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Towards a Definition of Life: The Impossible Quest?

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Abstract "Life" is an empirical concept whose various definitions and phenomenological characterizations depend on historical frameworks. Although analysis of existing literature suggests that attempts to define life will remain, at best, a work in progress, the history of biology shows that some efforts have been more fruitful than others. There is a major distinction between natural selection—which is clearly a defining trait of biology—and the changes that result from purely physical chemical evolution, which can be observed in non-biological complex systems. Accordingly, it can be concluded that life cannot be understood without considering the presence of genetic material and Darwinian evolution. This shows the usefulness of the suggestion that life can be considered as a self-sustaining chemical system (i.e., one that turns environmental resources into its own building blocks) that is capable of undergoing natural selection.

Keywords Life's definition · Autopoiesis · Complexity · Natural selection

1 Introduction

Perhaps as never before in the history of science, "life" has been transformed into a value-ridden term that sits in the center of a tense debate, as shown by the (not always well informed) discussions on abortion, euthanasia, transgenic organisms, and synthetic biology, to name just a few. In spite of the spectacular developments in our understanding of the molecular processes that underlie biological phenomena, we still lack a generally agreed definition of life, and not for want of trying (see, e.g., Rizzoti 1996; Pályi et al. 2002). As Nietzsche once wrote, there are concepts that can be defined, whereas others only have a history. This is not surprising: as argued by Immanuel Kant, precise definitions are achievable in mathematics and philosophy, but empirical concepts such as "life" can only be made explicit (cf. Fry 2002) in ways that are strongly dependent on historical circumstances. Eighty years ago, for instance, when the role of nucleic acids was largely

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unknown, proposals on the emergence of life included a wide array of possibilities based on the random emergence of autocatalytic enzymes, on autotrophic "protoplasm," and on the step-wise evolution of heterotrophic microbes from gene-free coacervates (cf. Lazcano 1995).

It has been argued by many that attempts to define life may be a useless endeavor, bound to fail (Cleland and Chyba 2002). Indeed, attempts to address the definition of living systems have often led to nothing more than phenomenological characterizations of life, which are then 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). This can become a unsolved burden for biological sciences, as shown, for instance, by the intense debates on the ultimate nature of the microscopic structures in the Martian meteorite Allan Hills 84001, or those found in early Archean sediments and that not all accept as fossils.

2 Life as a Self-Sustaining System

Since the nineteenth century, metabolism has been recognized as a central trait of life, a conclusion that has led us to consider viruses and other subcellular biological entities as nonliving. The recognition that life's continuous production of itself is based on networks of anabolic/catabolic reactions and energy flow led Maturana and Varela (1981) to define life as an autopoietic system, i.e., as an entity defined by an internal process of self-maintenance and self-generation. A 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. As discussed in the following, 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 2007).

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, which is a trait common to all living beings. 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). This is illustrated, 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 octanoid acid derivative have been shown to catalyze the hydrolysis of ethyl caprylate. The resulting caprylic acid is incorporated into the micelle walls, leading to their growth and, eventually, to their fragmentation, during several "generations" (Bachmann et al. 2002).

However surprising, replicative micelles and liposomes do not exhibit genealogy or phylogeny. Albeit due to different processes, 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 (1992) these systems replicate without transmission of information, i.e., they lack heredity. This is in sharp contrast to living beings. Organisms may be recognized as the ultimate example of autopoietic systems (Margulis and Sagan 1995). However, the properties that form 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, and since life is neither the outcome of a miracle or of rare chance event, proper understanding of the minimal properties required for a system to be considered alive require the recognition of the evolutionary processes that led to it. The appearance of life was marked by the transition from purely chemical reactions to autonomous, self-replicating molecular entities capable of evolving by natural selection. How did this take place? At what point in time was the difference between a chemical system and the truly primordial, first organisms, established?

3 Life and the RNA World

The lack of an all-embracing, generally agreed definition of life sometimes gives the impression that what is meant by its origin is defined in somewhat imprecise terms, and that several entirely different questions are often confused. 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. This is no longer a dominant point of view: four of the central reactions involved in protein biosynthesis are catalyzed by ribozymes, and their complementary nature suggest that they first appeared in an RNA world, i.e., that ribosome-catalyzed, nucleic acid-coded protein synthesis is the outcome of Darwinian selection of RNA-based biological systems, and not of mere physico-chemical interactions that took place in the prebiotic environment.

The discovery and development of the catalytic activity of RNA molecules, i.e., ribozymes, has given considerable support to the idea of the "RNA world," a hypothetical stage before the development of proteins and DNA genomes. During this stage, alternative life forms based on ribozymes existed. This does not imply that wriggling autocatalytic nucleic acid molecules were floating in the waters of the primitive oceans, ready to be used as primordial genes, or that the RNA world sprung completely assembled from simple precursors present in the prebiotic soup. In other words, the genetic-first approach to life's emergence does not necessarily imply that the first replicating genetic polymers arose spontaneously from an unorganized prebiotic organic broth due to an extremely improbable accident, or that the precellular evolution was a continuous, unbroken chain of progressive transformations steadily proceeding to the first living beings. Many prebiotic cul-de-sacs and false starts probably took place, with natural selection acting over populations of primordial systems based on genetic polymers simpler than RNA, in which company must have been kept by a large number of additional organic components such as amino acids, lipids and sugars of prebiotic origin, as well as a complex assemblies of clays, metallic ions, etc.

However, it is true that the arguments in favor of an RNA world have led many to argue 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, or in the origin of cryptic and largely unknown pre-RNA worlds. Not all accept these possibilities: there is a group of scientists that favors the possibility that life is a self-maintaining emergent property of complex systems that may have started with the appearance of self-assembled autocatalytic metabolic networks initially lacking genetic polymers (Kauffman 1993).

These different viewpoints reflect a rather sharp division that emerged between those who favor (1) the idea that life is an emergent interactive system endowed with dynamic properties that exist in a state close to chaotic behavior, and (2) those who are reluctant to adhere to a definition of living systems lacking of a genetic component whose properties reflect the role that Darwinian natural selection and, in general, evolutionary processes, have played in shaping its the central characteristics. From a biologist's viewpoint, however, neither the nature of life nor its origin can be understood in the absence of an evolutionary approach.

4 Complexity and the Nature of Life

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 the deeply rooted intellectual tradition that led physicists to search for all-encompassing laws that can be part of a grand theory, one that encompasses many, if not all, complex systems (Fox Keller 2002). Unfortunately, in some cases invocations of spontaneous generation appear to be lurking behind appeals to undefined "emergent properties" or "self-organizing principles" that are used as the basis for what many life scientists see as grand, sweeping generalizations with little, if any, relationship to actual biological phenomena (Fenchel 2002).

Self-assembly is not unique to biology, and may indeed be found in a wide variety of systems, including 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, for instance), and in the autoorganization of lipidic molecules in bilayers, micelles, and liposomes. 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 is that such all-encompassing principles, if they exist at all, have so far remained undiscovered (Farmer 2005). This has not stopped a number of researchers from attempting to explain life as a continuously renewing, complex interactive system that emerged as self-organizing metabolic cycles that did not require genetic polymers. It is unfortunate that many proposals on an autotrophic origin of life and of living systems as complex systems on the verge of chaos have turned out to be creative guesswork or empty speculation.

However, complexity models have promised much but delivered little. Evidence for the spontaneous origin of catalytic system and of metabolic replication would indeed be exciting (Kauffman 1993) if it could be established. It is true that under given conditions the self-organization of lipidic molecules into liposomes, for instance, can lead to the spontaneous formation of microenvironments which may have had significant roles in the emergence of life. But they are not alive, even if they replicate.

Prebiotic organic compounds very likely underwent many complex transformations, but there is no evidence that metabolic cycles could spontaneously self-organize, much less replicate, mutate, and evolve. Theories that advocate the emergence of complex, self-organized biochemical cycles in the absence of genetic material are hindered not only by the lack of empirical evidence, but also by a number of unrealistic assumptions about the properties of minerals and other catalysts required to spontaneously organize such sets of chemical reactions (Orgel 2000). However complex, systems of chemical reactions such as the formose reaction are not adapted to ensure their own survival and reproduction; they just exist. Life cannot be reduced to one single molecule such as DNA or a population of replicating ribozymes, but current biology indicates that it could not have evolved in the absence of a genetic replicating mechanism ensuring the stability and diversification of its basic components.

5 The (Evolutionary) Emergence of Life

Following his 1946 conversations with Einstein on the underlying biochemical unity of the biosphere, John D. 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" (cf. Brown 2005). History, in biology, implies genealogy and, in the long term, phylogeny. This requires an intracellular genetic apparatus able to store, express and, upon reproduction, transmit to its progeny information capable of undergoing evolutionary change. The most likely candidates for this appear to be genetic polymers.

A good case can thus be made that Darwinian evolution is essential for understanding the nature of life itself. Accordingly, 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 tentative definition, which was the outcome of a discussion group convened by NASA in the early 1990s, has been rejected by a number of authors who argue on different grounds that a single definition is impossible (Luisi 1998; Cleland and Chyba 2002). Life cannot be defined on the basis of a single trait, but since natural selection is indeed a unique feature of living systems, the basic nature of living systems cannot be understood without it.

The suggestion that life can be understood as a self-sustaining chemical process capable of undergoing Darwinian evolution is consistent with the well-known fact that cyanobacteria, plants, and other autotrophs are not only self-sustaining, but also very much 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 primordial metabolic routes that allowed it to use as precursors environmental raw materials (such as CO_2 and N_2, for instance). This appears unlikely to many biologists. An alternative possibility is that the first living entities were systems capable of undergoing Darwinian evolution (i.e., endowed with genetic material capable of replication, change, and heredity) whose self-sustaining properties depended on the availability of organic molecules already present in the primitive environment. Although this can be read as an update of the hypothesis of the prebiotic soup and the heterotrophic origin of life, those involved in the study of emergence of living systems have to ponder not just on how replicative systems appeared, but also how they became encapsulated and how metabolic pathways evolved (Lazcano 2007).

6 Conclusions

Research into the origin and nature of life is doomed to remain, at best, 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. As Gould (1995) once wrote, to understand the nature of life, we must recognize both the limits imposed by the laws of physics and chemistry, as well as history's contingency. It is easy to understand the appeal of autopoiesis and complexity theory when attempting to understand the basic nature of living systems. However, there is no evidence indicating how a system of large or small molecules can spontaneously arise and evolve into nongenetic 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 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, life cannot be understood in the absence of genetic material and Darwinian evolution.

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