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To be or not to be alive: How recent discoveries challenge the traditional definitions of viruses and life

Patrick Forterre

Institut Pasteur, Unité de Biologie Moléculaire du Gène chez les Extrêmophiles, Département de Microbiologie, F-75015, Paris, France

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ABSTRACT

Three major discoveries have recently profoundly modified our perception of the viral world: molecular ecologists have shown that viral particles are more abundant than cells in natural environments; structural biologists have shown that some viruses from the three domains of life, Bacteria, Eukarya and Archaea, are evolutionarily related, and microbiologists have discovered giant viruses that rival with cells in terms of size and gene content. I discuss here the scientific and philosophical impact of these discoveries on the debates over the definition, nature (living or not), and origin of viruses. I suggest that viruses have often been considered non-living, because they are traditionally assimilated to their virions. However, the term virus describes a biological process and should integrate all aspects of the viral reproduction cycle. It is especially important to focus on the intracellular part of this cycle, the virocell, when viral information is actively expressed and reproduced, allowing the emergence of new viral genes. The virocell concept theoretically removes roadblocks that prevent defining viruses as living organisms. However, defining a "living organism" remains challenging, as indicated by the case of organelles that evolved from intracellular bacteria. To bypass this problem, I suggest considering that all biological entities that actively participate in the process of life are living.

1. Introduction: how recent discoveries impact the debate over the living/non-living status of viruses

Scientists often describe the material world using concepts first developed by human beings to describe their environment and mode of existence. However, these concepts may take on very different meanings when translated into a world far beyond human experience. For example, the concepts of space and time have different meanings for us, in our daily life, and for astrophysicists dealing with general relativity. Quantum mechanics also highlight major confrontations between human experience and reality at the ultramicroscopic level. Similar problems came to the forefront in biology when scientists began to try to apply concepts such as "life" and "organism", to the world of microbes (Dupre & O'Malley, 2009, Pradeu, 2010). The case of viruses is especially interesting because biologists have argued for more than one century about their living and organismal status (Helvoort, 1994, Kostyrka, 2016, Méthot, 2016).

Viruses use the same macromolecules (proteins and nucleic acids) as cellular organisms for the reproduction and expression of genetic information. This indicates that viruses and cells fit into the same historical process that we call "life". Viral genomes may consist of RNA (a situation encountered only in viruses) or DNA. They have a reproductive cycle with two characteristic phases. In the extracellular phase, the viral genome remains inactive within a viral particle, also known as a virion, until it encounters a susceptible cell that can be infected. In the intracellular phase, the viral genome may temporarily remain silent (as a free chromosome or integrated into the cellular chromosome) or be actively expressed and replicated in the infected cell. When activated, these coupled processes lead to the production of infectious virions (viral particles), which serve as vehicles for the dissemination of viral genomes. In virions, the viral genome is encased within a protein coat, which may differ in complexity

E-mail address: forterre@pasteur.fr.

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between viruses, with some containing or surrounded by a lipid envelope and/or decorated with polysaccharides.[1]

The nature and definition of viruses, especially their "living" status, have been the focus of heated debates among biologists for decades (Helvoort, 1994, see Kostyrka, 2016, and Méthot, 2016). Recently, these debates have become more acute following three startling discoveries. First, it has been demonstrated that viral particles outnumber cells by one or two degrees of magnitude and that viral genes greatly outnumber cellular genes in most environments (Kristensen, Mushegian, Dolja, & Koonin, 2010, Suttle, 2013). Viral genes also massively integrate into cellular genomes, greatly influencing cellular evolution (Forterre & Prangishvili, 2013). Second, the sharp distinction between viruses infecting prokaryotes (bacteriophages) and eukaryotes was put upside down by the discovery of evolutionarily related viruses infecting cells from the three domains of life, Bacteria, Eukarya and Archaea (Abrescia, Bamford, Grimes, & Stuart, 2012). Finally, the traditional view of viruses as submicroscopic entities has been challenged by the discovery of giant viruses infecting Amoeba, such as Mimivirus and Pandoravirus (Philippe et al., 2013; Raoult et al., 2004; see also Claverie and Abergel, 2016). Here, I critically review how these discoveries have led to new proposals about the nature, definition, and origin of viruses, trying to emphasize the philosophical aspects of these debates. I will argue that we should probably modify the meaning of common concepts, such as life or organisms, when applied to biology, in order to make them useful for an objective description of nature, and introduce new concepts (such as the virocell concept) to prevent some of the ambiguities inherent to current paradigms.

2. The traditional view of viruses assimilated to their virions

2.1. The "virus/virion" paradigm

The name "virus" was traditionally used both as a concept and as a general term to name concrete objects (viral particles) within the material world. This often led to a narrow concept of virus assimilated to viral particle (also called virion). This assimilation is general and pervasive for both historical and practical reasons (Forterre, 2012b) and will be referred to as the "virus/virion" paradigm hereafter.[2] Historically, the origin of the "virus/virion" paradigm can be traced back to the discovery of viruses, because the term "virus" was first used to describe the infectious entities able to pass through a Chamberland porcelain filter that was known to retain bacteria (Bos, 1999). Practically, virions can be isolated and purified, allowing their biochemical analysis and their observation. As a consequence, they can be visualised and used to illustrate and popularize the virus concept with pictures in publications, textbooks and conferences.

By contrast, viruses have no specific form in the intracellular phase, with their components being dispersed among those of the infected cell. As a consequence, the intracellular phase has been largely excluded from traditional virus definitions. For example, Jacob and Wollman (1961) defined a virus as "*a genetic element enclosed in a protein coat*". The "virus/virion" paradigm has indeed influenced most definitions of a virus. For example, Lwoff (1957) claimed that viruses carry only one type of nucleic acid (either RNA or DNA), whereas cells carry two types: DNA for information storage, and RNA for gene expression. However, this affirmation is correct only in the framework of the virus/virion paradigm, because, like cells, DNA viruses undergo transcription to generate viral messenger RNA! The resulting viral mRNAs belong to the virus just as much as cellular mRNAs belong to the cell. Thus, all DNA viruses actually possess both types of nucleic acid, DNA and RNA. Most virologists would deny that they identify the virus with the virion, but in fact they are constantly liable to do this implicitly. The best example is provided by the work of environmental virologists who have traditionally determined the number of viruses in a given environment by counting the number of viral-like particles (assimilated to viruses) by epifluorescence microscopy (Forterre, 2013).

Originally, the virus/virion paradigm was not contradictory with the idea that viruses are living because the mysterious entities that crossed the Chamberland filters displayed all the classical properties of life: reproduction, multiplication and evolution by natural selection. However, once it was realized that virions are not tiny cells but giant macromolecular complexes, viruses were frequently considered to be simple biological "objects", intermediate between living and non-living entities, existing "*at the threshold of life*" (Bos, 2000) or not living at all (Morange, 2011; Moreira and Lopez-Garcia, 2009; Van Regenmortel, 2003).

2.2. A special case of the virus/virion paradigm: viruses as replicators

In apparent contradiction with the "virus/virion" paradigm, viruses have been traditionally classified according to the nature of their nucleic acid (Baltimore, 1971). Several authors indeed used to define viruses primarily on the basis of their genomes. This happens, for instance, when viruses are considered to be "pure genetic information" (Rohwer & Barott, 2013) or when they are primarily defined as "parasitic genetic elements" (Koonin and Wolf, 2013) or replicators (Jalasvuori & Koonin, 2015; see also Koonin and Starokadomskyy, 2016). These definitions can be viewed as particular forms of the "virus/virion" paradigm in which the virion is assimilated to the viral genome, located within the capsid. This is well illustrated by the fact that naked RNA molecules infecting plants are recognized as viruses (e.g. Narnaviruses) by the International Committee on the Taxonomy of Viruses, ICTV.[3] These infectious RNA have been called recently "*capsidless viruses*" by Dolja and Koonin (2012). In that case, the viral genome is implicitly assimilated to a "virion", since it corresponds to the "infectious element" triggering the infection.

Historically, the view that confuses virus and their genomes probably explains why the "escape theory" became the dominant explanation for the origin of viruses in the second half of the last century (see section 2.5). Hence, in this theory, the origin of viruses is linked to the autonomization of some part of cellular chromosomes (prokaryote or eukaryote) that becomes a selfish replicator, the acquisition of a proteinic capsid to form a virion being a secondary event.

2.3. The "virus/virion" paradigm minimizes the role of viruses in biological evolution

A significant consequence of the "virus/virion" paradigm is that most biologists profoundly underestimate viral "creativity" (i.e. the opportunity for emergence and selection of novel traits encoded by viral genomes). This is probably because viruses, confounded with their virions, are assimilated to passive, inert objects (Forterre, 2011). As a consequence, it is often assumed that all (or almost all) viral genes are derived from the cellular hosts (the "viral pickpocket"

[1] The different types of virion morphologies, which can be quite diverse, are illustrated on the ViralZone website (Hulo de Castro et al., 2011).

[2] For previous critiques of the "virus/virion" paradigm, see Bandea, 1983, Claverie, 2006, Forterre, 2011, Van Regenmortel, 2010.

[3] These infectious RNA molecules only encode an RNA replicase homologous to that of RNA viruses.