Orig Life Evol Biosph (2010) 40:119–120
DOI 10.1007/s11084-010-9189-y

EDITORIAL NOTE

Defining Life: Conference Proceedings

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Received: 14 September 2009 / Accepted: 15 September 2009 /

Keywords Definition of life · History of science · Origin of life · Philosophy of science

Foreword

This Special Issue of *Origins of Life and Evolution of Biospheres* contains papers based on the contributions presented at the Conference "Defining Life" held in Paris (France) on 4–5 February, 2008.

The main objective of this Conference was to confront speakers from several disciplines—chemists, biochemists, biologists, exo/astrobiologists, computer scientists, philosophers and historians of science—on the topic of the definition of life. Different viewpoints of the problem approached from different perspectives have been expounded and, as a result, common grounds as well as remaining diverging arguments have been

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identified. In addition to individual talks, two large roundtables gave ample room for speakers to discuss their diverging viewpoints. This volume collects almost all the contributions presented during the Conference and provides a rich spectrum of renewed answers to the ever-standing question “What is Life?”. Besides the arguments directly regarding this question, more philosophical or historical reflections are also proposed in this issue that were not presented during the Conference. This volume also offers a synthesis written by J. Gayon taking each contribution into account.

To conclude this foreword, we would like to thank all the participants and speakers who made this Conference a most stimulating event. Each provided novel ideas to “Defining Life” while highlighting the extreme difficulty to reach a consensus on this topic. We are also very grateful to the French CNRS Interdisciplinary Program *Origines des Planètes et de la Vie* (Origins of Planets and Life) for its generous support, as well as to the National Museum of Natural History in Paris for hosting the Conference. We also thank Alan W. Schwartz for generously offering this space for publishing the Proceedings of the Conference.

Orig Life Evol Biosph (2010) 40:121–130
DOI 10.1007/s11084-010-9190-5

Software Replica of Minimal Living Processes

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Received: 4 January 2009 / Accepted: 21 April 2009 /

Abstract There is a long tradition of software simulations in theoretical biology to complement pure analytical mathematics which are often limited to reproduce and understand the self-organization phenomena resulting from the non-linear and spatially grounded interactions of the huge number of diverse biological objects. Since John Von Neumann and Alan Turing pioneering works on self-replication and morphogenesis, proponents of artificial life have chosen to resolutely neglecting a lot of materialistic and quantitative information deemed not indispensable and have focused on the rule-based mechanisms making life possible, supposedly neutral with respect to their underlying material embodiment. Minimal life begins at the intersection of a series of processes which need to be isolated, differentiated and duplicated as such in computers. Only software developments and running make possible to understand the way these processes are intimately interconnected in order for life to appear at the crossroad. In this paper, I will attempt to set out the history of life as the disciples of artificial life understand it, by placing these different lessons on a temporal and causal axis, showing which one is indispensable to the appearance of the next and how does it connect to the next. I will discuss the task of artificial life as setting up experimental software platforms where these different lessons, whether taken in isolation or together, are tested, simulated, and, more systematically, analyzed. I will sketch some of these existing software platforms: chemical reaction networks, Varela's autopoietic cellular automata, Ganti's chemoton model, whose running delivers interesting take home messages to open-minded biologists.

Keywords Artificial life · Autopoiesis · Chemoton · Computer simulations

Introduction to Artificial Life

Proponents of artificial life have chosen to resolutely neglecting a lot of materialistic and quantitative information deemed not indispensable to focus on the rule-based mechanisms

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making life possible, supposedly neutral with respect to their underlying material embodiment, and to replicate them in a non-biochemical substrate. In artificial life, the importance of the substrate is purposefully understated for the benefit of the function (software should "supervene" to an infinite variety of possible hardware). Minimal life begins at the intersection of a series of processes which need to be isolated, differentiated and duplicated as such in computers. Only software development and running make possible to understand the way these processes are intimately interconnected in order for life to appear at the crossroad. Artificial life obviously relates to exobiology since the later cannot restrict itself to a mere materialistic view of life in order to detect it elsewhere. The material substrate could be something totally different and the presence of life must be suspected through its functions, much before being able to dissect it. Artificial life does not attempt to provide an extra thousandth attempt definition of life, any more than do most biologists. "Defining" is a sociological endeavor which consists in grounding something semantically rather weak on a stronger semantic support. The rejection of an authoritative definition of "life" is often compensated for by a list of functional properties which never finds unanimity amongst its authors. Some demand more properties, others require fewer of those properties that are often expressed in terms of a vague expression such as "self-maintenance", "self-organization", "metabolism", "autonomy", "self-replication", "open-ended evolution". A first determining role of artificial life consists in the writing and implementing of software versions of these properties and of the way they do connect, so as to disambiguate them, making them algorithmically precise enough that, at the end, the only reason for disagreement on the definition of life would lie in the length or the composition of this list and on none of its items.

Beginning at the next chapter, I will sketch the history of life as the disciples of artificial life understand it, by placing these different lessons on a temporal and causal axis, showing which one is indispensable to the appearance of the next and how does it connect to the next. The task of artificial life is to set up experimental software platforms where these different lessons, whether taken in isolation or together, are tested, simulated, and, more systematically, analyzed. I will outline some of these existing software platforms whose running delivers interesting take home messages to open-minded biologists.

The History of Life Seen by Artificial Life

Appearance of Chemical Reaction Cycles and Autocatalytic Networks

In order for a system to emerge and maintain itself inside a soup of molecules which are potentially reactive and contain very varied constituents (which could correspond to the initial conditions required for life to appear i.e. the primordial soup), this reactive system must form an internally cycled network or a closed organisation, in which every molecule is consumed and produced back by the network. A network of this kind will be materially closed but energetically open if none of the molecules appears in or disappears from the network as a result of external factors, whereas energy, originating in external sources, is necessary for the reactions to start and take place. The presence of such a energy flux, maintaining the network far from the thermodynamic equilibrium, is needed since, without it, no reactive flow would be possible circulating through the entire network. A reaction cycle thus acts as a chemical machine, energetically driven from the outside. The network transforms as much as it "keeps on" all the chemical agents which it recruits. Biologists generally agree that a reactive network must exist prior to the appearance of life, at least to catalyze and make possible the other life processes such as the genetic reading and coding; it is open to external influences in terms of matter and energy, but necessarily contains a series of active cycles. They are most often designated as “metabolism” or “proto-metabolism”, the most popular and active advocates of this “metabolism-first” hypothetical scenario of the origin of life being: (De Duve 2002; Ganti 2003; Maynard Smith and Szathmary 1999; Kauffman 1993, 1995; Shapiro 2007; Dyson 1999).

In my lab (Lenaerts and Bersini 2009), we give priority to the study of chemical reaction networks viewing them as key protagonists in the appearance of life. These chemical reaction networks where the elements are the molecules participating in the reactions and the connections the reactions linking the reacting molecules to the molecules produced are generally characterised by fixed point dynamics, the chemical balances during which the producers and the products mutually support each other. The attractors in which these networks fix themselves are as dynamic—the concentrations slowly stabilize—as they are structural—the molecules participating in the network are chosen and “trapped” by the network as a whole. These networks are perfect examples of systems which combine dynamic (the chemical kinetics in this case) and metadynamics (the network topological change), as new molecules may appear as the results of reactions while some of the molecules in the network may disappear if their concentration vanishes in time.

We have programmed the genesis of these chemical reaction networks by adopting the Object-Oriented (OO) programming paradigm. The OO simulator aims to reproduce a chemical reactor and the reaction network which emerges from it (like shown in Fig. 1). This coevolutionary (dynamics + metadynamics) model incorporates the logical structure of constitutional chemistry and its kinetics on the one hand and the topological evolution of the chemical reaction network on the other hand. The network topology influences the kinetics and the other way round since only molecules with a sufficient concentration are allowed to participate into new reactions. Our model is expressed in a syntax that remains as close as possible to real chemistry. Starting with some initial molecular objects and some initial reaction objects, the simulator allows us to follow the appearance of new molecules, the reactions in which they participate as well as the development of their concentration over a period of time. The molecules are coded as canonical graphs. They are made up of atoms and bonds which open, close or break during the reactions. The result of the simulation consists in various reaction networks, unfolding in time, and whose properties can be further studied (for instance the presence of cycles or of a particular topology such as scale-free or random).

One of these reaction schemes, more than just cycling, can further be autocatalytic, when a product of the reaction cycle is the double in concentration of one of the reactant: a + b -> a + a. This is for instance the case of the so-called Formose reaction (that Ganti and Szatmary have discussed at large in (Ganti 2003)), during which a two-carbon molecule, reacting twice with a monomer composed of one carbon, leads to a four-carbon molecule, which then splits in order to duplicate the original molecule. As will be discussed later, Ganti has been the first to connect and synchronize these two replication processes: chemical and genetic, in order for the cell to simultaneously duplicate its boundary, its metabolism and its informational support. In the presence of autocatalysis, the kinetics amounts to an exponential increase and, more interestingly, when various autocatalytic cycles enter in antagonistic interaction, turns out to be responsible for symmetry breaking (one of the cycle, randomly favoured initially, wins and takes it all). The early origin of life should not be studied without taking account the self-organization of chemical networks, the emergence and antagonism of autocatalytic cycles and how energy flows drive the whole process. Such chemical networks are for

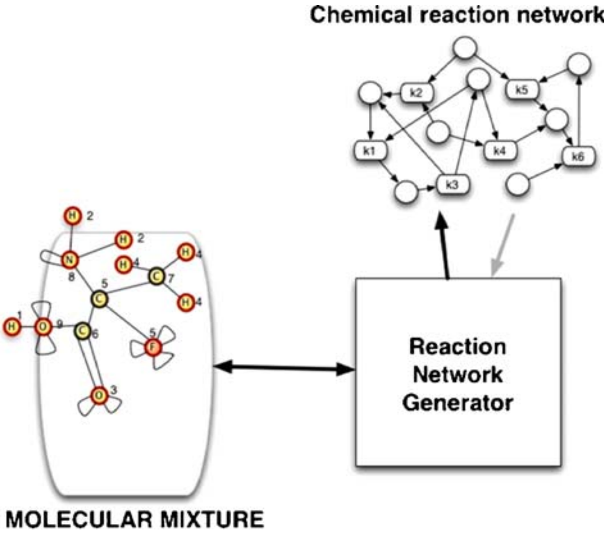

Fig. 1 The OO chemical simulator developed by Lenaerts and Bersini (2009). On the left, the molecules are represented as canonical graphs. On the right, the outcome of the simulator is an evolving reaction network which can be studied in its own right (the presence of cycles, the type of topology...)

instance interesting to understand the onset of biological homochirality as the destabilization of the racemic state resulting from the competition between enantiomers and from amplification processes concerning both autocatalytic competitors (one left-oriented and the other right, see (Plasson et al. 2007)). The chemical reaction network under study (shown in Fig. 2) is made up of polymerization and depolymerization reactions. In the additional presence of epimerization reactions allowing the transformation of a right-hand monomer in a left-hand one and vice-versa, the concentration of one family of monomers (for instance the left one) vanishes in favour of the other. The flux of energy is transferred and efficiently distributed through the system, leading to cycle competitions and to the stabilization of asymmetric states.

Production by this Network of a Membrane Promoting Individuation and Catalysing Constitutive Reactions

The appearance of a reaction network of this kind undeniably creates the stability necessary for exploiting its constituents in many reactive systems such as the ones dedicated to the construction of membranes or the replication of molecules carrying the genetic code. This network also acts as a primary filter as it can accept new molecules within it, but can equally well reject other molecules seeking to be incorporated within it. They will be rejected, as they do not participate in any of the reactions making up the network. Nevertheless, It would seem fundamental that a living organism of any kind can be differentiated from another. The best way of successfully completing this individuation and to be able to distinguish between these networks is to revert to a spatial divide, which can only be produced by some form of container capable of circumscribing these networks in a given space. Biochemists are well acquainted with an ideal type of molecule, a raw material for these membranes in the form of lipidic/amphiphilic molecules or fatty acids, the two extremities of which behave in an

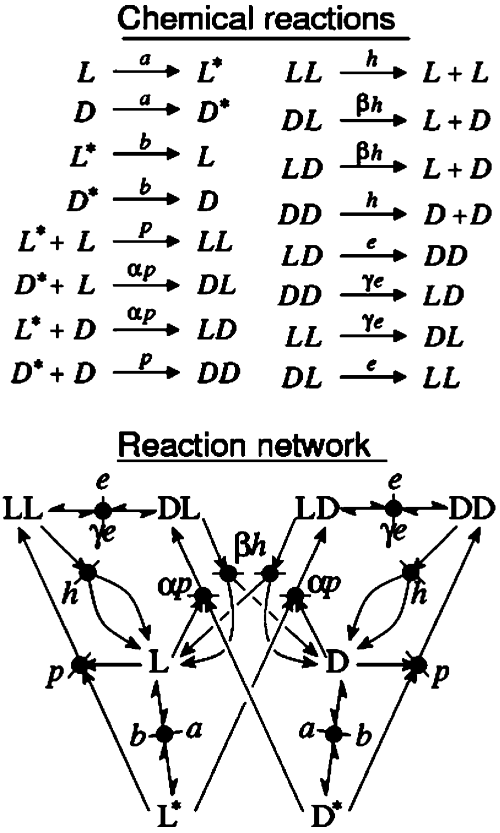

Fig. 2 The prebiotic chemical reactor system responsible for a homochiral steady state studied by Plasson and Bersini. The complete set of reactions is indicated containing activation(the necessary energy source), polymerisation and hydrolysis (which together shapes the cycles) and epimerization (which induces the competition between the enantiometers)

antagonistic fashion—the first hydrophilic, attracted to water, and the second hydrophobic, repulsed by it. Quite naturally these molecules tend to assemble in a double layer (placing the two opposing extremities opposite to each other), formed by the molecules lining up and finally adopting the form of a sphere to protect the hydrophobic extremities from water. Like soap bubbles, these lipid spheres are semi-permeable and imprison the many chemical components trapped during its formation. They do however actively channel in and out the most appropriate chemicals for maintaining themselves.

In assimilating living organisms to autopoietic systems, Varela et al. (1974) were the first to insist that this membrane should be endogenously produced by the elements and the reactions making up the network (for example lipids would come from the reactions of the network themselves) and would in return promotes the emergence and self-maintenance of the network. The membrane can help with the appearance of the reactive and growing network by the frontiers that it sets up, the concentration of certain molecules trapped in it or by acting as a catalyst to some of the reactions due to its geometry or its make-up. Basically, autopoiesis requires a cogeneration of the membrane and of the reactive network which it "walls up". The network presents a double closure—one chemical, linked to the cycling chain of its reactions and another physical, due to the frontiers produced by the membrane. In the cellular automata model of Varela (Varela et al. 1974; McMullin and Varela 1994) illustrated in Fig. 3, there are three types of particles

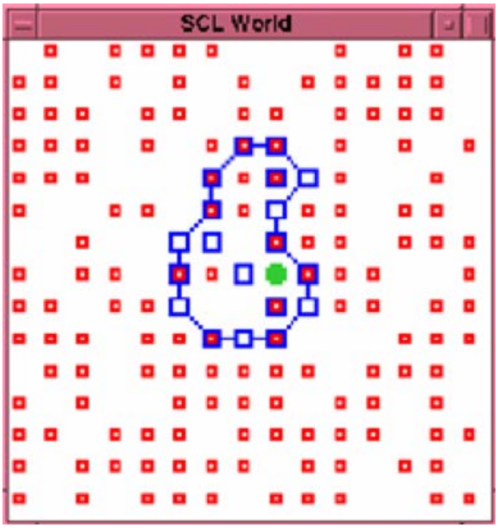

Fig. 3 Simulation by means of a cellular automata of the autopoietic model originally proposed by Varela. The minimal cell can easily be seen together with the catalysts and the substrates that it encapsulates

capable of moving around a two-dimensional surface; “substrates”, “catalysts” and “links”. The working and updating rules of this cellular automata produces minimal versions of reactive systems, physically closed and confined by means of a membrane, which is itself produced by the reactive system.

In the food steps of Varela, considering life impossible without a way for individuation and compartmentalisation, the constitution of the membrane by simple self-organisation or self-assembly processes of bipolar molecules (hydrophilic and hydrophobic) has become a very popular field of artificial life in its own right. It is indeed rather simple to reproduce this phenomenon in software (like illustrated in Fig. 4). You need water molecules that just randomly move, in blue in the figure. You need two kinds of sub-molecules (call then A and B) which when meet form, though the only authorized additive chemical reaction, an A-B molecule (A is hydrophobic and B hydrophilic) whose two poles are connected by a small string. You need also to adjust the degree of repulsion between A and water, of attraction between B and water, the strength of the string of the A-B molecule and the random component (akin to the thermal noise)

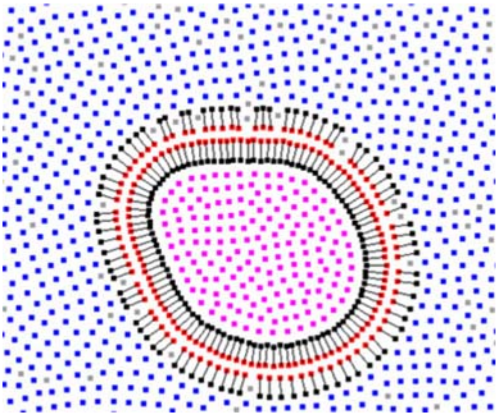

Fig. 4 Simulation of a minimal cell based on A-B (A is hydrophobic and B hydrophilic) and water molecules. All molecules move in reaction of repulsive forces of different intensity and thermal agitation. The *pink dots* are the A, the *grey dots* are the B that do connect to give A-B (represented in *red* and *black*) by a simple chemical reaction. The *blue dots* are the water molecules

to add at each of the intermolecular forces. Nevertheless, the final outcome turns out to be rather robust. The bi-layer of B-A/A-B molecules will very naturally and spontaneously form such as for real cells.

Again as for the Varela's minimal cell, the closure turns out to be quite delicate to obtain. One very simple way to obtain it is to locate the source of A sub-molecules (the pink dots in the figure) in a singular point so that the closed membrane will simply surround that source, the circular shape being the local minimal of the mechanical energy connecting all A-B together. Like in Varela's model, and somewhat paradoxically, the source needs to be circumscribed by the membrane for that same membrane to close on itself. However, in contrast with this autopoietic model, once in place the membrane cannot deteriorate and thus no further internal chemistry is required to endogenously produced what would be needed to fix it. Ultimately this membrane must exhibit some selective channelling in and channelling out (akin, for some authors (Luisi 2002), to a very primitive form of cognition) providing its internal metabolism with the right nutrients and the right evacuating way out so as to facilitate the cell self-maintaining. These two software models raise interesting questions for the biologists like: how are the molecular parts of the membrane generated (endogenously or exogenously) and is this cogeneration of the membrane and the internal metabolism the signature of minimal life?

Self-replication of this Elementary Cell

Self-replication, or the ability of a system to produce a copy of itself on its own, is one of the essential characteristics which has most intrigued and impassioned disciples of artificial life, beginning with the second father of computing: John Von Neumann, after Turing. Departing from the elementary cell introduced in the preceding chapter, and in the interest of an unbroken narrative, it is possible to imagine a simple scenario leading to self-replication. The closed circuit of chemical reactions could be destabilized by some kind of disturbance, causing a growth in concentration of some of its constituents, including those involved in the formation of membranes. This would also be the case provided all the reactions of the metabolism turn to be autocatalytic entailing the concentration exponential growth of all its molecular elements (including again the membrane constituents). The membrane and the elements which it captures begin to grow (as illustrated in Fig. 5) until they reach the fatal point where the balance is upset. This is followed by the production of a new cell produced by and from the old one. When the new one comes, it quickly grows fast enough to catch up with the "generator" and "nursing" cell, as a chemical network is capable of some degree of self-regeneration due to its intrinsic stability; each molecule

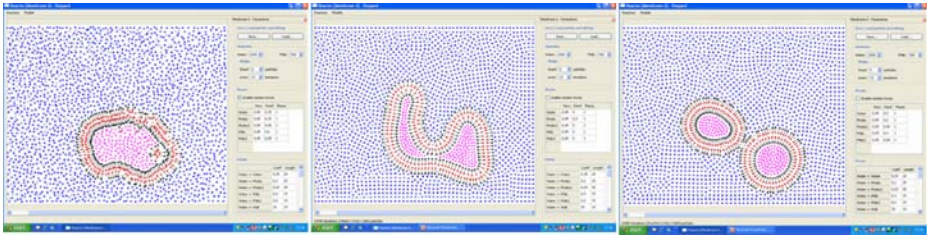

Fig. 5 The elementary minimal cell of Fig. 5 in a process of self-replication induced by the growing and the division of the chemical metabolic network together with the membrane individuating it. A lot of random thermal noise is here indispensable to destabilize the initial cell

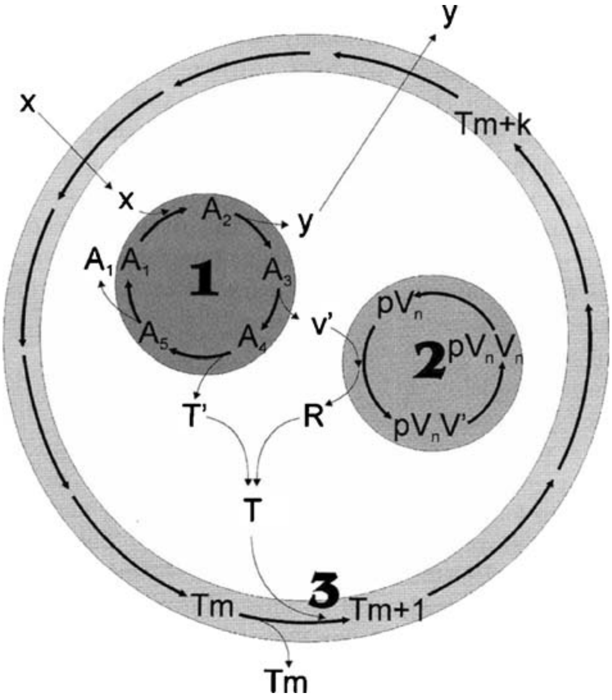

Fig. 6 The schematic representation of Ganti's chemoton. One can easily see the three autocatalytic subsystems: the metabolism, the membrane and the information template, chemically coupled

looks around for another that it can couple up to. This reconstitutes the natural chain reaction of the whole. The new membrane and the new chemical network reconstitute on their own by helping each other. Again, obtaining such duplication is far from obvious since, any cell being intrinsically stable, only a thermal but quite unnatural agitation would do the job. Alive hackers ought to find some more convincing mechanisms including the genetic template in the years to come.

Rather than this elementary form of chemical self-replication coupled to the physical self-replication induced by the growth and division of the membrane, life has opted for a more sophisticated physico-chemical version of it, more promising for the evolution to come: self-replication by the interposing of an "information template". Each element of the template can only couple itself with one complementary element. The new coming elements will as a whole naturally reconstitute the template they were attracted to, causing then the replication of the entire template. In the 50s, Timor Ganti, (Ganti 2003), a largely misunderstood researcher, but nevertheless a key precursor of artificial life, proposed a first minimum mathematical system, named "chemoton", represented in the Fig. 6. This is the first abstract computational proto-cell that we know, construed by Ganti as the original ancestor of living organisms. It possesses three autocatalytic chemically linked sub-systems; a metabolic network, a membrane and an information template responsible for scheduling and regulating self-replication. They all three grow exponentially until to reproduce and essentially depend on each other for their existence and their stability. The metabolism feeds the membrane and the template, the membrane concentrates the metabolites, the template mechanism dictates the reproduction of the whole. The triadic ensemble is indeed capable of a whole self-replication and tries to computationally answer questions about the three sub-systems and their interdependency, such as "how does the self-replication of the template automatically accompanies the self-replication of the whole". This complex software object, the "chemoton", has also become these recent years the topic of many software developments and experimentations and is emblematic of artificial life at its best.

Conclusions

Parallelism, functional emergence and adaptability are the conditions necessary to allow these new biologically inspired artefacts to emerge, to "face the world". We are jumping straight into the robotics branch of artificial life (Brooks 1990). The interfacing with the real world required by these robots needs a parallel information reception mechanism, because the environment subjects it to a constant bombardment of stimuli. They have to learn to organize and master this avalanche falling on their perceptions. They have to learn to build their own concepts, fed and stimulated by this environment, and which, in return allows them to master it. The conceptual high level cognitive processes are born out of motor-sensory interactions and serve to support them. Cognitive systems extend at new levels what the minimal cell in the primitive soup does, with a flow of matter and energy crossing straight through, maintaining itself by selectively integrating this influx to form a closed reactor network and the membrane enclosing it. Like the simplest membrane, they do not passively receive a predetermined world, but integrate it in a way which is adapted to their structure and their maintenance in the world.

To the philosopher, at each attempt at a definition of life, artificial life makes a hard move to achieve a computerized version in conformity with this definition. For the sceptic, unhappy with this computerized "lining", the question now becomes how to refine his definition, to complete it or to renounce the possibility that there is no definition which cannot be computerized. The other possibility, doubtless more logical but more difficult for many philosophers to accept would be that life poses no problem for a computer snapshot since it is computational at its roots. The beneficial effect of such an attitude is to help de-sanctify the idea of life in its most primitive form, when it is the privilege of the most elementary organisms, and not, as in more evolved organisms, when it underlies the manifestation of consciousness. By referring a philosophical article which has become famous in the artificial intelligence community (Nagel 1974), if a computer cannot know what it is like to be a bat, living like one could be much more within its reach.

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Orig Life Evol Biosph (2010) 40:131–136
DOI 10.1007/s11084-010-9191-4

Defining Life: Connecting Robotics and Chemistry

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Received: 13 January 2009 / Accepted: 15 May 2009 /

Abstract Life is commonly referred as open systems driven by organic chemistry capable to self reproduce and to evolve. The notion of life has also been extended to non chemical systems such as robots. The key characteristics of living systems, i.e. autonomy, self-replication, self-reproduction, self-organization, self-aggregation, autocatalysis, as defined in chemistry and in robotics, are compared in a dialogue between a chemist and a robotitian.

Keywords Aggregation · Autocatalysis · Autonomy · Chemical evolution · Robotics · Self-organization · Self-replication

Introduction

Defining life is a difficult task and the intriguing and eternal question "What is life?" has not yet received a commonly accepted answer, even for what could be defined as minimal life, the simplest possible form of life (Luisi 1998). On the occasion of a Workshop on Life, held in Modena in 2003, each member of the International Society for the Study of the Origins of Life was asked to give a definition of life. The 78 different answers occupy 40 pages in the proceedings of the workshop (Palyi et al. 2002). In this query, the connection with chemical systems was implicit, although the concept of life is also used in robotic sciences. This paper aims to compare the two approaches in a dialogue between a chemist (A.B.) and a robotitian (M.T.).

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Defining Life

A.B. Perhaps the most general working definition is that adopted in October 1992 by the NASA Exobiology Program: “Life is a self-sustained chemical system capable of undergoing Darwinian evolution”. Implicit in this definition is the fact that the system uses external matter and energy provided by the environment. In other words, primitive life can be defined, *a minima*, as an open chemical system capable of self-reproduction, i.e. making more of itself by itself, and also capable of evolving. The concept of evolution implies that the chemical system normally transfers its information fairly faithfully but makes a few random errors. These may potentially lead to a higher complexity/efficiency and possibly to a better adaptation to changes under the existing environmental constraints.

M.T. Robots are physicochemical machines which have to preserve the integrity of their structure while being faced with infinite variable constraints within an environment which can degrade them. The mandatory characteristic of robots is autonomy. To fulfill the requirement of autonomy, these physicochemical machines must be able to categorize in a coherent way the infinite variety of shapes of objects which are perceived by their sensors. It is not necessary for an autonomous robot to be able to reproduce itself, self-reproduction being only a secondary property. Evolutionary robotics, based on self-reproducing mechanisms, appears therefore to be a restricted branch of robotics. It is suggested that the mandatory notion of autonomy could help to create “chemical” life in a test tube.

Self-Replication Versus Self-Reproduction

A.B. The concept of self-replication is borrowed from the molecular biology of DNA, that is transferring the sequence information to a daughter chain *via* template polymerization. The daughter chain is not a true image of the mother chain but rather a “negative” so that a second step is required to obtain a true copy of the original. Primordial living systems were perhaps able to produce true copies in one step. One can therefore imagine autocatalytic growth of specific sequences on mineral surfaces followed by chain cleavages generating new chain primers. So far, no such sequence information amplification *via* chain elongation has been obtained in the laboratory.

M.T. From the point of view of evolutionary robotics, the self-replication of a DNA strand can be seen as the self-reproduction of a list of characters or a ‘robotic genome’ pertaining to a mother robot, which would transmit fortuitously-acquired functional features to a daughter robot. This mother genome is decoded by a specific computing module or controller to monitor functions, such as “forward”, “backward”, etc. The self-reproduction of the characters of a robotic genome can be spontaneous, like footprints in clay.

However, the functions attached to these genomic characters cannot be transmitted spontaneously to the daughter robot without the help of a technician. This is because the relative positions of the various characters of the genome known by the mother controller are strictly indistinguishable by the daughter controller. This factor of “indiscernibility” between the localization of the characters is due to the fact that the mother and daughter robotic genomes do not occupy the same position in space, thus requiring a new additional descriptor of the genome (Watanabe 1985). Self-reproduction of the robotic genome, in terms of function, is thus impossible. Therefore, evolutionary robotics is not a pertinent mechanism for the creation of autonomous robots.

The impossibility of transferring functions can perhaps be connected to the difficulty in obtaining self-replicating RNAs in a test tube.

Organization and Self-Organization

A.B. Amphiphilic molecules, with a hydrophobic hydrocarbon tail and a hydrophilic polar head, self associate spontaneously in water to form vesicles or micelles. Harold Morowitz (Morowitz 1992) postulated that vesicles were the first step toward the origin of life. Examples of autocatalytic micelle growth have been published by the group of Luisi (Bachmann et al. 1992). The formation of vesicles is a passive response to environmental conditions. They do not really store hereditary information and cannot therefore evolve by natural selection. However, Szostak (Hanczyc et al. 2007) found that clay particles, such as montmorillonite, can help the vesicles to assemble and, in the process, to bring bound RNA into the interior of the vesicles, thus providing information to the vesicular system. Computer modeling by Doron Lancet (Shenhav et al. 2005) may also help to support this vesicular life. Even more ambitious, the "minimal cell project" aims to synthesize a cell model that has the minimal number of components in order to be defined as living. Liposomes are used as shell membranes and attempts are made to introduce a minimal genome (Luisi 2007; Solé et al. 2007).

M.T. A robot is autonomous if it is able to face alone the various deleterious and useful constraints of its environment. The concept of autonomy implies being able to distinguish between order and organization. Order results from stereotyped attractive physicochemical processes, i.e. spontaneous interactions possibly accelerated by catalysts, induced by physical laws, like the association of sodium with chlorine in sodium chloride. These spontaneous reactions are inescapable events due to the combinational properties of matter. Organization results from opportunistic physicochemical processes, which have the basic property of being able to categorize the infinite variety of object shapes perceived by a system and for which the system has no particular physicochemical affinity.

In the view of the above distinction, vesicles made of amphiphilic molecules (Désaubry et al. 2003) are by no means self-organized structures; they are only ordered structures considering the physicochemical affinities between their elements. Thus, these vesicles alone cannot be considered as approaching living species. Similarly, dissipative structures far from thermal equilibrium (Prigogine 1969) are only ordered and are not self-organized structures capable of generating life, as generally asserted. The same holds for the cyclic networks of Stuart Kaufman (Kaufman 1993), which only lead to more or less complex ordered objects. All these prebiotic candidates do not have any of the opportunist functions characterizing life. The interactions shaping their organization relate only to elements sharing more or less pre-established affinities.

Aggregation and Selective Aggregation

A.B. Strictly homochiral polypeptides, with alternating charged hydrophilic and hydrophobic residues, are soluble in water. At neutral pH, the charged side-chains are ionized and the charge repulsion impedes the formation of ordered conformations. Addition of salt produces a screening of the charges and allows the polypeptide to adopt a β-sheet structure (Brack and Orgel 1975). The polypeptide chains aggregate into asymmetrical bilayers with a hydrophobic interior and a hydrophilic exterior because of hydrophobic side-chain clustering.

Aggregation of alternating sequences to form β-sheets is possible only with homochiral (all-L or all-D) polypeptides. When increasing amounts of L-residues are introduced into a racemic alternating polypeptide, the proportion of β-sheets increases and there is a good relationship between the percentage of the β-form and the amount of L-residues in the polymer. The molecules can be described as a mixture of β-sheets and disordered segments. Those segments containing six or more homochiral residues aggregate, thus forming stable nuclei of optically pure β-sheets surrounded by heterochiral unordered segments. In these polypeptides containing both L-and D-residues, only those segments containing six or more homochiral residues aggregate to form stable optically pure β-sheet islands surrounded by heterochiral unordered segments (Spach and Brack 1979).

M.T. Aggregation of polypeptide chains leads to an ordered object. Owing to their nature, these ordered structures have stereotyped properties that are antithetic to the nature of life, which implies opportunist actions. These attractive interactions between identical molecules result from their reciprocal recognition that differs radically from the recognition process of a robot, which recognizes objects for which it has no particular physicochemical affinity.

To undertake relevant actions to ensure the durability of its structure, the robot must therefore make the distinction between the various objects perceived by its sensors. However, according to the ‘indiscernibility principle’ of the formal theory of ‘Pattern recognition’ (Watanabe 1985), it is actually possible to prove that « for any physical system—whatever its complexity—two unspecified objects having no specific physicochemical affinities with the system are basically strictly indistinguishable one from the other ».

It appears therefore logically impossible to build an autonomous robot by implementing only mechanisms that involve necessary physico-chemical attractive interactions between elements, like those generating the vesicles.

Catalysis, Autocatalysis and Competition

A.B. “All replicating systems are, by definition, autocatalytic and all autocatalytic systems result, in some sense, in replication” (Orgel 1992). Autocatalysis is observed when the coupling of two reactants A-o and •-B is catalyzed by product A-B of the reaction. Different templates have been tested (Terfort and von Kiedrowski 1992; Wintner et al. 1994; Burmeister 1998). In most cases, the rate of the autocatalytic growth did not vary in a linear sense. The initial rate of autocatalytic synthesis was found to be proportional to the square root of the template concentration, i.e. the reaction order in these autocatalytic self-replicating systems was found to be 1/2 rather than 1, a finding in contrast to most autocatalytic reactions known so far. The reaction is slowed down by the fact that the A-B/A-B duplex produced is more stable than the starting A-B/A, B triplex. Two preformed fragments of a peptide have been demonstrated to be autocatalytically ligated by the whole peptide acting as a template (Lee et al. 1996; Severin et al. 1997). Moreover, the replicated molecules contain only two “letters” and therefore a very low level of information. As for the writing, the use of bifunctional letters allows the information to be infinitely enriched:

$$\bullet{-}A - o + \bullet{-}B - o \rightarrow \bullet{-}A - B - o$$

Now it becomes possible to enrich the information by simple lengthening of the chain. On the other hand, the coupling reaction must be highly selective since bifunctional molecules can also lead to the unwanted combinations •-A-A-o, •-B-B-o and •-B-A-o. Self-replication must therefore combine autocatalysis and information transfer. Autocatalytic reactions are particularly attractive since they might amplify small enantiomeric excesses, of extraterrestrial origin, for example, to homochirality (Shibata et al. 1998). Some investigations are also focusing on autocatalytic systems adsorbed on mineral surfaces (Orgel 1998; Luther et al. 1998).

So far, the replication of a complete peptide sequence fed with a mixture of amino acids has not been yet achieved. Orgel (Orgel 2000) examined the plausibility of theories that postulate the development of complex chemical organization without requiring the replication of genetic polymers such as RNA. He emphasized the implausibility of the suggestion that relatively pure, complex organic molecules might be made available in large amounts *via* complicated, self-organizing, autocatalytic cycles.

M.T. A catalyst (or enzyme) is a substance which increases the rate of an already existing physicochemical reaction. The problem to be solved is not the replication of the object RNA, whether or not accelerated by a catalyst, but rather the replication of all of its functional information.

In the field of evolutionary robotics, the functional self-reproduction of the robotic genome is logically impossible to achieve. *Mutatis mutandis*, that would imply that the functional self-reproduction of RNA, whether or not accelerated by an enzyme, is a mechanism that cannot develop spontaneously. For a daughter reading the instructions (bases) of the duplicated object RNA in order to build new proteins, these instructions are logically indistinguishable one from another, whereas those of the RNA source were perfectly decipherable by the mother.

Conclusion

M.T. Autonomy is the basic feature for robotic life rather than functional self-reproduction which is logically impossible to achieve. The empirical way to build an autonomous robot requires the help of a human operator: a car becomes autonomous when a driver takes over the controls. To solve the problem of autonomy, one could imagine equipping the robot with a sensitive controller having ‘reactive features’ corresponding to particular feelings experienced by human beings, such as pain, pleasure, etc. An elementary robot equipped with a controller device possessing a ‘reactive feature’ to temperature, would be able to systematically move away from any hot object which threatens its integrity. A specific sensitivity to temperature would make it indifferent to the non-deleterious hot objects encountered, thus bypassing the ‘indiscernibility principle’, which prevents such a coherent operation.

If we apply these theoretical and experimental results derived from the analysis of robotized systems to chemical living structures, current research dedicated to the origin and evolution of life, which consists of building increasingly complex ordered systems presenting chemical dynamisms characteristic of life, would thus be doomed to failure.

Based on the assumption that in order to be autonomous any physicochemical system must have reactive features, it would be necessary to search for specific structures in living organisms whose architecture or structure, would allow the emergence of such reactive features. From the knowledge of the geometry and the nature of living structures which have the property to be ‘sensitive’, one could then try to create artificial sensitive structures in the laboratory that would generate a machine made up of sensors and actuators leading to autonomy and ultimately to life.

A.B. Obviously, some words have not the same meaning or importance in chemistry and in robotics. For example, the word autonomy implies the capability of making more of itself by itself as well as the capacity to escape deleterious factors in the surroundings. In fact, making more is also a way of ensuring the survival of a chemical species. Evolution is a key factor in the chemical approach, whereas it is secondary for robotics. However, the two approaches have in common the search for "reactive features". The short homochiral sheet-forming peptides represent a preliminary result in this direction. When diluted by non-sheet forming sequences, they form small reactive islands resisting deleterious environmental conditions. More productive sensitive features are still to be discovered to come closer to self-replicating chemical systems.

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DOI 10.1007/s11084-010-9192-3

DEFINING LIFE

Is it Useful to Have a Clear-cut Definition of Life? On the Use of Fuzzy Logic in Prebiotic Chemistry

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Received: 22 December 2008 / Accepted: 12 May 2009 /

Abstract Many scientists, including one of the authors of the present paper, have devoted time to try to find a definition for life (Bersini and Reisse 2007). It is clear that a consensus will never be reached but, more importantly, it seems that the issue itself could be without major interest. It is indeed impossible to define a "natural" frontier between non-living and living systems and therefore also impossible to define dichotomic criteria which could be used in order to classify systems in one of these two classes (living or non-living). Fuzzy logic provides a natural way to deal with problems where class membership lacks sharply defined criteria. It also offers the possibility to avoid losing time with unnecessary controversies such as deciding whether a virus is, or is not, a living system.

Keywords Darwin · Fuzzy logic · Lamarck · Origin of life · Species

Introduction

At first glance the question raised in the title of this paper could seem surprising. Indeed, it is generally considered that, in order to undertake good scientific research, objects and concepts should be well defined. Many people, including scientists, believe that it would, for example, not be possible to be a good physicist without being in possession of a precise definition of some basic concepts. This is in fact not true. Physics Nobel laureate Richard Feynman clearly pointed out that: "*It is important to realize that in physics today, we have no knowledge of what energy is*" (Feynman et al. 1963, p4–2). He also pointed out, regarding the lack of a definition for "time": "*Maybe it is just as well if we face the fact that time is one of the things we probably cannot define (in the dictionary sense) and just say that it is what we already know it to be: it is how long we wait*" (Feynman et al. 1963, p5–1).

As soon as we are convinced that, even in physics, precise definitions of concepts are not always required, we should be able to accept that it is also possible to be a good

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biologist without a rigorous definition of a living system. In fact, in the majority of general treaties devoted to biology or biochemistry, the words "life" and "living" are never defined. It is probable that biologists in front of the definition of these words face the same quandary as Augustine, in front of the definition of time, as stated in his Confessions (book 11): "*What then is time? If no one asks me, I know. If I wish to explain it to one that asked, I know not*". Biologists know what a living system is and they do not need to define it. When a definition is requested, they frequently limit themselves to a list of properties shared by many, if not all, living systems. Implicitly, biologists like physicists agree with the statement of the well known Dutch physicist Hendrik A. Kramers who said: "*In the world of human thought generally, and in physical science in particular, the most important and most fruitful concepts are those to which it is impossible to attach a well-defined meaning*" (Dresden 1987, p539).

In this context, it is interesting to try and elucidate why certain scientists wish to be in possession of a clear-cut definition for the terms "life" and "living" (Bersini and Reisse 2007). These scientists are generally not biologists but in essence members of one of three communities: scientists searching for the presence of extraterrestrial living systems, scientists involved in research related to artificial life, including the building of "*in silico* living systems", and scientists interested by the origin of life on Earth. Before focusing on why scientists interested in the origin of life on Earth wish to have a definition for "life", and also why this quest is essentially without hope, we will briefly state the reasons why the members of the two other communities are searching for a definition.

The discovery of living systems on an extraterrestrial body, inside or outside our Solar system, would be a major event. It is clear that in order to search for traces of extraterrestrial living systems it is essential to know how to classify them as such. Generally, scientists involved in this type of research focus their interest on the search of probable molecular components of living systems or metabolic products of these. The search for the presence of liquid water on Mars and the search for oxygen and ozone in the atmosphere of extra-solar planets, illustrate this type of approach.

The development of sophisticated computer programs and micro-machines has lead to the design of virtual objects and robots, which exhibit certain behavioral characteristics similar to those observed in living systems. The specialists working in these fields need a definition of living systems which is as broad as possible in order to be able to qualify their objects as living. They do not consider that the presence of components such as water and organic molecules is a significant criterion. They insist on properties and functions of their systems, which, for them, are similar to those of living systems.

Is it Necessary, or Even Possible, to Find a Definition of Life Acceptable for Scientists Interested in its Origin?

From a materialistic point of view, a living system is a highly complex form of matter, a supra-molecular assembly exchanging matter and energy with its surroundings. Scientists interested in the elucidation of the steps leading to the origin of life, focus their search on the transition between a molecular assembly which is not yet living and a molecular assembly which can be described as living (Luisi et al. 1996; Luisi 2006). It consequently seems fully justified to try to define the frontier between a non-living and a living system. A difficulty however automatically arises, difficulty which presents many similarities with those encountered by Darwin and Lamarck in their attempts to find a definition for a biological species. These two illustrious scientists modified profoundly our way of thinking about the living world and about the place occupied by *Homo sapiens* in this world. Both naturalists were interested in classification. Classification requires clear-cut criteria with which one can decide if a particular object is a member of category A or of category B. Faced with the task of finding criteria which could enable the classification of animals into species, Darwin and Lamarck both came to the conclusion that these criteria always result from some arbitrary agreement, that they are never offered by nature itself. In his book *Philosophie zoologique* first published in 1809 Lamarck wrote: *« But these classifications from which many have been so well imagined by the naturalists and the divisions and sub-divisions they introduce, are artificial means. Nothing like that, I insist, can be found in nature...*"(Lamarck [1809] 1994, p79). Darwin wrote in his book *The origin of species by means of natural selection* first published in 1859: *≪I look at the term species, as one arbitrarily given for the sake of convenience to a set of individuals closely resembling each other, and that it does not essentially differ from the term variety, which is given to less distinct and more fluctuating forms≫* (Darwin [1859] 1978, p108). He also wrote: "*Certainly no clear line of demarcation has as yet been drawn between species and sub-species—that is, the forms which in the opinion of some naturalists come very near to, but do not quite arrive at the rank of species; or again, between sub-species and well-marked varieties, or between lesser varieties and individual differences. These differences blend into each other in an insensible series; and a series impressed the mind with the idea of an actual passage"* (Darwin [1859] 1978, p107).

Lamarck and Darwin both came to these conclusions not only through their careful observation of the living world, but also because they were convinced that species change with time (by variation inside a population and natural selection for Darwin) and that new species arise necessarily from previous ones. For an evolutionist, the separation between species cannot be absolute and time independent. If a species A evolves from a species B, at some stage some individuals must have been partially A but also, partially, B. As pointed out by Darwin: "*No one definition* [of species] *has yet satisfied all naturalists; yet every naturalist knows vaguely what he means when he speaks of a species*" (Darwin [1859] 1978, p101).

On the basis of these remarks, it seems necessary to ask another question: is it possible to draw a clear-cut frontier between a non-living state of matter and a living system? Our answer is without hesitation no. The transition from non-living to living, at the so-called origin of life, must have evolved through systems which were "not yet living" but already "not fully non-living". This means, and this is the main point that we wish to make, that Aristotelian logic should not be used by people interested in the origin of life.

Aristotelian logic is based on three axioms considered as self-evident:

- the law of contradiction which states that "x" cannot be both "A" and "non-A";
- the law of identity which states that "x" will always be "x";
- the law of excluded middle which states that "x" must be "A" or "non-A".

These three axioms are not compatible with an evolutionary description of the living world and they are also in contradiction with an evolutionary description of the transition from non-living to living. Between the prebiotic world and the biotic world, a "partially prebiotic/partially biotic" world must necessarily have existed. As soon as Aristotelian logic cannot be applied to differentiate non-living from living, any definition of life, or any definition of a living system must necessarily result from an agreement. Consequently, it is highly improbable that a consensus will ever be reached and as a result the concept "living" will remain ill-defined and thus, according to Kramer, an important and fruitful concept (Dresden 1987, p539).

On the Use of Fuzzy Logic in Prebiotic Chemistry

It is possible to deal with ill-defined concepts by using a non-Aristotelian logic called fuzzy, or multi-valued, logic. An excellent introduction to fuzzy logic is given in a chapter of Rouvray's book (Rouvray 1997) devoted to the treatment of uncertainty in the physical sciences. A few very illustrative quotations related to the concept of vagueness in science are given in this chapter. One is from Bertrand Russel who in 1923 said: "*apart from representation...there can be no such things as vagueness or precision; things are what they are and there is an end of it*" (Russel 1923). Another is from Williamson who said: "*vagueness is indeed one manifestation of the fact that our classification are not fixed by natural boundaries*" (Williamson 1989).

The description of nature is, in certain cases, unavoidably vague and, as scientists, we must accept that frequently Aristotelian logic cannot be applied and must be replaced by fuzzy logic. It is widely recognized that Zadeh was the first to introduce the concept of the fuzzy set which is at the basis of fuzzy logic (Zadeh 1965). He defines a fuzzy set as "*a class of objects with a continuum of grades of membership*". According to Zadeh, the concept of fuzzy set could provide "*a natural way of dealing with problems in which the source of imprecision is the absence of sharply defined criteria of class membership*". It is clear that biological species are fuzzy sets and, for reasons previously discussed, prebiotic systems and living systems are also examples of fuzzy sets. Fuzzy logic allows partial set membership rather than crisp set membership or non-membership. If an object is without doubt in class "A", its membership will be 1; if it is without doubt in the class "non-A", its membership will be 0 in class "A"; it can however also be characterized by a different membership value, which means that it is partially member of class "A" but also partially member of class "non-A".

Even if fuzzy logic can help us deal with vague issues, and even if vagueness or imprecision can be useful in science, an excess of imprecision is not acceptable. A limit must necessarily be fixed in order to define the 0 and 1 values for membership to the class "living system". We could decide that a membership of 1 is restricted to systems classified today as Bacteria, Archaea or Eukarya. This decision could be accepted by any scientist, and also non-scientist, interested in the origin of life on Earth and furthermore does not require a definition of life. On the basis of this, a cat, a sequoia or a bacteria would be characterized by a membership of 1 in the class "living system". A virus would however be characterized by a membership lower than 1 in this class. However, in order to determine its membership value an agreement must first be found for a membership scale. This is a very important aspect of fuzzy sets: the degree of membership will vary with the choice of classification criteria. This is however not a major drawback as what is important is to be able to apply a logic which is not constrained by the law of excluded middle. In science, we must reject the use of concepts or methods that generate false problems! Deciding whether or not a virus is a living system, is an example of a false problem which originates from the vain attempt to try to define, in a very precise way, what "living system" means. Of course, a virus does not posses all the attributes of a unicellular organism but it has some of these attributes and, as we will see later, on the basis of our definition of the zero value of the membership scale, a virus is indeed characterized by a non-zero membership in the class "living system".

Scientists interested in prebiotic chemistry will most probably accept that a hypothetical vesicle which can be prepared under physico-chemical conditions compatible with what is known about Earth's primitive hydrosphere, can be considered as a partially living system, as it corresponds to a plausible step towards a first unicellular organism. As in the case of a virus, the degree of membership of this vesicle to the class "living system" will depend on chosen criteria. This degree of membership will generally be considered to be high by those working on artificial membranes while those interested, for example, in the origin of prebiotic polynucleotides will most probably challenge this stance. For them, important criteria are information and catalysis and a hypothetical RNA-type polymer, able to catalyze its own synthesis (autocatalysis) and other reactions, would most certainly be considered an important step towards a first unicellular organism. An ensemble of such molecules confined in a small volume, would undoubtedly be considered by them as a partially living system with an associated membership higher than 0. The confinement of these RNA-type polymers inside the vesicle previously described would probably have an even higher membership value (be considered as "more alive") than the two sub-systems taken separately. This membership would however remain lower than 1, because, as previously mentioned, we suggest that the 1 value only be given to Bacteria, Archaea and Eukarya.

Regarding the zero on the living system membership scale, and coming back to the vesicles and the RNA-type polymers, it is possible to find what is common to these systems, and also to every living system on Earth today. These two "partially living" systems (i) are composed of organic molecules and liquid water; (ii) are ensembles of interacting or reacting molecules and (iii) have properties which are different from those of the isolated components. It is precisely because the two systems have these three characteristics that we have considered that their membership in the class "living system" is higher than 0. On the basis of these three simple criteria considered together we can now decide if a system has a non-zero membership to the class "living systems" and we therefore have a definition for the 0 of the membership scale.

The criteria presented above to define the zero of the membership scale are of course just a suggestion and others might wish to recommend other criteria, but the concept of collective properties of supramolecular ensembles of organic molecules immersed in liquid water has many advantages. Indeed, with these criteria, pure liquid water, ensembles of amino acids, nucleic bases, polypeptides, polynucleotides, ribose, polysaccharides or their water solutions have a membership of 0. On the contrary, a water solution of RNA molecules, which act as templates for their own reproduction, in a reactor containing nucleotides and enzymes would be considered as partially living with, consequently, a membership in the class "living system" higher than 0. A system composed of peptide nucleic acid (PNA) polymers interacting with single stranded DNA in liquid water leading to double helical molecules would also be described as partially living, even if PNA is not a component of the living world today. The membership of this system would be non-zero because the duplex resulting from the molecular recognition of DNA by PNA has properties which are different from those of the isolated polymers dissolved in water. This means that even in an extraterrestrial environment with liquid water and organic molecules, the criteria could be used to qualify the non-zero membership of hypothetical organic supramolecular systems, even if the polymers used as information support or as catalysts were not DNA, RNA or polypeptides. For extraterrestrial systems new criteria would necessarily be required to define the 1 value of a membership scale, and these criteria will probably differ from the ones used to describe the transition from "non living" to "living" on Earth. We prefer not to consider here exotic forms of life, with silicon in place of carbon or liquid methane in place of water (Schulze-Makuch and Irwin 2006), because for reasons discussed elsewhere (Bruylants et al. 2009), such a scenario is, from our point of view, not at all realistic.

The case of artificial "living systems" presents similarities with the issues just discussed for extraterrestrial life. A robot, despite its performances and the similarities of these performances with those of an organism, is not a living system in the biological sense.

Specialists of artificial life are certainly interested in defining, for their own work, a membership scale. They would be obliged to define what is, for them, an artificial living system which has a membership of 1 in the class “living systems”. For a biologist, the cell is the archetype of a living system while for people working in robotics, dogs and men seems to be their archetypes. This clearly highlights that the membership scales must necessarily be different for the scientist interested in the origin of life, on the one hand, and for the engineer developing robots, on the other. This however does not mean that these scientists and engineers have nothing to learn from each other: it means that attempts to compare, on the same scale, the membership of a vesicle and the membership of a robot in the class “living systems” has no heuristic value.

Conclusions

Cats and dogs are different species and today nobody would challenge this conclusion. However mammals living on Earth in the past must have been the ancestors of both cats and dogs. Therefore for the evolutionist, the division of cats and dogs into different species is without any particular interest; what is important for the evolutionist is to be able to explain the divergence of an initial population into two separate populations. In the past, some mammals were necessarily “not yet fully cats” or “not yet fully dogs”.

Scientists working on the origin of life are evolutionists interested in steps of evolution which preceded the first population of prokaryotes and they are exactly in the same position as biologists. They are interested in the sub-systems, of various levels of complexity, which were the components of the systems which were, for the first time, able to reproduce themselves, to compete, to evolve and to become the first population of cells from which all forms of life originated on the surface of the Earth. These sub-systems were not yet living but they were already partially living.

It seems clear that it will never be possible to obtain a clear-cut definition for the concepts “life” and “living” which can satisfy all scientists. Life, and especially the progressive transition from non-living to living matter, is a concept to which traditional Aristotelian logic cannot be applied. Fuzzy logic provides a natural way of dealing with these types of problems in which class membership lacks sharply defined criteria.

Acknowledgements G.B. thanks the Belgian Fonds de la Recherche Scientifique—FNRS for a post-doctoral fellowship.

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Orig Life Evol Biosph (2010) 40:145–149
DOI 10.1007/s11084-010-9193-2

Towards an Autopoietic Redefinition of Life

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Received: 31 December 2008 / Accepted: 5 June 2009 /

Abstract In this paper we develop the autopoietic approach to the definition of the living developed by Maturana and Varela in the Seventies. Starting from very simple observations concerning the phenomenology of life, we propose a reformulation of the autopoietic original definition of life which integrates some of the contemporary criticism to it. Our definitional proposal, aiming to stimulate the further development of the autopoietic approach, expresses what remains implicit in the definition of the living originally given by Maturana and Varela: life, as self-production, is a process of cognitive coupling with the environment.

Keywords Autonomy · Autopoiesis · Cognition · Life · Structural coupling

Premise

There is a growing number of works dedicated to the definition of life. They often contain a plurality of definitional proposals belonging to different disciplines. They tend to start from a set of abstract, theoretical assertions, with little reference to the phenomenology of life.[1] Here, we want to take a quite different approach, relying on phenomenological observations rather than speculative considerations. In order to do so, we go where life has on our Earth the simplest

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[1] For example, the book edited by Palyi et al. (2002) contains several pages of definitions of life, proposed by chemists, biologists, philosophers, geologists, medical doctors, astronomers, Russian orthodox religious leaders, as well as Indian theologians… See Luisi 1998, which includes a long list of references on the subject.

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possible expression, namely, at the level of unicellular organisms. We watch how a living cell works, and we see whether we can elicit from these phenomenological, simple observations a definition of cellular life. We wonder then whether and to what extent this cellular definition is also valid at other, macroscopic levels. We apply this procedure following and partially reorienting the research pathway covered by Maturana and Varela in the Seventies. The result is a reformulation of their definition of the living which aims to solicit further developments of the autopoietic definitional approach (Maturana and Varela 1973).

From the Phenomenology of the Cell to the Theory of Autopoiesis

Let us start from the simple question: *How does the biological cell, as the minimal form of life, work?*

This question, as basic as it may be, brings us to an apparent paradox. Inside any simple cell there take place thousands of transformations, but, in spite of that, the cell maintains its own identity, at least during all the homeostasis period. How is this possible? For the scientific observer the answer is simple. This depends on the cell's capability of re-generating from the inside all the components transformed—be they ATP, glucose, aminoacids or proteins—at the expense of matter and energy coming from the medium. This is our first phenomenological observation, and the most important one. To the observer, the cell appears as a physico-chemical system which has the ability to exploit external energy and matter to carry out an internal activity of self-production and self-maintenance, consisting in the permanent re-generation from within of all its components and its own boundary.

This very simple remark provides the basis of the so-called theory of autopoiesis developed by Maturana and Varela (1973), according to which this activity of self-production—«autopoiesis»—is common to all the livings—it is what the minimal biological unit shares with other living beings.[2] As Maturana puts it in a recent interview (Poerksen 2004):

"When you regard a living system you always find a network of processes or molecules that interact in such a way as to produce the very network that produced them and that determine its boundary. Such a network I call autopoietic. Whenever you encounter a network whose operations eventually produce itself as a result, you are facing an autopoietic system. It produces itself. The system is open to the input of matter but closed with regard to the dynamics of the relations that generate it."

Maturana here touches upon the peculiarity of the theory of autopoiesis, which is to point out the dynamical mechanism allowing the living process of self-production. The idea is that of a close chain of operations of synthesis and destruction of components, within which each operation triggers and integrates the other in such a way that the concatenation of process (*re*)-generates itself through the production of its own components. This theoretical perspective, usually condensed in the notion of *organizational closure*, constitutes the core of Maturana and Varela's definition of the living as «autopoietic system». We can formulate it as follows:

(1) An autopoietic system is organized as a network of production processes (transformation and destruction) of components which produces the components which, through their interactions and transformations, permanently regenerate and realize the network of processes, constituting a concrete topological unit defined by a boundary.[3]

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[2] We dealt elsewhere with the theoretical and epistemological construction of the theory of autopoeisis (Luisi 2006; Damiano 2009).

[3] This is a simplification of the rather complex original formulations given in Maturana and Varela 1973.

Although this definition holds for the basic autopoietic systems -i.e. the «first order autopoietic systems» given by living cells- it has broader implications. Indeed, it does not focus on the «structure» of the cell, that is, on its components, which are undergoing a continuous transformation. It focuses instead on the «organization»[4] of the life's basic unit, that is, on the invariant functional relations which connect its elementary components into the persistent global unity able to produce itself.[5] According to Maturana and Varela, this specificity offers to **(1)** the capability of defining the whole living domain, as it makes **(1)** able to provide a *general characterization* of the cellular system—that is, valid for every kind of cell—and therefore a *fundamental characterization* of all the living beings. The idea of the two authors is quite intuitive. The cellular organization is not the only form of the biological organization, but it can be considered the basic one. It is present in the other two (known) forms of living organization, i.e. multicellular and social. According to the theory of autopoiesis, they respectively belong to (ii) «second order» and (iii) «third order autopoietic systems», corresponding to (ii) multicellular organisms and (iii) their social aggregates, whose organization does not merely contain the cellular one, but was generated by its transformative evolutions. In this sense, defining the cellular organization amounts to producing a *fundamental* definition of the whole biological domain: a definition of the basic organizational form of the living, in which specific organizational definitions, about multicellulars and their social aggregates, are contained—and from which they can be derived by conceptual transformation.[6]

Here lies the main hypothesis of autopoietic biology, which affirms that the definition of the autopoietic system holds for every living structure: if a physico-chemical system is living, then it is autopoietic and, conversely, if it is autopoietic, it is living (Maturana and Varela 1973). Accordingly, if we substitute in **(1)** «autopoietic unit» with «living system», we provide a definition of cellular life which aims to be valid also for all forms of macroscopic life. At this point, a somewhat simpler form can also be proposed:

(2) A living system is a system capable of self-production and self-maintenance through a regenerative network of processes which takes place within a boundary of its own making.

It is an original definition of life, with many specificities we cannot treat in detail here.[7] For our definitional purposes it is enough to notice that it implicitly proposes criteria to distinguish the living from the non-living. As already pointed out by Luisi et al. (1996), these criteria can be summarized as shown in Table 1.

Autopoietic Organization: A Necessary and Sufficient Notion for Defining Life?

Maturana and Varela have always claimed that the notion of autopoietic organization, here summerized in **(1)**, is necessary and sufficient for characterizing living systems (Maturana and Varela 1973, 1984).

In the last years, independently, two groups of researchers (Bitbol and Luisi 2004; Bourgine and Stewart 2004) examined critically this statement and came to the conclusion

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[4] As we will point out shortly, according to the theory of autopoiesis the "organisation" of a system is the relational frame which defines the system as a unit of components (Maturana and Varela 1984).

[5] On the complementary concepts of «structure» and «organization» in the theory of autopoiesis, see Maturana and Varela 1984; Ceruti 1989; Zeleny 1981; Bich and Damiano 2008.

[6] The term «fundamental», referred to the characterization or the definition of the living, can be considered here as a synonym of «generative» (cf. Damiano, 2009, chap. 3 and 4).

[7] Cf. footnote 2.

Table 1 Criteria derived from the definition of the autopoietic system (adapted from Luisi et al. 1996)

1. Boundary	The system is defined by a semi-permeable boundary which permits a discrimination between the inside and the outside of the system (a discrimination relative to relevant components of the system).
2. Reaction network	The boundary components are being produced by a network of reactions which takes place within the boundary.
3. Interdipendency	The network of reactions is generated by conditions produced by the existence of the boundary itself, i.e. 1 and 2 are interdependent.

that the notion of autopoiesis expresses a necessary, but not a sufficient condition for defining life. They agreed that all livings are characterizable as autopoietic systems, but denied the converse. In fact they were able to show the existence of artificial systems—generated not only by simulation, but also in chemical laboratory, such as self-reproducing micelles or vesicles (Luisi 2006)—that respect the autopoietic definition but cannot be considered living. In particular, these authors highlighted that some artificial systems can satisfy the criteria of distinction between living and non-living derivable from the notion of autopoiesis (see Table 1), but lack something essential to be alive: the adaptative interaction with the environment, which is described by the theory of autopoiesis as a «cognitive» interaction (Maturana and Varela 1973, 1984).

Maturana and Varela have dealt extensively with «cognition», and defined it as the recursive interaction of the autopoietic unit with the its *ambience*. They described it as a self-regulating coupling of the system with the environmental context: an active coordination of the internal autopoietic processes with the environmental dynamics which allows the system to conservatively react to external variations. For Maturana and Varela it corresponds to a permanent self-determinated modification of the system's patterns of activity which, seen from the outside, appears as «intelligent adaptive behaviour» (selective assimilation of nutrients available in the environment, overcoming of obstacles while moving in the environment, etc.). Conceived this way, the act of cognition is an act which, literally, permits life, as it dynamically integrates the organic structure of the living systems in the environment. Maturana and Varela thus came to the strong conclusion that «life is cognition»—that there is no life without cognition. (Maturana and Varela 1973).

But the primary literature contains possibly confusing elements. Although the two authors have always claimed that autopoiesis and cognition are «two aspects of the same process, the process of life», in their production, the theme of cognition has been developed after the autopoietic definition of life - and in this sense separately. Consequently, it often seems difficult to understand precisely how cognition fits with autopoiesis, or how to consider the relation between autopoiesis and cognition (Bitbol and Luisi 2004).

Bitbol and Luisi argued that we cannot attach the label of «living» to a system which, even if it is autopoietic according to the criteria indicated in Table 1, lacks the cognitive aspect. Their conclusion was that a system, in order to be living, must be grounded in an internal metabolic network which is capable of interacting in an adaptive way with the environment. This reflects Maturana and Varela's notion that the living has to have the cognitive ability to couple its own self-production process with those of the environment, an aspect of the biological systems left implicit in the autopoietic definition of life.[8] We do not have the room here to discuss all the implications. Let us just notice that, to express necessary and sufficient conditions for life, the autopoietic definition has to include a

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[8] Here we mean all the definitions given in common works of Maturana and Varela.

reference to cognition. How then can our previous definition(s) of life be changed, in order to take into account this new aspect?

The Proposal

We propose the following reformulation:

(3) An autopoetic system is organized as a network of production processes which produces the components which, through their interactions and transformations, permanently regenerate the network of processes constituting the system itself as a concrete topological unit, separated from its medium by a boundary and related to it through cognitive or adaptive coupling.

Or, in the simpler version:

(4) A living system is a system capable of self-production and self-maintenance through a regenerative network of processes which takes place within a boundary of its own making and regenerates itself through cognitive or adaptive interactions with the medium.

In doing so, we propose a definition of the living based on the theory of autopoiesis which, in its final form, also takes care of the notion of cognition, that is, of the adaptive interaction with the environment. This links autopoiesis not only to metabolism, but to evolution as well, and in a sense, to more traditional ways of thinking life.

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Orig Life Evol Biosph (2010) 40:151–160
DOI 10.1007/s11084-010-9194-1

Defining Life: The Virus Viewpoint

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Received: 27 January 2009 / Accepted: 15 May 2009 /

Abstract Are viruses alive? Until very recently, answering this question was often negative and viruses were not considered in discussions on the origin and definition of life. This situation is rapidly changing, following several discoveries that have modified our vision of viruses. It has been recognized that viruses have played (and still play) a major innovative role in the evolution of cellular organisms. New definitions of viruses have been proposed and their position in the universal tree of life is actively discussed. Viruses are no more confused with their virions, but can be viewed as complex living entities that transform the infected cell into a novel organism—the virus—producing virions. I suggest here to define life (an historical process) as the mode of existence of ribosome encoding organisms (cells) and capsid encoding organisms (viruses) and their ancestors. I propose to define an organism as an ensemble of integrated organs (molecular or cellular) producing individuals evolving through natural selection. The origin of life on our planet would correspond to the establishment of the first organism corresponding to this definition.

Keywords Archaea · Evolution · Mimivirus · Origin of life · Virus

Introduction

What is life? This question, asked by Schrödinger sixty years ago (Schrödinger 1944), is still on the agenda. When Crick claimed that he and Watson had discovered “the secret of life”, he suggested that “life is DNA”, the aperiodic crystal wisely predicted by Schrödinger a few years before the discovery of the double-helix. Since then, reductionists and holists have opposed themselves in giving priority either to the genetic material, or the metabolic network to define life. Many attempts have been made to find a definition of life that could be operational not only for terrestrial life, but for any form of “life” present in the universe, a definition that could help us to recognize a *bona fide* extraterrestrial “life” if we encounter

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it one day. In my opinion, such a definition is by essence biased by an idealist prejudice, reminiscent of Plato and Socrates' ideas. It seems to imply that life is an ideal form, concrete examples of life being various "shadows" of this ideal. I will adopt here the view that, up to now, life is only a terrestrial phenomenon, a characteristic of terrestrial "living organisms". In fact, there is no life without living organisms and all presently known living organisms are thriving on planet Earth. If one day we hopefully meet friends from another world, it will then be possible to define "life" in term of the common properties shared by organisms from both planets.

For the moment, the only materialistic way to define life is to start from the objects that exhibit this extraordinary property: being alive (or having been alive, once such objects are dead). In that sense, the question, "are viruses alive?" is clearly at the heart of the debate. The answers to this question have varied in time, depending of our knowledge about viruses and our definition of life. Over the last decades, the answer has been often negative and viruses have been usually relegated to the periphery of the living world, being mainly considered as «dangerous» curiosities. They have been considered as by-products of cellular life, having probably originated as escaped genes from cellular organisms. However, this situation is rapidly changing, following several discoveries made either by chance or by the effort of a few pioneers, and general advances in molecular biology (including the outcome of the genomic and post-genomic era) that have recently contributed to revise the position of viruses in the living world. Times are changing and viruses, once only considered as side-products of cellular evolution, are now at the center of many debates on the early evolution of life on our planet (Forterre 2002, 2005, 2006a, b; Brosius 2003; Bamford 2003; Bamford et al. 2006; Claverie 2006; Koonin et al. 2006; Ryan 2007; Raoult and Forterre 2008).

Viral Particles Are the Most Abundant Biological Entities in the Biosphere

It has been realized quite recently that viral particles are by far the most abundant biological entities on our planet (Suttle 2007). Indeed, they are ten times more abundant than bacterial cells in the upper ocean. This has been deduced in the nineties from examination of water samples by electron microscopy or epifluorescence optical microscopy. More recently, the abundance and diversity of viruses has been confirmed by the abundance and diversity of their genes in metagenomic studies (Edwards and Rohwer 2005). The fact that viruses are more abundant than their targets is not surprising, since every single cellular species is infected by many diverse viral species (as we know very well from the case of our own species, *Homo sapiens*) and the infection of a single cell always produces a high number of viral particles. However, the data have impressed biologists and contributed to a renewal of interest in virus research. The ecology of viruses, their roles in major geochemical cycles, and in controlling the diversity of population are now active research fields (Suttle 2007).

Surprising Diversity in the Morphology of Viral Particles

Our initial view was that of a curious but monotonous world. Viruses (confused with viral particles, see below) were essentially either small spheres (sometimes with spikes as in TV cartoons featuring the AIDS virus), or strange Lunar exploratory module (LEM) with a head, a tail, and sometimes legs (as in the case of the T4 bacteriophage and related myoviridae). Specialists (virologists) were aware of the existence of filamentous viral particles, or pleomorphic types of capsids (as in the case of vaccinia or poxviruses), but these were considered as exceptions. This has changed now, with the discovery, during the last two decades, that viruses infecting hyperthermophilic archaea (members of the third domain of life, see below) produce viral particles with a morphology that is completely different from the classical head and tailed structure of bacteriophages (Prangishvili et al. 2006). Some of their virions are either flexible or rigid filaments that superficially resemble those of viruses infecting bacteria or eukarya, but they form clearly distinct families (for instance, they are all double-stranded DNA viruses, whereas eukaryotic filamentous viruses are all RNA viruses). Other viral particles show morphotypes previously never seen in the viral world, such as lemon-shaped, or bottle-like structures. The most spectacular example is the virus ATV (*Acidianus*-Tailed-Virus) whose virion undergoes the first known case of extra-cellular development (Häring et al. 2005). The virions produced by ATV infected cells are lemon-shaped particles that can be stored for months at room temperature without any change in their morphology. However, as soon as there are incubated at high temperature (above 70°C) they undergo a drastic structural reorganization, with the formation of two long tails at opposite ends of the central body (Häring et al. 2005).

A New Virus Classification Inferred from the Three Domains Concept

The unique archaeal viruses, isolated from terrestrial hot springs and infecting organisms living at temperatures between 79 and 105°C, are not just mere curiosities. Their discovery has led to revise the classification of viruses and their relation to cellular organisms. Traditionally, viruses have been classified according to the prokaryote/eukaryote dichotomy. Historically, this binary division of the living world was proposed in 1962 by Stanier and Van Niels, following the discovery of major structural differences between bacterial cells and those of animals, fungi, plants and protists (for an historical account of this proposal and its epistemological consequences, see Sapp 2005, 2006). In bacterial cells, the genetic material (DNA) is present within the cytoplasm, being directly in contact with ribosomes, where messenger RNAs are translated into proteins. In contrast, in the cells of animals, fungi, plants and protists, the genetic material is located within a "nucleus", being separated from the cytoplasm by a nuclear membrane. Cells with a nucleus have been called eukaryotes (true nucleus) whereas cells without nucleus have been called prokaryotes (meaning before the nucleus) suggesting that they predated eukaryotes. This proposal was accepted with enthusiasm by cell biologists, but also by the pioneers of the molecular biology revolution, as a novel concept with an explanatory power much greater that older classifications favored by botanists or zoologists, such as the five kingdoms of Whittaker. Unfortunately, the concept of prokaryote had a very negative effect on virology by splitting the viral world between viruses infecting prokaryotes (bacteriophages) and viruses infecting eukaryotes (simply called viruses). It was concluded from this dichotomy that these two viral categories had different origins, bacteriophages having originated from bacterial genomes (or plasmids) and viruses from eukaryotic genomes (for instance, retroviruses from retro-elements).

However, in contradiction with this hypothesis, most viral encoded proteins, especially those involved in the replication of viral genomes, have no specific relationships with those of their hosts (Forterre 1992, 1999; Villarreal and DeFilippis 2000; Filée et al. 2002, 2003; Miller et al. 2003; Forterre et al. 2007). In contrast, viruses infecting very different hosts and producing virions with various morphologies sometimes encode similar proteins that have no homologue in the cellular world (Forterre 1999, 2005, 2006b; Koonin et al. 2006).

The importance of these viral specific proteins (*viral hallmark proteins*, *sensu* Koonin et al. 2006) was underestimated for a long time. Since viruses were supposed to have originated from cells, the existence of real viral genes was denied (all viral genes were supposed to have originated from cells). In contrast, genomic data have shown that the huge majority of viral genes have no cellular homologues, indicating that viral genes represent a unique pool of genetic diversity.

Surprisingly, the prokaryotic concept, proposed in 1962, still functions as a paradigm for most biologists, more than 30 years after it was shown to be wrong in 1977, thanks to the work of Carl Woese and colleagues (sometimes referred to the Urbana School) (Pace 2006). In the seventies, Carl Woese applied the techniques and concepts stemming from the molecular biology revolution of the sixties to decipher the parental relationships between all living organisms. He finally demonstrated that the division of the living world between prokaryotes and eukaryotes was misleading in term of natural classification (Woese and Fox 1977). He showed that a group of organisms previously considered to be bacteria, according to their "prokaryotic phenotype" (they have no nucleus) was in fact no more related to bacteria than to eukaryotes in terms of their ribosomes (more precisely their ribosomal RNA). Although all ribosomes (the cellular organelles that synthesize proteins) are homologous in the living world, there are three versions of them. Woese and Fox concluded that living organisms should therefore be divided into three primary lineages, originally called eubacteria, archaebacteria and eukaryotes (Woese and Fox 1977). Later on, Woese and colleagues proposed to replace this nomenclature by a new one: bacteria, archaea and eukarya, to prevent further confusion between the two prokaryotic domains (archaea are not "strange" or "old" bacteria", but a domain with equal taxonomic status compared to bacteria and eukarya) (Woese et al. 1990). This trinity concept has now been corroborated by comparative biochemistry and comparative genomics. Amazingly, although archaea superficially resemble bacteria when they are examined under the microscope, they are much more similar to eukarya when they are analyzed at the molecular level (Forterre et al. 2002, for recent monographies on archaea, see ref. Cavicchioli 2007; Garrett and Klenk 2007). For example, there are 33 ribosomal proteins that are common to archaeal and eukaryotic ribosomes but are absent in bacteria (Lecompte et al. 2002).

The discovery of unique viruses infecting archaea also corroborates the three domains concept from the virus perspective. Indeed, most viruses infecting archaea have nothing in common with those infecting bacteria, although they are still considered as "bacteriophages" by many virologists, just because archaea and bacteria are both prokaryotes (without nucleus). A first step in a natural classification of viruses was thus to get rid of the dichotomy between bacteriophages and viruses, and to superimpose a viral trichotomy to the cellular trichotomy. David Prangishvili and myself have thus suggested to classify viruses into three categories, archaeoviruses, bacterioviruses and eukaryoviruses (Forterre and Prangishvili 2009).

Viruses Are Ancient and Have Played a Major Role in Biological Evolution

The last common ancestor of archaea, bacteria and eukarya is today usually called LUCA (the Last Universal Common Ancestor, or the Last Universal Cellular Ancestor). The ubiquitous existence of viruses infecting members of the three cellular domains strongly suggests that the cellular lineage of LUCA and the other cellular lineages living at that time were already victims of viral attacks. In fact, it is likely that viruses originated before LUCA, when cells still had genomes made of RNA and not DNA (DNA, which is a chemically modified form of RNA, could have appeared only after the emergence of complex proteins capable of modifying RNA, see Forterre 2005 and references therein). If viruses were already present in the biosphere when LUCA was living, one would expect to find some common features between viruses that now infect members of different domains. This is precisely the case. In particular, some archaeoviruses, bacterioviruses and eukaryoviruses share homologous capsid proteins and/or ATPases for protein packaging, suggesting that they all evolved from a common virus that existed at the time of LUCA of even before (Bamford 2003; Baker et al. 2005; Bamford et al. 2006; Krupovic and Bamford 2008). Based on such homologous features of their virions (defined as the virus "self" by Dennis Bamford), it has been possible to already identify three major viral lineages that probably originated independently before the time of LUCA (Bamford et al. 2006). Viruses are therefore very ancient, and the ancestral virosphere was probably already diverse and abundant at the time of LUCA. To explain why modern viruses are clearly different from one domain to the other (as previously seen in the case of archaeal viruses) we have suggested that the three ancestral populations of cellular organisms at the origin of the modern domains have randomly selected at birth three different parts of the ancestral virosphere (Prangishvili et al. 2006). The presence of a few viruses of common origin (with similar "self") in the three selected virospheres would explain the presence of homologies between some viruses infecting different domains.

The idea that viruses are very ancient and have co-evolved with the three cellular lineages from the time of LUCA and even before has recently led to several hypotheses posing that viruses have played a major role in several critical evolutionary transitions. For instance, it has been suggested that DNA and DNA replication machineries first originated in the viral world (Forterre 1999; Villarreal and DeFilippis 2000; Forterre 2002), that virus-induced transition of cells with RNA genomes into cells with DNA genomes triggered the emergence of the three cellular domains (Forterre 2006), that the nucleus of eukaryotic cells originated from a large DNA virus (Takemura 2001; Bell 2001), or even that the selection pressure to prevent the entry of virions promoted the evolution of cell walls (Jalasvuori and Bamford 2008). All these hypotheses are not easily testable, but recent findings make them reasonable. Indeed, it has been shown that cellular proteins playing very important roles in modern organisms may have a viral origin. For instance, phylogenetic analyses have revealed that the RNA polymerase, DNA polymerase and DNA helicase that transcribe and replicate DNA in modern mitochondria were recruited from a virus that was originally integrated into the genome of the bacterium at the origin of the mitochondria (Filée and Forterre 2005). More recently, it has been shown that placentation in mammals is initiated by a protein, syncitin, encoded by a retrovirus integrated in mammalian chromosomes (De Parseval and Heidmann 2005; Prudhomme et al. 2005). There are many other examples of the role that viruses have played in recent cellular evolution (for reviews, see Ryan 2007; Brosius 2003; Villarreal 2005). Brosius wrote, for instance, that "*the interaction of hosts with retroviruses, retrotransposons and retroelements is one of the eternal conflicts that drive the evolution of life*" (Brosius 2003). Prangishvili and myself have recently extended his argument, concluding that the conflict between cells and viruses has been (and still is) the major engine of life evolution (Forterre and Prangishvili 2009).

The Nature of Viruses

For a long time, viruses have been defined by their virions, the viral particles produced during infection. The confusion between the virus and the virion is still apparent both in the media (the AIDS virus on TV is shown as a sphere with spikes—the virion) and in the scientific literature (when it is claimed that viruses are ten times more abundant than bacteria in the ocean, it is meant that viral particles are ten times more abundant). As a consequence of this confusion, viruses were first defined as simple entities (for instance with a single type of nucleic acid, as in the famous André Lwoff's definition, Lwoff 1957), without any metabolic activity. Since some virions can crystallize, viruses were considered as molecular (not cellular) entities. Many definitions of life being based on the cellular theory "*Omniae cellula e cellula"* (for instance, in his Nobel lecture, Anfré Lwoff wrote *"an organism is constituted of cells"* Lwoff 1967), viruses were not usually classified as living organisms.

The confusion between the virus and the virion was first criticized by Claudiu Bandea who considered that the intracellular phase of the virus life cycle is the ontogenetically mature phase of viruses (Bandea 1983). As Bandea wrote in a landmark paper "*in this phase the virus shows the major physiological properties of other organisms: metabolism, growth, and reproduction. Therefore, life is an effective presence*". The proposal of Bandea was ignored until recently, when the discovery of the giant mimivirus by Didier Raoult and his colleagues (La Scola et al. 2003; Raoult et al. 2004) focused the attention of virologists on the viral factory. Eukaryotic viruses that replicate in the cytoplasm form complex localized viral factories to replicate their genome and produce virions (Novoa et al. 2005, Miller and Krijnse-Locker 2008). The viral factories of the mimivirus are spectacular and their size is similar to the size of the nucleus of the virus host, the amoebae *Acanthameba polyphaga* (Suzan-Monti et al. 2007). The virion of mimivirus is itself much larger than all previously known viral particles, being visible under the light microscope and its size being similar to those of small cells, such as mycoplasma. Jean-Michel Claverie pointed out that the viral factory corresponds to the real viral organism, whereas the virion corresponds to the mechanism used by the virus to spread from one cell to others and that to confuse the virion with the virus would be the same as to confuse a sperm cell with a human being (Claverie 2006).

One can wonder why the confusion between viruses and their virions became a paradigm in virology. This is probably because our modern conception of viruses was mostly elaborated following the work on "bacteriophages" performed in the fifties by the "phage group" in the USA and André Lwoff in France. Indeed, bacterioviruses did not produce viral factories and the viruses seemed to disappear (being reduced to their genomes) during the intracellular phase of their life cycle, known as the "eclipse phase". Interestingly, Lwoff wrote forty years ago that the virus transforms the entire infected cell into a viral factory (Lwoff 1967). If we consider now that the virus and the virion should not be confused, his sentence can be read: bacterioviruses (and archaeoviruses) transform the infected cell into a virion factory, i.e. into a virus! Many lytic viruses indeed trigger the degradation of the host genome. In that case, after destruction or inactivation of the cellular genome, when the viral genome is the only one that is expressed, one can really consider that the infected "cell" is no more a bacterium, but a virus with a cellular appearance. A nice example of this conversion is provided by cyano-bacterioviruses (cyanophages) that encode their own photosynthetic proteins to replace the decaying cellular ones in order to get the proper energy required for the production of virions (Bragg and Chisholm 2008 and references therein). The former cyanobacterial cell thus becomes a photosynthetic virus. We observed recently the same type of conversion in the case of a virus infecting a hyperthermophilic archaeon (Bizet *et al.* 2009). This virus destroys the genome of its host and produces spectacular intracellular structures that break the cell envelope to prepare the release of its virions.

If infected archaea and bacteria are indeed transformed into *bona fide* viruses, one can conclude that infected eukaryotic cells in which viral factories have taken control of the cellular machinery became viruses themselves, the viral factory being in that case the equivalent of the nucleus. By adopting this viewpoint, one should finally consider viruses as cellular organisms. They are of course a particular form of cellular organism, since they do not encode their own ribosomes and cell membranes, but borrow those from the cells in which they live.

The question, "are viruses alive?" is typically a philosophical question, meaning that it is our choice to decide if viruses are living entities or not. For a growing number of evolutionists and virologists, viruses should definitely be considered as living entities since they exhibit all features typical of terrestrial life: they are made of the same macromolecules as cells from archaea, bacteria or eukarya, and they have co-evolved with members of these three domains according to the scheme of Darwinian evolution. Amazingly, the recent discovery that the virion factory of the mimivirus can be infected by another virus (sputnick) has also been taken as an argument in favor of the living nature of viruses (only living organisms can become ill) (La Scola et al. 2008; Pearson 2008). Finally, considering viruses themselves as cellular organisms reconciles the idea that viruses are living with the classical definition of living organisms as cellular organisms (Lwoff 1967). To take into account the idea that viruses represent a *bona fide* form of life, Didier Raoult and myself have recently proposed to divide the living world into two major groups of organisms, ribosome encoding-organisms (the descendants of LUCA, archaea, bacteria and eukarya) and capsid-encoding organisms (the viruses) (Raoult and Forterre 2008).

What is Life?

Although the definitions of life have evolved continuously depending on the progress of our knowledge in biology, this is clearly not a scientific question, but a philosophical one. Definitions of life have always been based at a given time on the philosophical background of scientists as well as the scientific background of philosophers. As a consequence, the answer to the question, "what is life?" will always be given in a particular philosophical framework. Personally, although dialectic materialism is now out of fashion for historical and political reasons, I like the definition of life proposed in the 19th century by Frederich Engels in his posthumous book *Dialectics of Nature*. For Engels, "*life is the mode of existence of albuminoïd bodies*" (Engels 1883). At the time of Engels, it was a prescient insight to focus the definition of life on proteins (albuminoïds), considering that the real nature, diversity and role of proteins were then practically unknown. At first sights, a modern version of this definition could be: "life is the mode of existence of informational macromolecules (proteins and nucleic acids)". However, the term "albuminoïd bodies" asks for more. Albuminoïd bodies could be translated in modern time as "a physical entity based on organic molecules, molecules that are produced by living entities, let's say … an organism". So I would give the following definition of life: '*life is the mode of existence of living organisms*'. If one only considers present terrestrial life, one could conclude that "*life is the mode of existence of ribosomal and capsid encoding organisms (REO and CEO)*". However, we would like to reach a definition that would also include ancient terrestrial life (predecessors of modern REO and CEO), especially in the framework of discussions about the origin of life. So the question remains, what is a living organism? According to Lwoff (1967) "*an organism is an integrated system of interdependent structures and functions*".

I will define here a living organism as an entity formed by the functional integration of several "organs", corresponding to the structure and functions of Lwoff's definition. By analogy with multicellular organisms that are composed of several organs (skin, liver, brain and so on), unicellular organisms can be defined as composed of several molecular machines and/or structures (metabolic networks, ribosomes, replicons, capsid, membranes and so on). A living organism can thus be defined as: "*a collection of integrated organs (molecular machines/structures) producing individuals evolving through natural selection*".

The simplest viruses encode two different "organs", a replicon, allowing genome multiplication, and a capsid, i.e. a complex structure allowing not only to protect the viral genome in the extracellular space, but also involved in the entrance and exit mechanisms of virions in and out of the cell. All viruses encode sophisticated mechanisms to divert the organs of the infected cells, such that these organs become part of the viral organism during infection.

One can try to use our definition of organisms to approach the problem of the origin of life itself. Modern cells descending from LUCA and their viruses are all complex organisms, and LUCA itself has been the product of a long history (for a recent review, see Forterre and Gribaldo 2007). Life indeed already existed before the emergence of capsids and ribosomes. This is the reason why I included the ancestors of LUCA in my definition of life. At some point one should have to imagine the nature of primitive cells to include their features in our definition. The precise moment when life originated corresponds to the appearance of the first individuals formed by at least two integrated molecular organs (possibly a primitive metabolic network and a membrane) co-evolving through natural selection.

Although the definition of life is a philosophical question, the choice of a definition has a great impact in the definition of scientific programs. The definition of life proposed here implies that the goal of biology should be to explore and understand exhaustively (*via* combining reductionist and integrative approaches) the mode of existence of living organisms and to understand their history (evolution being the cornerstone of biology). Above all, a program to study "the origin of life" should focus on looking, theoretically and experimentally, for the mechanisms that led to the emergence of the first living organisms on our planet.

Acknowledgments I thank Michel Morange for the invitation to participate to the 2008 meeting on life definition in Paris. I am grateful to David Prangishvili, Didier Raoult and Simonetta Gribaldo for fruitful discussions.

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Orig Life Evol Biosph (2010) 40:161–167
DOI 10.1007/s11084-010-9195-0

Which Way to Life?

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Received: 15 January 2009 / Accepted: 12 May 2009 /

Abstract If the emergence of life is seen as the evolutionary transition between the non-living and the living, then it may be meaningless to draw a strict line between these two worlds. A comparison between the metabolic- and genetic-first origin-of-life proposals is made. A comparison of the empirical evidence used in favor of the metabolic-first and genetic-first theories of the origin of life shows that many of the observations and experimental findings that are used to argue in favor of one or another view are equally consistent with the premises of both theories and do not unambiguously support neither of them. However, current biology indicates that life could not have evolved in the absence of a genetic replicating mechanism insuring the stability and diversification of its basic components.

Keywords Origin of life · Metabolism first-genetic first theories · RNA world

Introduction

It is generally accepted that any explanation of the origin of living systems should attempt, at least implicitly, to propose the definition of a set of minimal criteria for what constitutes a living organism. However, this has proven to be an elusive intellectual endeavor, and not for lack of trying. The absence of such definition sometimes gives the impression that what is meant by the origin of life is described in somewhat imprecise terms, and that several entirely different questions are often confused (Lazcano 2008).

Despite the seemingly insurmountable obstacles surrounding the understanding of the origin of life, or perhaps because of them, there has been no shortage of discussion about how it took place. A cladistic approach to the origin of life is not feasible, since all possible intermediates that may have once existed have long since vanished. Phylogenetic analyses based on comparative genomics provide important clues on very early stages of biological evolution, but it is difficult to see how its applicability can be extended beyond a threshold

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that corresponds to a period of cellular evolution in which protein biosynthesis was already in operation, i.e., the RNA/protein world (Becerra et al. 2007).

Since the attributes of the first living entities are unknown, it is not surprising that an inventory of current views on the origin of life reveals a mixture of opposites of every kind, including the imaginative possibility that terrestrial life did not emerge on the Earth but was transferred from another planet. As summarized by Eschenmoser (2008), two major camps can be recognized among those working on the origins of life, i.e., those assuming that the emergence of autocatalytic "metabolic" cycles in the primitive Earth was essential for the appearance of genetic systems, and those that assume the priority of genetic polymers endowed with catalytic properties. These two different viewpoints reflect a rather sharp division between those who favor the idea that life is an emergent interactive system endowed with dynamic properties that exist in a state close to chaotic behavior, and 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 central characteristics. As argued here, when the evidence that is used in favor either of the metabolism- or the genetic-first theories is placed side by side, it is evident that it is not possible to draw a firm conclusion: many of the current observations and experimental findings are consistent with the premises of both possibilities and do not unambiguously support one theory or the other (Table 1).

Genes Versus Coacervates

In a series of papers published during the First World War, the American physicist Leonard Troland (1917) argued that the origin of life was the outcome of the random formation of a self-replicating enzyme-like molecule that had made its sudden appearance in the primitive oceans. A few years later Hermann J. Muller explicitly adapted Troland's hypothesis to propose that life appeared with the abrupt, random formation of a single, mutable gene endowed with catalytic and autoreplicative properties (Muller 1926).

Muller's proposal was brilliantly reductionist, and was contested by Alexandr I. Oparin and others in a now largely forgotten debate. Their controversy became an entangled debate in which science, philosophy, and politics mixed in an excruciating discussion that was shaped in part by the Cold War atmosphere (Lazcano 2008). In sharp contrast with Muller's ideas, Oparin (1938) argued that the essence of life was metabolic flow. For him, life must be seen, in the dialectical sense, as a special form of the motion of matter, always in flow, which included enzymatically based assimilation, growth, and reproduction, but not nucleic acids, whose genetic role was not even suspected during the 1930's. Biological inheritance was assumed by Oparin to be the outcome of growth and division of the coacervate drops he had suggested as models of precellular systems.

Oparin and Muller came from different scientific backgrounds and almost opposite intellectual traditions, so their common interest in the origin of life did nothing to assuage their opposing views. Oparin was a convinced evolutionist, and, like many of his contemporaries, his original genetics were pre-Mendelian. The evolution of Muller's and Oparin's ideas on the nature of life ran parallel to the molecularization of biology that would dominate research for many decades. For Muller, a staunch neoMendelist trained in Morgan's group, the essence of life lies in the combination of autocatalysis, heterocatalysis, and mutability, i.e., evolvability. According to Muller (1966) the gene material alone, i.e., DNA, possesses these faculties, and it is therefore legitimate to call it living material, the present-day representative of the first life.

Table 1 A summary of the different lines of evidence used to argue in favor of the metabolism-first and genetic-first proposals for the origin of life. Conclusive evidence for either view is still lacking. As shown in the second column, the available observations and empirical findings that have been used to support one view are equally consistent with the other alternative

	Supported by	Key demonstration
Metabolism-first	Basal position in phylogenetic trees of thermophiles Wide distribution and conservation of Fe–S clusters Replicative liposomes with protein-synthesizing machinery Abiotic synthesis of metabolic intermediates Non-enzymatic transformations of metabolic intermediates Cyclic chemical reactions (for instance, the Belousov-Zhabotinskii reaction) Formose reaction Cyclic production of $(HCN)_4$ from HCN and H_2CO	Self-assemblage of enzyme-free multi-step chemical cycles, formed within the constraints of prebiotic chemistry, capable of utilizing organic compounds or CO_2. Enclosure within membranes not essential, but should exhibit multiplication and the ability to form complex enzymatic networks
Genetic-first	Abiotic synthesis of biochemical monomers and oligomers Non-enzymatic template-directed reactions Ribozymes and in vitro evolution of RNA systems Synthesis of alternative genetic polymers (v. gr., PNAs) Abiotic synthesis of metabolic intermediates Non-enzymatic transformations of metabolic intermediates Cyclic chemical reactions (for instance, the Belousov-Zhabotinskii reaction) Formose reaction Cyclic production of $(HCN)_4$ from HCN and H_2CO	Synthesis of genetic polymers within the constraints of prebiotic chemistry, capable of evolving by replication with variation. Does not requires enclosure within membranes nor autocatalytic properties, but should be able to evolve using environmental precursors.

The catalytic versatility of RNA molecules clearly merits a critical reappraisal of Muller's viewpoint, but there are many different definitions of what the RNA world was. The discovery of ribozymes does not imply that wriggling autocatalytic nucleic acid molecules ready to be used as primordial genes were floating in the primitive oceans, 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.

There are many indications of the robustness of the RNA world hypothesis. The list includes the recent report by Lincoln and Joyce (2009) showing that a ribozyme that catalyzes the RNA-template joining of RNA can be modified leading to two ribozymes that catalyze each other's synthesis from a total of four oligonucleotide substrates. These cross-replicating catalytic RNAs undergo self-sustained exponential amplification in the absence of proteins or other biological materials. However, the problem of how RNA came into being is still an open one. It is possible that some type of self-replicating polymer may have preceded RNA, but this remains a major unanswered issue.

As summarized in Table 1, the genetic-first views of the origin of life would be strongly supported with the synthesis, within the constraints of prebiotic chemistry, of genetic polymers capable of evolving by replication with variation. Although the possibility that membranes were essential from the very beginning is supported by empirical evidence (Mansy et al. 2008), the genetic-first proposal does not requires enclosure within compartments, but such hypothetical model system should be able to evolve and promote catalysis using environmental precursors (Table 1). There is convincing evidence suggesting that the genetic code and protein synthesis first evolved in such an RNA world, but the question of the ultimate origin of primordial functional protein-encoding sequences in RNA-dominated systems remains open and needs to be addressed.

What Came First?

With few exceptions like the views advocated by Sidney W. Fox and others (cf. Fox and Dose 1977), during the years that followed the Miller-Urey experiment attempts to understand the origin of life were shaped to a considerable extent by the unraveling of the molecular details of DNA replication and protein biosynthesis. During the past 15 years this situation has changed, due in part to a reaction against molecular biology reductionism, and in part to the adherence to all-encompassing views based on complexity theories and self-assembly phenomena. The background of current metabolic views lies not in Oparin's proposals, but in the attempt to extrapolate to biology the deeply rooted tendency in physical sciences to search for all encompassing laws that can be part of a grand theory that can explain many, if not all, complex systems. It is unfortunate, however, that 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 many life scientists see as grand, sweeping generalizations with little relationship to actual biological phenomena (Fenchel 2002).

The many examples of self-organizing physical systems that lead to highly ordered structures demonstrate that, in addition to natural selection, there are other mechanisms of ordered complexity that operate. 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, in cyclic chemical phenomena (such as the Belousov-Zhabotinsky reaction) and, quite significantly, in the autoorganization of lipidic molecules in bilayers, micelles, and liposomes (Table 1). There are indeed some common features among these systems, and it has been claimed that they follow general principles that are in fact equivalent to universal laws of nature (Kauffman 1993). Perhaps this is true. The problem is that such all-encompassing principles, if they exist at all, have so far remained undiscovered. This has not stopped a number of researchers to attempt to explain life as a continuously renewing complex interactive system that emerged as self-organizing metabolic pathways that at first did not require genetic polymers.

However, 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. What is lacking is the confirmation that metabolic (or protometabolic) routes can replicate and evolve. As summarized by Leslie Orgel in a posthumous paper, 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 autocatalytic chemical reactions (Orgel 2008).

As argued by Orgel (2008), as of today the only known prebiotic example of an autocatalytic system is the formose reaction, i.e., the polymerization of formaldehyde to yield a complex mixture of sugars including ribose. Additional examples may include the formation of HCN tetramer from HCN in the presence of formaldehyde (Schwarz and Goverde 1982), as well as the triose-ammonia reaction described by Weber (2007) in which a mixture of glyceraldehyde with ammonia produces pyruvaldehyde and a complex mixture of nitrogen-containing compounds, which in turn can enhance the rate of production of pyruvaldehyde if added to a fresh solution of glyceraldehyde. However, these systems do not prove by themselves that primordial metabolism came before genetic polymers. In other words, if autocatalytic cycles ever existed, they are not competitive with a genetic system. On the other hand, it is reasonable to assume that different prebiotic components underwent many complex transformations, and if self-sustaining reaction chains did arise on the early Earth, they could have played an important role in enriching the prebiotic soup in components not readily synthesized by other abiotic reactions or delivered from space.

There is a clear lack of simple continuity between the biosynthetic and the (possible) prebiotic pathways (Lazcano and Miller 1999). For instance, abiotic amino acid formation is by the Strecker synthesis or the Bucherer-Berg reaction, which are very different from transamination and the reverse Krebs cycle. The prebiotic synthesis of purines is from HCN (Oró 1960) and not from glycine, formate, and NH_3. Only the amino imidazole carboxamide ribotide in the biosynthetic pathway is similar to the amino imidazole carbonitrile synthesized in the prebiotic pathways. Additional examples include (a) the decarboxylation of orotic acid which yields uracil (Ferris and Joshi 1979); (b) the chemical synthesis of glutamic acid from α-ketoglutarate, ammonia and reducing agents (Morowitz et al. 1995); (c) pyrrole synthesis from UV-irradiated δ-aminolevulinic acid (Szutka 1966); (d) pyrimidine synthesis from dihydroorotic acid (Yamagata et al. 1990); and (e) the production of acetic acid from the hydrolysis of the activated thioester CH_3–CO–SCH_3 formed from the NiS/FeS-mediated reaction of CO and CH_3SH (Huber and Wächtershäuser 1997). The similarities between these reactions and their enzyme-mediated counterparts do not necessarily indicate an evolutionary continuity between prebiotic chemistry and biochemical pathways, but may reflect chemical determinism. These processes are similar because may they be the unique way in which given reactions can take place. The possibility that these reactions took place on the primitive environment does not disprove the view that genetic polymers played a key role in the emergence of life.

The evidence supporting the contention that metabolic cycles can undergo spontaneous self-organization is quite limited, and there is no indication that they can replicate, mutate and evolve. Complex systems of chemical reactions such as the formose reaction are not adapted to ensure their own survival and reproduction—they just exist. The key demonstration that life could have appeared in the absence of genetic polymers would be the self-assemblage of enzyme-free multi-step chemical cycles, formed within the constraints of prebiotic chemistry, capable of utilizing organic compounds or CO_2 (Table 1). It can be argued that enclosure within membranes was not essential (but would certainly help), but such hypothetical chemical cycles should exhibit multiplication and the ability to form complex enzymatic networks. Until this is demonstrated, the idea that metabolism came before genetic polymers remains a speculation with little support from what biology shows today. Life cannot be reduced to one single molecule such as DNA or a population of replicating ribozymes, but current biology indicates that it could have not evolved in the absence of a genetic replicating mechanism insuring the stability and diversification of its basic components.

Conclusions

The remarkable coincidence between the monomeric constituents of living organisms and those synthesized in laboratory simulations of the prebiotic environment appears to be too striking to be fortuitous. Nevertheless, at the time being the hiatus between the primitive soup and the RNA world is discouragingly enormous. If the origin of life is seen as the evolutionary transition between the nonliving and the living, then it is meaningless to attempt to draw a strict line between these two worlds (Lazcano 2008). The appearance of life on Earth should, therefore, be seen as 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.

The intellectual dichotomy between among those claiming that the appearance of the first life forms depended on informational oligomeric compounds, i.e., the so-called genetic approach, and those that argue that it was based on autocatalytic metabolic cycles has been transformed into a dialogue of the deaf. Instead of engaging in footling arguments about when exactly did life start, the recognition that it 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 nonliving entities. Some systems may not be “half-alive”, but they can exhibit some of the properties we associate with living entities.

As in other areas of evolutionary biology, answers to questions on the origin and nature of the first life forms can only be regarded as inquiring and explanatory rather than definitive and conclusive. This does not imply that all origin-of-life theories and explanations can be dismissed as pure speculation, but rather that the issue should be addressed conjecturally, in an attempt to construct not a mere chronology but a coherent historical narrative by weaving together a large number of miscellaneous observational findings and experimental results (Kamminga 1986). 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, and the most likely candidates for this appear to be genetic polymers.

Acknowledgements I am indebted to Professor Albert Eschenmoser for several conversations regarding some of the issues described here. Support from CONACYT-Mexico (project 50520-Q) to A. L. is gratefully acknowledged.

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DOI 10.1007/s11084-010-9196-z

DEFINING LIFE

On What It is to Fly Can Tell Us Something About What It is to Live

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Received: 20 February 2009 / Accepted: 12 June 2009 /

Abstract The plurality of definitions of life is often perceived as an unsatisfying situation stemming from still incomplete knowledge about 'what it is to live' as well as from the existence of a variety of methods for reaching a definition. For many, such plurality is to be remedied and the search for a unique and fully satisfactory definition of life pursued. In this contribution on the contrary, it is argued that the existence of such a variety of definitions of life undermines the very feasibility of ever reaching a unique unambiguous definition. It is argued that focusing on the definitions of specific types of 'living systems'—somehow in the same way that one can define specific types of 'flying systems'—could be more fruitful from a heuristic point of view than looking for 'the' right definition of life, and probably more accurate in terms of carving Nature at its joints.

Keywords Definition of life · Living systems · Origin of life · Pluralism

Introduction

Definitions of life abound in the literature. Simultaneously, there is much debate among scientists and philosophers to find 'the' right definition of life. Yet, should we really worry about the existence of such a plurality of definitions and work towards a unique definition of life? In this contribution, I propose two arguments that account for such a diversity of definitions of life: a 'methodological argument' that has to do with the methods of definition, and a 'natural argument' stemming from research on physico-chemical systems at the border-line between inanimate matter and life. I argue that, instead of searching for 'the' right definition of 'life', one ought to focus on defining types of 'living systems', for not only living systems might come with varying degrees of 'lifeness' but also with varying means for achieving this 'lifeness'.

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On the Many Definitions of Life

The literature is replete with definitions of life. Already in the 1970s, Carl Sagan noticed that there was no commonly accepted definition of life and that there was a clearly discernible tendency for each biological discipline to define life in its own terms (Sagan 1970, 985); at that time, Sagan identified physiological, metabolic, biochemical, genetic and thermodynamic definitions of life. More recently, following the work of Palyi et al. (2002, 15–56), Popa catalogued over ninety different definitions of life, from the 1850s to today (Popa 2004, 197–205). Some of these definitions are rather short, others much more intricate.

A closer look actually shows that they tend to fall into two broad categories. One finds ‘list-based definitions’ that define a living system in terms of a list of putative necessary and sufficient properties. Such properties typically include growth, reproduction, self-repair, energy-harnessing capability, matter-harnessing capability, variation capability, information capability and so forth (see for instance: Oparin 1961; Bernal 1967; Monod 1970; Crick 1981; Mayr 1982; de Duve 1991; Farmer and Belin 1992; Koshland 2002; Morange 2003). On the other hand, one also finds ‘model-based definitions’ that define living systems on the basis of a model that describes the very functioning of such living systems (see for instance: Maturana and Varela 1973; Ganti [1971] 2003; Ruiz-Mirazo et al. 2004). In such cases, the properties of living systems are only secondary in the sense that they are nothing but a consequence of the functioning of the model. Whichever way one may adopt to classify definitions of life, the end-result is straightforward: definitions of life abound.

Such a situation is often perceived as being unsatisfactory: there is indeed much debate about the relative strengths and weaknesses of definitions of life when compared to one another, about the adequacy of such and such definition when it comes to capturing the ‘essence’ of life. There is also much debate about the existence of physical, chemical or biological counterexamples that seem to defy both the sufficiency and necessity of any of these definitions (e.g. Luisi 1998; Ruiz-Mirazo et al. 2004). Many discussions focus on finding ‘the’ right definition of life. For instance, Cleland and Chyba argue that, in order to reach ‘the’ correct definition of life, one first needs to have a theory of life, somehow in the same way that one needs a molecular theory of water to correctly define water as H_20 (Cleland and Chyba 2002). And, besides intellectual satisfaction, specific motivations for finding ‘the’ right definition of life are often put forward, including for instance use in astrobiology (to define whether one finds life or not elsewhere than on Earth), use in artificial life (to decide whether specific *in silico* systems do qualify as being alive or not), or use in synthetic biology (to decide whether specific ‘wet’ *in vitro* systems are alive or not).

In what follows, I argue that there are good reasons for such a plurality of definitions of ‘life’, and furthermore that the debate could benefit from tackling, instead, the question of defining ‘types of living systems’.

Definitional Pluralism

Two arguments can explain why there is such a plurality of definitions of life: first, a ‘methodological argument’ that borrows from logic and linguistics, and that concerns the art of defining; and second a 'natural argument' based on an analysis of the variety of functionalities that can be harnessed to sustain life-like processes[1].

The 'methodological argument' stems from the simple observation that, there exist, in logic and linguistics, quite many methods for reaching definitions of terms, and that such methods may generate indeed quite distinct definitions of any given term. For instance, Clark and Welsh, in their logic manual (1962), list a number of such methods and types of definitions. One can first distinguish between 'lexical definitions' and 'stipulative definitions': whereas the first ones give or explain the meaning of a word by referring to the linguistic usage of this very word by certain people at certain places and times, the second ones deliberately assign a meaning to a word (Clark and Welsh 1962, 175–181). As a matter of fact, 'stipulative definition' is the principal sort of defining that is at stake when one claims that arguments can be settled by clarifying definitions, and, in this respect, the various definitions of life belong to this class of 'stipulative definitions'. But there are also many ways to elaborate a 'stipulative definition' of any given word. Clark and Welsh catalogue no less than eight methods of definition: the 'synonymous method', the 'method of analysis *by genus and differentia'*, the 'relational or synthetic method', the 'denotative method', the 'range method', the 'ostensive method', the 'implicit method' and even the so-called 'regular method' (Clark and Welsh 1962, 182–192)[2]. As a result, it is no surprise that multiple definitions of any given term might co-exist.

Indeed, the variety of methods of definition can certainly explain part of the observed plurality of definitions of life: for instance, the approach of many proponents of 'list-based definitions' of life definitely borrows from the 'method of analysis *by genus and differentia'* in so far as such definitions list specific properties that are supposed to set apart living systems from other types of physico-chemical systems; on the other hand, the approach of proponents of 'model-based definitions' of life is more akin to the 'relational or synthetic method' in so far as living systems are, in this case, defined by being related to particular models and their way of functioning.

The 'natural argument' stems from the diversity of physico-chemical systems that appear to populate the bordering zone between non-life and life. There is indeed quite a wide disagreement about whether certain systems are alive or not. One of the most frequently discussed cases is that of viruses. For some, viruses should not count as living systems in so

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[1] It can also be argued, as a third argument, that 'life' is a folk concept that does not correspond to a natural kind, and that, as a result, it is no surprise that no right definition of life can be singled out (Machery, forthcoming). In this contribution, I will focus on a more scientific viewpoint.

[2] The 'synonymous method' consists in defining a word by giving another word which is its synonym ('chat' in French means 'cat' in English); the 'method of analysis by *genus et differentia*' consists in giving the name of a larger class (the *genus*) of which the thing to be defined is a subclass, and giving a property (*differentia*) which sets it off from other members of the larger class (a 'bachelor' is an 'unmarried adult man'); the 'relational or synthetic method' defines a word by relating the thing meant to some other thing we are familiar with (the color 'blue' can be correlated with a given set of light waves); the 'denotative method' proceeds by giving a list of examples of things the word applies to (a 'card game' is something like bridge, poker or twenty-one); the 'range method' defines a paradigm case and deviating borderline cases (a 'Labrador retriever' can be defined by presenting typical specimens and borderline specimens); the 'ostensive method' defines a word by presenting an object ('this is a thermometer'); the 'implicit method' defines a word by using it (the word 'hemisphere' can be defined by saying: 'the diameter of a circle cuts the circle into two equal hemispheres'); the 'regular method' defines a word by giving the rule for its use (the rule for 'we' is that it is used by the speaker to refer to himself or herself and at least one other person). For more details, see for instance Clark and Welsh (1962, 182–192).

far as they lack proper metabolic activity (see for instance Luisi 1998; Ruiz-Mirazo et al. 2004). Yet, for others, they should: in particular, recent research is challenging the traditional view of a virus pictured as a rather static strand of nucleic acid encapsulated in a capsid, replacing it by that of a quite active and alive 'viral factory' (see for instance Forterre 2010, this volume). There is also substantial debate about whether self-replicating strands of RNA, as hypothesized in the 'RNA world' scenario (Gilbert 1986), could count as being truly alive or not. For some, such an RNA strand would be capable of replication, possibly with variation thanks to replication errors, and therefore would be subject to natural evolution, hence alive (see for instance Luisi 1998). For others, on the contrary, self-replicating RNA strands would be far from qualifying as living systems: at best would they be self-replicating and variation-capable systems; yet they would lack metabolic activity and would also not be enclosed in any membrane-like compartment (see for instance Shapiro 1986; Segré et al. 2001). Similarly, one can imagine the debate about the status of a physico-chemical system that would be capable of metabolic activity yet incapable of replication; an extreme example could be that of an organism that would comprise a planet in its entirety; yet another that of self-sustaining vesicles. One can also question whether a self-replicating system that would have a compartmentalization and a metabolic activity, but that would be devoid of any genetic code, might be called 'living' or not: most likely 'no' if one defines life on the basis of a genetic code, and 'yes' if one defines life on the basis of a metabolic activity. And the debate goes on about whether certain particular natural systems should be included or not within the restricted circle of 'living systems'.

What this debate illustrates, above all, is the wide range of properties and of ways of expressing these properties that might be called upon to define 'what it is to live'. Indeed, it appears today that the transition from 'inanimate matter' to 'life as we know it' is likely to be a very gradual process, involving multiple steps and spanning over millions of years (see for instance de Duve 1991). In this respect, there would therefore be no sharp point in time corresponding to the appearance of life: rather then resulting from a sudden emergence, 'life' is likely to be the outcome of a continuum of 'more-or-less alive' systems. Similarly, one can also argue that there still exist today physico-chemical systems that could be assessed as being more or less alive than other systems (as is the case, for instance, of viruses when compared to archae, bacteria or eukarya). In a sense therefore, there would be no clear-cut historical transition between non-living and living systems, nor any clear-cut delineation between current, be they natural or artificial, non-living and living systems. As a result, it can be argued that there are degrees of 'lifeness', that the property of 'being alive' or of 'pertaining to the class of living systems' is a matter of degree that cannot be captured within a framework resting on classical logic and the law of bivalence, but rather within a framework resting on fuzzy- or multi-valued logic (see Bruylants et al. 2010, this volume): in such a case, physico-chemical systems may receive a score between 0 and 1 representing their degree of being alive. The upshot of the approach is to take into account the latest scientific knowledge about the origin of life, that is to say the very likelihood of a gradual transition from inanimate matter to life, and to formalize this continuum of 'lifeness'. Yet, the evaluation of any system along a 0-to-1 scale seems to imply that being more-or-less alive is a question of degree along a one-dimensional axis. Yet, is there indeed such a one-dimension along which to be 'more-or-less alive' or rather several dimensions, some of them potentially getting lost when projected onto a single axis?

As a matter of fact, a system can be more-or-less successful at replicating or reproducing itself, or more-or-less successful at metabolizing components or energy tokens from given sets of available nutrients and energy sources, or even endowed with a more-or-less sophisticated membrane. For instance, it appears very likely that, over time, membranes evolved very much in complexity: the abiotic synthesis of amphiphilic molecules, such as fatty acids, and their concentration and self-assembly might have resulted into vesicles, likely to be the first types of membranes encountered on the primitive Earth; yet such vesicles are very sensitive to concentration, temperature and pH (e.g. Monnard and Deamer 2002); the addition of other molecules such as sterols or amphiphilic polypeptides could have resulted, in a second step, in more robust vesicles, stable across varying chemical conditions, and larger as well (e.g. Luisi 2002); in a third step, the insertion of specialized transporters and active catalysts might have led to vesicles able to create and maintain chemical disequilibria; and the subsequent additions of other more complex organic compounds such as polysaccharides, energy-transduction components or surface-layers components would have resulted in the appearance of the extremely sophisticated and multi-function membranes of current organisms (e.g. Ourisson and Nakatani 1994). One can therefore hypothesize the appearance of many different types of membranes of increasing complexity and performance. It might also be the case that only certain types of membranes are sophisticated enough to host life. In any case, the type of membrane that a particular physico-chemical system has might lead to qualify this system as more-or-less alive depending, in part, on the performance of this type of membrane: for instance, more-or-less alive because of being more-or-less stable across varying chemical conditions, or because of being more-or-less capable of creating a chemical disequilibria etc. Similar performance scales could be put together for other major features of living systems: more or less efficient catalytic activity, more or less sophisticated metabolic pathways, more or less robust informational polymers etc. Such scales may then explain how a system might be more-or-less alive along several dimensions: for instance, a system might be capable of more-or-less successfully replicating, or more-or-less successfully metabolizing components. In addition, it might prove to be the case that in order to be, for instance, optimally replicating, one also needs to be successfully metabolizing, i.e. that in order to reach higher degrees of ‘lifeness’, then one needs to integrate and couple between themselves several of the above-mentioned dimensions. In sum therefore, it appears that the transition from inanimate matter to life is not a matter of a sudden jump but rather a matter of degrees, and that furthermore, such transition is not a matter of degrees along a single dimension but rather along several dimensions. As a result, defining ‘life’ becomes less relevant than defining specific ‘types of living systems’ that would characterize each of these dimensions and their inter-relatedness. Such an approach could also account for the current plurality of definitions of life. It is also commonplace in other fields of human enquiry. For instance, the multiple ways one can fly—more-or-less successfully!—have led to a plurality of definitions of the term ‘aircraft’.

Different Types of ‘What It is to Fly’

It seems one would know what flies and what doesn’t, and that there is a clear-cut definition of ‘what it is to fly’: birds fly, as do aircrafts, but stones don’t, neither do laptops. Yet, from paper airplanes to long-haul passenger aircrafts, there appears to be a wide range of performance and diversity of ‘what it is to fly’. Dictionary-type definitions would say that to fly, in this semantic context, is “to move or be moved through the air by means of wings or a machine”[3]. Yet, such a generic definition has numerous counter-examples: hot-air

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[3] See for instance the entry ‘Fly’ in *Longman Dictionary of Contemporary English*, Longman (1981).

balloons do not have wings nor a machine, neither do dandelion seeds, and yet they do fly. A similar problem arises when defining 'what it is to fly' as when defining 'what it is to live': stipulative definitions of such concepts fail to capture all necessary and sufficient conditions in which the terms should apply. Yet, a closer look at those 'flying systems' tells an interesting story.

In particular, the study of man-made flying systems—'aircrafts'—reveals a great diversity of flying performances or 'degrees of successfully flying', to say the least[4]. For instance a propeller aircraft like the four-seat, single-engine, fixed-wing *Cessna 172 Skyhawk*, one of the most popular flight training aircraft in the world today, is likely to be qualified as a better flying system then the *Blériot n° XI* which crossed the Channel exactly 100 years ago[5]: both are single engine, fixed-wing aircrafts, yet the *Cessna* can carry more passengers, at a higher altitude and over longer distances than the *Blériot* could. One can therefore imagine a scale alongside of which could be measured the degrees of 'what it is to fly'. Such a scale would take into account a mix of flight performance parameters: distance, speed, cargo load or number of passengers, energy consumption, maintenance costs, durability, handling in adverse weather conditions etc.

A closer look at the story of aviation reveals that there is much more to 'what it is to fly' than just a single one-dimensional flight performance scale. There are indeed several drastically different dimensions along which such performance could be measured, in short several ways of 'what it is to fly': one can glide; one can use a propeller to generate thrust and dynamic lift; or one can also take advantage of buoyancy. The existence of such a diversity of means of flying has led to a plurality of definitions of 'flying systems'. For instance, one can first distinguish between 'aerostats', such as hot-air balloons, and 'aerodynes', such as modern commercial airplanes: whereas 'aerostats' are lighter than air and can take advantage of buoyancy to achieve sustained movement through the air, 'aerodynes' are heavier than air and fly only by deriving lift from dynamic motion through the air.

Also, within 'aerodynes', one can distinguish those that are powered, such as propeller airplanes, from those are not, such as gliders. One can also distinguish those that have fixed wings from those that have flexible wings, or even those that have rotary wings: for instance, among 'unpowered aerodynes', one can find fixed-wing gliders, usually simply called 'gliders', but also flexible-wing gliders like so-called 'hang gliders' or 'paragliders', or even rotary-wing gliders like 'rotor-kites' or 'gyrogliders'.

A somehow similar, but more complex, classification holds for 'powered aerodynes'. In addition to using fixed-wings, flexible-wings or rotary-wings as means of providing lift, some 'powered aerodynes' might use other sources of lift, maybe more or less successfully. For instance, 'ornithopters' fly by flapping their wings somehow similarly to what birds do[6]; and aircrafts like the 'flying bedstead' relies on jet lift, with engine thrust directed downwards, as a means of providing lift[7].

And there are also hybrid 'lighter-than-air/heavier-than-air' aircrafts. Among those are hybrid airships that combine characteristics of 'heavier-than-air' and 'lighter-than-air'

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[4] A similar argument could be made on the basis of *naturally* occurring flying systems, from birds to seeds, to even bacteria in cloud droplets (on the later, see for instance Sattler et al. 2001).

[5] Blériot crossed the Channel on July 25th 1909, reaching Dover from Calais in 37 minutes. See for instance Winchester (2007).

[6] See for instance www.ornithopter.org

[7] This was for instance the case of the *Rolls-Royce Thrust Measuring Rig* of the 1950s, or the NASA *Lunar Landing Research Vehicle* of the 1960s.

technology, like helicopter/airship hybrids intended for heavy lift applications or dynamic lift airships intended for long-range cruising[8].

This brief aeronautical survey illustrates not only that 'flying systems' can be more-or-less flying, i.e. that there are degrees of performance relative to flying, but also that flying can be achieved by quite different means and quite different arrangements of these means. The existence of some many different ways and degrees of flying has led to (1) a rather simple generic high-level definition of 'what it is to fly', accompanied by (2) dozens of more specific 'niche' definitions covering special ways and degrees of 'what it is to fly'. And, whereas the high-level definition captures the key features of flying without the ambition to fence off all possible counter-examples, the niche definitions specify much more precisely the types of 'flying systems', essentially on the basis of their functioning.

Different Types of 'What It is to Live'

In a similar way, the plurality of definitions of life could be accounted for by the existence of, not only performance degrees of living systems, but also the diversity of means and ways of functioning of such living systems. As a result, one should not worry so much about finding 'the' right definition of life: like the definition of 'to fly', the definition of 'to live' is likely to be prone to countless exceptions, no matter how well-crafted such definition might be: the reason is that there appears to be different ways thanks to which a chemical system might qualify as living. Instead, focusing on the definitions of more precise types of living systems—like one can define types of aircrafts—could prove to be more fruitful in terms of heuristics and more accurate in terms of carving Nature at its joints.

Indeed, different predicates can be defined to explicate 'what it is to live' when applied to particular types of physico-chemical systems. For instance, some of the major predicates may include:

- *Replicating*: property of a system that catalyzes the synthesis of systems that are identical to itself,
- *Vario-replicating*: property of a system that catalyzes the synthesis of systems that are nearly identical to itself (the 'nearly' could be further specified, for instance 95% molecule-to-molecule identity),
- *Metabolizing*: property of a system that harnesses energy sources to produce chemical components while maintaining itself,
- *Encoding*: property of a chemical system that utilizes a molecular informational code,
- *Encapsulated*: property of a chemical system that possesses a membrane which, in turn, provides a degree of isolation of the system from the environment, etc.

Accordingly, as a matter of illustration, the RNA-world would be populated by 'vario-replicating systems'; on the other hand, hydrothermal vents might have given birth to 'metabolizing systems'; and a current unicellular organism would qualify as an 'encapsulated metabolizing encoding and vario-replicating system'. Of course, the precise definitions of each predicate can be fine-tuned, as well as the list of these predicates. In addition, more fine-grained predicates could be devised to capture further distinctions

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[8] For instance, one can refer to the *P-791* of Looked-Martin ("Lockheed Martin's Secretly Built Airship Makes First Flight", *Aviation Week*, 5 Feb. 2006) or the *Aeroscraft* project of Aeros (www.aerosml.com) among others.

between types of ‘living systems’, as scientific investigations reveal them. For instance, in the case of energy appropriation, one could define (on the basis of e.g. Popa 2004):

- *Catalytic*: property of a chemical system that catalyzes specific chemical reactions,
- *Autocatalytic*: property of a chemical system that catalyzes specific chemical reactions, some of which catalyze in turn the synthesis/restoration of the initial catalysts (reflexive activity),
- *Energy-transducing:* property of a chemical system that can transform one energy form into another energy form (and potentially store energy),
- *Energy-regulating:* property of a chemical system that can regulate the pace of energy flow.

Of course such definitions are still largely open and upcoming scientific research will tell which specific predicates are the most suited to describe the types of living systems (it is advances and failures in aeronautics that have revealed which ways of flying were possible and also more effective, and that have therefore shaped the predicates used to describe the great diversity of flying systems: aerostat/aerodyne, powered/unpowered, fixed-wing/flexible-wing/rotary-wing etc.). In any case, I argue that there are, at least, three major reasons for focusing on defining ‘types of living systems’, and no longer on defining the higher-level property of ‘life’.

First, defining and explicating types of living systems should facilitate communication of scientific results, between scientists (in particular of different disciplines), as well as between the scientific community and the general audience (for instance in order to avoid hastily reached conclusions of the sort ‘the secret of life has been discovered’ or ‘traces of life have been discovered on Mars’). This should also help laypersons realize how complex the transition from inanimate matter to life can be, and which key functions are required for a chemical system to gradually reach the performance of some of the most basic living systems.

Second, focusing on types of living systems and their key properties may have a heuristic value as it may help map out and investigate alternative ways of putting together life-contributing functions: after all, it is not by copying Nature and the flight of birds that man best managed to fly, but by devising a ‘powered fixed-wing aircraft’; as a matter of fact, man-made ornithopters proved much more complex to build; furthermore, focusing on buoyancy instead of dynamic lift made possible the first manned free-flights in hot-air balloons a century before the first flights in ‘powered fixed-wing aircrafts’[9]. Similarly copying Nature may not prove to be the best way for synthetic biology to make headway in creating novel *in vitro* living systems.

Third, such a pluralistic definitional strategy might also prove to be a more truthful way to carve Nature at its joints: the wide diversity of definitions of life as well as the numerous debates between scientists about the relative importance of specific sets of properties or models over others might indeed be interpreted as pointing, if anything, towards the existence of different ways and degrees of ‘what it is to live’.

Conclusion

In this contribution, I proposed that two arguments can help explain the existence of a plurality of definitions of life: first a ‘methodological argument’ related to the diversity of possible

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[9] The first recorded free flight with human passengers onboard a hot-air balloon was on November 21, 1783 when de Rozier, along with Marquis Francois d'Arlandes, flew the balloon built by the brothers Montgolfier in Annonay, France. On the other hand, the Wright brothers made the first sustained, controlled, powered heavier-than-air manned flight at Kill Devil Hills, North Carolina, USA on December 17, 1903. See for instance Winchester (2007).

methods of definition, and second a ‘natural argument’ stemming from the diversity of properties exhibited by border-line systems in between inanimate matter and life. Whereas, for some, the plurality of definitions of life is perceived as an unsatisfying situation that is to be remedied, I proposed that focusing, instead, on defining types of living systems might prove more fruitful and accurate as a way of accounting not only for different degrees of ‘lifeness’ or ‘living performance’, but also of accounting for the different means that physico-chemical systems might manage to harness in order to live. Like flying, living might indeed come not only in different intensities but also in different flavors.

Acknowledgments I am very grateful to the participants to the *Defining Life* conference organized in Paris in February 2008, for very stimulating discussions. Support from the *CNRS interdisciplinary program* “Origines des planètes et de la vie” and from the *Fondation Louis D.* of the *Institut de France* is gratefully acknowledged.

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DOI 10.1007/s11084-010-9197-y

DEFINING LIFE

The Resurrection of Life

Michel Morange

Received: 16 January 2009 / Accepted: 22 May 2009 /

Abstract The question of life was progressively put aside in the second half of the 20th century with the rise of molecular biology, but has recently re-emerged. Many scientists and philosophers consider that there is no place for this question within biology; that the distinction between living and non-living is arbitrary; and that progress in synthetic biology will finally put this question out of people's minds. I will argue that there is something wrong with the arguments supporting these statements. There are no reasons to exclude the question "What is life?" from biology. But the nature of the question has dramatically changed recently. Instead of being a search for the principles of life, the answer is now sought in the description of the historical process that has coupled the now well-established characteristics of organisms.

Keywords Emergence · Molecular biology · Natural kind · RNA world · Synthetic biology

Introduction

The question of life—the search for a definition, a clear distinction between life and non-life—vanished during the development of molecular biology. It has recently re-emerged. Does this question have a place within biology? And what kinds of answers are presently looked for?

Death and Resurrection of Life

The question of life was actively raised by many biologists and physicists in the 1930s, culminating in Erwin Schrödinger's book *What is Life?* in 1944 (Schrödinger 1944). The question disappeared with the rise of molecular biology, and with the conviction of molecular biologists, including Francis Crick (Judson 1996) and Jacques Monod (Monod 1971), that an answer had been found. Retrospectively, we can see that there was a confusion between two different statements: nothing more than physics and chemistry is needed to explain the present

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characteristics of organisms, and the physicochemical description of present organisms is sufficient to explain how life emerged. I will come back on this confusion in the conclusion.

The re-emergence of the question of life is clearly visible in the titles of recently published articles and books. The diminishing place of molecular biology in the biological landscape, the fading of the informational vision as well as the rise of systems biology have all contributed. The hypothesis proposed by Norman Pace and Terry Marsh (Pace and Marsh 1985), and later by Walter Gilbert (Gilbert 1986), of an RNA world preceding the present DNA and protein world dramatically changed the problem of the origin of life, but also the vision of what life is: in an RNA world, information does not have the same meaning and place as in the DNA and protein world. Finally, the question of life was re-addressed by scientists working in fields peripheral to biology, who had not been immersed in the same informational bath: specialists in artificial life; new researchers in the life sciences trained in physics or computer science, who joined the efforts of biologists with the development of genomic and post-genomic projects; and researchers participating in exobiology projects.

Has the Question of Life a Place in Science?

There are two main arguments used by those who consider that the question "What is life?" has no place in science. The first is philosophical: the category "living being" is not a "natural kind". The demarcation between life and non-life is the product of human history, not of evolutionary history. Such a position has been supported by Norman Pirie (Pirie 1957), Michel Foucault (Foucault 1971) and more recently by Evelyn Fox Keller (Keller 2002), and by some of the new "synthetic biologists". Two linked arguments are put forward, one historical and the second more practical. The question of life is relatively recent: it emerged at the end of the 18th century. The second argument is that, in the near future, either from observations collected by exobiologists or from the work of synthetic biologists, we will be confronted by objects situated at the borderline between animate and inanimate. Their existence will challenge the clear separation between life and non-life, and whether or not we call them living will be a human decision.

The strength of these arguments is less than it would seem. The question of life was never absent from the minds of those studying organisms. One of the first to ask it was one of the first zoologists—Aristotle. Questions in science are not permanently raised with the same urgency, but this does not mean that these questions are no longer posed. The second argument is apparently weightier. If the projects of synthetic biologists succeed in a more or less distant future—and there are no reasons for them not to succeed—the existence of intermediate (between non-life and life) beings will become a reality. Will the existence of these "things" difficult to label or not as organisms be a valid argument for abandoning the distinction between life and non-life? Quite the opposite I think: the existence of intermediate beings 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.

The second reason for excluding the question of life from biology has been precisely expressed by François Jacob (Jacob 1982). Scientific knowledge—in contrast with other forms of knowledge, such as philosophy—has always progressed by focusing on questions of limited scope, and renouncing big issues. To speak plainly, the question of life is a waste of time for working scientists. There is a confusion in this statement between two different kinds of questions. The first questions are those addressed by scientists every day at the bench: it is obvious that answers will only be obtained if the questions are of a limited scope, and that the question of life is not a valid thesis topic for a graduate student! But science, as a human global enterprise, is more than the accumulation of focused studies. Big questions are a part of scientific investigation, even if they are put aside in daily scientific work.

Science, and in particular biology, cannot eschew the big issues, and provisional answers are permanently provided, in a kind of subliminal form. Such answers are crucially required for scientists working on the origin of life, or searching for traces of life on planets and exoplanets.

The big issues are a part of science. To abandon them to non-scientists would be a catastrophe for the public image of science. It would reduce the attractiveness of scientific studies among young people, and project an overly practical image of scientific knowledge, an image that is already all too prevalent in the public mind and in the media.

What Kind of Answers are Sought?

It is obvious that the kinds of answers sought must be open, in the sense that they must not be limited by the present state of knowledge. What is needed is more a framework than a precise, well-defined answer.

Answers will be provided by different specialists, working on different projects—the origin of life on Earth, the search for extraterrestrial life. They will be contextual, and for this reason partially different. But there is no valid reason to consider that the coexistence of different answers will be the ultimate state of the enquiry, and to exclude *a priori* possible strong connections between these narrowly oriented answers.

But the most important characteristic of these answers is that they will be presented as scenarios by which the different characteristics of life—the capacity to reproduce, the permanent exchange of material and energy with the environment, complex macromolecular structures—have developed and been associated in the historical development of life (Morange 2008). The first molecular biologists, Francis Crick and Jacques Monod, were not wrong when they said that the secret of life had been solved, and the characteristics of organisms explained. The question of life is no longer a mystery. But what remains to be understood is the way these well-defined characteristics have emerged, and been coupled. There has been a dramatic shift in the past fifty years: the question of life is no longer a search for principles of life, but a historical question. 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?".

This is a dramatic change, because it makes the question of life a scientific question, fully accessible to scientific enquiry. Life is on the way to being "naturalized". And the most ambitious projects of synthetic biologists, such as those of Craig Venter, will probably be successful in the near future!

Acknowledgements I am indebted to Dr. David Marsh for critical reading of the manuscript, and to Stéphane Tirard, Antonio Lazcano and Florence Raulin for allowing the publication of this contribution.

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Necessity, Futility and the Possibility of Defining Life are all Embedded in its Origin as a Punctuated-gradualism

Radu Popa

Received: 25 December 2008 / Accepted: 21 April 2009 /

Abstract The criteria used for defining life are influenced by various philosophical visions about life, ranging from holism to reductionism and from mechanistic-reductionism to vitalism. Using different scenarios about the origin and evolution of life as well as properties of energy-dissipative systems, artificial life simulations and basic tenets of xenobiology, guidelines can be established for formulating a definition of life. A definition of life is proposed that is parametric, non-Earth-centric, quantitative and capable of discriminating ‘living entities’ from ‘life’. Living entities are defined as self-maintained systems, capable of adaptive evolution individually, collectively or as a line of descend. Life is a broader concept indicating that the capacity to express these attributes is either virtual or actual. At least four major phase transitions can be recognized during the origin of life (reflexive activity; self-regulated homeostasis; the advent of informatons and the origin of adaptive evolution); these make the origin and evolution of early life an example of ‘punctuated gradualism’. Such phase transitions can be used to identify a boundary in early evolution where life began. This contribution identifies the step in the evolution of a dynamic system when digital control of the system’s state becomes dominant over analogical control, and genetic information is irreversibly used for adaptive evolution, as the boundary between non-living and living systems.

Keywords Automaton · Informaton · Life definition · Origin of life · Phase transition

Introduction

For many reasons life remains a concept very difficult to circumscribe and to agree upon. During the Origin and Early Evolution of Life (OEEL) some of the parameters essential for understanding life may have been part of a *phenomenological continuum* (Bedau 1998), starting with lifeless chemical systems and ending with living biomolecular networks. Alleging this as true means that no sharp threshold can be assigned to the non-life to life

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transition. Consequently, some authors prefer to believe that a definition of life is a matter of convention (similar to arbitrarily choosing a specific shade of gray within a long and smooth gradient between white and black as the actual white/black boundary). Henceforth, the way we describe the origin of life has consequence on our capacity to reveal and focus on its evolutionary stages and its definition. I will refer to this as: "*the dilemma of endless gradualism*". Because no single event fully explains the transition from non-life to life, explaining the phenomenon of life may only be complex, (including numerous physico-chemical forces, events, and achievements), rendering any brief definition insufficient. Many lifeless systems show a few properties that are frequently used to diagnose life (including: growth, preservation of information, feedback regulation, controlled handedness and use of energy dissipation to maintain organization), yet their composition is dissimilar from that of biological life forms. Hence, the composition of the living entities may be a feature independent of the attributes making them alive. This suggests that an objective and universal definition of life has to be non-Earth-centric, and dissociated from any specific chemistry (such as DNA, proteins, carbon, water or covalent bonds).

Yet, this type of generalization makes a more "down to Earth" analyst doubt its applicability. The living state may be an emergent property within networks that have reached some high and specific threshold of organization and complexity. This implies that life may be an unavoidable byproduct in the evolution of many systems, (including artificial life simulations), henceforth the question: "Why is the universe around us (or at least our planet) not more richly populated with many other types of life?" One argument frequently used against the feasibility of a definition of "life" is that we do not have enough information, or have not reached a sufficient scientific maturity to explain the complexity of life. Last but not least, the role of the human psyche, morals and goals cannot be underestimated when such far reaching commitment as "*the ultimate and irrevocable definition of life*" is at stake. Due (arguably) to an innate bias toward spiritualism, many humans are not prepared to accept that a materialistic definition of life could ever be satisfactory, and will downplay any commitment or agreement on this issue. Also, many researchers are more comfortable being on a continuous trek toward understanding life, rather than settling on an ultimate definition. Some might argue that a definition of life will remain out of reach until the last details of the question of the origin of life have been solved completely.

The Futility and Necessity of Defining Life

According to Stuart A. Kauffman (1993) the existence of a self-sustainable chemical system requires a high level of complexity; here complexity is interpreted as a measure of the diversity of internal components, and the specificity of their position in the network, their activity and their interactions. The dilemma in this case is that if the "life-required complexity threshold" is set too high (as Kauffmann's analysis suggests), on the one hand, simpler systems (*i.e.* those obeying the 2nd law of thermodynamics) could never have evolved toward increased organization and complexity, while, on the other hand, the random origin of a system complex enough to be alive faces impossible odds. For example if the origin of life required 100 steps, and each step had a conservative probability of ~0.1, the odds for a living entity to originate would have been extremely low ($\sim 1/10^{100}$). This is a very small number even if one takes into account the whole of space, atoms and time in the universe. Henceforth, whether life originated in one spectacular event, or as a succession of many small steps, may be less relevant than questions such as: "How to address this low probability predicament?" or "Why did life originate at all?" It was often claimed that some form of "*organizing* *principle*" (*e.g.* molecular Darwinism, a self-rewarding polymeric sequence, or a selfish gene) may have been part of early evolution and may have pushed pre-living networks to evolve toward increased order and complexity in contradiction with simplistic thermodynamic expectations. The fundamental physical drivers behind such organizing trends remain hotly debated. In one model, the organization of energy dissipative systems may be a response to the disequilibrium between the geometric increase in volume of the universe, and its arithmetic production of heat (Chaisson 2002; Popa 2004). If we want to understand how various *physical agents* (natural forces or organizing principles) may have controlled the evolution of pre-living systems, relative to agents controlling the evolution of living systems, we have to identify thresholds in evolution where chemical networks may have became alive (*i.e.* establish unambiguous and quantifiable boundaries between the non-living and living state). Presently, a large number of models exist that try to simulate properties of bio-molecular networks by using computational means. Developing a definition of life is not just an abstract quest, but a practical need as well, because it will ease establishing goals and monitoring progress in the field of artificial life.

The argument has been proposed (though it is not explored here), that defining life may be unnecessary or even erroneous in some specific cases (Cleland and Chyba 2002, 2005). Pushing this argument we can land into another extreme position where a definition of life may be viewed as impossible. Alleged causes for this difficulty vary. Until about 50 years ago (prior to the present scientific revolutions in microanalytic biochemistry and molecular biology), adventuring into defining life appeared overambitious. It can also be claimed that, because the only form of life we have seen so far is "biological life on Earth", we are not in a position make a generalization. Though such arguments are often dismissed as subjective, a sharp distinction between non-life and life may be difficult to find for objective reasons as well; for example if the OEEL was a phenomenological continuum (*i.e.* an example of endless gradualism). It is often claimed that biological life has something to it that is unique. Indeed, evidence shows that no other complex energy dissipative system in nature (fire, growing crystals and fluid vortices) ever evolved to become alive; also, so far none of the many models of primitive chemical networks (Eigen 1971; Rosen 1973; Gánti 1975; Luisi and Varela 1990; Fontana 1992; Pargellis 1996; Bro 1997; McMullin and Varela 1997; Kunin 2000; Szathmáry 2002) ever self-evolved toward higher organization and life. Without external support these systems always drift toward states with increased entropy. If no true boundary between non-life and life exists, and we are required to resort to a convention, then such definition may appear artificial or irrelevant. It is also possible that our present understanding of how life originated is fundamentally flawed in some way. Solving this problem may require a novel dogma about prebiotic evolution and an origin of life model that actually works. Last but not least, the comprehensiveness and the relevance of a short syntax-coerced dictionary type of definition may be insufficient for something as complex and diverse as life. As Lauterbur puts it: "*definitions are...like a fisherman's net: too small to encompass Leviathan, but with a mesh too large to hold many of the denizens of the deep*" (Lauterbur 2002).

The Search for a Universal Definition of Life

Stances about how life should be interpreted cover two broad philosophical dimensions:

- Holism (or generalism), in opposition to reductionism (or minimalism); and
- Dialectical-materialism, in opposition to vitalism (Fig. 1).

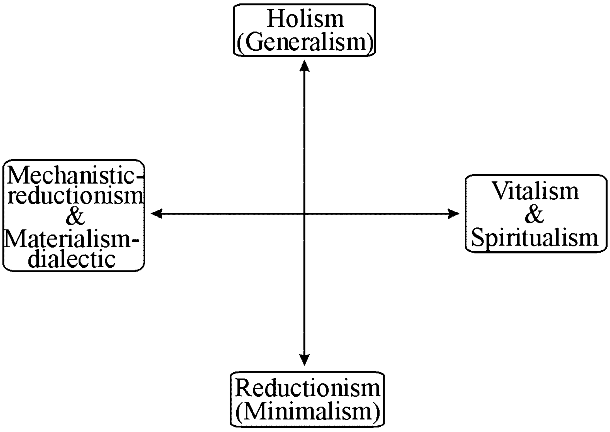

Fig. 1 Visions about how life should be understood and interpreted vary greatly across a two dimensional landscape. The x axis represents the range of opinions concerning the material/immaterial basis of being alive; the y axis concerns the balance between life being a phenomenon caused by fundamentally simple mechanisms, in opposition to life as an emergent (collective) property of system complexity

Holistic interpretations of life are function- and purpose-related views, explaining life as a collective property, and can be summarized in: "*nothing is alive in a cell except the whole of it*" (Olomucki 1993). Reductionism tries to distil life to very simple, small scale, fundamental, and minimalist mechanisms or forces that may fully explain it. Vitalism and spiritualism are rooted in the belief that life is due to some transcendental principle of organization, esoteric force, or supernatural will, that are beyond our power of observation or understanding. Mechanistic-reductionism and Dialectical-materialism consider that life is a fully logical phenomenon, and that, even if we cannot explain it today, we will eventually in the future. When this will occur, life will be proven to have been caused by unambiguous laws of nature and its origin to have occurred in very specific interactions and environmental circumstances. These materialistic visions also state that in the future, (given more knowledge and computational power) we will be able to experimentally produce artificial life forms. Based on these various stances about life, different authors have proposed definitions of life in ways that reflect their specialty, goals and targeted audience. When such definitions of life are formulated they appear in a couple of forms: parametric (a collection of more general or particular attributes of life forms), cybernetic (a numerical analysis of the properties of life), cellularist/genetic (a small list of the most important features, generally resulting from a diagnostic of life on Earth) and non-Earth-centric. A large collection of definitions of life now exist covering a wide array of such stances and choices (Muller 1955; Gánti 1975; Tamponnet and Savage 1994; DeLoof and Broeck 1995; Maynard Smith and Szathmáry 1995; Lahav 1999; Buiatti and Buiatti 2001; Nevo 2001; Rosslenbroich 2001; Apte 2002; Pályi et al. 2002; Szathmáry 2002; Popa 2004; Schultze-Makuch and Irwin 2004).

No definition of life was ever interpreted by peers as "just right". Different observers will often perceive other's philosophy as far fetched, inadequate or insufficient, and other's definition as too narrow, too broad, too vague, too mathematical, too materialistic or too impractical. The most pragmatic scientists will simply avoid such quandary and qualify "life" as "biological life as we know it on Earth" together with the very common statement "*I recognize when I see it*". Albeit this is apparently a safe and non-engaging position, it is also anthropocentric and mistaken because it excludes anything from being actually alive until it is discovered. Yet the quality that makes something alive should remain independent of its revelation. Opinions are also strongly divided about what types of systems may belong under the large umbrella we call life. Are natural viruses alive? If yes, how about prions and viroids? Are computer-based life simulations alive? If the natural viruses are alive, are then computer viruses alive as well? Definitions already exist of different broadness. Defining life as "any material system that undergoes Darwinian evolution ... capable of self reproduction, and mutation followed by selection based upon stored information" (McKay, 1994), will include aliens but disregard computer life and viruses. At another extreme, defining life as "any reproducible system capable of adaptive evolution" appears too broad and includes systems that are not metabolically active.

Life Properties in the Eyes of Xenobiology

Xenobiology is an approach toward understanding life and its origin, while ignoring the material composition of the biological life on Earth (Popa 2004). As a discipline xenobiology establishes goals and means at the intersection between Biology, Artificial life and Astrobiology (Fig. 2). Xenobiology posits that some non-biological systems and some system manifestations that show some life-related properties (fire, growing crystals, fluid vortices, viruses, computer games, socio-economical system, art and religion), are essential for understanding life and its origin. Some of the postulates and lessons of xenobiology are useful guidelines in formulating a definition of life:

- The OEEL cannot be attributed to any singular event, molecule or gene. The OEEL is a matter of environmental conjecture and driving forces, and is the climax of a long series of changes. Henceforth, life should not be presented as an "out-of-context exceptionally unique phenomenon", but as a likely achievement of a dynamic system situated on a specific evolutionary path. Also, understanding life requires no esoteric explanation.
- The OEEL involved both causality and probability. No physical discontinuity existed between the physical drivers controlling the origin of life and the drivers of macroevolution, and the OEEL was punctuated by a number of phase transitions. Henceforth, life ought to be presented as a natural process, (rather than some Earth-

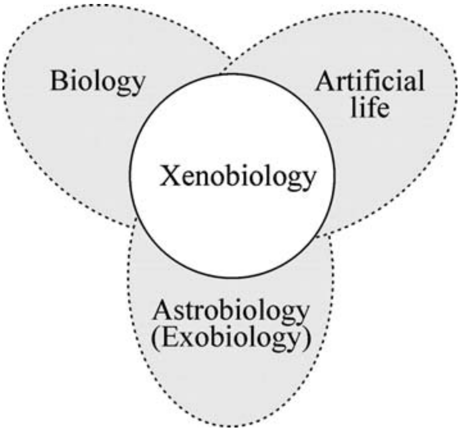

Fig. 2 Xenobiology is an interpretation about the nature and origin of life situated at the intersection between biology, astrobiology and artificial life

bound exception), and the most important phase transitions are useful markers to search for a non-life/life boundary.

- Although composition is important to circumscribe the environmental and adaptive limits of the living entities, when viewed at the perspective of an entire universe, the living state can be achieved from many possible compositions. Consequently, life's definition should invoke no particular compound or structure, but remain broad and non-Earth-centric.
- At the mechanism level, the OEEL is the outcome of increase in organization supported by a system-controlled dissipation of entropy; hence, as a natural phenomenon, the OEEL has to be explained at the intersection between disequilibrium thermodynamics and the theory of information. Still, none of the major facets of life (such as energy flow, organization, homeostasis, genetic information and evolution) is actually primordial; they all coevolved. Thus, ranking their primordiality has to include an appropriate deductive elimination.
- Although in order to be useful it has to remain specific and take advantage of measurable parameters, a definition of life should not become so analytic as to lose perspective of the big picture, such as ignoring the purpose-like nature of life and physical drivers of its origin.
- 'Living entities' and 'life' are different concepts, with distinct meanings and properties.

Fulfilling Requirements of a Definition for Life

Based on the above, an appropriate description of life should be on the side of mechanistic-reductionism (rather than vitalism or spiritualism), and in middle ground between holism and reductionism. At least two definitions are apparently needed; one for 'living entities' (as physical realities), and another for 'life' (as an abstract concept identifying a functional achievement in the behavior of living entities). As far as selecting a type of definition and its specific elements, I favor one that is parametric, non-Earth-centric, quantitative, and that identifies living entities with energy dissipative dynamic systems that have reached a specific evolutionary threshold. Because the maintenance of any out-of-equilibrium state by a system requires energy to alleviate the entropic effects of the 2nd law, the capacity for increased energy flux and entropy dissipation is implicit, and thus redundant in definitions using terms such as 'self-maintenance' or 'homeostasis'. If criteria are adequate, formulating a definition may simply require choosing the best combination of life-diagnostic factors from the numerous definitions that already exist. My preference goes for:

> "*Living entities are self-maintained systems, capable of adaptive evolution, individually, collectively or as a line of descend*".
> "*Being alive is the state of expressing these capabilities*".
> "*Life is a concept indicating that the capacity to express these attributes is either virtually or actually present*".

The fact that life evolved from lifeless systems may leave the impression that a clear objective boundary between non-living and alive systems may actually not exist. Yet, only some of the features that evolved during the OEEL were gradual changes. Others were remarkable phase transitions (Maynard-Smith and Szathmáry 1995). This view interprets the OEEL as an example of '*punctuated gradualism*' and aims to put the '*dilemma of endless gradualism*' to rest. The measurable consequences of these phase transitions can be used to identify an unambiguous boundary when the non-living became alive, while the underlying causes of these events can be used to study physical conditions pushing life into originating.

Four of the most notable phase transitions in the OEEL are:

- Implementation of “*reflexive activity*”: this includes any activity that connects an energy flux with the activity of maintaining the state of a system; this phase transition is likely to have created a mutually conditional relationship between “system organization” and “system functioning”, and made the organization controllable from within even in abiotic systems (Popa 2004);
- Reaching enough complexity level to allow most mechanisms of system control to be internalized (Kauffman 1993); hence allowing systems to evolve from expressing local or small scale feedback regulation (*i.e.* keeping system states under significant external control), toward homeostasis (*i.e.* the preservation of the system state being dominated by self-control);
- Evolution of automatons into informatons. Automatons are self-controlled systems based on analogical feed-back mechanisms; at best, these systems can only assume one state (or a very small number of related states), and have limited liberty to constrain these states. Informatons are self-controlled systems dominated by digital (genetic or cryptic) controlling mechanisms. The transition from automatons to informatons opened the gate toward sizable increase in the capacity of what is referred in the bibliography as “*meaningful information*” (Yockey 2002). Meaningful information is the information capacity of the organized part of the system. Digital information has the great benefit of compressibility, and thus can offer more liberties to control the state of a system. It may also be used to construct a virtual reality (*i.e.* a package of instructions regarding the different states a system may assume, and how to respond to various environmental contingencies). Eventually, each system space can harbor a collection of different states (one real and others that are virtual), the sum (and succession) of which is known in the field of “*qualitative dynamics*” as a “*quasi-state*”.
- The transition from pre-Darwinian evolution (*e.g.* molecular Darwinism, self-rewarding polymeric sequences, or selfish gene evolution) to genuine Darwinian (*i.e.* adaptive) evolution. This phase transition created a never-ending landscape of learnable functional contingencies within systems of finite space size, by expanding the variability of information across the variable time, and producing memory about past experiences.

Many scientists regard Darwinian evolution as the best diagnostic feature of living systems. Yet, as a phenomenon Darwinian evolution is not a physical cause but a consequence; the only cause of it that is internal to the system is genetic variability. Henceforth: “*The boundary in evolution where a non-living dynamic system becomes alive is marked by the dominance of genetic information (informaton) over analogical controllers (automaton), and the use of genetic information for adaptive evolution*”.

Conclusions

As any definition of something as complex as life the interpretation given here teaches something about the essence of being alive, yet may remain one of many other perspectives, rather than an absolute and ultimate truth. The goal any good definition of life should hope to achieve, is not to find an appeasing middle ground or overwhelming approval, but to cover most ground, not loose perspective of the general while not dismissing the particular, to be rooted on a balanced and evidence-supported vision of nature, be broad yet specific, a fair and quantitative interpretation of life in all its possible forms. We may never agree on a final definition of life, which could remain forever a matter of personal perspective. The measure of one's scientific maturity may actually be his/her latest "*definition of life*", and the acceptance that it is never ultimate.

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Orig Life Evol Biosph (2010) 40:191–193
DOI 10.1007/s11084-010-9199-9

DEFINING LIFE

Searching for an Exo-life in the Solar System

François Raulin

Received: 4 December 2008 / Accepted: 7 April 2009 /

Abstract How to define life? This very brief paper tries to bring some elements of answer to the question—essential for exobiology—with some chemical considerations.

Keywords Definition of life · Exobiology · Prebiotic chemistry · Replicating macromolecules

From Exobiology to the Origin of Life on Earth and the Definition of Life

Exobiology, the study of life in the universe, in particular the study of its origin(s), evolution and distribution in the whole universe, as well as the study of processes and structures related to life, is a very interdisciplinary field centered around the different aspects of LIFE. One the fundamental question of exobiology is how to define life. Indeed the quest for another life, one of the main goal of exobiology, implies to have available a definition of what is looked for. Similarly, the study of the origin of life on Earth, which is also part of exobiology, requires to be able to differentiate a non-living system from a living system, and to identify the level of chemical evolution at which a system is leaving the world of inanimate matter and can be considered as "living".

The question of the definition of life usually seems so obvious, that we are always surprised by the difficulty of the exercise when we try to answer the question. Identifying a living being is not always easy, even at the macroscopic level. Look at the ivy on the wall of a house. It seems immobile, as an inanimate object, far from the living world. Of course, if we change the time scale of observation and look at it for days, we will see that it moves slowly, which may be considered, as its very complex and regular structure, as a sign—but not an evidence—of life. And if we move from the macroscopic to the microscopic scale, then we see cells which move and duplicate: a strong indication of the presence of a living system.

Adapted from Raulin (2007).

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A Chemical Definition?

Much has already been said on how defining life and how difficult it is to answer the question. In fact, the definition of life given by a scientist is often directly linked to his own field. Life can be defined as the cell, for a cell biologist, as nucleic acid for a molecular biologist, as a system kept far from equilibrium by an energy flux for a thermodynamician. The prebiotic chemist Leslie Orgel (1975) called living systems CITROENS, not the name of the French car company, but as "Complex Information Transforming Reproducing Objects that Evolve by Natural Selection". Note that the scientists who are supposed to know the best the living systems, the biologists, usually do not try to give a definition of life: the 800 pages book "Le traité du vivant" by Jacques Ruffié (1982) does not include any.

The main difficulty of defining life lies in the absence of several elements in the set "Life". Indeed, so far we have only one example, one unit: the terrestrial life. Of course, there is an apparent wide diversity of life on Earth, and many differences between terrestrial living systems: at the macroscopic scale, in structure, morphology, appearance, but also in the processes involved: heterotrophic life, autotrophic life, oxygen producers, methanogens, etc… However, all living systems on Earth have common properties, at the macroscopic level and, first of all, at the molecular one. They are made of the same carbonaceous materials, built on the same molecular models, and use the same fundamental macromolecules, carriers of the genetic information (nucleic acids) and chemical and structural information (proteins).

Thus one approach which is often followed for defining life, is to list the common properties of all terrestrial living systems particularly those which seem more specific of the living world. I personally select three main properties from such an approach. The first is the level of complexity and the large quantity of information which is stored in a living system. The second is the property of replication, which can be done with changes, allowing the system to adapt to the constraints of its environment. And the third is this possibility of evolution, by natural selection, allowing the species to stay alive and to evolve, eventually with an increase of its complexity and level of stored information.

On the Earth, the set of these properties is specific of very complex chemical systems based on carbon chemistry and liquid water. They are the result of a long chemical evolution which preceded the biological one on Earth, about four billion years ago. A subtle chemical cooking, using carbon compounds, liquid water and energy, all present in the primitive environment of the Earth, yielding the first replicating macromolecules, and then the first living cell. All living forms present on Earth today have a common ancestor: "LUCA" the Last Common Universal Ancestor. But there was probably a pre-LUCA world, an RNA world, where RNA was playing simultaneously the roles of DNA and proteins. And before there was probably a pre-RNA world, with replicating macromolecules similar to present nucleic acids, but using simpler and more robust nucleotides. The later were the first living systems, a link between prebiotic chemistry and life. This chemical origin of life, could justify a chemical definition of life: life is a complex chemical system able to replicate and to evolve through a natural selection.

The Search for Life Elsewhere

The terrestrial scenario of the emergence of life and the resulting chemical definition of life can be used as a reference to search for life elsewhere. We may be too much limiting when looking for extraterrestrial life based on carbon chemistry and liquid water, but—at least—we know that life does exist with these ingredients, and we understand some of the processes which allowed life to emerge from chemical evolution and the associated planetary environmental conditions. We thus look for planetary bodies where liquid water and carbonaceous matter are or have been simultaneously present.

This is very likely the case of Venus and Mars, which were quite similar to the Earth more than three billion years ago. Since that time Venus has experienced a dramatic warming, due to a diverging greenhouse effect. The planet lost most of its water, and its surface is today too hot for living organisms and even for most organic compounds. If life arose on Venus, it has disappeared today, as well as its hypothetical traces. Mars also experienced paramount changes: it lost most of its atmosphere, and the surface liquid water bodies. However, a large fraction of Mars surface or close subsurface has not been renewed, and could still include traces of passed life. Moreover the present surface conditions are hostile but the subsurface may be habitable and may still house life. Life may also be present in the internal ocean of Europa, or even the deeper one of Titan, or in the internal liquid water reservoir of Enceladus. These hypothetical extraterrestrial lives are supposed to be based on carbon chemistry but may use organic replicative polymeric molecules different from those of present terrestrial life. Indeed, if life on Earth evolved from a pre-RNA world to an RNA world and the current DNA world, we may envisaged a similar prebiotic/primitive life evolution in these extraterrestrial environments, starting from an "Exo-pre-RNA world" which could even imply nucleotides different from the (still unknown) nucleotides of the Earth pre-RNA world. If life did not evolve as far as it did on Earth, and the extraterrestrial biological evolution did not passed this first level, we have to search for molecular traces of this Exo-pre-RNA chemical life on the potential extraterrestrial habitats.

Conversely, finding such traces, for instance on Mars, should provide essential information on the origin of life on Earth, by a comparative molecular biology approach. It should also help understanding the initial steps of biological evolution. And, with a second element in the set "Life", it should help us to define what is life.

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Orig Life Evol Biosph (2010) 40:195–202
DOI 10.1007/s11084-010-9200-7

DEFINING LIFE

What Possible Life Forms Could Exist on Other Planets: A Historical Overview

Florence Raulin Cerceau

Received: 6 February 2009 / Accepted: 12 May 2009 /

Abstract Speculations on living beings existing on other planets are found in many written works since the Frenchman Bernard de Fontenelle spoke to the *Marquise* about the inhabitants of the solar system in his *Entretiens sur la pluralité des mondes* (1686). It was an entertainment used to teach astronomy more than real considerations about the habitability of our solar system, but it opened the way to some reflections about the possible life forms on other planets. The nineteenth century took up this idea again in a context of planetary studies showing the similarities as well as the differences of the celestial bodies orbiting our Sun. Astronomers attempted to look deeper into the problem of habitability such as Richard Proctor or Camille Flammarion, also well-known for their fine talent in popular writings. While the Martian canals controversy was reaching its height, they imagined how the living forms dwelling in other planets could be. Nowadays, no complex exo-life is expected to have evolved in our solar system. However, the famous exobiologist Carl Sagan and later other scientists, formulated audacious ideas about other forms of life in the light of recent discoveries in planetology. Through these few examples, this paper underlines the originality of each author's suggestions and the evolution and contrast of ideas about the possible life forms in the universe.

Keywords Exotic life forms · Planets habitability · Plurality of worlds · Xenobiology

Introduction

As far back as Antiquity, philosophers and men of science (Anaximander, Lucretius) studied the subject of life on other worlds. Later, physicists and astronomers such as Huygens or Newton have dwelt upon the same fascinating theme. The history of the plurality of worlds can't forget the dissenting Dominican Giordano Bruno who was burnt at the stake in 1600 for, among other things, having supported the idea of infinity of worlds.

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The plurality of worlds became popular when heliocentrism supplanted geocentrism, since the Earth could be no more considered as the center of the universe. Other worlds could be regarded as inhabited and speculations could be put forward on the model of creatures living on our planet.

With the development of astronomical techniques of observation, astronomers took an active interest in a new concept named "habitability", dealing with the conditions of planetary environment combined with the possibilities for life to exist (Raulin Cerceau 2006). Comparisons were made between the other planets of the solar system and the Earth. It was the time of the first maps of Mars and the idea of a Martian life was expanding, from the canals controversy to the hypothesis of a Martian vegetation. Life was supposed to be possible nearly everywhere in the solar system. Limitations came from spectroscopy when astronomers realized that the atmospheric conditions—more or less suitable for life—on each planet were a determining factor. Of course, our age of space exploration led to a new definition of "habitability" and to reconsider the way to conceive the life forms likely to exist on various planetary environments.

Bernard le Bovier de Fontenelle's Plurality of Worlds

The French philosopher and writer Fontenelle (1657–1757) was famous for popularizing science and philosophy in a lively and elegant way. His *Entretiens sur la pluralité des mondes* (Conversations on the Plurality of Worlds) (Fontenelle 1686) offered an explanation of the Copernicus' heliocentric model of the universe in popular language. It was an immediate success. The book presented a series of conversations between a gallant philosopher (Fontenelle himself) and a Marchioness. The question about life on other worlds was raised and one of the main problems to be discussed was the following one: are the inhabitants of these planets like us or are they quite different?

Here is Fontenelle's view. The inhabitants of the solar system are very different from one planet to another. On the Moon, where there is no water, no cloud, no protection against the Sun, the *Selenites* live beneath the surface in deep wells that perhaps could be seen through our telescopes. But the Marchioness looks very doubtful about the humming and hawing coming from his pleasant teacher concerning the description of life on the Moon: "it's a lot of ignorance based on very little science", she asserts. She has the feeling that Fontenelle is going to populate all the planets and she is at once overwhelmed by the "unlimited number of inhabitants likely to be on all these planets". How can we imagine these planet dwellers, so various indeed if nature is opposed to repetitions? Fontenelle enjoys himself imagining that differences increase as the planets become more and more distant from the Sun.

For instance, on Venus, where heat and sunlight are more intense than on our planet, the climate conditions are very favorable to love affairs. The Venusians (named *Céladons* and *Silvandres*) are clever and lively but all are infertile, except a very little number of procreators and the Queen who is extremely prolific. Millions of children are descended from her and this fact is quite similar to the bee kingdom on the Earth. The Marchioness looks very amazed!

Fontenelle spends very little time on the case of Mars, a planet which seems to be very similar to the Earth. According to him, Mars has nothing special and it's not worth mentioning it.

Jupiter, Saturn and their moons seem to be more interesting and are worthy of being habitable. The inhabitants of Saturn, very far from the Sun, are very wise and phlegmatic. They never laugh and they need a whole day to answer the least question one asks them.

What about far away in the universe? All the stars are so many suns lighting up a world. Fontenelle's plurality of worlds seems finally to be so probable that the Marchioness appears disheartened by such a diversity of living beings…

Fontenelle offers to the reader a very broad plurality of living worlds. Its merit is to have been the first to popularize in a pleasant style the idea of diversity of life in the universe.

Camille Flammarion's Diversity of Beings

> *"Terrestrial life is not the type of other lives. An unlimited diversity reigns over the universe".* (Flammarion 1891)

The French astronomer Camille Flammarion (1842–1925) founded the Juvisy Observatory (France) in 1883 and the *Société Astronomique de France* (SAF) in 1887. He was a very prolific writer. Above all, he was well-known for his *Pluralité des Mondes habités* (Plurality of Inhabited Worlds) published in 1862, when he was only twenty years old. This book, translated in many languages, explained the conditions of habitability of earthlike celestial bodies discussed from the astronomical, physiological and philosophical viewpoint (Flammarion 1862). A comparative study of the planets of our solar system led him to state that "the Earth was, considering its physical characteristics, a planet of medium kind, without anything remarkable." Following this idea, life would have been present everywhere in the solar system. In the chapter entitled *Humanity in the Universe*, Flammarion studied the case of other *humanities* likely to exist on other worlds, while raising the question of anthropomorphism.

Most of Flammarion's successful books dealt with the question of planet habitability seen from the scientific angle. Sometimes however, Flammarion devoted himself to fiction. A few of his narratives were turned towards the description of imaginary worlds though punctuated with scientific observations and philosophical reflections. Such was the case in *Uranie* (Urania) published in 1891, in which the narrator met the statue of the heavenly Muse *Urania* and felt under her spell. It gave rise to a debate on the diversity of life in the universe, as follows.

One night, *Urania* took her admirer off towards a sidereal journey to visit a selection of other worlds filling the universe. She wanted to show him some of astronomical truths, invisible to anyone else on Earth. While approaching other suns, the narrator was captivated by the amazing diversity of the living beings populating the planetary systems. None of them had an earthly human form. The Muse behaved like a teacher of the plurality of worlds:

> *"To be in a condition to understand the infinite diversity displayed in the different phases of creation, it is necessary to cast aside all terrestrial feelings and ideas."*
> As examples of this diversity, the Muse asserted that *"life is earthly on the Earth, Martian on Mars, Saturnian on Saturn, Neptunian on Neptune,—that is to say, appropriate to each habitat."* (Flammarion 1891)

On one world, the *human beings* enjoyed the organic faculty of those insects endowing the capacity to sleep in a chrysalis state and to metamorphose themselves into winged butterflies. On another world, the inhabitants had a sixth sense which might be called magneto-telegraphic, by virtue of which the thought became outwardly manifest and could be read upon a feature which occupied the same place as a forehead. With such a magnificence of the spectacle, the Muse wanted to demonstrate that astronomy inevitably led to the study of universal and eternal life and that anthropomorphism had to be excluded from this context.

In this book, Flammarion made use of imagination to make the reader aware of the problem of life's diversity on other worlds. However, his aim was obviously scientific even if the narrative form was poetic. Contrary to most of his contemporaries, he dismissed any form of anthropomorphism when he described the other inhabitants of the universe. Other worlds meant other conditions of habitability and necessarily other forms of beings: "Beings are born on each world in close correlation with its physiological state" (Flammarion 1865). The plurality of worlds supported by Flammarion was then also a plurality of life forms.

Richard Proctor's Planetary Worlds

The British astronomer Richard A. Proctor (1837–1888) is best remembered for having produced one of the earliest maps of Mars in 1867 and for having written many popular books. Among them, *Other Worlds Than Ours, The Plurality of Worlds Studied Under The Light of Recent Scientific Researches*, published for the first time in 1870, immediately attracted attention not only of the scientific world but also of a very wide audience. Proctor used a poetical description to show what astronomy taught us about the Sun and its planets. He also discussed the probability that other worlds could be inhabited.

However, according to Proctor, difficulties arise when the discussion comes to the possible forms of life (Proctor 1870). Habitability would be the key argument able to answer this question, even if it is quite hard to know the conditions under which these beings could live. In Proctor's opinion, habitability could nevertheless be defined in considering analogy with the Earth, i.e. parameters resembling those existing upon our planet. Proctor also integrated the Darwinian theory of biological evolution into his reasoning in order to see if life would be possible in very exotic environments. He underlined that we have learned from Darwin's theory that slight differences between two regions of the Earth could lead to life forms differently adapted. Moreover, there are places on the Earth where species belonging to other regions would quickly perish. He deduced from what our planet taught us about evolution that other worlds could be the abode of living creatures but they would support life in other ways.

Proctor studied the habitability of every planet of the solar system. He suggested that the existence of organized forms of life depended on the conditions supposed to have an effect on the planetary surface, such as climate, seasons, atmosphere, geology, gravity. For instance, the physical conditions of Venus—size, location in the solar system, density, rotation, seasons, heat and light received from the Sun- seemed to show very close resemblances to the Earth. Arguments coming from analogy allowed him to conclude that this planet could be inhabited. Proctor assumed that Venus could be the abode of creatures as far advanced in the scale of evolution as any existing upon the Earth.

However, it clearly appeared that the best candidate to be the abode of life was Mars, "the miniature of our Earth" (Proctor 1870). Of course, at that time, among all the celestial bodies observed in our solar system, Mars had been examined more minutely and under more favorable circumstances than any object except the Moon. The surface of Mars was supposed to be covered by oceans and continents (the darker regions were assumed to be seas and the lighter parts continents). The Martian geography—or *areography*—was intensively studied and seemed to demonstrate the presence of a vast equatorial zone of continents, seas and straits: no doubt remained as to the interpretation of the features looking like land or water. Mars seemed to offer very strong analogies with the Earth and everything appeared possible regarding the forms of life likely to be on its surface. With seasons equivalent to terrestrial ones, water vapor in the atmosphere and forms of vegetation growing abundantly, Proctor's Martian world was perfectly fitted for complex life.

Proctor admitted also life on Jupiter. The giant planet might be inhabited by "the most favored races existing throughout the whole range of the solar system" (Proctor 1870), thanks to the very symmetry and perfection of the system which circles round it. It had been proposed at that time that the huge dimensions of Jupiter and its distance from the sun led to the conclusion that Jovians must be of the giant kind. Their eyes would have been in accordance with the weakness of the sunlight: less light, larger pupil and larger eyes, and then larger body. But Proctor did not support this hypothesis. Because of gravity and in order to make a *Jove-man* as active as our terrestrial counterpart, he underlined that we would have to give to these beings a size comparable to pygmies'one. However Proctor wanted to stay under the control of exact knowledge. He though we could only claim that "the beings of other worlds are very different from any we are acquainted with, without endeavoring to give shape and form to fancies that have no foundation in fact (Proctor 1870)."

Carl Sagan and Edwin Salpeter's Sinkers, Floaters and Hunters

> *"Nature is not obliged to follow our speculations. But if there are billions of inhabited worlds in the Milky Way Galaxy, perhaps there will be a few populated by the sinkers, floaters and hunters which our imaginations, tempered by the laws of physics and chemistry, have generated."* (Sagan 1980)

Since Flammarion or Proctor's time, the idea of plurality of worlds has significantly evolved. Exobiology was born in the 1960s as a result of the space exploration and its confrontation to the problem of biological contamination and planetary protection. In the meantime, the developments in genetics and molecular biology led to clarify the major components of the living systems. In this new context, planetary studies and advances in biology benefited to the speculations about life forms on other worlds. The historical debate continued with modern "pluralists" such as the American astronomer Carl Sagan (1934–1996) who contributed to the establishment of Exobiology as a credible science among institutional research programs.

Three years after the first fly-by of Jupiter by a space probe (Pioneer 10), Carl Sagan and Edwin Salpeter envisaged in 1976 the possibility of exotic biota in the upper regions of Jupiter's atmosphere (Sagan and Salpeter 1976). They proposed that other metabolic strategies such as chemoautotrophy or photoautotrophy would have to be employed by organisms present in the Jovian atmosphere. They discussed many aspects of a possible Jovian biology and deduced from the supposed composition of Jupiter's atmosphere (thought to present some similarities to the primitive terrestrial one) that organic molecules might be falling from the upper strata to the lower ones. They suggested that life could exist at a level of the Jovian atmosphere where descending organic molecules could be captured and used for energy (Schulze-Makuch and Irwin 2004). But how organisms could subsist in an environment so turbulent and, in the depths of the atmosphere, subjected to excessive heat?

Sagan and Salpeter made comparisons between ecology in the Jovian atmosphere and ecology in terrestrial oceans (food chain existing at three different levels in our oceans, i.e.

photosynthetic plankton, fishes, predators). The three hypothetical Jovian equivalents of these organisms were named “sinkers”, “floaters” and “hunters” by Sagan and Salpeter. They imagined that the sinkers could be carried by convection to cooler layers of the atmosphere and that the floaters could behave like our terrestrial hydrogen balloons: the deeper a floater is carried, the stronger is the buoyant force returning it to the higher, cooler, safer regions of the atmosphere (Sagan 1980). The bigger a floater is, the more efficient it will be. Finally they imagined very large floaters, a few kilometers size, likely to be eaten by hunters attracted by their organic composition.

Sagan admitted that one cannot know precisely what life would be like in such a place, but he and his colleague just wanted to see if, within the laws of physics and chemistry, a world of this sort could possibly be inhabited (Sagan 1980). If Sagan’s Jupiter world seems today a little bit eccentric, Sagan’s main fruitful initiative was to consolidate the search for life elsewhere, especially the starting up of the first Exobiology experiments on Mars.

Dirk Schulze-Makuch and Louis N. Irwin’s Xenobiology

Nowadays, Exobiology is looking for life-as-we-know-it or similar to it, based on carbon chemistry and liquid water as solvent, in outer space in every suited place accessible to our technology. Of course, this assumption is based on the fact that we would not be able to draw a reliable conclusion from experimental results no comparable to the ones biochemical or biological known on Earth. In spite of this, very few (theoretical) attempts to imagine alternative forms of life with other parameters than the terrestrial ones have been suggested by scientific authors since Exobiology was created.

The geologist Dirk Schulze-Makuch (Washington State University-USA) and the biologist Louis N. Irwin (University of Texas-USA) recently studied the possible pathways followed by life on other worlds, as alternatives to life-as-we-know-it on Earth (Schulze-Makuch and Irwin 2004). They questioned the possibility of a silicon-based life, a substitute to the carbon-based life known on our planet, a hypothesis previously suggested in the 1960s by V.A. Firsoff (Firsoff 1963, 1974). The best form offered by silicon for an exo-life would be a series of silicon hydrides, the silanes, consisting of Si-H and Si-Si single bonds. However the conditions required to make possible a silane-based life seem to be very restrictive: little or no water in liquid form, very low temperatures, little or no oxygen, suitable solvent such as methane, restricted abundance of carbon (Schulze-Makuch and Irwin 2004). According to these authors, the Saturnian moon Titan could meet these criteria, except the low abundance of carbon (but perhaps the cold and reducing conditions on Titan could lead silicon to have an advantage over carbon). However, no silane has been detected in Titan’s atmosphere, in spite of more than five years of closed observation of Titan.

Life-as-we-know-it requires water as solvent and the search for the origins of life and exo-life is usually focused on chemical reactions occurring in aqueous environments. However, if there is a consensus on the point that life positively needs a solvent, other solvents could replace water under environmental conditions very different from those existing on Earth. As soon as 1954, the British geneticist J.B.S. Haldane suggested the possibility of building proteins, nucleic acids and polypeptides using liquid ammonia as solvent. Firsoff studied other pathways for exo-life and compared synthesis reactions in water-based, ammonia-based and water-ammonia liquid mixtures (Firsoff 1963). More recently, F. Raulin suggested that “ammono” analogs of terrestrial biomolecules in which NH groups replaced oxygen atoms might yield an equally viable pseudo-biochemistry on Titan (Raulin et al. 1995; Raulin and Owen 2002 and refs included). As for Schulze-

Makuch and Irwin, they studied the physical and chemical properties of ammonia and the acceptable conditions allowing the formation of prebiotic macromolecules in such a solvent (Schulze-Makuch and Irwin 2004). Likewise, non-polar solvents like methane (CH_4) and ethane (C_2H_6) offering interesting properties are presently under consideration since the results of the Cassini-Huygens mission related to Titan (Brown et al. 2009). Ch. McKay and H.D. Smith have suggested a possible life in Titan's hydrocarbon lakes using as an energy source the conversion of hydrocarbons into methane (McKay and Smith 2005).

Besides this, Schulze-Makuch and Irwin have proposed that life could be possible in the Venusian atmosphere (Schulze-Makuch and Irwin 2002), a hypothesis previously put forward by Sagan (1961), Morowitz and Sagan (1967), and Grinspoon (1997). Sagan made the assumption that if life based upon carbon-hydrogen-oxygen-nitrogen chemistry ever developed in the early history of Venus, it must subsequently have evolved to subsurface or atmospheric ecological niches (although he was not convinced that life ever arose on Venus). Schulze-Makuch and Irwin suggested that during the time period when liquid water was stable on the surface of Venus, life may have evolved independently or been delivered by meteorites from Earth or Mars (Schulze-Makuch and Irwin 2002). Changes in environmental conditions could have led primitive organisms to be adapted to other habitats.

The clouds of Venus could have then offered an acceptable ecological niche to microorganisms. This idea could be supported by some parameters: the dense atmosphere of Venus could be more stable and more richly endowed with organic molecules; on this planet, H_2S might serve as nutrient source. However, the problem of this type of habitat is the question of a suitable solvent for the support of life-sustaining reactions. The clouds of Venus (at altitudes between 48 and 70 km) consist primarily of sulfuric acid droplets. In the lower cloud level, they contain large droplets similar in size to cloud droplets on Earth which could act as solvent and provide energetic reactions (involving H_2S and CO_2) sustaining a microbial life (Schulze-Makuch et al. 2004).

Schulze-Makuch and Irwin's Venusian putative world, attractive though it was, is not (yet) a part of the future Astrobiology programs intended for planetary exploration.

Conclusion

Until the beginning of space exploration, science and speculation were mixed together when philosophers or astronomers talked about life forms on other worlds. In spite of this, some assumptions have led to look more deeply into the problem of habitability on other worlds. Habitability has rapidly been perceived as the key question to understand what kind of living beings could be adapted to other planetary environments. It also led to a critical examination of the nature of life and the place of anthropomorphism in the way to imagine other "humanities".

Would human imagination be more fruitful than Nature? A question asked by Flammarion who thought that it was more probable that natural processes, thanks to flexibility in forces and variability in effects, could produce a larger variety of living beings than imagination. Nowadays, as claimed by Carl Sagan himself, imagination could still be needed to envisage some of the possibilities by which living systems could be manifested. Thus the uncertain limit between scientific parameters and conjectural thought seems to be very thin.

At the time of the first planetary explorations, Exobiology envisaged larger possibilities about the environmental niches supposed to be the best candidates to shelter hypothetical life forms. Xenobiology looked for alien forms in habitats more exotic than terrestrial-like planets. This concept was widely accepted until the 1980s. After this date however, NASA's Exo/

Astrobiology goals became more pragmatic and mainly focused on the search for life based on liquid water, with chemical or biological parameters closely linked to terrestrial ones.

Eventually, Exo/Astrobiology projects—at least in the solar system- are conceived with the idea that we know what and where to search for alien organisms. While becoming more and more concrete, this science studying the possible life forms on other worlds is mainly based on the terrestrial example: a view that could obviously be discussed and that is closely linked to our classification of "what is living" and "what is not". The definition of life could be then a crucial point to both specify and extend the field of possibilities leading to identify the experiments necessary to detect other life forms in the universe.

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Orig Life Evol Biosph (2010) 40:203–213
DOI 10.1007/s11084-010-9201-6

Defining Life or Bringing Biology to Life

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Received: 27 February 2009 / Accepted: 24 June 2009 /

Abstract In the present, post-genomic times, systemic or holistic approaches to living phenomena are compulsory to overcome the limits of traditional strategies, such as the methodological reductionism of molecular biology. In this paper, we propose that theoretical and philosophical efforts to define life also contribute to those integrative approaches, providing a global theoretical framework that may help to deal with or interpret the huge amount of data being collected by current high-throughput technologies, in this so-called 'omics' revolution. We claim that two fundamental notions can capture the core of the living, *(basic) autonomy* and *open-ended evolution*, and that only the complementary combination of these two theoretical constructs offers an adequate solution to the problem of defining the nature of life in specific enough—but also encompassing enough—terms. This tentative solution should also illuminate, in its most elementary version, the leading steps towards living beings on Earth.

Keywords Basic autonomy · Open-ended evolution · Life definition · Systems biology · Origin of life

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Introduction

As part of the living world, we naturally have an intuitive grasp on life. Such a primordial or inherent intuition usually tells us that living beings share some property, some basic dynamic attribute that is responsible for their forms and functions, that brings forward their robustness, their responsiveness or their capacity for growth and reproduction… Aristotle was the first philosopher that developed a rational concept of life, which he based on the abstract idea of an animated or active “form”. But this unified idea of the living was almost forgotten, in favour of a view of nature as three separated “kingdoms” (mineral, vegetable and animal), where the distinctive character and commonalities of all biological entities were partly lost. The achievement of a new unified concept of life, which encompassed a whole phenomenological world, separate from physical and chemical systems, required a long process of both theoretical and empirical research. In fact, the interpretation of life as a unitary phenomenon, as a common quality or type of organization that could group together a vast domain of natural systems is relatively modern.

Life, in this sense, can be regarded as ≪an invention of the 18th century≫, like philosopher and historian Foucault (1966) said; an invention consolidated during the 19th century, thanks to the development of microscopy and the experimental (chemistry-based) techniques that allowed the detection of some of the material and organizational features shared by such a variety of systems. This unitary conception, of course, received further support from evolutionary theories, which—also during the 19th century—provided evidence of the fact that all present organisms come from a common ancestor. The disproval of spontaneous generation of microorganisms in extant conditions and the Darwinian principle of divergence consolidated the picture of all living beings belonging to a huge family (historically related in a tree-like structure) since Haeckel’s time.

Nevertheless, even if it was the combination of results coming from experimental and evolutionary approaches in the—then emerging—field of biology what made possible to establish a first unitary notion of the living (as a separated domain with regard to the non-living world), each of those two approaches put forward a rather different way of conceiving the living phenomenon. They were actually representatives of two alternative traditions or methodologies of work in the general practice of biology: on the one hand, the physiological approach, focusing on how material parts can put and keep together an organism; and, on the other hand, the natural history approach, looking into shared morphologies or adaptations that phylogenetically connect the organisms. In terms of Mayr (1982), the first would be a biology of ‘proximate causes’ (functional biology) whereas the second (evolutionary biology) would deal with ‘ultimate causes’. Two of the major achievements in 20th century biology, the modern synthesis and the discovery of the fundamental molecular mechanisms responsible for the functioning of any living cell, corroborate the validity of that general portray up to our days.

Often we do not realize to what an extent our present view of life reflects an implicit cut, linked to this dual tradition in biology. But, in fact, living systems tend to be regarded from two distinct perspectives (Maynard Smith 1986): (i) as individual organisms in a continuous self-producing activity (metabolism) and in continuous interaction with their respective environments, including other organisms; and (ii) as populations, species or ecosystems following longer-term evolutionary pathways, making up different branches of the whole tree of life (the biosphere: past, present and future).

Our more ‘spontaneous’ view is certainly the first, because we regularly observe other systems, like us, acting, reacting, behaving in—more or less—unexpected ways, struggling for survival, dying, etc. under different environmental conditions. And we can extrapolate this to other cases, like microorganisms, further away from our personal experience, but which also hold together and respond—more or less—coherently to external stimuli. The second, instead, is more of a culturally—or scientifically-inherited conception: we have *become used to* interpreting life as a result of evolution (rather than the contrary). Dobzhansky's (1973) celebrated sentence «nothing makes sense in biology except in the light of evolution» is a good example to illustrate how far we see into living beings, now, through a scientific background that provides us with a more global and elaborate perspective, in which the features and behavior of individual organisms gain much deeper meaning. Thus, even though most of what we can directly *observe* in biology is still provided by living individual entities, what we *comprehend* involves other abstract categories that go beyond the time and space occupied by single organisms (e.g. genomes, phylogenetic histories, fitness landscapes, evolving ecologies, and so on), and has enabled a richer re-interpretation of our spontaneous conception.

Nevertheless, that primary tension between the physiological and evolutionary views remains there: who dares to say, at the beginning of the 21st century, that it has been resolved? Quite the contrary, it might be increasing right now. Modern biology was constructed on concepts like species, population, gene, adaptation, etc. (Keller 2000), supposed to be scientifically more sound or rigorous than the idea of organism, or functionally organized system (which had virtually disappeared from biological theory (Morange 2003)). However, by themselves, those apparently more scientific concepts have not carried enough explanatory power, at least under the strict light of molecular-reductionist approaches. As a result, we are witnessing (Etxeberria and Umerez 2006) a return to more holistic/organicist positions (like before molecular biology's revolution, with authors like Woodger, Needham, Waddington or Bertanlanffy),[1] but with more operational power this time.[2]

In this new context, where more and more scientists are becoming aware of the limits of traditional strategies in biology (*Science* special issue on systems biology 2002; Westerhoff and Palsson 2004; Moya et al. 2009), integration seems to be the key word. Integration both (i) as the necessary complement of analytic/decompositional (molecular-reductionist) methods and (ii) as the most adequate approach to reconcile different conceptions of the living and construct a new theoretical framework in which the tension between them is well-channeled: that is, productive. The aim of this paper is to show how efforts to define life may contribute to such an enterprise, somehow giving cohesion or bringing biological sciences together.

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[1] Actually, this new enthusiasm for a systemic view of life has even older roots. Around the end of the 18th century, Kant argued that an organism is a system comprised of a whole and parts, where the whole is the product of the parts, but the parts, in turn, depend upon the whole for their own proper functioning and existence. He understood a mechanism as an operational unit in which the parts exist for one another in the performance of a particular function (what today might be called the "working principles" of a machine). Instead, an organism would be a functional and a structural unity in which the parts exist for and by means of one another in the expression of a particular entity (or identity). Thus, the emergence of parts in an organism is a result of internal interactions, rather than the assembly of preexisting parts, as in a mechanism or in a machine.

[2] Operational power in terms of new methodologies of work (combining *in silico* and *in vitro* strategies) that make possible to study complex holistic systems, like living systems, in radically novel ways (Moreno et al. 2010). This is, in fact, reflected in the (re-)emergence of new research fields, like systems biology (Serrano 2007) or synthetic biology (Peretó and Català 2007).

Grasping the Core of Life: Autonomy in Evolution

If we accept that biology is at a historical crossroads, perhaps it would be wiser to keep a cautious attitude, wait for events and advances to happen, and in some ten or twenty years, once the synthetic approaches have delivered their first full results, or an extraterrestrial mission has found proof of alternative living forms, come back to the question of the nature of life. Actually, there are several good reasons (Cleland and Chyba 2002, 2007), to believe that things might not be ripe enough to try to enwrap life into a definition. In particular, we lack examples of life that do not depend on—or are not directly related with—life as we know it on planet Earth. Therefore, we cannot be sure to what extent ours is a representative case, and it will remain difficult to know with certainty how a general theory of biological phenomena should be constructed until those different examples (at least one) are synthesized in the lab or found elsewhere in the universe.

Having said that, we consider that the present situation in biology is not at all like the one (in 17th century chemistry) of trying to define—or find the true nature of—water when the molecular theory of matter had not yet been developed (Cleland and Chyba 2002). The amount of accurate scientific data and knowledge about living systems available these days is enormous. So much so that it is becoming really hard to assimilate. Of course, the discovery of some system or phenomenon that we unanimously agree to regard as an alternative form of life, when it comes (if it eventually comes), will have deep implications and change profoundly our worldviews and our conception of the living. But, meanwhile, efforts to put together explicitly, in a distilled way, what our day-to-day increasing biological knowledge is telling us about the actual concept of life should not be abandoned. Quite the contrary, they should be encouraged, as part of what biology is really lacking right now: more encompassing approaches that contribute to integrate the huge amounts of data and relevant information being continuously generated.

As we have argued in more detail elsewhere (Ruiz-Mirazo et al. 2004; Ruiz-Mirazo and Moreno 2010), current scientific knowledge gathered from the diversity of living entities on Earth, and the diversity of investigations carried out on them, enables us to start discerning what is necessary and what is contingent in their organization and, in that way, achieve eventually a more complete or congruent characterization of the phenomenon of life, in its minimal general sense.

From our perspective, the key concepts to grasp the fundamental core of the living phenomenon are 'basic autonomy' (Ruiz-Mirazo and Moreno 2004; Ruiz-Mirazo et al. 2004) and 'open-ended evolution' (Ruiz-Mirazo et al. 2004, 2008). Autonomy, in this minimal (bio-)chemical sense, covers the main properties shown by any living system at the individual level: (i) self-construction (i.e., the fact that life is continuously building, through cellular *metabolisms*, the components which are directly responsible for its behaviour) and (ii) functional action on/through the environment (i.e., the fact that organisms are *agents* that necessarily modify their boundary conditions in order to ensure their own maintenance as far-from-equilibrium, dissipative systems). Open-ended evolution, in turn, covers the properties of life as a collective-historical phenomenon, i.e., as an intricate network of interacting individuals (organisms), bringing about other similar individuals, and undergoing a long-term process of change which allows for an indefinite increase in their complexity (always under the constraints given by a finite physical-chemical world). But, more importantly, according to the way we define and use these concepts, a process of open-ended evolution could not occur except in the context of a population of autonomous systems; and, conversely, the unfolding of autonomous systems and their long-term maintenance depends on the fact that they get inserted in an open-ended evolutionary route.

Therefore, this general conception somehow tries to bring together the main results and theoretical legacy of those two traditions in biology to which we were referring previously. On those lines, life would be (Ruiz-Mirazo and Moreno 2010) ≪a *complex network of self-reproducing* autonomous *agents whose basic organization is instructed by material records generated through the* open-ended*, historical process in which that collective network evolves*≫, which comes basically from the realization that collective-evolutionary and individual-systemic aspects of the living are so deeply intertwined that cannot be set apart. Any living being that we know (so far) cannot exist but in the context of a global network of similar systems. This is clearly reflected in the fact that genetic components (which specify the metabolic machinery and organization of single biological entities), in order to be functional, have to be shaped through a process that involves a great amount of individual systems and also many consecutive generations, or reproductive steps.

Someone would object that this is an Earth-chauvinist conception, not audacious enough as a generalized or universal notion of the living. However, even if the concrete evolutionary pathway followed by biological systems on our planet were unique and full of contingent aspects, the *type* of evolutionary process that living organisms are engaged in (i.e., open-ended evolution) results from a set of general conditions with far-reaching consequences. In particular, as explained a bit further below, we claim that those conditions could actually be crucial for the robust, long-term sustainability of any living phenomenon as a whole (i.e., of any biosphere).

As argued in a previous paper (Ruiz-Mirazo et al. 2004), in comparative terms, our proposal is more restrictive, more demanding than the standard conception/definition of life (Joyce 1994): 'autonomy' in that sense requires—and provides—more than the bare 'self-maintenance' of a chemical network (especially when that self-maintenance is understood as the direct consequence of a molecular genetic program: see Luisi's (1998) criticism). Equally, the definition above leads to specific requirements for candidate systems that go beyond those coming from the autopoietic (Varela et al. 1974) or the chemoton criteria (Gánti 1975), for instance.

Furthermore, our definition also comprises a particular hypothesis to tackle the problem of the origins of living systems. There is no space here to go into a detailed account of it but, according to our general scheme, between chemical autocatalytic networks and full-fledged biological cells, a series of complex transitions in suprachemical but still 'infrabiological' systems (Szathmáry's *sensu*), both at the level of individual autonomous systems (from 'basic' to 'hereditary' autonomous systems) and at the level of their collective interactions (competitive/selective dynamics, primary food/recycling-webs, ecopoiesis), have to take place. The highly sophisticated molecular and organizational constraints required to implement genetic mechanisms (necessary for a fully open-ended evolution) would make these more plausible in the latest stages of the origins of life, whereas autonomous cellular systems (which would solve other crucial problems, like the control on matter-energy resources necessary to keep a far-from-equilibrium component-production system running) would play the bridging role. As conceptually proposed by Oparin (1924), the complete scheme of those transitions under primitive Earth conditions and the explanation on the articulation of the suprachemical/infrabiological subsystems (e.g. templates, boundaries, catalytic networks), would represent a first step towards a coherent narrative on the origin of life.

On the Importance of the Evolutionary Dimension

Therefore, during the process of life emergence, proto-metabolic autonomous systems would generate mechanisms that make possible the articulation of a network of systems beyond the ontogenic, individual organization and particular histories of each of them. This also involves radical changes in the way those proto-metabolisms are run, going from coupled autocatalytic cycles (probably already self-enclosed in a vesicle) to genetically-instructed, enzymatic pathways, interconnected and regulated in complex ways, within a cellular organization that controls very efficiently the flow of matter and energy through it. But, more importantly, it involves some reliable way to keep and transmit the complexity generated on the way (i.e., hereditary/reproductive mechanisms) so that the resulting population of systems can undergo, overall, a process of indefinite production (and, thus, potential increase) of complexity—throughout the onset of natural selection (de Duve 2005a,b).

The evolutionary dimension, then, brings with it a different, longer-term, time scale (a history beyond a particular organism's lifetime) and a different, much wider space scale (collections of similar, geographically spread systems, reproducing and—sooner or later—competing for limited resources: i.e., ecosystems), but has also crucial implications at the individual level, because it is a very special type of metabolic organization (what we call 'genetically-instructed metabolism') that can sustain all this. Of course, evolutionary aspects have to be regarded as 'capacities' in so far as concrete individual organisms are concerned. Gánti (1987) was very aware of this and that is why he proposed the distinction between 'absolute or actual' life criteria and 'potential' life criteria. The former apply to «every living being at every moment of its life without exception»; and the latter, «not being necessary criteria for the living state of the individual organisms, are indispensable with regard to the surviving of the living world» (Gánti 1987, p. 68–69).[3] And such a distinction also helps to overcome problems posed to life definitions by certain borderline cases (e.g.: resting seeds, a frozen tissue culture, sterile animals, etc.).

However, it should not be forgotten that evolution constitutes not only a capacity or a process of change but comprises a real complex collective network at work. Evolution is «the derivational history of organism-environment complexes», as Oyama (2002) has nicely expressed. In other words, organisms develop a complex biophysical environment around them that, in turn, plays a fundamental role in their individual development. As recently pointed out by Dupré and O'Malley (2009), life is the consequence of the intersection of lineage (evolution) and metabolism (individuals), and cooperation is as important as competition in the constitution of living matter. So we find here two entangled processes, happening at different rates and locations, but mutually dependent, since neither can be actually understood without referring to the other.

Therefore, it is the progressive construction of a complex meta—or supra-systemic organization what explains the creative potential of evolution. In contrast with the apparent fragility/instability of complex physico-chemical systems, life is able to steadily maintain much higher levels of structural and relational complexity. And this is achieved through the ongoing triggering of trans-generational changes in the organization of its individuals and their effects, as agents, on the environment. Actually, if it were not for the invention of evolution, nature most probably would not be able to overcome a preliminary threshold of complexity, below which—as von Neumann (1949) already anticipated—that complexity could not maintain itself or thrive. At a certain point in the process of origins of life evolution becomes, somehow, intrinsic to it: like a cyclist that can only keep the balance by pedaling,

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[3] Among the absolute life criteria Gánti includes: inherent unity and stability, metabolism, information-carrying subsystem and program control; and the potential criteria would be: growth and reproduction, capability of hereditary change and evolution, mortality.

life maintains itself, in the long run,[4] by its own evolving. As a result, biological systems, in that 'minimal core' sense, apart from being much more complex than inert systems, hold the potential—not the tendency, but the potential—to become ever more complex.

In those lines, it is quite remarkable that, starting from the first modes of selective evolution dynamics in the most simple 'proto-organisms', through the invention of systems with reliable heredity (hypothetical RNA world), origins of translation and genetic code (DNA-RNA-protein world), post-transcriptional editing processes, symbiosis, sex, development, and so on, the mechanisms of evolution have themselves evolved.[5] In other words, the genesis, through evolution, of new forms of organism and collective (meta-individual) organization has modified, in turn, the strategies of evolution. For sure, evolutionary changes do not just result from the operation of novel mechanisms, but also from the use of former ones, which are almost never completely erased. As a matter of fact, in the history of life that we know, increasingly complex organism types have developed by means of conserving and building upon the previous, simpler ones—i.e., through a process of 'tinkering' and making use of different functional-hereditary mechanisms. Nevertheless, the new evolutionary pathways tried by complex organisms are often "orthogonal" or incommensurable with regard to the old ones. So, even if there is a basic set of common mechanisms working along the whole evolutionary history of life on Earth, evolution is, itself, a process in evolution. This is the idea behind the notion of 'evolvability' (Conrad 1979; Kirschner and Gerhart 1998).

Consequently, when the problem of evolution is brought to the fore nowadays, it is quite different from what biologists had in mind a century ago. The main challenges faced these days are: (i) to determine additional evolutionary mechanisms, complementary (or perhaps, in some situations, alternative) to natural selection, showing what could be their relationship with the latter; and (ii) to understand the way in which main evolutionary transitions occur, i.e., precisely, to find out how the process of evolution itself changes in time. Nothing much, so far, is well-established about these issues, but, as we try to explain in the next section, autonomy is surely involved in both.

On the Importance of the Individual Dimension

Natural selection, genetic drift, gene flow, etc., the traditional mechanisms by which population genetics and evolutionary theory in general, up to date, have provided explanations for the great diversity of living forms on Earth, do not seem to be enough to account for many of their complex structural and dynamic features. Different authors, from different perspectives, have made this pretty clear over the years (D'Arcy Thomson 1992 [1917]; Wimsatt 1980; Buss 1987; Kauffman 1993; Salthe 1993; Goodwin 1994; Weber and Depew 1996; Gould 2002). Most of this critical work, together with recent advances in the field of 'evo-devo' (Raff 1996; Laubichler and Maienschein 2007), points

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[4] For shorter-term, individual system maintenance can be ensured through other strategies, more related to the question of autonomy (see next section).

[5] It is now widely accepted that the mechanisms of evolution (especially as far as phenotypic variation or plasticity is concerned, i.e., adaptability, generation of new functionalities, etc.) have themselves evolved (Conrad 1979; Wagner and Altenberg 1996; Kirschner and Gerhart 1998). The reason for these evolutionary changes seems to be the robustness and flexibility of the processes involved, which make them particularly suitable for complex development and physiology.

in the direction that evolutionary theory, in order to be fully explanatory, needs to merge, in a sort of 'new synthesis', with a theory of the organization of individual organisms.[6]

Traditionally, the phenomenological level of organisms had been privileged by evolutionary theory itself, as it was considered that they were the actual units of selection. The reasoning behind was that, in order for natural selection to be applicable there had to be reproducing entities with a high enough cohesion or functional integration, so that the effects of their interactions with the environment and mutual competition for resources determined the survival of each of them, separately taken. However, in more recent years, that classical view was strongly challenged by authors claiming that natural selection could be also working at other levels: e.g., below, at the level of biomolecules (the gene, in particular, Williams 1966; Dawkins 1976), or above, at the level of groups or species (Wynne-Edwards 1986; Gould and Eldredge 1988). In any case, the general outcome of that debate was the overall acceptance (except for the always present radical voices) that natural selection could be acting, in parallel, at multiple levels of the biological hierarchy (Brandon and Burian 1984; Sober and Wilson 1994)

Nevertheless, the question of whether organisms deserve a special place in biological theory is not confined to the problem of units of selection (Ruiz-Mirazo et al. 2000). Instead, we claim that the more significant connection between the idea of organism and its evolutionary dimension is related to the understanding of all major biological transitions in terms of changes in the type of organization of the systems involved.

Now, if the idea of organism turns out to be crucial to understand the living, we should ask what is its basic organizational structure, its minimal and common set of properties, from the most simple unicellular examples to the more complex ones. In its most elementary general expression, an organism is a collection of parts (molecules, cells, and so on) that put together an integrated whole, according to an arrangement that allows it to *act* in its environment in order to maintain and reproduce itself. Thus, the organization of organisms implies that the component parts and processes of the organized entity are not only responsible for producing each other and the whole, but get actually subjugated under the power of that entity to carry out global, highly coordinated, actions: i.e., to behave like an *agent*.

As we mentioned above, a minimal autonomous organization already involves these two deeply interconnected spheres that define an organism: the functional integration of processes and components making up the system, and the asymmetric interactive loop with the environment, which makes it actually an agent (in Kauffman's 2000, 2003, words: a system «acting on its own behalf»). Similarly to what we said about life at the collective level (which maintains itself because it keeps evolving), at the individual level organisms maintain themselves in so far the underlying biosynthetic machinery keeps running and interacting with the environment; otherwise they simply disintegrate. Living beings are, ultimately, chemical systems that do not stop synthesizing components, and with those components they synthesize some others, build up their cells and organs, repair informational/control devices, or produce the fuel (the type of energy required) to grow, move, capture nutrients and other energy resources, etc. All the functional actions they

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[6] Some of the authors we just mentioned would consider that a theory of self-organization could be enough for the purpose, even if its integration within the standard evolutionary framework remains problematic (Edelman and Denton 2007). Indeed, a lot of processes, shapes or functional patterns that we observe in biological systems (at many different phenomenological levels) reflect self-organizational principles, so their weight should not be underestimated. But, beyond self-organization, the constitution of an organism requires a more cohesive type of organization, as we try to explain below.

perform, inwards and outwards, cycle around that ongoing (self-building, self-repairing and self-reproducing) biochemical intra- and inter-cellular machinery.

Final Remarks

Biological knowledge is not hindered any more by our own difficulties or inability to obtain extensive data from living systems. Rather, the frontier of understanding seems to move away with the continuous accumulation of information in present days. Theoretical and philosophical efforts to define life may contribute to the holistic or synthetic approach necessary to make sense out of that huge amount of information being collected by the different fields and research traditions in biology. Our proposal, on those lines, is that the core of life can be captured by two fundamental constructs: autonomy and open-ended evolution. Although autonomy may initially appear as a high level concept (with too many extra-biological connotations), in its minimal sense ('basic autonomy') it provides just the necessary explanatory power to account for the complex material organization underlying any organism. After all, in the biological domain it is individual organisms that more obviously self-maintain, self-repair and reproduce, adapt and act functionally on their environment. Nevertheless, the wider historical and collective-evolutionary perspective must not be disregarded, or assumed to be of secondary importance. In fact, it is the complementary combination of the two perspectives that offers the adequate solution. A conception of autonomy that comprises both *functional integration* and *agency* is suggested as crucial to develop a theory of evolutionary transitions that may lead to ever more complex organisms, taking into account the increasingly elaborate and indirect relationships established between system and environment. Such an encompassing theoretical framework should also illuminate, in its most elementary version, the precursory steps of life on Earth.

Note Added in Proof Vasas et al. (2010) have recently explored the limits of evolution in self-sustaining autocatalytic networks. Their results support our view that the absence of a reliable system to keep and transmit complexity (i.e. the absence of genetic records) fundamentally constrains the potential to evolve. Nonetheless, self-sustaining, compartmentalized autocatalytic networks (or 'basic autonomous systems' in our terms) still represent the most plausible scenario as the initial bridge between self-organizing and living phenomena.

Acknowledgements The authors of this paper would like to thank the editors of the special issue for their assistance and, in particular, Michel Morange, who read a previous version of it and made several comments for improvement. Funding for this work was provided by grant IT-250-07 from the Basque Government, grants FFI2008-06348-C02-01, BFU2006-01951/BMC, BFU2005-03477/BMC from the Spanish Ministry of Science and Innovation (including FEDER funds) and grant FP7-KBBE-2007-212894 (TARPOL project) from the European Union. KRM holds a *Ramón y Cajal* Research Fellowship.

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Orig Life Evol Biosph (2010) 40:215–220
DOI 10.1007/s11084-010-9202-5

Origin of Life and Definition of Life, from Buffon to Oparin

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Received: 25 May 2009 / Accepted: 12 August 2009 /

Abstract Many theories on origin of life at the end of the XIXth century and the beginning of the XXth, generally use conceptions of life instead of explicit definitions of life. This paper presents ideas on the origin of life as studied by Buffon (1707–1788), Lamarck (1744–1829), Darwin (1809–1882), Huxley (1825–1895), Oparin (1894–1980) and Haldane (1892–1964). We show that their conceptions on the evolution of matter and life reveal their conceptions of life rather than their definitions of life.

Keywords Buffon · Darwin · Haldane · Huxley · Lamarck · Oparin

Introduction

One of the relevant characteristics of many theories on origin of life of the end of the XIXth century and the beginning of the XXth, is the fact that they generally use conceptions of life, instead of explicit definitions of life. In the works of Buffon, Lamarck, Darwin, Huxley, Oparin or Haldane, we can see how their thoughts about the origin of life are included in complete theories on the evolution of the Earth and the evolution of life and reveal their complex conceptions of life.

Buffon: Life as Organized Matter

In his *Histoire Naturelle* (1749), the French naturalist Buffon did not define life but gave a very complete theory of life based on important concepts. His concept of *organic molecules* is a central point of his theory. He claimed that these microscopic entities are alive and constitute all organisms in nature. Indeed, plants receive *organic molecules* in soil with

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their roots and animals receive *organic molecules* when eating plants and others animals. When they die, living organisms release their molecules in soil.

O*rganic molecules* are also central in the concept of species proposed by Buffon. He claims that during the generation of living organisms, *organic molecules* are responsible for the transmission of the *interior mold* that indicates the organization of each species*,* In this way, Buffon's species concept belongs to a very large view about life. According to him, species are not only collections of living beings at a specific moment, but also the perpetuation of these collections through time, generation after generation.

At the end of his career, in his *Epoques de la Nature*, Buffon introduced a new concept of time to describe the history of the Earth and thus abandoned cyclic time for sagittal time (Buffon 1778). In spite of this new historical view, he remained "fixist" and continued to claim that species do not change in other species, even if some reversible changes could occur in each species. In the first ages of the Earth, when temperature was sufficiently cold, organic molecules produced spontaneous generations and produced each species. Depending on his fixist conception, each new form belongs to a definitive *interior mold*.

Therefore in Buffon's view we can underline that life is a property of matter. Nature produces life and this production finds its place in sagittal history of the Earth.

Lamarck: Life as Transformable Organization (Adapted from Tirard 2006)

We have to distinguish two periods in Jean-Baptiste Lamarck's life. This French naturalist was indeed fixist until 1802. But from this date, he supported a new theory based on evolutionary processes retrospectively named transformism, which he defended all his life (Lamarck 1802). In the presentation of his theory, he gave a short definition of life: "Life is an order and a state of things in the parts of every body that possesses it. Life allows or makes possible the performance of organic movement, and, as long as it subsists, effectively counteracts death." (Lamarck 1802 p. 71). However, this is more in the mechanisms of the evolutionary process described by Lamarck that we can perceive his complete conception of life. Indeed, his definition makes sense when he continues saying that animalized matter is in a gelatinous state, between solid and liquid states, a state in which transformation of structure can occur. The first characteristic of living matter is the presence of "vital orgasm", a particular force that maintains molecules separated in spite of universal attraction. The causes of this "vital orgasm" are the uncontainable fluids: electricity and heat. The latter mainly maintains space between molecules.

At this stage during animalization, that is to say during spontaneous generation process, Lamarck considers that the gelatinous matter obtains capacity of contractility as simplest polyps. Following, transformations, induced by action of containable fluids, gases and water are the second step of the process. In the formation of polyps the second fluid is the most important. The continuous flow of water through the gelatinous matter induces the formation of a larger pore. That is the first expression of habit in the evolutionary process described by Lamarck. This pore, progressively enhanced, constitutes the first primitive digestive tube.

We claim that Lamarck's description of animalization of matter is a synthetic presentation of his entire evolutionist or transformist theory. This description indeed uses the fundamental concepts of his theory: fluids, habits and modification. With these concepts Lamarck can explain all transformations of organisms from animalcules to mammalians.

With Lamarck, we see that the definition of life depends on transformation processes that include spontaneous generation as well as species formation.

Darwin: Life as Historical Process

In *The Origin of Species* Darwin did not give any definition of life (Darwin 1859). His approach to life concerned proofs and causes of evolutionary processes of species, but he was not directly interested in any physical or chemical characterization of life. We will note that with Darwin, life becomes an historical process. However, he emphasized that no clues remain from the beginning of this process: there is no fossil of those very old times. In the last lines of his book, he asserts that "There is grandeur in this view of life, with its several powers, having been originally breathed into a new forms or into one; whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being evolved." (Darwin 1859, in 1985 pp. 459–460). However, in this book, he gave no more details about the origin of life. It was only in his famous letter to Hooker that he described a hypothetic primordial phenomenon: "It is often said that all the conditions for the first production of a living organism are now present, which could have been present. But if (and oh what a big if) we could conceive in some warm little pond with all sort of ammonia and phosphoric salts,—light, heat, electricity &c, present, that a protein compound was chemically formed, ready to undergo still more complex changes, at the present day such matter would be instantly devoured, or absorbed, which would not have been the case before living creatures were formed." (Darwin 1871 in Calvin 1969 p. 4).

These sentences are very informative about his conception of life. It seems that concerning the chemical nature of life, Darwin agreed with a protoplasmic concept based on albuminoidal substances and admitted that they could emerge spontaneously in nature. The most interesting point in his analysis is the impossibility for these substances to subsist: present life prevents emergence of new life. This constraint is a pure consequence of the historical nature of life. Darwin's conception of life could perhaps be summarized as to the importance he gave to historicity: life is an irreversible process and an event that can't be repeated, because life itself changes the condition of each step of the process.

Life and Evolution of Matter

During his entire career, Louis Pasteur (1822–1885) defended the idea of a barrier between inert and living matter (Pasteur 1994). At the beginning of the 1860s, his experiments and his debate with Félix Pouchet (1800–1872) showed that spontaneous generations do not exist and comforted his own conviction about limits of life. For most of the scientific community, these results led to definitively giving up the spontaneous generation theory. However thinking about a very simple and unique primitive ancestor still remained of a great difficulty. Indeed, as suggested by Darwin, there was a necessity to imagine a process between inanimate and living matter with a kind of progressive evolution of matter.

In this way, during the second part of the XIXth century, studies of the chemical and physical properties of living matter produced several central concepts. For example, in his famous text, *On the Physical Basis of Life*, Thomas Huxley identified life with its constitutive matter, i.e. the protoplasm. He described the link between elementary chemical constituents and complex organic matter present in the cell and claimed that life lies in the properties of the protoplasm (Huxley 1868).

This conception of life permitted the development of theories of evolutionary abiogenesis (Tirard 2005). These theories conceived progressive evolution of matter, which represented the first step of a global evolution of living beings. At the end of the XIXth and at the beginning of the XXth century, biologists or chemists (Haeckel 1879,1897, Chamberlin & Chamberlin 1908) formulated several short suggestions, but the most important hypotheses came in the 1920s.

Life in Evolution of the Earth

Alexander I. Oparin and John B. S. Haldane developed independently the first complete scenarios on the evolutionary abiogenesis in their texts respectively published in 1924 and 1929 (Oparin 1924, Haldane 1929). Oparin described the evolution of the Earth and the evolution of matter leading from mineral to organic matter and then to a form of primitive life. He claimed that in the primitive atmosphere and primitive oceans, organic matter became more and more complex. Oparin gave an interesting description of this evolution and said that appropriate conditions would arise “by chance” and “lead to the formation of a gel in a colloidal solution.” His description of the process was as follows:

> “The moment when the gel was precipitated or the first coagulum formed, marked an extremely important stage in the process of spontaneous generation of life. At this moment material, which had formerly been structureless, first acquired a structure and the transformation of organic compounds into an organic body took place. Not only this, but at the same time the body became an individual. […] With certain reservations we can even consider the first piece of organic slime, which came into being on the Earth, as being the first organism. In fact, it must have had many of those features, which we now consider characteristic of life. It was composed of organic substances, it had a definite and complicated structure which was completely characteristic of it. It had a considerable store of chemical energy enabling it to undergo further transformations. Finally, even if it could metabolize in the full sense of the word, it must certainly have had the ability to nourish itself, to absorb and assimilate substances to form its environment, for this is present in every organic gel.” (Oparin 1924 in Bernal 1967, p. 233).

Afterwards, some bits of gel progressively isolated themselves and the biggest incorporated the smaller.

Five years later, in 1929, Haldane proposed a very similar scenario concerning the primitive conditions on Earth, but with some particularities about primitive life. He used modern notions of biology, like “genes”, and invented the term “prebiotic soup” to designate the primitive ocean. Regarding his conception of life, the important fact is that he claimed that primitive chemical reactions can produce some “half living molecules”:

> “The first living or half-living things were probably large molecules synthesized under the influence of the Sun’s radiation, and only capable of reproduction in the particularly favorable medium in which they originated. Each presumably required a variety of highly specialized molecules before it could reproduce itself, and it depended on chance for a supply of them.”(Haldane 1929, in 1991 p.108)

In 1936, Oparin wrote a book about his theory, enriched with a lot of details and complements (Oparin 1936). He used the notion of coacervate experimentally described by Burgenberg de Jong (1932), which suggested a model of living entities. We could also present Alexandre Dauvillier’s photochemical conception of life or John D. Bernal’s hypothesis, which suggests that primitive chemical reactions happened on clays as support and catalyst.

All these scenarios include life in a large evolutionary process and explore some ways of chemical complexification leading to primitive living forms comparable to the present ones. Theses scenarios are in fact concepts of life, which depend on characteristics observed in present life and on hypothetic primitive conditions too.

Conclusion: Reconstructing the Past or Defining Life?

Undoubtedly, the puzzle of the origin of life results in a problem about the past of our planet, which contains an important historical dimension. This historical status of the problem of the origin of life was emphasized by Haldane in 1929: "The question at issue is 'How did the first such system on this planet originate?'. This is a historical problem to which I have given a very tentative answer on the not unreasonable hypothesis that a thousand million years ago matter obeyed the same laws that it does today."

In the same way, Bernal in 1951 wrote that the problem of the origin of life was "at the same time historical and physiological."

Is the definition of life an absolute necessity for scientist working on origin of life? It seems that it is possible to explore past and hypothetical processes of the emergence of life with the help of theoretical and experimental ways without any circumscribed definition of life. However, a lot of approaches of the origin of life seem included in wide conceptions of life, which depend on the historicity of life.

In 1924, Oparin concluded his famous work with these words:

> "What we do not know today we shall know tomorrow. A whole army of biologists is studying the structure and organization of living matter, while a no less number of physicist and chemists are daily revealing to us new properties of dead things. Like two parties of workers boring from the two opposite ends of a tunnel, they are working towards the same goals. The work has already gone a long way and very, very soon the last barriers between the living and the dead will crumble under the attack of patient work and powerful scientific thought."

Therefore, Oparin described in this quotation the gap in which the problem of the origin of life remains. Necessity of experiments is obvious, but because of complexity and historicity, the experimental exploration of this gap needs an accurate point of departure, precise primitive conditions, and an orientation, i.e. the present life. Scientists can perhaps hope to find a definition of life somewhere in this tunnel.

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Orig Life Evol Biosph (2010) 40:221–229
DOI 10.1007/s11084-010-9203-4

What is Life? Defining Life in the Context of Emergent Complexity

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Received: 25 October 2008 / Accepted: 7 April 2009 /

Abstract Erwin Schrödinger defined life not only as a “self-reproducing” aperiodic crystal of DNA coding for proteins but within the context of living entities increasing their order by dissipating matter/energy gradients to maintain themselves away from equilibirium. Since then most definitions of life have focused on the former. But living cells do more than replicate their DNA. Cells also have membrane barriers across which metabolites must move, *via* which energy transduction as well as information processing occurs, and within which metabolic transformation occurs. An approach of complex systems dynamics, including nonequilibrium thermodynamics, may provide a more robust approach for defining life than a “naked replicator” at the origin of life. The crucial issue becomes the process of emergence of life from pre-biotic chemistry, concomitant with the emergence of function, information, and semiosis. Living entities can be viewed as bounded, informed autocatalytic cycles feeding off matter/energy gradients, exhibiting agency, capable of growth, reproduction, and evolution. Understanding how life might have emerged should sharpen our definition of what life is.

Keywords Complex systems dynamics · Defining life · Emergence · Nonequilibrium thermodynamic · Origin of life

Introduction

The attempt to define life goes back to the ancient Greeks. For Democritean philosophers the question of what is life and consciousness was problematic since living entities exhibited phenomena not seen in non-living matter. In contrast, for Aristotle the persistence of living beings in the face of the apparent flux of the material world was an irreducible and paradigmatic phenomenon (Smith 1976). René Descartes radically reconceptualized the “problem of life” by his dualism of matter and mind; the definition of life was to be sought in the mechanistic

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interactions of matter. There was a vitalist reaction to such a mechanistic programme during the nineteenth and early twentieth centuries, ranging in approach from Romantic anti-materialists through chemists seeking a new type of Newtonian force (a “vital force”) to materialists with an intuition of the importance of the organized whole for living phenomena.

At the dawn of the twentieth century Sir Frederick Gowland Hopkins, the first Professor of Biochemistry at Cambridge University rejected the naïve reductionism of the mechanists as well as the crypto-vitalism of those biologists who saw protoplasm as irreducible. In his address to the British Association for the Advancement of Science given in 1913, Hopkins articulated the conceptual foundations of a molecular approach to life in which he viewed the cell as a chemical machine whose transformations were catalyzed and regulated by enzymes, obeying the laws of thermodynamics, but having *organized* molecular structures and functions. “The living cell is not a mass of matter composed of a congregation of like molecules, but a highly differentiated system: the cell, in the modern phraseology of physical chemistry, is a system of co-existing phases of different constitutions” (Hopkins 1913, [1949] p. 151). He went on to conclude that “Life is a property of the cell as a whole, because it depends upon the organization of processes” (Hopkins 1913 [1949] p. 152).

The physiologist J.A. Haldane argued that such organization as seen in living systems was disanalogous to the order seen in physical and chemical systems, though he rejected the notion of a vital force as being just another form of reductionism (Haldane 1931). At about the same time Lancelot Hogben argued that the reductionist approach that the biochemists were developing was the way to make progress in understanding the nature of life (Hogben 1930). For Hogben science did not have to be complete but was a work in progress and he had faith that in time conceptual tools might be developed to deal with the organized complexity of living beings. J. H. Woodger argued for the need to develop a theory of biological organization, stating that “by cell I shall understand a certain type of biological organization, not a concrete entity” (Woodger 1929 p. 296, emphasis in original). For Woodger living organisms could be scientifically defined but he argued that defining life was outside of the limits of science as was the problem of the origin of life. N.W. Pirie, a protégé of Hopkins argued in 1937 that life could not be adequately defined by a list of qualities, nor even of processes (Pirie 1937). The necessary theoretical tools for complexity, information and organization were not in place at this time.

It was at this stage of the discourse that Erwin Schrödinger attempted to answer the question “What is life?” in his lectures at the Dublin Institute for Advanced Studies in 1943. His answer was formulated in specific molecular terms (Schrödinger 1944). The first issue he considered was how order could produce order when statistical ensembles of molecules quickly become disordered. He proposed that the molecules of heredity were ‘aperiodic solids’ which had embedded in their structure a ‘miniature code.’ The second issue was how order could be produced from disorder. He postulated that a cell could produce internal order, or ‘negentropy’ if its processes could produce greater disorder in its environment. That is, a cell must operate away from thermodynamic equilibrium. Schrödinger then tied these two aspects together by claiming that an organism was able to concentrate a “stream of order” on itself in its organization and in the ‘aperiodic solids’ or chromosome molecules, thereby escaping decay into atomic chaos.

Defining Life in Terms of Its Emergence as a Complex System

During this same period speculations abounded about the possibility of scientific research on the origin of life. It was the demonstration by Stanley Miller and Harold Urey that some amino acids could be synthesized under what were then considered to be plausible pre-biotic conditions that scientific exploration of the origin of life began (Miller 1953; Bada and Lazcano 2004; Bada 2004; Johnson et al. 2008). Attempts to understand the origin of life depend upon having a definition of life. Thus there is an explicit relationship of attempts to model the origin of life and to define it (for recent reviews see Luisi 2006 and Weber 2007). Much origin of life research has assumed, following Miller and Urey, that the emergence proteins and their catalytic versatility were the crucial step toward life (Fox 1965, 1988; Wicken 1987; Kumar and Oliver 2002; Leman et al. 2004). It has been shown that random-sequence proteins have a high probability of assuming a preferred tertiary structure and can exhibit some weak catalytic activity even as it has been shown that many different amino acid sequences can code for proteins with essentially the same structure and activity (Shakhnovich and Gutin 1990). Thus a highly specific informational content is not necessary for a polypeptide sequence to serve as a catalyst. But recently more emphasis has been on the pre-biotic synthesis of nucleotides and RNA with a concomitant rise of molecular replication as the defining event for life to arise (Woese 1967; Orgel 1968, 1992; Cech 1986, 1987a, b; Joyce and Orgel 1993; Gesteland and Atkins 1993). Others have stressed the importance of membrane-like structures produced by amphiphiilic molecules derived from carbonaceous meteors striking the early earth thereby providing phase separation and possibilities of energy transduction by chemiosmotic mechanisms (Deamer and Pashley 1989; Deamer 1992; Chen and Szostak 2004). This latter is important as it provides one specific mechanism by which energy gradients could be coupled to complexifying pre-biotic systems to move the systems away from chemical equilibrium.

Such considerations point toward several important features of the process of the emergence of life. There needs to be an energy source (gradient) and a mechanism of energy capture such that the entropy of the system decreases even as the entropy of the system + environment increases. Abiotic processes initially need to produce the component molecules, but these molecules subsequently are produced by autocatalytic networks that emerge, whether they be composed of polypeptides, polynucleotide, or a mixture of both. Also there needs to be an osmotic barrier that defines the inside and environment of the living system while providing matter/energy coupling across it. Whether these arise sequentially or simultaneously, these factors must all be considered when attempting to define any putative scenario for the emergence of life. Such transitional proto-cells need some manner of reproduction and information processing, though these need not be identical with those mechanisms seen in present-day organisms (Kauffman 1993).

As has been explored through computer simulations and some laboratory experiments, autocatalytic cycles can complexify over time to achieve a condition of catalytic closure in which all components of a complex chemical system, including the catalysts, are produced by at least one reaction of the network (Kauffman 1993, 2000, 2008; Lee et al. 1997). Such complexification occurs when matter/energy fluxes exceed certain critical values, resulting in the emergence of macroscopic structures that more effectively dissipate energy (entropy) than microscopic processes (Wicken 1987). Hurricanes, Benard cells, the Belousov-Zhabotinskii reaction, living cells, and ecosystems are all examples of dissipative structures that arise by processes of self—(or more accurately system-) organization (Morowitz 1968, 1992, 2002; Tyson 1976; Peacocke 1983; Swenson 1989, 2000; Casti 1994; Sole and Goodwin 2000; Harold 2001; Schneider and Sagan 2005). Many lines of empirical evidence demonstrate that self-organization is a phenomenon, and not just a mathematical concept, of cellular organization (Misteli 2001). Patterns of cellular and subcellular order and complexity reflect constraints of chemistry and natural laws, including those being studied by complex systems dynamics (Kauffman 1993, 2000, 2008; Denton et al. 2002).

In sufficiently complex systems, self-organization and selection are in fact mutually entailing processes that work together in a parallel and distributive manner to produce emergent macroscopic organization and phenomena (Kauffman 1993; Depew and Weber 1995; Weber and Depew 1996; Weber and Deacon 2000). With complexity, arising either by self-organization in natural systems or by design in artifactual systems, comes redundancy and parallelism that can give minimal functionality of the whole, even if component parts are imperfect; with minimal functionality comes a selective pressure for improved components over time (Challet and Johnson 2002; Weber and Depew 2004). In such complex systems the whole is defined by closure conditions; for emergent living systems physical closure was provided by the osmotic barrier and chemical closure by the catalytic closure. Stuart Kauffman has proposed that an ensemble of polypeptides, such as that proposed by Jeffrey Wicken, could roughly cover the 'catalytic task space' needed for a catalytically closed system, albeit with weak specificity or efficiency; through processes of self-organization and selection such ensembles of protein and/or RNA catalysts would be expected to gain in specificity and efficiency even as they begin to exhibit minimal aspects of agency to move up or orient toward nutrient gradients or down or orient away from gradients of toxins (Kauffman 2000, 2004). Such autonomous agency would be expected to be an emergent property of protocellular systems as well as, of course, present-day living systems (Kauffman 2000, 2004).

Three kinds of emergence can be distinguished in complex systems (Weber and Deacon 2000; Deacon 2003). First-order emergence is just the synchronic supervenience of the macroscopic on the microscopic, as in wave propagation in a fluid; second-order emergence is diachronic self-organization of energy dissipative systems, such as a snowflake or the Belousov-Zhabotinskii reaction; third-order emergence is diachronic with biasing across iterations or generations, as in biological development and evolution. This latter can be characterized as 'self-referential self-organization' in which semiosis emerges. "So life, even in its simplest forms, is third-order emergent. This is why its products cannot be fully understood apart from either historical or functional concerns" (Deacon 2003, p. 300). We might then imagine the emergence of life as a transition from second-order emergence to third-order emergence in a complex chemical system under the right initial and boundary conditions.

Developing a Research Programme for the Emergence of Life

As befits a problem of complex nature, a number of parallel lines of research are being pursued in the quest to develop a theoretical understanding of the possible routes for the emergence of living systems. One main avenue or research explores the role of catalytic polymers (protein and/or nucleic acid) in autocatalytic cycles coupled with thermodynamic work cycles (Kauffman 2000, 2008; Deacon 2006). Another pursues a proto-cell first assumption and explores the minimum requirements for cellular life (Morowitz et al. 1991; Morowitz 1992; Luisi 2006). Of course many researchers are continuing to pursue the RNA-world assumption (Gesteland and Atkins 1993). Also, possible geochemical processes that might have played an important role in the transition from abiotic chemistry to proto-cellular chemistry are being studied (Martin and Russell 2003; Russell 2007).

Kauffman's original model for the origin of life involved describing protein sequence space with his NK model (N being the particular amino acids in a sequence and K the interactions between them) (Kauffman 1993). Such a sequence space was then mapped onto a catalytic task space in which each reaction can be catalyzed in some degree by a relatively large sphere of sequences. Such ensembles of catalytic polymers participate in autocatalytic cycles and at some point the ensemble of such activities becomes sufficiently complex for catalytic closure to occur. Such ensembles, whether free standing or encapsulated in vesicles, can grow and reproduce even in the absence of central templates coding for the catalysts. However, when templates emerged, they would stabilize information about more efficient catalysts. Originally Kauffman assumed that such a prebiotic system would be out of equilibrium but later was more specific about the need for an energy source and actual thermodynamic work to be done (Kauffman 1993, 2000). Terrence Deacon has proposed an "autocell" model in which some proteins provide encapsulation and others catalyze the formation of proteins and their encapsulation, although how the system is driven thermodynamically is not directly addressed (Deacon 2006). Laboratory exploration of these scenarios is underway (Kauffman personal communication; Deacon personal communication). Kauffman argues that the origin of life was not an improbable event, but "lawlike and governed by new principles of self-organization in complex webs of catalysts. Such a view has many implications. Among them, the template-replicating properties of DNA and RNA are not essential to life itself (although these properties are now essential to *our* life). The fundamental order lies deeper, the routes to life are broader" (Kauffman 1993, p.xvi, emphasis in original).

David Deamer has argued for a protocell-first model in which amphiphilic molecules, perhaps derived from carbonaceaous condrites, form the starting point for the emergence of life:

> Amphiphiles -> protocells -> directed synthesis -> prokaryote. At the protocell stage there would be a direct coupling with an energy source such that the protocell is viewed as a dissipative structure:
>
> Protocell + nutrients + energy -> protocells + waste + heat (entropy) (see summary in Deamer et al. 2002 and in Morowitz 1992).

In this view the protocells can grow and reproduce by exploiting nutrient and energy gradients while producing entropy even before a directed synthetic system is established. In Harold Morowitz's view, it is the emergence of both of Schrödinger's criteria (molecular coding and nonequilibrium thermodynamics) that yields true life (Morowitz 1992). However, the thermodynamic requirement takes precedence in the process of emergence of life for the conditions for the emergence of coding macromolecules. The putative amphiphilic-vesicle precursor to protocells can show autocatalytic self-replication (Bachmann et al. 1992; Luisi 2006). Plausible membranes for protocells composed of non-phospholipid amphiphiles in which polynucleotides can replicate have been shown to allow passage of nucleotides across their osmotic barrier during high-temperature excursions that are then incorporated into the growing nucleotide chain (Deamer 2008; Mansy et al. 2008; Mansy and Szostak 2008). Further, amphiphilic vesicles derived from meteorites, when supplemented with polycyclic hydrocarbons, also from meteorites, pump protons in the presence of light thus demonstrating the fundamental method of energy coupling (chemiosmotic) seen in all cells (Mitchell 1961; Deamer 1992; Harold 2001; Prebble and Weber 2003).

Such amphiphilic vesicles could be the "cradle" in which true life emerged, with these protomembranes being replaced by the phospholipids of true cells after such phospholipids were synthesized by photochemical reactions or by the proto-metabolism of the protocells. But another possibility is that iron-sulfur membranes that could be produced in the primitive oceans of early earth when hot, reduced-alkaline waters produced by thermal vents mixed with cooler, more oxidized and acidic waters containing carbon dioxide and iron-sulfur compounds from above (Martin and Russell 2003; Russell 2007). Such membranous structures form in the laboratory and there is evidence they have formed in the past in nature. Such iron-sulfur membranes are naturally acidic on the outside but alkaline inside, creating a chemiosmotic proton gradient. Further, such membranes have the catalytic and chemical potential for oxidation-reduction reactions that have been proposed as important in the emergence of life (Wächtershäuser 1988a, b, 1992, 1997). Possibly this was the cradle of life in which later acquisition of phospholipids allowed living systems to escape this cradle and colonize the planet.

Pier Luigi Luisi has developed a research programme exploring the properties of random polypeptides and polyribonucleotides, as well as determining the requirements for a minimal cell. He and his colleagues have generated 10exp9 random polypeptide sequences of the 10exp65 possible for a 50-mer peptide. About a quarter fold into globular structures, some of which may have weak catalytic activity (for a review of this work see Luisi 2006 and references therein). A possible scenario for the emergence of life in the Luisi programme would include selection among sequences for solubility and physical stability as well as their contribution via their catalytic efficiencies to the autocatalytic networks and nonequilibrium thermodynamic cycles in which they are embedded.

Implications for the Emergence and Definition of Life

Though thermodynamics provides the driving force for self-organization in complex chemical systems, it is the kinetic mechanisms that afford the pathways of emergence. In the transition to living systems there is a shift to an extreme expression of kinetic control in which thermodynamic requirements play a supporting rather than a directing role. Replication is an instance of this extreme kinetic control. From this emerges the teleonomic character of living entities. Non-living chemical reactions, driven by thermodynamics, explore the state space in an ergodic fashion; in contrast, living systems explore a combinatorially large space of possibilities through evolutionary processes.

Ensembles of protocells, either as free-standing vesicles or as iron-sulfur membranous compartments, could be viewed as the "cradle" for the emergence of life in which complexification of autocatalytic sets of polymers give rise to metabolism. In such ensembles mutual stabilization of 'generic' proteins and nucleic acids over time could lead to the emergence of molecular specialization of coding templates and catalysts. Thus weakly heritable analogic information about protometabolism in proteins could become stabilized as digital information in nucleic acids, resulting in a chemical selection for enhanced efficiency of autocatalytic cycles of energy use and entropic dissipation. There would be an enormous selective advantage (physical and chemical) for those entities that could "remember" information that enhanced autocatalytic activity and dissipative efficiency by encoding it in RNA and later DNA. Thus natural selection of the reproductively fit would be emergent from the chemical selection of the efficient (Depew and Weber 1995; Weber and Depew 1996; Weber 2007).

In complex systems, such as those that gave rise to living systems, not only is the whole defined by closure conditions (physical and catalytic) but there is redundancy and parallelism. Thus, even weakly incipient functional patterns of structure and interaction can persist due to greater stability and/or efficiency. With functionality comes pressure for improved structures/stability/efficiency, through an on-going process of selection and self-organization. Therefore, in thinking about the origin of life we should not expect one function to be perfected, say replication, before others appear. Rather, we should expect that there was an inherent holism in the process by which cellular life arose. Rather than expect that we can develop a single narrative trajectory for the emergence of life we should explore all possible routes of chemistry and proto-biochemistry to develop a range of plausible scenarios, as well as keeping in view the range of phenomena associated with living systems. Further, we should not conflate natural and artifactual systems but anchor our research on the emergence of life and natural selection in the natural laws and processes of thermodynamics and kinetics, thereby driving a conceptual wedge between natural organization and design.

If there is not grandeur in this view defining life and its emergence, at least there is reasonable hope for progress, through application of the tools of experimental science, computer simulations and complex systems dynamics, towards developing a more general theory of emergence. Such an approach holds the promise of developing a more general biology, one that is not constrained by what we know of the specific chemistry of life on earth. Is there a fourth law of thermodynamics awaiting discovery that favors the emergence of life as described by autocatalytic cycles capable of reproduction and evolution, performing thermodynamic work cycles away from equilibrium, and exhibiting autonomous agency? If the roads to life are indeed deep and broad, might they be even deeper and broader than we anticipate. For now, attempting to understand the emergence of life on earth is a daunting project, but we should not lose sight of broader issues raised by A-life and exobiology and seek to define life in its essentials a broadly as possible (Weber 2007, 2008). Such a definition should include more than macromolecular replication but reproduction more generally within a phase-separated space and encompass not only thermodynamic necessity and kinetic chance but also the complex systems' characteristics of evolvability and agency.

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Orig Life Evol Biosph (2010) 40:231–244
DOI 10.1007/s11084-010-9204-3

Defining Life: Synthesis and Conclusions

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Received: 16 August 2009 / Accepted: 5 September 2009 /

Abstract The first part of the paper offers philosophical landmarks on the general issue of defining life. §1 defends that the recognition of "life" has always been and remains primarily an intuitive process, for the scientist as for the layperson. However we should not expect, then, to be able to draw a *definition* from this original experience, because our cognitive apparatus has not been primarily designed for this. §2 is about definitions in general. Two kinds of definition should be carefully distinguished: lexical definitions (based upon current uses of a word), and stipulative or legislative definitions, which deliberately assign a meaning to a word, for the purpose of clarifying scientific or philosophical arguments. The present volume provides examples of these two kinds of definitions. §3 examines three traditional philosophical definitions of life, all of which have been elaborated prior to the emergence of biology as a specific scientific discipline: life as animation (Aristotle), life as mechanism, and life as organization (Kant). All three concepts constitute a common heritage that structures in depth a good deal of our cultural intuitions and vocabulary any time we try to think about "life". The present volume offers examples of these three concepts in contemporary scientific discourse. The second part of the paper proposes a synthesis of the major debates developed in this volume. Three major questions have been discussed. A first issue (§4) is whether we should define life or not, and why. Most authors are skeptical about the possibility of defining life in a strong way, although all admit that criteria are useful in contexts such as exobiology, artificial life and the origins of life. §5 examines the possible kinds of definitions of life presented in the volume. Those authors who have explicitly defended that a definition of life is needed, can be classified into two categories. The first category (or standard view) refers to two conditions: individual self-maintenance and the open-ended evolution of a collection of similar entities. The other category refuse to include reproduction and evolution, and take a sort of psychic view of the living. §6 examines the relationship between the question of the definition of life and that of the origins of life. There is a close parallel between the general conceptions of the origins of life and the definitions of life.

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Keywords Definition · Life · Origins of life · Philosophy

“Life”: A Primarily Intuitive Notion

Before any attempt to define life for scientific or philosophical purposes, it is worth recalling that we are all able to instantly recognize life, discriminating the animate from the inanimate seems to be a remarkable cognitive capacity of all human beings. We recognize animals by movement and shape, and plants by the repeating patterns of leaves and stalks. James Lovelock, in his intellectual testament *The Vanishing Face of Gaia* (Lovelock 2009), insists on this primarily intuitive aspect of the question of how we recognize that something is alive: “our survival and that of our species depends upon a fast and accurate answer to the question: is it alive? (…) The power of our life-detector proves itself when we look into a fast flowing river from a bridge: the constant motion of the water flashes in our eyes as eddies and waves reflect sunlight from the river, yet if the water is clear we can see a fish, especially if it is swimming upstream against the flow, and we know that it is alive. Should you think this easy and obvious and boring, try to design a life-detection device that would detect the presence of that fish. It is far from easy, yet life detection is a free part of our mental equipment…” (Lovelock 2009 p. 125). This “mental equipment” shows itself extremely early in the development of the child, especially when it comes to detecting animals. On the one hand, it is deeply rooted in organic evolution: almost all animals are able to recognize prey and predators in some way. On the other hand, the cognitive capacity of humans to recognize living beings is tremendously refined and improved by learning, and by all sorts of technical devices and scientific knowledge. But, on the whole, this intuitive capacity makes us able to recognize as “living beings” a huge diversity of beings, with different patterns of shape and of movement, from bacteria or the cells that compose our body to macroscopic creatures such as elephants, maples and ourselves. Of course, this intuition is not infallible. The 17th and 18th century’s microscopists doubted whether they were observing real microscopic creatures or non-organic bodies submitted to Brownian motion. Similarly, in the 18th century, there were a lot of discussions about whether spores were “alive” or not: did they represent a form of “latent life”, or were they able to “resuscitate” (Tirard 2003, 2010)? Today, we have similar doubts if we ask: is a virus a living being? Is an ecosystem—or even the biosphere as a whole—“alive” and (perhaps not exactly the same question) a “living being”?.

In spite of such doubts about borderline cases, the recognition of “life” has always been and remains primarily an intuitive process, for the scientist as for the layperson. In that respect, “life” should be carefully distinguished from other highly abstract terms commonly encountered in science, such as “matter” or “energy”. It is often stated that many, if not all fundamental terms in science are difficult to define. Thus it should come as no surprise, the argument goes, that “life”, perhaps the most abstract term in biology, is hardly definable. However, likening it to terms such as “matter” or “energy” is ill-founded. Firstly, although we have a number of intuitive representations of matter and energy—mostly rooted in particular cultures—we do not have as immediate and cosmopolitan an intuition of them as we have of what it means to be “alive”. Secondly, in contrast with physical terms such as “force” and “energy” in physics”, or “gene” in biology, “life” does not function as a theoretical concept in modern biology. That is to say, it is not a term designating a non observable entity that intervenes in fundamental hypotheses able to explain classes of phenomena. As shown in this volume, the concept of life raises important theoretical questions in contemporary science, but these questions do not seem to reduce to questions of explanation. Thirdly, an important aspect of the intuitive notion of life is its antagonistic aspect: what counts is the opposition between "living" and "non-living", more than a special content attached to the abstract notion of "life". The reason for this is that for an infinity of practical situations, biological and social, we *need* to be able to discriminate between living and non living beings. We should not expect, then, to be able to draw a *definition* from this original experience, because our cognitive apparatus has not been primarily designed for this. At best, psychology and the cognitive sciences could provide a list of the discriminating criteria that humans use for recognizing life in varied situations.

A number of authors in this volume mention this intuitive character of the category of life. But, as indicated in the title, the problem addressed in this special issue is that of *defining* life. The issues, then, are: why do modern scientists (biologists, but also other scientific disciplines) feel it necessary to define this concept? And, if this task is justified, how can we move from our powerful intuition of life to a genuine concept of life, which may or may not confirm our intuition, but should be based on other grounds? These are the major questions behind all the contributions of this fascinating collection of essays. As easily seen by the reader, the disagreements between the authors are deep, and this is what makes the whole volume so exciting. Furthermore, as an outsider, I would like to say that have highly appreciated the format of the papers: all seem to have adopted the implicit rule of "making a statement" and of defending it in a restricted number of pages. This shared attitude confers on the volume the interesting aspect of map of the relevant questions and answers within the present state of knowledge. In the rest of these concluding remarks, I will explore the terrain charted by this map, taking short trips along three routes: (1) should one define "life" and why? (stakes); (2) how is life defined? (intellectual resources); (3) what is the relation between defining life and the problem of the origins of life? (a particular scientific question). However, before carrying out this analysis, I will propose a few reflections on "defining" in science in general, and on the problem of "defining life".

Science and Definition

Christophe Malaterre (this volume) offers an interesting reflection on the general question of the methods commonly used for reaching the definition of any term. This subject has been extensively treated by logicians and linguists (e.g. Clark and Welsh 1962; Robinson 1950). First, one should distinguish between lexical definitions and stipulative definitions. Lexical definitions explain the meaning of a word by referring to its effective usage in explicit contexts. This is what dictionaries commonly do, but so do historians, and anyone who has doubts about what a given word means. Stipulative definitions, also called "legislative" definitions" (Robinson 1950), deliberately assign a meaning to a word, for the purpose of clarifying arguments. A stipulative definition may agree with the common use(s) of a word, but it may also contradict it (or them). A stipulative definition often consists in adopting one of the many current meanings of a word, but it can also settle a totally new convention for the utilization of this word. Anyway, adopting a stipulative definition is adopting a rule: "by the word *x*, we mean…". Scientific definitions are most often stipulative. If you apply this distinction to the present volume, you will easily see that both lexical and stipulative definitions are used. For instance, André Brack (this volume) relates that on the occasion of a recent meeting of the International Society for the Study of the Origins of Life, each member was asked to give a definition of life. 78 different answers were given, that occupy 40 pages of the proceedings of the meeting (see Palyi et al.). If we make use of such a document, we are discussing lexical definitions, because we are saying that this or that biologist, or chemist, or roboticist, in this or that precise context, has used the word "life" in this or that sense. But when the same André Brack adheres to the working definition adopted in 1992 by the NASA Exobiology program ("Life is a self-sustained chemical system capable of undergoing Darwinian evolution"), he posits a stipulative definition. I will let the reader determine whether the various definitions of life given in this special issue are lexical or stipulative. (S)he will probably observe that there is an unusual amount of "lexical" attitude. This may come as a surprise in a scientific context, but this is also a clear sign that there is no scientific consensus on the definition of life, and that scientists feel the need of adopting a critical attitude toward this subject.

But it is not enough to define the notion of definition. From the viewpoint of epistemological analysis, perhaps a more important issue is why defining is important in science, and what its limits are. In his reflection on essentialism, the philosopher Karl Popper has provided a powerful critical tool (Popper 1945). For Popper, essentialism (a word coined by himself) is a conception of scientific knowledge that privileges questions of the sort "What is a certain sort of thing?", or "What is its true nature?". Privileging such questions leads to a practice based upon the idea that the essential task of science is to define, in the sense of expressing the essence of something. Popper considers that this attitude has been the major source of sterility in the history of science as well as in philosophy since Antiquity. Genuine knowledge, for Popper, does not consist in defining terms and then deducing something from these fundamental statements (as in Aristotle's demonstrative method), but in formulating empirically testable *hypotheses*. Science does not aim at revealing essences through definitions, but at describing and explaining the behavior of things in given circumstances, through conjectural universal laws. This does not mean that definitions are unimportant. They are necessary, of course, but only from a pragmatic point of view : we need definitions for the purpose of clear communication. What we need is not to tell "what something is" but "what we mean by something" in a given scientific context. Definitions should always be understood in a nominalist, non essentialist, manner; they are no more than "useful abbreviations". With an admirable pedagogical sense, Popper says that definitions "should be read, not from left to right, but from right to left". By this he meant (for instance), that what counts is not "What is life?" but "What do we call life?". What counts are the hypotheses that we make about observable phenomena; definitions should be subordinated to this primary goal of science (Popper 1945, II: 1–24).

I feel uncomfortable about what can be made of such provocative thought by the specialists on the origins of life, exobiology and robotics who have written for the present volume. If I try to apply Popper's recommendation, it seems that one should not try to define "life" in a realistic way. Popper might add that life is not a scientific concept any more than "matter" is, because this term is not part of hypotheses that genuinely attempt to account for given classes of observable phenomena. But he might also admit that it is justified to propose a stipulative definition able to orient our research on the origins of life, or on objects similar to terrestrial living beings on other planets.

Philosophical vs Scientific Definitions of Life

Bruylants, Bartik and Reisse (this volume) rightly observe that "in the majority of general treatises devoted to biology, the words 'life' and 'living' are never defined". This relates to the very history of biology as a discipline. The circumstances within which the word "biology" was created and applied to a new scientific discipline are now well known (for a historiographical summary, see Gayon 2008). To sum up in a few words, the word itself has been known in a Latin form (*biologia*) since at least the 17th century in German speaking universities, where it was conventionally used for obituaries. "Biology", then, was the name for a narrative of the entire life of someone. In 1766, Christian Hanov, a disciple of the philosopher Christian Wolff, used it (in Latin again) in the title of a big treatise in which he advocated the idea of a science devoted to the study of the most general laws common to plants and animals (for this important historical discovery, see McLaughlin 2002). This fits well with a common claim among historians of science, according to which the idea of a science entirely and exclusively devoted to the phenomena of life and to living beings, emerged in the second half of the 18th century. It also puts back the origin of the word more than three decades earlier than the traditional account does. In fact, when Treviranus, Lamarck and Bichat solemnly introduced the word "Biologie" in German and in French, their proposal did not come from nowhere. Both the word "biologie" and the idea of a science encompassing the phenomena of life in all its dimensions (general laws, classification, and history) already existed. But it was only in the years following 1840, after the philosopher Auguste Comte had popularized the word, that it really began to be widely used. I have proposed elsewhere (Gayon 1988) an explanation for the reasons why ever since Comte, the term "biology" has been used more and more in the very sense that Hanov, Treviranus, Lamarck and Bichat had proposed: a science that studies all and only the different forms and manifestations of life. The tremendous success of this word has nothing to do with the more or less awkward attempts of these authors do define life; it has resulted from the fact that 19th and 20th centuries indeed developed several theories that were general enough to encompass the entire spectrum of phenomena and beings that we commonly (and intuitively) name "life". The cellular theory was the first step. Then came the evolutionary theory, and, finally biochemistry and molecular biology, which showed that all known living beings are made of the same stuff (nucleic acids, proteins, etc.), and exhibit a remarkable metabolic unity (universal existence of quasi-universal mechanisms and metabolic pathways). Note that none of these sub-disciplines of biology ever tried to define life. But all of them have definitively shown that there are very strong reasons to believe that living beings share a number of properties that distinguish them from any other natural beings, and that justify the existence of a methodologically autonomous science. Of course, from this knowledge that we all share today, it would be tempting to infer some general definition of life. Such a definition would consist in extracting the most general doctrines from cellular biology, evolutionary theory, biochemistry, and molecular biology. Almost all current definitions of life are more or less convincing attempts to do this. Some insist on membranes and metabolism, others on reproduction and evolvability, others on the basic "building blocks" of life (organic molecules). Still others attempt to provide a formula as abbreviated as possible. Among these are the NASA definition quoted above, or the phenomenological definition proposed by Damiano & Luisi in this volume.

All these attempts amount to saying (I apologize for the crudeness of my formulation): "Hey, colleagues! Haven't we created a great science over the last two centuries? There is no doubt that 'biology' has succeeded beyond all expectation to develop a number of general theories that tell us what the living beings that we know have in common. Let us summarize them in the most compact formula, and we will feel more comfortable with the margins of life: the origins of terrestrial life, other possible forms life elsewhere, viruses, ecological entities, and, why not, artificial life". I cannot avoid thinking here of Popper's reflections evoked earlier: what counts are empirically testable hypotheses and theories. Thus, if we want to speak of vital phenomena, the best thing to do is to begin with the available theories. But, if we want to go further and provide a general definition of life, we must be aware that it cannot be more than a stipulative definition, in relation with particular scientific theories. Such a definition will always be conventional, and for this reason, the wisest attitude that we may have is to accept that it is open to change, in response to new knowledge. If we do not accept this, Popper would probably go on, we must be aware that we enter into the realm of metaphysics.

At that point, I would like to observe that, if on the whole biologists have avoided defining life for approximately two centuries, they nevertheless inherited a very long philosophical tradition that offered them genuine definitions of life. Since a number of scientists today claim that they need, as scientists, to elaborate a definition of life, it may be worth recalling what the major philosophical models of life have been.

Philosophers did not wait for the advent of biology for constructing general conceptions of life (in the trivial sense of animals and plants). In reality, the major theoretical possibilities seem to have been exhausted before the 19th century. Georges Canguilhem, in a legendary article (Canguilhem 1968), identifies three major concepts of life, each associated with an outstanding philosopher: life as animation, life as mechanism, and life as organization.

Animism is certainly the oldest and the most universal notion of life. It defines and explains life by a specific principle, the soul. Aristotle has provided the most impressive elaboration of this conception. Perhaps his most important statement is that the soul is the cause of life in the sense that it is the coordinated exercise of all the body's capacities to act. Soul, Aristotle says, is for the entire body what sight is for the eye. The soul is thus both the ensemble of functions, and their coordination. Many other versions of animism have been given: sometimes the soul is an entirely immanent power (as in Aristotle), sometimes, it is rather an independent power that governs the body in a more Platonic way (as in Stahl's thinking). The important point is that the conception of life as animation posits that living beings have properties that distinguish them from all other natural beings, and thus require a special type of explanation.

The concept of life as mechanism makes exactly the opposite postulate. According to it, all vital functions are no more than mechanisms, and the living body itself is a machine. While it is much more complicated than any artifact made by humans, it does not require a special type of theoretical principle to explain its functioning. Descartes has given this conception its most elaborate form. The mechanistic concept of life is founded on a representation of nature which does not admit a real distinction between non living bodies and living bodies. Pushed to its limits, the mechanistic concept of life leads to the avoidance of the word "life". This is exactly what happens in Descartes' works.

The last philosophical concept of life consists in emphasizing organization, and consequently, it identifies living beings with "organisms". This conception developed throughout the 18th century, and led to the invention and spread of the word "organism", which became common at the beginning of the 19th century. It came as a sort of *tertium* for both animists and mechanicists, because it relies upon both mechanistic intuitions (the living body as similar to an organ—the musical instrument that is able to play by itself, on the basis of its own mechanisms), and upon animist ideas ("organization" and "organism" come for the Greek word *organon*, which signifies a means with respect of an end—whence the finalistic connotation of these words). Immanuel Kant, in his *Critique of Judgment*, has provided a remarkable philosophical elaboration of this conception. He proposed to equate the notions of "natural purposiveness" and "organized being" (the context making clear that organized beings are living beings). An organized being, Kant explains, is a being in which any part is both a means and productive cause for the others.

Such a being is different from a machine, in which every part is a means relative to the others, but is not "produced" in any sense by them. In the same text, Kant also insisted that "organized beings" are able to "self-organize" (self-maintain, self repair and self-reproduce). In addition to the fact that Kant's reflection upon organization had a tremendous influence upon a number of biologists in the 19th century and part of the 20th century, modern biologists of the 19th and the 20th centuries have massively adopted the spirit of this conception through the equation that they have made between "living being" and "organism". We can hardly imagine someone denying that living beings are "organisms". I do not believe that this is a pure matter of convenience.

Beside these three philosophical concepts of life, I doubt that anything really new has been produced since the advent of biology. Our representation of life remains structured, on the one hand, by the immediate or intuitive notion of life that I have evoked at the beginning of this paper, and, on the other hand, by the three philosophical concepts of animation, mechanism, and organization. Of course the scientists who today want a *definition* of life want more than this; they want a *scientific* concept of life. But I would be very much surprised if their search for such a scientific definition were not influenced by these old philosophical schemas. Most probably, most of them would say that, of course, they adhere to the organizational concept of life, but that they also want this concept to be more precise in terms of the formal and/or empirical properties able to make it operational for scientific purposes. Nevertheless, I am not sure that all scientists would definitely refuse either the mechanistic or the animist concept of life. For instance, when I see that several authors in this volume deny that any realistic definition of life is possible, and say that any definition is a matter of convention, or of degree (e.g. Forterre or Bruylants/Bartik/Reisse), I tend to think that, ultimately, they feel more comfortable with the Cartesian or mechanistic view of life rather than anything else. Similarly, Damiano/Luisi's emphasis upon the presence of a "cognitive" element in their definition of life makes me irresistibly think of Aristotle's bio-psychic concept of the soul. But I may be wrong. The important point, anyway, is that modern scientists (as well as philosophers) should be aware of the strength of the three philosophical models of life that I have briefly examined. All three are a common heritage that structures in depth a good deal of our cultural intuitions and vocabulary any time we try to think about "life".

Should One Define Life? What is at Stake?

So far, I have formulated a few personal views on the subject of this volume. I have insisted upon the strength of our immediate intuition of life, on the pitfalls of definitions in general in science, and upon traditional philosophical concepts of life that are part of the common heritage of present science. In some cases, I have ventured to indicate cross-relations with some contributions of the present collection of essays. I will now come closer to the content of the volume, and provide, as far as I can, a categorization of the recurrent problems and solutions that have been proposed. As said earlier, it seems to me that three major questions have been discussed: Should we define life, and why? If so, what kind of definition should we adopt? And, finally, how does the question of definition relate to that of the origins of life? These three questions are in fact closely interrelated. Not every question has been discussed by all participants in the volume. But, taken jointly, they confer a high degree of interaction between the various papers.

Let us begin with the question of whether and why one should define life or not. No doubt, this question has been the most hotly debated among the authors.

Two authors provide historical information that profitably contextualize the enthusiasm for defining life in today’s science. Stéphane Tirard observes that a number of major authors who have explored the problem of the origin of life from the 18th to the 20th century, either with the aim of offering hypotheses, or with that of denying its relevance, have done so without having any well-circumscribed definition of life. Although he is cautious, as any historian should be indeed on such subjects, Tirard tends to believe that this has been a rather general rule until recently. Thus, over approximately two centuries, just as the biologists in general, the specialists of the origin of life seem to have been able to think about and work on the problem of the origin of life without being haunted by defining life. Florence Raulin-Cerceau complements nicely these negative results of Tirard’ enquiry. She insists upon the highly speculative character of research on the origin of life until the last decades of the 20th century. Especially, she observes (as does François Raulin) that after 1980, the research programs in astrobiology, especially those of NASA, became much more pragmatic than they were before. Therefore, instead of imagining exotic forms of life elsewhere, they “mainly focused on the search for life based on liquid water, with chemical or biological parameters closely linked to terrestrial ones”.

More generally, almost all authors seem to admit Bersini’s and Reisse’s (2007) assertion that the necessity of defining life has resulted from the converging needs of three domains of research that have developed spectacularly over approximately the past two or three decades: exobiology (formerly “astrobiology”), artificial life, and origins of life. Thus it is not in the traditional areas of biology that the quest for a definition of life has developed. All authors also agree that these three domains have generated the need for an operational criterion, as unequivocal as possible, for pragmatic reasons: exobiologists need it because without it they would hardly know what they are looking for on other planets; and all three disciplines need it for the mutual benefit they derive from their many interactions with each other, as well as with chemists, biologists, geologists and paleontologists. I would like to make several observations about this consensus. First, there is something very plausible about this pragmatic demand. It makes sense to try to build an operational criterion if three different disciplines claim that they want to identify life outside the scope of our common intuitions about living beings (inquiries into the origins of life deal with objects outside the temporal scope of these intuitions, exobiology deals with ones that lie outside of their spatial scope, and robotics and artificial life deal with ones that lie outside of their material scope).

Secondly, it is worth recalling that giving a definition and giving an operational criterion are not necessarily the same task. A definition is a theoretical construction, ideally founded on some or several characters that we believe to be essential to the thing defined, even if we do not adopt a realistic or platonic stance relative to definitions. A good definition is one that captures something important in terms of the conceptual content of the term defined. Of course, we may call the set of distinctive elements that such a definition identifies a “criterion”. But this should not be confounded with offering a reliable criterion for the purpose of diagnosis. For instance, having “hair” is a good criterion for distinguishing mammals from all other vertebrates. But we would hardly accept this criterion as sufficient for a definition of Mammals (if such a definition can be provided—this is another matter). It is exactly the same for life. A number of scientists seem to be satisfied with the NASA definition of life, already mentioned: “Life is a self-sustained chemical system capable of undergoing Darwinian evolution”. But, as Radu Popa observes, the capacity to evolve (with the implicit ideas of reproduction, imperfect replication of some information, and competition in populations) is probably more a consequence than a definitional element of living systems. Therefore, Popa adds, this element should not be retained in a genuine definition of life; it is a “diagnostic feature”, not a definitional element. This being said, I do not deny that diagnostic criteria may be tremendously important in practice. But one should never forget that a good definition requires more, even for a methodological nominalist, such as Popper.

Among those authors who have expressed their skepticism about the possibility of any clear-cut and unequivocal definition of life, several have endorsed what Christophe Malaterre calls “definitional pluralism”. I identify two different sorts of this pluralism in the papers in this volume. They are not exclusive, and sometimes coexist in the same authors. The first sort of pluralism is what I would call methodological, because the various definitions are necessarily anchored to particular scientific contexts. This attitude is illustrated by Malaterre himself, but also by Michel Troublé, a roboticist who has a fascinating dialogue with the chemist André Brack. In contrast with many specialists of artificial life, Troublé doubts that robotics deals with objects similar to chemical systems. Consequently, he concludes that the discourses of chemists and biologists, on the one hand, and roboticists on the other, are “heterogeneous”. Another kind of pluralism can be found in Bruylants/Bartik/Reisse and in Malaterre. These authors propose to think of the distinction between living and non-living, not in terms of a sharp boundary (whence the air of skepticism towards any harsh operational criterion), but in terms of “degrees and modes of lifeness” (Malaterre). They mean by this that if we look at the borderline cases of prebiotic evolution, exobiology and robotics, the problem is not whether this thing is alive or not, but whether it is “more or less” alive, and what makes it so. Bruylants/Bartik/Reisse go in the same direction. They propose a scale on which “0” means that a given entity is definitely not alive, and “1” means that we have not the slightest doubt of it being alive. For instance, all past or present bacteria and eukarya would be attributed a value of lifeness of 1 on this scale. This version of pluralism could be labeled as “gradualism”. Note that this gradualism needs not to be thought of in terms of a linear scale, a sort of resurrected *scala naturae*. Modern science does not need that. Rather it is a methodological pluralism, admitting that degrees of lifeness may have developed (or may develop today in the world of artifacts) along many lines, and require some sort of fuzzy logic (Bruylants/Bartik/Reisse).

One aspect of this proposal which I like very much is the parallel made between the living/non living distinction and the failure of evolutionary biologists to define the category of species. Although species are immensely important for evolutionary biology as well as in practice, there is no “golden rule”, as Darwin said, for unequivocally defining the concept of “species”. There are various ways of “being a species” in nature, because there are various modes of discontinuity between the past and present collections of organisms (e.g. common descent, intersterility, ecological disruptions, etc.). It is probably wise to adopt a similar attitude towards “living” and “non-living”. I do not see why the collection of living beings should be totally distinct from the collection of the non-living ones, whereas at all levels, taxonomic categories fail to define clear-cut boundaries.

Nevertheless, there is a possible strong objection to such a perspective. A number of authors, perhaps including some in this volume, are convinced that a clear-cut boundary does exist between the living and the non-living, because the difference is not a matter of historical science, but a matter of physics, or something close to it—it is described by a nomological science, not an “idiopathic” science.[1] These authors think that some highly abstract property is the signature of life, and is the result of some kind of jump or bifurcation in the behavior of a certain sort of dynamic system. Of course, if living systems rely on *sui generis* properties that universally belong to them in virtue of laws of nature, the problem of defining life amounts to identifying these laws, and (not the same question), to

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[1] Nomological science: a science based on universal statements of unrestricted scope (laws). Idiopathic sciences: sciences dealing with events that happen only once.

delineating the conditions under which such systems can be generated. There is no need to insist that this remains an open question in the context of present science—theoretical as well as experimental. But it is obviously an important open question.

How is Life Defined?

As already mentioned, a number of definitions of life have been proposed, catalogued and discussed in recent years. Palyi et al. (2002) have listed around forty definitions; Popa (2004) has listed and discussed ninety. Such an inflation of definitions makes me think of the incredible number of definitions of species that have been found in past and present literature. In his authoritative review, Mayden discusses eighteen different concepts of the biological species used by biologists, all of which are considered as operational (Mayden 1997). A number of authors, however, admit between twenty and thirty acceptable concepts, whereas Lherminier and Solignac (2000) have listed ninety two "definitions of authors" in past and (principally) contemporary literature. These numbers are in good agreement with Bruylants', Bartik's, and Reisse's parallel made between the unending attempts to define both the category of species and the boundary between a non-living state of matter and a living system. Bruylants/Bartik/Reisse also observe that most authors who try to define this boundary content themselves with giving a list of properties shared by all (or at least many) well-known terrestrial living systems. Such lists are variable. Some authors insist on components and on their coupling (macromolecules such as nucleic acids, proteins interacting in an aqueous solvent, etc.), others on thermodynamic properties, others on the necessity for a living system to exhibit some sort of metabolism within the limits of a partially permeable membrane, others on reproduction and replication (or either metabolic cycles or precise material structures), and the majority propose a combination of any of such criteria.

But some authors adopt a more theoretical attitude, and claim that a genuine universal definition of life is possible, one that is of course able to include all terrestrial beings, past or present, that we recognize as "living beings", but also anything that would deserve the name of "living system", be it manufactured in our test-tubes, on our screens, or possibly existing anywhere else in the universe. In the present volume, at least four papers represent that camp, the camp of the "definers": Ruiz-Mirazo/Peretó/Moreno, Popa, Bersini (with reservations, see below), and Damiano/Luisa. Brack could also be added, but he makes clear that his adoption of the NASA definition results from a purely pragmatic, rather than theoretical, motivation -detecting life outside the Earth. It is thus interesting to look at these definitions, and classify them.

All these definitions proceed *genus et differentia*; they enunciate an essential property that delineates a larger class, and then one or several other properties which define life as a subclass of this larger class (on this method, see Malaterre's interesting comments on the various methods of definition). Each definition can also be equivalently interpreted as a conjunction of properties such that the conjunction is a necessary and sufficient condition for a given entity to be called a "living system". All these definitions are brief and they closely resemble each other. It is worth it then to reproduce all of them.

Here is Ruiz-Mirazo/Peretó/Moreno's definition (reproducing the definition given by Ruiz-Mirazo and Moreno 2009):

> "[Life is] a complex network of self-reproducing autonomous agents whose basic organization is instructed by material records generated through the open-ended, historical process in which that collective network evolves."

In this definition, the authors insist on the importance of both the individual dimension and the evolutionary dimension. Functional autonomy and self-reproduction are each essential to individual living systems. But they are not enough; the open-ended history of living systems in collective networks is also part of the definition. This is typically an "holistic" or "synthetic" definition.

Here is now Brack's definition (reproducing the definition given by NASA program of exobiology):

> "Life is a self-sustained chemical system capable of undergoing Darwinian evolution."

This definition basically expresses the same requirements as the previous one. But, since it explicitly aims at providing a practical touchstone for recognizing living systems, it sounds less theoretical in comparison with Ruiz-Mirazo/Peretó/Moreno, who try to explicate the two parts of this operational definition. The only difference is the reference to a particular theory of evolution ("Darwinian evolution"), an element that Ruiz-Mirazo et al. probably find too restrictive. Nevertheless, Ruiz-Mirazo *et al.* clearly refer to the evolution of "collective networks". It is hard to imagine such an evolution without processes such as random sampling and selection.

Popa provides one definition for "living entities", one for "being alive", and one for "life":

> "Living entities are self-maintained systems, capable of adaptive evolution, individually, collectively or as a line of descent."
> "Being alive is the state of expressing these capabilities."
> "Life is a concept indicating that the capacity to express these attributes is either virtually or actually present."

The two last definitions are in fact closely dependent on the definition of living entities. They do not bring anything new in terms of necessary and sufficient conditions. They make one think of Aristotle's distinction between the two senses of *entelecheia* (first and second entelechy) when he proposes a definition of both the soul and life in his *De Anima* (II, 2). Being alive means expressing effectively, at a definite time, the capacities of living entities. Life is a name for these capacities as such, whether expressed or not. This being said, Popa's definition resembles very much the two previous ones. Individual self-maintenance and evolutionary history are equally important.

Bersini does not propose an explicit definition of life. But he claims that the current theoretical definitions by chemists and biologists depend too much upon the particular "hardware" (molecules, membranes, metabolic pathways, etc.) that support them in living systems. Therefore he proposes a purely formal and functional approach to the properties commonly invoked by chemists and biologists, *i.e.*: *"self-maintenance", "self-organization", "metabolism", "autonomy", "self-replication", "open-ended evolution"*. Thus, although Bersini claims that "artificial life does not attempt to provide an extra thousandth attempt of definition of life, any more than do most biologists"; his paper suggests that he accepts the previous definitions as a provisional working tool. But we clearly understand that he would be just as pleased to set up experimental software platforms able to implement other requirements.

Finally, Damiano and Luisi propose the following definition:

> "A system is living when [it] is self-maintaining due to a regenerative network of processes taking place within the boundary of its own making, and which has a cognitive adaptive interaction with the medium."

This definition is clearly quite different from the previous ones. First, we see that it does not refer at all to reproduction and evolution. This is clearly an individually-centered definition. Secondly, it explicitly introduces an element that is absent from or (only implicit) in the other definitions: the interaction of a living being with its "medium" or (if I interpret it correctly) its environment. Nevertheless this difference may be negligible, since the previous definitions implicitly postulate something like a "milieu" of some sort. Thirdly, and most importantly, Damiano and Luisi insist on a "cognitive element". According to them, this cognitive element is a necessary complement to Maturana's and Varela's definition of autopoietic systems, which they summarize: "*A living system is a system which is capable of self-production and self-maintenance through a network of regenerative process from within a boundary of its own making.*" Another significant difference with the previous definitions is the method that produces it, according to Damiano and Luisi. They claim to rely upon "phenomenological observation" rather than "speculation". In fact, they take for granted that the biological cell is "the minimal form of life". Such a method means that they try to identify the essence (in any sense you wish, scholastic or phenomenological) of present terrestrial life as everyone understands it today. Although I do think that this reflection is very much in the metaphysical mood of what Popper condemned so energetically, I must confess that it is philosophically very interesting. Such a definition might well be listed as a fourth (and fascinating) philosophical definition of life, beyond the three that we have listed above. This definition looks like a mixture of the animist (or Aristotelian) definition and the organizational (or Kantian) definition. Beyond its reflective interest, I doubt that such a definition can either provide a diagnostic criterion for life, or found a theoretical program, whereas Maturana's and Varela's definition would probably do these two things.

Therefore, to summarize, we can fairly say that those authors who have explicitly defended that a definition of life is needed, and have coherently offered one, can be classified into two categories. The first category includes Ruiz-Mirazo/Peretó/Moreno, Brack, Popa, and, to a lesser degree, Bersini. More or less crudely, all refer to two conditions: individual self-maintenance and the open-ended evolution of a collection of similar entities. This category could be labeled as the standard view among theoretical biologists. The other category is represented by Damiano and Luisi, who refuse to include reproduction and evolution, and take a sort of psychic view of the living, which also emphasizes the environment. This definition makes me think of previous thinkers such as Uexküll. In my subjective opinion, it is a philosophical interpretation as much as an operational definition.

Definition of Life and Origins of Life

Although the subject of the present collection of essays is not the origins of life as such, it is obvious that this subject is the main theoretical motivation behind the entire volume. Furthermore, a majority of authors are known as specialists of the origins of life, either as practicing scientists, or as philosophers and historians of that subject. We should not be surprised then, to find echoes of the major theoretical debates that characterize present research on the origins of life. These debates pervade the entire volume. They are most explicitly treated in Bruylants/Bartik/Reisse, Lazcano, and Weber. But, as already noted, they can be identified in all papers.

I will be brief on this topic, and just point out its relationship to the problem of the definition of life. Lazcano provides a very illuminating description of the central debate that has structured the field of the origins of life for more than half-a-century. This debate is familiar to all readers of OLEB. With the risk of oversimplifying, there are two camps. One emphasizes the importance of metabolic cycles and the emergence of vesicles whose membranes partially isolate these metabolic cycles. Oparin and Haldane are the founding fathers of this school of thinking. The other camp focuses primarily on macromolecules able to store genetic information, and perhaps to have both auto-catalytic and hetero-catalytic capacities. Lazcano seemingly favors the second school, but he clearly says that no firm conclusion can be drawn from available data in favor of either the "metabolic" camp or the "genetic polymers" camp.

One funny thing in the volume is the self-confidence with which other authors in this volume claim that the state of present science has established beyond reasonable doubt that one or the other school is the good one. Please do not take this as an ironic remark. What I mean is that the very content of the volume confirms Lazcano's appreciation of the state of knowledge.

The relation between this fundamental debate and the problem of the origin of life is quite simple (although, again, being a non-specialist, I am aware of oversimplifying). It seems clear that if you emphasize theoretical entities such as metabolic cycles, vesicles and membranes, and some sort of compartmentalization, you privilege a functional approach to the question of what living beings are. Such an approach fits well with the idea that what must be explained is the emergence of individual self-maintained systems. If this is the case, the emergence of life comes down (in a broad philosophical formulation) to the emergence of individuality. On the other hand, if you insist on the replication of polymers, on the reproduction of assemblies of some kind of molecules, and on the evolution of populations of something, you will probably be led to emphasize a notion of life in terms of collectives, descent, and history of related collectives.

This dividing line is echoed in the definitions of life (or living systems) that we find in this volume. Most often, the authors choose a syncretic attitude; they emphasize both individuals and evolution. But this is not always the case. Some require only the first element, and insist that the second one is only a consequence, or, more precisely perhaps, a more or less remote outcome. As I see it, the problem is entirely open.

In conclusion, as a philosopher, I should say that I have been fascinated by the debates developed in this volume. They illustrate a style of interaction between science, philosophy and history that is really exceptional. After reading all the contributions, I am convinced more than ever that contemporary scientists remain exceedingly dependent upon what I called the intuitive or spontaneous intuition of life—an outstanding piece of our cognitive equipment. Perhaps, fifty or one hundred years from now, we will not need to use the word "life" for the kind of problems that we discuss today in terms of "the origins of *life*", or of whether there is *life* of some sort in extraterrestrial habitats or in our refined technological constructs, such as robots and the like. We will then have more operational, and more abstract tools, and we will consider our past discourse on "life" with the same indulgence and condescendence as physicists and chemists speak today of "matter." It will be a useful word in practice, but not a scientific concept, except in very precise contexts where, in fact, you could just avoid the word (as, for instance, when we oppose "matter" and "energy"). When this point will be reached, life will be no longer a concept for the natural sciences, but just a convenient word in practice, in the kind of world that we inhabit. "Life" will be a folk concept. Its specialists will be no longer chemists, biologists, and roboticists; life will be a subject for psychology, cognitive science and anthropology. Is this a sad dream or an exciting one? It is just an idiosyncratic positivist's dream!

Acknowledgements I would like to thank Rachel Bryant (University of Toronto, Department of Philosophy), for her suggestions and for her wonderful linguistic revision.

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