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ORIGINAL PAPER

Some conceptual issues in the transition from chemistry to biology

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Abstract The transition from chemistry to biology is an extremely complex issue because of the huge phenomenological differences between the two domains and because this transition has many different aspects and dimensions. In this paper, I will try to analyze how chemical systems have developed a cohesive, self-maintaining and functionally differentiated system that recruits its organization to stay far from equilibrium. This organization cannot exist but in an individualized form, and yet, it unfolds both a diachronic-historical and a synchronic collective dimension. I will argue that, far from being a problem, these different dimensions of the phenomenon of life, appear as a consequence of the nature of this individualized organization.

Keywords Far-from-equilibrium self-maintaining organization · Functional diversity · Individualization · Synchronic collective organization

1 Introduction

The transition from chemistry to biology is an extremely complex issue. First, because of the huge phenomenological differences between the two domains; second, because this line of research must overcome the problems posed by the fact that the appearance of life on Earth erased all evidence of the hypothetical variety of intermediate forms of organization leading from chemistry to life; and third, because this transition has many different aspects and dimensions (see below). How to organize all these questions into a unifying line of research? What guidelines

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should we follow for detecting the most important issues that may help our understanding of the transition from the chemical to the biological domain? This undertaking most likely requires a definition, or at least a rough outline, of what we mean by systems which show a minimal form of life. Yet, "life" is a polysemic, multifarious phenomenon: it appears in the form of individualized, cohesive systems as well as collective, physically-unbounded networks; as actual organizations as well as entailed sets of diachronic/historical processes. Thus, the biological domain has several complementary and entangled dimensions: individual and collective, synchronic and diachronic. In other words, although the most striking characteristics of living systems appear essentially in organisms, these cannot be fully constituted without forming part of evolutionary processes and ecological webs.

If no attempt is made to unify the different aspects of the phenomenon of life, we will lack a defined target for our research, a clear point of reference towards which to head. The development of a unified concept of life should be based on our current knowledge of biological phenomenology, moving backwards from there in an attempt to "deconstruct" this highly complex concept in order to grasp its "chemical core".[1]

My purpose in this paper is to analyze some of the fundamental—hence, philosophical—problems associated with the earlier stages of the transition from chemistry to biology, and to contribute to building a unifying conceptual framework, thus helping to move scientific research forward in this domain. The questions explored are: the origin of functional organizations; the emergence of individuality and its self-reproduction; and our understanding of the emergence of evolution and its role in the unfolding of the multidimensionality of biological phenomenology. While conceptually different, all these questions are in fact closely related and indeed, the main challenge of this line of philosophical research is precisely to untangle the many-threaded web that ties them all together. There are, of course, several other key issues in the origin of life, such as the emergence of genetic information, agency and regulation; or the origin of cooperative and symbiotic interactions, the importance of which is undeniable. I focus on the aforementioned questions for two reasons: firstly, because (as I will argue), they are more fundamental; and secondly, because these questions have received less attention than the others.

The structure of the paper is as follows: in the next section I will explore the most basic differences, from the thermodynamic perspective, between chemical and biological systems, namely, the capacity of the latter to use their own organization to remain in a far-from-equilibrium state. In the third section I will analyze the logical structure of this organization, showing that it is a self-maintaining network of chemical processes sustained by a set of internally generated and maintained constraints, and that this structure is what enables potential functional diversity. The

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[1] I will not discuss here the problem of whether life could or should be defined for developing a useful research program in the Origin of Life domain. First, because in this paper I will only try to explain the emergence of certain (in my view, fundamental) properties of life *as we know it in our planet*; and second, because I am just focusing only in the earlier steps of the biogenic process, and therefore, I am not endorsing here any claim about which could be the requirements to call something a full-fledged biological system.

next section argues that such a form of organization can only exist in an individualized, strongly integrated way, thus constituting the basic unity for self-reproduction and evolution (fifth section), while at the same time generating a complex and entangled diachronic and synchronic system (sixth section). Finally, at the end of the paper I will try to summarize and bring together the main conclusions drawn in these different sections.

2 The starting point: a chemical far-from-equilibrium *organization*

Chemical systems consist of processes of molecular transformation. These transformations—called chemical reactions—encompass changes that only involve the positions of electrons, with no change in the nuclei. Interestingly, these transformations—chemical reactions—can recruit some of the resulting products to yield new processes of transformation. Thus, new chemical entities are created and new chemical properties are in turn brought forth, and the cycle continues. Therefore, in the chemical domain, processes and entities are linked and serve to reinforce each other, yielding a combinatorial process.[2] This, in theory, allows for the creation of an indefinite, open-ended variety of chemical entities.

Yet in practice, the creativity of the non-biotic chemical world depends on a number of different factors. On the one hand, too high a throughput of energy precludes the formation of large, complex molecules based on covalent bonds. On the other hand, too low a throughput of energy results in reactions tending to yield only the more thermodynamically stable components. Thus, the transition towards life requires a very specific scenario, in which processes occur within a very narrow range of conditions. Moreover, this scenario includes not only chemical processes, but also other types of macroscopic and microscopic geological and physical processes (Nisbert and Sleep 2001). Indeed, we must assume that on Earth (and perhaps elsewhere in the universe also), about 4000 my ago a set of very special circumstances occurred, providing not only a temporal and spatial scenario which fell within the aforementioned energy range, but also several local macroscopic geo-chemical forms of far-from-equilibrium stabilities (i.e., hydro-thermal cycles). Together, a very rare and complex set of astronomical and geological factors produced a highly exceptional set of macroscopic boundary conditions (Ward and Brownlee 2004), which in turn enabled an exceptional process of chemical complexification. Only once these complex macroscopic conditions have been met should the focus shift to the microscopic (molecular) framework. Why? Because only at this scale could recursive feedback occur between forms of dissipative stability and molecular increases in complexity (i.e. autocatalytic reactions leading to the production of more complex catalysts, leading in turn to the production of new catalytic reactions, etc.). And the reason why this "virtuous circle" could happen only at a microscopic scale is that, in order to have an entailment of reactions, a large number of different types of molecules are required in close

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[2] This combinatorial process is in turn enhanced by the phenomenon of catalysis (a catalyst is a chemical element that increases the rate of a reaction without being consumed).

proximity. Hence, this "virtuous circle" constitutes the starting point that may have led to the earlier proto-biological systems, namely, what I call "organizationally differentiated" chemical systems capable of remaining in a far-from-equilibrium state. Or in other words, a type of chemical system capable of using its own (however minimal) organization to remain in a far-from-equilibrium state.

Why am I focusing on this capacity? Contrary to what happens in the non-biotic world, where systems remain far-from-equilibrium only because of a set of external Boundary Conditions, over which they have no influence, the biological world is a domain populated by systems in which chemical reactions are selectively driven to produce functional compounds while avoiding the myriad of side reactions that chemical and thermodynamic laws permit.[3] In other words, in the biological domain, processes occur permanently in far-from-equilibrium conditions, because they use their own organization to do so. But how can this be done? And what would be the minimal form of chemical system capable of remaining in a far-from-equilibrium state?

To answer these questions, let us begin with the concept of reaction cycles. A reaction cycle is a set of reactions that generate a loop. A reaction cycle usually works because at least one reaction is driven by a catalyst, and when this is the case, it is called a catalytic cycle. If at least one of the reaction products is also a reactant, and therefore a catalyst in the same or in a coupled reaction of the cycle, the cycle is called an autocatalytic cycle. An autocatalytic reaction loop emerges as a consequence of the exploration of a chemical environment's structure and the reactivity space of its starting components, and connects intermediate products (substrates as opposed to catalysts) in a cyclic pathway. Now, if the forward and reverse reaction rates are such that each chemical species is being created at the same rate as it is being destroyed, the system is in equilibrium. Yet, in an autocatalytic cycle, the reactions are under kinetic control, namely, reactions are driven by catalysts to produce certain compounds that are not the most stable equilibrium compounds, and therefore the system is driven away from equilibrium. This of course requires a set of special boundary conditions and a continuous supply of energy (Pascal et al. 2013).

Within the field of the Origins of Life, researchers have focused on two different types of reaction cycles: self-replicating autocatalytic cycles, and self-maintaining autocatalytic ones. Both, in fact, are far-from-equilibrium, kinetically-driven reactions (because they are autocatalytic), yet the former focuses on the generation of a diachronic entailment of structures, where the core idea is the cyclic copy of a target structure driven by the catalytic action of this structure on itself (see also Sect. 5), whereas the second focuses on the generation of a synchronic organization: a cyclic set of different entailed reactions. Whereas the former aids the study of the origin of the genetic process, the second aids the study of the emergence of metabolism. As Eschenmoser (2007) has pointed out, "another type of reaction loop that can emerge as a consequence of the exploration of a chemical environment's structure and reactivity space is one that driven by the free energy of starting

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[3] A side reaction is a secondary or subsidiary reaction that takes place simultaneously with the reaction of primary interest.

materials, connects intermediate products (substrates as opposed to catalysts) in a cyclic pathway: such a cycle is referred to as an autocatalytic *metabolic cycle*." (p 311. Italics in the quotation).

So why should we focus on "metabolic" SM cycles, rather than on "genetic" or self-replicating cycles? Well, because the latter focus on the replication of molecules, which by itself cannot explain the appearance of chemical systems capable of remaining FFE. Pross (2003, 2009), for example, has argued that given adequate environmental variety, a process which increases the structural complexity of the replicators may in turn lead to the appearance of what he calls a "variety of catalytic effects" that can be recruited by the system to gather environmental energy resources and use them for its own maintenance. As he says, "the emergence of more complex replicators would not be kinetically sustainable if the added complexity were unable to provide some kinetic advantage - complexity must provide some existential advantage. It now seems clear that the kinetic advantage that longer sequences could provide would not have stemmed from any inherently greater replicating ability associated with the longer sequences (Spiegelman's experiment demonstrated that) but, rather, through a variety of catalytic effects that some particular sequences might have afforded." (Pross 2003, p. 401). But the concept of catalytic networks, or the more abstract "catalytic task space" (Kauffman 2000, pp. 13–14), involves a framework in which the focus is not on diachronic populations of molecules competing for faster replication, but rather on synchronic systems of different reactions forming an integrated organization. In other words, a set of molecules that have diverse catalytic effects on each other, as a means of coordinating the particular locations, times and speeds at which their chemical transformations occur (Moreno and Ruiz-Mirazo 2009).

This is why we should focus on the first case, namely that of "metabolic" SM cycles. In other words, in order to understand the OL we should pay attention to how chemical processes gather together in a cohesive, self-maintaining whole. Why should we link the concept of self-maintenance with that of organization? Because a prebiotic chemical system cannot remain stable unless the arrangement of reactions constituting the system contribute to its own maintenance. That is why, in the prebiotic context, a chemical system able to remain stable in far-from-equilibrium conditions must necessarily be a self-maintaining organization. Moreover, the concept of "organization" implies a system whose parts are related to each other so as to achieve a *goal* or *purpose* (that is why it is said that a given system is "well" or "badly" organized). Now, a prebiotic system, if it remains stable, is an "organization" because the arrangement of reactions constituting the system *contributes to its own maintenance*. In other words, in the prebiotic context, a chemical organization is synonymous with a self-maintaining organization.

This concept is very important for our purpose, because it will help us understand how a chemical system becomes capable of remaining stable in far-from-equilibrium conditions. In other words, it will help us understand how it manages to become less and less dependent on external environmental conditions and, at the same time, how it can increase its internal complexity. In the aforementioned case of an autocatalytic cycle, the catalyst acts as an internally created constraint, since the outcome of the action of the catalyst leads to its re-production, and therefore, to the cyclic maintenance of the set of reactions. The cycle is therefore not only maintained by the external Boundary Conditions, but also (albeit in a minimal sense) by the catalyst, and the catalyst is maintained by its own action. Yet, to maintain a system in far-from-equilibrium conditions, the system has to (1) capture and (2) organize matter and energy so as to keep its organization going. And this requires something more than a mere autocatalytic cycle. Indeed, as we shall see, this requires an organization constituted by many differentiated catalytic reactions and other coupled processes. But here the key point is a paradoxical circularity: the system has to organize the energy flows of its environment so as to maintain a precarious (due to its dissipative nature) organization; yet at the same time, it has to use this organization to harness usefully (on its own behalf) external energy (and material) resources.

Some minimal form of self-maintaining organization is therefore a requirement for starting the transition from chemistry to biology. I have already analyzed the very special conditions required for starting a process of chemical evolution, where the focus lies in the formation of chemical reaction cycles. Martin and Russell (2003) have suggested that many chemical reaction cycles would have appeared on the primitive Earth, driven by the sun or geothermal energy. For instance, a constant flow of energy and micro-porous surfaces would have favored the appearance of chemical cycles leading to the formation of relatively complex organic compounds, and some of these compounds may have been recruited as catalysts. Therefore, in order to be a relevant starting point in the origin of life, a chemical organization must gradually take over (at least partially) the boundary conditions that enable its existence. In other words, it must “use” or “recruit” its own organization for its own maintenance. But which kind of chemical cyclic organization provides the conditions to be able to capture and adequately manage energy flows in order to maintain the cyclic reactions that constitute them? This question leads us to the next section.

3 Minimal metabolism and the origin of functional diversity

An obvious requirement of the origin of life is that we must start with systems that fulfill a twofold condition: firstly, they must, in principle, be simple enough to emerge spontaneously from a set of material aggregates under the conditions of the primitive Earth. This means that we need to conceive of a set of plausible boundary conditions which would enable the spontaneous appearance of chemical systems endowed with, in at least a very simple way, a self-maintaining organization, even though such systems were probably preceded by many other systems whose maintenance was essentially dependent on boundary conditions that were much more complex than themselves. Secondly, and at the same time, *they must* also possess the capacity to increase their organizational variety.[4] For example, perhaps some of the components involved in the basic self-maintaining cycle can generate a

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[4] And of course, they should also be able to preserve organizational innovations. But we will discuss this question later.

physical border, which in turn ensures better conditions for recursive self-maintenance; or/and perhaps the basic self-maintaining cycle generates some components (i.e. catalysts) that make the processes follow chemically unlikely pathways; or perhaps they coordinate their inter-conversion processes in space and time so as to increase the number and variety of reactions and components involved in the organization. Thus, the idea is that in order to be a candidate for prebiotic evolution, a chemical system must be organized in such a way that it harbors a potential variety of internal constraints that contribute in different ways to the self-maintenance of the system (Moreno and Ruiz-Mirazo 2009). This is what, in fact, is implicit in the idea of a metabolic organization.

Let me explain this further. Albeit at a minimal level, what we are looking for is a type of organization that allows both a minimal form of functional differentiation and the potential to increase it. Certainly, what the organization we are looking for should fulfill is the generic framework which will allow for open functional diversification (although the effective actualization would, of course, require many additional modifications). As we have seen, in order to maintain itself in far-from-equilibrium conditions, a system must use its internal organization; and in particular, it must use constraints for capturing matter and energy, so as to keep the whole organization going. In short, it must produce something "useful" or "functional" (Mossio and Moreno 2010).

More technically, we could justify the use of functional terms in this early stage of prebiotic evolution as follows. An internally produced constraint C has a (specific) function in a chemical organization because it contributes to the maintenance of the system that produces it; thus, C is there by virtue of its effects. This is consistent with the teleological dimension of the concept of function in biology: we say that X has a function (F) insofar as X exists because it does F (e.g. the heart exists because it pumps blood). Bickhard and Christensen have proposed a way to naturalize the idea of function within the framework of self-maintaining systems. According to these authors, functions are contributions that the constitutive parts of a far-from-equilibrium system make to its maintenance: "the contributions that a self-maintenant system makes to its own continued existence are, in that sense, *functional* for that system: They serve the general function of helping to maintain the existence of the far-from-equilibrium system. Derivatively, any components or parts of a system (…) serve such a function insofar as they make such a contribution. Serving a function, in this sense, is necessarily relative to the system whose maintenance is being contributed to." (Bickhard 2000). Mossio et al. (2009) have argued that, in order to speak about functions in a system, the idea of *differentiation* (both in terms of the parts of the system and their specific contribution to its global self-maintaining dynamics) becomes crucial, and therefore, mere physical–chemical dissipative structures do not have functions because they do not have organizationally distinguishable parts. What specifically characterizes an organizationally differentiated self-maintaining system is that it is constituted by a set of constraints (catalysts, membrane, etc.) that harness the energy flows so as to maintain and re-generate that same set of constraints. It is in this context that we can talk about organizational differentiation, in the sense of an organization harboring (at least a minimal form of) functional differentiation or functional diversity. Thus, functional differentiation would emerge when a set of constraints come together in a sort of mutually reinforcing effect, and lies at the heart of a new set of more robust self-maintaining dynamics (Mossio and Moreno 2010).

How can this minimal organization lead to a more complex type of chemical organization capable of remaining stable? Well, this could be achieved if a chemical system were capable of producing a set of different but interdependent constraints. In such a system, the action of each constraint would be to harness underlying chemical interactions in order to produce another constraint, and so on until the process comes full loop in a recursive manner. Indeed, biological cells are functionally differentiated chemical systems, because their self-maintenance is ensured by a large number of highly complex, mutually dependent enzymes which act as constraints and are internally produced and maintained.

Formulated in chemical terms, this idea corresponds to the abstract concept of "reflexively catalytic network", a system of cyclic reactions where every reaction is catalyzed by at least one molecule involved in any of the reactions of the system, and where every reactant is produced within the system from a small core of components (Hordijk and Steel 2004).[5] The main difference between a reflexively catalytic network and the small molecule autocatalytic cycles described in the previous section is that the former is constituted by modular catalysts showing thus a much more interesting capacity to display functional diversity. Thus, by internally synthesizing its own constraints, the system becomes capable of performing a diversified modulation of its own self-maintaining dynamics. And it is in this organizational context that different constraints can make *distinguishable contributions* to the global maintenance of the system. In sum, once we have an organization of this type, functional differentiation can subsist, at least in principle, indefinitely.

4 Individuality

In the two preceding sections we have seen that the origin of life requires a form of organization capable of managing energy flows so as to remain stable in far-from-equilibrium conditions and harboring at least a minimal level of functional diversity. However, this organization requires a way to manage the exchange of matter and energy between itself and its environment. In this scenario, the only way to achieve this aim is through a selectively permeable compartment.[6] A selectively permeable compartment is necessary for ensuring concentrations and generating a differentiated and adjustable internal environment (in terms of volume, pH and chemical composition, etc.) that fosters the creation of a metabolic process (and conversely).

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[5] Though a reflexively catalytic network has not yet been produced in vitro, different theoretical studies suggest that it is likely that systems achieving reflexive catalytic closure could have appeared before a RNA stage (Hordjik et al. 2012; Vasas et al. 2012). These models are based on the pioneer work of Kauffman (1986).

[6] Prebiotic compartments would probably be the result of spontaneous assembling of amphiphilic molecules in water (Deamer 1985; Deamer & Dworkin 2005).

By creating a separation between the inside and outside of the system, compartments produce concentration gradients (Mitchell 1961; Harold 1986), pH and oxidation–reduction differences (Morowitz 1981, 1992; Chen and Szostak 2004). And these differences could be used as energy storage mechanisms, eventually supporting endothermic transformations and against gradient active solute transport (as those utilized in all extant cells (Skulachev 1992). Therefore, encapsulation emerges as a necessary condition for the evolution of a primitive metabolic (or "proto-metabolic"[7]) organization, capable of both managing the energy flows required for the maintenance of the system (Ruiz Mirazo and Moreno 2004) and of developing internal organizational differentiation. In turn, the encapsulated proto-metabolic organization would be a tool for the evolution of a compartment, providing catalysts and other compounds that enable the emergence of selective permeability.[8]

However, the coupling of self-assembled compartments with autocatalytic proto-metabolic networks was by no means a trivial achievement. It was likely the result of a long process of essays and mutual transformations.

> "Numerous times in prebiotic chemistry, there may have occurred the chance insertion of complex reaction systems, developed in different chemical contexts, into various self assembled compartments (e.g. into the internal aqueous phase and/or membrane of lipid vesicles). However, such structures would have been unlikely to result in stable functional protocell systems since the membrane would probably not possess the correct composition, nor contain the correct molecular machinery (selective channels, carriers, ion pumps, mechanisms to transduce external energy into a form usable by chemical reactions, etc.) in order to meet the permeability, catalytic and energy requirements to keep the metabolism running, and at the same time avoid e.g. osmotic burst. Equally, the metabolic processes would probably not be able to synthesize all of the key system components enabling division into equally functional offspring. The first systems with the ability to robustly maintain themselves far-from-equilibrium (and with the ability to divide in a controlled way into equally functional progeny) could only have existed as such if they were encapsulated and their internal (proto-metabolic) organization and compartment were tightly integrated" (Shirt-Ediss 2016, p. 85).

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[7] De Duve (2007) uses the term "proto-metabolism" for those chemical networks driven by catalysts that, whatever their nature, cannot have displayed the exquisite specificity of present-day enzymes and must necessarily have produced some sort of "dirty gemisch".

[8] The origin of far-from-equilibrium maintenance of chemical organizations also raises the problem of the interplay of individuated systems and collective networks, or in other words, of sets of different types of individual systems in conjunction with environmental compounds, interacting together as a long-term self-maintaining collective system. This is an important issue in the field of Origin of Life because the early appearance of a collective proto-ecological network would in turn permit metabolically less complex individual systems. As discussed by Morowitz (1992) and Morange (2008), metabolic simplicity depends on the chemical demands of the environment and, as a consequence, there is not *a* minimal metabolic network. Thus, a highly stable and chemically rich environment is less demanding than a more changeable and chemically restricted one. However, the trade-off between metabolic and environmental complexities during the early evolutionary stages has yet to be explored. I will discuss later (Sect. 6) the close and complex relationship between the individual and collective dimensions in the origin of life.

If, in addition, the encapsulated system is capable of reproduction and inheritance, it could also yield a process of evolution driven by a very primitive form of natural selection (I will discuss this question in next section).

The encapsulation of a self-maintaining chemical system has far-reaching organizational implications since its viability imposes significant changes on both parts (compartments and metabolic networks) in order to enable a functional coupling between them. A very simple compartment (for example, a self-assembled vesicle) would be a limiting factor for the evolution of an enclosed autocatalytic network because of its inability to allow a selective control of the inside-outside transport (which, for example, would lead to an osmotic burst). However, if the compartment becomes more complex—including, for example, functional short peptides (Ruiz-Mirazo and Mavelli 2008) and allowing selective transport—then both parts may reinforce their respective and complementary functionality and evolve towards an integrated system.

Such a system would be an *integrated* organization, because a selectively permeable compartment would become a functional constraint that acts globally and, it could therefore be said, in some sense "controls" all the remaining constraints/functions of the system. Interestingly, this selectively permeable compartment is in fact a composed constraint (i.e. the self-assembled vesicle plus the local constraints inserted into it); yet, because the action of these different constraints affects the inner processes conjointly, they could be seen as forming an integrated global constraint. Under these conditions, the compartment is what ensures the global cohesion of the system, because it affects the activity of all the different local constraints within it. But, as explained earlier, the compartment does not act merely as a global physical border; on the contrary, it must be associated with other constraints that, together, establish a set of global roles. The different roles of the compartment, such as the selective forms of permeability and the mechanisms of its shrinkage or growth (and reproduction when that happens, see next section), exemplify this global "control" of the system.

Thus, encapsulation of a proto-metabolic system defines a minimal form of individuality in terms of cohesion, physical boundedness and organizational asymmetry with its environment. A selectively permeable compartment affects all the functions of the system and it is for this reason that an encapsulated self-maintaining system (a protocell[9]) is an organizationally integrated system. In other words, the interdependent set of constraints that we described in Sect. 3 must themselves be globally constrained. Consequently, a clear distinction is created between the whole set of encapsulated processes and the rest of the world. Indeed, such an encapsulated system *acts on its own behalf*, i.e. it ensures the maintenance of its identity through the selective control of transport processes, which in turn

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[9] A protocell is any experimental or theoretical model that involves a self-assembling compartment linked to chemical processes taking place around or within it (Rasmussen et al. 2008; Ruiz-Mirazo 2011). Here, I use the concept of protocell in a slightly more specific sense, as a far-from-equilibrium, self-maintaining compartmentalized system with some prebiotic properties, such as growth, autocatalytic activities or reproduction.

functionally modifies its constitutive processes in accordance with environmental circumstances.

In sum, self-maintaining protocells realize a minimal form of biological individuality, because they are a specific and physically bounded set of processes achieving a cohesive and functionally integrated entity; and in turn, the properties of being able to remain in far-from-equilibrium conditions and harbor functional differentiation (as well as, where appropriate, to self-reproduce in order to become a unit of selection in evolution) follow on from this cohesive organization. All these features prefigure the origin of what, in biology, is considered the paradigmatic form of individuality, namely, the organism, understood as an integrated, physically cohesive entity that embodies the most relevant biological properties (metabolism, reproduction, growth and development, homeostasis and response to stimuli).[10] In sum, the emergence of individualized organizations was a fundamental step in the transition from chemistry to biology, because they were both a source and a locus of complexification through prebiotic evolution, an early unit of selection and a minimal form of organismality.

5 Self-reproduction and the beginning of evolution

So far we have analyzed the transition from chemical systems to biological ones by focusing on which causal structure could have supported increasingly complex and integrated chemical systems. In this enquiry we have highlighted the circular self-maintaining logic of the *actual* organization of these systems. Yet, it is very likely that the lifespan of these systems would have been very limited and therefore, once disintegrated, innovations would have been lost. Hence, while the creation of an individuated, cohesive, self-maintaining form of organization is a fundamental step in the transition from chemistry to biology, what is equally important is the emergence of a mechanism ensuring the maintenance of their specific identity beyond their individual lifespan. This mechanism was self-reproduction (coupled with some form of heredity). Only in this way could individuated, self-maintaining systems ensure a long-term entailment between their successive organizations, transmitting innovations and allowing a cumulative historical process.

However, while reproduction is necessary for *genealogically* explaining the appearance of increasingly complex prebiotic systems, it *logically* requires, as we shall argue, the emergence of a cohesive individuated system (Maturana and Varela 1987). Let us clarify first the difference between reproduction and replication (Moreno and Etxeberria 1992). Replication is the construction of a copy of a

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[10] In the Stanford Encyclopedia of Philosophy, Wilson and Barker (2016) define organism as a contiguous living system, capable of some degree of response to stimuli (“agency”), reproduction, growth and development, and homeostasis.

thermodynamically conservative structure (a procedure through which a structure maintains a conservative order, i.e. a static one).[11] Reproduction, on the other hand, involves the construction of a separate copy of a *far-from-equilibrium organization* (i.e. what is duplicated is a dynamic, dissipative order). Hence, self-reproduction is a phenomenon in which the system itself is the "agent" that triggers the copy process that concludes when a spatially separate —yet similar—entity is produced. Since the new system is similar to the original, the process can be repeated indefinitely (providing the environmental conditions permit it).

Now, since we have argued that the transition from chemistry to biology relies fundamentally on far-from-equilibrium organizations, self-reproduction is naturally of great interest to us, and we will deal with replication only to the extent that the complexity of the former process requires the participation of this mechanism. Therefore, self-reproduction implies two things: (1) that what will be reproduced is the organization of the type of system in question as a whole; and (2) that the cause/mechanism of reproduction will be the organization of the system itself. This means that self-reproduction requires an identity, a "self" that first triggers the copy process and then becomes its result.

But how does a self-producing organization become a self-re-producing one? Self-reproduction occurs when an individualized system is organized in such a way that the deployment of its continuous process of self-production (i.e. the entailment of different reactions of synthesis and degradation) generates growth and, once a certain size threshold has been reached, the compartment (and what is contained inside) divides into two new units. Needless to say, all these processes must be organized (spatially and temporally). Reproduction is strongly related to self-maintaining organization because reproduction is not only a copy of a "form" (as could be said of the genetically controlled reproduction of present day cells), but also a continuity of the material entailments of the metabolic organization of the system. As Griesemer (2002) has pointed out, the reproduction process involves the material connection between the reproducer and the reproduced system. And in fact, when certain conditions occur, the growth and division of a protocell becomes an inevitable consequence of its own self-maintaining dynamics: autocatalysis causes the production and accumulation of different types of components within the system, and the cellular nature of this causes division to occur spontaneously once a critical size has been reached and the system has become unstable. Thus, from this perspective, reproduction is the specific path taken in certain self-maintaining systems to ensure the continuity of their functional organization, which maintains itself over time. The occurrence of reproduction may be explained in terms of the time relation between the production and decay of the constitutive components in a

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[11] Template replication is a typical example. In fact, the basic mechanism of replication by template can be found in relatively simple systems, like the growth of crystals. Modular templates like RNA or DNA are a specific form of this mechanism. The process of copy by template is grounded in the morphological and chemical properties (i.e. a conjunction of form and materiality) possessed by certain polymers, especially nucleic acids. In these molecules, nucleotides polymerize one by one, following the guidelines set by the template string; no instructions are required to explicitly determine the form of the final set, because the reconstruction of the sequential configuration of the original molecule is ensured by the complementarity principle of nucleotide bases.

self-maintaining organization. If the rate of replacement of the constitutive components is faster than their decay, the self-maintaining cycles of the system will prompt it to establish reproductive cycles: the system will grow and reproduce; otherwise, it will disintegrate (Zepik et al. 2001). That is why self-reproduction is a derived form of the ongoing process of an organization's self-maintenance.

As shown by Mavelli and Ruiz Mirazo (2013), when certain parameters are met, simple protocells will spontaneously settle into a stationary reproducing regime, characterized by regular growth and a division cycle, including the maintenance of a certain standard size and chemical composition across generations. According to these authors, under these particular conditions, protocells generate anosmotic synchronization between membrane and core volume growth that in turn produces a stationary reproduction regime. Therefore, even in simple forms of self-maintaining organizations which lack template components, reproduction with a certain degree of identity transmission can occur (although of course, the fidelity of the reproduced copies would be very low).

The consequence of self-reproduction is that the organization persists beyond the lifetime of individualized protocells; and processes which occur at a populational level may be causally connected to the strictly individualized organizational level through a diachronic process that transcends the lifespan of individuals. This in turn paves the way for the appearance of an evolutionary mechanism based on some preliminary kind of competitive dynamics.[12] Once encapsulated organizations ("protocells") capable of reproducing with a certain form of inheritance had developed, the appearance of populations of protocells may have led to a primitive form of evolution by natural selection; this in turn could have favored those systems whose functional integration happened to be more efficient, while eliminating others. There are a variety of combinations in which the functional components of these systems may contribute to their maintenance and reproductive success. This variety ensures a minimal, yet wide enough, phenotypic space for selection to actually operate as an evolutionary mechanism without running into "dead ends" or bottlenecks of too low complexity (Arnellos and Moreno 2012). However, in these earlier stages, the mechanism of natural selection was not yet fully operational (Godfrey-Smith 2009).[13] Indeed, there was a bottleneck in the evolution of protocells: as organized complexity increased, its preservation became more and more difficult. Therefore, only those systems that developed specific mechanisms to stabilize and retain their increasing organizational (and, therefore, structural) complexity with a fairly high degree of reliability could begin to unfold new and

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[12] Evelyn Fox Keller (2009, 2010) has suggested that some form of historical accumulation of complexity preceded evolution by natural selection. What Keller is trying to stress is that what is needed for a primitive form of evolution is the existence of systems with properties that contribute to their persistence, which will be enough to trigger a different (simpler) selection process for stability and persistence. In other words, adaptation mechanisms, which result in the generation of stabilities in a system, are enough for the operation of simpler evolutionary-competitive dynamics that will result in different degrees of maintenance of those stabilities.

[13] As argued in Moreno and Ruiz-Mirazo (2009), there are several experimental cases (e.g. Walde et al. 1994; Segre and Lancet 2000; Chen et al. 2004) which have shown that multiplication, variation and heredity would constitute a necessary but not sufficient set of conditions for what is commonly understood as evolution by natural selection.

higher degrees of complexity and, furthermore, lay the groundwork for ensuring their long-term maintenance. As formulated by Darwin himself, evolution by natural selection requires reliable heredity, which we know now, in turn assumes the emergence of much more complex components (sequentially based templates), and a decoupling between these components (the "genotype") and their functional expression (the "phenotype"), which in turn implies a much more complex form of organization (namely, full-fledged organisms).

Yet, from our perspective, evolution, which is usually seen as a causal mechanism (or driving force) that explains the transition from chemistry to biology, is itself a consequence rather than a cause of the emergence of the earlier forms of proto-biological organization. Obviously, this does not belie the fact that, once it emerged, evolution by natural selection operated as a driving force in the transition towards life. My claim is, rather, that evolutionary mechanisms appeared gradually and were themselves the result of the emergence of increasingly complex and integrated self-re-producing systems. And in turn, these organizations brought forth increasingly efficient forms of evolution, so that, both the organization of individual systems and their form of evolution, evolved together. This would mean that Darwinian evolution appeared gradually and was itself the result of the appearance of increasingly complex forms of organization. For, as C. Hooker (2015, p. ix) has recently pointed out, "it may be evolutionary selection that provides the thrust, but it is organization that provides the lift".

6 The emergence of synchronic collective organizations: ecological webs

As we have seen, the process of individuation involves the development of processes that paradoxically go beyond it, implying a trans-individual framework in spatial and temporal terms: evolution establishes intergenerational entailments between protocells, thus creating the conditions for the long-term sustainability of increasingly complex forms of organization. Though based on the individual reproduction of each individual protocell, evolution is understood as the intergenerational change of *populations*, because the process necessarily involves large numbers of individuals and therefore what matters is the statistical average of the hereditary changes.

But the combination of individual action and evolutionary process in turn generates the conditions required for the emergence of another, very different, form of trans-individuality: the ecological domain. By that I mean the long-term yet *synchronic community* of different types of protocells mutually affecting their environmental conditions so as to ensure the conditions necessary for their global long-term maintenance. Although evolution (based on heritable reproduction) creates the possibility of the long-term sustainability of increasingly complex prebiotic organizations, manifested through protocells, the creation of collective ecological webs is another, no less important, condition of this long-term sustainability. I develop this idea further below.

Presumably, protocells would establish webs of interactions amongst themselves. The first reason for this is that the environment of protocell populations would soon become full of a variety of organic compounds resulting not only from the release of chemicals (“waste”) generated by their self-maintenance, but also from the disintegration of protocell organizations. Since the evolution of protocells leads to the proliferation of an inevitably varied set of metabolic entities, the environment would become increasingly full of a variety of organic compounds. This fact would lead either to a dead end, due to the continuous increase in the number of protocells and the limited resources available in the environment, or to the creation of a web of metabolic dependencies between the individuated systems. Moreover, as Guerrero (1995; Guerrero et al. 2002) and Ruiz-Mirazo et al. (2004) argued, this proto-metabolic complementarity between different types of prebiotic metabolizing organisms would resolve the problem of needing to “clean” the environment of an increasing amount of non-digestible organic waste. And more recently, Briones et al. (2015) remarked along the same lines that:

> “Thanks to the fundamental connection between the membrane and the metabolism, a continuous flow of energy and matter between each system and its environment began to occur. This would have prompted a movement of substances between different protocells living in close proximity, which is essential because each compartmentalized system would have been slightly different from the others, and none would have been able to produce all the molecules needed. Moreover, lacking mechanisms for the reuse of certain basic chemical compounds, sooner or later a global crisis would have occurred due to depletion of available resources. Therefore, moving on from their earlier steps, groups of protocells began to establish ecological relationships with each other: the beginning of life not only marked the beginning of evolution, but also the beginning of ecology.” (p. 266, my translation).

It is therefore a sensible hypothesis that, over time, some individuated systems, if forming dense and diverse enough populations, would have established functional interactions and more or less stable collective networks. Although as yet there is little empirical evidence supporting this, some experiments (Carrara et al. 2012; Stano et al. 2014) have observed the formation of protocell colonies that may have favored solute capture and vesicle fusion, creating a positive feedback loop between “individual” systems and the “colony”. Since this individual-collective interdependency could appear in even very simple protocells, it is likely that in subsequent steps this interaction would have been reinforced and complexified. It is therefore probable that once protocells became more autonomous self-maintaining systems, capable of internally generating more complex compounds, a relatively dense set of these compounds began to grow up around them, and some of these components would have been captured and recruited by other protocells if they proved functional for them. As a result, sooner or later, a web of metabolic dependencies would have been established among them.

What matters in ecological interactions is the fact that the self-maintenance performed by a specific type of protocell affects the energy and material inflow of another type of protocell, whose own self-maintenance in turn affects another group of protocells and so on until the loop is closed, thus forming a network of interactions. The importance of this closed network of ecological interactions lies in the fact that they enable the long-term sustainability of a diversified community of protocells in both energy and material terms. The action of each type of protocell ensures that the flux of energy and matter necessary for its own maintenance, as well as that of the other types of protocells, is constrained so as to be indefinitely maintained (providing certain geological and astronomical conditions are met: for instance, the network is ultimately driven by a stable external energy source, such as the sun). Ecological systems are therefore a kind of “biologically constructed environment” (Dagg 2003). And this is where a new form of circular causality appears: individualized self-re-producing systems, through their different forms of metabolism, create the mechanisms and the “microscopic” interactions that allow the emergence of a long-term—yet synchronic—macroscopic self-maintaining network (an ecosystem) that in turn helps to ensure the long-term maintenance of differentiated individualities (because it affords them the possibility of sustaining evolution), as well as the environmental conditions required for developing more complex metabolic organizations.

7 Conclusion

In this paper I have addressed only some of the philosophical problems related to the earlier steps of the transition from the chemical to the biological world. Here I have proposed a conceptual framework for understanding the origin of life with a precise order of events. As argued, this order is based on logical and physic-chemical reasons, and therefore, it would be universally valid. Yet, as mentioned in Sect. 2, the “starting point” of prebiotic evolution on our planet was possible due to a very complex and specific set of conditions; and we don’t have so far a sufficient knowledge to evaluate how likely similar conditions could be met in other planets. And second, despite our recent advances in understanding the hypothetical earlier steps of prebiotic evolution through experiments in vitro and, especially, through computational models, we need much more experimental progress; for example, as mentioned in Sect. 3, no experimental evidence of reflexive catalytic networks has been obtained so far.

Within the conceptual framework that I have developed here, we have seen that the transition towards life implies the gradual emergence of a complex phenomenon that unfolds in different dimensions, and which can only be understood through the entangled relationships which exist between these dimensions.

There are a number of different “driving forces” that have played a crucial role throughout the transition from chemical systems to biological ones. Natural selection is, of course, of paramount importance in this story, but we should not forget that natural selection operates only by selecting among actual viable organizational novelties. Thus, prior to natural selection comes the constitution of functional loops that act as virtuous circles, trapping external compounds capable of maintaining and reinforcing them and generating new components inside; in short, facilitating their global persistence. This is why we have focused on the idea of a far-from-equilibrium, self-maintaining organization. Self-reproduction is often mentioned as another fundamental mechanism in the transition from chemistry to biology, because it ensures the statistical survival of innovations and involves the formation of long-term organizational entailments, thus enabling a cumulative historical process (evolution). But self-reproduction itself is ultimately the expression of a special form of self-maintaining organization endowed with a form of cohesive individuality. From this perspective follows that organization and evolution depend on each other. Last, but not least, populations of individualized self-maintaining organizations would inevitably generate synchronic collective self-maintaining ecological networks.

Hence, if life is a multifarious phenomenon, individual and collective, a synchronic organization and a historical process, then it is vitally important to understand what underlies all this. We will never understand how life began and why it has this multidimensional phenomenology unless we focus on its organizational nature as a cohesive, far-from-equilibrium, self-maintaining, functionally-differentiated and self-individualized chemical system.

Obviously, life as we know it, even in its simpler forms, is much more than that. Its capacity for open-ended evolution, at the collective-diachronic level, and, at the individual level, for adaptive agency, requires the introduction of several key innovations. But I hope I have, at least, developed the conceptual scheme for understanding how nature built the chassis of the biological phenomenon.

References

Arnellos, A., & Moreno, A. (2012). How functional differentatiation originated in prebiotic evolution. *Ludus Vitalis, 37*, 1–23.

Bickhard, M. H. (2000). Autonomy, function, and representation. *Communication and Cognition—Artificial Intelligence, 17*(3–4), 111–131.

Briones, C., Fernandez, A., & Bermudez de Castro, J.M. (2015). *Origenes. El universe, la vida, los humanos.* Barcelona: Critica.

Carrara, P., Stano, P., & Luisi, L. (2012). Giant Vesicles “Colonies”: A model for primitive cell communities. *ChemoBioChem, 13*, 1497–1502.

Chen, I. A., Roberts, R. W., & Szostak, J. W. (2004). The emergence of competition between model protocells. *Science, 305*, 1474–1476.

Chen, I. A., & Szostak, J. W. (2004). Membrane growth can generate a transmembrane pH gradient in fatty acid vesicles. *Proceedings of the National Academy of Sciences of the United States of America, 101*(21), 7965–7970.

Dagg, J. (2003). Ecosystem organization as side-effects of replicator and interactor activities. *Biology and Philosophy, 18*, 491–492. doi:10.1023/A:1024128115666.

De Duve, C. (2007). Chemistry and selection. *Chemistry & Biodiversity, 4*(4), 574–583.

Deamer, D. W. (1985). Boundary structures are formed by organic compounds of the Murchison carbonaceous chondrite. *Nature, 317*, 792–794.

Deamer, D. W., & Dworkin, J. (2005). Chemistry and physics of primitive membranes. In P. Walde (Ed.), *Prebiotic chemistry* (pp. 1–27). Heidelberg: Springer.

Eschenmoser, A. (2007). Question 1: Commentary referring to the statement ‘‘the origin of life can be traced back to the origin of kinetic control?’’. *Origins of Life and Evolution of the Biosphere, 37*(4–5), 309–314.

Fox Keller, E. (2009). Self-Organization, Self-Assembly, and the Inherent Activity of Matter. In S. H. Otto (Ed.), *The Hans Rausing Lecture 2009* (Uppsala University, Disciplinary Domain of Humanities and Social Sciences, Faculty of Arts, Department of History of Science and Ideas).

Fox Keller, E. (2010). It is possible to reduce biological explanations to explanations in chemistry and/or physics. In F. J. Ayala & R. Arp (Eds.), *Contemporary debates in philosophy of biology* (pp. 19–31). Oxford: Wiley.

Godfrey-Smith, P. (2009). *Darwinian populations and natural selection*. Oxford: Oxford University Press.

Griesemer, J. R. (2002). What is "Epi" about epigenetics? In L. Van Speybroeck, G. Van de Vijver, & D. De Waele (Eds.), *From epigenesis to epigenetics: The genome in context* (pp. 97–110). New York: New York Academy of Sciences.

Guerrero, R. (1995). Vida arcaica y ecopoyesis. In F. Morán, J. Peretó, & A. Moreno (Eds.), *Los Orígenes de la Vida* (pp. 225–243). Madrid: Editorial Complutense.

Guerrero, R., Piqueras, M., & Berlanga, M. (2002). Microbial mats and the search for minimal ecosystems. *Int Microbiol, 5*(4), 177–188.

Harold, F. M. (1986). *The vital force: A study of bioenergetics*. New York: Freeman.

Hooker, C. (2015). Foreword. In A. Moreno & M. Mossio (Eds.), *Biological autonomy. A philosophical and theoretical inquiry* (pp. i–xiii). New York: Springer.

Hordijk, W., & Steel, M. (2004). Detecting autocatalytic, self-sustaining sets in chemical reaction systems. *Journal of Theoretical Biology, 227*(4), 451–461.

Hordjik, W., Steel, M., & Kauffman, S. (2012). The structure of autocatalytic sets: Evolvability, enablement, and emergence. *Acta Biotheorica, 60*, 379–392.

Kauffman, S. (1986). Autocatalytic sets of proteins. *Journal of Theoretical Biology, 119*(1), 1–24.

Kauffman, S. (2000). *Investigations*. Oxford: Oxford University Press.

Martin, W., & Russell, M. J. (2003). On the origins of cells: A hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells. *Philosophical Transactions Biological Sciences, 358*, 59–85.

Maturana, H., & Varela, F. (1987). *The tree of knowledge: The biological roots of human understanding*. Boston: Shambhala Publications.

Mavelli, F., & Ruiz-Mirazo, K. (2013). Theoretical conditions for the stationary reproduction of model protocells. *Integrative Biology, 5*(2), 324–341.

Mitchell, P. (1961). Coupling of phosphorylation to electron and hydrogen transfer by a chemi-osmotic type of mechanism. *Nature, 191*, 144–148.

Morange, M. (2008). *Life explained*. New Haven: Yale University Press (original edition (2003): *La vie expliquée. 50 ans après la double helice*. Paris: Odile Jacob).

Moreno, A., & Etxeberria, A. (1992). Self-reproduction and representation. The continuity between biological and cognitive phenomena. *Uroboros, 2*(1), 131–151.

Moreno, A., & Ruiz-Mirazo, K. (2009). The problem of the emergence of functional diversity in prebiotic evolution. *Biology and Philosophy, 24*(5), 585–605.

Morowitz, H. J. (1981). Phase separation, charge separation and biogenesis. *BioSystems, 14*(1), 41–47.

Morowitz, H. J. (1992). *Beginnings of cellular life: Metabolism recapitulates biogenesis*. New Haven & London: Yale University Press.

Mossio, M., & Moreno, A. (2010). Organizational closure in biological organisms. *History and Philosophy of the Life Sciences, 32*(2–3), 269–288.

Mossio, M., Saborido, C., & Moreno, A. (2009). An organizational account of biological functions. *British Journal for the Philosophy of Science, 60*, 813–841.

Nisbert, E., & Sleep, N. (2001). The habitat and nature of early life. *Nature, 409*, 1083–1091.

Pascal, R., Pross, A., & Sutherland, J. (2013). Towards an evolutionary theory of the origin of life based on kinetics and thermodynamics. *Open Biology, 3*, 130–156.

Pross, A. (2003). The driving force for life's emergence: kinetic and thermodynamic considerations. *Journal of Theoretical Biology, 220*(3), 393–406.

Pross, A. (2009). Seeking the chemical roots of Darwinism: bridging between chemistry and biology. *Chemistry—A European Journal, 15*, 8374–8381.

Rasmussen, S., Bedau, M. A., Liaohai, C., Deamer, D., Krakauer, D. C., Packhard, N. H., et al. (Eds.). (2008). *Protocells: Bridging nonliving and living matter*. Cambridge (MA): MIT Press.

Ruiz Mirazo, K., & Moreno, A. (2004). Basic autonomy as a fundamental step in the synthesis of life. *Artificial Life, 10*(3), 235–259.

Ruiz-Mirazo, K. (2011). Protocell. In M. Gargaud, R. Amils, J. C. Quintanilla, H. J. Cleaves, W. M. Irvine, D. Pinti, & M. Viso (Eds.), *Encyclopedia of astrobiology* (Vol. 3, pp. 1353–1354). Heidelberg: Springer.

Ruiz-Mirazo, K., & Mavelli, F. (2008). On the way towards 'basic autonomous agents': stochastic simulations of minimal lipid-peptide cells. *BioSystems, 91*(2), 374–387.

Ruiz-Mirazo, K., Peretó, J., & Moreno, A. (2004). A universal definition of life: Autonomy and open-ended evolution. *Origins of Life and Evolution of the Biosphere, 34*, 323–346.

Segre, D., & Lancet, D. (2000). Composing life. *EMBO Reports, 1*(3), 217–222.

Shirt-Ediss, B. (2016). *Modelling Early Transitions Toward Autonomous Protocells*. PhD Dissertation. University of the Basque Country, San Sebastian.

Skulachev, V. P. (1992). The laws of cell energetics. *European Journal of Biochemistry FEB., 208*(2), 203–209.

Stano, P., de Souza, T. P., Carrara, P., Altamura, E., D'Aguanno, E., Caputo, M., et al. (2014). Recent biophysical issues about the preparation of solute-filled lipid vesicles. *Mechanics of Advanced Materials and Structures, 22*(9), 748–759.

Vasas, V., Fernando, C., Santos, M., & Kauffman, S. (2012). Evolution before genes. *Biology Direct,*. doi:10.1186/1745-6150-7-1.

Walde, P., Goto, A., Monnard, P. A., Wessicken, M., & Luisi, P. L. (1994). Oparin's reaction revisited: enzymatic synthesis of poly (adenylic acid) in micelles and self-reproducing vesicles. *Journal of the American Chemical Society, 116*, 7541–7547.

Ward, P., & Brownlee, D. (2004). *Rare earth: Why complex life Is uncommon in the universe*. New York: Copernicus Books.

Wilson, R.A., & Barker, M. (2016). The Biological Notion of Individual. In E.N. Zalta (Ed). *The Stanford Encyclopedia of Philosophy* (Spring 2016 Edition) URL = <http://plato.stanford.edu/archives/sum2016/entries/biology-individual/.

Zepik, H., Blöchliger, E., & Luisi, P. L. (2001). A chemical model of homeostasis. *Angewandte Chemie Int Ed, 40*(1), 199–202.