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Viruses as living processes

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ABSTRACT

The view that life is composed of distinct entities with well-defined boundaries has been undermined in recent years by the realisation of the near omnipresence of symbiosis. What had seemed to be intrinsically stable entities have turned out to be systems stabilised only by the interactions between a complex set of underlying processes (Dupré, 2012). This has not only presented severe problems for our traditional understanding of biological individuality but has also led some to claim that we need to switch to a process ontology to be able adequately to understand biological systems. A large group of biological entities, however, has been excluded from these discussions, namely viruses. Viruses are usually portrayed as stable and distinct individuals that do not fit the more integrated and collaborative picture of nature implied by symbiosis. In this paper we will contest this view. We will first discuss recent findings in virology that show that viruses can be 'nice' and collaborate with their hosts, meaning that they form part of integrated biological systems and processes. We further offer various reasons why viruses should be seen as processes rather than things, or substances. Based on these two claims we will argue that, far from serving as a counterexample to it, viruses actually enable a deeper understanding of the fundamentally interconnected and collaborative nature of nature. We conclude with some reflections on the debate as to whether viruses should be seen as living, and argue that there are good reasons for an affirmative answer to this question.

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1. Introduction

It is still often assumed that life is composed of discrete, genetically homogeneous, organisms, either single cells or the descendants of a single originating cell in the case of multicellular organisms. This assumption accords well with the orthodox metaphysical thesis that the world is composed of things, or substances. These things are typically thought of as fairly stable entities, and as bearers of properties. Although these properties can change, some subset of them must persist if the entity itself is to persist. Things are thought of as having reasonably clear boundaries, and their important properties, the properties that determine their continued existence, as being intrinsic, i.e. as being grounded on features that lie entirely within those boundaries.

Realisation of the near omnipresence of symbiosis, however, is one factor that has presented severe problems for this background position (Dupré, 2012; chap. 7, 11). Widespread symbiosis threatens the clarity of boundaries between organisms, and even the uniqueness of these boundaries. This paper starts from a position articulated in Dupré and O'Malley (2009): the typical living system consists of interconnected and collaborating segments of many genetically distinct lineages. Humans, for instance, comprise, as well as the lineage of 'human' cells derived from an original zygote, numerous lineages of symbiotic bacteria, archaea, and fungi. These vary in the extent to which they are mutualistic, commensalistic or parasitic; often the same organism can play different such roles at different times (Méthot & Alizon, 2014). The boundaries of the organism, which may or may not be taken to include some or all of these symbionts, may be to some extent indeterminate. The realisation of the integrated nature and blurred boundaries of organisms has led to claims that traditional (substance-based) metaphysical accounts of individuality should be replaced with a

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process ontology, as the only 'philosophy of organism' that can make sense of the biological phenomena as we now know them (see for instance (Henning, 2013)).

Whilst the adoption of a process ontology might be thought of merely as an epistemological strategy our claim here is an ontological one: biological systems *are* processes.[1] It is not just that biological things are complexly interrelated with other biological things. These relations are necessary for the persistence of the biological system. Whereas persistence is the default state of a thing, the persistence, or stability, of a process requires explanation; it is actively maintained. The stabilisation of multicellular organisms, in particular, has been found to depend not only on internal processes, but also on the interactions between its symbiotic constituents, which leads us to argue that all or most of these should be seen as parts of the overall process that constitutes the organism. The organism, thus broadly construed, can then be seen as a stable eddy in the flow of interconnected biological processes (see also (Dupré, 2012; chap. 4, 5)).

The aim of this paper is to explore the role of viruses in relation to this general processual view of life. Viruses have usually been seen as distinct individuals that are entirely competitive among themselves, and entirely harmful to anything else unlucky enough to be affected by them. Given this understanding it is not clear how viruses could fit into the more integrated and interdependent picture of life that we have just sketched. They are rather seen as distinct entities that follow their own intrinsic (and pathogenic) agenda.

We want to challenge this view on two counts: first we will claim that viruses should be understood very much in the same way as other lineages in the flow of living systems. As we will discuss in Sections 2–4, recent research in virology shows that there are also 'nice' viruses. Often, as is very familiar, the intersection of viral processes with organisms is destabilising and pathogenic. But viruses also make important contributions to the stability, or health, of the hosts they intersect with. Symbiotic systems therefore may include viruses as well as plants, animals and microbes (this point is elaborated by Pradeu (this issue), a paper highly complementary to ours).

Second we will argue that viruses have to be seen as processes. Viruses pass through an intricate and specific sequence of states or activities that must be seen as an ongoing and repeated series of cycles (Sections 5–8). Specific stages of the cycle might have significant stability (for instance the virion stage), but this stability is temporary, and the fact that there are (perhaps very many) such temporarily stable entities can only be understood by reference to their role in the larger process that *is* the virus. This processual nature of viruses will be elaborated in more detail in the second half of the paper.

Bringing both the processual nature of viruses and their intermittent 'niceness' to the fore will show that viruses are not counterexamples to the integrated and dynamic picture of biological systems advocated here and elsewhere (Dupré, 2012). Indeed, the example of viruses serves to reinforce (and further inform) a processual view of biological systems. Viruses, or so we will claim, are vital and omnipresent constituents of the larger flow of interconnected processes that make up biological systems.

2. The microbiome and its benefits

Not long ago, it was standard to think of a multicellular organism as a lineage of differentiated cells, originating from a founder cell, typically a fertilised egg. Microbes, especially bacteria, were generally thought of as potential enemies, poised to invade and attack the multicellular system. It gradually became clear, however, that multicellular organisms are typically populated by vast numbers of microbial residents and that these often do little harm. Perhaps they are just passengers, taking advantage of a warm and well-resourced niche. But it was also clear that in exploiting these resources some bacteria also provide some benefit. In the case of animals like cows, which rely on digesting such recalcitrant molecules as cellulose, it was long known that this was only possible with the help of resident bacteria, and here can be seen the beginnings of a shift in perception of microbes from dangerous threat to necessary symbiont.

More recently, it has become clear that microbial symbionts do far more than just these often essential contributions to digestion. They are involved in the modulation of development, and play a central role in the development and homeostasis of the immune system (Chu & Mazmanian, 2013; Round & Mazmanian, 2009; Spasova & Surh, 2014). They have even been found to connect to the central nervous system (Bravo et al., 2012). In plants, hugely complex systems of bacteria and fungi modulate the interface between the plant's roots and the surrounding soil (Philippot, Raaijmakers, Lemanceau, & van der Putten, 2013). These insights have contributed to a major philosophical reconsideration of the concept of the biological individual, with some researchers arguing that multicellular organisms are typically massively symbiotic individuals or, as they are sometimes known, *holobionts* (the concept of holobiont is discussed in Mindell, 1992; Rohwer, Seguritan, Azam, & Knowlton, 2002; Rosenberg, Koren, Reshef, Efrony, & Zilber-Rosenberg, 2007).[2] The human microbiome, according to some, consists not of passengers, but of parts of an integrated individual.

Importantly, according to this integrated view of the biological individual, the organism itself in its stable state turns out to be a product of a myriad of interactions between host and microbes. The body then is not just the passive and pre-existing vessel that can host a bacterium; it is shaped and maintained by the interaction with its 'guests'.

The human body, however, is not only populated by bacteria, archaea and fungi but also by viruses. It is difficult to provide a good estimate of the number of virus particles within the human body, but as techniques have developed for finding them, results have been more or less consistent with the analogical inference from simpler systems studied that there are about ten times as many virus particles as cells (Brüssow & Hendrix, 2002). This might immediately raise a question how, if viruses are as uniformly nasty as the standard view supposes, we manage to stay alive at all.

3. Viral collaborators?

As pointed out at the beginning of this paper, there is evidence that the resident community of viruses provides services to biological systems; possibly even such vital services that we should consider them, like many bacteria, to be integral parts of complex symbiotic biological organisms.

Apart from the very obvious fact that they frequently fail to kill us, there is a general reason for supposing that the vast numbers of viruses or virus-like particles found in the human body are an integral part of the system rather than a reservoir of predators, generally kept sufficiently under control to allow the system to function. This is that the composition and size of the virome seem to be remarkably stable (see Section 5 for a more detailed discussion of the term 'virome'). If viruses were primarily hostile, then we would expect their numbers to oscillate in the way analysed in the

[1] For more on the distinction between epistemological and ontological processism see (Rescher, 1996).

[2] More general philosophical discussion is provided in (Dupré & O'Malley, 2009; Bouchard & Huneman, 2013; Pradeu & Carosella, 2006).

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classic Lotka/Volterra predator/prey models; but this appears not to be the case (Minot et al., 2011; Reyes et al., 2010; Wylie, Weinstock, & Storch, 2012). In fact the virome responds gradually and in a systematic way to changes in diet (Minot et al., 2011), which rather suggests a positive functional response to environmental change.

There is of course no denying that the way viruses reproduce and maintain their own life cycles is not very nice for the host: generally when they have used a cell for their own reproductive purposes they kill it as they leave. But it is also possible that this very killing of cells is functional for the larger system of which a virus is part. Cells after all die all the time, and stabilising a complex system including cells of many kinds will very centrally involve mechanisms for killing cells that are surplus to the requirements of the system. Apoptosis, or programmed cell death, is for this reason an essential process in multicellular organisms.

The fact noted above, that phage populations and strains remain stable within an individual implies a stable ecological relation between these and their bacterial hosts, and it seems very likely that this is functional for the whole system. It is debated whether bacteria have any equivalent of apoptosis, and since bacterial communities almost invariably coexist with phages, it is plausible that stable relations between the two have evolved in many cases, especially where these are functional for a larger system of which both are part.

The simplest targeted cell destruction role to attribute to viruses would just be the killing of hostile invaders. And indeed there is evidence for such a role. Barr et al. (2013) provide evidence for a coevolved relationship between metazoan mucosal surfaces and phages. They describe a chemical binding between elements in the mucus and phage capsids, resulting in an enriched ratio of phages to bacteria on mucal surfaces. This, they plausibly suggest, protects the metazoan from external bacterial invasion while also providing the phages with a location richly provided with host bacteria. Importantly, it is not just the regulation of cell numbers that matters here. The bacteriophages provide a non-host derived immunity to the host which can be crucial to its survival. The viruses that target prokaryotes indirectly support the immune system of the host by taking over some defence work.

There are many other ways in which viruses are now known to help their hosts, mostly, it seems, by playing roles similar to that of some bacteria, for instance in the regulation of gut morphology and function or the shaping of the immune system. Such ‘stabilising’ effects of viruses on their hosts are discussed in more detail by Pradeu (this issue) and we will not further dwell on this point here.

What we want to focus on in the next section is another manner in which viruses might provide benefits to their host or to populations of hosts and that is in the context of DNA flow between cells. In these examples it is the dynamic nature of the systems involved rather than the stabilities created which matters most.

4. The benefits of a flow of DNA

DNA, we often think, is trapped deep in the heart of the cell. It, or its copies, is passed on to more or less identical cells when cells divide. In this process the DNA doesn’t escape the cell; it is just that the cell splits, and the DNA moves on in two separate prisons.

Surrounding the flow of DNA is a penumbra of the closely similar nucleic acid RNA, the molecule through which DNA sends its developmental and metabolic orders into the surrounding biological action (indeed some of it has long been known as “messenger” RNA). The DNA, however, trapped in its sequence of cell nuclei, is separated from the outside world by two membranes, the nuclear membrane and the cell membrane, precisely regulating the molecular milieu in which it lives. In the process of mitosis, or cell division, the DNA briefly escapes its inner membrane (at least in those organisms undergoing open mitosis, see (Guttinger, Laurell, & Kutay, 2009)), but it never passes beyond the outer membrane of the cell. This is the vertical flow of nucleic acids through evolutionary time, and the flow often conceived as accumulating the aeons of evolutionary wisdom and carrying it forward to the ever more complicated and well-adapted organisms that exist today.

But there is also a horizontal flow. Viruses carry on their life cycles by entering cells, reproducing there, then leaving to find new cells to invade. Although typically the viral DNA does not remain in the invaded cell, which is very often killed in the course of the encounter, sometimes it does. Retroviruses, for instance, have a single-stranded RNA genome which is reverse-transcribed after infection into double-stranded DNA and inserted into the host genome. After insertion the viral DNA is treated by the host like its own DNA, meaning it is transcribed and reproduced together with the rest of the host genome.

Importantly, in some cases retroviruses can become entrapped in the host genome and turn into what is known as endogenous retroviruses (ERVs). Over time this has resulted in a significant addition of DNA sequence to mammalian genomes and it is estimated that up to 8% of the human genome actually consists of ERVs (Griffiths, 2001; Lander et al., 2001). This means that significant proportions of the DNA in eukaryotic organisms originally entered its cell-line by way of a virus.

This horizontal flow of nucleic acids is vast. Think of the 10^{29} or so bacteria that are estimated to live in the Earth’s oceans, an inconceivably large number, but not as large as the 10^{30} phages, the viruses that prey on them (Suttle, 2007; Whitman, Coleman, & Wiebe, 1998). 10^{30} phages, it is estimated, would cover hundreds of light years placed end to end, so the scale of this horizontal flow is vast indeed (see also Morgan, this issue). Not much of this would need to establish itself in the vertical flow to make a significant impact on the evolutionary process. And in fact it is becoming increasingly clear that there is just such an impact. Among microbes (bacteria, archaea, and to some extent single-celled eukaryotes) lateral gene transfer, to a large extent mediated by viruses, is undoubtedly important, and has led many theorists to question whether the traditional representation of evolution as a ‘tree of life’ portraying the vertical relations between kinds of organisms is defensible or even meaningful. Microbes have acquired their DNA from a variety of ancestors (Bapteste et al., 2009).

Horizontal exchange of DNA between bacteria can also be mediated by plasmids, circular pieces of DNA that are distinct from the main genome and which are typically found in bacteria (for an overview see (Sherratt, 1974) or (Smillie, Garcillán-Barcia, Francia, Rocha, & de la Cruz, 2010)). Like viruses, plasmids can move from cell to cell. Some have the ability to generate a pilus, a process that enables them to transfer to another cell by the quasi-sexual process of conjugation. Others rely on the assistance of other plasmids. Well-studied plasmids provide their host cells with useful functions, such as antibiotic resistance, virulence, or nitrogen fixation. They thus can provide a reserve of access to such functions within a bacterial community without the energetic costs of every member of the community maintaining these resources. The ability of a community to respond to a threat such as an antibiotic by distributing a resource held by a few members of the community is far more efficient than requiring every member of the community to be independently equipped to respond to any likely threat. Indeed, there is an obvious parallel with the division of labour between cells of different kinds in a multicellular organism, a parallel that lends some support to the hypothesis that bacterial communities may themselves be best seen as multicellular individuals.

This mode of function is well established for the case of microbial communities such as biofilms. But as we have already noted, complex eukaryotes are all or almost all in fact symbiotic systems

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involving microbial consortia as well as a lineage of eukaryotic cells (Dupré & O'Malley, 2009). So if transfer of genetic material is important to the functioning of microbial communities, it is important to the functioning of us. When, for example, we consume antibiotics to combat harmful bacteria that are damaging us, antibiotic resistance plasmids that help our symbiotic communities resist this threat are likely to be good for us—though needless to say they also carry the risk of being co-opted by the pathogenic bacteria the antibiotics are intended to destroy.

It may be, in fact, that the virome functions as a vast storehouse of genetic resources. Minot et al. (2011) compared the results of a metagenomic analysis of the human virome with a database of known antibiotic resistance genes, and found 614 matches. Wylie et al. (2012) sum up the situation: "like bacterial plasmids, bacteriophages serve as reservoirs for mobile genetic elements in bacteria. In turn, this suggests that bacteriophages may affect human health by contributing to or changing the metabolic capabilities of the resident bacterial community." As one of us has suggested elsewhere the best way to think of the human genome itself may be as a database or library of resources that can be used in multiple ways by the cell (Dupré, 2005; see also Noble, 2006). From this point of view we might then see the virome as a reserve warehouse of genetic resources; or to vary the metaphor slightly, the genome as the open shelves of the library, with the virome as the stacks—though the genome here must be interpreted to include the 99% of the human genes that reside in the microbiome.

An even more speculative thought is that the ability of microbes, specifically our symbiotic microbiome, to recruit genetic resources from the biotic environment may be a much more efficient way of responding to environmental contingencies than evolution by random genetic variation and selection. One minor example of this is the acquisition of genes from marine bacteria by the gut bacteria of Japanese people that enable them to digest seaweed (Hehemann et al., 2010). The diversity of roles played in the functioning of complex symbiotic systems by bacterial consortia suggests that this could turn out to be a frequent type of occurrence. If so, it is likely that viruses or plasmids are the agents responsible for this kind of traffic.

In summary we see then that in addition to the vertical travel of DNA down the generations of a cell there is a vast stream of nucleic acids moving between cells. And though generally the interactions between these streams are transient, there is enough long-lasting interaction that a substantial proportion of the DNA in the vertical stream arrived there by intersection with the horizontal stream. What once seemed to be an isolated system going in one direction only (vertical DNA flow) is actually much more open and flows in several directions at the same time.

Given this tight interconnection between viruses and their hosts it seems at least a plausible hypothesis that viruses in complex multi-organismic systems are vital functional parts of the whole. As we have seen in the first part of this paper, they may well play essential roles in regulating the numbers of different cell kinds, especially microbial kinds, and immunological roles in eliminating deleterious cells, certainly potentially hostile microbes. They may well also play important roles in mediating the transfer of genetic resources, surely between symbiotic microbes, and possibly even between the latter and cells in the eukaryotic host. And more generally, as discussed by Pradeu (this issue), viruses can also support the development of their hosts and help them survive under challenging conditions.

5. The human virome

In the previous sections we have repeatedly referred to the 'virome' without specifying in detail what is meant by this term. In part this is because the question of how to define the virome has no straightforward answer. The problems with the term, as we want to show in this section, hang together with the issue of how we think of the ontological status of viruses (which we will discuss in Section 6).

The suffix '−ome' is now widely used to refer to a class of biological entities of some general kind found in a particular biological context. The 'liver transcriptome' for instance is the set of transcripts (i.e. the RNAs corresponding to transcribed DNA sequences) that can potentially be found in liver cells. Following this use of the suffix the set of viruses found associated with humans would therefore be called the 'human virome'.

We indeed find the term used in this sense in the life sciences, for instance in Delwart (2013), who writes: "It is now conceivable that all viral species commonly infecting human[s] (i.e., the human virome) will soon be determined". The fact of infection itself does not tell us whether the presence of the virus is detrimental, beneficial or of no further consequence to the host. It also does not tell us whether the infection results in a prolonged or only temporary presence of the virus in the host system. (The only restriction in this definition lies in the term 'commonly', which suggests that 'uncommon' human viruses will not be counted as part of the human virome.)

Other scientists use the term virome in a more restricted sense, referring only to the *viral component* of the microbiome, the latter being defined as the set of all microbes (bacteria, archaea, fungi and viruses) stably associated with an organism (Wylie et al., 2012; see also Lecuit & Eloit, 2013).

Defining the virome as a sub-set of the microbiome implies a different understanding of the set of viruses to which it refers. The human microbiome, as we have noted, is not just a list of microbes that infect (or have the potential to infect) humans, but a complex set of organisms that display a more stable association with the human host. What counts as a part of the human virome would then be limited to viruses that have a *stable* association with the human body (be it beneficial, detrimental or neutral with respect to the survival of the host).

A third and even more restricted understanding of the term virome follows from a more restricted understanding of the term microbiome. A highly cited article on the human microbiome project begins: "The human microbiome project (HMP) reflects the fact that we are supraorganisms composed of human and microbial components" (Turnbaugh et al., 2007). Later, the same article notes: "The collective genomes of our microbial symbionts (the microbiome) provide us with traits we have not had to evolve on our own". This understanding of the microbiome appears specifically to exclude purely harmful microbes – and therefore also any harmful viruses, if we treat the virome as part of the microbiome. Crucial to this definition, then, is the idea of 'good' or 'bad' microbes.

These examples, in summary, show different ways of understanding the term 'human virome', the first depending on a distinction between (common and uncommon) *infections*, the second on the notion of a 'stable' association between virus and host and the third depending on a notion of the 'goodness' of a virus. Very probably there are others.

All of these distinctions have their own problems, but the most intriguing is the idea of a 'good' virus. As we have discussed in Sections 3 and 4, we now know of many cases where the presence of the virus has beneficial effects on the host. But does this mean that there is a set of viruses that are good for us and another set that harm us? And is this a dichotomy with which we can define sharply the term 'virome'?

In line with what we know about bacterial symbiosis, recent insights into the roles played by viruses suggest that such a classification is not possible. Whether a virus is good or bad for us, just as for a bacterium, is not a characteristic that it carries

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like an essence. Whether a bacterium or a virus is 'good' or 'bad' is always a question of what it *does*, and not merely a question of intrinsic properties. Some more general philosophical reflections on the ontological status of viruses will help to strengthen this point.

6. What are viruses?

Viruses are extremely diverse in their structure and complexity. Generally they are fairly specific in their choice of hosts, and it appears that just about every kind of cell can be host to some kind of virus. Some viruses contain genomes that may code for as few as two proteins (see, for instance, Nogawa et al., 1996). At the other extreme are the recently identified giant DNA viruses such as the mimivirus, with genomes larger than those of many bacteria.[3] When we think of the viruses that occupy our environment, as countable things in the ocean or in our bodies, we are probably thinking of virions, the stable state in which viruses exist when they are not actively engaging with cells. A virion contains a central core of nucleic acid, RNA or DNA, single- or double-stranded, its genetic material. This is surrounded by a protein coat, or capsid, which both serves to protect the viral genes, and has surface features that enable it to bond to appropriate host cells. Some viruses also contain the capsid within a phospholipid bilayer membrane that is typically captured from the host cell in the process of exiting through the host cell membrane. Others contain a lipid layer directly surrounding the central, genome-containing, area. The stability and inactivity of the virion lends intuitive support to the common claim that viruses are not living things.

But the virion state is neither the only state in which viruses exist, nor is it strictly speaking inactive (see Claverie & Abergel; and Forterre, this issue). The virion can attach itself to a suitable host cell where it initiates a series of events that typically lead to the destruction, or lysing, of the cell and the production of hundreds or thousands of new virions. The details of these changes are again diverse. In some cases the virion enters the cell complete with its protein coat, in other cases this is abandoned and only the genetic material enters the cell. Various molecular events may follow, but in most cases the transcription and translation machinery of the cell is eventually hijacked for the copying of the viral nucleic acid and the production of viral proteins. Some of these proteins may be involved in the process of redirecting the activities of the cell's genome. The virion in some cases will self-assemble automatically, in others it will require the assistance of special proteins. In the case of the very large viruses such as mimivirus, much of the translation machinery is actually encoded by the virus.

The one thing that is constant throughout these changes is the viral genome. One natural thought is therefore that the virus should simply be identified with its genetic material. Unlike more complex living systems there is a stage in its life cycle within the cell in which it is, apparently, reduced to nothing but its genes. The genome might be seen as the viral essence, with various attachments, notably the capsid, as contingent additions at various stages in the life cycle. This, however, is not a tenable position for several reasons.

The first problem concerns the existence of many viruses in a so-called latent state within the host cell. In some cases, for example of herpesviruses, the latent state consists of 'episomes', the viral DNA taking a circular form that is then tethered to the host chromosome. In this state the viral DNA must elude the repair mechanisms of the host genome, and can undergo mitosis alongside the host DNA. To this end it undergoes chromatinization similar to that of the host chromosome, and is subject to epigenetic modification (see, e.g., Lieberman, 2008). Under these circumstances, it is questionable whether the viral genome is properly to be seen as a distinct entity, rather than an addition, if unwelcome, to the host genome.

This question is more pressing when one considers retroviruses, for instance human immunodeficiency virus (HIV). HIV, in the virion state, is a single-stranded RNA virus. When it invades a cell it is reverse transcribed into double-stranded DNA, and inserts itself into the host genome. First, though the inserted DNA is isomorphic to the HIV RNA, it is, nonetheless, a different chemical. Second, the question whether inserted DNA is a distinct entity rather than an addition to the host genome is very hard to answer. If one is tempted to insist that it is a distinct entity, one might reflect that large parts of eukaryote genomes originated from viral insertions or intra-genomic replications of viral genomes, as discussed above for the case of ERVs. For substantial periods after their initial entrapment, ERVs may continue to express themselves as viruses, producing virions that can infect other organisms. In time they typically lose this ability and may either become genomic junk or, frequently, may be adapted to serve vital functions in the host organism. A number of ERVs are expressed in the mammalian placenta, for example, and appear to serve important functions, possibly exploiting viral techniques for modifying host reactions to alien genomic elements (Haig, 2012). At what point does an ERV cease to be a virus, and become part of the genome into which it has been inserted? The lack of any clear answer to this question suggests that the question is in some way poorly posed.

7. Going viral

The problem underlying the question just raised is similar to the one we encountered when trying to define the virome: drawing clear boundaries is not possible as long as we presume that a virus is some sort of stable thing with given properties. In the same way that we cannot use that picture to come to an understanding of the 'goodness' or 'badness' of a virus, we cannot use it to decide whether ERV DNA is a virus sitting inside a genome or not. Or so we want to claim here.

The problem is that identifying the virus with anything less than a cycle is bound to lead to failure. A single thing, for instance an episome or a virion, is always less than the actual virus. It is only part of what makes the virus. What matters is not the DNA molecule itself but what it *does* (or can do) in a particular context: qualifying as viral is a matter of doing characteristic things, such as invading cells and replicating, rather than having a particular intrinsic property. This is just as well, since there are no properties that a virus has at every stage of its life cycle.

And this is where the question at the end of the last but one paragraph misfires: an ERV is a virus just as long as it maintains the capacity to contribute to a viral process. Whether it lives in a host genome is immaterial. In the case of viral latency as an episome, the episome should count as viral because occupying that state, and expressing the genes that it expresses to maintain itself during latency, are things that some viruses do to maintain their life cycles.

We suggest that rather than trying to provide a set of characteristics that qualify something as a virus, we should concentrate on the activities that constitute the viral life cycle. In other words, we should see viruses as processes rather than things. Rather than worry whether an episome, or a piece of naked DNA replicating in its host cell is a virus, we should simply recognise that it is part of the viral process and it is because of this belonging to a specific process that it qualifies as 'viral' DNA.

The desirability of the process perspective is highlighted by the difficulty in counting viruses. Here we don't refer to practical

[3] Amazingly, it appears that there are even viruses that attack these giant viruses (see La Scola et al., 2008). The authors of this report suggest that these 'virophages' might be seen as vehicles for moving DNA between giant viruses.

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difficulties (though these are considerable!) but conceptual difficulties. There is no problem (again conceptually) in counting virions. A single virion enters a cell and at some later, perhaps much later, time, some number of virions emerge from the remains of the lysed cell. How many viruses were present in the intervening time? Suppose the virus exists as multiple episomes and passes through several events of mitosis. Many of the resultant cells die before the next stage of viral replication is activated. All the cells are infected, but are some more infected than others, with more viruses, if they have a greater number of episomes? Is the death of one of these cells also the death of a specific number of viruses? It is not that one could not choose to attach answers to these questions but it is not clear why one would want to. We are interested in the unfolding of a process rather than in tracing the careers of discrete entities, or things.

One final point will conclude the present brief discussion on the nature of viruses. The boundaries between viruses and related entities are not easy to define. One very important class of related entity is the plasmids, which we have already discussed in more detail in Section 4.

Plasmids are generally considered to be differentiated from viruses by their lack of a capsid; they consist of naked DNA. But as we have noted, viruses do not have capsids at all stages in their life cycles. In fact, like viruses, some plasmids can attach to a host eukaryotic genome in the form of an episome. In this state, indeed, they are not strictly naked, as they must undergo the chromatinization necessary for replication in mitosis in the host genome. So what is the difference between a viral and a plasmid episome? The answer, obviously, is that they are parts of processes that differ at other stages of their life cycles. So again, the only way of understanding the generally intended limits of the concept of a virus is to recognise that a virus is a process.

8. Are viruses alive?

It remains hotly contested whether viruses should be counted among the living (see Claverie & Abergel; Forterre; Koonin; Van Regenmortel; Kostyrka, this issue). It is not entirely obvious why this is a question that anyone should care deeply about. It sounds rather like either a matter of fairly arbitrary definition, or a relic of an earlier time when being alive was associated with some fundamental ontological difference from merely physical matter. The question, however, may help to bring the different strands of our discussion together and allow us to further clarify the concept of living systems as being inherently processual.

Elsewhere (Dupré & O'Malley, 2009) one of us has argued that standard reasons for denying that viruses are alive are misguided. In brief, the problem is that most of the criteria involved would exclude from the category of the living much that we almost universally agree should be included. One central example is the criterion of autonomy. Without going into great detail about what exactly this criterion involves, the fact that viruses require essential resources from the host cell for their reproduction is often taken to exclude them from the category of the living. But given that most or all eukaryotic organisms, including ourselves, depend on a multitude of symbiotic organisms for our survival and, a fortiori, reproduction, it would appear that on this criterion we are not alive either—presumably a reductio ad absurdum of the criterion in question.

The main thesis of that earlier paper is that living systems are constituted by complex interactions between lineage-forming elements of many different kinds. Sometimes, perhaps almost always, these elements include viruses. In that paper we suggested that viruses were living when active in these larger systems, but not when in the dormant virion state. Van Regenmortel (this issue) argues that a virus active in a larger living system is no more a living entity than any other *part* of the system, an organelle or an organ. It is not clear whether a great deal hangs on which side of this debate one prefers, given that it is doubtful that there is any sharp living/non-living distinction. However, there is an obvious difference between a virus and an organelle: a virus is part of a process distinct from the organism in which it is at a particular time active. It has a history that intersects that system for a particular period of time, and may continue in another system.

There are two issues that need to be revisited in this discussion of the status of viruses, namely a focus on collaboration and an emphasis on process, the two key notions that we mentioned at the beginning of this paper. Collaboration is a prominent feature of any biological system, even if no viruses are involved. Symbiotic bacteria are a key example of agents that work together with other organisms to form holobionts. As a consequence, the actual agent (for instance the cow that is said to digest cellulose) has now to be understood as something more complex, as it is the larger symbiotic system that should be said to do the digesting.

We encounter the same issue in the virus examples discussed above. We have seen that in many cases an organism cannot do what it does without viruses being actively engaged inside it. And the virus in turn cannot maintain its own cycle without the processes going on inside the cell. But the virus examples seem to take us further than the examples of symbiotic bacteria. If we simply look at the interplay between bacteria and multicellular organisms there might still be a temptation to look at what is going on as a collaboration between two stable things, each with its own properties. Like a TV set and a DVD player that work together to achieve a particular task, the bacteria and the host cell come together as two pre-existing machines that are somehow compatible and work together.

But the example of viruses helps to reinforce the more general point that such a simple picture of collaboration has to be expanded. The collaboration we see between virus and host is not a simple interaction between two stable things, but has to be understood as a collaborative interaction between processes. As we noted above, the virus itself can only be understood if it is depicted as a cycle, and the horizontal and lateral flow of genetic material has shown that the host itself is not a 'pure' and/or stable entity in itself. Both 'things' that come together in the collaboration are intrinsically fluid and temporarily stabilised entities (processes). And the activity we are interested in (be it digestion or the maintenance of a reproductive cycle) turns out to be a *product* of a coming together of different processes.

In all of the above the coming together of entities (processes) has played a key role. But what comes together may also separate again. We have pointed out, for instance, that a key difference between a virus and an organelle is that the former can re-emerge from the cell and continue its own life cycle. If we adopt the perspective of a process ontology we can make sense of the constant merging and separating, because processes can certainly merge into a single process and may even maintain their identity sufficiently to part company again. A slightly fanciful example might help to illustrate this point.

Imagine that two battles, both parts of the same war and hence involving the same armies, intersect. In each battle the Oceanians are driving the Eastasians backwards, but in different directions. In each case the retreating army is following orders to retreat to a particular rallying point, and their pursuers are under orders to follow them in the direction they are retreating. The battles cross, and continue in their different directions. In the areas in which they cross, however, the combatants are engaged in both battles. When they encounter an enemy they will not, we suppose, enquire as to which battle that soldier is fighting before deciding whether to engage; they are all equally enemies, to be killed if possible. If

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soldiers accidentally wander into a battle in which their army is engaged, they are liable to become part of the battle. In the case imagined this is just what has happened to all the combatants in both battles who find themselves in the zone of intersection.

The point of the example is that it is a teleological element, in this case the intentions or orders of the combatants, that enables the processes to re-emerge from their intersections. By contrast, it is hard to imagine two streams of water merging, flowing together, and then separating again, to reconstitute the very same processes that were the original merging flows. After the convergence there is nothing that identifies a particular molecule with the flow from which it originated. In the case of the soldiers their intentions achieve this continuity through the period of merger.

This, we suggest, is the right way to think of the intersection of a virus with its host organism, more specifically in the case where the host survives its interaction with the virus. We have two processes which, for a time, merge into a coherent process and which may, thereafter continue as separate processes (or, often, as one host process and many viral processes). A particular entity, say a viral episome, may be part of more than one process, for example mitosis as part of the lineage of cells in which it is resident, and viral reproduction, the process which will separate off again at some later point.

But viruses surely don't have intentions in the same sense as conscious beings have them, so how can we claim that the battle example is a good guide for our thinking about viruses? It is important to note that in the battle example the intention does not merely describe an end state at which the soldier eventually arrives somehow or other. The soldiers must keep their goals in mind and allow these to guide their actions; if the soldiers forget their orders then the process will quickly break down.

This is important because it brings the idea of a process extended through time into the picture. We should not just think of the final goal, but also of the beginning of the process and the activities that tie together its various stages; where one is coming from matters as much as where one is going. The same view, we claim, applies to the virus example. A virus does not, of course, have a memory any more than it has intentions. But there nevertheless is a certain coherence and interconnectedness between the different activities that we label 'viral' and which we take to constitute a viral life cycle. The genes an episome expresses, for instance, are expressed to maintain the viral life cycle. The function of the episome is therefore not just defined relative to the actual system in which it finds itself (a mitotic cell for example), but it is related to the future and the past of the virus (thought of as an active cycle). We cannot understand what makes the episome a *viral* DNA if we don't take into account the whole cycle or process that is the virus. In contrast, a mere DNA plasmid is not working as part of this viral cycle and this is where it clearly differs from a viral episome.

This nicely resonates with how Nicholas Rescher describes processes (Rescher, 1996). Rescher introduces a view of processes as being defined by a *functional unity*; there is a 'programmatic structure' that characterises and unifies a process. Interconnected activities that form a functional unity are key to his understanding of processes: "A process is made into the item it is not through its continuing ("essential") properties, as with a classically conceived substance, but by its history, by the temporal structure of its descriptive unfolding across time. The identity of a process is constituted through a sequential pattern of action […]" (Rescher, 1996, p.41).[4]

We see such a functional unity also in the case of viruses but not in the case of the two water streams that combine and separate again. In the case of the two intersecting streams of water we do of course have some form of structure, the physical boundaries that help us identify the two streams. But nothing in this structure makes the streams reform after the intersection. The viral life cycle has a stronger unity than this, as it manages to intersect with other processes and re-emerge again.

What gives the process 'its' structure is a difficult question. What is clear in the case of the virus-as-process is that it cannot simply be the DNA (or any of the other entities that are part of the viral cycle), because we have seen that the entity captured by the idea 'virus' is much larger than simply its genome or other specific stages; it is always a whole cycle, i.e. a running process or overarching activity, that defines the virus.

This process-centred perspective provides a very different understanding of activity and function in biological systems from merely the interaction of discrete individual things, a difference that is ultimately evolutionary. The episome is part of a process that has a pattern (the cycle) and it is this cycle that has evolved its distinctive trajectory. The interconnectedness between different parts of such processes has developed over evolutionary time and is what unites these stages into the larger whole that we refer to as the virus. It is in this coherence that we find the analogy to the intention and memory that determine the soldier's continued participation in a particular battle. At the same time, the persistence of this process has come to depend on multiple interactions with further living processes that have each their own cyclical structure and mode of persistence. Crucially, the virus may both have its independent cyclical structure and be a necessary part of a larger system with which it interacts. Hence there need be no unique division of biological activity into distinct, non-overlapping processes.

The notion of the independent active cycle that has evolved over time also brings us back to the living vs. not-living question. We do not suggest that an entity is living simply by virtue of being part of a living system. What more is required? The key is, again, to recognise the essentially processual and interconnected character of life. We should not try to decide whether an entity, a traditional substance, has a set of properties that qualify it as living, but rather to identify activities that sustain both conceptually and actually separable processes in the characteristic and extraordinarily efficacious ways characteristic of life as we know it. If we simply consider viruses as *particles* then there is no doubt that they are seriously deficient in the qualities needed to sustain living processes. On the other hand, as we have seen above, viruses *do* have the capacity to contribute powerfully to such sustenance. The key to reconciling these observations is once again to adopt the processual perspective. It is the viral *process* (and not simply a virus particle) that can take on a functional, or even essential, role for the processes it intersects with (for instance by regulating bacterial cell numbers (Section 3)).[5] And as some of these latter processes are unquestionably living processes, for example ourselves, it would seem odd to deny the status of living to the viral processes that interact with them in this life-sustaining way. Virions, then, are not living things certainly, but they are stages of living processes.

9. Conclusion

Viruses raise questions on many different levels. There is, for instance, the question of whether they are good or bad for us, as

[4] Another approach to this problem is through Reichenbach's concept of genidentity, as discussed in (Guay & Pradeu, 2016).

[5] We think in general that the grounding of capacities in relational and dynamic aspects of entities or systems is an important feature that a processual perspective helps to emphasise and articulate (for further discussion see also (Guttinger, in press)).

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figured in the discussion of the term 'virome'. There is also the question of whether viruses belong to the realm of living things, with which we ended this paper. And there is of course the issue of what a virus actually is.

For all of these issues a substance ontology has little to offer. If we take things and their fixed set of properties to be fundamental we find it hard to come to any answers to these various problems of classification. One reason for this is that the substance standpoint assumes an essentialism and/or individualism, neither of which squares well with the interconnected picture of the biological world that the natural sciences are painting for us.

Switching to a focus on processes allowed us to make sense of distinctions that are often used in the natural sciences, for instance the distinctions between a plasmid and a viral episome or between a good and a bad virus. What matters in both these cases is that the 'thing' we are talking about is a process that can often mix with and become part of other processes and hence contribute to a range of outcomes at the same time. What keeps the viral process separate from the other processes with which it is intertwined is the interconnectedness that its different sub-processes display and to which we have referred above using Rescher's term of 'functional unity'.

Clearly more work is needed to further develop this idea of a functional unity. How is it brought about and how is it maintained? On what basis do we attribute it to some part of the biological flux, and are we even sure what it is that we are attributing?

But even though there still are many open questions related to this unity, there are also some preliminary insights we can take away from the above discussion of viruses. One insight is related to the question of what provides the unity we observe in the case of viruses but not the intersecting streams of water. If we could find an essential property that defined the virus, the problem would be easily solved. But the only candidate for such a property is the genome and as we have argued, the genome cannot serve this purpose. As we have seen, the viral life-cycle should not be understood as some sort of material thing or as a mere succession of different states of one material thing that gives the cycle its unity. Rather, the process of the cycle as a whole *is* the virus. And the viral life-cycle is one of the many processes that may come together to form yet another stable pattern to which we usually refer as 'organism'.

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