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Are viruses alive? The replicator paradigm sheds decisive light on an old but misguided question

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ABSTRACT

The question whether or not "viruses are alive" has caused considerable debate over many years. Yet, the question is effectively without substance because the answer depends entirely on the definition of life or the state of "being alive" that is bound to be arbitrary. In contrast, the status of viruses among biological entities is readily defined within the replicator paradigm. All biological replicators form a continuum along the selfishness-cooperativity axis, from the completely selfish to fully cooperative forms. Within this range, typical, lytic viruses represent the selfish extreme whereas temperate viruses and various mobile elements occupy positions closer to the middle of the range. Selfish replicators not only belong to the biological realm but are intrinsic to any evolving system of replicators. No such system can evolve without the emergence of parasites, and moreover, parasites drive the evolution of biological complexity at multiple levels. The history of life is a story of parasite-host coevolution that includes both the incessant arms race and various forms of cooperation. All organisms are communities of interacting, coevolving replicators of different classes. A complete theory of replicator coevolution remains to be developed, but it appears likely that not only the differentiation between selfish and cooperative replicators but the emergence of the entire range of replication strategies, from selfish to cooperative, is intrinsic to biological evolution.

1. Introduction

"Alcohol-based hand sanitizers kill most types of bacteria, viruses and fungi in a few seconds" — claims a random ad in a family magazine. Regardless of the technical (in)accuracy of this statement, its anonymous author(s) has unwittingly answered, in the affirmative, a question that over several decades had been debated by many scientists: *Are viruses alive?* The logic here is simple and arguably undefeatable: you cannot kill something that is not alive. Much the same argument was made by a science writer in the top scientific journal *Nature*, on the occasion of the discovery of virophages, viruses that parasitize on other, giant viruses of amoeba. The same simple reasoning applies: if something can be sickened and eventually brought to death, it surely is alive to begin with (Pearson, 2008). In an influential conceptual paper stimulated by the discovery of giant viruses and virophages that parasitize on them, Raoult and Forterre classify viruses as one of the two fundamental categories of organisms (capsid-encoding organisms, in contrast to the ribosome-encoding organisms, i.e. cellular life forms), with the obvious implication that viruses are living beings (Raoult & Forterre, 2008). However, the opposite view has been forcefully propounded as well: viruses cannot be considered alive because of their inability to reproduce without a cellular host (Lopez-Garcia, 2012; Moreira & Lopez-Garcia, 2009). Each of these viewpoints certainly reflects distinct, important features of viruses: they combine "animate" (reproduction and the ensuing evolution) and "inanimate" features (lack of autonomy, existence of an inert state). This dichotomy fuels the perpetual "life vs non-life" debate among researchers, and even more so among scientific journalists and interested members of the public.

Certainly, the answer to the question "Are viruses alive?" depends on the definition of life or of the "state of being alive".

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Although this issue has been pondered at length for centuries, there is no generally accepted definition of life or "aliveness" (Trifonov, 2012, 2011), and it has been argued that such definitions are neither feasible nor needed (Bruylants, Bartik, & Reisse, 2010; Koonin, 2012; Szostak, 2012). Simple examples from different areas of biology show that a sharp boundary between the living and non-living (or animate vs inanimate) entities is but an illusion. Growing bacteria and archaea are certainly alive. However, many if not most of them enter a dormant (persistent) state under starvation and other forms of stress (Lewis, 2010; Wood, Knabel, & Kwan, 2013). The dormant cells have greatly reduced metabolic activity and are either able or unable to resume growth and division depending on the environmental conditions as well as random factors. Are dormant cells alive or not? Intuitively people are inclined to answer "yes": dormant cells are clearly not dead, because we can resume their growth under given conditions. But, from a biochemical standpoint, they dramatically differ from truly alive cells. Therefore, dormant cells exist in some third, "inert" state that is neither truly "alive" nor inanimate. Even more dramatically, Gram-positive bacteria, such as *Bacilli* and *Clostridia*, as well as cyanobacteria, sporulate under adverse conditions (Adams, 2000; Galperin et al., 2012; Paredes, Alsaker, & Papoutsakis, 2005). Spores are virtually inert biochemically and again, may or may not come back to active reproduction. Are they alive or dead? Or do they represent the third state as well? Thus, the "dead-alive" dichotomy in the classification of biological entities seems to present unsolvable conandra whereby the borders of life cannot be clearly defined.

Interestingly, the apparent paradoxes with respect to "aliveness" are not limited to prokaryotes. For example, micro-animals tardigrades can survive prolonged incubation in outer space where no biochemical reactions are possible (Jonsson, Rabbow, Schill, Harms-Ringdahl, & Rettberg, 2008). However, upon the return of the satellite to Earth, some of the tardigrades survived and even were able to produce offspring. Should they be admitted as "alive", in the regular sense, during this exposure? Many other situations in biology can be invoked, where a rational answer to the question "Is X alive or not?" is out of reach, but those mentioned above should suffice to make the point that this question generally does not allow a yes-or-no answer.

In the above discussion, we conflate the issue of the state of aliveness (whether or not a given object can be considered alive or not) with that of the category of animate (as opposed to inanimate) objects (whether or not a given object belongs to the category of living beings). In general, the two issues are distinct: a dead organism certainly still belongs within the living category. However, when it comes to viruses, these different aspects of aliveness are entangled and are typically discussed jointly. Indeed, viruses can be viewed as not belonging to the category of living beings because they are incapable of autonomous reproduction and extracellular virions are in a dormant (inert) state.

Given that the question on the "aliveness" of a particular class of entities is generally unanswerable (although for many objects the answer can be "intuitively obvious"), this appears to be a non-question. In contrast, in general, it is not difficult to delineate the range of biological phenomena. Although sometimes we cannot give a defendable answer to the question "is X alive?", we argue that it is always possible to tell whether a particular entity belongs to the realm of biology. Such an answer can be given within a fundamental concept that can be denoted the Replicator Paradigm, which we discuss in the following sections, with an emphasis on viruses.

2. The replicator paradigm

All life that is currently known centers around DNA or RNA molecules, replicating carriers of genetic information which all share fundamentally the same chemical structure. The regular structure of nucleic acids and the complementarity between purine and pyrimidine bases make nucleic acids uniquely suited for replication (and other processes that involve sequence copying, such as transcription). Replication with fidelity above the error catastrophe threshold (sometimes called the Eigen threshold) ensures inheritance of genetic information and automatically entails evolution via both selection and random drift (Eigen, 1971; Koonin, 2011; Szathmary & Demeter, 1987). Distinct, partly autonomous replicating units are known as replicators, a concept and a term that have been originally proposed by Richard Dawkins (Dawkins, 1982, 1976), and are widely used in theoretical modeling of evolution at different levels (Godfrey-Smith, 2000; Griesemer, 2000; Hull, Langman, & Glenn, 2001; Maynard Smith & Szathmary, 1995; Nanay, 2002). A key facet of the replicator concept as considered here is the (partial) autonomy with respect to genome replication.

Clearly, replicators are tightly linked to two other major biological concepts, the replicon and the genome. A replicon is literally a unit of replication (Jacob, 1993; Jacob & Brenner, 1963). The major difference from a replicator is that not all replicons possess any degree of autonomy, and conversely, a replicator does not have to be a single replicon. The concept of genome is effectively isomorphous with the replicator concept, but with a different emphasis: a genome is the entirety of nucleic acid sequences that are stably associated with a given replicator (we avoid speaking of "genetic information" here because parts of the genome often are not informative in the strict sense). Thus, each genome corresponds to a replicator that can encompass multiple replicons, e.g. in eukaryotes.

The (partial) replicative autonomy is the key feature that makes each replicator a distinct unit of evolution which employs a specific evolutionary strategy and evolves along a unique trajectory. Certainly, the autonomy of replicators is never complete, and no replicator can survive in isolation. The degree of a replicator's autonomy can be readily measured by the repertoire of the components of the replication machinery (enzymes and other proteins required for replication) that are encoded in the replicator genome, and by the presence of dedicated replication and/or transposition signals. Replicators form a continuum along the autonomy axis although with some degree of arbitrariness, distinct classes ranked by the level of autonomy can be envisaged (Fig. 1 and Table 1).

At the left end are "quasi-replicators", such as prokaryotic toxin-antitoxin (TA) and restriction-modification modules, ORF (Open Reading Frame)-less Group I self-splicing introns and mini-inteins, that have neither specific replication or transposition signals nor genes for any components of the replication machinery. Nevertheless, these entities possess properties that promote their survival and in some cases survival of other replicators on which they parasitize. A case in point are the TA modules that are "addictive" to prokaryotic cells because when the TA element is lost, the cell is killed by the toxin (Gerdes, Christensen, & Lobner-Olesen, 2005; Makarova, Wolf, & Koonin, 2009) (see Table 1). The Group I introns are ribozymes that catalyze their own excision and splicing of the flanking exons as well as reverse splicing which provides for limited spread to ectopic sites (Nielsen, 2012; Nielsen & Johansen, 2009). Mini-inteins are an extremely peculiar variety of parasitic or commensal quasi-replicators that autocatalytically excise from the target genes at the protein level while carrying no signals for replication or transposition (Mills, Johnson, & Perler, 2014; Starokadomskii, 2007).

Immediately to the right of the quasi-replicators are viroids, arguably, the simplest bona fide replicators. Viroids are small RNA molecules of only 400 nucleotides or so that encompass signals for replication initiation by the host DNA-dependent RNA polymerase or the RNA-dependent RNA polymerase of the "host" virus but

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