42]</sup> and interrogate their chemical requirements in a geochemical context.

## A Focus on Metals

Investigating the role of environmental factors in the natural selection of the elements through the lens of bulk CHNOPS elements may not be fully revealing. They are perhaps *too* essential. For life-as-we-know-it, their biological proportions are apparently decoupled from environmental changes (even when nutrients like phosphorous and nitrogen are considered to have limited primary productivity across geologic timescales.<sup>[43–45]</sup>). Yet life is apparently more flexible with regard to metals.<sup>[22]</sup> The biological metallome varies across different organisms and thus has likely varied across time.<sup>[20,46–48]</sup> Metals catalyze key, pervasive and/or primordial biosynthetic and energy transduction processes.<sup>[3,7,14,16,49]</sup> Understanding how environmental metal availabilities have produced the preconditions for life and modulated the continued evolution of the biosphere over Earth history is critical. For instance, astrobiologists have long studied the circumstances in which life can originate.<sup>[50–57]</sup> Yet, major remaining open questions are whether there are unique (and perhaps indispensable) metal needs for driving prebiotic chemical synthesis, and whether the metal needs of prebiotic processes correlate with obligatory biological metal utilization. Furthermore, with the discovery of thousands of new exoplanets and the ever-improving capability to characterize their fundamental physical properties, we will inevitably find planets that cross broadly defined habitability thresholds despite differing in important aspects from Earth.<sup>[58,59]</sup> One future way to constrain exoplanetary targets for further exploration will be by incorporating the search for specific metals in observations and measurement techniques that future space missions – whether remote or in situ – will employ.

## Paleomolecular biology and a case for molybdenum

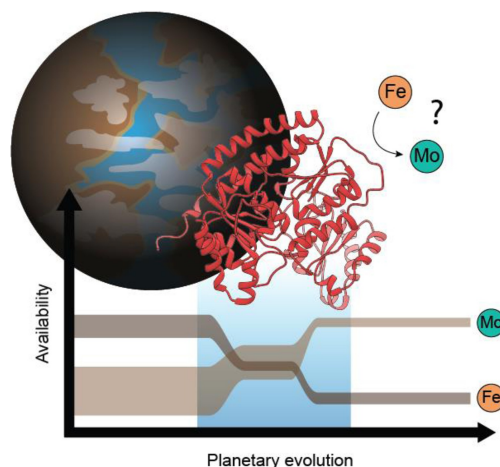
Here, we highlight the most common biochemical mechanism that obtains biologically essential N from the environment (N-fixation), which we argue is a prime focus area for astrobiologists interested in Earth-metal-life interplay. N-fixation is essential for life as we know it. A reduced-capacity form of this process can be driven by entirely abiotic atmospheric processes,<sup>[60]</sup> but it is unknown when the crucial metabolic capability to fix nitrogen emerged in life's history.<sup>[36,60–62]</sup>

N-fixation provides an exemplary case for understanding the evolution of metal usage in biology. The most common modern pathway uses molybdenum as a primary cofactor,<sup>[61,63]</sup>

and the biosphere as we know it would not exist without this metal. Yet, Mo is exceedingly rare on Earth's surface and most especially in Earth's ancient oceans when this biochemical mechanism likely first evolved.<sup>[1–3]</sup> Thus, it has been widely thought that early variants of this metabolic process were Mo-independent, and perhaps solely reliant on iron, which was substantially more abundant than Mo in oceans for the first half of Earth history (Figure 1).<sup>[3,64,65]</sup>

This story is so simple and elegant that it is almost a dogma, making Mo the type-example of an element for which it is often thought that biochemical use and evolutionary adaptation were tightly coupled to changes in environmental availability. However, this story is at odds with recent biogeochemical and genomic discoveries that imply that the Mo-dependent mode of N-fixation was ancestral and potentially operating despite early Mo scarcity. Phylogenetic reconstruction has indicated that modern Mo-independent pathways for N-fixation likely evolved from the Mo-dependent pathway.<sup>[66,67]</sup> Notably, recent research has focused on reconstructing molecular sequences based on the genomic record, with constraints provided by the reconstruction of ancient environments from the geologic record.<sup>[40,68]</sup> For example, features of reconstructed ancient N-fixing enzymes indicate ancestral specificity for a Mo-cofactor.<sup>[17]</sup> Such studies have the potential to be validated experimentally by the resurrection of ancient, synthetically engineered biosystems.<sup>[40–42]</sup> Finally, nitrogen isotope signatures from preserved sediments are consistent with having been produced by the Mo-dependent mode of N-fixation,<sup>[69]</sup> dating well before Mo is thought to have become bioavailable.<sup>[70]</sup>

Taken together, these studies suggest that the evolution of Mo usage in N-fixation might not have been so tightly



**Figure 1.** Over the course of a planet's evolution, the environmental availabilities of biologically useful elements such as transition metals can influence natural selection. For instance, the abundances of molybdenum and iron species would likely fluctuate as a function of surface oxygenation, as has occurred over Earth history.<sup>[1,2]</sup> If such metals are essential for biogeochemical processes, their availabilities would also be expected to modulate habitability at the planetary scale. The degree to which availability drives the selection of particular metals can be investigated by reconstructing ancestral metalloenzymes and investigating their paleomolecular characteristics in a biogeochemical context.

governed by environmental availability after all. Rather, evolution may have discovered the utility of Mo early on, allowing it to become ecologically important despite its scarcity in Earth's early oceans. A potentially *universal* preference for Mo in early and modern N-fixation may need to be considered in assessments of planetary habitability. Yet given that other metal-dependent pathways for N-fixation do exist on Earth today (such as those solely dependent on Fe),<sup>[71]</sup> other scenarios can be imagined in which different elements might be preferentially utilized by early life.

### Implications for the search for life

Metal availability is determined by planetary geophysical and geochemical processes – especially differentiation and subsequent geodynamic and tectonic evolution – and by planetary formation processes that determine bulk planetary chemical inventories. However, the distribution of metals is extremely heterogeneous on and near the Earth's surface. Hence, the intersection of exoplanet geophysics and geochemistry, as well as planet formation, shapes our understanding of which planets are and are not likely to be habitable.<sup>[72–76]</sup>

Understanding Earth-life metal utilization dynamics can provide necessary guidance as to how we should explore the universe, allowing us to ask more sophisticated questions about the habitability of subsurface oceans on icy worlds, and meso- and micro-environments, such as on Mars.<sup>[77–79]</sup> Assumptions that couple global metal and geochemical abundances with the modern frequency of biological cofactor utilization may need to be reconsidered to incorporate the possibility that global metal availability and pervasive cofactor utilization can be entirely decoupled. For instance, if it does look like rare metals such as Mo are used for critical metabolic or other chemosynthetic functions, we may have to consider that use of these metals arose in fairly restricted circumstances where they were abundant, or that such use evolved in particularly unique niche environments. General assumptions about a correlation between abundance of a cofactor or substrate and its utilization and uptake in biological systems may need to be revisited through laboratory studies utilizing different metals. Studying the paleomolecular record can help us to assess past biochemical preferences of life using data independent of the geological record. If, as hypothesized for the Mo scenario in N-fixation, laboratory resurrected enzymes exhibit specificities toward metals that are thought to have been scarce early in Earth history, a disconnect between biological metal selection and global metal abundances would be supported. This emerging field of paleomolecular biology is necessary to understand how these two independent records of life, biology and geology, impacted one another in complicated and nuanced ways.

## Viewpoint: Explore Alternate Possibilities of Modern Biochemical Operation

The geochemical records of ancient Earth, and our increased understanding of factors that drove the chemical origins of life, permit us to explore alternate possibilities of biochemical operation. Investment into the development of novel experimental techniques that can probe the importance of major elements in both the pre-biological and biological modes of chemosynthesis is essential to constraining the pervasiveness and architectural variability of life in our universe. We therefore advocate a robust, interdisciplinary program of exploring beyond modern biology's atomic and molecular limitations.

Life is a highly specialized arrangement of atoms and molecules that, by acting in concert, avoid a collapse to equilibrium.<sup>[80]</sup> Perturbing this arrangement (i.e., substituting for alternative catalytic or biophotonic cofactors, alternative phosphorylation compounds, etc.) is often limited by life's tight tolerances that arise from within these networks of constraints. It is possible, however, that Earth life's specific chemical arrangement represents only one particular solution among many possible such solutions with similar behavioral properties. By generating novel interfaces between self-organizing biotic and self-organizing abiotic chemical systems, entirely novel chemosynthetic capabilities can be uncovered that are not limited by life's extant genetic, enzymatic and metal co-factor-catalyzed molecular architecture. Specific techniques that have demonstrated promise in generating and probing such novel interfaces include:

- genetic and enzymatic molecular resurrection through phylogeny;<sup>[17,40,81]</sup>
- generating genetic libraries that are subjected to laboratory selection experiments for identification and generation of novel alien chemistries and metabolisms;
- continuously driven systems of (likely self-organizing) prebiotic compound synthesis as proto-metabolic proxies;<sup>[80]</sup> and
- targeted genetic perturbation of highly conserved cellular modules with synthetic genes, with accompanied multi-level (genetic, enzymatic and metabolite concentration) monitoring of cellular adaptive responses.<sup>[82–85]</sup>

Taken together, these novel methods are likely to generate entirely new experimental means of perturbing, analyzing, decoupling, and constraining the fundamental elemental constituents that enable living systems to persist and flourish. By extension, the data generated can directly inform the targeted and strategic use of observational and laboratory resources to guide the search for forms of life in our universe that may be quite dissimilar from our own. Because of metals' unique role in mediating fundamental processes such as nitrogen fixation, metal-focused biochemical studies are not only important for origins of life, prebiotic chemistry and early life investigations, but can play a key role in the next generation of exoplanetary investigations.



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## Conflict of Interest

The authors declare no conflict of interest.

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