

Dreaming of a Universal Biology: Synthetic Biology and the Origins of Life

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Abstract: Synthetic biology aims to synthesize novel biological systems or re-design existing ones. The field has raised numerous philosophical questions, but most especially what is novel to this field. In this article I argue for a novel take, since the dominant ways to understand synthetic biology's specificity each face problems. Inspired by the examination of the work of a number of chemists, I argue that synthetic biology differentiates itself by a new regime of articulation, *i.e.* a new way of articulating the questions and phenomena it wants to address. Instead of describing actual existing biological systems, the field aims to describe biological possibilities. In the second part I corroborate this hypothesis through a comparison between early research in the field of the origins of life and contemporary synthetic biologists, who are not so much interested in the historical origin of life on Earth, but rather in a universal biology of the possible origins of any life whatsoever.

Keywords: *synthetic biology, universal biology, origins of life, biological possibilities.*

1. Introduction

Synthetic biology is one of the most recent developments within the life sciences. The field has many birthdates, but as an institutionalized field it was launched in the early 2000s and stabilized around 2010 (Raimbault, Cointet & Joly 2016). Typically, the field is defined as the application of engineering to biology in order to (re)design biological systems. Historically, it has drawn inspiration either from engineering or from synthetic chemistry (see Campos 2009, Bensaude-Vincent 2013).

According to some scholars, synthetic biology raises new philosophical questions, mainly by its new method of synthesis. This is not only argued for by philosophers (*e.g.* Malaterre 2013), but also by a number of synthetic biologists, who similarly claim that “synthesis as a research strategy can drive discovery and paradigm shift in ways that observation and analysis cannot”

(Benner *et al.* 2010, p. 374). Others are not convinced that synthetic biology raises new philosophical questions. Humans have always shaped and designed their biological environment. What are cows and corn but artificial constructions, produced by human intervention? Synthetic biology might claim to intervene in nature in novel manners, but even this can be doubted (O'Malley 2009, Lewens 2013).

Much thus depends on three questions: (a) does synthetic biology implies something new? (b) if so, in what way? (c) and finally, what is philosophically at stake? I will argue that (a) there is something specific to synthetic biology; (b) that what this is differs from the dominant narratives about synthetic biology, and (c) that this deserves philosophical attention, since it raises novel philosophical questions.

The dominant narratives will be described in Section 2, followed by why I believe they are inapt. I will propose an alternative interpretation of the specificity of synthetic biology, namely that it resides in what I will call its *regime of articulation*: the way it articulates questions about living systems. My central claim is that synthetic biology is characterized by a focus, not on describing *actual* existing living systems, but on describing *possible* living systems. I will defend this claim in three forms. The *weak claim* is that there are (at least) two ways of describing relevant phenomena in the life sciences, either focusing on actual or on possible living systems. The *moderate claim* is that within synthetic biology the latter is dominant. The *strong claim* is that this shift is a product neither of a natural progress nor of a theoretical choice. Rather it is linked to a shift in the experimental system (Rheinberger 1997), more particularly in its engagement with experimental objects such as protocells or minimal cells.

Although my hypothesis is that this can be defended for most parts of synthetic biology, in this paper I will mainly defend it for chemical protocell synthesis. I will argue for this by contrasting earlier examples of biologists and chemists working on the origins of life, more particularly the work of Stanley Miller and J.D. Bernal (Section 3), with recent synthetic biology groups, such as the group of Stephen Mann and of Pier Luigi Luisi (Section 4). At the end of Section 4 and in the conclusion I will draw some philosophical implications from this novel perspective on synthetic biology.

2. What is Particular to Synthetic Biology?

The specificity of synthetic biology has been described in many ways. I follow Schmidt's (2015) suggestion and cluster them in three dominant narratives. Either the novelty of synthetic biology resides in the fact that it applies

engineering principles to the life sciences (Endy 2005, Képès 2011). Let us call this the *engineering narrative*. Or, what is novel is that the field is working with artificial biological systems, which are not found in nature (Benner *et al.* 2010). Let us call this the *artificiality narrative*. Finally, a third narrative states that synthetic biology is actually not something new, but a radicalization of existing biotechnology (O'Malley 2009, Lewens 2013). This I will call the *biotech narrative*. Similar to Schmidt, my claim is that all three narratives fail to properly delineate the specificity of synthetic biology.

2.1 Problems with dominant narratives

What is wrong with the engineering narrative is threefold. First of all, it is an open question whether synthetic biology is really applying engineering principles to biology. Some have argued that there is a discrepancy between what synthetic biologists say and what they do: they speak about rational principles, but in practice their work resembles tinkering and kludging (O'Malley 2009, Calvert 2013). Secondly, historians have pointed out how engineering and biology have met before in history, often indeed linked with the dream to control and create novel living systems (Pauly 1987, Campos 2009). Such attempts were moreover not restricted to microbiology, but engineering has also had its influence in agriculture, plant science, and pharmacology (Curry 2016, Crowe 2019). Thirdly, there is a strong diversity in conceptions of engineering at work in these debates, which begs the question *which* engineering is applied to biology (Simons 2020a).

The artificiality narrative faces similar problems. For instance, one could argue that synthetic biology hardly deals with genuine artificial systems. Most, if not all, biological systems synthetic biologists work with are derived from nature. A telling example is that of Craig J. Venter's famous announcement to have created the first 'artificial cell' (Gibson *et al.* 2010). This claim was immediately criticized since only the genome was synthesized in a lab (and most of it was copied from an existing cell). The machinery of the cell (the organelles, the membrane, *etc.*) was simply taken over from an existing natural cell (see Simons, forthcoming). One could still argue, however, that synthetic biology combines existing, natural systems in ways they never occur in nature, and are therefore artificial (Benner *et al.* 2010). The problem is that this kind of artificiality is hardly novel in the life sciences. Also traditional breeding methods produce artificial living systems not found in nature (Lewens 2013). Such artificiality is even more striking in 20th century experimental biology, for instance in cell cultures (Landecker 2009) or purified DNA (Barnes & Dupré 2008).

The failure of these two narratives have let some to argue that synthetic biology is nothing new, but merely a continuation of earlier biotechnologies

(Lewens 2013). However, the problem with this third narrative is that it makes us incapable to detect new philosophical issues raised by synthetic biology. This is the main concern of Evelyn Fox Keller, who worries that though biology never just describes ('sees') but also always intervenes in ('touches') its objects, maybe

the pendulum has swung too far. While there may be – arguably, even can be – no looking without touching, it does not follow that looking and touching are the same. [...] It erases distinctions between a variety of conceptual aims that may not sort by old boundaries but may still sort in ways that need marking. Perhaps nowhere does my unease surface more clearly than in thinking about the new interdiscipline of synthetic biology. [Keller 2009, p. 294]

Similarly, Schmidt argues that the biotech narrative “prevents an exhaustive characterization of the new technoscientific wave” (Schmidt 2015, p. 7). Synthetic biology is highly interdisciplinary and shares many characteristics with related technoscientific fields such as nanotechnology and robotics (Simons 2020b). These links must be accounted for. Therefore, I wish to propose a candidate to characterize synthetic biology which is able to acknowledge previous elements of engineering and artificiality, while also situate its novelty within this new technoscientific wave.¹

2.2 A shift in its regime of articulation

What I want to argue for is that synthetic biology is characterized by a shift in what I would like to call its *regime of articulation*. ‘Articulation’ is here used in a technical way, mainly inspired by constructivist philosophies of science. Following suggestions by Latour (2004), Despret (2002), and Rouse (2015), a regime of articulation refers to the way in which a scientific practice theoretically and technically shapes the kind of questions it finds meaningful to ask and answer. As Rouse suggests, articulation is not a matter of correcting earlier mistakes, but replaces a “silence rather than error” (Rouse 2015, p. 208):

In many scientific domains [...] earlier generations of scientists could not have erred because the relevant errors were not yet even conceivable. In the most striking cases, scientists’ predecessors either had no basis whatsoever for making claims within a domain or could only make vague, unarticulated claims. [Rouse 2015, p. 294]

My hypothesis is that synthetic biology is characterized by a shift from *articulating the actual* to *articulating the possible*, *i.e.* synthetic biologists are more interested in exploring what living systems possibly could do rather than what they actually do. Whereas earlier biologists were not interested, dismissive, or simply silent about questions concerning biological possibilities, within a field such as synthetic biology these questions have become central.

Such a shift has already been sporadically noted by commentators. Michel Morange, for instance, highlights how synthetic biology is translating historical questions of evolutionary biology ('How has life evolved?') into experimental questions, due to new technologies and approaches. According to him, "synthetic biology can help evolutionary biologists explore possibilities that have not been realized by existing organisms" (Morange 2009, p. S53). In a similar vein, Malaterre argues that

What appears to be distinctive of synthetic biology's route to knowledge is that it broadens the perimeter of systems that can be manipulated beyond those that are naturally-occurring, and that it does so in an empirical space of biochemical possibilities that is truly large and so scarcely sampled by nature. [Malaterre 2013, p. 355]

Similar remarks are found in the work of synthetic biologists themselves. In a paper in *Nature*, Michael Elowitz and Wendell Lim similarly argue that the discipline of biology is expanding "from a discipline that focuses on natural organisms to one that includes potential organisms" (Elowitz & Lim 2010, p. 889).

Elowitz and Lim are part of the engineering strand of synthetic biology. I want to focus, however, on contributions by chemists to synthetic biology, since I believe that they illustrate this shift even clearer. A good illustration of this is Steve Benner (Benner *et al.*, p. 2010; see Koskinen 2017). Benner has been studying 'alternative genetic systems' since the 1980s as a chemist. His work deals with artificial chemical structures that have the same functions as our familiar DNA and RNA molecules, but start from a fundamentally different design. Benner aims, for instance, to evaluate the Watson-Crick model of natural DNA: how necessary are the structural aspects of the bases and the sugar-phosphate backbones? Is it possible to replace the backbone with a different sugar (resulting in a form of XNA)?

According to Koskinen what is fundamentally at work here is the use of what he calls 'how-possibly models' (Koskinen 2017, p. 493). Synthetic biologists such as Benner are not interested in actual biological systems, but

use how-possibly models to study what may be called potential biological systems. I argue that in the hands of bioengineers, how-possibly models are not just speculations or eliminable scaffolds towards one how-actually model, but rather *design hypotheses* for a field whose ultimate goal is to build novel biological systems and 're-wire' existing ones. Apart from their more traditional explanatory purpose, how-possibly models can function as ways of studying, and ultimately concretizing, biological possibilities. [Koskinen 2017, p. 494]

Similarly, I have argued elsewhere that the work on minimal genomes can be interpreted in a similar way, in the sense that biologists such as Craig Venter are mainly interested in *possible* minimal life, rather than actual existing min-

imal living systems (Simons 2020b). From this literature, the hypothesis comes forward that synthetic biology tends to articulate its phenomena in a different and novel manner, since they are ultimately interested in *biological possibilities*. These possibilities are moreover *metaphysical* possibilities, rather than, for instance, studying epistemic possibilities.

My paper wants to expand and support this hypothesis further through the novel case of protocell biology. Protocell biology is a rather small sub-field of synthetic biology (Raimbault, Cointet & Joly 2016). Nonetheless, it deserves our attention for at least three reasons. First of all, it can bring literature on synthetic biology into contact with that of the origins of life and astrobiology. These interactions are currently absent, despite the fact that they overlap concerning topics about *possible* forms of life. Secondly, it can correct an overemphasis among commentators on the engineering subfields of synthetic biology. Thirdly, it can therefore shed light on the enigma of how synthetic biology can consist of what at first sight looks like a strange alliance between engineers and chemists. These chemists, just as the engineers in the above examples, share an interest in studying possible forms of life.

For these reasons I will, in the next session, focus on how protocell biology should be situated in relation to the field of the origins of life. First (in Section 3) I will describe how the question of the origins of life was conceptualized in the middle of the 20th century, by authors such as Stanley Miller and J. D. Bernal. In Section 4, I will contrast this with two contemporary examples, namely the Mann group and the Luisi group. As stated before, I wish to argue for three theses: (a) that there are two regimes of articulation at work here; (b) that within synthetic biology only one of them is dominant; and (c) that the reason for this resides in shifting experimental practices, allowing synthetic biologists to engage with novel experimental objects, such as minimal cells and protocells.

3. Articulating the Actual Origins of Life

My aim is to juxtapose two episodes in the origin of life research, namely research at the heights of molecular biology (1950s) and more recent research that is aligned with synthetic biology (2000s). My claim is not that my argument is applicable to the whole field of the origins of life. Here I will only focus on synthetic biology. I therefore leave out other work on the origins of life, such as the work of Leslie Orgel, Timor Gnani, Manfred Eigen, or Stuart Kaufman (see Kauffman 2011). I thus do not claim that the historical question of the origins of life has disappeared completely nor that the question of

the possible origins of life was never posed before synthetic biology entered the scene. Rather I juxtapose these two groups to highlight how there are (at least) two ways how to pursue the question of the origins of life, and how in synthetic biology the question is different from how it was understood by earlier influential authors.

3.1 Miller, Bernal, and the actual origin of life

The most famous experiment linked with the question of the origin of life is probably the 1953 Miller-Urey experiment, conducted by Stanley Miller under supervision of Harold Urey, which showed that under certain conditions complex amino acids can spontaneously be formed out of simpler chemicals (Miller 1953). However, this experiment was certainly not the start of the field, but must be situated in a longer tradition.

What it shared with its immediate predecessors was the way in which the problem of the origin of life was understood or, in my technical term, articulated. An influential author was the Russian biochemist Alexander Oparin, who in 1924 proposed a theory in which life on Earth could be explained as a product of a chemical evolution, following a number of simple steps (a variation on the famous ‘primordial soup’ theory). A few years later, the British biologist J.B.S. Haldane published a similar hypothesis, with the result that this position is known as the Oparin-Haldane hypothesis (Falk & Lazcano 2012, Tirard 2017).

In order to understand Stanley Miller, it is thus important to appreciate what was at stake for Oparin and Haldane. Their specific framing of the question of the origin of life came out of a (perceived) clash between the work of Louis Pasteur and Charles Darwin. Through a range of experiments, Pasteur discredited the theory of spontaneous generation, which claimed that life could spontaneously arise out of non-living materials, such as maggots from rotting meat. Pasteur demonstrated that living beings could only arise out of other living beings. On the other hand, Darwin’s theory of natural selection suggested that there must have been an ‘origin of species’. But subsequent discoveries, showing the complexities of even a single cell, seemed to show that an “impassable abyss existed between the living and the dead” (Oparin 1924, p. 203). This conflict made neo-vitalistic theory, such as in Hans Driesch’s work, or the theory of panspermia, according to which life has been eternally present in the universe, gain popularity. Authors such as Oparin or Haldane wanted to offer an alternative both to vitalism and to a very strict kind of continuous materialism. According to them there was material novelty through a range of small jumps.²

The same kind of framing is found in Miller’s work. For instance, he starts a later article, written together with Urey, as follows:

Since the demonstration by Pasteur that life does not arise spontaneously at the present time, the problem of the origin of life has been one of determining how the first forms of life arose, from which all the present species have evolved. [Miller & Urey 1959, p. 245]

Miller is concerned with the problem of uncovering the organic compounds and steps required to end up with living organisms. The bulk of his papers is therefore concerned with identifying the exact historical conditions on Earth when life came into being (*e.g.* whether there were oceans, whether oxygen was present, *etc.*). Miller does discuss the possibility of life on other planets, but in the form of the question whether the right chemicals, temperature, *etc.* are present on other planets as well.

It is thus important to realize that his work is concerned with experimentally articulating and investigating the original historical conditions of Earth in order to show that life can spontaneously arise. If alien life forms were to be discovered, this would be “one of the most marvelous feats of 20th-century science,” but only because as a consequence, “the thesis that life develops spontaneously when the conditions are favorable would be far more firmly established and our whole view of the problem of the origin of life would be confirmed” (Miller & Urey 1959, p. 251). That this life might have a fundamentally different chemistry is rarely considered, and even in the rare cases that it is, not seen as a relevant possibility. Such a question was raised by Enrico Fermi (from the Fermi paradox) in one of Miller and Urey’s seminars, but the answer was brief and telling. When Fermi asked, “I understand that you and Miller have demonstrated one path by which life might have originated. Harold, do you think it was *the* way?” Urey replied, “Let me put it this way, Enrico. If God didn’t do it this way, he overlooked a good bet!” (quoted in Lazcano & Bada 2008, p. 376).

3.2 The importance of molecular biology

Besides the question of spontaneous generation, another issue was also at play and became more dominant with the rise of a new player in the field: molecular biology. What became important was a tension between diverse accounts of the origin of life which crystallized in two opposing viewpoints, namely

those who favor the idea that life is an emergent interactive system endowed with dynamic properties that exist in a state close to chaotic behavior, and those who are reluctant to adhere to a definition of living systems lacking a genetic component whose properties reflect the role that Darwinian natural selection and, in general, evolutionary processes, have played in shaping its central characteristics. [Falk & Lazcano 2012, p. 387]

Due to the dominance of molecular biology, the second, genetic viewpoint prevailed. Through the subsequent realization that cells and even bacteriophages were complex beings on their own, in need of both processes of metabolism and replication, the question became how a form of life could come into being that possessed both DNA and proteins. It seemed that one of them needed to come first, leading eventually to the popular 'RNA world' hypothesis: in this first stage of evolutionary history there was only RNA, possessing both genetic material and catalytic properties.

Molecular biology gained momentum in the 1960s, but so was the study of the origin of life. The first international conferences took place in 1957 (Moscow) and 1963 (Florida). A clear case where the study of the origin of life and molecular biology merged was the work of J.D. Bernal, who also translated the work of Oparin into English. In *The Origin of Life* (1967), Bernal starts from the idea that origin of life research "is a speculative science and not by any means observational or experimental science, although observation and experiment are used in its study" (Bernal 1967, p. 3). It is thus "necessarily a work of imagination, but of imagination controlled by science" (*ibid.*, p. 5). The reason for this is the fundamental nature of the phenomena that are to be articulated and explained by this research. The book is concerned with *life as it exists on Earth*. It is "an attempt to produce a plausible history of the origins of these chemical-physical processes on the actual Earth surface" (*ibid.*, p. 7). Rather than a question of synthesis, of exploring possibilities, it is a "process of the logical reconstruction of the earlier forms of life" (*ibid.*, p. 2).

But why is Bernal interested in the origin of life? What seemed to be at stake is a new issue raised by molecular biology, which offers us the "basis for the development of a new generalized biology, not depending on the peculiar forms existing on Earth" (*ibid.*, p. xv-xvi). At first, this might look very similar to the universal biology propagated by synthetic biology (as we will see), but it is in fact radically different. Bernal is interested in a specific universality of life, but different from the one at work in contemporary synthetic biology: he is not concerned with the question of a chemical universality of life, but rather a genetic-biological universality.

Molecular biology has shown that all life-forms, no matter their evolutionary contingencies, share DNA. It is thus a matter of "recognizing the unity of life on Earth" (*ibid.*, p. 4), but only as opposed to the evolutionary and development contingencies that distinguish an elephant from a giraffe. Both might look different, even have different genes, but the fact that both have genes and share DNA is what is universal. If the question is raised whether there would be life on other planets, it is a question concerning whether *life chemically similar to that on Earth* would exist there: "We may yet find on other planets, schemes of life which are different, but probably only

in the detail of their chemical reactions, not in the essentials of the types of process or in their chemical elements that are involved in them” (*ibid.*, p. 161).

There is thus an eye for contingency, but framed through the lens of a particular regime of articulation: life is a historical phenomenon which starts from the same fundamental principles, but evolution and natural selection can create all kinds of surprises. The question of whether the chemistry is contingent in any sense is not raised or dismissed as an irrelevant and speculative question. It only appears in the margins, namely at the end of chapters or in question sections. For instance, at a certain moment, Bernal wonders “whether the processes required in the origin of life are necessary or contingent” and he answers as follows:

Both explanations must be true in some measure, first, because any structures widely different from those of minimal energy would be unstable and unlikely to have a long life and, secondly, because there is not only one form of life but a wide multiplicity of forms. These may vary widely in small matters, but not in basic biochemistry. [*Ibid.* p. 34]

Similarly, in appendix 4, which reproduces a questions-and-answers session of a conference paper ‘Molecular Matrices for Living Systems’ from 1963:

Q1: Is life necessary or contingent? A: The simpler [forms] are and the more complicated are not. Molecules such as adenine are apparently necessary. The forms of any particular organism is not. It is contingent on the accidents of organic evolution. [*Ibid.* p. 299]

Q31: Is life on Earth a fair sample of life types on any hydrosphere? A: Probably. [*Ibid.*, p. 302]

Bernal is thus quite explicit in his claim of chemical necessity and evolutionary contingency. The question of the origin of life is one of finding out what the actual historical chemical steps were of life on Earth, which can be logically reconstructed through a speculative endeavor because they seem to be logical necessary. If there is contingency, it seems to be only at work on the level of evolutionary history. Chemical contingency is not considered to be relevant.

4. Articulating the Possible Origin of Life

Let me contrast this with recent research by synthetic biologists, which start from a radically different regime of articulation. My story starts in 2003, with “two back-to-back workshops – one held jointly at Los Alamos National La-

laboratory (LANL) and the Santa Fe Institute (SFI), the other in Dortmund, Germany, at the Seventh European Conference on Artificial Life” (Rasmussen *et al.* 2004, p. 963). Both workshops aim to study the transition from nonliving to living matter, which “is usually raised in the context of the origin of life”. These workshops, however, aimed to take

a broader view and asked how simple life forms could be synthesized in the laboratory. The resulting artificial cells (sometimes called protocells) might be quite different from any extant or extinct form of life, perhaps orders of magnitude smaller than the smallest bacterium, and their synthesis need not recapitulate life’s actual origins. [Rasmussen *et al.* 2004, p. 963]

It is thus concerned with a similar problem as before, but its approach is different. We encounter here the specific subdiscipline of synthetic biology, namely “protocell biology” (Mann 2013) or “protocell systems biology” (Solé, Rasmussen & Bedau 2007), which “aims at the construction of a chemical life-like ensemble in the form of an artificial cell system able to self-maintain, self-reproduce and potentially evolve” (Solé *et al.* 2007, p. 1727). To study these processes, they focus on objects called ‘protocells’, often defined as “the simplest instances of autonomous cell-like structures” (Solé, Rasmussen & Bedau 2007, p. 1725). As a concept, ‘protocell’ dates back to the 1960s, but in the early decades it was mainly discussed in theoretical journals, such as *BioSystems* and *Journal of Theoretical Biology*. Only at the turn of the century, when new fields like synthetic biology came into being, did “protocell models enter the laboratory” (Dzieciol & Mann 2011).

The result of this transformation of protocell research is a reinvestment of these authors in the investigation of the origin of life, for which they believe they can offer experimental means to answers its questions. Simultaneously it implies a number of significant shifts in comparison with earlier origin of life research. First of all, the definition of the essence of life shifts from the genetic variant to the more systematic variant: life is defined not by a certain molecule or by DNA, but by a range of abstract criteria. Rasmussen and colleagues, for instance, argue that in order for a protocell to be alive, it must

(1) use free energy to convert resources from the environment into building blocks so that it can grow and eventually divide. (2) have the growth and division processes at least partly controlled by inheritable information. (3) allow the inheritable information to change slightly from one generation to the next, thereby permitting variation of the growth and division processes and thus allowing selection and hence evolution. [Rasmussen *et al.* 2013, p. 585]

Secondly, this results in a shift in focus from *actual* life on Earth to *possible* forms of life, “the problem of defining life, not only as we know it, but as it could exist or might exist on other planets, or even as it might at some future time be synthesized in a terrestrial lab” (Ruiz-Mirazo & Moreno 2011, p. 3).

Such a definition, they add, must “be universal, in the sense that it must discriminate the necessary from the contingent features of life, selecting just the former” (*ibid.*, p. 6).

The result of these three shifts, the experimental and its two conceptual consequences, is a central conflict surrounding the question of the origin of life: can protocells synthesized in the laboratory tell us anything about how life on Earth *actually* came into being? Is the question of how life actually came into being even an answerable question or is it doomed to remain inconclusive? While the first worry would be expressed by more traditionally-minded researchers, the second is characteristic of a new generation of synthetic biologists.

Such a divergence was present in the first workshops in 2003, which “started with some tension between the origin of life perspective and the more general concern with synthesizing the simplest possible artificial cells” (Rasmussen *et al.* 2004, p. 965). A similar doubletalk is present in more recent papers, arguing on the one hand that synthesizing protocells “will deepen our understanding of the essence of cellular life and its origin on Earth” while at the same time acknowledging that “solutions found in the laboratory need not be chemically similar or even directly relevant to the actual molecular assemblies that led to the origin of life on Earth” (Szostak, Bartel & Luisi 2001, p. 387).

What we see at work is a struggle over what the origin of life research should actually be about: is its object *actual* or *possible* biology? For those who are interested in how life actually came into being on Earth, laboratory syntheses are deemed irrelevant:

There are no agreed upon prebiotic conditions to begin with nor is it obvious which molecular building blocks were and were not available. [...]. Perhaps most frustratingly, we may not be able to recognize success if a laboratory made protocellular system were constructed that faithfully mimicked Earth’s first cells. [Del Bianco & Mansy 2012, p. 2125]

The question always remains, in the words of Steven Benner (2012, p. xvi): “Did life emerge on Earth in this way?” But Benner favors the alternative perspective. After listing a whole range of similar problems, he adds that we should “attempt to resolve these problems by ignoring them, accepting (perhaps arbitrarily) the chemist’s question (How *might* life have originated?), its approach to answer the question, and the standards of proof that chemists accept” (Benner 2012, p. xvi). Let me explore what this means by focusing on the work of Stephen Mann and Pier Luigi Luisi.

4.1 Stephen Mann and universal biology

Stephen Mann describes his own work as ‘protobiology’ or ‘protolife science’ (Dzieciol & Mann 2011, p. 80; Mann 2013, p. 155). He defines this field as “the search for the minimal organizational logic that is sufficient for the emergence of matter with a basic level of systems autonomy, ultimately capable of undergoing evolutionary change” (Mann 2013, p. 159). The work of Mann and his group consists in the chemical exploration of protocells in the laboratory, testing which particular properties of life can be reproduced and mimicked in a chemical way. Life is seen through a formal lens, namely as “as a systems property that is maintained under non-equilibrium conditions by flows of energy and matter from the surrounding environment” (Dzieciol & Mann 2011, p. 80). Mann even goes so far as to argue that “the ultimate criterion that defines life” could be found in a “form of organizational logic” which “has been described using various terms, such as autopoiesis (self-production), autocatalytic self-maintaining metabolic networks, or metabolic closure” (*ibid.*, p. 81). Such criteria are not limited to terrestrial biology, rather the ambition is to aim for a “framework for a universal biology that penetrates deep into the history of life on the Earth” (Mann 2012, p. 2140).

These claims could bring forth the impression that this kind of research is unrelated to that which preoccupied Miller or Bernal. But Mann and his colleagues see their work as a continuation of this tradition, solving the problems that were left unanswered by their predecessors. Mann even starts one of his review studies with an overview of the current state of the art on the origin of life (Mann 2012), while the other opens with the claim that

It is ironic that modern biology – considered by many to be the pre-eminent science of the 21st century – tells us everything we know about life as it exists today, but nothing substantial about its origin on the early Earth some 3.5-3.8 billion years ago. [Mann 2013, p. 155]

Moreover, he argues that “a study of biology offers no illumination on the origin of life – on how life first emerged in a physical universe” and that

there remains an intractable discontinuity at the base of the reconstructed tree of life, where all current knowledge of biology becomes effectively bottlenecked such that the origin of life appears impenetrable and mysterious. Metaphorically speaking, the tree of life appears rootless. [Mann 2013, p. 155]

Although biologists cannot solve these problems, the tools to answer these questions reside in the hands of another group, namely the chemists, who must play a central role, “along with colleagues in synthetic biology, complexity science and systems engineering” (*ibid.*, p. 156). But through this gesture, the problem of the origin of life has been redefined, since to find out

the exact processes by which life on Earth came into being is deemed impossible:

Thus, the irrevocable erasing of prebiotic signatures by Archean geochemistry, the fragmentary and rudimentary nature of models of the early Earth atmosphere and oceans, the sheer impossibility of reconstructing local chemical conditions, and the perceived weakness of the underlying theories are sufficient reasons to halt a concerted chemical approach to solving the origin of life. (*Ibid.*, p. 155)

What was originally a *historical* question is transformed into an *ahistorical* one. Or, to put it in Mann's own words, we are faced with "reframing an etiological problem with an ontological one" (*ibid.*, p. 156).³ This implies "a shift away from 'Stanley Miller-type' experiments in which highly speculative scenarios of early Earth reaction conditions are probed, to more judicious and systematic investigations that are breaking new ground by attempting to solve old problems with new chemistries" (*ibid.*). Or to quote him more extensively:

is it possible for life to emerge through fundamentally different organizational, operational and evolutionary mechanisms, or are the core criteria of terrestrial biology – membrane-based cellularity, semi-conservative DNA/RNA-mediated self-replication, protein-regulated metabolism, Darwinian evolution, non-equilibrium energization – invariant and axiomatic? This wider perspective necessitates *an intellectual shift away from the historical impasse* associated with the study of the origin of life specifically on Earth *to a broader perspective* concerned with the generic transformation of inanimate matter to a life-like state. And by focusing attention towards the possibility of generating alternative models of life in the laboratory that are *essentially devoid of historical content* – that is, without needing to anticipate too many unknown boundary conditions – it should be possible for chemists to contribute significantly to understanding the origin of life as a general physical phenomenon, *even if the actual origin of life as it occurred on the early Earth remains unresolved*. [*Ibid.*, emphasis added]

We are thus confronted with a redefinition of the question of the origin of life in function of the new experimental and synthetic possibilities in the lab. The question is not anymore how life factually came into being on Earth, but rather the question of the underlying principles of the possibility for life. Synthetic biology aims for a *universal biology*.

The notion of universal biology, however, is ambiguous and needs clarification. There have been several different varieties of universal biology. Nonetheless, they have something in common: "universal biology is *the multidisciplinary study of the noncontingent properties of life as guided by biological theory and constrained by the universe*." (Mariscal & Fleming 2017, p. 122) But to clarify this further, Mariscal & Fleming (2017) distinguish three programs,

which I will name *ontological*, *epistemological*, and *methodological universal biology*.

Ontological universal biology concerns the universal aspects of its object of study, *life*. It is interested in finding features common to all forms of life, regardless whether they exist in the universe or are yet to be actualized. Mariscal & Fleming (2017) give the example of Craig Venter's work on the creation of novel artificial minimal cells (see Simons 2020b). *Epistemological universal biology* rather concerns the universal aspects of the science, *biology*: biological theories or laws that are universally applicable. Examples are universal Darwinism, claiming that all living systems in the universe obey Darwinian principles of evolution (Dawkins 1982), or Kauffman's substrate-neutral understanding of biology based on complexity theory and self-organization (Kauffman 2000). Finally, *methodological universal biology* concerns the universal applicability of biological concepts outside of biology proper, e.g., to investigate the structure of the universe at large. Mariscal & Fleming (2017) give the example of Dan McShea's work on teleology as a product of the structural hierarchy in a system, which McShea (2012) himself had applied both to biology and the formation of solar systems.

Protocell biology seems to fall under the first group, where universal biology is understood as aiming to articulate and explore the physico-chemical properties of any life whatsoever. The particular contingencies of terrestrial life are left aside. Such a universal biology redistributes the experimental landscape. Whereas previously the relevance of formal and artificial biological systems in the life sciences could be questioned, since any connection between the proposed model and life on Earth could be contested, this kind of criticism becomes irrelevant. No matter what one creates in the lab, it is an instantiation of the universal biology and therefore relevant. In that sense, protocell biology differs from Koskinen's (2017) take on synthetic biologists as aiming for how-possibly explanations. Both differ from historical explanations of life (how it actually happened), but how-possibly explanations (how it could have happened otherwise) also differ from how-universally explanations (which we take would hold true for all life everywhere) (see Scharf *et al.* 2015). The latter two become central in synthetic biology, though they might not always perfectly align with one another.

4.2 Luisi and the question of contingency

I wish to explore another dimension of protocell biology through the work of the Luisi group, namely in what way protocell biologists study possibilities. Pier Luigi Luisi describes himself as "a chemist who left his original avenues of polymer chemistry to move towards biochemistry and biology" (Luisi 2007, p. 603). He considers his own work as "chemical synthetic biology"

(*ibid.*, p. 604) and is mainly concerned with the question of the origin of life, or ‘the emergence of life’ as Luisi calls it. His starting point is, “the perception of a shift in the field of the origin of life, a new ‘Zeitgeist’” (Luisi 2006, p. xi).

In what does this new *Zeitgeist* consist? Mainly in a number of shifts in techniques and instruments in biochemistry, going back to the 1990s, such as “the discovery of the self-reproduction of micelles and vesicles” (Stano & Luisi 2010, p. 3639). Micelles and vesicles are molecular structures that automatically form a membrane, typically through a contrast between hydrophilic and hydrophobic parts. While protocells remained theoretical entities for a long period, structures such as liposomes (spherical vesicles) gave these entities a concrete translation in chemical entities which chemists and biologists could articulate and interrogate in the laboratory. Or, in the words of Luisi, “one additional reason for this rise of interest lies in a diffused sense of confidence that the minimal cell is indeed an experimentally accessible target” (Luisi, Ferri & Stano 2006, p. 12).

Luisi speaks of ‘minimal cells’ rather than ‘protocells’. There is a slight but important difference between both notions. While ‘protocells’ refer to life-like biochemical entities that possess some, but not all, properties of a living cell, ‘minimal cells’ are rather “defined as a system that has minimal and sufficient structural conditions for life” (Luisi 2002, p. 209). Luisi describes his own approach as a “semi-synthetic approach to minimal cells” which “involves the use of extant genes and proteins in order to build a supramolecular construct based on lipid vesicles” (Luisi 2007, p. 605). He thus synthesizes a cell chemically, namely the vesicle, but adds parts of living cells, such as ribosomes, to these vesicles.

But what are the questions Luisi is trying to address by studying minimal cells? In short, his reply is the following:

It may bring an answer to the questions of whether life is possible with less complexity, whether life is indeed an emergent property arising from the non-living, whether in the history of cell evolution final living cells had indeed as precursors ‘limping’ half-living cells [...]. Even if we are not able to explain how life originated on Earth, we may be able to give a good answer to such questions. [Luisi 2006, p. 270]

This passage must be unpacked because three things are at stake. A first factor is that of complexity. Minimal cells are interesting and relevant because, contrasted with natural cells, they illuminate “the question of whether or not such complexity [of natural cells] is really essential for life, or whether or not cellular life might be possible with a much smaller number of components” (Luisi, Ferri & Stano 2006, p. 1). Minimal cells provide a way to go beyond the evolutionary contingencies of cells to the central properties of life. The goal is thus to *falsify a necessity*: certain properties are necessary for life. Re-

moving these forms highlights how these complexities are contingent and not necessary.

Secondly, there is the question of the emergence of life: how does living material emerge out of non-living material? This comes close to what was the central question for Oparin and Miller. Luisi does refer favorably to both of them. “However, the main hypothesis, that cellular life derives from inanimate matter, has not been demonstrated yet. It must then be considered still a working hypothesis.” (Luisi 2006, p. 268) He is thus interested in showing how chemically “life developed by itself – without any transcendental help” (Luisi 2002, p. 208). Here the goal seems to be a *confirmation of a possibility*.

And thirdly, “the general question ‘theoretically, how much can the structure of modern cells be simplified?’ is related to the question about the structure of the early cells” (Luisi 2007, p. 610). This brings us back to the question of the origin of life. But Luisi has redefined what kind of phenomena are at stake here. In an editorial, Luisi describes how his own bottom-up approach is of crucial importance,

in those fields of enquiry where the ‘object’ of the investigation is not available. This is the field of origin of life, where all intermediate steps leading to the evolution of early macromolecules, metabolic networks, primitive cells are largely unknown and cannot be studied classically. Bottom-up approaches allow us to probe, certainly in a minimal way, the huge field of reactions, paths, and structures that were potentially viable when life evolved on Earth, and possibly understand what have been the most important milestones in molecular and protocellular evolution. [Luisi, Chiarabelli, & Stano 2014, p. 6]

The aim is not to offer a historical explanation of the origins of life, since that is deemed impossible, because “the sequence of our macromolecules of life – enzymes, RNA, and DNA – are the products of the vagaries of contingency and by definition it is then impossible to reproduce them in the laboratory” (Luisi 2006, p. 268). Similar to Mann, life is rather defined through a number of formal criteria, unconnected to terrestrial biology: “self-maintenance (metabolism), self-reproduction, and evolvability” (Luisi 2007, p. 610). The “universality of the living” can best be grasped through “the theory of autopoiesis” (Lucantoni & Luisi 2012, p. 385).

Luisi frames this through the opposition between determinism and contingentism: “why has a certain type of molecular form been selected in the construction of life – and not another?” (Luisi 2006, p. 13) The determinist claims that the chemistry of terrestrial life is necessary and could not have been otherwise; all life requires it. This was the (implicit) position of someone like Bernal. The contingentist, however, argues that terrestrial biology is based on chemical contingencies and that a universal biology is not bound to it. Luisi considers himself part of the second group, and questions any form of determinism: “it would only make sense if the construction of life was

demonstrably a preferential, highly probable natural pathway: but this is precisely what we do not know” (*ibid.*, p. 6). Once again the question thus becomes one of a falsification of a necessity. The goal, however, is a universal biology: by trying to show the contingency of properties of life, synthetic biologist will end up with a list of properties that resist such ‘falsifications’, *i.e.* the universal properties of life.

More concretely, this way of framing the question of the origin of life is at work in Luisi’s project on Never-Born Proteins (NBPs). The starting point is the idea that

the proteins existing in nature are only an infinitesimal part of the possible polypeptide sequences [...]. One might say, for example, that the ratio between the possible and the actual protein sequences corresponds, in order of magnitude, to the ratio between the size of the universe and the size of a single hydrogen atom [...]. As trivial and old as it is, this consideration elicits some interesting questions about the origin of life, one of which being why and how these “few” extant proteins were selected during evolution. [Luisi 2007, p. 606]

The determinist would argue that the proteins used by terrestrial biology are the only viable ones, due to some as yet undefined special properties. The contingentist, however, would argue that other options were available, but that only the current chemical pathways were chosen through a historical accident. Luisi interestingly adds that “[o]f course we have many still unknown proteins on Earth, but clearly the question of the non-selected NBPs has quite a different flavour” (*ibid.*, p. 606-607). The question thus concerns *unknown possibilities* rather than *unknown actualities*.

What Luisi actually did in his experiments was to explore the realms of NBPs through the phage-display method: you synthesize the DNA parts that would express NBPs and put the DNA in bacteriophages. Subsequently you let the phages infect living cells in order to force the machinery of the cell to express these novel proteins. You thus end up with NBPs of which you could study the specific properties.⁴ What Luisi was interested in was especially the folding of proteins: do terrestrial proteins fold differently than NBPs? If they do, this might corroborate the determinist position. However, Luisi’s results suggest that the proteins used by terrestrial biology are not special and do not seem to stand out in the larger realm of NBPs. Therefore, the data “permit to break a lance in favor of the scenario of contingency” (*ibid.*, p. 607).

But a second conclusion is also present: “If ‘our’ proteins are the product of contingency, then with all probability, the pathway to their prebiotic synthesis cannot be reproduced in the laboratory” (*ibid.*, p. 608). If the chemistry of our terrestrial biology is contingent, this is seen as a disqualifying factor. Its origin is no longer deemed to be an object of genuine scientific study.

Such contingencies could not be reproduced in the laboratory, at least not in a systematic and reproducible way (since each iteration would result in different proteins). Does this then mean the end of the origin of life research? Are we reaching the borders of science, a historical science which possesses neither laws nor data? Surprisingly the answer is no. Synthetic biologists can continue their work, if only they shift towards another question, that of exploring possible ways in which life could come into being, aiming for a universal biology:

the synthesis of exactly ‘our’ proteins on Earth is doomed by contingency – we cannot hope to find out the exact conditions that determined the final sequence of a given protein or a nucleic acid from our Earth. Once this bitter assertion is accepted, we should at least attempt experiments that show that the prebiotic synthesis of *some* specific sequence in many identical copies is possible. [Luisi 2006, p. 82]

4.3 Experimental systems for modal properties

This new generation of synthetic biologists thus engage with the old historical question of the origin of life, but in a radically different manner. The difference resides not so much in a radically different theory. Rather, what has shifted is the realm of phenomena deemed relevant to be studied. For Miller or Bernal it was about articulating the actual historical origin of life on Earth. For authors like Mann or Luisi it is about the possible origin of life.

As stated in the introduction, the strong claim I wish to defend is that to understand this shift in regimes of articulation, a shift in experimental practices is important, related to the possibility to synthesize. As was illustrated with the case of Luisi in particular, the technical possibilities to synthesize and manipulate vesicles allowed for a transformation of proto- and minimal cells from theoretical to experimental entities. They became “an experimentally accessible target” (Luisi, Ferri & Stano 2006, p. 12). Luisi even gives a brief history of this novel experimental object and how minimal cells only recently became something more than pure theory:

The story of the minimal cell on the basis of liposomes started in the early 1990s mostly in my laboratory at the ETH Zürich, where we set up methods to perform complex molecular biology reactions inside liposomes, for example the polymerase chain reaction [ref], or the incorporation of the entire ribosome machinery inside liposomes with the production of the first polypeptide chain [ref]. I believe the term ‘minimal cell’, related to the synthetic biology using liposomes, appeared in that 1995 paper with Oberholzer [ref]. [Luisi 2006, p. v]

Or, to put it philosophically, protocells became a new accessible ‘epistemic thing’ (Rheinberger 1997). Following Rheinberger, epistemic things come

with a novel experimental system, resulting in transformations of the relevant techniques and questions as well. What enabled the shift in synthetic biology from actualities to possibilities is thus these new experimentally accessible cell-like systems that can be synthesized, transformed, and analyzed in laboratories. Through them questions about biological possibilities, which were in the past dismissed as irrelevant or purely speculative, are translated into meaningful experimental questions that can be readily answered through the novel synthetic methods.

What kind of modal properties can be studied through this new experimental system? There are several options. First of all, there is the option of a *falsification of a necessity*. This new method of synthesis allows biologists to show experimentally that a property of life is not necessary, that it could be otherwise. Synthetic biologists can be interested in this for several reasons: either it shows how the existing theories are inadequate, since they assume its necessity; or, if it cannot be falsified, it brings them a step closer to finding the universal properties of life. Secondly, there is the *confirmation of a possibility*: showing that something that we thought was impossible, or never thought about, is nonetheless possible. This could be interpreted along Koskinen's examples of how-possibly models. In more recent work, Koskinen has explored this theme further through a number of themes from philosophy of science. First of all, there is the multiple realizability thesis (Koskinen 2018). The work of synthetic biologists could then be interpreted as the exploration of how the same biological function could be realized through different means: either the natural way or its artificially designed counterpart. This is applicable to origins of life research as well, mainly if it is occupied with studying alternative origins of life.

Secondly, in a more recent paper Knuuttila and Koskinen (2020) suggest the useful notion of semifactuality: what synthetic biologists are interested in is not just 'what-if-things-were-different' questions (counterfactuals), but often also 'even-if-things-were-different' questions (semifactuals). They want to know whether something that is true in the actual world is also true in slightly different possible worlds, e.g. whether DNA and XNA can have the same function or, as in the case of Luisi, whether the proteins used by life would be the same in slightly different worlds. The new experimental system of synthetic biologists enables them to translate these questions about modal properties into questions that can be experimentally pursued.

5. Conclusion

In this article, I have argued through the case of research in the origin of life how synthetic biology can be characterized by a shift in its regime of articulation, from one focusing on the actual and contingent terrestrial biology towards one focused on a universal biology. The questions of the origins of life thus shifts from ‘what has happened?’ to the question ‘what has possibly happened?’. Let me reiterate that my claim is not that the old historical question of the origins of life was completely abandoned. There are still biologists trying to answer this question. My claim is rather that the question of a universal biology has become more dominant in synthetic biology.

Such a shift from actuality to possibility can also be seen at work in other projects in synthetic biology, such as xenobiology (Koskinen 2017) and synthetic genomics (Simons 200b). Nonetheless, what protocell biology brings to the table is the link with debates on universal biology and behind questions about ‘what has possibly happened?’ questions concerned ‘what has necessary happened?’ or ‘what has universally happened?’ are at work.

Moreover, I have tried to argue that the reason for this shift towards biological possibilities is not just a matter of biologists having reached a point where they understand terrestrial biology and now subsequently want to know what is universal. As critics of universal biology have noted before, the things we do not understand about terrestrial biology are still nearly limitless (e.g. Sterelny 1997). So why then focus on universal elements? The hypothesis that I defended is that the answer is a shift in its experimental system (Rheinberger 1997): new accessible targets such as vesicles, combined with stronger synthetic methods, made these questions about biological possibilities experimentally meaningful. Similarly, the prediction is that in other synthetic biology projects the main reason for this shift is related to shifts in experimental systems as well, mainly the rise of genomics which is linked with the increase in use of computers and big data sets (see Stevens 2013, Leonelli 2016).

To end, let me briefly highlight two further avenues of research to which this hypothesis give rise. First of all, this perspective allows us to better understand the somewhat strange alliance within synthetic biology between often practically-minded engineers and theory-minded chemists such as Mann or Luisi. Synthetic biology is sometimes seen as split between these two groups, often with the result that most attention is paid to the engineers at the expense of the chemists. My hypothesis, however, allows us to see how both groups can actually be aligned, since both see it as their task to explore biological possibilities.

Secondly, this perspective also enables us to situate synthetic biology within the broader technoscientific wave (Schmidt 2015, Simons 2021b).

Many technosciences can be characterized by an interest in exploring possibilities, often without a concrete interest to go beyond a mere proof-of-principle (Bensaude-Vincent & Loeve 2018). Nanotechnologists are interested in what nanomaterials can do; roboticists are interested in what robots are capable of. Similar to synthetic biologists they smoothly combine an interest in fundamental research and practical applications. Focusing on the shift in its regime of articulation enables us therefore to understand what is specific to synthetic biology while at the same time also situating it in more recent technoscientific developments.

Notes

- ¹ Schmidt proposes his own candidate, namely *late modern technologies* which aim for “the idea(l) of harnessing self-organization for engineering purposes” (Schmidt 2015, p. 1). Although I do not disagree with this candidate, I wish to supplement it with an analysis of synthetic biology that highlights not only how its object, but also its ambitions and methods have changed.
- ² An important factor here is the broader political context of the USSR. Oparin’s view is influenced by a form of ‘dialectical materialism’. Oparin claims that “Dialectical materialism makes it possible to accept the material basis of life without having to regard every phenomenon not included in physics and chemistry as vitalistic or supernatural” (Oparin 1961, p. 5). It has been noted “that many of those who contributed to the early-20th century philosophical breakthrough in the study of the origin of life were Marxists: notably Oparin, Haldane, the virologist N.W. Pirie and the English physical chemist J.D. Bernal” (Fry 2005, p. 27). This seems to be an instance where political ideology played a *positive* and *productive* role for scientific research.
- ³ In a more recent paper, the group of Dieter Braun speaks of a choice between an “archaeological approach” and a “synthetic approach,” opting for the latter since “the laws of physics and chemistry are universal. Hence, if a synthesis pathway is discovered that, *e.g.*, nucleotides can be synthesized in high yield and purity using a limited set of conditions, the same set of conditions would have produced the same result at the emergence of life.” The old question, “the historical Origin of Life question, *i.e.*, how exactly life on Earth emerged, will remain hidden and speculative” (Agerschou, Mast & Braun 2017, pp. 61-62).
- ⁴ In addition, they added the tripeptide PRG in the DNA strands in order to prevent the enzymes of the cells from digesting the NBPs. They also looked at ‘never-born’ messenger RNAs, which in properties seem not that different from the actual m-RNAs terrestrial biology uses.

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