

ABOUT VARIOUS DEFINITIONS OF LIFE

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Abstract. The old question of a definition of minimal life is taken up again at the aim of providing a forum for an updated discussion. Briefly discussed are the reasons why such an attempt has previously encountered scepticism, and why such an attempt should be renewed at this stage of the inquiry on the origin of life. Then some of the definitions of life presently used are cited and briefly discussed, starting with the definition adopted by NASA as a general working definition. It is shown that this is too limited if one wishes to provide a broad encompassing definition, and some extensions of it are presented and discussed. Finally it is shown how the different definitions of life reflect the main schools of thought that presently dominate the field on the origin of life.

Dedicated to Prof. Dieter Seebach for his 60th birthday

1. Introduction

One might think that among the many people working in fields of prebiotic life, artificial life, cell models and the like, one finds many references to a definition of life in the literature. These researchers should know what they are researching or what they are trying to reproduce in their laboratories. This is not the case: actually definitions of life are rare (some definitions are cited in Chyba and McDonald (1995)*, by Folsome (1979), or in the recent book edited by Rizzotti (Rizzotti, 1996)), and those which are given are not very popular. The reason why this is so would already be *'per se'* an interesting argument of discussion. It would also be interesting to follow how these few definitions have changed in the course of the years, as these changes automatically reflect how science values have moved with time (e.g. proteins versus nucleic acids, metabolism versus self-replication, etc.)**. An analysis of the various definitions of life given in history is, however, out of the framework of the present short article. Some old definitions of life, which are relevant for the arguments presented here, will be given without further comments as footnotes.

* One interesting and often forgotten definition I would like to add without further comment goes back to M. Perret in the early fifties (Perret, 1952). This definition was later taken up by J. D. Bernal (1965). It reads: *'Life is a potentially self-perpetuating system of linked organic reactions, catalyzed stepwise and almost isothermally by complex and specific organic catalysts which are themselves produced by the system'*.

** I find particularly fascinating the definition of life given 1894 by Engels (yes! Friedrich Engels of Karl Marx' memory) and particularly what he says about life and chemistry (Engels, 1894). His definition reads: *'Life is the existence form of proteic structures, and this existence form consists essentially in the constant self-renewal of the chemical components of these structures'* (Engels knew about Haeckel's work, who in turn knew about Rolle's ideas – none of them at that time had a clear notion of what proteins really were).

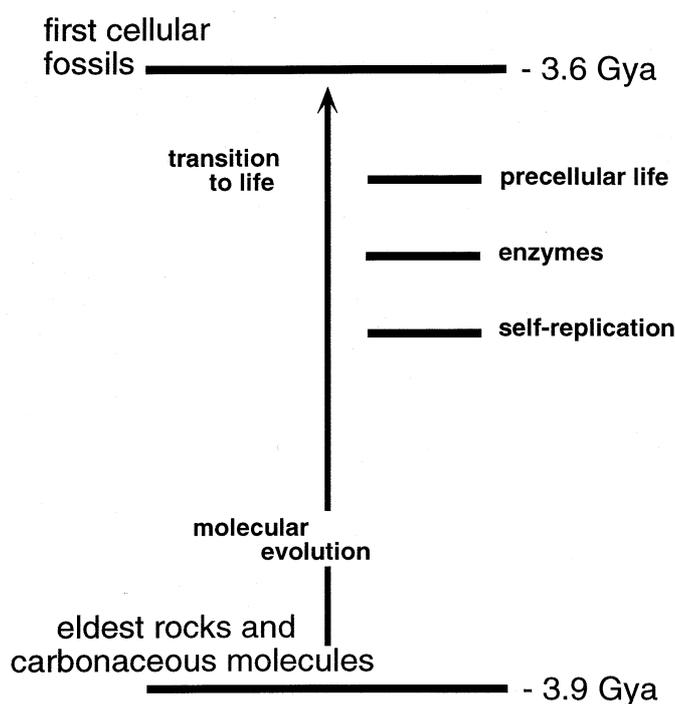


Figure 1. Oparin's scenario of transition to life, with the two signposts we can experimentally rely upon, the dating of the eldest carbonaceous rocks, and the dating of the first fossil cells; and the three way-stations to the transition to life along the pathway of molecular evolution, self-replication, enzymes and pre-cellular life. The assumption here is that a macromolecular system with the property of self-replication is more probable – and therefore may have occurred prior to – a full fledged enzymatic system (ribozymic or proteinaceous).

At first sight, the problem of defining life should be easier for us in the field of origin of life by the self-imposed restriction to deal only with *minimal life*, i.e., the simplest possible form of life. This restriction makes it possible to ignore all those very beautiful and very difficult properties of human life (intelligence, consciousness, ethics, etc). As trivial as this observation may be, it is the one which we should keep repeating to the public, as much misfeeling towards the field of the chemistry of life comes from the unconscious and confusing equivalence between life and 'spirit'.

In this short paper, I would like to reconsider some of the concepts underlying the definition(s) of life, with the aim of possibly fostering a new discussion on the subject.

In order to have a general prospective of the situation, let us consider Figure 1. This represents the view which we all widely accept (although not demonstrated yet). Accordingly, the living originates from the inanimate matter throughout a continuous process of increase of molecular complexity and organization – a process loosely referred to as 'molecular evolution'.

The first one to propose this idea in a written form was Darwin himself – you remember his little warm pond full of salts and other good ingredients – which later on should become famous as prebiotic soup. But Darwin didn't think too much about origin of life; some of the contemporary scientists who popularized his view, however, did it for him, most notably Ernst Haeckel, who stressed that there is no difference in qualities between the inanimate and the animate world ('Anorgane und Organismen') and therefore there is a natural and continuous flux from the one to the other (Haeckel, 1866); and Friedrich Rolle, who most clearly advocated that life derives from the inanimate (Rolle, 1863)*.

But in the chemical literature not so much is known about Rolle and Haeckel – or Lamarck. The first name of note for us is Alexander Ivanovic Oparin, who in 1928 wrote his famous book 'The origin of life' (Oparin, 1928), the one in fact who pushed the idea into modern science. In fact, I will refer to Figure 1 as Oparin' scenario*, as he is certainly the main responsible for our time. Implied with this is not the particular chemical scenario of Oparin' (for example the methane atmosphere) but the general concept of transition to life as a process which goes spontaneously from the inanimate matter to the first living cells.

According to this view, transition to life is a *continuum*, a process which moves between the two signposts ca. 4.5–4.6 billions years ago (origin of Earth) and 3.6–3.7 billions years ago (first cellular fossils). Actually, as the beginning of the transition to life one should take the age of the eldest rocks, about 3.9 billions years ago, when the Earth had reached a certain stage of geological equilibrium. Concerning the final signpost, one may argue that at this time life was already full fledged, since these fossils look remarkably similar to modern cyanobacteria. Then, the beginning of life forms must have started earlier. In conclusion, then, as diagrammatically represented in Figure 1, the transition to life should encompass a period of only a few million years or even shorter (Lazcano and Miller, 1993).

The consideration that the mark 'life' must with all likelihood have preceded cellular life suggests the existence of some forms of life which we do not know presently. This indicates that in the study of origin of life we have not simply to consider *life-as-it-is-now* (cellular) but to include *life-as-it-initially-was*, namely some transient forms that have preceded cellular life. And actually the picture becomes even more complex – and more challenging – if we include (why not?) artificial life, namely *life-as-it-could-be* (Langton, 1992). Notice that these italicized

* A citation from this 1863 work is worth mentioning: (my translation) 'The hypothesis of an originary arising of life from the inanimate matter ... can at least offer the advantage to explain natural things by natural pathways, thus avoiding to invoke miracles, which are actually in contradiction with the foundations of science'.

* A. I. Oparin himself gave a description of life based on six properties: (1) capability of exchange of materials with the surrounding medium; (2) capability of growth; (3) capability of population growth (multiplication); (4) capability of self-reproduction; (5) capability of movement; (6) of being excited. He also added however some additional properties, such as the existence of a membrane (a cardinal principle for him); and the interdependency with the milieu (Oparin, 1961). About the semantics of *description vis-à-vis definition*, see footnote 5.

domains are not so far from each other; once we accept the statement (Eschenmoser and Kiskakürek, 1996) that *'the aim of an experimental aetiological chemistry is not primarily to delineate the pathway along which our (natural) life on Earth could have originated, but to provide decisive experimental evidence, through the realization of model systems ('artificial chemical life') that life can arise as a result of the organization of the organic matter'*, then the difference between artificial life and chemical origin of life is less dramatic.

When we look at Figure 1 trying to be un-prejudiced, we realize that Oparin's proposition is extremely bold. The idea that molecules, without the help of the intelligence of enzymes and the memory of DNA, should spontaneously assemble into molecular structures of increasing complexity, order and functionality, is actually against all chemical and common sense experience. At least, it is so in simple closed systems: which implicitly suggests that Oparin's scenario must be an open system which receives energy from the outside. We have some good ideas on where the energy can come from – think for example of the proposition on the origin of reductive power by Wächtershäuser (1990). Also, we have several ideas about the origin of the small moieties – amino acids and nucleobases and perhaps sugars. The problem with Oparin's proposition is elsewhere: the first problem concerns the origin of optical activity, as in fact, if we want to be honest, we have no chemical idea on how this may have happened. However, as an interesting form of general consensus – we decide to ignore this problem and proceed to the next one. This concerns the origin of functional macromolecules, such as enzymes and nucleic acids, and then their subsequent interactions to build supramolecular complexes, up to the genetic code and the protein biosynthetic apparatus.

In order to deal somehow with this extreme difficulty, we need to make use of some assumptions. In Figure 1 the bold Oparin' pathway is interrupted by three reasonable 'way stations' – whereby the term reasonable means that there is a kind of general consensus today that this is a reasonable assumption: one intermediate – a way station – may have been an enzyme-free process of *macromolecular self-replication* – which in turn might have led to a successive way station of macromolecular catalysis. The cell membrane might have appeared at this stage, or even earlier, to facilitate the primitive metabolism which led to enzymes (Morowitz, 1992).

Even with the simplification of minimal life and way stations, it is clear that the process leading to life is a continuum process, and this makes an unequivocal definition* of life very difficult. In fact, there are obviously many places in Oparin's pathway where the marker 'minimal life' could arbitrarily be placed: at the level of self-replication; at the stage where self-replication was still accompanied by chemical evolution; at the point in time when proteins and nucleic acids began to interact; when a genetic code was formed, or when the first cell was formed, or

* Some philosophers of science of strict Aristotelian observance may even object to the use of the term *definition* (this in fact should be based – they would say – on *genus proximus et differentia specifica*) – and they would then rather use the term *description*.

any intermediate stage that can be conceived of. All these successive way stations have not been indicated in Figure 1b – but it is clear that, once we have reached the stage of enzymes, the way to get to life is still long and difficult.

In view of this arbitrariness on where to put the marker, is any definition equally good? Surely not, as one definition may be more meaningful than another, depending on what you want to do with it. In fact, the following criteria appear important: a definition of life should permit one to discriminate between the living and the non-living in an operationally simple way and it should not be too restrictive (i.e., the discrimination criterion should be applicable over a large area and should be capable of including life as it is as well as hypothetical previous forms). All forms of life we know about should be covered by such a definition. Once decided upon, the definition should also help to design experiments on the production of minimal life in the laboratory, consistent with the definition. It should help space explorers in the attribution of the term ‘life’ to novel biological forms. Finally of course it should be logically self-consistent. The criterium of discrimination between living and non-living should clarify ‘difficult’ cases, such as a virus, which generally is not included in the list of the living; a dead cell, which has still a lot of nucleic acids; and a growing crystal; ... and others.

2. The ‘NASA Definition of Life’

In light of these criteria, let us examine the applicability of a definition used by the Exobiology Program within the National Aeronautics and Space Agency as a general working definition of life. It is one of the very few which one finds in a written form and perhaps for this reason it enjoys considerable popularity – it is for example often cited in origin of life meetings. This working definition goes as follows (Joyce, 1994):

- (1) *‘Life is a self-sustained chemical system capable of undergoing Darwinian evolution’.*

This definition was used before by Horowitz and Miller (1962). Implicit in this definition is the fact that the system is driven by an external source of energy – as nobody, not even in the field of the origin of life! – intends to violate the second principle of thermodynamics. In other words, the self-sustaining proceeds at the expenses of transformation of nutrient/energy provided by the environment. Most probably definition (1) was created to define life at the molecular level. In fact, some of the adherents to the RNA-world would probably be satisfied by a definition of minimal life at the level of

- (2) *a population of RNA molecules (a quasi-species) which is able to self-replicate and to evolve in the process.*

Among the criteria mentioned above, the criterion of generality and broadness is the first to come at odds with the ‘NASA definition’. It is in fact a definition

applicable only to systems which obey the Darwinian mechanism, and all possible forms of imputed life which are not in such a scheme are *a priori* excluded from consideration. Also notice that this means to exclude *single specimens* from consideration. In fact, classic Darwinian evolution generally applies to a *population*, i.e., one has to have a large number of organisms (or elements of the system) which differ from one another in some genotypic feature. The term Darwinian has also a strong historical implication; it immediately brings in the notion of generations of populations which follow one another. It is known that some people will not even consider the notion of life outside a contest of population, but this would be too restrictive, as certainly one should be able to define whether one single individual entity is *per se* living or not. In other words, a strict Darwinian view leaves out, automatically, the case of *life-here-and-now* and therefore it would be difficult to apply it to an individual blob found by space explorers in another planet. Even if they were to find a colony of the things, should they wait perhaps a few million years to observe the Darwinian evolution? In other terms, the definition is also at odds with the criterion of practical operationability. Of course, here is where the use of the vague term '*capable of*' helps, as it is probably meant to indicate that it may be just enough to look at the genetic material and see whether Darwinian-like mechanisms might, in principle, be operative.

Does this definition help the difficult cases, for example, is a virus living or not? The answer would be yes if one considers the potentiality of Darwinian evolution; the answer would probably be no concerning the self-sustainability – but in order to say no we would have to qualify more strictly the term *self-sustained*, e.g., by excluding the mechanisms which lie outside the virion itself.

But the more general and interesting point which emerges from this examination is the question of life at the level of a single object and in the here-and-now connotation. Even without leaving our planet with the astronauts, there are interesting cases where the term life may potentially apply to a single specimen. Is our planet (by some considered to be self-maintaining and self-regenerating) living – as Lovelock (1979, 1988) and more recently Margulis and Sagan (1995) are proposing? Can one create robots or other artificial life artifacts which might be called living? Would a self-reproducing cellular system with a primitive metabolism and without genes – as Oparin (1938) or Dyson (1985) have suggested be living? Or, alternatively, Pirie's 1953 statement comes to mind. 'If we found a system doing things which satisfied our requirements for life but lacking proteins, would we deny it the title?' (Pirie, 1953). And who is to say that these questions do not make sense, or are irrelevant? In fact, one may choose not to consider all these possibilities, (but: by which criterion is this elimination made?) and the problem of defining life becomes then a little easier. However, a more open-minded view would certainly demand a more general definition, one that also allows for the analysis of the life/non-life issue at the level of a single specimen and in non-Darwinian systems.

3. Going beyond the 'NASA-definition' and concluding

The simplest way to approach this would be to delete the term 'Darwinian' from the 'NASA definition'. Let us try that:

- (3) '*A system which is self-sustaining by utilizing external energy/nutrients owing to its internal process of component production*'

where the term self, as usual, indicates that is the system itself that does it from within, and the more general term *production* has been preferred to the too specific and too vastly used terms reproduction or replication*. Production can in fact include reproduction as a particular case. The term *generation* might be perhaps equally good. The qualification 'by utilizing external energy/nutrient' might be perhaps eliminated – as is rather trivial – on the other hand, a link with the medium may sound useful.

The above definition includes all present forms of cellular life, as well as a molecular system such as a self-replicating RNA family (the components are in this case the RNA molecules and the nutrients the mononucleotides or smaller fragments). It also includes Gaia but does not include a virus (as it does not make its own components from within; a self-sustaining chemical reaction, or a growing crystal, are also not included in this definition of minimal life for the same reason, a robot which makes other robots by assembling pieces furnished by other machines would also not be living in force of definition (3).

Definition (3) includes definition (1) but since it does not contain the Darwinian or genetic specification, it allows for *coded life* as well as *non-coded life*. Since the notion of population has disappeared, it can be used to analyze single specimens, including non-molecular systems, such as Gaia or a robot.

The problem with definition (3) is that it may be non specific enough, particularly to those who may like to take a sharp side in the debate. Let us follow this point a little more in detail. There are two main constituents among scientists who study the origin of life. One is that of the adherents to the notion of compartmentation, whereby – in analogy to the existent forms of life on this planet – it does not make sense to talk about life without the notion of boundary; the other much larger party is of course those of the RNA-world, according to whom it does not make sense to talk about life without mentioning the nucleic acids and the corresponding genetic information.

We can amend definition (3) to take into account these specifications (and restrictions) to:

- (4) '*a system which is spatially defined by a semipermeable compartment of its own making and which is self-sustaining by transforming external energy/nutrients by its own process of components production*'.

* Note incidentally the difference between the terms reproduction and replication: replication means making identical copies, reproduction implies a more generic statistical apparatus. This goes back to Dyson (1985) and has been recently reposed (Luisi, 1994).

This corresponds to the definition of minimal life given originally by the proponents of autopoiesis (Maturana and Varela, 1980; Fleischaker, 1988; Luisi, 1993). It is interesting to recall at this point that the original definition of minimal life in autopoiesis does not mention evolution, but not because this is considered irrelevant, but for another, more subtle reason: that mutation, evolution and also reproduction are seen as a *consequence* of the logic of the living, which is expressed by a self-maintaining and dynamically self-regenerating system. In other words, once we have a self-sustaining homeostatic system, according to the autopoietic view, this may (or may not) mutate, evolve, reproduce – depending on its actual internal mechanisms. But this too clever argument may well be the reason why the theory of autopoiesis did not gain much support among molecular biologists and adherents of the RNA-world in particular. Autopoiesis has been freshly re-emphasized by Margulis and Sagan (1995). Notice that the emphasis on the compartments eliminates from the business all systems without boundary, for example all molecular systems such as a ‘naked’ family of self-replicating RNA – as the walls of the little warm pond, or the glass of the reaction vial, do not qualify as ‘boundary of its own making’. The Gaia may, however, be included. All these restrictions are due to the effect of choosing a specific definition.

Let us now consider the geneticist’s view, by expanding definition (3) possibly without using the term Darwinism. For example we could say that life is:

- (5) *‘A system which is self-sustaining by utilizing external energy/nutrients owing to its internal process of component production and coupled to the medium via adaptive changes which persist during the time history of the system’.*

The boundary here is not mentioned, not because the geneticists consider it irrelevant, but because they consider it non essential for the essence of life – something useful yes, but probably a later comer. A comment on the ‘adaptive change’* seems to me relevant: although genes are the most obvious way to view adaptation, they may not be required in principle. Suppose for example that the network system which is responsible for self-maintenance has many different stable subsystems (or structural states of existence), and that perturbations from the outside world trigger a transition from one sub-state to another. Such accessible multiplicity of structural states would be a kind of gene-less, or uncoded, adaptation. This has not been produced in the laboratory, which sets actually a challenge for experimentalists in the field.

Of course definition (5) includes in principle definition (4), and vice,versa. But the point here is one of ‘political’ emphasis; and I am sure that some authors may recognize themselves more in one than in the other specific definition. This difficulty in setting the question between these two types of definitions (the one with boundary and the one based on self-replication alone) reflects well the present

* I owe this comment to Walter Fontana (private communication).

day' situation, which is characterized by a division in two main schools of thought – the compartmentalist's view and the molecular geneticist's view. Consider also that this differentiation corresponds to a deeper cultural division – although this may not always be at a conscious level. The autopoietic view can in fact be brought back to the cultural stream of system theory, – with emphasis on self-organization, complexity, and Gestalt ('the whole is more than the sum of the parts', etc.). The other view is more strictly reductionistic, certainly more old-fashioned, with the advantage of a larger transparency. And it is perhaps good that each author identifies her/himself with the one or the other definition. Just to know where one stands.

Why should one have a definition of life? There is first of all the intellectual pride in catching with words a difficult concept one is working with. But, more importantly, a definition of life illustrates an experimental program: once you have the intellectual clarification of the definition in front of you – there you have a challenge to implement it in the laboratory. As we should not forget that, notwithstanding our positivistic optimism, the pathway of Figure 1 is still an unproven hypothesis. With regard to this, let me cite again Friedrich Rolle, who wrote about the hypothesis of the transition to life from the inanimate (Rolle, 1863 – my translation): 'The general reasons for this assumption are really so impellent, that no doubt soon or later will be possible to show this possibility in a clear and broader scientific way – or even to repeat the process by the experimentation'.

This was said over 130 years ago, and still nobody has yet made minimal life from the inanimate organic matter.

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