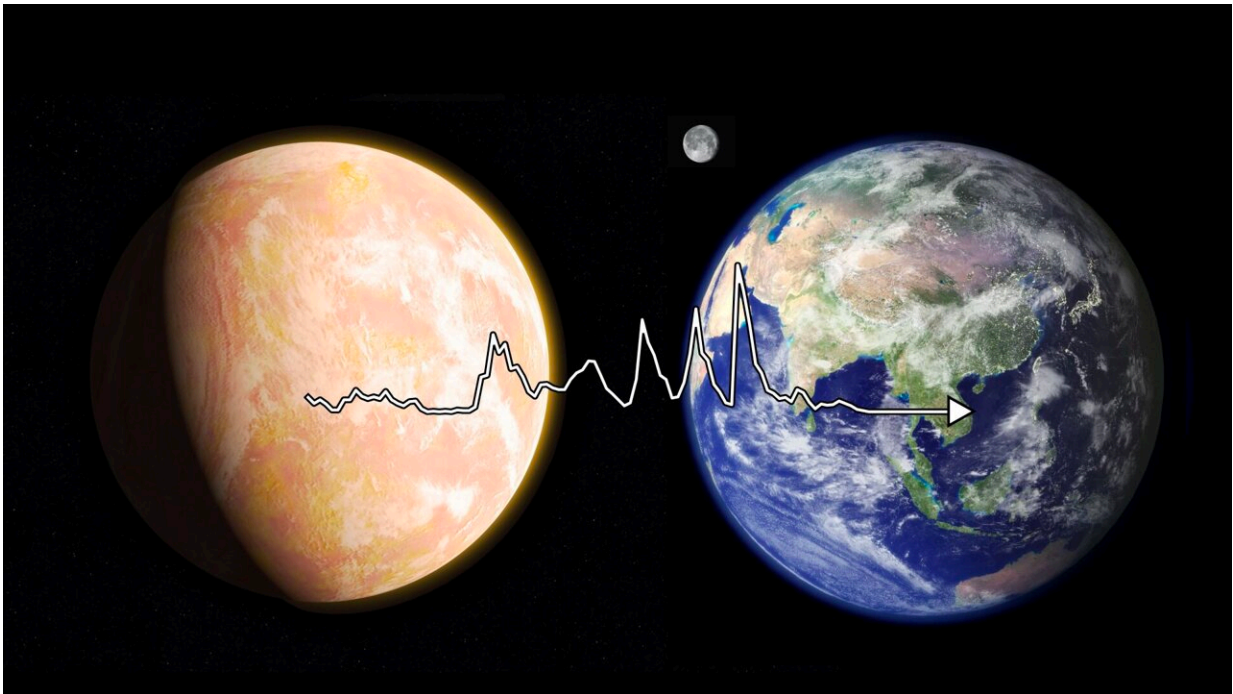


Scientists uncover a multibillion-year epic written into the chemistry of life

May 28 2024



Metabolism is the "beating heart of the cell". New research from ELSI retraces the history of metabolism from the primordial Earth to the modern day (left to right). The history of compound discovery over time (white line) is cyclic, almost resembling an EKG. Credit: NASA's Goddard Space Flight Center/Francis Reddy/NASA/ESA

The origin of life on Earth has long been a mystery that has eluded scientists. A key question is how much of the history of life on Earth is

lost to time. It is quite common for a single species to "phase out" using a biochemical reaction, and if this happens across enough species, such reactions could effectively be "forgotten" by life on Earth.

But if the history of biochemistry is rife with forgotten reactions, would there be any way to tell? This question inspired researchers from the Earth-Life Science Institute (ELSI) at the Tokyo Institute of Technology, and the California Institute of Technology (CalTech) in the US. They reasoned that forgotten chemistry would appear as discontinuities or "breaks" in the path that chemistry takes from simple geochemical molecules to complex [biological molecules](#).

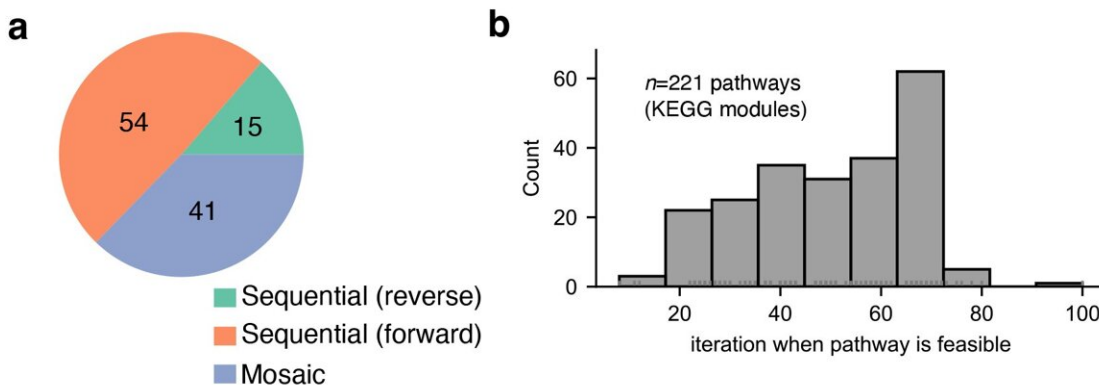
The early Earth was rich in simple compounds such as [hydrogen sulfide](#), ammonia, and carbon dioxide—molecules not usually associated with sustaining life. But, billions of years ago, early life relied on these simple molecules as a raw material source. As life evolved, biochemical processes gradually transformed these precursors into compounds still found today. These processes represent the earliest metabolic pathways.

In order to model the history of biochemistry, ELSI researchers—Specially Appointed Associate Professor Harrison B. Smith, Specially Appointed Associate Professor Liam M. Longo and Associate Professor Shawn Erin McGlynn, in collaboration with Research Scientist Joshua Goldford from CalTech—needed an inventory of all known biochemical reactions, to understand what types of chemistry life is able to perform.

They turned to the Kyoto Encyclopedia of Genes and Genomes database, which has cataloged more than 12,000 biochemical reactions. With reactions in hand, they began to model the stepwise development of metabolism.

Previous attempts to model the evolution of metabolism in this way had

consistently failed to produce the most widespread, complex molecules used by contemporary life. However, the reason was not entirely clear. Just as before, when the researchers ran their model, they found that only a few compounds could be produced. The research is [published](#) in the journal *Nature Ecology & Evolution*.



To construct a model of the evolutionary history of metabolism at the biosphere scale, the research team compiled a database of 12,262 biochemical reactions from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. Credit: Goldford, J.E., *Nat Ecol Evol* (2024)

One way to circumvent this problem is to nudge the stalled chemistry by manually providing modern compounds. The researchers opted for a different approach: They wanted to determine how many reactions were missing. And their hunt led them back to one of the most important molecules in all of biochemistry: adenosine triphosphate (ATP).

ATP is the cell's energy currency because it can be used to drive reactions—like building proteins—that would otherwise not occur in water. ATP, however, has a unique property: The reactions that form

ATP themselves require ATP. In other words, unless ATP is already present, there is no other way for today's life to make ATP. This cyclic dependency was the reason why the model was stopping.

How could this "ATP bottleneck" be resolved? As it turns out, the reactive portion of ATP is remarkably similar to the inorganic compound polyphosphate. By allowing ATP-generating reactions to use polyphosphate instead of ATP—by modifying just eight reactions in total—nearly all of contemporary core metabolism could be achieved. The researchers could then estimate the relative ages of all common metabolites and ask pointed questions about the history of metabolic pathways.

One such question is whether biological pathways were built up in a linear fashion—in which one reaction after another is added in a sequential fashion—or if the reactions of pathways emerged as a mosaic, in which reactions of vastly different ages are joined together to form something new. The researchers were able to quantify this, finding that both types of pathways are nearly equally common across all of metabolism.

But returning to the question that inspired the study—how much biochemistry is lost to time? "We might never know exactly, but our research yielded an important piece of evidence: only eight new reactions, all reminiscent of common biochemical reactions, are needed to bridge geochemistry and biochemistry," says Smith.

"This does not prove that the space of missing biochemistry is small, but it does show that even reactions which have gone extinct can be rediscovered from clues left behind in modern biochemistry," concludes Smith.

More information: Joshua E. Goldford et al, Primitive purine biosynthesis connects ancient geochemistry to modern metabolism, *Nature Ecology & Evolution* (2024). [DOI: 10.1038/s41559-024-02361-4](https://doi.org/10.1038/s41559-024-02361-4)

Provided by Tokyo Institute of Technology

Citation: Scientists uncover a multibillion-year epic written into the chemistry of life (2024, May 28) retrieved 22 June 2024 from <https://phys.org/news/2024-05-scientists-uncover-multibillion-year-epic.html>

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