Cambridge University Press
978-0-521-76131-4 - Origins and Evolution of Life: An Astrobiological Perspective
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# Part I

## What is life?

 

# 1

# Problems raised by a definition of life[1]

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## Introduction

Looking for a definition of life raises various issues, the first being its legitimacy. Does seeking such a definition make sense, in particular to scientists? I will successively refute the different arguments of those who consider that looking for such a definition makes no sense, and then propose good reasons to do just that, but also add some caveats regarding what sort of definition is sought. After considering definitions proposed in the past, I will examine various present-day definitions, what they share and how they differ. I will show that the recent suggestion that viruses are alive makes no sense and obscures discussions about life. Finally, I will emphasize two important recent transformations in the way life is defined.

## Philosophical and scientific legitimacy of a definition of life

Two questions immediately emerge. Are we seeking a definition of life or a definition of organisms? And what kind of definition should be sought? Two types of definition are, in fact, traditionally distinguished. A definition may aim to give the essential characteristics that causally explain the existence of the category of objects considered. Or a definition may be of more limited scope: to establish a list of properties that are necessary and sufficient to define this category of objects and to distinguish them from objects belonging to other categories. If one adopts the first kind of definition it will be possible to define life. If one opts for the second, one will look for a definition of organisms. I will support the idea that these two kinds of definition are somehow equivalent, at least in the case of a definition of life. If the properties necessary and sufficient to define 'living objects' are well chosen they will constitute a 'causal' definition of life.

More serious are the philosophical objections raised against the possibility of finding such a definition. The main argument is that organisms do not constitute a natural kind of category, but rather one constructed by humans. This was expressed by Norman Pirie in 1957: 'My attitude, which might be labelled empirical nihilism, is that the statement that

[1] This contribution was inspired by a series of essays on defining life published in OLEB vol. 40 (2010).

a system is or is not alive is a statement about the speaker's attitude of mind rather than about the system, and that no question is scientifically relevant unless the questioner has an experiment in mind by which the answer could be approached.' (Pirie, 1957). It was also recently formulated again by the philosopher Evelyn Fox Keller (Keller, 2002) and found support from some biologists working in the new discipline of synthetic biology. It is frequently proposed that in a more or less near future, biologists will be able to synthesize 'objects' intermediary between non-life and life, and that the decision to call them living will be a purely human one. The idea that there is a 'minimal' form of life is an illusion. There are many different minimal forms of life, but also subliminal forms intermediary between life and non-life.

Doubts about the possibility of defining life are supported by historical studies. Michel Foucault argued that life did not exist before the 'invention of biology' at the beginning of the nineteenth century (Foucault, 1966). Less affirmative, the philosopher Georges Canguilhem has simply remarked that the question of life was not seriously discussed before the last decades of the eighteenth century. He added that the discussions about the question of life also disappeared at the end of the twentieth century, after the development of the new molecular vision of life (Canguilhem, 1982).

I consider that these arguments are of limited value and should not prevent us looking for a definition of life. I will try to deconstruct them, starting with the historical ones.

Foucault's statement is a clear deformation of historical facts. Aristotle discussed the question of life. What is true, and rightly underlined by Canguilhem, is that the intensity of the discussion has varied greatly from one period to another. But that answering this question was no longer a priority does not mean that it had fully disappeared. The question of life is a historical question, linked in a complex way with changes in the study of organisms.

The philosophical argument is ontological, and for this reason it is impossible to demonstrate that it is wrong. But there is also no way to demonstrate that it is right. Is it really necessary to address such ontological issues and to make of organisms a 'natural kind'? What is necessary for our purpose – in searching for a definition of life – is to consider that organisms have a set of properties that unambiguously distinguish them from other objects of the natural world. And that this set of properties can be sufficiently well defined for the search for objects on other planets having these properties to be a valuable goal and for such newly discovered objects unambiguously to be called 'living'. There is a recurrent confusion stemming from misinterpretation of the word 'convention', which is viewed as equivalent to 'arbitrary'. A definition of life will be conventional, in the sense that it will be an intersubjective agreement. This does not mean that this agreement is not based on rational arguments.

The existence of intermediary stages between life and non-life, either natural or created by synthetic biologists, is not an objection to the definition of life. If one admits – and it seems difficult not to! – that life appeared from non-life, there were surely objects that were intermediary between life and non-life at one or another time in the process. The decision to call these objects 'alive' or not will clearly be a human decision. But not because the set of properties that they have to possess to be called 'alive' is ill-defined, but rather because these objects probably did not have all these properties in a stable way. The existence of categories is not incompatible with the existence of intermediary states. The problem has been nicely described by Radu Popa under the name of 'the dilemma of endless gradualism' (Popa, 2004): it is easy to designate objects that are alive and objects that are not, but it is probably possible to go from one to the other by a gradual transformation.

This is a general philosophical difficulty, encountered also, for instance, when attempting to define consciousness or a species. There are different ways to try to solve this difficulty. To conclude that the adjectives 'living' and 'non-living' have no significance is not the right conclusion. A second possibility is to suppose that, in a gradual continuous process, there are nevertheless 'thresholds' or 'phase transitions'. The problem with this solution is that the latter expressions are metaphoric and do not provide any clue to the nature of the change. Another possibility would be to abandon traditional logic for fuzzy logic, in which between being A (1) and not being A (0) there is a continuum of values between 1 and 0. The problem with fuzzy logic is that everything is both true and false and the most absurd propositions such as 'viruses are alive' cannot be shown to be wrong. My feeling is that a more qualitative solution has to be sought, in which an object can be A, or non-A or intermediate between A and non-A. The limits to our logic are not the fact that A and non-A cannot be clearly distinguished, but rather that in our Universe a historical process can generate A from non-A. To be alive means to be alive for a relatively long period of time. It seems reasonable to admit that the first living systems were alive for very short periods of time. To be alive requires a certain stability, but there is no way to define a minimal duration below which a system might not be called alive and beyond which it might be called alive. This tight association between 'to be alive' and 'duration' explains why the capacity to reproduce is an obligatory component of a definition of life (see later). Reproduction is the only way to provide a living system with a sufficient stability.

Scientific objections to a search for a definition of life are also diverse, but of a different nature. The first one is historical. To search for a definition of life is likened by many scientists to a search for a principle of life, and therefore to the vitalist movement. Historians have long shown that the vitalist movement was diverse and that many of its supporters in the eighteenth and nineteenth centuries were simply opposed to the mechanistic–reductionist programme of Descartes and Galileo; not in principle for many of them, but in practice, because this reductionist project was premature and ill-adapted (Canguilhem, 1994). Most contemporary biologists nevertheless consider vitalism as a crime against science. It is obvious that looking for a definition of life, looking for a list of properties associated with life, does not mean that organisms are not natural objects, nor that behind their properties a 'principle of life' is hidden somewhere.

The second objection seems stronger, and has been advocated in particular by François Jacob (Jacob, 1982). Science has always progressed by focusing on questions of a limited amplitude – in contrast with, for instance, philosophy. By so doing, scientists have been able to construct a solid form of knowledge. The question of life is too large to be a scientific one.

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This argument is true in the sense that the search for a definition of life is not comparable to the work that scientists do every day at the bench. And finding a good definition cannot be a PhD project! But it does not mean that finding a definition of life is not a scientific objective. It only means that it is an objective of a different nature, distinct from the day-to-day questions raised by scientists; a question which nevertheless must remain in the minds of biologists.

Another argument, closely linked with the previous one, is that looking for a definition of life is a waste of time; it is far more useful to ask 'small' questions, and to answer them by precise experiments. Once again, there is a confusion between experimental questions and questions that belong to a science, without being questions that are directly addressed by experiments.

Another objection is the apparent heterogeneity of the answers that are presently proposed (Popa, 2004). These answers are specific to one discipline or subdiscipline of biology, the answer of a biochemist being different from the answer of a geneticist. Such differences have been shown by historians to have persisted throughout the twentieth century (Kamminga, 1988). Another slightly different version of the same objection is to consider that the question of life will be asked for different purposes, for instance by astrobiologists constructing a device to be put aboard a space probe, or chemists studying prebiotic reactions, and that the answers will always be, for this reason, contextual and different. The fact that the answers are biased by the scientific training or field within which they are posed is obvious, but the error is to consider that these biases will remain forever barriers in a search for a common definition of life. The limits of these provisional definitions do not mean that the production of a consensual definition, including all the aspects that have been underlined by these partial definitions, is not possible. What is clear is that a valid definition of life cannot belong to a single discipline. It has to be shared by different disciplines, biochemistry as well as genetics, chemistry and physics.

The last objection appears radical. Discussing the nature of life makes no sense. What is needed is the elaboration of an experimental device thanks to which the distinction between living and non-living objects would be unambiguous. This was one of the arguments of Norman Pirie (Pirie, 1957). The only way for scientists to answer questions is by doing experiments. The logical flaw in this reasoning is that, to construct such experimental devices, the researcher must have a theoretical idea about what it is 'living'. What will be inserted in this experimental device are these preconceived ideas, and the results of the experiments will only confirm them.

### Good scientific and societal reasons to search for a definition of life

In contrast to the fallacy of the previous objections, there are excellent reasons to try to answer the question 'What is life?'. The first and major reason, which I will develop later when specifically examining the case of viruses, is that the absence of a definition leaves us defenceless when absurd statements are made on the living or non-living character of such and such objects. A definition, however imperfect it may be, is a framework to which it is possible to refer.

A second good reason is that scientists constantly answer this question: not explicitly, but implicitly. A simple example will clearly demonstrate that it is impossible not to adopt an implicit definition of life. A meeting was organized by the Royal Society in London for 3–4 December 2003. The title was: 'The molecular basis of life: is life possible without water?'. The answer to this question is crucial in selecting the planets and satellites of the Solar System to be explored as a priority in the search for traces of life. How is it possible to answer the question on the place of water in living systems without an idea of the main characteristics of a living system? Since a definition of life is clearly necessary, in particular in astrobiology, it is better for the discussion to make it explicit instead of keeping it implicit.

It is also crucial to have an answer, however imperfect, to the question 'What is Life?' for the relations between scientists (and, in particular, biologists) and the lay public. The latter would not understand that this question is not high on the list of biologists' priorities. The right attitude for scientists is not to reject this question as non-scientific: this would create complete misunderstanding. It is to explain why the answer is difficult and what characteristics are considered today as essential for a system to be called 'alive'.

By doing this, biologists will occupy a place too often left to 'mavericks', journalists, amateurs, people without a satisfactory scientific training who propose categorical and frequently wrong answers to the question 'What is life?' and also a door for creationists to give their own non-scientific answer.

The tendency, common among scientists, to consider that this is a 'philosophical' question, and therefore one that does not belong to science, has the same consequence. Philosophers propose answers not informed by recently acquired scientific knowledge and for this reason these answers are at odds with scientific practices. Scientists must not dictate to philosophers what they have to say about life, but they have to do their best to ensure that this philosophical discourse is not in conflict with current scientific knowledge.

An additional argument in favour of a 'natural' place for the question of life within science is the need to attract to science the best minds of the next generations. They will not be seduced by the technological achievements of science, but by the ambition to address the most fundamental issues at the boundary between science and philosophy. When they receive their scientific training they will rapidly learn to delay seeking answers to these fundamental questions and that the progress of science results from focusing on small limited questions, accessible to experimental practice. These fundamental questions will not be abandoned, but left to one side, ready to be taken up again as soon as important scientific breakthroughs have been accomplished. In such a way, the dreams that support any scientific career will not be dashed, but simply tempered by the strict rules that any scientific work has to obey.

While the search for a definition of life has its place in science, this does not mean that any definition is acceptable. Such a definition has to be 'open', in the sense that it must not be limited by our present knowledge, which there is no reason to consider complete. When definitions of life were proposed in the nineteenth century, proteins seemed to be its essential components. For molecular biologists of the 1960s, DNA was placed at the pinnacle. Today, one considers that living organisms, using other macromolecules, may have preceded life on Earth and exist on other planets. To define precisely the nature of the macromolecules present in organisms in a definition of life would therefore be a mistake.

Looking for a definition of life must not be considered to reflect the belief that life is common in the Universe. It does not mean that the process of formation of organisms was a deterministic one: it may be that the conditions favourable to the emergence of life are rarely encountered in the Universe.

## Successive answers to the question of life

My objective will not be to provide a full description of the answers that have been provided so far, but to point to some of their characteristics. Two strategies can be used in a search for a definition of life. The first is to observe the characteristics of organisms present on Earth and to try to isolate the most fundamental ones. The other is more abstract, less tied to observations made on extant organisms. It aims to define abstract characteristics that organisms ought to possess, independently of their precise material constitution. This second approach has been favoured by researchers working on artificial life (Varela, 1979; Ganti, 2003). Most of the historical definitions of life were the product of the former approach.

The most traditional one is that of Aristotle: 'By life we mean self-nutrition and growth (with its correlative decay)' (Aristotle, 1941, 555). One can retrospectively see in this definition an emphasis on two characteristics of life that we will show are still essential in our present vision: the fact that organisms permanently exchange with their environment and that life – in organisms as well as at the global level – is a historical phenomenon.

As we previously saw, the second half of the eighteenth century and the first years of the nineteenth century were a crucial period for the question of life.

One of the most popular definitions was proposed by Bichat in 1802: 'Life is the totality of functions that resist death' (Bichat, 1994). Its weakness is its rhetorical nature, the answer being sought in its apparent opposite, death, the definition of which is unfortunately no more obvious than the definition of life!

More important, and significant for future developments, is the impetus given at the same time by Immanuel Kant, Georges Cuvier and many others in considering organisms as systems, in which the explanation of the functions of the different parts cannot be reached independently of the role they fulfil in the whole organism.

The systemic vision of life has persisted up to the present time, but is complemented by the emphasis placed on reproduction. Buffon was the first to place reproduction at the core of living phenomena, but it was through Darwin's contribution that reproduction became the central mechanism in the evolution of life: the occurrence of chance variations and the differential reproduction of organisms harbouring these variations is the mechanism that drives the evolution of organisms. The progressive description of the chemical components present in organisms – proteins, DNA – in the middle of the twentieth century pressed biologists to give these informational macromolecules a pre-eminent place in the definition of life.

The result of this complex history is that, as we have already outlined, there are many current definitions of life. However, two characteristics of life clearly predominate (Joyce, 1994). The first is that organisms are 'autopoietic systems', chemical systems able to maintain themselves by permanently synthesizing all or most of their components (Varela, 1979). The notion of autonomy is essential to characterize these self-maintaining systems (Ruiz-Mirazo and Moreno, 2009). The second is the capacity of organisms to reproduce. These two characteristics are the legacy of the two historical traditions that we described previously, enriched by improved knowledge of the mechanisms involved. Throughout the twentieth century, these two traditions were clearly supported by two groups of disciplines, chemistry and biochemistry on one side, genetics and evolutionary biology on the other.

Most biologists would agree that these two characteristics are important, but would disagree on their relative importance. Biochemists, for instance, would consider that the existence of a self-sustaining chemical system is the basis of life and that the capacity to reproduce is a consequence. Conversely, geneticists would emphasize that the capacity to reproduce came first, maybe in the simple form of self-replicating macromolecules, and that the metabolic side of life emerged later to support the reproductive system.

Disagreements also emerge as to whether or not it is necessary to combine other properties to generate a living system. Are the complex macromolecular structures present in organisms part of a definition of life? Is it possible to consider that the formation of these complex macromolecular structures was the consequence of the improvement of primitive, already living, chemical reproducing systems or, conversely, that the existence of self-maintaining and reproducing systems would not have been possible without the invention of these complex macromolecular structures? In particular, the existence of a self-maintaining chemical system is due to the presence within organisms of highly efficient catalysts, which all are macromolecules.

Similarly, it is obvious that a system has, in one way or another, to be insulated from its environment. The formation of cellular membranes can be considered as the necessary condition for the existence of such systems, or as a last step in the evolution of complex systems that already existed thanks to the confinement of their components in space, for instance on mineral surfaces. The formation of membranes will be considered as a fundamental step, if they are believed to have been the primeval place where energy was produced.

The invention of genetic information can also be seen as a way to reproduce pre-existing systems more faithfully; or the *sine qua non* for the emergence of a system able to reproduce. The existence of genetic information and the complex interactions between organisms and their environment make it reasonable to attribute a certain form of cognition to any organism. Is cognition a part of the definition of life (Bitbol and Luisi, 2004)? There is a long philosophical tradition that the capacities exhibited by 'higher organisms' have to be included in a minimal definition of life.

Is it also necessary to emphasize that the reproduction of organisms has to be imperfect to generate variants susceptible to be screened by natural selection? It seems difficult to imagine what 'perfect' reproduction would be. More significant, but difficult to be precise about, is the necessity for the rate of variation to be intermediate between two extreme values: too low a value will prevent the generation of enough variations and too high a value will rapidly lead organisms to utter disorganization of their most fundamental functions.

The discussions are not closed, but some trends are clearly visible. The 'informational' vision of many molecular biologists is not as dominant as it was some years ago; dominant to the point of considering that the riddle of life had been definitively solved with the discovery of genetic information and of the genetic code.

The fading of the informational vision is due to the immediately disappointing results of genome sequencing; and also to the hypothesis that an RNA world preceded the present DNA and protein world – in which RNA is not informational in the same sense as DNA is. The contributions of specialists of artificial life, who emphasize the functioning of organisms as systems, did not abolish the role of information in organisms, but put an end to the identification of life with the existence of genetic information.

Similarly, the vision of organisms as self-maintained chemical systems, which was put aside during the development of the informational vision of molecular biology and the dominant place of genes, made a comeback with the increasing number of projects in astrobiology. For the detection of extraterrestrial forms of life will be totally dependent on the capacity of organisms to exchange matter and energy with their environment, not on their capacity to reproduce. Personally, I consider that the two properties – a self-maintaining chemical system and reproduction – are necessary and sufficient to define life; necessary, because a self-maintaining chemical system can be transiently alive, but will not be stable enough to support life; sufficient, at least provisionally, because the addition of other properties depends on scenarios that have not yet been validated. A useful distinction was introduced by Tibor Ganti (Ganti, 2003) between a criterion considered as absolute – the capacity of organisms to self-maintain – and one considered as actual – the capacity to reproduce. The first allows definition of a system as alive, whereas the second is required for the existence of life.

## Are viruses alive?

After they were distinguished from bacteria, viruses were considered in the first decades of the twentieth century as alive. They were the simplest living organisms, and for this reason models to characterize the most fundamental properties of organisms (Morange, 1998). Otherwise, it would be impossible to understand the role that bacteriophages and the tobacco mosaic virus played in the rise of molecular biology (Creager, 2002).

But difficulties accumulated in the 1930s: it was impossible to cultivate viruses except in the presence of living cells. Viruses were progressively considered as parasites. At the end of the 1950s, André Lwoff stated the differences between viruses and organisms: the absence of a metabolism – the lack of a molecular machinery able to translate the information contained in their DNA or RNA genomes (Lwoff, 1957).

There have been recent attempts to give life back to viruses. The first reason for this is the increasing evidence that horizontal gene transfer, due in most cases to viruses, played an important role in the evolution of life. Such genetic transfer, by viruses or plasmids, still plays an important part in the rapid adaptation of microorganisms to new environments, such as the addition of antibiotics. It is admitted that at the early stages of life, at the time when the last universal common ancestor (LUCA) of all extant living forms existed, these genetic exchanges might have been so extensive that it would be more appropriate to talk about a community of genes shared by organisms than of a collection of independent organisms. The recent systematic search for viruses and bacteriophages has revealed not only their abundance, but also the diversity of the genes they harbour, with no related sequences found in extant organisms. A possible interpretation of these data is that viruses are the remnants of a living world that pre-dated LUCA.

The way of considering viruses has also changed. During its cycle a virus may replicate within cells in particular structures called viral factories, which are sometimes surrounded by a membrane. It has been suggested that these viral factories represent the true nature of the virus, whereas the virions are only inactive states during their cycle. Hence the hypothesis that cells invaded by viral factories, in which the virus has reoriented all the synthetic capacities of the cells towards their own propagation, might be called 'virocells' and have a living status comparable to that of 'traditional' cells, now called 'ribocells' (Raoult and Forterre, 2008).

Large viruses of sizes comparable to bacteria have been discovered (Raoult *et al*., 2004). These mimiviruses have large genomes containing hundreds of genes. In addition, they can themselves be parasitized by other viruses (La Scola *et al*., 2008). These observations led their authors to propose that mimiviruses are alive and that the world of life contains a fourth kingdom, in addition to Archaea, eucarya and eubacteria.

I consider with others that, despite their importance, viruses remain strict parasites (Moreira and López-García, 2009). There is no symmetry between a virocell and a ribocell. The first needs the second: the reverse is not true. To consider viruses as living creates much useless confusion. Nothing in the definition of life or in the non-living nature of viruses has to be changed to acknowledge the importance viruses had in the evolution of organisms.

## A crucial time for the definition of life

Since antiquity, multiple definitions have been proposed. Despite the accumulation of observations, the present ones are not utterly different from those that preceded them. Is there real progress in this desperate search for a definition of life?

My conviction is that the search for a definition of life cannot be considered independently from two other issues – the origin of life and the capacity to 'master' living phenomena. Both have experienced a dramatic evolution in the twentieth century. The fears generated by the development of genetically modified organisms bear witness to this new capacity to modify organisms. Researchers working in synthetic biology also have the ambition to synthesize artificial organisms in a more or less distant future; and this ambition does not seem unreasonable.