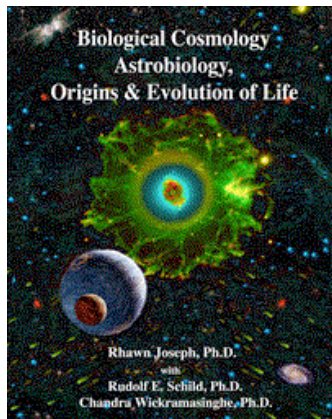


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## Just Like the Universe the Emergence of Life had High Enthalpy and Low Entropy Beginnings

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### Abstract

Life was forced into being to resolve the disequilibrium between atmospheric carbon dioxide and the reduced (electron-rich) solid surface of our planet. Metabolic pathways that hydrogenate carbon dioxide and the phylogenies of selected metalloenzymes that are involved in the synthesis of acetate or methane from CO<sub>2</sub> and H<sub>2</sub> are considered with respect to the initial conditions at ~ 4.3Ga along with the availability of the requisite mineral clusters then in an effort to understand the mechanisms by which life first emerged. A congruence exists between the structures of minerals likely to have been available to the roots of life's evolutionary tree and the metalloenzymes with the longest

pedigree as gleaned both from phylogenetics and the simplest metabolic pathways. These resemblances suggest that the mineral clusters could have simply been co-opted by short peptides to produce proto-enzymes with superior catalytic activities, though still not measuring up to the effectiveness of coded enzymes further up the evolutionary roots. Nevertheless, even though such prototypical enzymes could have facilitated hydrogenations, for geochemistry to transform to biochemistry, still more energy would have been required to quicken the reactions as in the anaerobic microbiological synthesis of acetate and methane today. Such microbes—the acetogens and methanogens— generate a proton-motive force to drive their metabolisms over kinetic barriers. We appeal to a submarine alkaline hydrothermal spring as the most likely place where hydrogen fuel could have first reduced atmospheric carbon dioxide dissolved in the early ocean, with the extra push needed to quicken the hydrogenations coming from the proton gradient acting across the inorganic margins of the hydrothermal mound, i.e., with the ambient proton-motive force. We note that, in strong contrast to the "organic soup" concept, the sources of the energies *and* inorganic materials required for organic life to emerge and complexify in the high enthalpy hydrothermal environment would have been effectively inexhaustible and have been delivered in a low entropic state.

**Keywords:** acetyl-coenzyme A pathway, Big Bang, compartmentation, early evolution, last universal common ancestor, LUCA, origin of life, metalloenzymes, molybdenum, proton-motive force, tungsten

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## 1. Introduction

### *Per aspera ad astra*

For tens of thousands of years, looking up to the stars on a dark night, humans have known there was a Universe (Belmonte 2010; Pankenier 2010; Šprajc 2010). Mankind has come a long way from early myths and explanations of our Cosmos and its history (e.g. Scherzer, 1857; George 2003) to our present understanding of cosmology from what is generally taken to be the Big Bang, through inflation, star and galaxy formation to the structure and workings of the manifold of objects in the sky. It was not until after the combination of insights from general relativity and particle physics that the current cosmological model took shape, eventually incorporating observations such as the cosmic microwave background radiation or the red shifts of distant objects. Cosmology has now come up with a rather detailed description of what the initial conditions of the Universe may have looked like very shortly after the theoretical Big Bang, and how this Universe evolved ever since (Weinberg, 2008). Astronomy experimentally is testing this theoretical description by going increasingly back in time towards our Universe's birth 13.7 billion years ago via the observation of luminous objects at increasing red shifts, i.e. further and further away. For an extended period of time prior to when the first stars ignited, the "conventional matter-side" of our Universe was dominated by neutral hydrogen gas. Unfortunately, this non-ionized hydrogen absorbed photons in basically the full visible spectrum thereby screening off information about the early Universe, by blocking out the transmission of light and leading to what is called the "dark age" of the Universe, that is, the first 300 thousand years to half a billion years after the Big Bang (Ouchi and Atkinson, 2009). One of the main challenges for modern experimental cosmology therefore lies in the search for, and then scrutiny of, sources of information reaching us from within or before the dark age that we might eventually connect up observational and theoretical approaches back to the very beginnings of our Universe, and even before (Carroll, 2006, 2010).

Early humans not only saw the stars above but also the biosphere that they were a part of and similarly made efforts to figure out explanations for how all this life came into being. The geochemical sciences have begun to work out the initial conditions of early planet Earth in the course of the last few decades, i.e. about half a century later than when the foundations of modern cosmology were spelt out. Correspondingly, many scenarios for the origin of life put forward during the 20th century and prior to the major advances of Earth sciences, were based on plausibility arguments rather than on the empirical facts that take into account the physico-chemical boundary conditions of the environment in which life emerged. In contrast to these earlier ideas, the scenario for life's origin in an alkaline hydrothermal setting proposed in 1989 (Russell et al., 1989, 1994 et seq.) directly builds upon the geological and

geochemical evidence. The origin and early evolution of life in the present endeavor shares a number of common features with the Big Bang cosmological model, not least in the difficulties in looking beyond where, for whatever reason, the trail of evidence goes cold (Figure 1) (Koonin, 2007). In the case of life this happens sometime before the emergence of the Last Universal Common Ancestor, the LUCA.

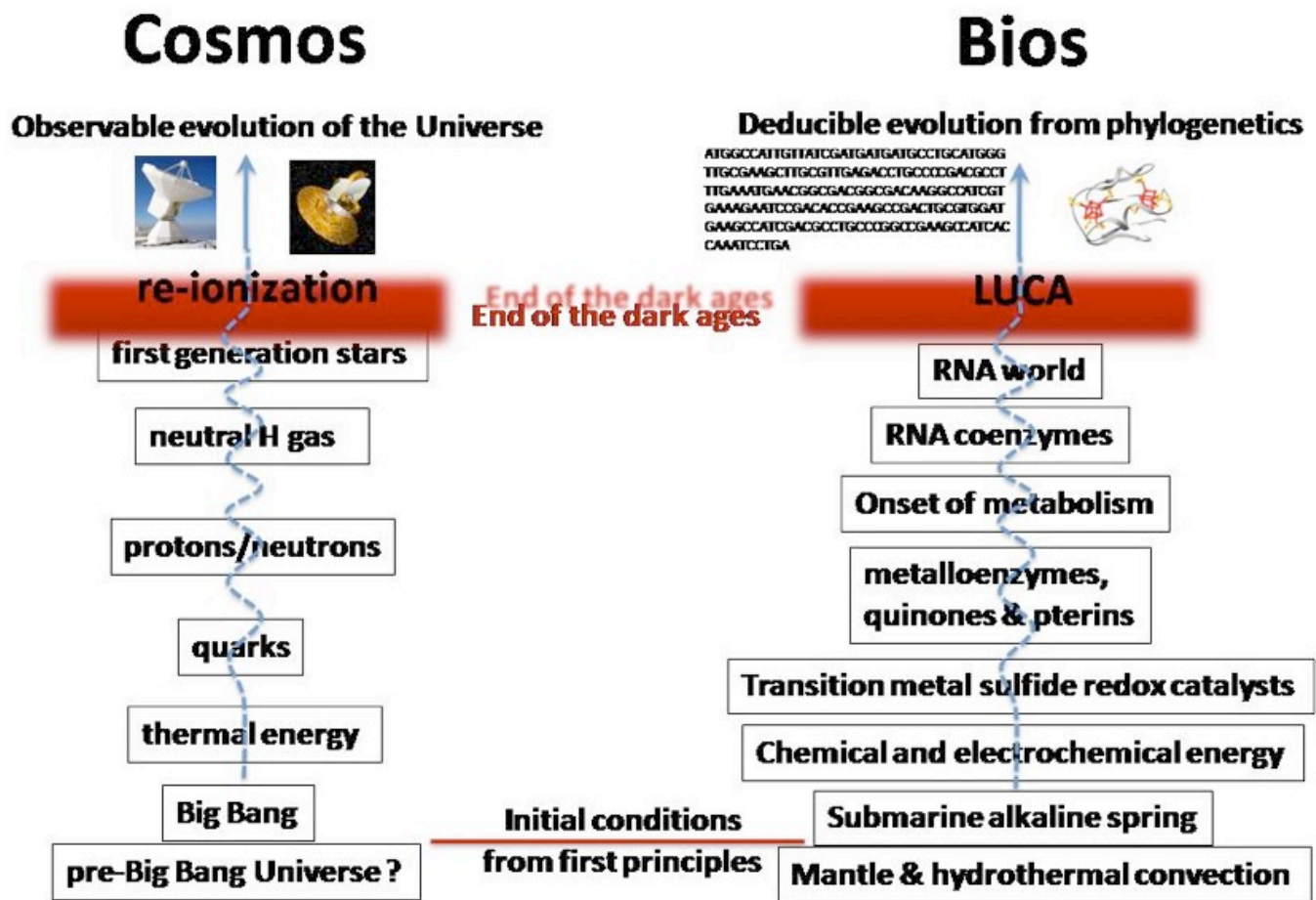


Figure 1. Comparison between the early evolution and complexification of the universe and of life (the bios) (Carroll, 2006, 2010; Martin and Russell, 2007; Koonin, 2007; Ouchi et al., 2009; Nitschke and Russell, 2009; Bromm et al., 2009). The emergence of metabolism marks a discontinuity with aqueous geochemistry and involves the reproduction of synergistic interactions driven by the ambient proton-motive force (e.g., Milner-White and Russell, 2010). A further, though less pronounced discontinuity is met as the RNA world adds the informative processes of replication and coding to the process of reproduction (Koonin, 2007; Yarus, 2010; cf. Trincher, 1965). Vertical distances are not meant to reflect a linear time scale but to emphasize the sequence of events.

## 2. Below the LUCA Horizon

If we accept that the universe operates as a cascade of energy dissipating systems, where on Earth (and elsewhere in the cosmos) might the energies commensurate with life's needs have been first focused and thereby discharged? We are aware of the requirement for boundaries and adversities ('aspera') that limit dissipation and promote selforganization, so that incoming energy might be expended and waste expelled. Thus for life to emerge, a partially open system is needed that can contain well-ordered structures bounded by some kind of wall or membrane—boundaries made continuously from materials in unlimited supply so that compartments could contiguously proliferate

and reproduce themselves in self-similar arrangements. The only inexhaustible materials that may be relied on for this purpose on the early Earth are silica, calcium, magnesium and/or carbonate that precipitate from aqueous fluids to form the necessary super- and infra-structures (Russell and Hall, 2006). The early ocean floor offers a setting for such a compendium of inorganic compartments to grow. Here, alkaline hydrothermal fluids of moderate temperature fed by a convective system of long duration, interact with the somewhat acidic ocean to precipitate entities comprising these and other molecules rendered insoluble as alkaline and acidulous waters meet, the entirety resulting in compartmentalized mounds growing on the floor of the Hadean Ocean (Figure 2).

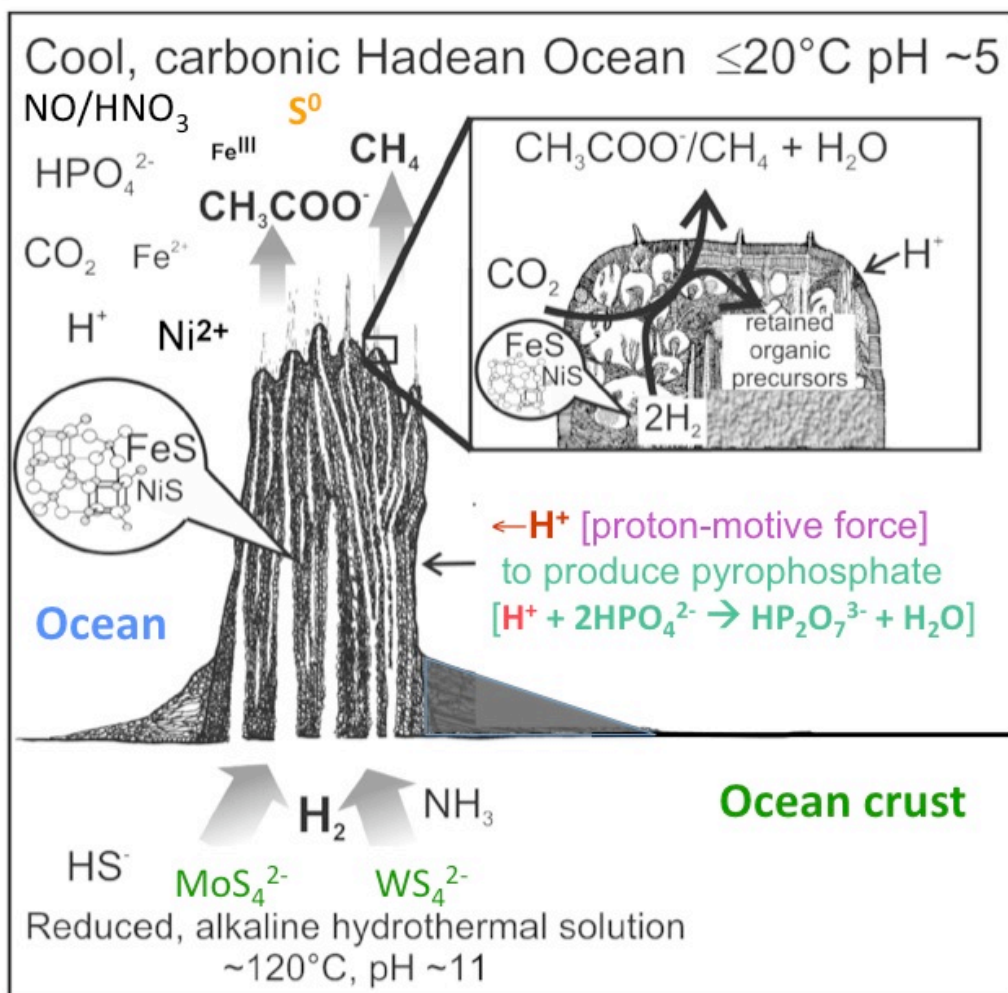


Figure 2. The hydrothermal mound where organic ions were produced, retained, reacted and self-organized to emerge as protolife i.e., where chemical and electrochemical energies were best discharged (cf., Morowitz and Smith, 2006). The earliest metabolizing system housed in inorganic compartments and the emerging autotrophs using similar mechanisms would have processed hydrogen and carbon dioxide to make acetate or methane (recast from Russell and Martin, 2004; Russell and Kanik, 2010).

Once these compartments are in place, disequilibria between hydrothermal hydrogen— the electron carrier bearing electrons from the oxidation of  $\text{Fe}^{\text{II}}$  (and traces of  $\text{Fe}^0$ ) from the crust—and volcanic  $\text{CO}_2$  dissolved in the ocean, may be resolved. The carbonic acid ocean also happens to induce a proton gradient wherever an alkaline solution is encountered—another, though all-transforming, potential energy source. The particular environment where these energies may have best been discharged over 4 billion years ago is at this mound, forming over the long-lived submarine alkaline hydrothermal spring. The mound acts as a catalytic reactor and affinity column where steep thermal and electrochemical gradients are induced that could drive a variety of chain reactions and concentration

mechanisms that, in certain circumstances, could lead to the onset of metabolism and eventually life (Russell and Hall, 1997, 2006; Baaske et al., 2007; Russell and Martin, 2004; Nitschke and Russell, 2009). There would be a myriad of such structures formed at alkaline springs in the early ocean, many of them going to waste, whereby the buoyant hydrogen would merely gravitate back to cold deep space. But some would act as omphali or hatcheries of life, though as we can glean from phylogenetics, there appears to have been only one singular surviving universal common ancestor. What were some of the characteristics of such reactors or hatcheries?

Conscious of David Garner's stricture that it is the inorganic elements that bring organic chemistry to life we consider the critical role that some of these elements must have played in the emergence of biochemistry from geochemistry (Martin and Russell, 2007). For  $\text{CO}_2$  to be reduced to organic molecules and for these to form polymers requires the involvement of electrons and protons. Our aim here is to show how the initial pathways to the simple components of a primitive organic cell might be beaten and with what— bearing in mind that survival requires containment across several scales. The so-called acetyl-coenzyme A pathway is the simplest of the known metabolic pathways and involves the least expenditure of energy (Fuchs et al., 1989; Berg et al., 2010). Its inputs are to biosynthetic molecules ordered in such a way as to maximize the outputs or products (see for example figures 6 and 7 in Russell and Kanik, 2010). The final products or effluents are likely to have been either acetate or methane, at least at first, though perhaps accompanied by sulfide and nitrogen. One tributary to the acetyl-CoA pathway involves the reduction of  $\text{CO}_2$  to a methyl group,  $-\text{CH}_3$ , the initial step requiring a molybdenum or tungsten sulfide complex (Figure 3). The other tributary leads to the simple reduction of  $\text{CO}_2$  to  $-\text{CO}$  using an iron nickel-sulfide complex (Figure 3). These two tributaries to the acetyl-CoA pathway converge at another nickel-sulfide cluster not unlike that involved in the initial reduction of  $\text{CO}_2$  to  $\text{CO}$ . Further steps use a complexed cobalt ion. Below we describe how these metals and sulfur might be supplied to the hydrothermal mound.

#### *Sources and uses of the Mo, W, Fe, Ni, Co sulfide constituents*

Given the relative scarcity of molybdenum ( $Z = 42$ ) and tungsten ( $Z = 74$ ) it is perhaps remarkable to find that these transition metals—available only in protoplanetary discs of third or fourth generation stars—were vital for a host of 2-electron redox reactions in the Last Universal Common Ancestor (Figure 3, top right scheme). In particular these elements were and are indispensable for overcoming the initial steps—those requiring high activation energies—along the mesothermal and hyperthermal tracks of the acetylcoenzyme A pathway respectively—the pathway that initially generated either acetate or methane (Fuchs, 1989; Thauer, 1998; Adams, 1998; Maden, 2000; Schulzke, 2005; Zerkle et al., 2006; Martin and Russell, 2007; Russell and Kanik, 2010, figures 6 and 7). At first sight the vanishingly small concentrations of these elements in acidic hydrothermal solution and in anaerobic Hadean Ocean water seems to pose a problem for early biochemistry (Douville et al. 2002; Williams and Fraústo da Silva, 2003). However, an advantage of the alkaline hydrothermal hypothesis is that these elements—soluble at high pH—would have been supplied directly, if present in the source rock, to the interiors of the compartments comprising the hydrothermal mound in the alkaline hydrothermal solution as oxythioselenomolybdenum or oxythioselenotungsten anions (Pourbaix, 1963; Garrels and Christ, 1965; Humenick et al., 1983; Helz et al., 1996; Newsom et al., 1996; Seward and Barnes, 1997; Becker et al., 2004). Here they would precipitate as mixed valence (IV and/or VI) sulfides/selenide/oxides as pH dropped, or be adsorbed in either state onto sulfides, clays, green-rust or organic molecules newly generated in the same milieu (Goldberg et al., 1998; Erickson et al., 2000; Bostick et al., 2003; Algeo and Lyons, 2006; Dahl et al., 2010). Although not analyzed for in fluids at a modern example of the kind of system we imagine for the early Earth, *viz.*, the Lost City springs (Kelley et al., 2001; Martin et al., 2009) empirical evidence for such a delivery lies in the fact that both elements occur in certain low temperature hydrothermal enrichments or groundwaters in mafic and ultramafic rocks where redox conditions would have been at the hydrogen/water boundary, *i.e.*, similar to conditions in the ancient ocean crust (Nekrasov et al., 1982; Appel, 1994; Arnórsson and Óskarsson, 2007; Russell et al., 2010).

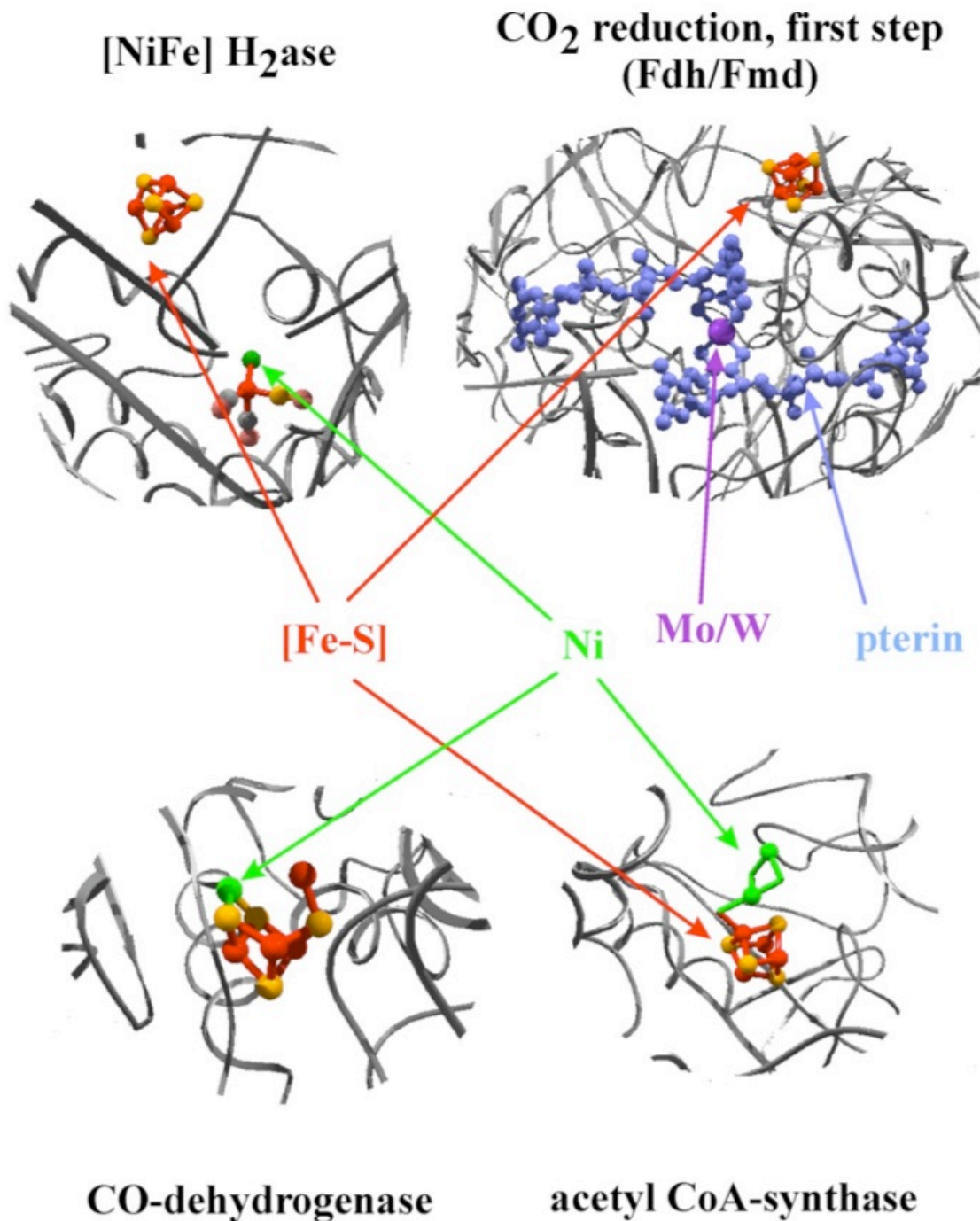


Figure 3. Active metal centers of key metalloenzymes involved in CO<sub>2</sub>-reduction by H<sub>2</sub> via the acetyl-CoA pathway and their immediate protein environment.

Unlike molybdenum and tungsten, the three other transition metals, iron and nickel (involved in the acetyl-CoA pathway, Figure 3) and cobalt (used in acetate and methane production), are all insoluble in alkaline solution. Instead, these transition metals are introduced to the carbonic ocean through ~400°C, sulfur-poor hot springs operating extensively at ocean ridge-crests (Lambert et al., 1998; Charlou et al., 2002; Douville et al., 2002). Once in the Hadean Ocean, these elements are likely to have remained supersaturated given its acidulous carbonic nature (pH between 5 and 6) only to be precipitated as sulfide clusters on meeting alkaline hydrothermal spring waters diffusing from the margins of the hydrothermal mound (Walker, 1985; Kasting, 1993; Lowell and Keller, 2003; Macleod et al.,

1994; Morse and MacKenzie, 2006; cf. Sigurdsson et al., 1987) (Figure 3 top left and bottom right and left). How might these various transition element sulfide clusters or nanocrysts have been put to work, and what can enzyme phylogenies tell us about the obscured roots of the evolutionary tree?

The ideas about the emergence of life we develop here have a long history. Feeling the way back to the root ends of the evolutionary tree, Traube (1867) and Leduc (1911) thought the deepest roots to have inorganic, perhaps silica, sheaths. And Eck and Dayhoff (1966) supported by Hall et al. (1971) found iron sulfide to lie at their very tips. The 4Fe-4S-proteins were held to be the enzymes with the longest pedigree, though the Ni-Fe hydrogenases are probably of the same age (Eck and Dayhoff, 1966; Volbeda and Fontecilla-Camps, 2005) (Figure 3 top left and bottom right and left). Moreover, oxidized 4Fe-4S-proteins (in ferredoxins) were, according to Daniel and Danson (1995), the earliest biological catalysts to mediate heterotrophic catabolism prior to the appearance of NAD(P)H. Exploration of these deep evolutionary roots has turned up further metalloenzymes wherein modules are mixed and matched to the other requirements of early metabolism (Beinert et al., 1997, Baymann et al., 2002; McGlynn et al. 2009). The iron sulfide structures found in these enzymes are convergent with those in metastable minerals likely to have occurred in the environment succoring early growth; mackinawite ( $[\text{Fe}_2\text{S}_2]_n$ ) and greigite ( $\sim[\text{NiFe}_5\text{S}_8]_n$ ) (Russell et al., 1989, 1994; Russell and Hall, 2006).

### *Provenances of energy and bulk materials*

Geologists since Darwin have known that the roots of the evolutionary tree were supplied with carbonic waters, and that the  $\text{CO}_2$  was originally exhaled from volcanoes (Osborn, 1917; Goldschmidt, 1952; Walker, 1984). And the ultimate fuels fed to the roots ends were hydrogen and protons (Russell et al., 1994). The overall reaction between hydrogen and carbon dioxide dissolved in ocean waters is theoretically exergonic. Indeed, aqueous geochemistry alone can facilitate the synthesis of methane, though tardily, in a common hydrolysis reaction that takes place in oceanic crust known as serpentinization (Russell et al., 1989, 2010; Proskurowski et al., 2008; McCollom and Bach, 2009). And taking electrons directly from nanoparticles of native iron rather than *via* the hydrogen carrier gas, acetate has been generated at the moderate temperatures to be expected in the alkaline hydrothermal system (He et al., 2010). It is just that life can make these reactions go so much more quickly. How so? Of course it is partly a matter of catalysis. As mentioned above, the enzymes catalyzing these reactions in extant species contain Ni, Fe, Co, Mo and/or W in their active centers. So once we have figured out how these inorganic centers promote catalysis in the fancy protein suits of the respective enzymes and how they are related to their still unclad precursors, we are on the way to understanding why life could expedite the methane or acetate reactions so effectively.

But even mere catalysis is not enough. Free energy values for the various reduction steps from  $\text{CO}_2$  through  $\text{HCOO}^-$  (formate) all the way to acetate or methane show that, while the full reaction to the end product is exergonic, its first step, i.e. the reduction to the formyl group, is substantially endergonic. Indeed, the comparison with an enzyme performing this first reaction step, only in reverse, indicates that the pH gradient building up at the barrier which separates the hydrothermal fluid from the ocean waters may be required to push the reaction over the barrier towards the formation of the formyl group (cf. Andrews et al., 1997). The mechanism of this extra push is still not worked out in detail but it seems very likely to us that it is somehow related to the versatile redox properties of the two-electron redox metals molybdenum and tungsten, properties which may appear counterintuitive or almost magical to someone unfamiliar with the equations of electrochemistry. Under specific circumstances, these redox centers in fact can split up their two individual redox half-reactions (i.e. single electron redox changes) in the way to "steal" reducing power from one step and inject it into the other step which then can transfer an electron to an acceptor with an electronegativity nominally even exceeding that of the donor. We have discussed this phenomenon in a previous article (Nitschke and Russell, 2009) and only want to add here that in analogous systems it has been shown that it is the electrostatic environment of the redox center which can induce these peculiar redox properties. It therefore does not seem far-fetched to us to assume that the influx of  $\text{H}^+$  ions towards the Mo/W catalytic centres provides the crucial energy accounting for the efficiency of this reaction and heralding the emergence of the first metabolic pathways. Such proton energy has been termed the proton-motive force, and is a feature of all autonomous life forms (Mitchell, 1967, Harold, 1986). In the same vein, this rationalizes why both Mo/W and the chemiosmotic potential are

indispensable for quickening the sluggish inorganic reduction of CO<sub>2</sub> to the high rates observed in living systems.

We have already noted that molybdenum and perhaps tungsten—although supplied in the alkaline hydrothermal solution—would have been in short supply in the anaerobic early ocean (Williams and Fraústo da Silva, 2003). Indeed, once reduced organic ring compounds were available that could take or dispense electrons, life would have been freed from the reliance on rare elements for the less challenging catalytic steps. Intriguingly both the thermodynamically uphill steps as well as the down-slope path from CO<sub>2</sub> to the methyl group involves organic ring molecules known as pterins (Thauer, 1998; Maden, 2000; Martin and Russell, 2007). However only those pterins involved in the uphill reactions have a molybdenum or tungsten catalytic center; the downhill pterins are without. We speculate that at the emergence of life the metals catalyzed all the steps of this tributary path, but later methanogens and acetogens could afford to dispense with them for the downhill steps.

### *The organic takeover*

We have seen how compartmentation, as a prelude to cellular life, was all-important for putting electrochemical and thermal gradients to work and for the retainment and selforganization of useful product. We have also touched on how metals and metal sulfide catalytic centers are ligated to particular organic structures (Figure 3). While it is beyond the scope of this paper to detail how nucleic acids and proteins were first formed and eventually took over the major tasks of metabolism, coding and guiding reproduction, here we merely emphasize that rendering the inorganic catalysts more efficient would also have required their sequestering i) to maximize their surface-to-volume ratio and prevent growth to nanocrystalline proportions, ii) to protect them from dissolution while allowing access to the catalytic centers and iii) to modulate their redox states and activities. The process of polymer growth and how peptides could act as sequestering agents in the form of partial compartments or "nests" is explained in a companion paper (Milner-White and Russell, 2010). Suffice to say here that for amino acids to link up as peptides requires another inorganic agent, *viz.*, phosphate. Phosphate exhaled from volcanoes would have been rained into the acidulous ocean and precipitated along with other entities as pH rose at the margins of the alkaline hydrothermal mound (Yamagata et al., 1991; Hagan et al., 2006; Russell and Hall, 2006). Once there amongst the other precipitates, the activity of water would have been low such that the ambient protonmotive force would have converted orthophosphate to its condensed form, pyrophosphate. Pyrophosphate energy can be spent by condensing amino acids to peptides which, in turn, can sequester further phosphate that it might be recharged with the proton-motive force to pyrophosphate again (Milner-White and Russell, 2010). Thus there is a synergistic relationship between peptide growth and pyrophosphate formation. Left-over peptides can then organize themselves around the metal sulfide centers, so improving their catalytic propensities as well (Milner-White and Russell, 2005, 2008). At the same time they could have acted as trusses and binding agents within the inorganic compartment walls while retaining active inorganic clusters, a step toward taking over the role of cell wall and membrane which is likely to have been proteinaceous anyway in the first instant (Milner-White and Russell, 2008).

Some of the nests harboring the inorganic "eggs" look very similar to the way these inorganic entities are sequestered by extant proteins. Of course, protein production requires coding by chains of nucleic acids. Prior to the LUCA it is likely this was facilitated simply by RNA arranged in the form of a nucleus to what is now the ribosome. Hsiao et al. (2010) have "peeled back" the large subunit of the modern ribosome to reveal its peptidyl transfer center which they take to be a molecular fossil predating the LUCA. The ribosome is noted for the extraordinarily conservation of RNA sequence, especially toward its core. While the center is devoid of protein it does include an unstructured peptide of uncertain function. But given the reliance of emergent life upon the inorganic elements it is intriguing to note that magnesium too is strongly enriched in the center of the large subunit where, in a framework of six ions, it acts as the RNA binding unit even to this day (Hsiao and Williams, 2009). Though at lower concentrations than at present, magnesium ions would have been available in the Hadean Ocean and at the mound, supplied from low temperature submarine springs and seepages and bicarbonate spring waters (Barnes and O'Neil, 1969; Mottl and Wheat, 1994; Elderfield and Schultz, 1996).

### **3. The LUCA Barrier**

It cannot have escaped the attention of readers having managed to hold on to this point that, while the direct link between present day's metalloenzymes and the inorganic minerals as well as between the simplest carbon fixation pathways (the above mentioned aceto- and methanogeneses) and the obvious primordial redox reaction of H<sub>2</sub> and CO<sub>2</sub> is straightforward, the subsequent evolution of metabolism described in the preceding paragraphs appears to be on less certain ground. Why is that? Why can't we just take the genes of the respective enzymes, determine their genealogy and thus retrace their evolutionary history back to the origins, very much as gene sequence-based phylogeny has elucidated the temporal and spatial origins of our own species and its subsequent migratory patterns? Evolutionary biology of the microbial world has in fact tried to follow the footprints in the paths of enzymes' evolution back to their roots (e.g. Castresana and Moreira, 1999). However, a specific characteristic of the early evolution of prokaryotes, the microbes which are the ancestors to all complex life, is to present an unfortunate barrier to this approach. "Family trees" of biological species and enzymes in fact converge at the Last Universal Common Ancestor. LUCA however, is predicted from these "genealogies" to already be a fully-fledged versatile organism, i.e. complex life quite evolved from its origins. This surprising observation is usually rationalized by unhampered transfer of genetic material within a community of primordial cells constantly scrambling the genetic heritage of this community and thereby to a large extent wiping out the deeper phylogenetic roots of these systems. Not unlike the quest of cosmology to read the past of the Universe beyond the re-ionisation horizon, gaining information about the origin of life via this top-down approach requires shining a light onto the dark age of the pre-LUCA world (Figure 1).

So are we really blind to how enzymes and metabolic reactions may have evolved prior to LUCA? There is indeed phylogenetic information reaching us from beyond the barrier and this is due to the fact that the "one-enzyme, one function" rule has been pitilessly demolished by evolutionary biology. Enzymes promoting a specific reaction have in the vast majority of cases "paralogs" which perform other, sometimes wildly different, tasks and therefore have to be grouped into so-called "superfamilies". Just to give an example, members of the superfamily which belongs to the above-mentioned enzyme performing one of the first steps in the reduction of CO<sub>2</sub> to acetate involving molybdopterin, also catalyzes a myriad of different reactions ranging from the reduction of polysulfides to the oxidation of arsenics (Duval et al., 2008). Whereas for a given family, LUCA represents the observation horizon, the composite genealogy of enzyme superfamilies can tell us which pathways have already bifurcated prior to the LUCA and in general which ones were there and which ones weren't and, moreover in certain cases, how they derive from each other (Vignais et al., 2001; Brugna-Guiral et al., 2003; Baymann et al., 2003; Duval et al., 2008; Ducluzeau et al., 2009). Then why not apply this approach to the very earliest metabolic pathways, that is, acetogenesis and methanogenesis? The enzymes catalyzing the first step to the formyl group are the molybdopterin enzymes mentioned above and referred to as formate dehydrogenase (Fdh) and formylmethanofuran dehydrogenase (Fmd) in aceto- and methanogenesis, respectively. Are Fdh and Fmd the same enzyme or do they represent two sister families in the vast superfamily and, if so, how are they related to each other? Figure 4 shows the composite phylogeny of these two enzymes. The topology of this family tree strongly suggests the following scenario: acetogenesis certainly has evolved prior to LUCA since the enzyme tree shows a clearcut congruence with the tree of species bifurcating into to distinct "domains" of organisms up from LUCA, the so-called "Bacteria" and "Archaea". The methanogenic enzyme does not show this pattern. It seems to have branched-off early, i.e. prior to LUCA from the acetogenic pathway but found its way only into the archaeal domain while being laterally transferred to Bacteria at much more recent times (and used by these for related but differing purposes). Although these preliminary observations need to be substantiated by more "densely leafed" trees, they support acetogenesis as the more important and possibly older ancestral pathway of carbon fixation (Martin and Russell, 2007; Yung et al., 2010).

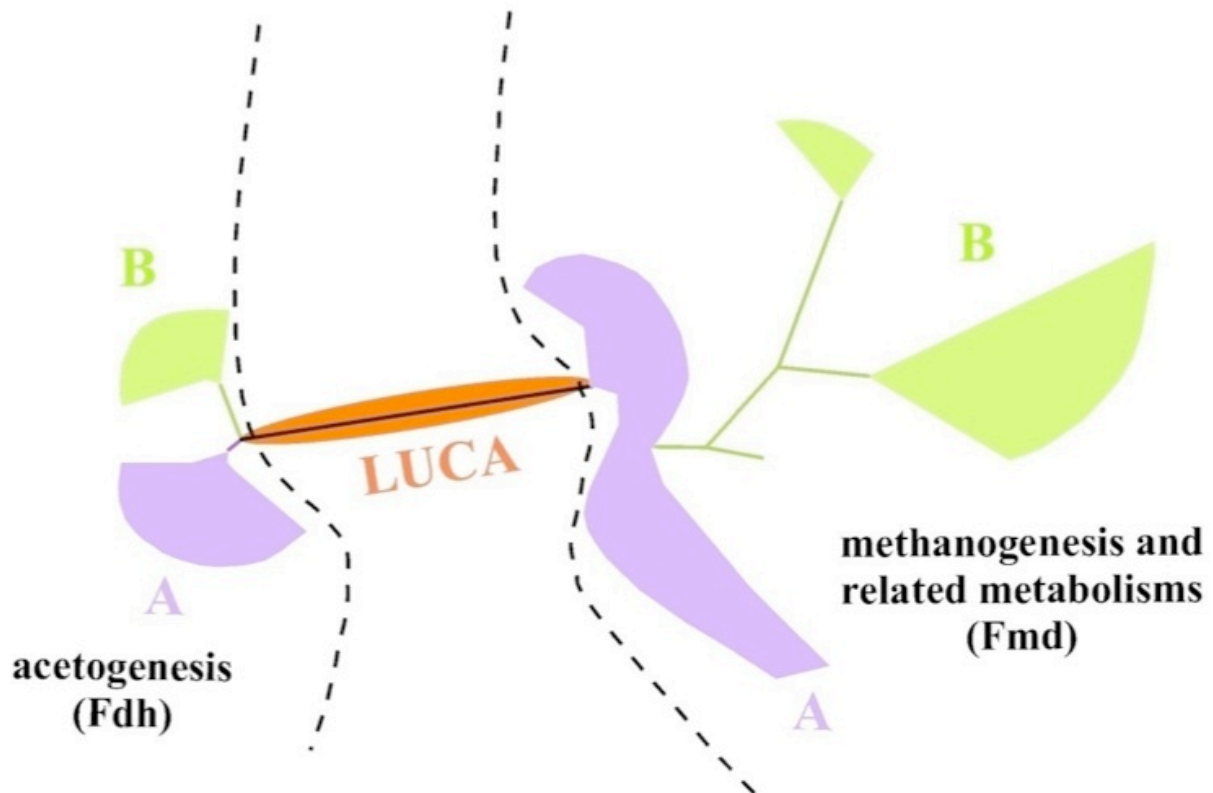


Figure 4. Schematic composite phylogeny (obtained by the neighbor-joining algorithm) of the large catalytic subunit in the molybdopterin enzymes formate dehydrogenase (Fdh) and formylmethanofuran dehydrogenase (Fmd) involved in aceto- and methanogenesis as detailed in the text. A (purple) and B (green) stand for Archaea and Bacteria, respectively. The detailed tree together with sequences, alignment details and tree-building procedures will be published in a dedicated article.

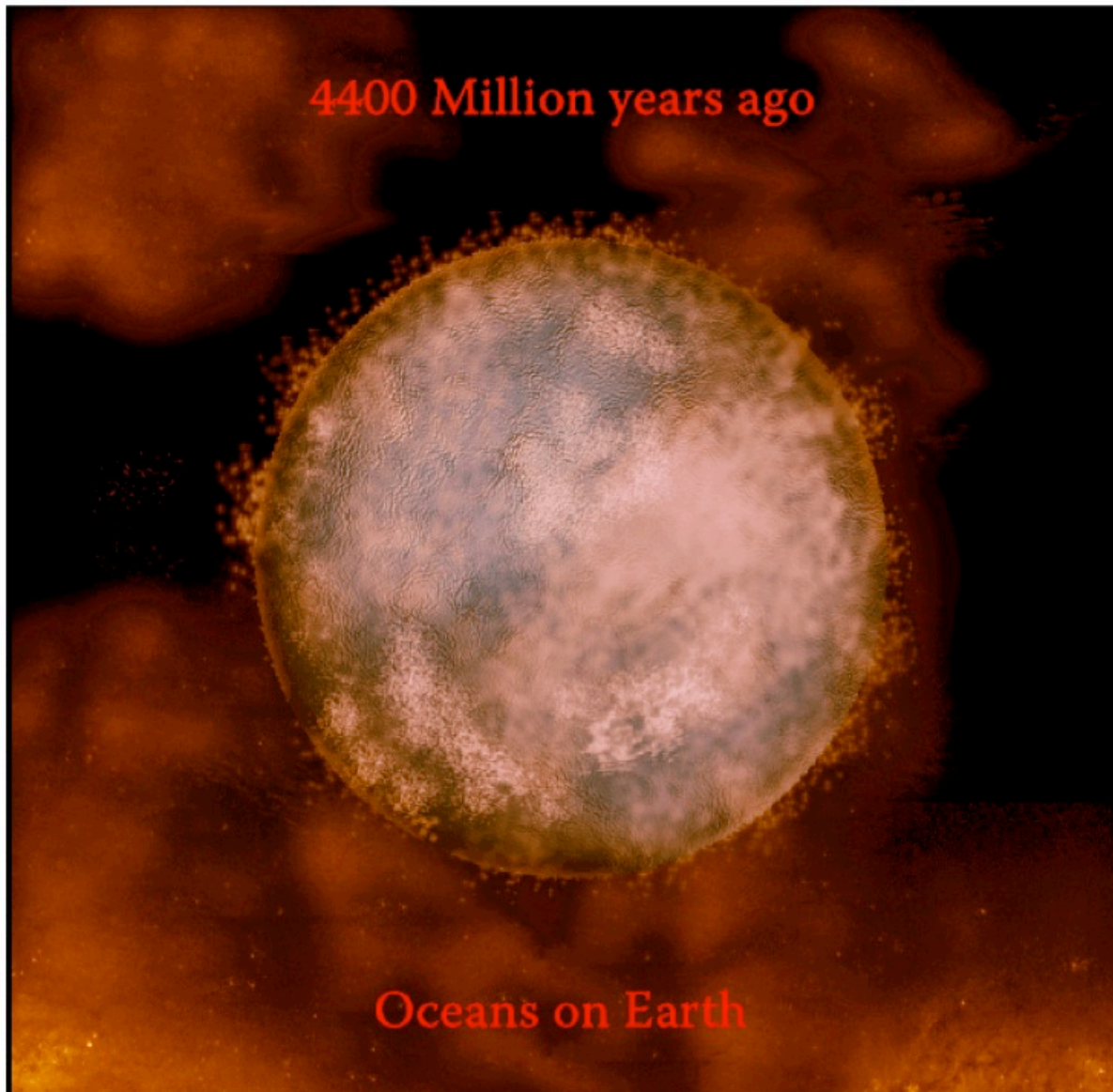


Figure 5. Planet Earth—a water world—between 4.4 and 4.3 Ga indicating its turbulent anaerobic atmosphere and hydrosphere subject to high UV and cosmic radiation and continual bolide impact. Modified from Rosing et al., 2006, with permission.

In order to close the gap step by step between the lessons gathered from extant life and the initial geochemical conditions we can bear in mind a more cosmic view of the problem that faces us (Figure 1). Terraqueous globes such as ours are effectively giant electrochemical cells with a potential output of up to a thousand millivolts or more (Russell and Hall, 1999; Ducluzeau et al., 2009). The negative electrode would comprise any part of the Earth's ocean floor where the electron rich interior surfaced, while the dispersed positive electrodes consist of the various more oxidized molecules—the gases such as  $\text{CO}_2$ ,  $\text{NO}$  and  $\text{SO}_2$  produced mostly at volcanoes and dissolved in the acidulous ocean as well as iron photo-oxidized to the ferric state at the ocean surface. All these entities, including the protons, could act as acceptors of electrons if they were to be accessible to the electrons available in those reduced iron minerals occupying the lithosphere. The question then arises, is there a particular place on Earth where this chemical and electrochemical energy could best be discharged? Again we are led to consider the alkaline submarine mound. It is here where hydrothermal hydrogen delivers the electrons from the reduced iron minerals in the oceanic crust as they themselves are oxidized with convecting ocean water. Thus, in electrochemical terms the mound

constitutes a hydrogen electrode. The semiconducting metal-bearing nanocrystals dispersed within the inorganic structures comprising the mound now split the hydrogen to electrons and protons which are conducted and transferred to reduce carbon dioxide to the organic molecules that form the components of emerging life. Or to put it yet another way, the giant electrochemical cell that is our planet may be broadly compared to an autotrophic microbe—reduced and basic within and oxidized and acidulous without. Thus we may imagine that life bubbled off the wet solid surface to quicken the reactions that were already being driven, though slowly, by the potential energies mentioned above (Figure 5 and 6). This bubbling off of a low entropy cell from an electrogeochemical fluctuation is reminiscent of the possible origin of the Universe as a false vacuum bubble born of a quantum fluctuation from the pre-Big Bang Universe (Figure 1) (Carroll, 2006, 2010; Koonin, 2007).

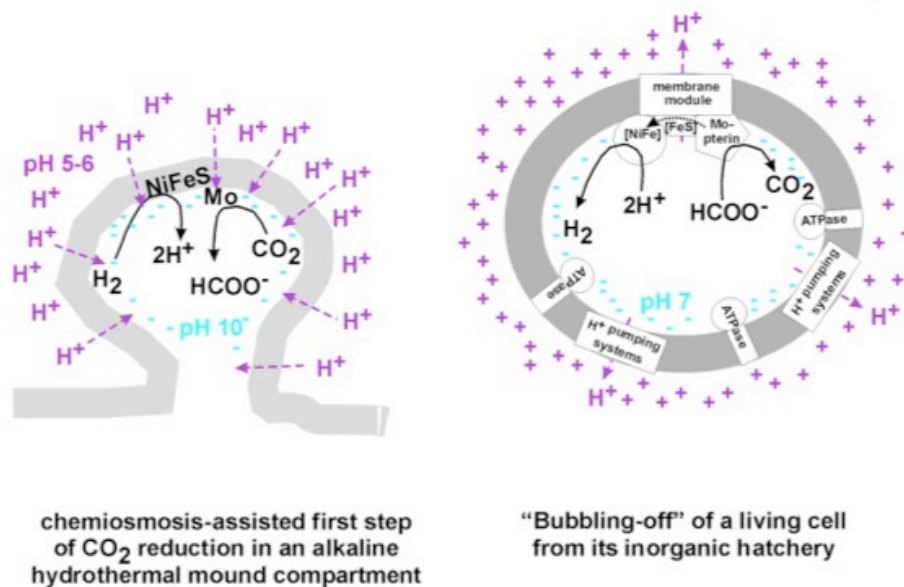


Figure 6. Sketches to show the notional "bubbling off" of life from the Earth's solid surface while maintaining a similar polarity of proton gradient (cf. Figure 5). a) demonstrates how the ambient protonmotive force (protons in the acidulous ocean are dammed up against the outer walls of the hydrothermal mound) acts across the boundary of a single compartment housing an emerging metabolism in alkaline solution derived from the hot spring while b) demonstrates the (necessary) replenishment of the proton-motive force acting across the membranes of living cells with the same vectors as the earliest metabolist as in a), though in this case generated through the concomitant outflow of protons and electrons to maintain charge balance. Electrons end up on the electron acceptors on the outside of the cell while the protons return back towards the cell's alkaline interior thereby driving substrate uptake (via membrane transporters) and energy storage (via  $H^+$ -translocating pyrophosphatases or ATP synthase). Based on Nitschke and Russell (2009) and Lane et al. (2010).

#### 4. Conclusions

(1) Very much as the observation of the Hubble constant sparked the Big Bang model, the alkaline hydrothermal origin of life scenario was inspired by what extant life looks like. For example, the fundamental functional entities catalyzing life's metabolism are in the vast majority of cases metals or metal clusters resembling minerals likely to have been available at the time life came into being on this or any other terraqueous globe massive enough to have retained a  $CO_2$  atmosphere (Russell and Hall, 1997, 2006; Russell and Kanik, 2010; Yung et al., 2010). Fundamental biological carbon fixation pathways, i.e. those allowing for the actual accumulation of "biomass" from the inorganic environment, strangely resemble simple inorganic redox equilibrations (Martin and Russell 2007) some of which have actually been observed in present day alkaline hydrothermal sites (e.g., abiotic methane at the Lost City alkaline hydrothermal springs; Kelley et al., 2001; Proskurowski et al., 2008). Moreover, the basic principle of energy

harvesting in all extant life, i.e. chemiosmosis (Mitchell, 1967) is a natural feature of the microcavities in hydrothermal mounds proposed to have been the hatchery of life (Russell et al., 1994; Nitschke and Russell, 2009; Lane et al., 2010).

(2) Unlike earlier "soup" scenarios stipulating accumulation of required basic building blocks in an open vessel such as a pond, lagoon or even an ocean, the hydrothermal mound hypothesis predicts a quick, explosive taking-off of life's complexity (Koonin, 2007). Both the Cosmos in the Big Bang cosmological model and the Bios in the chemiosmotic hydrothermal setting emerge from extremely high-energy initial conditions (Figure 1). For the Big Bang, this energy was thermal ( $10^{11}$  K) whereas in the mound it was chemical ( $\Delta G^{\circ} = 130$  kJ/mol) and electrochemical ( $\leq \sim 1,000$  millivolts) (Russell and Hall, 1997; 2006; Maden, 2000; Filtner et al., 2003; Ducluzeau et al., 2009). For both these singular cases, the high-energy start allowed for an explosively rapid early evolution. In both cases too, most of this energy ended up in high entropy forms (radiation in the early Universe, heat and planetary oxidation due to escape of  $H_2$  to space in the origin of life) (Carroll, 2010). Only an infinitely small amount of the total initial energy was converted into substantial decreases in entropy (matter and its inhomogeneous distribution in one case and metabolic pathways in the other) as allowed by the second law of thermodynamics (see discussions in Baaske et al., 2007; Nitschke and Russell, 2009; Pulselli et al., 2009). It is precisely this analogy in the emergence of order and structure from chaotic behavior which distinguishes the 'low entropy feed to the alkaline hydrothermal mound scenario' from previous hypotheses which all have life originating in a high entropy and low enthalpy environment. They therefore suffer from a lack of a thermodynamically viable driving force for the emergence of life which thus becomes an unlikely event comparable to the "infinite monkey theorem" with respect to typing the works of Shakespeare. In the thermodynamic settings of the alkaline hydrothermal mound scenario, by contrast, the emergence of metabolism serving to collapse the chemical and electrochemical disequilibria becomes inevitable: life cannot help emerging and extensively complexifying in this setting. The appearance of intricate feedback-controlled autocatalytic cycles then merely becomes a consequence in the autogenic alkaline hydrothermal model rather than a desperately crucial prerequisite for bootstrapping life out of the low enthalpy, high entropy environments of the older origin of life hypotheses (*pace* Luisi, 2006; Gibson and Wickramasinghe, 2010).

(3) Finally, we find the empirical approach of trying to work one's way back to the very roots of life from analyzing and comparing the setup, functional principles and phylogenies of selected enzymes faces a fundamental barrier analogous to the hydrogen re-ionization time horizon in cosmology. Our present contribution attempts to characterize the most fertile geochemical ground where these roots are most likely to have plumbed. For this we have unearthed the mineral structures most congruent with the active centers of the metalloenzymes and phosphatases and seen how they could have been co-opted, given the synergistic generation of organic molecules and polymers, to act as their nests that they might use the geochemical and electrochemical energies which happen to be commensurate with what we know of life's requirements for growing in the dark, safe from the deleterious effects of solar and cosmic radiation, bolides and the vagaries of the early Earth's climate. We conclude that a long-lived submarine alkaline spring issuing into an acidulous carbonic ocean acts as the best incubator for life's emergence—an incubator that attracts the discharge of those energies of the electrochemical cell of this, and any other terraqueous planet, massive enough to generate and hold onto a carbon dioxide atmosphere.

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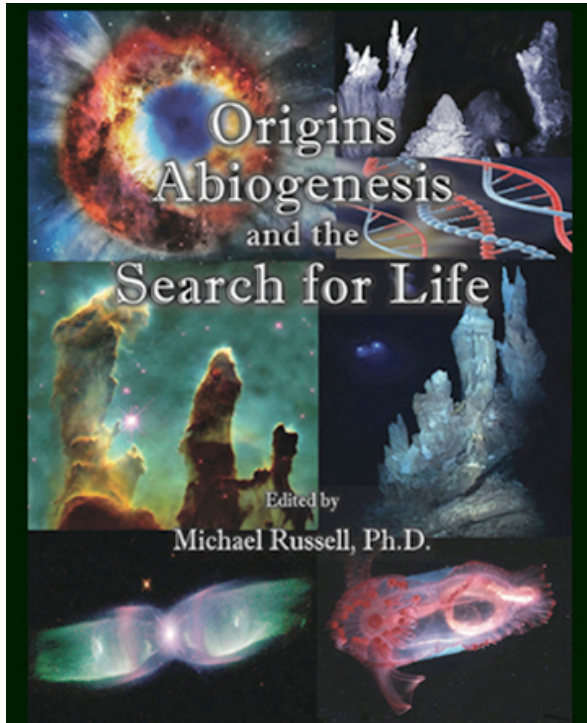
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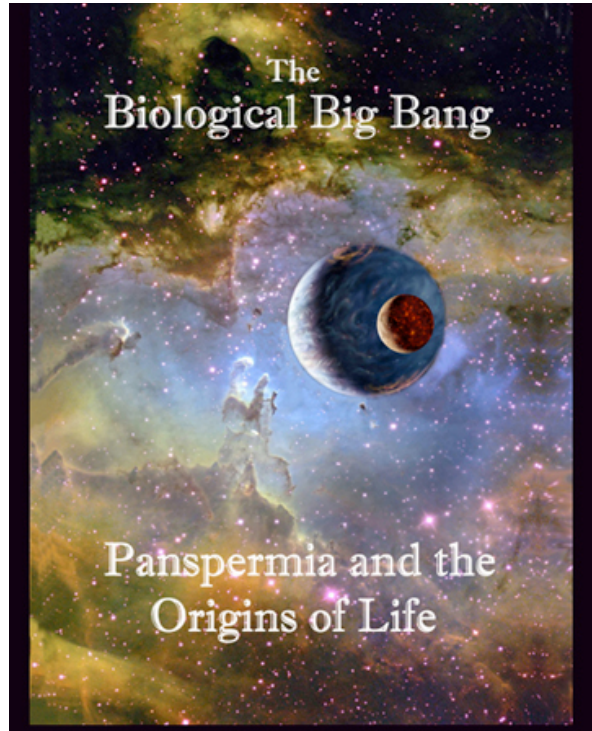
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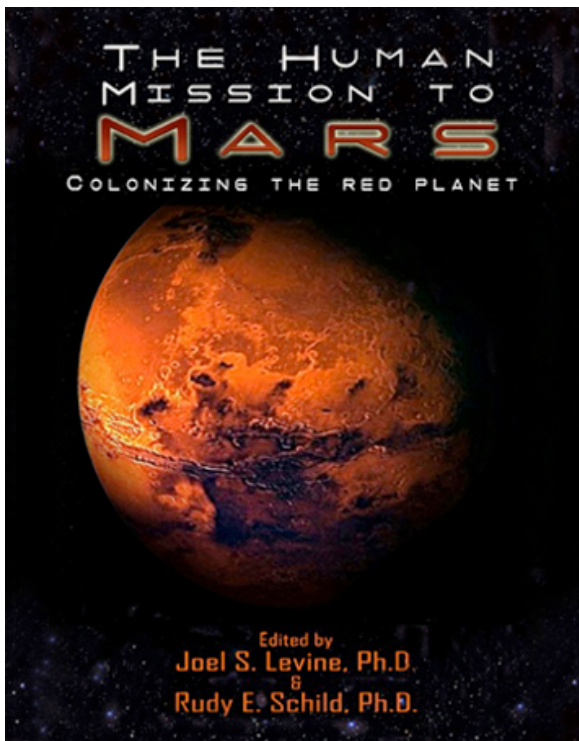
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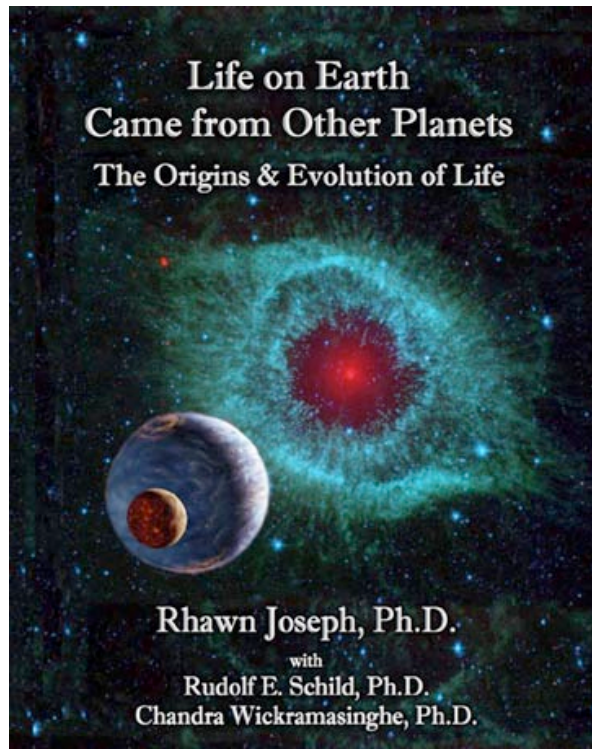
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