

The Origins Divide: Reconciling Views on How Life Began

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Did life begin in heat or cold, in a reducing or oxidizing atmosphere, at the ocean surface or in the deepest sea, with a membrane-enclosed genetic molecule or as a flat collection of chemical reactions on a rock?

Four and a half billion years ago, the planet Earth coalesced out of the gas and dust left over from the formation of the sun. For the next several hundred million years, the young planet was bombarded by comets and meteorites, volcanic eruptions raged across its surface, and its heat boiled the nascent oceans. But within about a billion years—and perhaps much earlier—life had arisen.

How nonliving chemicals transformed into living molecules is one of the biggest mysteries in science, and we might never know for sure how it happened. Deep divides in opinion are found in almost all areas of origin-of-life research. Did life begin in extreme heat or relative cold? Were its essential molecules synthesized in the prebiotic ocean, at the mouths of churning deep-sea vents, or did they rain down from space? Did the first life-form get its energy from the sun or from the chemical energy of minerals? Were inherited genetic molecules essential to the first life-form, or could life simply have been a chain of chemical reactions taking place on a rock?

“If we’re going to make any progress, we really have to be critically

honest about what we don’t know,” says geochemist George Cody, of the Carnegie Institution for Science in Washington, DC. “And that’s just about everything.”

The questions surrounding life’s origins are indeed vast and, for the most part, unanswered. A comprehensive explanation of the origin of life will require pinning down the beginnings of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), of proteins and lipid membranes, of genetic coding and metabolic machinery. In modern life, all of these molecules and processes are so intertwined that it’s difficult to imagine how any of them could have arisen without the others already in place. Chicken-and-egg problems abound.

But new technologies, hypotheses, and experiments are constantly surfacing, and each step reveals a bit more of the way the inanimate chemistry of Earth’s beginnings may have morphed into the remarkable variety of life we see today.

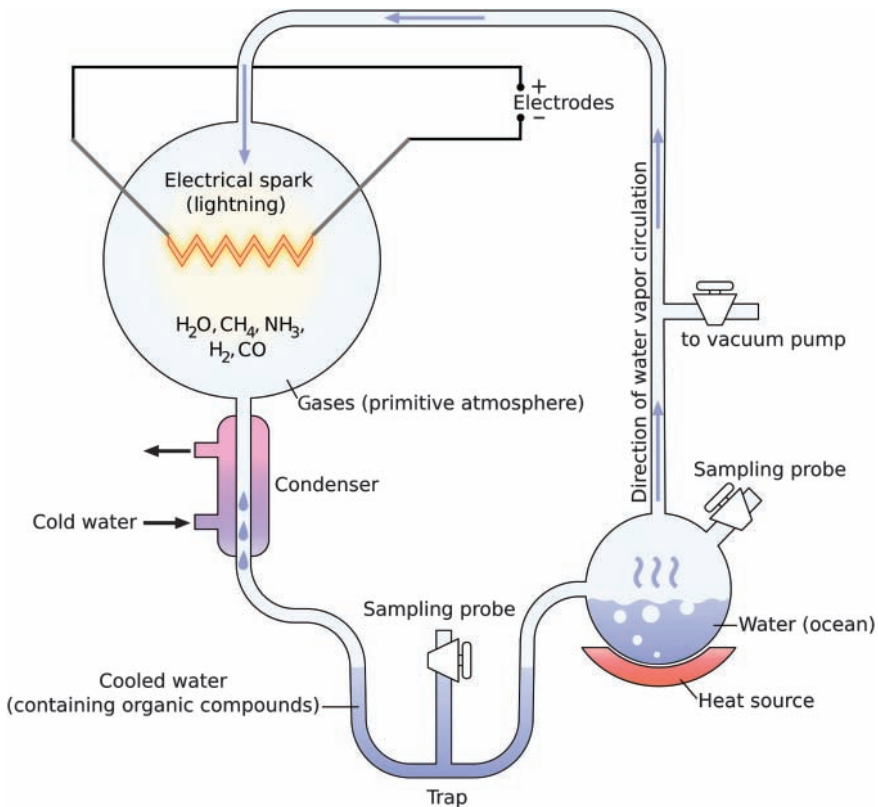
Beginnings

The basis of origin-of-life thought lies perhaps with Louis Pasteur’s disproof of spontaneous generation: If

life couldn’t arise out of nothing, then where did it come from? A few years later, Darwin speculated about chemical reactions in a “warm little pond,” and Alexander Oparin and J. B. S. Haldane independently took that idea a step further by proposing that life began in a primordial ocean of organic molecules.

Origin-of-life research didn’t get its experimental start, however, until the famed chemical synthesis experiments of Stanley Miller and Harold Urey, of the University of Chicago, were published in 1953. By sending an electrical current through a mixture of water, methane, ammonia, and hydrogen, they simulated what might have happened when lightning struck the oceans and atmosphere of ancient Earth. What they got—a mixture of key amino acids and other organic molecules—profoundly changed views of the origin of life. The origin of biology was now experimentally approachable.

Other groups soon conducted similar experiments, and in the following years, researchers managed to synthesize not only additional amino acids but also other essential biomolecules, including sugars, metabolic acids, and lipids.



By sending an electrical current through a mixture of water, methane, ammonia, and hydrogen, Stanley Miller and Harold Urey simulated what might have happened when lightning struck the oceans and atmosphere of ancient Earth. The resulting mixture of key amino acids and other organic molecules profoundly changed views of the origin of life. Graphic: User: Carny (he.wikipedia.org), User: Yassine Mrabet (en.wikipedia.org).

More recently, some research has suggested that Miller's synthesis might not have worked after all. Some data on the likely atmospheric composition of early Earth have suggested that it actually contained very little methane or ammonia, and was instead primarily composed of nitrogen and carbon dioxide—far less reactive gases. But other work has since countered that early Earth could have had a reducing atmosphere full of hydrogen. "Right now, you can have it either way, if you cite the appropriate papers," says organic chemist Jeffrey Bada, of the Scripps Institution of Oceanography in La Jolla, California.

The lack of confidence in the nature of prebiotic Earth's atmosphere holds back much origins research. Understanding Earth's early atmospheric composition could set rather stringent constraints on how and where life

might have arisen, but most of the first half-billion years of Earth's rock record has been recycled back into the interior of the planet. The early atmospheric record "just doesn't exist," says Jim Cleaves, also of the Carnegie Institution. "It leaves the whole problem open to speculation."

It's possible, however, that the atmosphere of early Earth may not end up being relevant to the origin of life. Work by Cleaves suggests that important molecules could have been synthesized locally at gas-belching volcanoes, even if the worldwide atmosphere wasn't supportive. "I'm not at all convinced that the composition of the atmosphere is a central issue," Bada says. "You can imagine local syntheses all over the surface of the Earth, so the composition of the global atmosphere might not matter."

Other researchers believe that life didn't originate on Earth's surface

at all. Since the 1977 discovery of elaborate ecosystems near deep-sea hydrothermal vents, many scientists have come to view this environment as perhaps uniquely suitable to nurturing the beginnings of life. At these vents, hot, mineral-rich water surges from the planet's interior into the cool ocean above. The chemical and thermal disequilibrium between these two water sources provides the energy that local microorganisms need to survive. "In my view, it seems like the most likely place to look for something interesting to occur," Cody says.

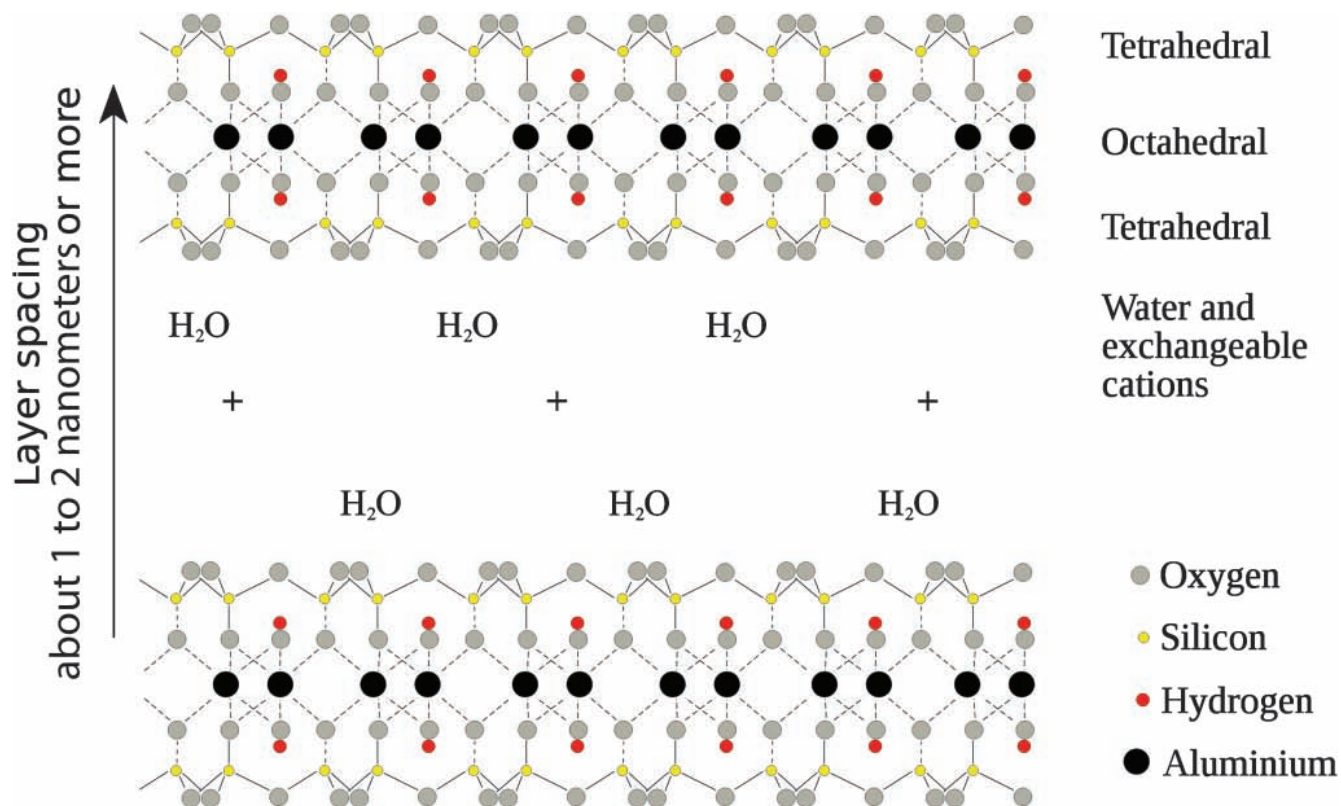
Miller and his students and colleagues have expressed doubt about marine vents' role in the beginnings of life, however. They claim that hydrothermal temperatures are too hot for essential biomolecules to survive, although "ventists" have countered that the surrounding cold ocean water would allow these molecules to remain intact.

Yet another possible origin of life's important biomolecules lies far beyond the surface of the Earth. Analyses of carbon-rich meteorites found on Earth have revealed amino acids and other important organic molecules that appear to have been synthesized in deep space and then delivered to Earth. Some scientists have also criticized this hypothesis, questioning whether significant amounts of organic molecules could survive crashing into the planet. But work from Jennifer Blank, of the SETI Institute in Mountain View, California, has suggested that although violent impacts may reduce the quantity of organics delivered to Earth's surface, they can actually induce chemical reactions that lead to a more diverse collection of biologically relevant molecules.

Many researchers now believe that life's basic building blocks came not from one place but from many: the early ocean and atmosphere, ancient volcanoes, the crust in the bottom of the ocean, and the reaches of deep space.

The origins of genetics

While basic building blocks such as amino acids and sugars may have



Many organic chemists have spent the past few decades trying to figure out how RNA could have spontaneously assembled from the simple organic molecules found on early Earth. One theory is that the structure of montmorillonite clay, diagrammed here, could have acted as a scaffold for the assembly of RNA from its building blocks. Graphic: Andreas Trepte, User: Itub (en.wikipedia.org).

been plentiful on early Earth, these molecules are a far cry from proteins, nucleic acids, and cell membranes—life's essential macromolecules. Much origins research over the past 50 years has focused on how these larger structures assembled themselves.

The question of how DNA and proteins could have arisen at first seemed intractable: DNA encodes proteins, but protein catalysts are required to synthesize DNA. Some researchers deemed this problem “solved” in the 1980s, when scientists discovered ribozymes, RNA molecules that can act as catalysts. These molecules can carry an organism's genetic information and also catalyze the replication of that information. After ribozymes' discovery, many origin-of-life scientists converged on a model of life's emergence known as the RNA world. Before DNA evolved, they believe, RNA both stored an

organism's genetic code and catalyzed its own reproduction.

With this view of life's beginnings, many organic chemists have spent the past few decades trying to figure out how RNA could have spontaneously assembled from the simple organic molecules found on early Earth. Work by James Ferris, of the Rensselaer Polytechnic Institute in Troy, New York, has shown that clays, especially one called montmorillonite, could have acted as scaffolds for the assembly of RNA from its building blocks, ribonucleotides. In a subsequent step, Jack Szostak, of Harvard University in Cambridge, Massachusetts, and his colleagues have illustrated how ribozymes might have evolved from short, noncatalytic stretches of RNA.

But proponents of the RNA world have long been plagued by a fundamental problem: Although they have found plausible pathways to string together

ribonucleotide subunits into RNA and then to “evolve” catalytic RNA, they couldn't explain the presence of the original ribonucleotides. Organic chemists have spent decades trying to synthesize ribonucleotides from their precursors of sugars, nucleobases, and phosphate groups. They've had remarkably little luck with this synthesis, which has prompted criticism of the idea that life really started with RNA.

In 2009, however, work from John Sutherland, of the University of Manchester, United Kingdom, presented a potential solution. His group managed to synthesize two of RNA's ribonucleotides by combining the components in a different way than had been done before. Instead of trying to attach the bases directly to the sugars, they set up the synthesis so that the mixture went through a series of hybrid intermediates before the final nucleotides

emerged. “We spent 14 years exploring all that potential assembly chemistry, and we were largely extremely unsuccessful,” Sutherland says. “But we discovered eventually that there was a way through.”

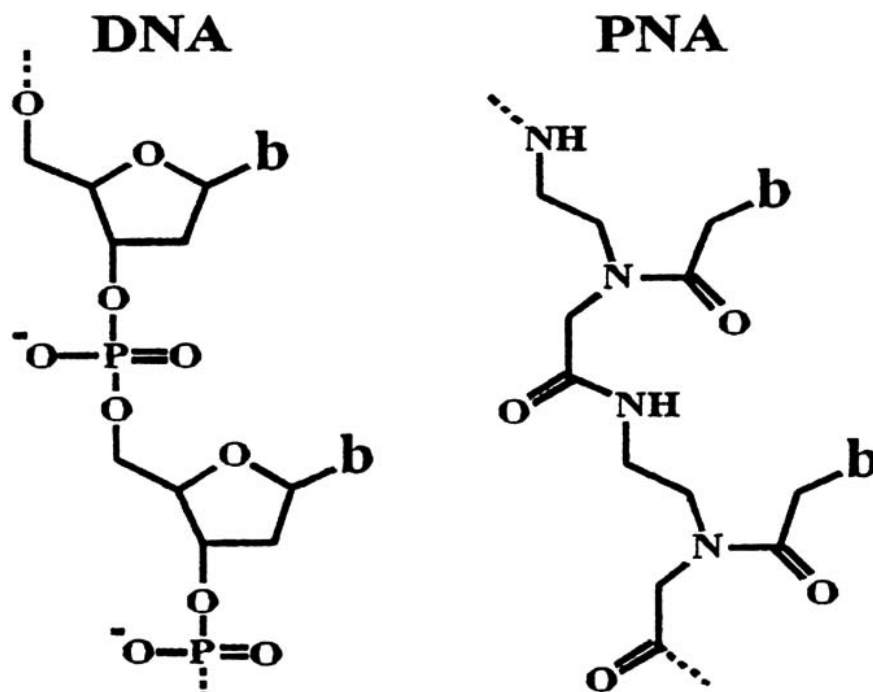
Not everyone is convinced, though. Sutherland’s work shows “absolutely beautiful organic chemistry,” says Cody, but the conditions under which they performed their experiments were likely not realistic representations of what early Earth looked like, he says. “There really isn’t anything plausible about the scenario.”

Elaborate experimental setups are a common problem in organic synthesis research into the origin of life, Cleaves says. Whenever researchers manage to synthesize an interesting molecule, “it’s such a complex and kind of contrived experiment, it’s hard to really swallow.”

Some researchers have suggested that a different genetic molecule came before RNA—something easier to assemble from small-molecule components. RNA is “much too complicated to have appeared out of the prebiotic soup,” Bada says. One possibility that chemists have toyed with is a molecule called peptide nucleic acid, or PNA. Instead of the sugar-phosphate backbone of RNA, this synthetic molecule has a backbone made of the amino acids found in proteins. Many chemists believe PNA would be far easier to put together from precursors.

Assembling any of these genetic molecules under plausible geochemical conditions is “the ultimate challenge in synthetic organic chemistry,” Bada says. “It’s not that it’s an intractable problem, it’s just that we’re ignorant of all of the potential chemistry that can take place under natural conditions.”

Whether the first genetic molecule was RNA or a simpler analog, researchers continue to disagree about the likelihood of such a molecule emerging from the prebiotic soup. “There have been some little successes here and there,” Cleaves says, “but I think the field is getting split now, between people who think



*Many chemists believe that peptide nucleic acid, or PNA, may have preceded RNA or other genetic molecules, since it would be far easier to assemble from small-molecule components. Figure © 1998 National Academy of Sciences, from *Proceedings of the National Academy of Sciences* 95: 2073–2076, used with permission.*

there is going to be some miraculous discovery of how you make RNA prebiotically and people who look at that and think, it’s just too complex.”

Among scientists who believe that nucleic acids could not have arisen spontaneously from organic precursors, many have aligned themselves with a drastically different idea of how life emerged.

Metabolism first

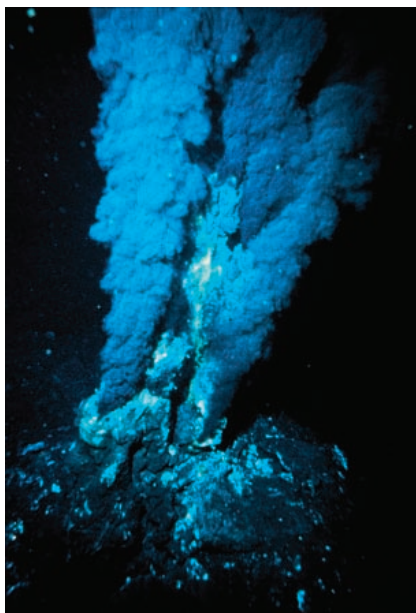
At the same time the RNA world hypothesis was gaining ground, a radically alternative concept of life’s origins surfaced—an idea that today underlies what many researchers consider to be the most fundamental divide in origin-of-life theories. “If we could answer this question one way or the other, it would put grounding under the whole field,” says Robert Shapiro, of New York University in New York City.

In 1988, a German chemist and patent lawyer named Günter Wächtershäuser published a groundbreaking paper on the origins of metabolism. In Wächter-

shäuser’s view, life began not with a genetic molecule synthesized from organic precursors in the environment but with a simple network of small-molecule chemical interactions capable of catalyzing its own replication.

Essentially, this “metabolism first” model proposes that life arose when very simple molecules such as carbon dioxide, hydrogen, and hydrogen sulfide reacted with each other on the common iron-sulfur minerals pyrrhotite and pyrite, probably at hydrothermal vents. With chemical energy harnessed from the minerals, the simple molecules combined into successively larger species. Some of these products catalyzed new reactions, and eventually, metabolic networks appeared, complete with feedback loops that allowed the networks to sustain themselves.

Metabolism-first proponents assert that no genetic mechanism was required for this first life-form, as faithful duplication of the entire metabolic network was built into the

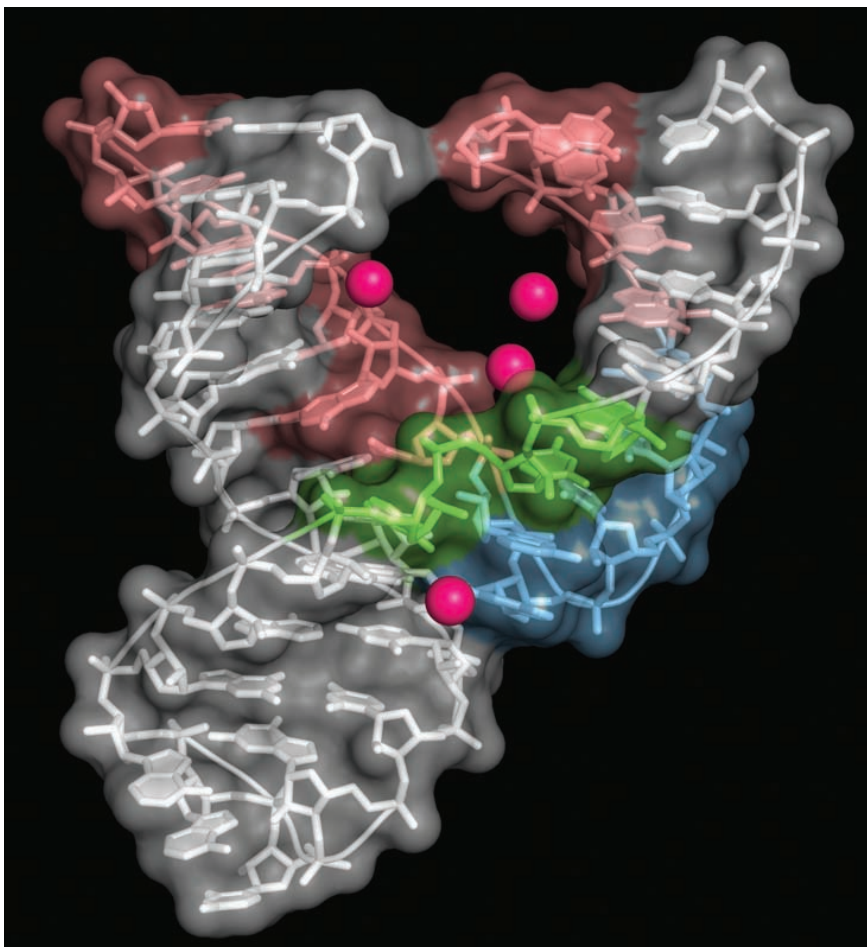


The metabolism-first model proposes that life probably arose at deep-sea hydrothermal vents, like the black smoker pictured here, when very simple molecules such as carbon dioxide, hydrogen, and hydrogen sulfide reacted with each other on the common iron-sulfur minerals pyrrhotite and pyrite. Photograph: OAR/National Undersea Research Program (NURP); NOAA.

cycle itself. Because of the mineral complexes he envisioned catalyzing the initial chemical reactions, Wächtershäuser named this conception of life's beginnings the iron-sulfur world.

Over the past decade or so, researchers swayed by the idea of metabolism before genetics have tried to find supporting evidence in the lab. They have found evidence that iron sulfide minerals can catalyze reactions that produce a variety of important organics, including acetate and pyruvate, both essential metabolic molecules.

Bada, however, echoes a complaint that has been directed at much of the research on genetic molecule synthesis: "You can do stuff in the lab, but it's not directly applicable to a natural process," he says. "Also, you might be able to do a reaction here or there, but any sort of comprehensive, sustained chemistry has never been shown."



The "RNA world" model arose with the discovery of ribozymes—RNA molecules, such as the self-cleaving hammerhead ribozyme depicted here, that can act as catalysts. Could these self-replicating molecules have evolved from short, noncatalytic stretches of RNA, or would an autocatalytic network of chemical reactions have had to come first? The pink spheres are Mg^{++} ions that stabilize the structure of the ribozyme. Graphic: Kalju Kahn and Esther Zhuang, University of California, Santa Barbara; created with PyMol (DeLano Scientific).

No complete metabolic cycle has yet emerged in the lab from mineral catalysis of small-molecule reactions, admits Harold Morowitz, of George Mason University in Fairfax, Virginia, but he's hoping that will change. He believes that life's first metabolic cycle may have looked very much like one still in existence in some primitive microorganisms: the reverse citric acid cycle. This cycle, which allows microorganisms to synthesize essential biomolecules from water and gas, is now helped along by protein enzymes. But Morowitz believes that sulfide minerals did the catalytic work in the beginning.

He and his colleagues have recently devised a hypothesis that extends the ideas of Wächtershäuser from iron sulfides to other so-called transition metals, including iron, nickel, cobalt, copper, zinc, manganese, and a few other elements. When small molecules or ions attach to these transition metals, the resulting complexes become effective catalysts; Morowitz and colleagues propose that these could have nudged along life's very first metabolic reactions. Their hypothesis also supports the idea of hydrothermal origins, as many of these metals are found in abundance at deep-sea vents.

Morowitz believes that evidence for such origins lies in current biology: The cores of many modern metabolic enzymes have clusters of atoms that look exactly like tiny bits of sulfide minerals. From iron in hemoglobin and cobalt in vitamin B-12 to the zinc that's incorporated in many proteins, these minerals are clearly an important, and perhaps ancient, part of biology.

Additionally, Morowitz believes that the chemical nature of these metals means that anywhere they're found in a supportive environment, catalytic networks—and therefore life—will emerge. He and his colleagues are currently working on lab experiments to try to show that the catalysis performed by these metals could lead to a metabolic system similar to the reverse citric acid cycle. If they can prove this experimentally, “the real excitement...is that metabolism is lurking in the periodic table,” he says. And here lies a fundamental, almost philosophical, divide between the genetics-first and the metabolism-first camps. The assembly of RNA or any other genetic molecule from the primordial soup was probably a unique, and perhaps unlikely, event. “You're invoking chance to an enormous degree,” Shapiro says.

In a metabolism-first world, however, the buildup of larger molecules from simple ones and the eventual emergence of interacting chemical networks could not only have happened many times and in many places on Earth but also may in fact have been a foregone conclusion, simply a result of the fundamental chemistry of carbon-based molecules, gases, and metals. If this is life, “the emergence of life is probably inevitable,” Morowitz says.

This viewpoint has vast implications for the probability of finding life elsewhere in the universe. Self-replicating genetic molecules such as RNA would

likely evolve only on worlds extremely similar to Earth, Shapiro says, whereas “metabolism-first people are free to imagine how life might exist on places like Titan, which is very different from us but seems to have a lot of reactive chemicals. Metabolism first is much more amenable to the idea that life can be very diverse.”

Some scientists, most notably Paul Davies, of Arizona State University in Tempe, have championed the idea that such diverse life may even exist on Earth—a “shadow biosphere” of life very different from anything we currently know, which we haven't recognized simply because we haven't been looking for it. “We may have been so fixated on studying our own kind of life that we may have missed that life operating on a different principle has existed right under our noses,” Shapiro says.

Other researchers, especially organic chemists, however, still resist the central conceit of metabolism-first models: that self-replicating chemical networks can be considered to be alive. “I wouldn't call that life. It might be interesting chemistry, but it's not alive,” Bada says. “In my opinion, our definition of life is that it can pass genetic information from one generation to the next.”

Others are uncomfortable with a strict divide between the origins of genetics and metabolism. “I think that's a false dichotomy,” Cody says. An autocatalytic network of chemical reactions “isn't necessarily life,” he says, but, on the other hand, “it's almost inconceivable that something like ribozymes could spontaneously emerge prior to other metabolic function. The systems have to be coordinated in some way.”

Systems chemistry

Researchers on both sides of the genetics–metabolism divide, as well as those who are hoping for some sort

of blend of the two ideas, are moving forward with new experiments, trying to see how far they can push organic syntheses along a believable road to simple life-forms.

Many origin-of-life scientists are now immersed in a fairly new approach they term “systems chemistry.” Instead of purifying and isolating chemicals before studying their interactions, systems chemists toss dozens or hundreds of chemicals together and see what emerges. Often, they find reactions and products that they couldn't have predicted simply from knowledge of each individual component of the mixture.

The Sutherland group used this approach to synthesize their ribonucleotides: By mixing together ingredients simultaneously, the chemicals reacted in important ways that they couldn't when each was added sequentially. By allowing complex mixtures of chemicals to interact, “you can get some tremendous synergies,” Sutherland says. “Ultimately, you might start getting emergent behavior. And that's really what interests everybody who's involved in origin of life.”

Metabolists are also using this method to see how catalytic networks might arise from complex mixtures of chemicals that are simply allowed to react over time. “You're not trying to force any results,” Shapiro says. “You take a look and see what nature wants.”

The emergence of unexpected behaviors from complex interactions is “an essential quality of life,” Cody says. “If we can study simple chemical systems and understand how these things emerge and what they do, at least we gain some insight into what probably happened, even if we can never replicate exactly what occurred on the pathway toward life as we know it.”

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