Viral niche construction alters hosts and ecosystems at multiple scales.

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Abstract

The classical picture of viruses focuses on pathogenic viruses damaging the host's cells and physiology and host-pathogen immune coevolution. However, a broader picture of viruses is emerging that includes weakly pathogenic, commensal or even mutualistic viruses and includes gross behavioural manipulations and viral effects on ecosystems. In this paper, we argue for a niche construction as unifying perspective on viral evolution. As obligate intracellular parasites, viruses are always modifying their environment, and these modifications drive evolutionary feedback between the virus and its environment across multiple scales from cells to ecosystems. We argue that niche construction will provide new insights into viral evolution, and that virology is a powerful source of empirical tests for niche construction.

Keywords: Niche construction, viruses, host-pathogen coevolution

Of niches and viruses

The classical picture of viruses centers on a pathogenic and obligate intracellular parasite that damages or destroys host cells and often has detrimental effects on the host while replicating and transmitting. This has led to a strong understanding of viruses such as influenza and human immunodeficiency virus (HIV), and provided a wide literature of theoretical and empirical work on viral evolution and epidemiology. However, viruses also display a startling range of effects on hosts and the wider environment of the host. These effects range from beneficial mutualisms and commensalisms to behavioural manipulations and even impacts upon global ecosystems. Such interactions with the host and its environment are even more surprising given that viral genomes are often compressed and lack machinery for protein synthesis.

Standard evolutionary theory can be used to provide explanations for these phenomena but

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does not emphasize the process of organism-mediated environmental changes that bias selection in viral systems. For example, some parvoviruses contribute to host aphid survival by creating winged morphs that aid in dispersal to neighboring plants (uninfected clones cannot grow wings) [1]. These winged morphs increase host availability by allowing aphids to colonise new plants in response to crowding and poor plant quality. The new selective pressures on viral transmission that result can be explained as viral adaptation to an environmental change (increased host availability), but this does not highlight that the virus itself caused this environmental change, nor that changes in evolutionary conditions apply to descendents far removed from the viruses responsible for production of the dispersal morphs. There is a growing list of viruses recognised to modify their own or others' selection in these complex ways, but while this has been discussed in the virological literature there has been little attempt to comprehensively explain and even predict their occurence.

Niche construction theory (NCT; see Box 1), which can be viewed as a generalisation of standard evolutionary theory, has the potential to incorporate all of these effects into a single explanatory framework. Adopting a niche construction perspective aids the study of viral evolution by providing new insights into the causes and consequences of viral manipulations of their host environment and beyond. Despite the number of reserachers working on niche construction, this perspective has not yet been applied to viruses in the evolutionary biology or ecology literature. Conversely, one of the strongest criticisms of niche construction is the paucity of empirical tests to date, but advances in virology allow us to directly manipulate many aspects of viral structure and function. Thus, we believe that viruses and niche construction need each other: niche construction assists in explaining viral evolution, and viruses provide a powerful platform for testing niche construction.

Box 1: Niche construction

Here we provide a brief introduction to niche construction and refer the reader to references [2, 3] for in-depth discussion of niche construction and its relation to standard evolutionary theory.

Niche construction is defined as the "process whereby organisms, through their metabolism, their activities, and their choices, modify their own and/or each other's niches" [4]. By modifying biotic and abiotic sources of selection in the their environment, organisms can modify their own selective pressures and those of other affected organisms in a feedback process that creates a genetic and ecological inheritance [Figure 2, and see Figure 2 of 3]. A popular example of niche construction is the turnover and consumption of soil by earthworms [2], which changes the soil chemistry, structure, aeration, drainage, and more. This benefits plants as earthworms enhance the recycling of plant nutrients, and earthworms in turn benefit from increased plant litter supply owing to increased plant growth. These changes have accumulated over generations such that earthworms now experience a different selective environment from that of their ancestors. One indicator of this change is that earthworms retain ancestral freshwater kidneys that do not show the adaptations one would expect of a land-dwelling organism (e.g. producing urine volumes similar to freshwater animals) [2].

Similarly, viruses can have effects on the host and beyond that will create multigenerational effects and feed back into the selective pressures experienced by descendant viruses. Many examples of niche construction in viruses, such as the aggression caused by rabies, will result in modified selection on the important viral traits of transmission and virulence. It is important to note, though, that viral fitness need not be increased (or even modified) for niche construction to occur. For example, GB virus C (GBV-C) has been found to inhibit the replication of HIV in a way that enhances the survival of the host, an effect strong enough that the use of GBV-C is being investigated as a potential biotherapy [5]. GBV-C is vertically, parenterally and sexually transmitted and might benefit from increased host survival, but even if no benefit to the virus were found, the effects on the host and the co-infecting HIV make this an example of viral niche construction.

A challenge to the use of niche construction for viruses lies in the broad definition of niche construction itself [6]. Viruses are obligate intracellular parasites and must heavily modify their host to survive; such modifications generally lead to increased demands on the cell for energy, materials and macro-molecular synthesis. Thus, every viral interaction with their host could be labelled as niche construction. Following discussion in [6], we suggest that a practical approach

to take is to ask 'when is it important or useful to emphasize the action of niche construction'? The modifications made to a host cell when it is used by the virus for injection and replication may meet the definition of niche construction, but these are already well-studied by standard theoretical and empirical approaches and need no further development in a niche construction framework. Instead, niche construction is most useful in analyzing interactions that extend beyond the effect of the virus on its immediate cellular environment (the innermost layers of Figure 1) to the physiology, behaviour, and broader environment of the host.

Figure 1 about here.

Glossary

Commensalism: a relationship between organisms in which one benefits without harming or helping the other(s). Viruses that persist in their host without causing disease or other detrimental effects to the host (i.e. viruses that escape immune surveillance) would be commensal.

Horizontal transmission: transmission between contemporaries in the same generation, such as the spread of influenza between humans via contact or sneezing.

Mutualism: a relationship between organisms in which all partners benefit.

Niche construction: an evolutionary process in which organisms modify their environments and so modify their own and others' selection pressures. See Box 1 for a detailed introduction to niche construction.

Obligate intracellular parasite: intracellular parasites are those which grow and reproduce inside host cells. Viruses cannot reproduce without the machinery for protein synthesis inside of the host cells, and so are reliant (obligated) on those cells.

Parenteral transmission: transmission of an infectious agent that occurs intravenously, for example through blood transfusions or intravenous drug use.

Pathogen: broadly, an infectious agent that causes disease. Pathogens include prokaryotes (e.g. bacteria), eukaryotes (e.g. fungi), and subcellular agents (viruses, prions).

Transmission: passing of an infectious agent from one individual to another. Viruses are transmitted by a number of routes, such as physical contact, fecal-oral via contaminated food or water, or via airborne transmission. Transmission can also involve an intermediate host or a vector (an agent, such as a mosquito, that carries the pathogen from one host to another).

Vertical transmission: transmission from parent to offspring, usually through the germ line of an infected individual.

Virulence: Here we define virulence to mean the ability of a pathogen species to cause disease, and in particular the increased death rate of a host due to the disease.

Why niche construction is important to viruses

Viruses are exemplars of rapid evolutionary change, with small genomes, massive population sizes and error-prone replication (especially in RNA viruses) allowing for fast and relatively wide exploration of sequence space [7]. The viral literature has emphasized straightforward environmental pressures (natural selection) as a cause of viral evolutionary change, usually immune pressures such as the yearly sequence evolution of influenza [e.g. 8]. Yet there is growing recognition that disease-causing viruses, while salient, are only a part of the organismal virome [9]. Together with the complex effects that viruses can have on hosts and beyond the host, there is a need for a comprehensive study of the network of evolutionary processes in which viruses are embedded. We suggest a new way to view viral interactions with the host on four levels of organisation (Figure 1). These levels are the effects on the host's cells, physiology (e.g. fever as a result of infection), the host's behaviour (e.g. aggression due to viruses such as rabies or borna virus), and the broader ecosystem [e.g. marine viruses affecting global CO_2; 10]. Evolutionary studies of viruses, such as the deep literature on transmission / virulence trade-offs, have tended to ignore these higher level effects on host and ecosystem. By focusing on biases in selection that emerge from changes a virus makes to its environment, niche construction can provide a

parsimonious and comprehensive explanation of complex interactions that bridge viral evolution and ecology [11].

Following this, an illuminating aspect of viral niche construction that is problematic under standard evolutionary theory is the difference in reproductive timescale between a virus and its host(s). Viral replication speed and population growth means that multiple generations pass before the host responds at the level of physiology or behaviour, and many more generations pass before effects are felt by the virus or other organsisms at the level of the ecosystem. This difference in timescale suggests that many host and ecosystem responses to viral manipulations are experienced as 'environment' from the perspective of the virus. Viruses present at the beginning of an infection may experience a dramatically different selective environment than viruses involved in transmission because of changes to host physiology or behaviour (e.g. increased opportunity for transmission in rabies), or in infections inspired in hosts affected by the gradually-accumulated ecosystem effects of the virus (e.g. marine viruses affecting global ocean and atmospheric CO_2 levels). Coevolution under standard evolutionary theory requires, by definition, reciprocal evolutionary change [11]; one organism causes evolutionary change in another, and in doing so results in evolutionary change to themselves. Viruses often result in significant changes in their hosts or ecosystems that result in evolutionary change to the virus but not the host. A host infected with rabies (Figure 2A) does not experience evolutionary change from the change in its behaviour (or does not do so on the same timescale experienced by the local viral population), but the virus experiences modified selection through the infection and across infections by its environmental modification. We argue that this is one way in which niche construction provides novel insights into viral evolution.

Odling-Smee et al. [3] (Table 1) list twelve insights derived from a niche construction perspective, and many of these apply to viruses. For instance, niche construction can lead to fixation of genotypes or phenotypes that would otherwise be deleterious or neutral, and many viral mutualisms are likely to be driven by this mechanism. As an example of this, panic grasses (*Dichanthelium lanuginosum*) that grow in geothermal soils in Yellowstone National Park, USA co-exist with a fungal endosymbiont (*Curvularia protuberata*) that it requires to survive. The fungus allows the grasses to grow in soils with temperatures greater than 50°C. However, it has

been discovered that the fungus relies on a virus (Curvularia thermal-tolerance virus, or CTV) to provide this thermal tolerance; fungi cured of the virus do not provide this service to their host grass.

Candidate niche-constructing viruses

To illustrate the concepts in the previous sections, we draw from the virological literature to non-exhaustively survey candidates for viral niche construction. Note that we are suggesting systems for which niche construction might be a useful perspective; both theoretical and empirical work is required to demonstrate that these are traits maintained or promoted by niche construction.

Figure 2 about here.

Many viruses have effects centring on host cells and physiology. For instance, mammalian viruses have evolved several strategies to manipulate the important Pl3K-Akt-mTOR signalling pathway in cells, affecting broad targets in cellular metabolism, growth, synthesis, and translation [12]. Retroviruses, especially endogenous retroviruses (ERVs), fit well into this category. Retroviruses such as HIV use reverse transcription to transcribe their RNA genomes into DNA which is then integrated into the host genome and undergoes normal cellular transcription and translation to replicate further. Endogenous retroviruses continue this by integrating into the host genome and passing vertically through the germline from parent to offspring, usually losing their ability to replicate. These modifications of the host genome on a temporary or permanent basis can shift host-virus interactions from antagonistic to commensal or even mutualistic. One striking example of this is placental ERVs [13], which likely evolved placental expression to allow vertical transmission of the virus, and in turn had their envelope proteins co-opted to develop mammalian placentas. This has occurred independently in multiple mammalian lineages [14], making this a reasonable candidate example of niche construction.

Another example of cellular and physiological modification working together comes from Polydnaviruses (PDV), which integrate into the genomes of ichneumonid and braconid parasitoid

wasps [15]. These viruses replicate in wasp ovaries and are injected into the wasp's host along with its egg. Virus-free eggs are encapsulated by the caterpillar host in a structure that prevents the egg from developing, but the PDV carried by the wasp carries genes to suppress this immune response. Experimental work has shown that eggs do not survive without the viral genes. Niche construction linking host physiological manipulations to transmission benefits in this way is likely common. For example, Norovirus causes severe vomiting and diarrhea and rhinovirus causes sneezing and coughing; both physiological manipulations receive feedbacks from dramatically increased transmission.

Niche construction acting at the level of the cell may even change the transmission route of a viral group. Flaviviruses are arthropod-borne viruses that replicate and cause disease in vertebrates and are usually spread by their arthropod vectors. However, insect-specific flaviviruses such as *Culex* flavivirus have evolved to spread directly within their arthropod hosts (parent to offspring) through eggs without requiring an intermediate vertebrate host [16]. Phylogenetic analyses of the flaviviruses suggest that this modification to insect-specific forms may have occurred multiple times, as there is no evidence of host-virus co-divergence, and resulted in multiple host-switching events [17]. Similar processes may interact with the effect of the virus on the host to modify viral selection pressures. For example, it is known that murine norovirus can shift between chronic and acute infection with a single point mutation in the NS1/2 protein [18]. Understanding the process of niche construction between effects on the host's physiology and subsequent viral transmission may help explain these changes.

Viruses also engage in powerful manipulations of host behaviour, which often feed back into selection on their transmission or virulence or into selection pressures on other organisms. The neurotropic RNA virus rabies (of the *Rhabdoviridae* family) causes encephalitis in the central nervous system of its animal hosts [19] that may result in large increases in aggression and aid in transmission through saliva. Niche construction can lead to the promotion and maintenance of these traits together by causing the first host manipulation (either the behavioural manipulation or transmission through saliva) to viral fitness when it acquires the second trait. Separately, they are difficult to explain; a placid animal transmitting through saliva does not aid viral fitness, and increased aggression does not benefit the virus without salivary transmission. However,

a protovirus causing aggression and biting as a side-effect of CNS infection would have made the acquisition of salivary transmission extremely valuable. Seoul virus (family *Bunyaviridae*), which causes increased aggression in male Norway rats [20] and is spread through bite wounds via saliva [21], may be a result of a similar niche construction process. Borna virus (family *Bornaviridae*) also causes increased aggression in multiple host species from horses to dogs [22], but here the method of transmission is not known with certainty.

Niche construction by viral manipulation of aggression is not limited to traits which transmit through biting. For instance, Kakugo virus is a picorna-like RNA virus that infects European honeybee (*Apis mellifera L.*) workers in Japan and causes significant increases in aggression. It has been suggested that this virus is responsible for the aggressive defense of European honeybee colonies against attacking Asian giant hornets (*Vespa mandarinia japonica*) [23]. Since Kakugo is likely transmitted by mites of the genus *Varroa* [24], this implies that the virus feeds back into host colony survival and the virus' transmission simultaneously. Though Kakugo has been found to a limited extent in North America [25], we can find no reports of such aggression in colonies outside Japan.

More speculatively, we can predict other niche-constructed behavioural manipulations that modify transmission. Aggression associated with strongly pathogenic viruses like rabies is easily spotted and consistent with a bias for disease-causing viruses [9], but many parasites manipulate social behaviour such as mating and social rank [e.g. 26]. Niche construction predicts that viruses manipulating sociality to enhance their transmission are possible, such as a sexually-transmitted virus modifying hormone production; such viruses will likely be vertically or sexually transmitted and weakly pathogenic, commensal or even mutualistic.

Viruses also drive large-scale population dynamics that contribute to niche construction processes for other organisms. One powerful example comes from bacteriophage-mediated virulence factors. The virulence of many pathogenic bacteria is enhanced by phages, and others even require phages to cause disease (reviewed in [27]). *Escherichia coli* and *Pseudomonas aeruginosa*, for instance, adhere to buccal epithelial cells and are enhanced by phage infection (e.g. phage FIZ15 for *P. aeruginosa*; see Table 1 of [27]). Phages also confer enhanced invasion, resistance to serum- and phagocyte-mediated innate immunity, and even antibiotic resistance. Some bacterial

pathogens also rely on phages for production of toxins, such as *V. cholerae*, which only produces toxin when genes are transferred from a lysogenic phage known as CTXΦ [27]. There is evidence that this act of viral niche construction affects not only cholera transmission (through diarrhea [27]), but may also drive seasonal cholera epidemics in humans [28]. The interplay of viral and bacterial population dynamics would create fluctuating selection pressures in both organisms. Similarly, it is known that bacteriophages follow and even drive the population dynamics involved in periodic cyanobacterial blooms [29]. Yoshida et al. [30] describe the association of cyanophages with the bloom-forming cyanobacteria *Microcystis aeruginosa*; some strains of *M. aeruginosa* produce potent hepatoxins called microcystins that are responsible for poisoning humans and other animals. Any regulation of bacterial populations by cyanophages in this system is likely to have selective effects on surrounding populations that can be studied.

Viral modifications of host cells or physiology can even have profound effects on the ecosystem at large. Just as beavers building a dam will influence selection on organisms in the surrounding ecosystem [2], viruses causing widespread population losses can significantly affect selection pressures experienced by other organisms. For example, rinderpest (Figure 2) is an RNA virus that produced a panzootic outbreak wiping out nearly every artiodactyl (cows, pigs, sheep, wildebeest, giraffe, gazelle, etc.) in Ethiopia and caused the Great Ethiopian Famine of the late 19th century [31]. This massive population loss caused knock-on effects throughout the region; as described in [31], a sudden lack of fertilizer (cow dung) brought planting and harvesting to a halt, led to an explosion in rat, locust, and caterpillar populations, encouraged smallpox outbreaks and killed as much as one-half to two-thirds of human populations in affected areas of East Africa. The disruption to the Eastern African ecosystem almost certainly changed selective pressures for a wide variety of organisms in the region, including the virus itself as host populations disappeared. A number of examples of disease-induced extinction have been observed [32], and from a niche construction perspective we predict that viruses will be important drivers of population dynamics in many host and non-host species, often with consequences that affect the virus itself.

On a global scale, marine viruses are responsible for significant horizontal transfer of core photosynthetic genes for cyanobacteria (host to phage, phage to host, and phage to phage: [33]). Along

with this, Thompson et al. [34] argue that cyanophages actually redirect host metabolism by the use of host-like metabolic genes in order to force the host to process carbon. This would allow the phage to increase the production of deoxynucleotides and increase replication by manipulating the cellular environment. Together with the potential upregulation of host photosynthesis by cyanophages [35] and the role of viruses in the 'biological pump' which increase the rate of CO_2 build-up in the atmosphere [36], the combined effects on marine photosynthesis and the global carbon may be highly significant (as in the example of earthworms above).

Why viruses are important to niche construction theory

While niche construction theory has been enthusiastically received in evolutionary biology [3, 37], it has been critcised on the grounds that theory has run ahead of empirical tests [6]. Viruses offer a compelling testbed for identifying and manipulating niche construction pathways because they evolve quickly and have small genomes, making it easy to identify and study their molecular pathways. Matthews et al. [11] call for experimental tests and a framwork under which to conduct them, and we argue that viruses present many powerful candidates for tests of niche construction (previous section).

An explicit example of the potential for new empirical work on niche construction comes from *Baculoviridae*, a family of invertebrate viruses that infect arthropod hosts. This virus causes a pathology in caterpillars known as "tree-top disease", in which the virus manipulates infected caterpillars to the top of its host foliage and liquefies the caterpillar after it dies from infection [38]. With experimental work demonstrating the genetic mechanisms underlying this effect [e.g. 38, 39] and a mathematical model that provides hypothesised a potential pathway for niche construction to promote and maintain these traits in Baculovirus [40], the stage is set for experimental manipulations to test niche construction as described in [11]. For instance, if the baculovirus-host system were modified so that the behavioural manipulation of the caterpillar was suppressed, removing the transmission advantage from liquefying the host on top of its foliage, we could predict that either or both traits would be quickly lost (and in fact, we know that plaque-derived cultures of these viruses almost always lose a gene associated with the manipulation [41]; this phenomenon remains to be shown experimentally).

Concluding remarks

The evolutionary study of viruses has a rich and productive history including bodies of theory and experiment on transmission and virulence, immune system coevolution, and epidemiological modelling. However, with new understandings of viral diversity and the often complicated interactions between virus and host has come the realisation that pathogenic viruses are only one part of the global virome and that viruses of all kinds can have sweeping effects on hosts, populations, and even globally. We believe that niche construction theory is a useful and practical lens through which to explain and unify these diverse phenomena into a cohesive and productive framework for theory alike. We also believe that virology and niche construction theory have much to offer each other; NCT offers a useful approach to the study viral evolution, and virology offers NCT many flexible experimental systems with which to put theory to the test.

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