

# **THE CREATION OF SYNTHETIC LIFE FROM SCRATCH: FUTURE REALITY OR UNATTAINABLE POSSIBILITY?**

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**ABSTRACT:** The origin of Life is one of the fundamental mysteries still unsolved by the modern science. The actual dominant orthodox scientific paradigm in Biological Sciences has as fundamental tenets that Life is a natural phenomenon as well as that the origin of Life would be an understandable event. Life apparently does not require of supplementary «vital principles» transcendent to the physical-chemical laws («materialistic forces») that govern non-living phenomena. No supernatural causes are required to explain Life. Here I have called this vision the mechanistic vital-less paradigm of Life. On the contrary the Vitalism is an old and discredited doctrine, which sustains that Life is a singular phenomenon that requires of the action of «vital forces» exclusives to living domain. The recent creation of a bacterial chromosome by Craig Venter's team and the successful transfer of it into a bacterium, where the native DNA has been replaced, has created the expectation of the creation of synthetic Life (SLife-Lab) from scratch could be a reality in the next years. However, despite this scientific notable milestone, the dream of the creation of autonomous SLab-Life (the so-called a second origin) has not been realized yet. Thus, in my opinion, an open question that still remains is this: Why it has not been SLab-Life created yet? Another question related to the previous is: Is Vitalism an idea completely dead? Here, I discuss these issues taking account a historical perspective.

## INTRODUCTION

### *What is Life?*

The question what is Life? Is the fundamental question in biological sciences [1]. The definition of Life has been always a difficult issue [2, 3]. Thus, even today there is not a definitive and complete definition of Life [4, 5]. Recently, I have proposed the following Life definition:

«In a nutshell, Life is a self-propagated order in a continuous struggle against second thermodynamic law (STL), driven by using an energy-matter flux that is “harnessed informatically” within the system boundaries to maintain order at the expense of the environment which pays the «entropic tax» required by the second law» [6].

Considering most explicitly the previous definition, to the modern science the living organisms that live in the terrestrial biosphere have the following essential characteristics [7]:

### *A möbiusware informational configuration*

Information processing and computational working is an essential quality of Life [8]. The living organisms are entities provided with soma, this means that living things are

systems that have hardware [9]. Interestingly, a «LEGO-principle» underlies in the construction of hardware of living organisms [10]. Thus, for instance, the basic entities of Life's hardware, the proteins, are polymers of 20 different aminoacids akin to LEGO pieces as the basic building construction blocks [10]. Remarkably, it has been recently constructed in the laboratory *E. coli* strains that are capable to synthesize proteins that incorporate other aminoacids in its aminoacidic sequence in addition of the canonical set of the twenty aminoacids [11].

Also, living organisms are *software* entities, i.e., that have genetic programs recorded into a physical medium as a sequence of nitrogen-containing bases into nucleotide polymers, DNA or RNA. These polynucleotides encode the instructions for the organismal formation and the self-reproduction (self-replication). The «information flux» in cells, the basic unit of Life, is encapsulated in the *Central Dogma of Molecular Biology*: DNA- > RNA- > Protein [12].

Proteins have enzymatic activity (i.e., chemical catalytic properties, as well as RNA [13]) and the ability to undergo structural self-organization in large macromolecular complexes [9, 14]. Thanks to these features, proteins endow the organism with organismal form, signalling pathway transduction, etc... that permit the living organism to carry out an active communication with the external environment, i.e., to actively react and generate adaptive responses to the changing environmental conditions adjusting its internal condition to new life situations [15].

At this point it is important to highlight that Life has a *möbiusware* informational configuration (Fig. 1) [6]. This means that the hardware (proteins) is required to synthesized

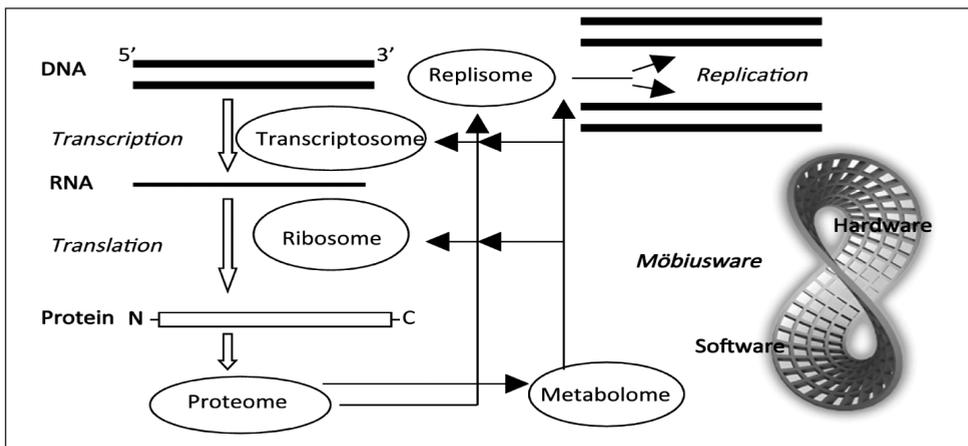


FIGURE 1: *The «möbiusware» informational configuration of Life.* Living organisms show this characteristic singular informational configuration. The software (genetic programs) is encoded (recorded) in DNA (a sequential informational polymer). The de-codification processes (transcription and translation) produce the main hardware of Life (proteins). Importantly the *möbiusware* configuration is achieved because the hardware (proteins, a polymer of aminoacids) form the cellular machineries required to this de-codification process (Transcriptosome and Ribosome respectively [9, 13, 69]) as well as to replication of DNA that encoded the software, the Replisome. In this way, this entanglement Hardware-Software can to be metaphorically visualized as Möbius's strip. A co-linearity exists between the nucleotide sequence in DNA and the aminoacidic lineal sequence of proteins i.e., both sequences show a «mirrored» configuration dictated by the genetic code. As how Life achieved this configuration is the main enigma to understand how Life (as we know it) actually began.

(self-replicate) the genetic material (the genetic material- hardware) that keep recorded the software (genetic programs), which is itself required to produce hardware. There is not hardware without software, and no software without hardware.

#### *Ability to harness energy-matter flux inside of boundary of system*

Life requires energy [9, 16]. Metabolism, a network of enzymatic catalyzed reactions, by harnessing in a controllable way an energy-matter flux (the living systems are open thermodynamic systems [7]) through boundary systems (constructed by the self-assembly of lipids substances [7]), allow the creation of internal order. Thus Life, by using energy, synthesizes its own organismal hardware and runs its reproduction (self-reproduction) upon increasing the environmental entropy (e.g., by producing waste product) in agreement to the government of second law of thermodynamics [17]. In the last term, the free energy used by living things comes from Sun's light radiation or from the energy liberated in REDOX reactions [9].

#### *Waterphilia*

Life requires water to flourish [7]. The chemical reactions inside and involving living systems are done in a watery environment.

#### *Evolution-ability*

A fundamental feature of living things is that they undergo adaptive Evolution [18] following a Neo-Darwinian process. In other words, that genetic variants arise in a population as consequence of randomly produced mistakes that occur during the copying process of genetic material (DNA or RNA, other process as genetic recombination increase the genetic variability in population) that are the raw material that undergo the scrutiny of the Natural Selection that selects the fittest variant for a determined set of environmental conditions [19]. In other words, Life shows evolvability, meaning that has the capacity to generate heritable, phenotypic variation that is susceptible to be naturally selected [20].

Taking account of these properties, it might appear self-evident that the construction the Slab-Life would be in principle an easy and attainable task. Why is it not like this? To give an answer it is necessary to make a short review on how the actual orthodox vision of «Vital-less» Life has been established.

#### THE RISE OF A VITAL-LESS VIEW TO ORIGIN OF LIFE

More than 400 extra-solar planets have been discovered in our cosmic neighbourhood so far [21]. The search of habitable earth-like planet is the goal of space missions as Kepler [22], and the quest for Life in doorstep Solar System and beyond is the principal goal of the recently created Astrobiology scientific discipline [23, 24]. The fundamental thought that underpins this passionate search is the conviction that Life «must» be a universal phenomenon, a *cosmic imperative* [25] and not a particular phenomenon exclusive to planet Earth. Life in everywhere i.e., there is not a particular or a special universal place for Life to emerge and to evolve. Here, I suggest naming Giordano-Bruno's principle to this idea [26]. But, which is the intellectual background behind of this scientific belief?

*From spontaneous generation to «Life comes from Life»*

During more of 2000 years, Mankind had considered (from sporadic, not controlled observations) the doctrine of the spontaneous generation, i.e., the belief that living organisms come from the spontaneous arrangement (i.e., its assembly) the inanimate matter into living matter. The fact that the spontaneous generation doctrine lasted during this long time was due to explicit support of the great authority of the Greek philosopher Aristotle [27]. Controlled experiments that were conducted in a modern scientific way by the Italians biologists Francesco Redi (1684) [28] and Lazzaro Spallanzani (1769) began to undermine this idea [28]. In 1828, the German chemist Friedrich Wöhler synthesized urea; an organic substance previously considered a genuine product of life forces that operate in living beings, from of inorganic materials and thus initiated the demise of Vitalism [29]. Finally, the elegant experiments of the French chemist Louis Pasteur in the 1860s convinced most scientists that organisms, including microorganisms, originated only from their parents and were not spontaneously generated from inanimate matter [29].

This fundamental natural fact was expressed by Rudolf Virchow in 1858 different famous dictums: the's *Omne vivum ex vivo* or *Omnis vita et vita* [30] which could be paraphrased as «Life comes from Life», meaning that all life arises from existing life. The work of the creation of the Life was left in the hands of God which had created independently the diversity of species of living creatures in his initial *ex nihilo* creation of World [31].

In 1859 the great English naturalist Charles R. Darwin [19, 31] and independently Alfred R. Wallace [31] suggested that, in addition of «Life comes from Life», also «Life becomes diversity». The different organismal forms of Life evolve into different species along the evolutionary timepath through of a natural simple conceptually mechanism: «descended with modification» and Selection Natural of adaptive modification, i.e., those that increase the organism's fitness. A strong claim of the Neo-Darwinian paradigm is that all diversity of Life in the Earth could be traced back to a unique last common ancestor, called LUCA [32]. In words of Darwin:

«Probably all the organic beings which have ever lived on this earth have descended from some one primordial form, into which life was first breathed» [33].

Thus, God was not necessary to create the living diversity of Life. Life is natural phenomenon.

On the other hand, the XX century was witness of significant milestone discoveries that have underpinned the modern way of understanding the molecular material basis of Life: the deciphering of DNA structure («the secret of Life» [34]), the elucidation of genetic code [35], the establishing of the Central Dogma of Molecular Biology [12], the molecular mechanisms that regulate the gene expression [36], and the creation of the synthetic genome from scratch [37]. After this accomplishment it appears that there is not any kind of weirdness in the Life phenomenon. Life is governed by the same laws and principles as the rest of matter in the Universe [29].

*The origin of Life became a treatable scientific problem*

However, all these understandings had created a profound intellectual and logical problem, as expressed in the following paradox: if in the Earth «Life comes from Life», then how the Life began from the inanimate matter? Thus, an immense gap (in its ontological status) opened between the inanimate and the living matter. How is it possible to close this gap? How did life emerge on Earth? [38].

A first glimpse of a scientific solution to this enigma was proposed in 1871 by Charles Darwin, when it shared in a letter to his friend, the botanist Joseph Hooker, his dreamy vision:

«But if we could conceive in some warm little pond, with all sorts of ammonia and phosphoric salts, light, heat, electricity, etc., present, that a protein compound was chemically formed ready to undergo still more complex changes, at the present day such matter would be instantly devoured or absorbed, which would not have been the case before living creatures were formed» [39].

A materialistic/mechanical start for Life was thus envisioned. However it was not until 1924 when the Russian biochemist Alexander I. Oparin challenged the dualistic view between animate matter and inanimate matter as two distinct realities, offering a detailed scenario for the natural materialistic emergence of Life [40, 41]. In 1929 the British biochemist and geneticist J.B.S. Haldane independently published a shorter and less-detailed paper that described possible scenarios for the emergence of life on primitive Earth [42]. As both theories had elements in common, they were later referred to as the Oparin–Haldane hypothesis [40]. This hypothesis supports the concept that Life emerged from a prebiotic soup or primeval broth that covered the Earth [40]. From an epistemological point view, this theory finally rescued the old idea of spontaneous generation displacing the place to spontaneous creation of Life to an early epoch of history of Earth.

That theory received support from the Miller's demonstration that organic molecules (e.g., amino acids) could be obtained by the action of simulated lightning on a mixture made of methane, ammonia, hydrogen and water vapour, which were thought at that time to represent Earth's earliest atmosphere [43]. Furthermore, later experiments of polymerization using hydrogen cyanide produced the nucleic acid bases adenine and guanine [44]. Thus, the production of monomers that constitute the chemical components of modern Life biochemistry is an easy issue.

From this and other fundamental laboratory experiment, the modern standard view of endogenous origin of Life in the Earth proposes that:

Organic compounds (aminoacids, sugar, etc...), the Life's LEGO pieces, accumulated in the primordial terrestrial oceans in a cold prebiotic broth (other places have been proposed, e.g., hydrothermal-vent settings [45, 46]) of pre-accumulated modules and underwent spontaneous polymerization, producing increasingly complex macromolecules (e.g., polymers, such as RNA, polypeptides, etc...) that eventually evolved to the ability to catalyze their own replication, «self-replication», in a prelude to the advent of DNA and proteins [47]. The evolution way to modern cells required that vesicles (formed by self-assembly of lipidic molecules) acted as a container capturing these molecules to generate early protocells [48]. Finally, it is thought that a protocell gave origin to the first genuine modern cell [49] (Fig 2). In fact an important, still debated issue is if Life started out with RNA alone (or RNA world) which would to make copies of itself without help from proteins, i.e., 'information became first', or was metabolism «the first one to emerge» (autotrophic origins) [50, 51] (Fig 2). However, it is clear that in the absence of a genetic replication mechanism ensuring the maintenance, stability, and diversification of autotrophic reaction chains generating energy, the incipient Life would have come and gone without leaving any direct descendants able to resurrect the process i.e., if Life had not achieved a *möbiusware* informational configuration, then Life had been gone with the wind.

Pervading to these theories has a principal change the substitution of the word generation for emergence. This is the *emergentism* view of Life [52] i.e., that is Life is an emergent product from mechanical processes. The main tenet of this thought current

could be well expressed with the following proposition: «The whole is more than sum of parts» and complexity [53] «more is different» [54] i.e., transitions in complexity generate emergence of a new behaviour, which has not been previously anticipated [54].

Variants of the prebiotic broth theory propose that the essential building blocks of life were synthesized in space and reached early Earth by comets (Fig 2) [55]. On the other hand, the most radical proposal is the panspermia hypothesis that sustains that Life arrived to Earth from other distant world as «seeds» (e.g., bacterial spores or even vegetative bacterial cells [56]) that germinated in the Earth [57]. Thus, panspermia proposes an extraterrestrial hypothesis to the origin of Life in Earth (exogenous origin). Evidently it has been argued that panspermia has not resolved the problem of first Life creation [58], as it simply transferred the question of its origin to other extraterrestrial places (Fig. 2).

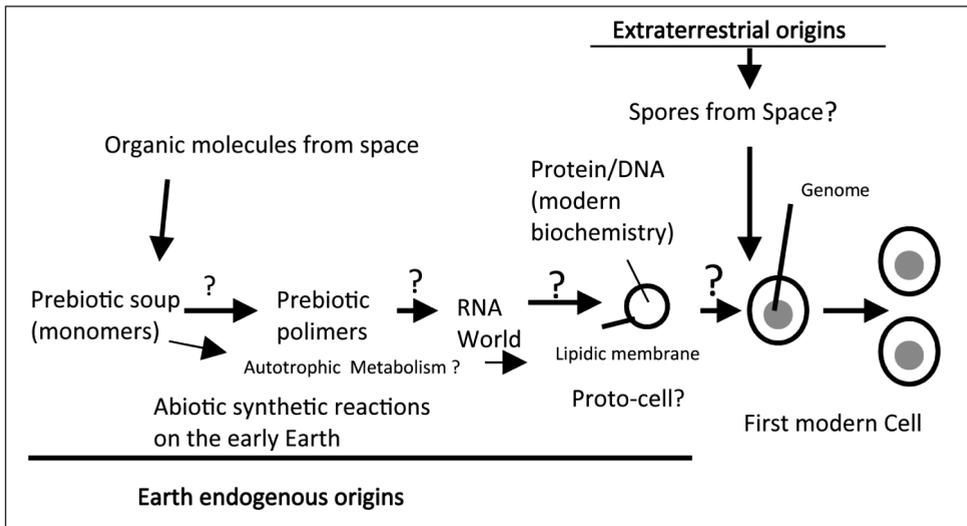


FIGURE 2: Schematic outlines of possible scenarios to Life start in Earth. The Orthodox view of Life origins claims that Life started in the Earth from successive evolutive self-organization steps from material synthesized in early Earth or/and from material supplies from the space. On the other hand, the main statement of panspermia is that Life arrived to Earth as biologically complete entities such as seeds or vegetative resistant microbial cells that grew and bloomed once they landed in the terrestrial oceans or in dry land. The interrogation shows the difficulty to understand the transition step. Figure adapted from the article of Bada and Lazcano [44].

#### LIFE FROM SCRATCH: A POSSIBLE OR IMPOSSIBLE SCIENTIFIC GOAL?

Taking account of the previous considerations, the question «why there is not synthetic Life in the Lab?» appears most relevant and intriguing. The scientific general opinion is optimistic because it is considered that the origin of Life is a tractable scientific problem [60]. However inside of scientific community there are dissident voices to this belief. Thus, in a recent article the authors made the following comment:

«There is an immense gap from prebiotic chemistry and the lifeless Earth to a complex DNA instruction set, code encryption into codonic sequences, and decryption (translation) into amino acid sequences» [61].

I also agree with this argument which could be paraphrased in another more abstract sentence, «the *möbiusware* configuration of Life creates this gap». How did the genetic code arise? How was born the colinearity between two completely different sequential polymers: the RNA or DNA in one hand and the other Proteins?

This question has not been satisfactorily answered yet. Nobody knows a solution for this enigma. Really, it is difficult to imagine the mechanism behind the creation of Life's *möbiusware* informational configuration.

The solution of the standard theory about the origin of Life is based on the idea that there was a necessarily long time period for that start. Thus, Geology tell us that the Earth originated approximately 4500 million years ago, and that the first fossil records of the first living may be present in ~3.5-billion-year-old rocks [62]. The chemical evolution that generated the *möbiusware* configuration must have occurred during this long arcane epoch. It is supposed that the gap was filled during this time.

To the majority of the scientific community, the creation of Slab-Life would be only a technical problem, but not an unattainable goal. The prevalent thinking is that production of Life in Lab is only a technical problem. But, from an empirical point of view, this belief is only an extrapolated idea, which still has not been experimentally proved.

### *Is Vitalism completely dead?*

Despite that Vitalism was discharged with being a scientific explanation of Life, the Vitalism doctrine was enthusiastically defended in the philosophical arena. The French philosopher Henri-Louis Bergson, in his book *L'évolution créatrice*, claimed that Life could never be explained by simply using mechanistic principles [63]. There was, he argued, an «*élan vital*» — a kind of vital force that was the ineffable current distinguishing living from inorganic material. Importantly, no imaginative manipulations of the inorganic molecules would permit the creation of any living thing [63]. Neither could it be artificially created by synthesizing molecules.

Even though that inside the academic biological science world it is considered that vitalism as a doctrine is dead, the claim for the Venter team of creation of a «synthetic cell» has opened an intense debate about this apparently forgotten issue (Fig. 3) [64]. Thus, the journal *Nature* gathered the opinion of reputed scientists about this particular [65]. Thus, to George Church:

«This milestone and many like it should be celebrated. But has the JCVI created 'new life' and tested vitalism? Not really. The semi-synthetic mycobacterium is not changed from the wild state in any fundamental sense. Printing out a copy of an ancient text isn't the same as understanding the language. We already had confidence in our ability to make synthetic DNA and get it to function in cells. The grand challenge remains understanding the parts of cells that help the DNA to function. This will be addressed by genetics, biochemistry and three-dimensional structures of the core life processes of biopolymer synthesis».

And to Steen Rasmussen (a participant in the seminar «Life, Evolution and Complexity»):

«Implementing a synthetic genome in a modern cell is a significant milestone in understanding life today. But the radical 'top-down' genetic engineering that Venter's team has done does not quite constitute a "synthetic cell" by my definition».

After the Venter's experiment, it still appears clear that vitalism doctrine is not dead yet (Fig. 3).

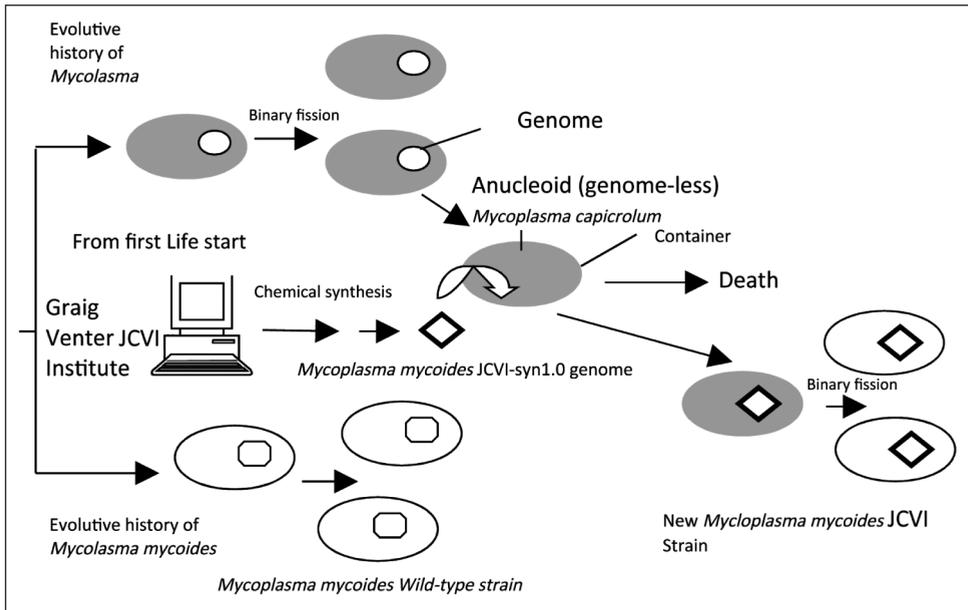


FIGURE 3: *The Graig Venter experiment.* A synthetic created genome (called 1.08–mega–base pair *Mycoplasma mycoides* JCVI-syn1.0 genome) [37] was transplanted in a *Mycoplasma capricolum* cell devoid of its own genome. The container cell (constituted by membrane plasmatic, endogenous ribosomes, etc...) that received the synthetic chromosome was provided by Life through the evolutionary history of *Mycoplasma* a lineage from of first Life start. The synthetic genome was able to take control of cellular activity providing information to growth and self-reproduction (binary fission). However, despite to this important technical achievement the question «is Vitalism completely dead or not?» still remains opened.

Would have undiscovered principles or laws from empirical sciences been necessary to explain how Life begun? Historically in science, there are many examples of how the impossibility of constructing machines unveiled the existence of «hidden principles» that forbade this possibility. Two most paradigmatic cases are the first and second thermodynamic laws. Behind of the impossibility of construction of perpetual motion machines were the first and second law of Thermodynamic [66]. In a similar way, if finally the creation of a Slab-Life device turns out to be impossible to construct, it will be necessary to revise our understanding of the vital phenomenon.

## CONCLUSIONS

It is clear that the creation of synthetic life in the laboratory is a crucial scientific issue that has many philosophical and ethical implications [67, 68]. I consider that we are in a historical moment to resolve the following dilemma: either in the next decades we attended to the creation of synthetic SLab-Life confirming therefore the Vital-less vision of Life or, on the contrary, it will be necessary to complete this paradigm by contemplating it from old vitalistic ideas. This would thus open the suggestion that, behind of Life phenomenon, there are perhaps specific «hidden vital principles», still

unknown to the experimental sciences, that in some inexplicable way prevent the creation of Life from scratch in the laboratory. The survival of the mechanistic Vital-less paradigm would be questioned. Vitalism would therefore revive as a «phoenix bird». Vital forces would be required for Life to start. Vital principles only operating in origin of Life would be invoked. Within the hope that one day it may be possible to understand and reconstruct the beginnings of Life on Earth, my opinion is that this may be far to be attainable. After all, perhaps the *Life is Life* dictum will be a profound reality. Time will tell.

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