

Why is Life the Way it Is?*

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The concept of the three domains of life (the bacteria, archaea and eukaryotes) goes back to Carl Woese in 1990¹. Most scientists now see the eukaryotes (cells with a true nucleus) as a secondary domain, derived from bacteria and archaea via an endosymbiosis². That makes the last universal common ancestor of life (LUCA) the ancestor of bacteria and archaea³. While these domains are strikingly different in their genetics and biochemistry⁴, they are nearly indistinguishable in their cellular morphology — historically, both groups have been classed as prokaryotes. In terms of their metabolic versatility and molecular machinery, prokaryotes are if anything more sophisticated than eukaryotes⁵. Yet despite an exhaustive search of genetic sequence space in virtually infinite populations over four billion years, neither domain evolved morphological complexity to compare with eukaryotes⁵. The evolutionary path to morphological complexity does not seem to depend on genetic information alone⁶. The most plausible explanation is that physical constraints stemming from the topological structure of prokaryotes blocked the evolution of morphological complexity in prokaryotes, and that the endosymbiosis at the origin of eukaryotes relieved these constraints⁶. In this lecture, I shall argue that the dependence of all life on electrical charges across membranes to generate energy explains the structural constraints on prokaryotes, and the escape from these constraints in eukaryotes⁷.

Keywords: Archaea; Bacteria; Eukaryotes; Tree of Life; Origin of Life; Bioenergetics; Membranes.

Just think for a moment about the sheer exuberance of life on Earth. It would be easy to imagine that anything that can exist does exist. Think about the extraordinary deception of stick insects, or the fleeting dance and vivid plumage of hummingbirds, the goofy grace of Platypus, the majesty of sequoia, or the magical wonders of the microscopic world — cells bustling about their business with whirling parts and secret purpose. Turn a stone in the Amazon and you may well find a new species, still undescribed by science. If not actually prohibited by the laws of physics, it seems as if virtually anything goes. Life is a riot of unfettered experimentation.

That perception is reinforced by the intricate interconnections in the tree of life. The ease of gene sequencing means that we now have complete genome sequences for thousands of species, giving an unprecedented insight into the evolutionary history of life on Earth. We can see that species are separated by numerous tiny differences in their gene sequences, and that all life on Earth shares a common ancestor

that arose close to 4 billion (4000 million) years ago⁸. Natural selection is a search engine that has explored every nook and cranny of the fitness landscape, coming up with intimate adaptations to every imaginable niche, and many others beyond the imagination. That old rhyme is true — big fleas have little fleas upon their backs to bite 'em. And little fleas have lesser fleas, and so ad infinitum.

Yet this perception is misleading. It might be true today, but we do not have to wind the clock back far for the situation to be very different. Just 500 million years ago there was little of this profligate exuberance on land — no trees, not even plants beyond a few lichens or mosses. No animals on land. Go back another 50 million years, and we are amidst that fabulous eruption known as the Cambrian explosion, when the first animals burst abruptly into the fossil record⁹. A little before that we see the mysterious fronds and flattened bags of the Ediacaran fauna, whatever they were, perhaps including a few jellyfish-like things (Figure 1)¹⁰.

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Origin of the germline – Cambrian explosion?



Cambrian animals – motile bilaterian predators, needed oxygen, fast tissue turnover, fast protein and mitochondrial turnover – high mitochondrial mutation rate

Once germline had evolved, supported greater division of labour and specialization

Figure 1. Ediacaran fauna and the Cambrian explosion. Courtesy of D.W. Miller paleoart.

And before that, nothing, or at least nothing much to see. In fact, there were plenty of single-celled organisms such as algae and simple fungal cells and amoeba-like cells¹¹. And lots of bacteria. Rewind the clock by another billion years, and even the more complex cells are nowhere to be seen. We are now close to 2 billion years ago, at another famous juncture in the history of life known as the Great Oxidation Event¹². The world was turning red with oxidised iron, the first tell-tale signs that bacteria — specifically cyanobacteria — had invented photosynthesis and were beginning to release oxygen into the atmosphere. Before even that, beating out a steady rhythm measured in hundreds of millions of years, life stretches back to the first stirrings in the fossil record, close to 4 billion years ago⁸. In other words, for four fifths of the history of our planet, life was not an exuberant riot of the imagination, but disturbingly staid, composed entirely of simple microscopic cells lacking any real morphological complexity. While most scientists would be excited to find such simple cells on Mars or Enceladus, these are far from the terrifying aliens that have long haunted the imagination. Most folk wouldn't be impressed.

So why did life take so long to take hold on Earth? In one sense the answer is staring at us from the tree of life itself. Most of the genetic variation across the tree of life is not in what amount to trivial differences between plants and animals — which are built from almost identical complex cells

with a nucleus — but between different types of bacteria. Not only bacteria. There is another group of cells that look more or less the same as bacteria, called 'archaea'¹. They're called that because when they were discovered, in the 1970s, they were thought to be even older than bacteria¹; but we now know that's not true³. Yet despite looking like bacteria, archaea are strikingly different in their genes and biochemistry, in some respects as different from bacteria as we are⁴. The point is that bacteria and archaea have searched through the genetic sequence space of life far more comprehensively than complex 'eukaryotic' cells (the type of cell that makes up all plants and animals, fungi and amoeba) ever did. If the problem of complexity could be cracked by genes alone — read by 'information' alone — then bacteria and archaea would have cracked the problem long ago¹³. Yet they didn't. They remain small and simple. There are no animals, plants or fungi made from bacterial cells, nothing that even approaches the size and sophistication of an amoeba. Of course, there can't be complexity without information, but information by itself doesn't explain the evolution of complex life, nor the endless delays in the history of life on Earth^{6,13}.

Presumably there are constraints on what genes can do. Those constraints could be linked with the environment. Animals can't thrive without oxygen, for example, so the simplest explanation is that life could not burst into its familiar exuberance until the oxygen levels in the atmosphere or

oceans had reached a critical threshold. There's undoubtedly some truth in that, but it doesn't explain why there are no giant multicellular bacteria or archaea; many of these cells can respire oxygen too, and so should gain the same benefits, but they still don't become large and complex. That means we can exclude both oxygen and genetic information: neither can be the secret ingredient that enabled the evolution of complex life⁷.

What is the secret then? The answer might lie in the very fabric of cells. There is a subtle constraint here, which relates to the 'powerhouses' of complex cells, the mitochondria. We have hundreds or thousands of these tiny structures in our own cells, which provide us with all the energy we need to live — they are the seats of respiration, where we burn food in oxygen and trap the energy released in a usable chemical form called ATP (which stands for 'adenosine triphosphate', but that is beside the point). Mitochondria have a little genome of their own¹⁴, whose provenance is one of the most obscure but fascinating stories in biology¹⁵. They have their own genes because they were once free-living bacteria, which moved into another cell, an archaeon⁵, and have remained there ever since. They have proliferated along with their host cells and are now arguably one of the most successful life-forms on the planet. But in the process, they lost their identity to the point that they are now barely recognizable as erstwhile bacteria.

Why would that matter? It matters because the way that mitochondria generate energy holds the clue to the whole history of life. Mitochondria are electric. Literally. They strip electrons from food and pass them down a sophisticated protein 'wire' buried deep within an insulated membrane, to oxygen (Figure 2). This current of electrons powers the pumping of protons (the charged nuclei of hydrogen atoms) across the insulated membrane. That puts an electrical charge on the membrane — each of the protons pumped out carries a positive charge. The system is like a hydroelectric dam, in which the membrane is equivalent to the dam, and the protons accumulate on one side of the dam as a reservoir. In a hydroelectric station the flow of water through a turbine powers the generation of electricity; in the mitochondria, the flow of protons through astonishing molecular motors (which rotate like real motors) drives the synthesis of ATP. The brilliant, genuinely eccentric Englishman who discovered this process, Peter Mitchell, called the electrical force generated by mitochondria the 'proton-motive force'¹⁶; others called it the 'most counterintuitive idea in biology since Darwin'¹⁷, and Mitchell duly won the Nobel Prize in 1978.

So: mitochondria are buzzing with a strong electrical field, the proton-motive force. They have a charge of about 180 milli-Volts across their membrane, which is just 5 millionths of a millimetre in diameter. That translates into a field strength of some 30 million Volts per metre, equivalent to a

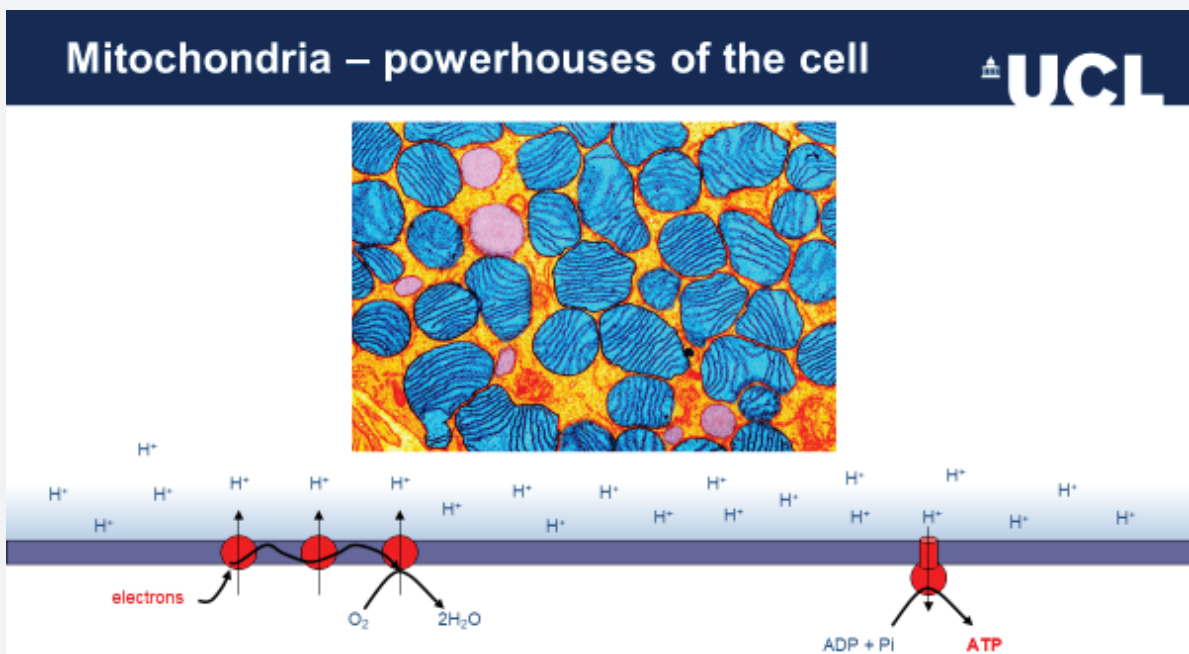


Figure 2. Mitochondria and cell respiration.

bolt of lightning¹⁸. To sustain this charge, we pump an extraordinary 10^{21} protons per second across the membranes of the 10 million billion mitochondria in our body, which have a combined surface area of about 4 football pitches. 10^{21} protons per second. That's a mere 2 orders of magnitude less than the number of stars in the known universe, every second.

If it were only large, highly evolved animals that were powered in such an extraordinary way, then these facts would certainly boggle the mind, but would not necessarily hold any deeper meaning. Mitochondria are miniature power stations, but animals have to be powered some way; so what? Well, I mentioned that mitochondria were bacteria once, and they inherited their proton pumping machinery from their ancient bacterial ancestors, whose free-living descendants still operate the same way. It turns out that all bacteria work the same way; and so do all archaea¹⁹. And it's not only respiration. The process of photosynthesis, in which plants, algae and photosynthetic bacteria tap the energy of the sun to form organic molecules and ATP, also works the same way, charging their membranes by coupling the transfer of electrons to the pumping of protons. Transport of molecules in and out of bacteria, archaea and mitochondria is also powered by the proton-motive force; even the rotating corkscrew flagellum, which powers bacterial motility like a turboprop engine, is driven by the proton-motive force²⁰. It's hard not to think

about Star Wars. Living cells are animated by an enveloping force-field. The force really is with you — or you're dead.

In short, the use of electrically charged membranes, and specifically the proton-motive force, is as widely conserved across all life as the genetic code itself²¹. That implies it is as important, as ancient, and perhaps as fundamental as the genetic code itself. That is an intriguing paradox because of the sheer complexity of the mechanism — how did sophisticated molecular machines like the rotating ATP synthase evolve in the first place? The mystery deepens. I mentioned that bacteria and archaea are deeply divergent in their genetics and biochemistry, including the chemistry of the membranes that bound the cells themselves (Figure 3). Most strikingly, these membranes use opposite-handed forms of the same crucial molecule (glycerol phosphate): archaea use the left-handed form and bacteria the right-handed^{4,22}. There is zero difference in their chemistry, just in the handedness, which means that choosing one hand over the other cannot be explained by any selective advantage, only by chance¹³. Presumably, given an arbitrary choice, ancestral bacteria randomly chose one hand while ancestral archaea chose the other, meaning that their shared common ancestor had... what? That common ancestor apparently utilized the proton-motive force and even had an ATP synthase, yet it did not have a modern membrane equivalent to either bacteria or archaea, but something else.

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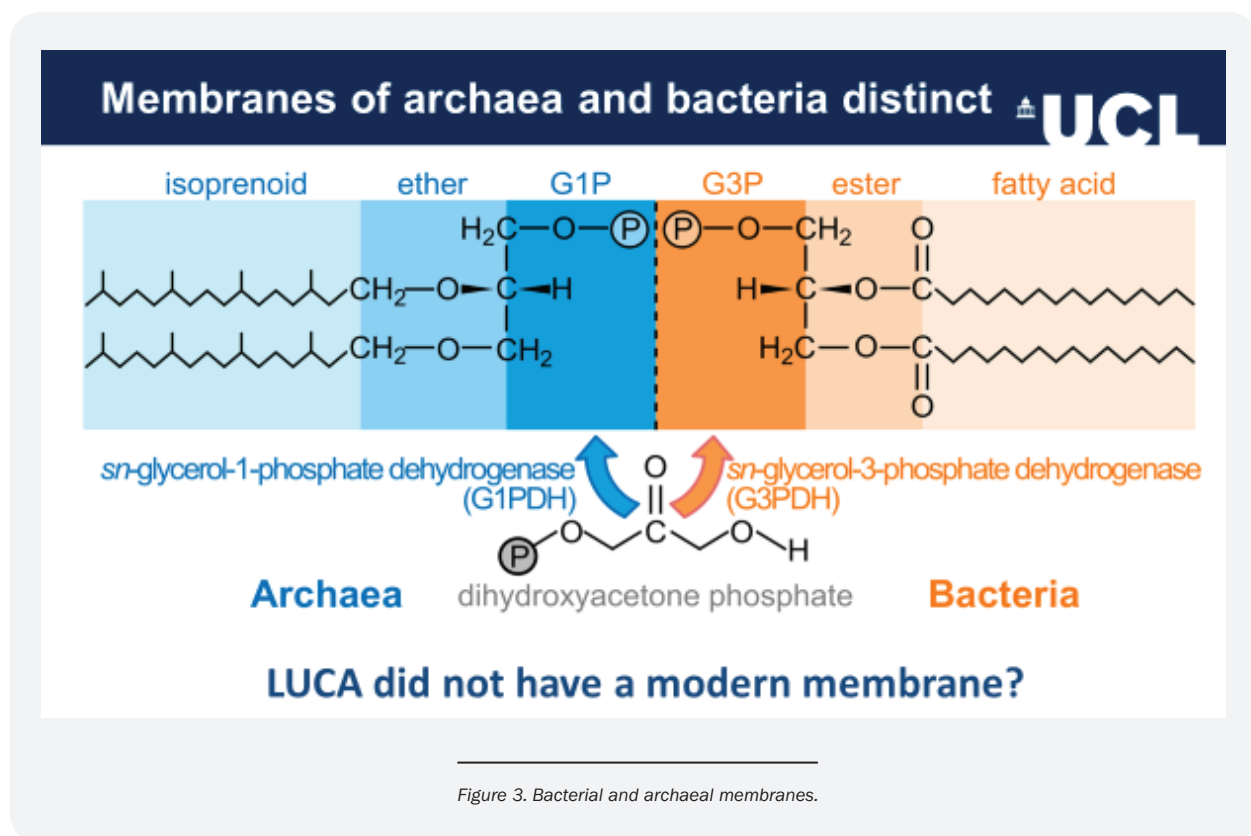


Figure 3. Bacterial and archaeal membranes.

This is the paradox: the common ancestor of life drew on the proton-motive force, but did not have a modern membrane²³. What was going on? I suspect that we are being bamboozled by the hypnotic fascination of the ATP synthase, and that the first use of the proton-motive force was not related to ATP synthesis but to something even more fundamental — growth. The deepest branches in the tree of life suggest that the first cells were autotrophs, meaning that they grow by converting gases such as hydrogen and carbon dioxide into organic molecules²⁴. This is how an ancient group of archaea, the methanogens, grow^{25,26}. These cells gain all the carbon and energy they need to grow from the reaction between carbon dioxide and hydrogen alone, but to do so they use a trick which, to my mind, offers a clue to the origin of life itself^{23,27}. The problem with growing from these gases is that they are not very reactive. Methanogens coax them into reacting using a protein that stands out for two reasons: first, it is a membrane protein that contains at its heart a few tiny iron-sulphide crystals, a type of mineral that is often found in hydrothermal vents²⁸; and second, the reaction is driven forwards by the proton-motive force^{29,30}. Unlike the sophisticated rotating motor that is the ATP synthase, the requirements are simple here: to drive growth, this protein needs hydrogen, carbon dioxide, iron sulphide crystals and the proton-motive force. And that humble combination points to a very specific environment where life might have started: alkaline hydrothermal vents^{4,31–34}.

Alkaline vents are not volcanic, nor especially hot, but are formed by a chemical reaction between rock and water, and specifically between the iron in minerals such as olivine, and water, giving rise to strongly alkaline hydrothermal fluids bubbling with hydrogen gas^{32,35,36}. This reaction only occurs when water meets the right sort of rock, which is now found mostly in the Earth's mantle, but can also be found close to the spreading centres of the mid-ocean ridges, and even on land where rocks deriving from the mantle have been thrust up onto the land, as in parts of Oman. The fluids produced by the reaction — think of caustic soda bubbling with hydrogen gas — are warm and buoyant. When formed deep down in the crust beneath the sea floor, the hydrothermal fluids bubble back up to the oceans above. There they mix and react with the ocean waters, with their distinct chemistry, and precipitate large and ornate vent structures, tall and spindly, reminiscent of the spires of gothic cathedrals³⁵.

These vents are not chimneys belching black smoke, as in the more familiar 'black smokers', but are more like a mineralised sponge — a labyrinth of interconnected micropores, with thin inorganic walls separating the pores³⁶. The minerals reflect the chemistry of the oceans as well as the hydrothermal fluids, and in modern vents are formed mainly of brucite (magnesium hydroxide), aragonite (calcium carbonate) or saponite (clay)³⁶. At the origin of life, 4 billion years

ago, the oceans were very different in their chemistry³². They contained plenty of dissolved iron, which only accumulates in the absence of oxygen, and they were acidic, with much more dissolved carbon dioxide than in modern oceans. As argued for many years by the geologist Mike Russell, these early alkaline hydrothermal vents must have been natural electrochemical reactors, even having a geochemically sustained proton-motive force³¹. Reactive hydrothermal fluids containing hydrogen gas percolated through pores with catalytic walls containing iron-sulphur minerals, mingling with mildly acidic ocean waters saturated in carbon dioxide³⁷. Acids are (by definition) rich in protons, alkalis deficient, so the steep difference in proton concentration between the hydrothermal fluids and the ocean waters generated a natural proton-motive force. A single pore deep within a vent is then analogous to a bacterial cell, with an alkaline interior bubbling with hydrogen gas surrounded by a thin barrier containing catalytic iron-sulphide minerals, and a more acidic exterior. There is a 'natural' proton-motive force acting across the thin barriers bounding the mineral cell^{23,37}.

But what use is that? There are various possibilities, but the one I like best is that even under abiotic conditions, the proton-motive force helps drive the difficult reaction between hydrogen and carbon dioxide to form organic molecules²⁷. This is not the place to go into the details of the chemistry, but in theory the difference in proton concentration across the iron-sulphide barrier should make both the carbon dioxide and hydrogen more likely to react with each other (Figure 4)²³. This is an experimentally tractable question, and we are trying to test it in the lab (Figure 5)³⁸. Unfortunately, it's premature to say for sure whether it works, and you'll just have to wait and see — like us. That's science. In the meantime, let's consider a few of the implications if it turns out to be true. These touch on the long, peculiar history of life on Earth and may speak to life on other planets too.

The key point is that life on Earth ultimately grows from the reaction between hydrogen and carbon dioxide. Cells can now glean their hydrogen from all kinds of places. Photosynthesis uses the energy of the sun to strip hydrogen from water, for example, and simpler forms of photosynthesis extract hydrogen from sewer gas (hydrogen sulphide) or rusty green iron hydroxides. But the simplest source of hydrogen is the neat gas bubbling out of alkaline hydrothermal vents. These vents should be ubiquitous on any wet rocky planet or moon, and there is good evidence that the same reactions are taking place on Mars as well as the icy moons of Enceladus and Europa³⁹. Beyond our solar system, the intensive search for exoplanets — planets orbiting a distant star — now suggests that there might be tens of billions of wet, rocky, earth-like planets in the Milky Way alone⁴⁰. Even their rock should be the right sort — the mineral olivine is ubiquitous in interstellar space⁴¹, and it likely constitutes a large part of many planets,

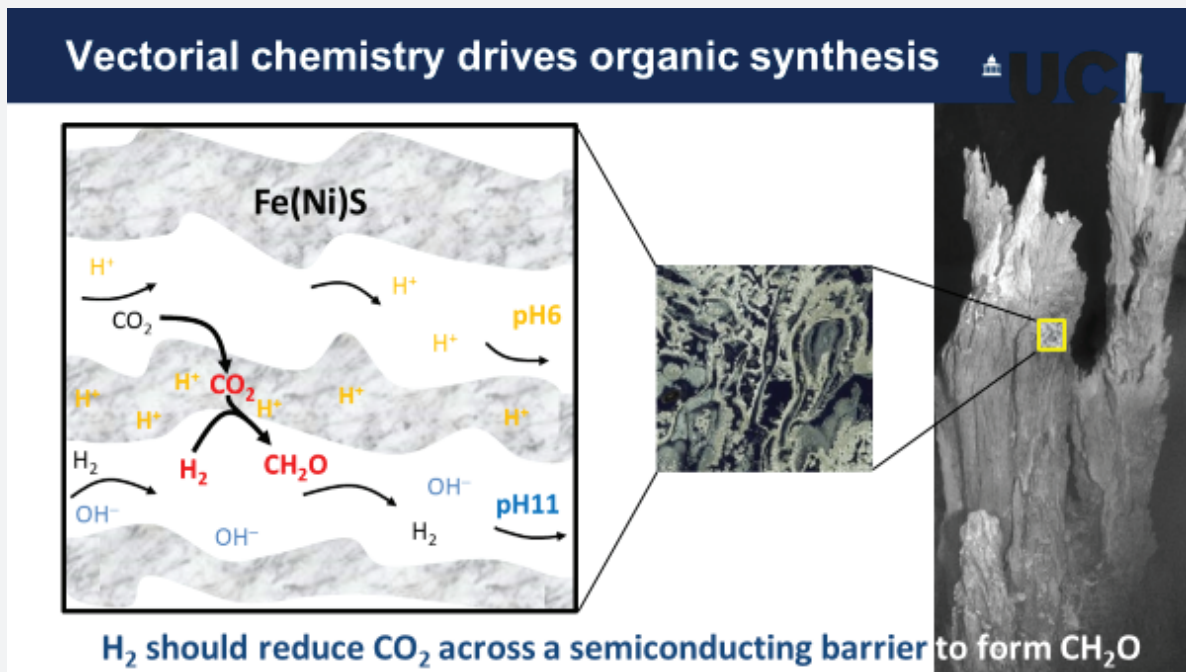


Figure 4. Natural proton-motive force in alkaline hydrothermal vents.

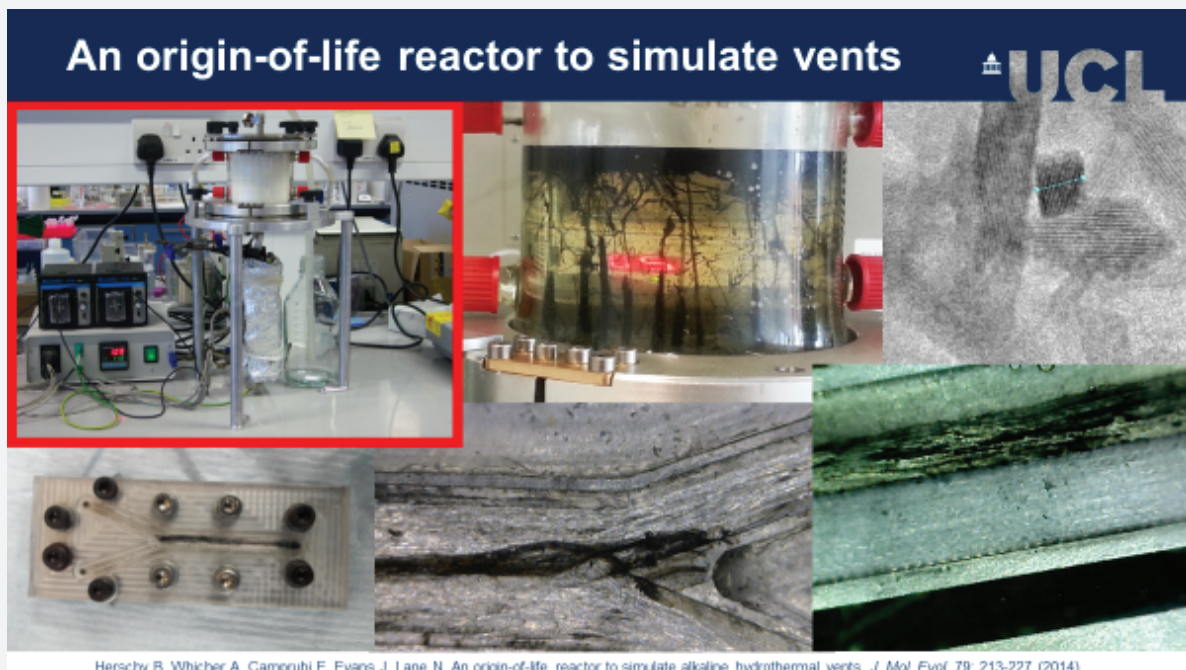


Figure 5. An origin of life reactor to simulate hydrothermal flow.

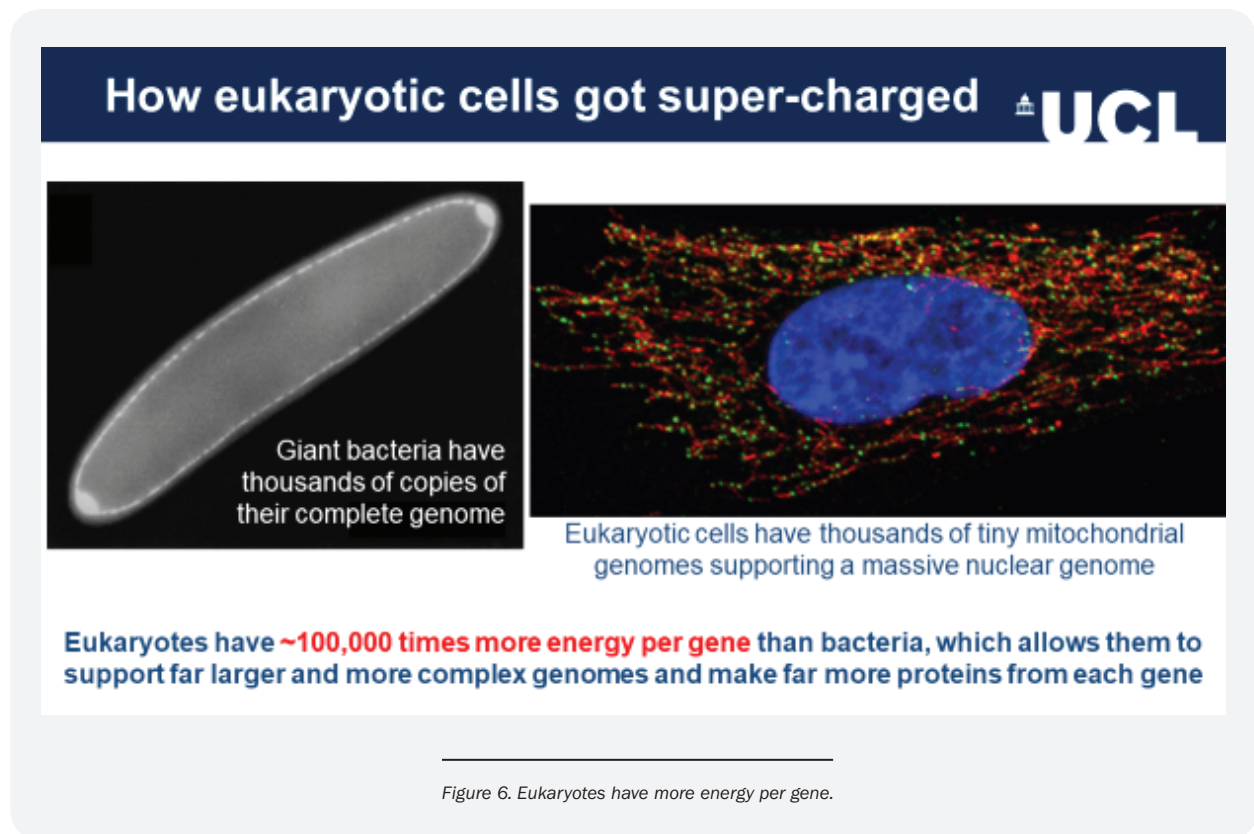
as it does the Earth's mantle. Water, too, is ubiquitous, and carbon dioxide is common in the atmospheres of planets in our own solar system; the fact that carbon is one of the most abundant elements in the universe means that carbon dioxide is likely to be common in the atmospheres of exoplanets too. That's important because any wet rocky world is likely to nurture the origins of life for the same reasons, and so face the same constraints¹³. It would be surprising if bacteria were not found extensively throughout the universe; but what about complex life?

I mentioned that the evolution of complex 'eukaryotic' cells on Earth was probably constrained by cell structure, and specifically the acquisition of mitochondria⁵. The reason arguably relates to the proton-motive force. Bacteria and archaea are enormously versatile in their biochemistry, and can live from almost any imaginable source of carbon and energy. Yet this virtuosity *depends* upon the proton-motive force. Without it they could not adapt so easily to radically different environmental conditions. Could it be that this very dependency, which offered them the world, also stunted their growth and evolution?

There's a good argument to say so — as bacteria become larger, they need more and more copies of their genome to control the potent proton-motive force across the widening

expanse of membrane⁵. That means bacteria gain no energetic advantage from growing larger, and indeed begin to lose the benefits of small size and faster replication⁷. Complex eukaryotic cells escaped from this bind when they acquired mitochondria^{5,7}. Mitochondria were bacteria, not merely extra copies of a genome, and they could compete among themselves to be inherited. They did what bacteria do, and jettisoned genes they didn't need, giving them a slightly greater chance of being inherited. Over evolutionary time, mitochondria lost most of their genes, and became specialised for energy production — each one produces as much ATP as a bacterium, but at a fraction of the normal bacterial overhead costs^{5,7}. And that allowed the host cell to accumulate new genes and to experiment with them in a way that had been unprecedented in the bacterial world^{5,13}. Gene loss from mitochondria gave eukaryotic cells virtually unlimited energy — at least 100,000 times more energy per gene than available to bacteria (Figure 6)^{5,13}. They could now sustain larger genomes, make many more proteins from each gene, and retain large families of duplicated genes, tinkering a bit with each one to craft new functions⁷. It was an explosive change. Energy no longer constrained evolution, and life became a riot of unfettered imagination.

If all that is true, then complex life may be rare elsewhere in the universe: life everywhere will face the same



constraints for the same reasons. It is not easy for bacteria to gain entry to other bacteria or archaea. Once inside, the chances of it all going disastrously wrong are very high⁷. From this point of view, it is not surprising that complex life evolved just once on Earth in 4 billion years of evolution. We are lucky to be here at all. And so if we ever meet any aliens from the other end of the universe, the first question I'd ask them is — do you have mitochondria too? I'll bet they do.

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