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The metaphor that viruses are living is alive and well, but it is no more than a metaphor

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ABSTRACT

Virologists often use anthropomorphic metaphors to vividly describe the properties of viruses and this has led some virologists to claim that viruses are living microorganisms. The discovery of giant viruses that are larger and have a more complex genome than small bacteria has fostered the interpretation that viral factories, which are the compartments in virus-infected cells where the virus is being replicated, are able to transform themselves into a new type of living viral organism called a virocell. However, because of the widespread occurrence of horizontal gene transfer, endosymbiosis and hybridization in the evolution of viral genomes, it has not been possible to include metaphorical virocells in the so-called Tree of Life which itself is a metaphor. In the case of viruses that cause human diseases, the infection process is usually presented metaphorically as a war between host and virus and it is assumed that a virus such as the human immunodeficiency virus (HIV) is able to develop new strategies and mechanisms for escaping protective host immune responses. However, the ability of the virus to defeat the immune system is solely due to stochastic mutations arising from the error-prone activity of the viral enzyme reverse transcriptase. The following two types of metaphors will be distinguished: an intentionality metaphor commonly used for attributing goals and intentions to organisms and the living virus metaphor that considers viruses to be actually living organisms.

1. Introduction

By the end of the 19th century, filtration experiments had clearly established that several infectious diseases were caused by agents smaller than bacteria and therefore invisible by light microscopy, which could not be cultured on conventional bacteriological media. Dimitri Ivanovsky in St Petersburg, Russia was the first to show in 1892 that the agent causing the tobacco mosaic disease was able to pass through a Chamberland sterilizing filter although he did not grasp the significance of his observation (Van Regenmortel, 2010a; 2010b). He remained convinced that he was dealing with a small bacterium rather than with a new type of infectious agent and thought that the filter he used might have had fine cracks allowing small spores of a microbe to pass through it (Witz, 1998). However, Ivanovsky's misinterpretation did not prevent Russian and other virologists to claim many years later that he was the father of virology (Lvov, 1993; Stanley, 1944). In 1898, Martinus Beijerinck in Holland repeated Ivanovsky's experiments but in addition he showed that the infectious agent in filtered tobacco sap was able to diffuse through several millimeters of an agar gel. This led him to conclude that the agent was not a microbe but was a contagious living fluid which he glorified with the Latin label *contagium vivum fluidum*. However, he also demonstrated that the agent could reproduce itself in a tobacco plant and he called the agent a virus. This led Dutch virologists a century later to claim that Beijerinck was obviously the father of virology (Bos, 1995, 1999).

In 1898, Friedrich Loeffler and Paul Frosch in Germany reported that the causative agent of foot-and-mouth disease in cattle also passed through a Chamberland-type filter but not through a finer grain Kitasato filter, from which they correctly concluded that the causative virus which multiplied within the host was a corpuscular particle and not an ill-defined living fluid. Beijerinck, however, did not agree with their interpretation that the virus was a small particle (Witz, 1998). This led German virologists to claim that Loeffler

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and Frosch should actually be considered the fathers of virology (Horzinek, 1995).

The discovery that viruses were a new type of infectious agent was thus attributed by virologists from three countries to scientific compatriots, which apart from nationalistic preferences illustrates the difficulty of agreeing on what constitutes a scientific discovery. A discovery is not simply making a novel observation such as the filterability of an infectious agent but requires in addition a correct interpretation of what is being observed since this is essential for grasping the significance of a new experimental finding. The controversy about who should be considered the father of virology reminds us that scientific facts are never obvious but need to be correctly interpreted.

The current debate on whether viruses are living is another case of disagreements that are fuelled not necessarily by new observations but by different ways of interpreting them. The present review will argue that such disagreements often arise from the tendency of many virologists to use anthropomorphic metaphors for describing more vividly the properties and behaviors of viruses.

In the third edition of their book *Principles of Virology*: *Pathogenesis and Control*, Flint, Enquist, and Racaniello (2009) pointed out that viruses do not actually "do" anything although many virologists succumb to the temptation of ascribing various actions and motives to viruses. They warned that while remarkably effective in enlivening a lecture or an article, anthropomorphic characterizations are inaccurate and often misleading. According to them, a multitude of anthropomorphic expressions should be banned because "Viruses cannot think, employ, ensure, synthesize, exhibit, display, destroy, deploy, depend, reprogram, avoid, retain, evade, exploit, generate etc". They also claimed that "infected cells and hosts do many things in the presence of viruses, but that viruses themselves are passive agents totally at the mercy of their environments" and they further admitted that because "it is extremely difficult to purge anthropomorphic terms from virology communications", they had to spend many hours removing such terms when preparing their textbook (Flint et al. 2009). It will be argued here that the claim that viruses are alive is only a metaphor based on several anthropocentric interpretations that are no doubt responsible for much of its appeal but which also makes it difficult for a scientific consensus to emerge. Metaphors are frequently used in scientific discourse and the role they play in shaping scientific concepts has become a major theme in the philosophy of science. However, this falls outside the scope of the present review and interested readers may want to consult Black (1962), Bradie (1999), Keller (2002) and Bailer-Jones (2002). Lily Kay (2000) in her history of the genetic code entitled *Who Wrote the Book of Life* described the many metaphors used by molecular biologists such as the language of life, DNA and protein codes, messengers, recipients as well as genetic information, which implied that genetic and verbal information systems were analogous. She pointed out that the Book of Life metaphor produced information without meaning, codes with no language, messages with no sender and writing devoid of authorship (Kay, 2000, p. 296). Since a human language is impossible without consciousness, a Book of Life without consciousness yielded numerous inadequate metaphors that are still widely used in biology. Metaphors may sometimes be useful as epistemic and theory-construction devices, but it is must be emphasized that they do not tell us how the world actually is (De Donato & Arroyo-Santos 2011; Hoffman, 1980).

The present review will first describe the orthodox view held by most virologists that viruses are subcellular, genetic parasites that do not self-replicate but are being replicated by the cells they have infected. The properties of living organisms as members of a reproductive lineage will then be analyzed. This will make clear why organisms are different from organs and other living tissues that are not functionally autonomous. Some biologists have suggested that a viral factory, which is the compartment in infected cells where virus replication takes place, is able to transform a virus into a living organism called a virocell. It will be argued that this putative ability of viruses to generate new types of living cells finds its origin in metaphors that attribute to viruses human-like capacities of intentional, goal-directed behavior. The Tree of Life (TOL) will then be described and it will be shown that viruses cannot be included in a universal TOL. Other metaphors will be discussed, for instance the interpretation that viruses are involved in battles and wars with their hosts and that the human immunodeficiency virus (HIV) is able to develop new strategies to escape the host immune system. Finally, it will be argued that design terminology is not appropriate for describing neither the behavior of HIV battling with host cells nor the attempts of scientists who try to develop an HIV vaccine by so-called rational design.

2. The nature of viruses: the orthodox view

At the present time, the majority of virologists still adhere to the view that viruses are subcellular, genetic parasites (Lwoff, 1957) that do not self-replicate or reproduce themselves but are being replicated, passively rather than actively, by the metabolic activities of the cells they have infected. The replication of viruses occurs through a process of copying carried out by parts of the cellular machinery of their host cells and this replication process is totally different from the process of fission that occurs when living cells reproduce themselves. When a virus infects a cell and the viral genome becomes integrated in the infected host, it may seem that the virus has become part of a living system although it is actually no more alive than other constituents of the host cell such as its genes, macromolecules or organelles. Most biologists accept that the simplest biological system that can be said to be alive is a cell and that cells always originate from other cells but that the individual components of a cell are not themselves alive. Virus particles, like genes, are inert outside cells but when the viral genome is integrated in an infected cell, it is able to instruct the cell to produce viral proteins and virions although it is still the cell that synthesizes them.

Many authors have discussed the nature and origin of life in terms of a series of hypothetical steps that could possibly explain the transition from non-life to cellular life in a prebiotic Earth through the spontaneous emergence of biomolecules, primitive membranes, metabolic networks and self-replicating systems (for a review, see Luisi, 2006). Once life had appeared, it spread over our entire planet without the need for periodical spontaneous generation events. However, even if one considers that something that evolves by natural selection is already alive, this still does not provide a clear-cut frontier between a non-living state of matter and a living system (Bruylants, Bartik, & Reisse, 2010), and the search for such a boundary has until now remained a futile exercise (see section 3). It is as difficult to ascertain at which moment life emerges as it is to decide at which moment it disappears upon the death of an organism.

Stanley in 1935 had suggested that tobacco mosaic virus (TMV) was a crystallizable molecule that lied at the borderline between chemistry and biology (Norrby, 2008; 2010). This raised the possibility that viruses could be alive and it was believed by some that if a protein could be a living infectious agent, viruses might hold the key to the origin of life. However, it was later shown that TMV was not a pure protein but a RNA-containing nucleoprotein (Bawden & Pirie, 1937) and it subsequently became clear that it was the RNA in the virus that was the infectious entity.

Viruses are considered to be biological entities because they possess a genome and give the impression to human observers of being able to adapt to particular hosts and biotic habitats. However, viruses do no not possess the functional autonomy that would allow them to actively evolve by themselves since they are passively evolved *by* the cells they have infected. Moreira and López-Garcia (2009) have suggested that this is somewhat analogous to human

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technology that does not evolve by itself but is evolved by humans. Viruses are usually not considered to be living organisms because they lack the capacity to capture and store free energy and do not possess the characteristic autonomy and self-repairing mechanisms that arise from the presence of integrated, metabolic activities (Van Regenmortel, 2010c). When a virus is replicated in an infected cell, it is the cell rather than the virus that actively produces virions and the virus may appear to be the active agent only because its nucleic acid is sometimes metaphorically described as the master molecule that instructs the cell to produce virions.

Although a virus has been defined as "a genetic element enclosed in a protein coat" (Jacob & Wollman, 1961), a definition that refers to a virus particle or virion, this does not mean that virologists tend to confuse viruses with virions. All virologists distinguish different stages in the replication cycle of a virus, such as an extracellular infectious state corresponding to virions, a replicating or lytic state in an infected cell corresponding to an eclipse phase when virions are no longer present, and a proviral, latent state when the viral genome has been integrated in the host genome but no virions are produced and no antiviral host immune response is elicited (Lwoff, 1957).

Whereas virions possess intrinsic properties such as size, mass, chemical composition and sequences of capsid proteins and nucleic acids, viruses in addition possess relational properties that arise by virtue of relations with other objects such as a host or a vector, which become actualized only during transmission and infection processes.

Virologists are well aware that a virus cannot be reduced to the chemical composition of a virion and although the chemical formula of a poliovirus particle has been described as $C_{332,652}$ $H_{492,288}$ $N_{98,245}$, $O_{131,196}$ P_{7501} S_{2340} (Wimmer, 2006), this reductionist formula reduces biology to chemistry and does not adequately represent the infectious entity poliovirus. (Van Regenmortel, 2010c). It would be equally absurd to state that Michelangelo's statue of David is nothing but a piece of marble (Van Regenmortel, 2004). The virion's composition, for instance, gives no information on the viral receptor binding site which is a conformational, relational structure dependent on the existence of a specific relationship with a host cell. This binding site which recognizes host cellular receptors is essential for initiating the infection process and arose during a process of biological evolution which culminated in the ability of the virus to infect certain host cells. To describe a virus, it is thus necessary to include properties other than the composition of virions and virologists have no difficulty in doing that (Van Regenmortel, 2000a, 2003). It is thus rather strange that Forterre (2010a; 2010b, 2010c, see also Forterre, this special issue) has argued that it was the supposed inability of virologists to distinguish between inert virions and actively replicating viruses that made them accept the view that viruses were inert, had no metabolism and could therefore not be living organisms. In reality, it seems that it is exactly the opposite that happened. Instead of referring correctly to the *replication cycle* of a virus, it became standard practice to speak metaphorically of the *life cycle* of a virus and it seems that some authors became convinced that since viruses went through a life cycle, they had to be alive. Bandea (1983), for instance, did not view the life cycle of a virus simply as a metaphor but claimed that "the living phase of the virus is the intracellular replication phase of its life cycle ". This living phase, according to him, exhibits the characteristics of metabolism, growth and reproduction present in all living organisms.

Before discussing the alleged living nature of viruses, it is important to analyze what is meant by a living organism.

3. Living organisms are the extension of the concept of life

Philosophers of biology as well as scientists disagree on whether life and living organisms should be considered a natural kind (Duncan, Bourrat, Deberardinis, & O'Malley, 2013; Dupre, 1981; Hacking, 1991; Rosenkrantz, 2001). A natural kind exists as a real category in nature independently of any human thinking or conceptualization, and classical examples are the chemical elements that reflect natural divisions in nature (Bird & Tobin, 2015). In the philosophical literature, water is often also considered to be a natural kind defined by the identity: water = H_2O, although this static definition in terms of a chemical composition is scientifically incorrect because it ignores the fact that water is a macroscopic entity that possesses properties such as viscosity and a melting point. A single H_2O molecule has no viscosity or melting point and also cannot form the hydrogen bond chains that are responsible for the fact that water is liquid at room temperature (Bird & Tobin, 2015; Marcus, 2009). In fact, since a single H_2O molecule is not water, such a definition cannot answer questions about the nature of water as a natural kind. In a somewhat analogous way, no definition of the concept of life can tell us if there is anything that all living organisms have in common, mainly because life is a cluster concept (see below).

Life is not a material entity, nor a force, nor a property but a conceptual object made up of the collection of all living systems, past, present and future (Mahner & Bunge, 1997; page 142). All living systems possess the property of being alive and the concept "life" corresponds to the mental representation of that property. Life can thus be said to be the extension of the predicate "is alive", the extension of a concept being all the objects that the concept refers to. Instead of analyzing the concept "life", biologists prefer to investigate which characteristics of organisms give them the property of being alive, because they expect that this will allow them to answer the question: what is a living organism (Van Regenmortel, 2010c).

Not all living entities are organisms since organs like hearts and kidneys that are considered to be alive are not organisms. One approach is to consider the class of living organisms as a cluster concept of properties (Dieguez, 2012; Hacking, 1991) that need not all be present in all the members of what is also often called a polythetic class (Beckner, 1959). Many of these properties tend to be present simultaneously because of underlying relationships between them that increase the probability that they will be found together. Defining life as a cluster concept overcomes the problem that it has not been possible to find a set of necessary and sufficient conditions for defining living organisms.

Living organisms may possess the following cluster of properties:

1. compositional and structural properties such as the presence of nucleic acids and proteins
2. the presence of a definite boundary such as a membrane, cell wall or shell which restricts the exchange of substances with the environment and allows selective interactions with it (Mahner & Bunge, 1997, p. 143).
3. functional properties such as the capacity to grow and develop, reproduce and repair themselves
4. the presence of metabolic activity and adaptation that arise from interactions with the immediate environment consisting of things that can be directly influenced by the living organism or may act upon it (Van Regenmortel, 2010c). The last two types of properties give living organisms the intrinsic autonomy that is their principal characteristic.

In order to be living, an organism must possess a certain number of these properties although it does not need to possess them all. This makes it possible to consider as organism sterile hybrids such as mules or plant seeds with a completely dormant metabolism but to exclude dead organisms since these consist only of the remains

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of living organisms that have ceased to exist (Rosenkrantz, 2001). Since living organisms may possess only some of the properties listed above, they can also be described as fuzzy sets defined as classes of objects with a continuum of grades of membership (Van Regenmortel, 2007a; Zadeh, 1965). Such sets do not conform to the axioms of Aristotelian logic known as the law of contradiction (a swan cannot be both white and non-white) and the law of excluded middle (a swan is either white or non-white) since they allow for the existence of intermediates between living and non-living organisms. This shows the futility of trying to solve the mystery of the origin of living organisms by identifying a clear-cut borderline between cellular life and non-life (Bruylants et al. 2010).

In addition, living organisms are also members of a reproductive lineage characterized by a life cycle and they must possess a functional autonomy that allows them to exercise control over themselves and to be at least partly independent from other organisms and environmental influences (Wilson, 2005). Organs and living tissues are not organisms because they are not functionally autonomous and do not reproduce themselves as members of a lineage. Organelles such as mitochondria and chloroplasts that were free-living organisms more than a billion years ago before they were incorporated into eukaryotic cells by endosymbiosis, are not considered to be living organisms today because they lack autonomy and a life cycle.

4. A viral factory which is the compartment in infected cells where virus replication takes place cannot transform a virus into a living organism

Viral factories have been well characterized in cells infected with viruses that belong to several viral families such as the *Poxviridae*, *Iridoviridae*, *Herpesviridae*, *Togaviridae*, *Bunyaviridae*, *Flaviviridae and Reoviridae* (Novoa et al. 2005). Viral factories are intracellular compartments in virus-infected cells where viral genome replication, transcription and translation take place as well the assembly of virus particles. They consist of perinuclear and cytoplasmic foci that recruit various cellular organelles such as mitochondria and cytoplasmic membranes, thereby creating a new compartment in the infected cell that allows efficient viral replication and morphogenesis. No viral factories have been identified in the case of viruses that infect bacteria and archaea, probably because the entire cell is transformed into a viral factory.

Since the formation of viral factories occurs after a cell has been infected by a virus, virologists who like to use anthropomorphic metaphors for describing the properties of viruses suggested that viruses were clearly able to manipulate and reprogram the infected cell and that they transformed the viral factory into a new type of living viral organism (Claverie, 2006; Claverie & Abergel, 2010; Forterre, 2010a; Claverie & Abergel, this issue).

Flint et al. (2009) warned of the dangers of using anthropocentric metaphors to ascribe actions and motives to viruses (see section 1) and heeding their advice could have avoided making the unjustified suggestion that a novel and complex cellular organelle that appears in a cell as a result of virus infection is able to transform a virus into a living organism. Claverie (2006) has claimed that one of the attractions of considering viruses as living viral organisms arising from viral factories instead of virions capable of undergoing a replication cycle, is that it makes it then easier to accept that non-living viruses could have originated from cells by the loss of certain cellular components and the subsequent progressive loss of certain functions. It may well make it easier but there is still no compelling reason for believing it.

On the basis of metagenomic analysis of genomes collected from the oceans, it is sometimes suggested that viruses are the most abundant biological entities on our planet. Forterre (2010a), however, pointed out that if viruses, as distinct from virions, are considered to be living cells, they cannot themselves be more abundant than cells since they can only represent a fraction of the cells on earth.

5. The metaphor of virocells does not transform viruses into cellular living agents

Since viruses lack ribosomes but always have a capsid that allows new hosts to be infected, Raoult and Forterre (2008), who consider viruses to be alive, proposed that the living world should be divided into two groups: the ribosome-encoding organisms (REOs) that include eukaryotic, archaeal and bacterial organisms and the capsid-encoding organisms (CEOs) that include all the viruses. The importance given to ribosomes for defining organisms reflects the creation by Woese, Kandler, and Wheelis (1990) of the three domains bacteria, archaea and eukaryotes that were differentiated because they all contained ribosomal proteins that were, however, of different types.

Since nucleic acids from either viruses or bacteria can infect hosts and be replicated, Raoult and Forterre (2008) made the somewhat unusual claims that there are no fundamental differences between these two types of nucleic acid-containing entities and that a virus can be entirely defined by its coding capacity. They proposed the following new definition of a virus: “Viruses are CEOs that are composed of proteins and nucleic acids that self-assemble in a nucleocapsid, do not multiply by binary fission and use an REO for the synthesis of their proteins and production of the energy and precursor molecules that are required for their life-cycle”. As could be expected, this new definition has not been widely accepted because it departs considerably from the orthodox view held by most virologists that in the absence of cells, viruses are nothing but inanimate, complex organic matter (Moreira & López-Garcia, 2009; Wolkowicz & Schaechter, 2008).

Forterre (2010a) subsequently introduced the terms “virocell” to characterize the cellular form of the virus and “ribocell” to designate the cell type of REOs. When viruses are defined as CEOs, i.e. organisms that produce virions, infection with a virion must somehow be able to transform an infected REO cell into a genuine viral, cellular organism, a transformation that occurs when the virus expresses itself into a cellular form (Forterre & Prangishvili, 2009; Forterre, 2012). Using another striking metaphor, the claim was made that the dream of a “normal” cell is to produce two cells whereas the dream of a virocell is to produce hundreds of new virocells through the dissemination of virions (Forterre, 2010a).

The proposal to divide the living world into REOs and CEOs was very much influenced by the discovery of the very large mimivirus with a diameter of about 600 nm that infects amoeba and possesses about 2.5 times more genes than the smallest known bacterium *Mycoplama genitalium* (La Scola et al. 2003; Raoult et al., 2004). Forterre took the view that a virus that is larger than many small prokaryotes, is visible with an optical microscope and is encoding about 1000 proteins simply had to be an organism. When mimivirus infects its amoeba host, it has been claimed that the infected amoeba becomes the virocell of mimivirus and, because of some superficial morphological similarity, that the viral factory of mimivirus can be assimilated to the nucleus of the virocell.

It seems that the virocell concept was invented to solve what was believed to be a contradiction, namely that viruses could be considered to be living organisms whereas all organisms are made up of cells. The virocell concept does indeed reconcile the idea that viruses are living with the classical view that all living organisms are made of cells, although a simpler way to resolve the contradiction would have been to accept that viruses are not organisms. According to Forterre, the virocell becomes a living viral organism

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during viral replication and virion assembly, i.e. when the host genome is either inactive, destroyed or altered by the expression of the viral genome and the original infected ribocell can no longer reproduce. When the infection results in a proviral latent state as in lysogeny, the viral genome is not expressed in the cell which then remains a ribocell. During this latent state, virions are sometimes produced and the cell is still able to divide by binary fission in which case the cell is considered to be a ribovirocell (Forterre, 2010a).

The supposed ability of viruses to do things such as "reprogramming" cells and "generating" new types of living cells finds its origin in metaphors that attribute to viruses a human-like capacity of intentional, goal-directed behavior that is able to control the evolution of life (Forterre, 2012). We often use intentionality metaphors for describing the behavior and activities of living organisms because of our tendency to explain all human actions in terms of their intended goals. To a human observer, organisms may appear to have goals and this may lead to the conclusion that their behavior is intentional. The fallacy of viewing a biological activity as intentional was made fun of by Rosenberg (1985, p. 44) when he pointed out that the phenomenon of heliotropism (i.e. the movements of a sunflower when it maximizes its exposure to the sun) is obviously not due to the plant's desire to increase the number of photons landing on its leaves since the phenomenon exists only because it contributes to the reproductive fitness of the organism. Darwinian evolution operates through selective retention of useful functional features and it appears to be goal-directed only by analogy with the intentionality of human behavior (Van Regenmortel, 2002). If viruses are viewed as living organisms, it may encourage the use of intentionality metaphors for describing their behavior but there is of course no justification for attributing imaginary intentions and goals to viruses.

6. The tree of life metaphor

Following the explosion of genomic sequence data, modern phylogenetic methods have revealed that horizontal gene transfer (HGT) is very common in archaea and bacteria. As a result, it becomes very difficult to discern any vertical gene transmission which is accepted to form the core of all lineages in a Tree of Life (TOL). In addition, non-tree like processes such as endosymbiosis and hybridization also contribute to obscuring the line of descent from parent to offspring.

It is commonly believed that trees of genes are able to reveal trees of species, although this may lead to a circular phylogeny since species need first to be established by taxonomists in order to enable molecular geneticists to know which genomes they should sequence and compare (O'Malley & Koonin, 2011). In one study that examined 191 species from all three domains of life, only 31 universal genes coding mainly for ribosomal proteins could be identified. Since prokaryotic genomes contain between 1000 and 4000 genes, building a tree on the basis of only 31 genes produces a TOL that takes into account only about 1% of the genome (Dagan & Martin, 2006; Doolittle, 1999).

Since the history of life is usually visualized as a history of bifurcating cell divisions that occur during genome replication, it is also possible to consider a TOL as a tree of cells or organisms instead of species. However, this can also lead to circular reasoning since the species tree which is now disguised as a tree of cells must be known beforehand although the aim of constructing the tree is actually to infer this species tree (O'Malley & Koonin, 2011). An alternative strategy is to replace the search for a universal TOL by the search for a web or for network models of sets of genes that could represent more complex evolutionary processes (Doolittle & Bapteste, 2007).

In line with the current emphasis on evolutionary developmental biology, Bapteste and Dupré (2013) have recently proposed that a living entity is also a developmental process consisting of specific temporal stages of stabilized biological processes. Genealogical trees can be constructed because reproductively linked sequences of similar entities form lineages within the limits of the branch of the tree in which they are located. However, Bapteste and Dupré (2013) stressed that the tree of life is a model of limited usefulness for analyzing the microbial world because of the widespread phenomenon of horizontal gene transfer (HGT) between different microorganisms. HGT blurs the vertical inheritance from parent to offspring and makes it virtually impossible to distinguish a tree of cells from a tree of genes.

It seems extremely unlikely that the evolutionary histories of the archaea, bacteria and eukaryotes could be united in a single TOL. The evolutionary origin in eukaryotes of mitochondria, cellular compartments, the nucleus and nuclear pores and the cytoskeleton have never been elucidated and the development of all these features may not be traceable if the genomes of extinct ancestors are not available for sequencing. If life already existed before the emergence of the last universal cellular ancestor and of capsids and ribosomes, it will be difficult or impossible to determine the exact moment when life originated (Forterre, 2010b). Over millions of years, genomes accumulate huge numbers of mutations and diverge beyond recognition by losing all information about ancestral sequences, the only exception being functionally essential regions that are subject to stabilizing selection. Although these difficulties will not stop speculation about possible evolutionary scenarios such as the suggestion that viruses could have existed before cells (Koonin, 2009), it may not be feasible to overcome the stumbling block known as the underdetermination of scientific theories caused by insufficient data since this is likely to make it impossible to adjudicate which theory is better than its numerous, possible alternatives (Stanford, 2013).

7. The metaphor of living viruses has no place in the TOL metaphor

The Tree of Life is usually interpreted as a metaphor to represent the history of life and proponents of the view that viruses are alive will obviously insist that viruses should be included in the tree. Forterre (2010a), however, conceded that in this case the Tree of Life could not be a tree in the strict sense of the term because viral evolution only partly occurs in a classical tree-like fashion. It is generally accepted that it is only possible to accommodate viruses and cells together in a universal network of life instead of a tree of life.

Life's early history concerns only microbial evolution and it seems impossible to explain the origin of life, prokaryote evolution and the prokaryote to eukaryote transition in terms of a single TOL (Martin, 2011). Evolutionary processes tend to erase the evidence of sequence similarities and since "there is more to evolution than will fit on any tree" (Martin, 2011), it is to be expected that viruses cannot be included in a single TOL. Different authors disagree about this conclusion with the debate centering mainly on the direction of HGT between cells and viruses, i.e. whether HGT occurs mostly from cells to viruses or the other way around (Forterre, 2010c). Since viruses or cells could have recruited their genes from cellular or viral lineages that are now extinct, different investigators reach different conclusions because they disagree about which proteins are of eukaryal, archaeal or viral origin (Filée et al., 2008; Moreira & Brochier-Armanet, 2008; López-Garcia & Moreira, 2009; Moreira & López-Garcia, 2009). It has even been suggested that viral genomes may act as invention factories for new genes (Ogata & Claverie, 2007) although the anthropomorphic metaphor of viruses being

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able to "create" new genes may not find general acceptance. Creativity is a human capacity and is also an attribute of an hypothetical Creator but seems out of place for describing the behavior of viruses.

Proponents of the view that viruses are living organisms may claim that they make that statement only in a metaphoric sense but they cannot escape the conclusion that TOL is a true metaphor. The suggestion of DJ McGeoch (Calisher, Horzinek, Mayo, Ackermann, & Maniloff, 1995) that viruses could be described as "mistletoe on the Tree of Life" is another appealing metaphor. Those who view living viruses only as a metaphor will agree that there is indeed no need to include viruses in the TOL metaphor.

8. Viruses are not involved in battles and wars against their hosts

Following the proposal that the living world could be divided in REOs and CEOs, it has been claimed (Forterre & Prangishvili, 2009) that these two branches of life have been at war with each other for a few billion years. These authors also suggested that this ongoing conflict between cells and viruses led to the invention of major novelties that shaped the development of life on our planet such as the invention or creation of DNA and the eukaryotic nucleus.

Explanations of biological phenomena and evolution often suggest that organisms possess human-like abilities that enable them to "create" novel mechanisms and entities, to "borrow" pre-existing successful cellular features and to "survive by winning fights and wars". Such metaphors arise because we tend to view human intentionality as the direct cause of human actions, an interpretation that leads to the generalization that the behavior and activities of all living systems can equally be explained in terms of goals and purposes (Van Regenmortel, 2007b). Any functional part of an organism that contributes to its survival is then interpreted as achieving a certain goal and this may sometimes foster the belief that organisms must have been designed by a deity to function in a preordained way. Organisms with their adaptations can indeed give the appearance of having been designed and this encourages the use of metaphors of goal-directed teleology for describing biological processes in terms of design and purposes (Ruse, 2002). Natural selection has now replaced a Creator as the most commonly accepted explanation for evolution although there is no selection but only differential survival and reproduction. Fitness, which corresponds to anything that increases the probability (but not the certainty) of survival and reproduction in a given environment (Millstein, 2002) is often regarded as the basis of selection, although fitness has been described as "another phantom of the human mind" (Hanke, 2004).

In reality, a biological function does not entail design for that function and functional descriptions do not require psychological notions of design and purpose (Allen & Beckoff, 1995). Attributing a purpose to organisms or viruses is entirely subjective since purpose has no real existence outside the mind thinking of it (Hanke, 2004) and the unscientific habit of supposing that all objects and events have purposes should be discouraged. A better formulation is to say that organisms are fashioned or shaped by selection pressures instead of invoking intentionality and purpose as explanatory concepts (Van Regenmortel, 2007b). Darwinian natural selection occurs blindly by preserving what is useful for living organisms in a given environment and eliminating what is not useful or harmful. It is equally inappropriate to try to explain the behavior of passive, non-living agents such as viruses by attributing to them imaginary intentions and goals that are assumed to help them overcome their enemies. It seems that biologists who believe that viruses are alive tend to have an "intentionalist" view of evolution and ascribe intentions to biological entities.

9. HIV is not trying to develop new strategies and mechanisms to escape the host immune system

In the case of viruses that cause human diseases, the infection process and its consequences are frequently described in terms of battles and wars between host and virus (Wick & Yang, 2013). Descriptions of these battles focus mainly on the ability of the immune system to restrict virus infection and eliminate virus-infected cells and on the assumed capacity of the virus to develop new strategies and mechanisms for evading immune responses. In recent years, the best known description of such warfare concerns the ability of the human immunodeficiency virus (HIV) to defeat the immune system and cause AIDS (Nowak & McMichael, 1995).

In the initial stage of HIV infection, the virus infects so-called helper T cells, bearing CD4 receptors recognized by the virions, which play an essential role in the emergence and maintenance of an effective antiviral response. Many helper cells are killed while macrophages engulf virus particles and degrade them into small peptides that find their way into grooves of proteins known as human leukocyte antigens (HLAs). Certain cells subsequently display the complexes of viral peptides bound to HLAs on their surface and this allows helper T cells that bear a unique receptor for the peptide to bind to it. This recognition process results in helper T cells secreting cytokines which are small molecules capable of activating other components of the immune system such as killer T cells and B lymphocytes. These B cells subsequently become plasma cells that secrete antibodies able to neutralize the virus. Activated killer T cells kill virus-infected cells that present HLA-peptide complexes on their surface, which will lead to a further decrease in the number of helper T cells.

A crucial question is why killer T cells and the secretion of antibodies able to neutralize the virus are unable to completely eradicate HIV whereas the immune system is often capable of doing so successfully in the case of many other virus infections (Hilleman, 2004). The answer has been found to lie in the extraordinary variability of the virus (Fraser et al. 2014). HIV is an RNA-containing retrovirus that uses a viral enzyme called reverse transcriptase to copy its RNA genome into double stranded DNA, thereby reversing the normal cellular process of transcription from DNA to RNA. The transcribed viral DNA is inserted into the genome of the host, where it directs the production of more viral RNA and viral proteins that are subsequently assembled into virions. It so happens that reverse transcriptase is a very error-prone enzyme that incorporates at least one mutation in every transcribed DNA copy. Since a billion HIV particles may be produced in an infected patient each day and the viral population is likely to double every two days in the absence of any immune control, this means that in 10 years, the virus is able to undergo as much genetic change as humans might experience in the course of millions of years (Nowak & McMichael, 1995). One consequence is that the probability of mutations arising that are more functional for the virus becomes extremely high. This is corroborated by the continuous production of viral variants and escape mutants that are able to evade the immune defenses of the host, for instance because mutated peptides presented at the surface of infected cells become undetectable by the body's immune system. Several years after the initial infection process, this usually leads to the almost complete loss of helper T cells and immune defenses in the host and to the onset of AIDS.

There is therefore no reason to suggest that HIV needs to continuously develop new strategies and mechanisms in order to escape the immune system defenses since its enormous variability on its own allows the virus in the end to completely evade immune control and drive disease progression. It must also be pointed out that the evolution of the host and of HIV occurs over totally

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different time scales, which diminishes the significance of what is sometimes said to be a momentous evolutionary battle between virus and host (Burton, Stanfield, & Wilson, 2005). Furthermore, since neutralizing antibodies typically appear only two to three years after the initial infection, the developing antibody response lags behind the rapidly diversifying virus, which probably explains why antibodies are unable to control the infection (Ackerman & Galit, 2013). Since viral resistance against antibody-mediated neutralization generally develops when autologous serum neutralization has faded, it has also been suggested that it is unlikely that such changes are driven by escape from autologous humoral immunity (Bunnik et al. 2009).

It is often stated that if we knew which successful strategies HIV has developed for defeating the immune system, that knowledge could reveal weaknesses in the immune defense system that may be exploited for designing an effective vaccine. That expectation seems to assume that HIV is able to develop or *design* effective mechanisms for winning the battle between virus and host because it possesses a human-like goal-directed capacity for winning battles in a metaphoric sense. It has been argued elsewhere (Van Regenmortel, 2015) that design terminology is not appropriate for describing the behaviour of 1) viruses that do not actively evolve but are passively evolved by the cells they have infected since their evolution is carried out by the metabolic machinery of cells (Moreira & López-Garcia, 2009) and 2) scientists who attempt to develop vaccines not by allegedly *designing* immunogens capable of eliciting neutralizing antibodies but only by *selecting* such immunogens empirically. If the production of stochastic mutations arising from the error-prone activity of reverse transcriptase is the only so-called "mechanism" used by HIV to defeat the immune system, there is in fact little hope that the strategy known as rational design will succeed in developing an effective HIV vaccine (Van Regenmortel, 2014a, 2015). The rational design of an HIV vaccine consists in determining the structure of a small region (i.e. an epitope) in a spike present on the surface of the virus that is recognized by an antibody that can neutralize the infectivity of the virus. It is then assumed that this epitope which is antigenic since it is recognized by the antibody will also be immunogenic, i.e. capable of eliciting the same type of protective antibody when it is used as a vaccine. This unwarranted expectation arises because antigenicity is confounded with immunogenicity, as if the ability of an epitope to bind to a protective antibody implies that it must also be able to induce protective antibodies when it is administered to an immunized host. Instead of designing vaccine immunogens, the vaccine developers are actually designing improved HIV antigens able to recognize a single antibody molecule (Van Regenmortel, 2015). In the case of HIV, the enormous antigenic variability of the virus as well as the requirement for extensive antibody affinity maturation for obtaining neutralizing antibodies invalidates an approach that is sometimes effective with other viruses (Van Regenmortel, 2014a, 2015).

The failure so far to develop an effective HIV vaccine is also due to the fact that vaccinologists tend to underestimate the polyspecificity of antibody molecules. The polyspecificity of an antibody refers to its ability to bind a variety of diverse epitopes in the same or in different antigens, a phenomenon that reflects the degeneracy of the immune system (Eisen & Chakraborty, 2010; Notkins, 2004; Sperling, Francus, & Siskind, 1983; Van Regenmortel, 2014b). Antibody polyspecificity is responsible for the fact that an epitope structure deduced from the structure of a complex between HIV and a neutralizing antibody will not necessarily reveal which immunogenic structure was recognized during the immunization process used to obtain the protective antibody. There is therefore no reason to expect that such an epitope would necessarily be an effective vaccine immunogen (Van Regenmortel, 2014a).

10. Conclusions

One unexpected finding of the present analysis of the use of metaphors for describing the properties of viruses is that metaphors that treat viruses as living organisms have an uncanny knack of becoming self-fulfilling prophecies with a life of their own. This makes it possible to add a few terms to the anthropomorphic lexicon (see section 1) condemned by Flint et al. (2009) and to say that viruses also do not dream, create, invent, design or borrow anything. Viruses would of course also find it difficult to survive since they are actually not living.

Although metaphors add a touch of poetic license to scientific arguments, they should be recognized for what they are since otherwise their users take the risk of being misled and embroiled in unhelpful controversies that may impede the progress of science.

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