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Essays

The Definition of Life: A Brief History of an Elusive Scientific Endeavor

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Abstract

In spite of the spectacular developments in our understanding of the molecular basis that underlies biological phenomena, we still lack a generally agreed-upon definition of life, but this is not for want of trying. Life is an empirical concept; and, as suggested by the many unsuccessful efforts to define it, this task is likely to remain, at best, a work in progress. Although phenomenological characterizations of life are feasible, a precise definition of life remains an elusive intellectual endeavor. This is not surprising: as Nietszche once wrote, there are concepts that can be defined, whereas others only have a history. The purpose of this essay is to discuss some of the manifold (and often unsatisfactory) definitions of life that have been attempted from different intellectual and scientific perspectives and reflect, at least in part, the key role that historical frameworks play. Although some efforts have been more fruitful, the lack of an all-embracing, generally agreed-upon definition of life sometimes gives the impression that what is meant by life's origin is defined in somewhat imprecise terms and that several entirely different questions are often confused. The many attempts made to reduce the nature of living systems to a single living compound imply that life can be so well defined that the exact point at which it started can be established with the sudden appearance of the first replicating molecule. On the other hand, if the emergence of life is seen as the stepwise (but not necessarily slow) evolutionary transition between the non-living and the living, then it may be meaningless to draw a strict line between them. Key Words: Definition of life—Prebiotic evolution—Self-sustaining systems—Darwinian evolution. Astrobiology 10, 1003–1009.

1. Introduction

In spite of the spectacular developments in our understanding of the molecular basis that underlies biological phenomena, we still lack a generally agreed upon definition of life; but, as shown by an overwhelming amount of discussions, this is not for want of trying (see, for instance, Rizzoti, 1996; Cleland and Chyba, 2002; Palyi *et al.*, 2002; Popa, 2004). Although phenomenological characterizations of life are feasible, a precise definition of life remains an elusive intellectual endeavor. This is not surprising: as Nietszche once wrote, there are concepts that can be defined, whereas others only have a history (*cf.* Lazcano, 2008). The purpose of this essay is, precisely, to discuss from a historical viewpoint some of the many (and often unsatisfactory) definitions of life that have been attempted from different intellectual and scientific perspectives, as well as to point out how the issue of the definition of life has often been put aside in biology, only to reemerge over and over again.

The lack of a definition of life can be in some cases a heavy burden for the biological sciences. This is shown, for instance, by the intense debates on the ultimate nature of the microscopic structures in the martian meteorite Allan Hills 84001; the endless discussions on whether viruses are alive or not; and more recently by the surprising achievements of synthetic biology, as demonstrated by the chemical synthesis of a complete bacterial genome and its incorporation into mycoplasma (Bedau, 2010; Deamer, 2010; Gibson *et al.*, 2010). It is also reflected on the value-charged debates influenced by major developments in biomedical research that bear upon abortion, euthanasia, and transgenic organisms, to name just a few.

It is has been argued that the publication of Schrödinger's *What is Life?* sparked the birth of molecular biology (for a critical review of this issue, see Yoxen, 1979). As discussed below, this was not really the case. In fact, following the publication of the double-helix model of DNA, the discussion of the definition of life disappeared from mainstream biology that focused on the molecular mechanisms underlying the replication of DNA and the synthesis of proteins. The search for a clear distinction between life and non-life

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vanished during the development of molecular biology. It is true that several distinguished molecular biologists, including Crick, Monod, and others (Morange, 2010), felt that a solution to the question of the nature of life had been found, perhaps because they shared with others the conviction that physics and chemistry were enough to explain not only the defining characteristics of organisms but also how life emerged. However, their attitude was often ambiguous. On one side, many molecular biologists assumed that the question of life had been solved and that organisms are nothing more than physical-chemical devices. On the other, they were also convinced that the secret of life resides in the existence of genetic information and the genetic code that translates this information, which are not found in mere physicochemical entities and are thus attributed to specific characteristics of organisms.

As shown by the many books and articles published during the past few years, the issue of the definition of life has not faded away but keeps bouncing back. Perhaps like never before in the history of science, the development of biosciences has led to a renovated discussion on the definition of life from new perspectives. But this has not always been a pressing issue. As argued here, since the 19th century most attempts to explain the origin of life have not been based on explicit definitions of life but, mostly, on intuitive conceptions of life that were not always made explicit. The different proposals on the origin of life suggested by Buffon, Lamarck, Darwin, Huxley, Oparin, or Haldane were part of their more elaborate theories on the evolution of Earth, but a critical reexamination of their writings also reveals their diverse conceptions of life, which they used without actually providing a precise definition of it. In fact, the issue of the ultimate nature of life and the search for its precise definition are questions that have emerged over and over again. Does the question of the definition of life have a place within contemporary life sciences? And what kinds of answers are presently looked for?

2. Conceptions of Life Rather than Precise Definitions

In retrospect, it is somewhat surprising to realize that from the 18th century until the first part of the 20th century some of the most influential naturalists and biologists discussed the origin and evolution of life without employing precise definitions, relying instead on rather broad conceptions of life, which included phenomenological descriptions and explanations (Tirard, 2010).

A significant case is the theory of life the French naturalist Georges Louis Leclerc, Compte de Buffon (1707–1788), developed in his *Histoire Naturelle* (1749), based on what he called *organic molecules* (hypothetical material units that should not be confused with what chemists today call organic compounds), which were consumed and transformed by the organism. Without actually providing a definition of life, Buffon claimed that, during the generation of living organisms, such hypothetical molecules were responsible for the transmission of the interior mold that indicates the organization of each species. Buffon's concept of species is part of a rather broad view of life and should not be seen as mere collections of living beings at a given time but also as collections that perpetuate through time, generation after generation.

As a fixist, Buffon argued that although some small variations can be recognized within species, there is no evolution. He suggested that during the earliest history of Earth, once the planet became sufficiently cold, the units that he had termed organic molecules produced spontaneous generations that led to different species, each of which is defined by a specific interior mold. Buffon's interest focused more on the organization of these small living entities and on the concept of species than on the understanding of the fundamental nature of life. The lack of a definition of life did not trouble Buffon, since for him matter produces what he had termed organic molecules, which he assumed were the simplest form of life.

Half a century later, Jean-Baptiste Lamarck described in 1802 his own theory explaining the transformation of species on the basis of their habits and the role of the environment on organisms. Lamarck assumed that the evolutionary process had started with the spontaneous generation of the simplest living beings, which was due to the animalization of subtle, gelatinous matter characterized by acquisition of the *vital orgasm*, a sort of agitation of matter (Tirard, 2006). Lamarck's writings make it clear that, for him, life cannot be reduced to a simple definition but should include a conception of transformation of organization of living beings and species.

Like most of his predecessors, Darwin put forth an explanation of the evolutionary process that lacked an explicit definition of life. Like many of his contemporaries, Darwin rejected the idea that putrefaction of preexisting organic compounds could lead to the appearance of organisms. Although he consciously avoided discussing the origin of life in the *Origin of Species*, the analysis of some other texts and of the correspondence he exchanged with friends and colleagues demonstrates that he took for granted the possibility of a natural emergence of the first life-forms (Peretó *et al.*, 2009). Although he never attempted to define life, some of the texts written by Darwin, including the correspondence he exchanged with friends and colleagues, demonstrates that he took for granted the possibility of a natural emergence of the first life-forms and the idea that organic compounds could form primitive and simple living beings. However, his remarks should not be read to imply that he was thinking in terms of prebiotic chemistry but rather that he recognized that the chemical gap separating organisms from the non-living was not insurmountable (Peretó *et al.*, 2009).

On February 1, 1871, Darwin sent a letter to his close friend Joseph D. Hooker, in which he wrote that

> it is often said that all the conditions for the first production of a living being are now present, which could ever have been present. But if (and oh what a big if) we could conceive in some warm little pond with all sorts of ammonia and phosphoric salts,—light, heat, electricity present, that a protein compound was chemically formed, ready to undergo still more complex changes, at the present such matter would be instantly devoured, or absorbed, which would not have been the case before living creatures were formed....

In other words, Darwin assumed that the presence of life, once it appears, is a new condition that prevents new formation of life (Peretó *et al.*, 2009). This is a key issue, because it underlies not only the fact that life is a part of its own environment but that the formation and the modifications of life, over time, introduce historicity and, therefore, irreparability and irreversibility in the conception of life.

Darwin's close friend Thomas Huxley, on the other hand, discussed in his famous 1869 lecture *On the Physical Basis of Life* the chemical and physical characteristic of the living matter, showing the importance of albuminoidal bodies in the constitution of what was then called protoplasma. This was not part of an explicit definition of life but a conception of the basis of life that reflects the extrapolation of a physicochemical vision to biological phenomena. This perspective is part of the theoretical framework that defined the contributions of Alexandr I. Oparin and John B.S. Haldane, who described the origin of life as a process that is part of the global process of the evolution of Earth. The key role that the evolutionary perspective provided by Oparin and Haldane has in shaping the current discussions on the origin of life is well known, as well as the way in which they discussed independently the fundamental characteristics of life in the context of the process of complexification of matter—but without actually attempting to define life.

3. Life Traits—toward an Empirical Definition?

Although phenomenological characterizations are feasible, a precise definition of life remains an elusive intellectual endeavor. This is not surprising: as argued long ago by Immanuel Kant, precise definitions may be achievable in mathematics and philosophy, but empirical concepts (as is the case for what life is) can only be made explicit through descriptions that depend on the historical context (Fry, 2002). Attempts to define life must distinguish between the simplest possible life-form and more complex organisms such as plants and animals. Definitions of life must be open and must not be limited by our current state of knowledge. Perhaps what is required is more a framework than a precise definition. Answers to the question of what is life will be provided by different specialists working on different problems and from diverse perspectives, ranking from the origin of life on Earth, to synthetic biology, to the search for extraterrestrial life. The answers will be contextual and, because of this, partially different. But there is no valid reason to consider that the coexistence of different answers will be the ultimate state of the inquiry and to exclude *a priori* possible strong connections between these narrowly oriented answers (Morange, 2010).

From the viewpoint of contemporary biology, a proper understanding of the minimal properties required for a system to be considered alive requires the recognition of the evolutionary processes that led to the system itself. The appearance of life was marked by the transition from purely chemical reactions to autonomous, reproducing entities capable of evolving by natural selection. How this process took place is not known; nor, of course, do we know the nature of the first living systems. At what point in time was the difference between a chemical system and the truly primordial, first organisms, established?

The discovery and development of the catalytic activity of RNA molecules, that is, ribozymes, has given considerable support to the idea of the "RNA world"—a hypothetical evolutionary stage before the development of proteins and DNA genomes during which alternative life-forms based on ribozymes existed. The different lines of evidence supporting the existence of an RNA world have led to proposals that the starting point for the history of life on Earth was the *de novo* emergence of the RNA world from a nucleotide-rich prebiotic soup.

These are extreme reductionist proposals that imply that life can be reduced to a single living molecule, that is, that life can be so well defined that the exact point at which it started can be established with the sudden appearance of the first RNA-replicating molecule. Such views have a long history. During a roundtable that was part of the now famous Darwin Centennial Discussions organized by the University of Chicago in 1959, Herman J. Muller stated that

> I think the most fundamental property distinguishing a living thing—and that can therefore be used to define life—is its ability to form copies of itself. We call this "reproduction," but such copies must also include innovations—mutations—that distinguish a given living thing from its parents.... Natural selection could not go on without the necessary basis of an ability or faculty of the material to copy not merely itself but its variations. That, I think, is the heart of life, and such material, when it arose, is rightly called "living." (Muller, 1959)

The criteria employed by Muller (1959) to define life (reproduction, mutation, and the capacity to transmit mutation) were rapidly rejected by many (Lazcano, 2010a). Of course, the lack of a generally agreed-upon definition of life sometimes gives the impression that what is meant by its origin is defined in somewhat imprecise terms, which leads to the assumption that traits that evolved subsequent to the appearance of life are, in fact, primordial. For instance, until a few years ago the origin of the genetic code and of protein synthesis was considered synonymous with the appearance of life itself. It is true that there are major exceptions. With surprising insight, Stent (1968) wrote that

> Though there is no guarantee, of course, that the first-reproducing genetic materials formed in the primordial soup of ancient oceans were nucleic acid, or any polymers even resembling polynucleotides, it has now become clear at least that probing into the origin of the genetic code—into ways in which it could have arisen without, like Athena, having sprung full-blown from Zeus' head—is likely to be a most profitable attack on this problem.

The available evidence provides considerable support to the approach suggested by Stent (1968). Indeed, four of the central reactions involved in protein biosynthesis, that is, amino acid activation, aminoacyl-RNA synthesis, peptide-bond formation, and RNA-based coding, are catalyzed by ribozymes, and their complementary nature suggests that they first appeared in an RNA world (Kumar and Yarus, 2001). This strongly supports the proposal that ribosome-catalyzed, nucleic acid–coded protein synthesis is the outcome of Darwinian selection of RNA-based biological systems and not of mere physicochemical interactions that took place in the prebiotic environment.

4. Life as a Self-Sustaining System

Since the 19th century, metabolism has been recognized as a central trait of life, a conclusion that has led to consideration of viruses and other subcellular biological entities as nonliving. It was the reason why Félix d'Herelle, co-discoverer with Frederick Twort of the bacteriophage, desperately tried to show that bacteriophages were able to assimilate foreign material, that is, they had a metabolism, in order to demonstrate that they were living entities (Summers, 1999). The recognition that life's continuous production of itself is based on networks of anabolic/catabolic reactions and energy flow led Maturana and Varela (1980) to define life as an autopoietic system, that is, as an entity defined by an internal process of self-maintenance and self-generation. As shown by Bernal's (1959) statement that life is "the embodiment within a certain volume of self-maintaining chemical processes," the idea of autopoiesis is not without historical precedents. However, for Bernal and some of his contemporaries like Oparin, the ultimate nature of living systems could not be understood in the absence of an evolutionary perspective (Lazcano, 2008). It is clear that reproduction was the *sine qua non* condition for life to persist, while replication can be understood as the molecular mechanism underlying reproduction of organisms.

Autopoietic systems are, by definition, self-maintaining and self-making. According to Tibor Gánti, however, self-maintenance is an absolute criterion for life, whereas reproduction is an actual one (Gánti, 2003). Although autopoiesis refers, and is limited, to minimal life-forms (Luisi *et al.,* 1996), it is a concept largely dependent on the existence of metabolism and, for many, independent of an evolutionary perspective. Cells and organisms made of cells are autopoietic and metabolize continuously, and in doing so continuously affect the chemical composition of their surroundings (Margulis and Sagan, 1995). Multicellular organisms, on the other hand, consist of units that are living systems in themselves and will remain so even if the entire system is destroyed (Szathmáry *et al.,* 2005) as shown, for instance, by the extraordinary success of organ transplants.

There are a number of physical and chemical analogues that have been considered autopoietic and that mimic some of the basic properties of life. One of the most enticing examples is that of the self-replicating micelles and liposomes described by Pier Luigi Luisi and his associates. For instance, synthetic vesicles formed by caprylic acid containing lithium hydroxide and stabilized by an octanoic acid derivative have been shown to catalyze the hydrolysis of ethyl caprylate. The resulting caprylic acid is incorporated into the micelle walls, which leads to their growth and, eventually, to their fragmentation, during several "generations" (Bachmann *et al.,* 2002).

Replication is an essential molecular property of living systems, but it does not suffice to define them. However surprising, replicative micelles and liposomes do not exhibit genealogy or phylogeny, which are traits found in all life-forms. The same is true of prions, whose multiplication involves only the transmission of phenotypes due to self-perpetuating changes in protein conformations. As underlined by Orgel (2000), these systems replicate without transmission of information, that is, they lack heredity, in sharp contrast with living beings. The ambiguity of the word "information" was responsible for a huge confusion. It is necessary to return to the definition given by Francis Crick in his famous 1957 lecture where he established the Central Dogma of molecular biology: "Information means here the precise determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein" (Crick, 1958; Morange, 2008a).

Organisms may be recognized as the ultimate example of autopoietic systems (Margulis and Sagan, 1995). However, the properties that lie at the basis of the self-sustaining abilities of living beings are the outcome of historical processes, and it is somewhat difficult for biologists to accept a definition of life that lacks a Darwinian framework. Regardless of their complexity, all living beings have been shaped by a lengthy evolutionary history. Accordingly, a proper understanding of the minimal properties required for a system to be considered alive requires the recognition of the evolutionary processes that led to it.

5. Physics and the Definition of Life

In 1944, Erwin Schrödinger published his famous book *What is Life?* It is generally believed that this volume (which includes but one single reference to biological literature) signals the start of the interest of physicists in the nature of life and heredity (*cf.* Yoxen, 1979). This is not really the case; Schrödinger's work is best understood as the culmination of a long tradition that attempted to explain the nature of life in purely physical terms (Lazcano, 2008). This is shown, for instance, in the manifold 19th century attempts to describe living systems based on magnetism, surface tension, radioactivity, and other physical phenomena (Keller, 2002). Although many of these attempts failed to recognize the uniqueness of living systems and the role of Darwinian evolution, they can be seen as part of the process of secularization of life sciences.

The ideas of Jerome Alexander, Stephane Leduc, and Alfonso L. Herrera epitomize this trend. Like many of his contemporaries, the Mexican Alfonso L. Herrera was convinced that life could be created in the laboratory and proposed an autotrophic theory known as *plasmogenesis*. Herrera devoted more than 50 years to experimenting with different kinds of substances, attempting to "illustrate the physicochemical concomitants of life" (Herrera, 1902). At first he used mixtures of water and oil (or gasoline) to understand the shape, size, and movement of cell-like structures. He would later refine his ideas and, despite the academic isolation in which he worked, developed his theory of "plasmogeny," which attempted to explain the origin of primitive photosynthetic protoplasm. This led him to experiment with formaldehyde and hydrogen cyanide derivatives like NH_4SCN (Herrera, 1942), a combination that we now know produces sugars and highly colored polymers, which unfortunately he mistook for photosynthetic pigments (Perezgasga *et al.,* 2003). Perhaps the most intense description of such attempts is found not in scientific reports but in the attempts of the somber Adrian Leverkühn to synthesize life that Thomas Mann so intensively describes in his novel *Doktor Faustus*.

Schrödinger's book, on the other hand, foreshadows the intensity of current attempts to extrapolate to biology the deeply rooted tendency of physicists to search for all-encompassing laws that can be part of a grand theory that encompasses many, if not all, complex systems. In a way, current attempts to explain the nature of life on the basis of complexity theory and self-assembly phenomena can be understood as part of this deeply rooted intellectual tradition (Keller, 2002). Unfortunately, in some cases invocations to spontaneous generation appear to be lurking behind appeals to undefined "emergent properties" or "self-organizing principles" that are used as the basis for what appear to be grand, sweeping generalizations with little, if any, relationship to actual biological phenomena (Fenchel, 2002; Lazcano, 2010a). Comparing the emergence of life to the percolation of a physical system is a wonderful metaphor, not a proper explanation (Morange, 2008b).

Self-assembly and complexification are not unique to biology and may indeed be found in a wide variety of systems, including computer-generated cellular automata, the complex flow patterns of many different fluids such as tornadoes, cyclic chemical phenomena (such as the Belousov-Zhabotinsky reaction and the formose reaction), and in the autoorganization of lipidic molecules in bilayers, micelles, and liposomes (*cf.* Farmer, 2005). There are indeed some common features among these different self-organized systems, and it has been claimed by a number of theoreticians that they follow general principles that are in fact equivalent to universal laws of nature. Perhaps this is true. The problem, as underlined by Farmer (2005), is that such all-encompassing principles, if they exist at all, have so far remained undiscovered.

This approach has led to a number of theoretical models and proposals on the origin and nature of life that can be considered, in a way, as the theoretical equivalent to Leduc's and Herrera's suggestions, "dignified" with the current prestige of mathematical approaches and computer modeling. Some of these attempts assume that life is a continuously renewing complex interactive system that emerged as self-organizing metabolic cycles that did not require genetic polymers, or as the result of mutual catalysis among lipidlike molecules of prebiotic origin, that led to the growth and cleavage of noncovalent protocellular assemblies displaying lifelike properties (see, for instance, Kauffman, 1993; Segré *et al.*, 2001).

However, mainstream evolutionary biologists and prebiotic chemists tend to be wary of explanations that assume that the emergence of life was the outcome of timeless mathematical or physical principles in which replication, selection, and adaptation play no role. Of course, they may be wrong. Such lack of interest does not imply a belief that the natural processes that led to the first life-forms were exempt from the constraints imposed by physics or that explanations on the appearance of life should be reduced to the issue of the emergence of nucleic acids or their precursors. However, in spite of a number of mesmerizing theoretical and experimental analogues (Morowitz, 1992; Kauffman, 1993; Segré *et al.*, 2001), what is known of biology suggests that the essential traits of living systems could not have emerged in the absence of genetic material with the capacity to store, express, and, upon replication, transmit to its progeny information that is capable of undergoing evolutionary change.

The basic assumption underlying proposals that metabolic networks arose prior to genetic components is based on the hypothesis that there are intrinsic phenotypic laws rooted in physical processes, that is, emergent self-organized systems (*cf.* Kauffman, 1993). Unfortunately, complexity models have promised much but delivered little. Evidence for the spontaneous origin of a catalytic system and metabolic replication would indeed be exciting—if it could be demonstrated. There is no evidence that metabolic cycles could spontaneously self-organize, much less replicate, mutate, and evolve.

It is true that the abiotic synthesis of a number of key metabolic intermediates has been achieved, sometimes under laboratory conditions that resemble those of hydrothermal vents or other extreme environments. Moreover, it is easy to assume that prebiotic organic compounds underwent many complex transformations. However, these observations do not demonstrate that self-organization of such compounds led to metabolic routes prior to the emergence of genetic material. In fact, the available experimental evidence that has been used to argue in favor of the metabolism-first theory is equally consistent with a genetic-first description of life, since these systems do not, in themselves, prove that primordial metabolism came before genetic polymers, and they may be explained by an updated version of the heterotrophic hypothesis that acknowledges the contribution of manifold environments in which the abiotic formation of organic compounds took place (Lazcano, 2010a,b).

6. Darwinian Evolution and the Definition of Life

After his 1946 conversations with Einstein at Princeton on the underlying unity, in terms of its biochemical processes, of life on Earth, Bernal wrote that "life involved another element, logically different from those occurring in physics at that time, by no means a mystical one, but an element of *history*. The phenomena of biology must be … contingent on events. In consequence, the unity of life is part of the history of life and, consequently, is involved in its origin" (Brown, 2005). History, in biology, implies genealogy and, in the long term, phylogeny (Lazcano, 2008). Phylogeny requires an intracellular genetic apparatus able to store, express, and, upon reproduction, transmit to its progeny information that is capable of undergoing evolutionary change. As biologists, it is somewhat problematic to imagine how this process could have started in the absence of some type of genetic molecules, whose chemical nature need not be restricted to the nucleic acids found in extant life-forms.

A good case can be made that Darwinian evolution is essential for understanding the nature of life itself, but is it enough? Life could be defined as a self-sustaining chemical system (*i.e.*, one that turns resources into its own building blocks) that is capable of undergoing Darwinian evolution (*cf.* Joyce, 1994). Such a definition of life implies that autotrophic organisms such as cyanobacteria and plants are clearly alive. But what about the first life-forms? Clearly, if at its very beginning life was already a self-sustaining entity capable of turning external resources into its own building blocks, then it must have been endowed with some type of primordial metabolic routes that allowed it to use as precursors environmental raw materials (such as CO_2 and N_2). An alternative possibility is that the first living entities were systems capable of undergoing Darwinian evolution (*i.e.*, endowed with genetic polymers capable of replication and heredity), whose self-sustaining properties depended on the availability of organic molecules already present in the primitive environment. Although this should be understood as an updated version of the hypothesis of the prebiotic soup and the heterotrophic origin of life, those involved in the origin of life have to ponder not just how replicative systems appeared but also how they became encapsulated and how the earliest metabolic pathways evolved (Lazcano, 2008).

7. Conclusions

Attempts to address the definition of living systems have often led to nothing more than phenomenological characterizations of life, which are in turn often reduced to a mere list of observed (or inferred) properties. These inventories are not only unsatisfactory from an epistemological viewpoint but may also become easily outdated and may fail to provide criteria by which the issue of life (and its traces) can be defined (Oliver and Perry, 2006).

Research in the origin and nature of life is doomed to remain, at best, as a work in progress. It is difficult to find a definition of life accepted by all, but the history of biology has shown that some efforts are much more fruitful than others. According to Gould (1995), understanding the nature of life requires a recognition of both the limits imposed by the laws of physics and chemistry as well as history's contingency.

It is easy to appreciate the appeal of autopoiesis and complexity theory when attempting to understand the basic nature of living systems. The sophisticated theoretical models derived from the perspective of self-organization theories have not been substantiated by unambiguous empirical evidence demonstrating that a system of large or small molecules can spontaneously arise and evolve into non-genetic catalytic networks. It is true that many properties associated with cells are observed in nonbiological systems, such as catalysis, template-directed polymerization reactions, and self-assemblage of lipidic molecules or tornadoes. Like fire, life can multiply and exchange matter and energy with its surroundings. It is true that living systems are endowed with properties of autopoeitic, self-organized replicative chemical systems. However, there is a major distinction between purely physical-chemical evolution and natural selection, which is one of the hallmarks of biology. In spite of many published speculations, the basic nature of life cannot be understood in the absence of genetic material and Darwinian evolution, and it is reasonable to assume that this was one of the defining properties of the first biological systems to appear.

Proposals that the first biological system was a single molecule capable of replication, mutation, and transmission of hereditary changes to its progeny can argue that life started when such a compound arose (Muller, 1959). However, if the origin of life is seen as the stepwise (but not necessarily slow) developmental transition between the nonliving and the living, then biological systems are the evolutionary outcome of a process that cannot be explained by spontaneous generation. We remain lamentably ignorant about major portions of the processes that preceded life, but there is strong evidence of an evolutionary continuum that seamlessly joins the prebiotic synthesis and accumulation of organic molecules in the primitive environment with the emergence of self-sustaining, replicative chemical systems capable of undergoing Darwinian evolution. In other words, the appearance of life on Earth should be seen as the evolutionary outcome of a process and not of a single, fortuitous event.

In a way, all those who have attempted to define life from a single perspective may be correct—but only partially. Life is certainly a complex, thermodynamically open, autopoietic system capable of undergoing Darwinian evolution; but we need to understand how these well-defined characteristics emerged and became coupled. There has been a dramatic shift in the past 50 years; the question of life is no longer a search for principles of life but has been transformed into a historical issue. The question is no longer "What characteristics are found in organisms but not in inanimate objects?" but "How were these characteristics progressively associated within objects that we call organisms?" (Morange, 2008b).

As summarized elsewhere (Lazcano, 2008), the recognition that life is the outcome of an evolutionary process constrained by the laws of physics and chemistry can lead to the acceptance that many properties associated with living systems, such as replication, self-assemblage, or catalysis, are also found in non-living entities. Some systems may not be "half-alive," but they can exhibit some of the properties we associate with life, like self-organization, replication, or Darwinian evolution. The existence of intermediate entities is the consequence of the existence of two well-defined categories, and it does not abolish their existence: evidence for these intermediate beings will help to define these two categories more precisely. This allows us, for instance, to discuss the issue of whether viruses are alive from a novel perspective. This question recently reemerged with the isolation of giant viruses and the accumulation of data demonstrating the richness and diversity of the viral world. Viruses were probably highly important actors in evolution, in particular, during its early steps, transferring genes from one organism to another. But they lack a metabolism and synthetic capacities. Calling them "alive" creates confusion; they obviously are on the inanimate side of the barrier between life and non-life.

Francis Crick and Jacques Monod were not wrong when they said that the secret of life had been solved and the molecular characteristics of organisms explained (Morange, 2010). The question of life is no longer a mystery. The question we need to address when inquiring into the nature of life is no longer "What characteristics are found in organisms but not in inanimate objects?" but "How were these characteristics progressively associated within objects that we call organisms?" We lack a definition of life—but one should not forget that in science it may happen that the most interesting questions are precisely those that cannot be answered.

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