Cheating in the viral world

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The success of many viruses depends upon cooperative interactions between viral genomes. For example, viruses that coinfect the same cell can share essential gene products, such as replicase, the enzyme that replicates the viral genome. However, when cooperation occurs, there is the potential for 'cheats' to exploit that cooperation. We suggest that: (1) the biology of viruses makes viral cooperation particularly susceptible to cheating; (2) cheats are common across a wide range of viruses, including viral entities that are already well studied, such as defective interfering genomes, and satellite viruses. Consequently, evolutionary theory developed to explain cheating offers a conceptual framework for understanding and manipulating viral dynamics. At the same time, viruses offer unique opportunities to study how cheats evolve, because cheating is relatively common in viruses, compared with taxa where cooperation is more usually studied, such as animals.

virus evolution | cheat | cooperation | social evolution | defective interfering genome | satellite virus

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Introduction

The existence of cooperation opens the door to cheats, which exploit that cooperation[1,2]. Cooperation can be observed at all scales of biology, from bacteria producing molecules that scavenge resources for the local group of cells, to the sterile workers in a colony of ants[3–5]. In contrast, examples of cheats, that exploit the cooperation of others, are much less common. The prevalence of cheating matters, because it determines the extent to which different individuals are in conflict over cooperation, and whether successful cooperation needs mechanisms to counter cheating[1,2,6,7].

Viruses may provide an exception, where cheating is relatively common. The simplest forms of cooperation in viruses occur when multiple viral genomes infect a host cell (Box 1; Fig. 1)[8]. Viral genomes encode gene products that convert the host cell's resources into more viruses. The benefits of many of these gene products are shared with all of the viral genomes infecting a cell, and so they are cooperative 'public goods'[9]. Viral genomes that avoid the cost of producing these gene products, but that still benefit from gene products produced by others, are cheats. Such cheats are common across a wide range of viruses, and include viral entities that are already well studied in the virology literature, such as defective interfering genomes, and satellite viruses[10–12].

The high prevalence of cheating in viruses poses novel evolutionary problems, which also have direct implications for our ability to manage viral infections. From an evolutionary perspective, why is cheating so common in viruses? Are there different types of cheats, that need different types of explanation? And can we use viral cheats to better understand the evolution of cheating more generally? From a virology perspective, the spread of cheats can have a substantial impact on the epidemiology and outcome of viral infections. Can evolutionary theory tell us how viral cheats will evolve and when they will spread? And can cheats be exploited or manipulated to help control viral infections?

We synthesise the relevant evolutionary and virology literatures, showing how similar issues have been examined in these two fields, but from very different perspectives. Bringing these bodies of work together offers novel insights, both for how cheating evolves, and for understanding viral dynamics. Specifically, we: (1) define cheating, and provide a detailed example of how this definition can be applied to viruses; (2) identify and classify the different kinds of cheating in the viral world; (3) discuss why cheating might be especially common in viruses; (4) examine how the prevalence of cheating in viruses poses novel problems for evolutionary theory; (5) apply ideas from social evolution theory, both to understand the evolution of viral cheats, and to assess their potential utility as therapeutic agents.

What is a cheat?

Cheats are individuals that exploit cooperators, by avoiding paying the cost of cooperation, while still benefiting from the cooperation of others[1,2]. The simplest possible form of cheating is to just not cooperate. For example, in bacteria, a common form of cooperation is to produce factors such as

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Box 1: How do Viruses Cooperate?

From an evolutionary perspective, cooperation is when a trait performed by one individual provides a benefit to another individual, and has evolved at least partly because of this benefit[9].

When multiple viral genomes infect the same host cell, there is an opportunity for cooperation between viral genomes[8]. This is because gene products encoded by one viral genome can produce a benefit that goes to all of the viral genomes inside the cell. For example, the replicase produced by one viral genome, to replicate that genome or its progeny genomes, can also replicate other (unrelated) viral genomes inside the same host cell (Fig. 1). Capsid proteins, required for building the capsid that transports viral progeny to new host cells, can produce a similar shared benefit, as can proteins that suppress the host cell's immune response, or indeed any viral gene product that provides a benefit to all of the viral genomes inside an infected cell (Fig. 1).

In some cases, viral cooperation can also extend beyond the cell, to include cases where benefits are shared between viral genomes infecting different cells. One example is when viruses suppress the release of interferon from host cells[55]. This suppression is costly to the viral genome encoding the gene for suppression, but it provides a public benefit by keeping the local population of host cells susceptible to infection by neighbouring viruses.

Evolutionary biologists sometimes use the term 'public goods' to refer to factors that provide a cooperative benefit to the local group of individuals[9]. Famous examples include iron-scavenging molecules produced by bacteria, acorns stored by cooperative woodpeckers, or humans contributing to some group task, such as hunting[5]. Virologists use the term 'trans-complementable' in an analogous way, to describe when gene products are shared between different viral genomes in the same cell[48].

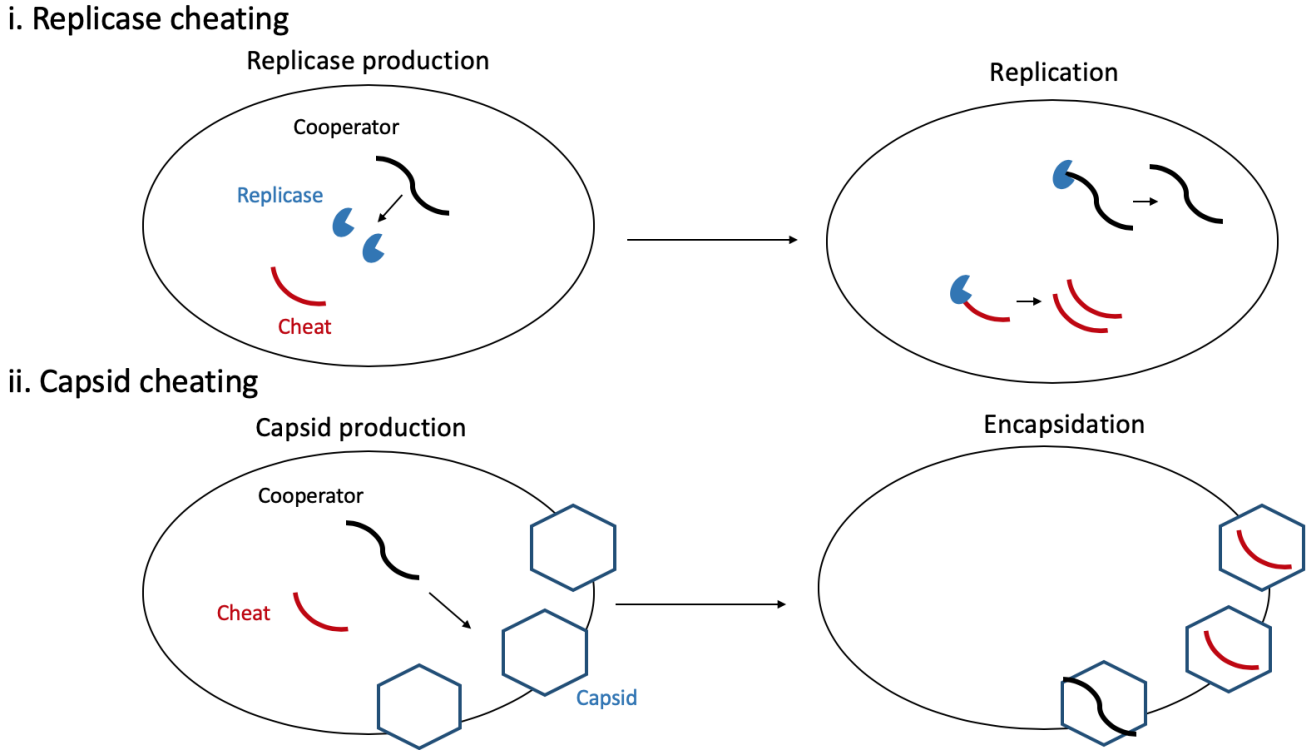

Fig. 1. Cooperation and cheating in viruses. In viruses, cooperation can occur when gene products produced by one viral genome provide a benefit to a different viral genome. When this occurs, the gene can be called 'trans-complementable' and the gene product a 'public good'. (a) The replicase enzyme replicates the viral genome to produce more copies. Replicases encoded by one genome can potentially replicate other viral genomes, including those that did not encode the replicase. A viral genome that is shorter, such as a cheat, is likely to be replicated more quickly than the longer cooperator virus genome. (b) Viral capsids are required to transport viral progeny to new cells. Capsids produced by one viral genome can be used by other viral genomes, including those that did not produce capsid proteins. Cheat genomes can be more likely to be incorporated inside capsids than full-length cooperator genomes[21].

iron-scavenging siderophores, that benefit the local group of cells[13–15]. Cheats that do not produce siderophores, but are able to uptake iron via siderophores produced by other cells, have been observed in both laboratory and natural populations of bacteria (Fig. 2)[16,17].

Cheating can also take more active or devious forms, such as in cuckoos and other avian brood parasites (Fig. 2). Here, individuals of one species trick parents of a different

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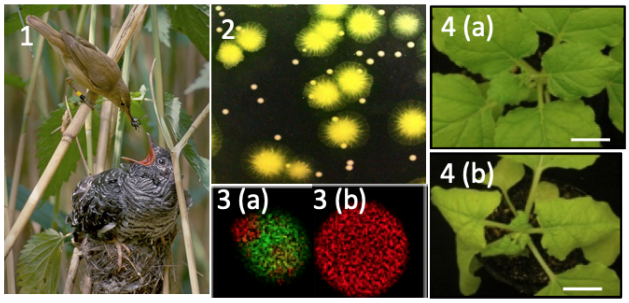

Fig. 2. Cheating throughout the natural world. Cheating occurs throughout the natural world, including in viruses: (1) the common cuckoo (*Cuculus canorus*) lays eggs in other birds' nests, here tricking a reed warbler (*Acrocephalus scirpaceus*) into taking care of a much larger cuckoo chick [107]; (2) Non-cooperative cheat individuals of the bacterial pathogen Pseudomonas aeruginosa (labelled in white) exploit iron-scavenging molecules produced by cooperators (labelled in green); (3) in Vesicular Stomatitis Virus (VSV), when a defective interfering cheat genome (labelled in green) is grown in a mixed infection with wild-type VSV (labelled in red), the defective interfering genome exploits replicase proteins encoded by the wild-type cooperator, resulting in a colony (a) that is dominated by the defective interfering genome, and grows less effectively than a colony consisting just of the cooperative wild-type (b)[108]; (4) in cucumber mosaic virus (CMV) infections, a cheat satellite (satCMV) exploits gene products encoded by the wild-type cooperator, substantially reducing the overall viral load and leading to less severe infections in plants infected by both cheat and cooperator (a) compared to plants infected by just the cooperative wild-type virus (b)[109].

species into neglecting their own chicks and instead feeding the brood parasite's chicks[18]. This trickery can range from cuckoo parents laying eggs that closely mimic those of the host species, to cuckoo chicks actively ejecting the offspring of the host parent. While examples such as these are clear and unambiguous examples of cheating, the extent to which cheating is prevalent in nature has proved contentious[2,19].

How to Test for a Cheat

A key step in investigating whether something is a cheat is to compare the growth rates of potential cooperators and cheats, on their own and in mixture[1]. If the potential cheat really is a cheat, then we would observe three results: (i) when grown separately, the cheat would not be able to exploit cooperation, and so would grow slower than the cooperator; (ii) when grown together, in a mixture, the cheat would be able to exploit and outcompete the cooperator; (iii) the exploitation by the cheat would reduce the growth of the cooperator, compared to when the cooperator is grown alone (interference)

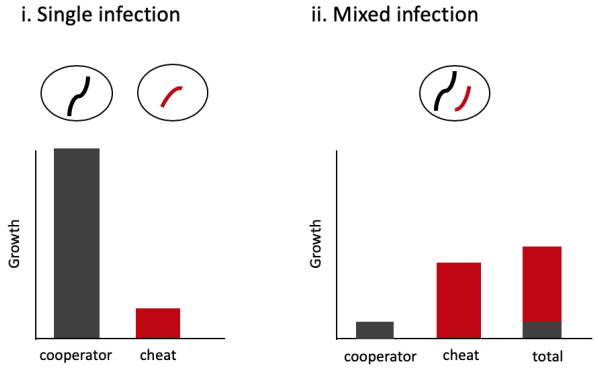

Fig. 3. How to test for a cheat. For two individuals to count as a cheat and cooperator respectively, three conditions must be met: (1) the cooperator must have a higher fitness than the cheat when each are alone; (2) the cheat must have a higher fitness than the cooperator when both are mixed; (3) the mixture containing both cheat and cooperator must have a lower fitness than when the cooperator was alone.

(Fig. 3).

For example, consider a viral genome that encodes a social trait such as replicase. Genomes that encode replicase are potentially cooperators, because replicases encoded by one viral genome could replicate other viral genomes infecting the same host cell (a 'public good') (Fig. 1; Box 1). In contrast, a genome that does not encode replicase represents a potential cheat, because it could exploit replicases produced by other genomes, without producing a replicase itself. If these two genomes do represent a cooperator and a cheat, then we would expect to see the three results given above: (i) when grown on their own, the replicase-encoding genome (cooperator) will have a higher growth rate than the genome that does not encode replicase (cheat); (ii) the genome that does not encode replicase (cheat) will have a higher growth rate than the replicase-encoding genome (cooperator) when both are grown together; (iii) the mixture containing both genomes will have a lower growth rate than when the replicase-encoding genome (cooperator) is grown on its own (Fig. 3).

An Example Viral Cheat

The mutant variant 'DI PV1' is a cheat of poliovirus. DI PV1 contains a large deletion that removes the entire capsid protein region (Fig. 4)[20,21]. Therefore, when grown on its own, DI PV1 produces no viral capsids, and so is unable to spread between host cells. However, when wild-type poliovirus and

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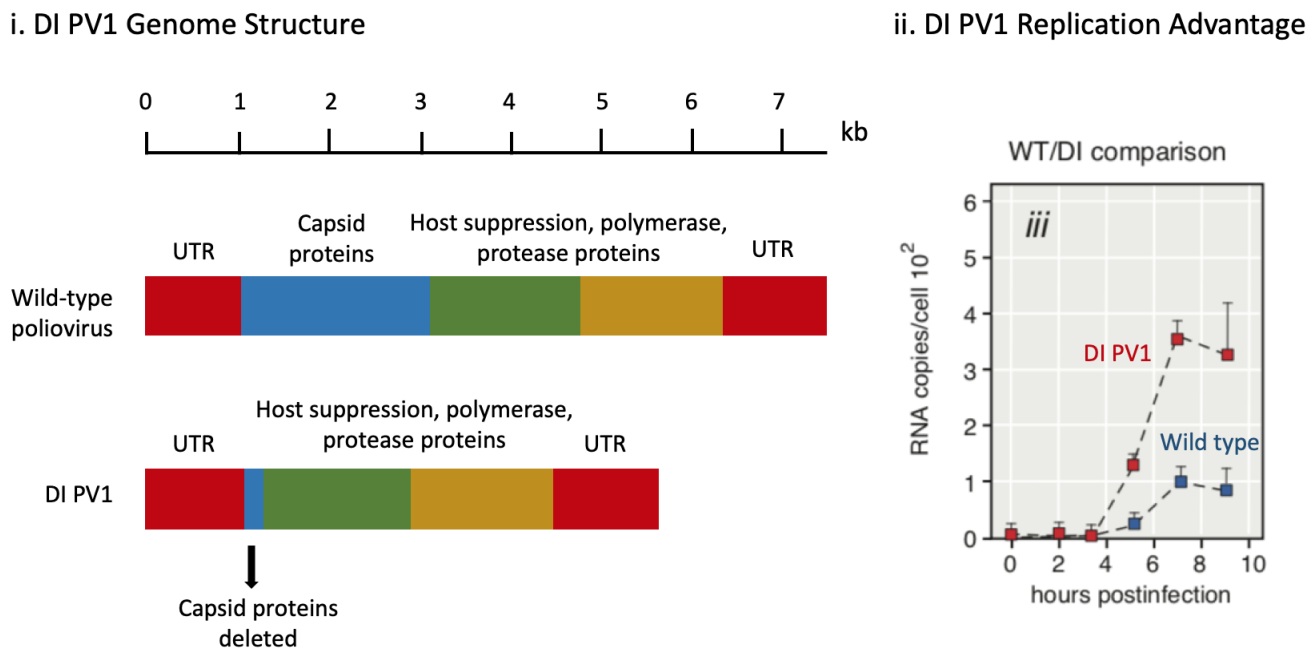

Fig. 4. DI PV1 is a model viral cheat. DI PV1, a defective interfering genome, is a cheat of poliovirus. (i) DI PV1 lacks the section of genome that encodes capsid proteins, resulting in a substantially shorter genome than the cooperative wild-type. (ii) Consequently, DI PV1 gains more than a 1,000-fold replication advantage over the wild-type cooperator when both coinfect the same cell (adapted from [21] Fig. 1).

DI PV1 are grown together, copies of DI PV1 can be incorporated into viral capsids produced by the wild-type cooperator. In coinfected cells, the shorter length of DI PV1 means that it is replicated substantially faster than the wild-type, and it is also able to enter virions more effectively than the wild-type. Consequently, DI PV1 is able to achieve more than 1,000 times as many genomes inside viral capsids as the wild-type cooperator, which is a huge fitness advantage [21] (Fig. 1; Fig. 4).

DI PV1 provides a clear fit to the evolutionary definition of a cheat. It avoids encoding a cooperative trait (producing capsid proteins), but it is able to exploit the cooperation of other genomes (by using capsid proteins they encoded). There are direct parallels between the experiments that virologists used to investigate DI PV1, with the experiments that evolutionary biologists typically conduct to examine cheating in bacteria[13].

In the virology literature, DI PV1 is a type of 'defective interfering genome'. Defective interfering genomes, such as DI PV1, are literally defined by the features that make them cheats – they are defective, because they grow less well on their own (result i of the three results that define a cheat), and they are interfering genomes because they exploit and interfere with the growth of the 'normal' cooperative strain (results ii & iii)[10].

When are Cheats Favoured?

The success of a cheat depends upon its ability to interact with and exploit cooperators. In viruses, this depends primarily on two factors related to population structure: the number of viral genomes that infect each host cell; and the extent to which these viral genomes originate from different cells. Viral cheats will spread best when multiple viral genomes, that come from different host cells, infect the same cells. In these conditions, viral cheats are more likely to be coinfecting a cell with a cooperator.

The relative frequency of coinfection involving different viral genotypes inside the same host cell depends on the biology of particular viruses. In tissue culture infections, coinfection rates can be extremely high for almost all viruses, often with hundreds to thousands of viruses infecting each host cell, and substantial mixing between viruses coming from different host cells. Consequently, viral cheats such as DI PV1 discussed above are extremely common in viral tissue culture infections.

In nature, many viruses have mechanisms that lead to multiple viral genomes infecting the same cell[22]. In many

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viruses, virions travel or stick together in 'collective infectious units'[23]. In most plant viruses, and in animal viruses such as HIV, Hepatitis C Virus, influenza, and measlesvirus, direct cell-cell transmission allows hundreds to thousands of viral genomes to infect the same cell simultaneously[23–28]. Quantitative estimates of the rate of coinfection have found that: in natural populations of marine Gammaproteobacteria, half of the infected bacterial cells contained multiple actively replicating phage species[29]; in turnip plants infected by cauliflower mosaic virus, each cell was infected by an average of two to 13 viruses[30]. Indirect evidence for coinfection include how a virus modified to be entirely dependent on coinfection grew robustly in guineapigs[31]; and the high rate at which reassortment and recombination occur in viruses such as influenza and HIV[32,33].

Where are Viral Cheats Found?

Cheats are common throughout the viral world, and exploit different kinds of cooperation (Fig. 5).

Intracellular public goods:

Most viral cheats exploit gene products that are shared among multiple viral genomes infecting the same host cell (intracellular public goods) (Box 1; Fig. 1). Defective interfering genomes, such as the DI PV1 example discussed above, are the most common example of such cheats, having been studied for decades, and described in tissue culture for almost all animal and plant viruses[10,34–36]. Defective interfering genomes emerge spontaneously during infections, by mutations that delete genes for intracellular viral public goods, such as the replicase enzyme, capsid proteins, or proteins that manipulate host cell machinery for the benefit of the infecting viruses. Defective interfering genomes are consequently much shorter than the wild-type virus, which can give them a substantial replication advantage in coinfection[37–43].

Satellite viruses are another common kind of viral entity that includes many intracellular public goods cheats. These are similar to defective interfering genomes in that they lack genes required for successfully infecting host cells. However, unlike defective interfering genomes, satellites have mysterious origins, usually sharing no sequence homology with the wild-type hosts they exploit, and sometimes encoding new genes not found in the wild-type virus[11,37,44,45]. Furthermore, satellites do not arise de novo in each infection, but instead they frequently transmit between hosts, surviving over long evolutionary timescales. Satellites can also have a range of effects on wild-type viruses, from pure exploitation (cheating) to more mutualistic interactions (not cheating), such as when they encode useful genes that the wild-type lacks. Satellites are very common in plant viruses, although they can also be found in animal viruses, including thse that infect humans[46,47]. Some satellite viruses, such as adeno-associated virus, and Mavirus, employ a 'sit-and-wait' strategy, in which they integrate into host genomes and become dormant, replicating only when a functional helper virus infects their host cell[48,49].

One of the most striking recent discoveries in virology has been the discovery of giant viruses and their associated satellites, the virophages[50,51]. Giant viruses have very large genomes that can be larger than some bacterial genomes, and construct capsids big enough to be seen with a light microscope[49]. Not long after giant viruses were discovered, virophages were found, which are a type of satellite virus that are entirely dependent on parasitising giant viruses, exploiting giant virus replication machinery to replicate themselves. Virophages would be cheats if they exploited social traits encoded by giant viruses, including shared gene products such as the replicase, or capsid proteins. This appears to be the case for some virophages, but not all. For example, Sputnik virophages use the giant virus host's genome replication machinery, whereas Mavirus encodes its own. Consequently, we would suggest that Sputnik is closer to our definition of a cheat, whereas Mavirus may be more of a non-social parasite.

Defective interfering genomes and satellites represent extreme forms of cheating, where the cheat has completely lost the ability to replicate on its own, and is entirely dependent on the cooperator. Less extreme forms of cheating are also possible in viruses, where the cheat does better when it exploits the cooperator, but can still survive on its own. For example, PhiH2 is a cheat of the phage Phi6, out-competing Phi6 in mixed infections and losing in single infections. However, PhiH2 is only a partial cheat, because it still retains some ability to replicate itself in the absence of Phi6[52]. This is analogous to many kinds of facultative cheating elsewhere in nature, such as when birds 'dump' eggs in nests of conspecifics, but still retain the ability to rear their own offspring, or when bacteria only partially downregulate the production of a public good[18,53]. Partial cheating may be rarer in viruses than in other organisms, perhaps because viruses' smaller genomes lend themselves more easily to simpler 'all-or-nothing' muta-

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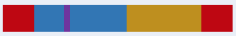
	Defective interfering genome	Satellite virus cheat	Point mutation cheat
Cooperator genome			
Cheat genome			
How is the cheat created?	Large deletion(s)	Independent origin, with a completely different genome sequence	A point mutation or small deletion leading to loss or change of function
Where found?	Almost all animal and plant viruses	Commonly in plant viruses and giant viruses, sometimes in viruses of bacteria and (phages), rarely in animal viruses	In phages, sometimes in animal viruses, difficult to say how common
Short vs long-sighted	Usually short, some evidence for long-term transmission	Long-term	Usually short, potentially long

Fig. 5. What do viral cheats look like?

tions that completely knock out a function, resulting in complete cheating[54].

Extracellular public goods:

In viruses, some gene products are shared between viruses infecting different cells (extracellular public goods)[12]. For example, many viruses encode proteins that block infected cells from releasing interferon, a signalling molecule that spreads to nearby cells and triggers antiviral defences. Blocking interferon provides a benefit to viruses in nearby cells, by keeping the local population of cells susceptible to infection. In Vesicular Stomatitis Virus (VSV), D51 is a cheat mutant that exploits this public benefit; it avoids the cost of blocking interferon, consequently replicating more quickly in infected cells, and spreads at the expense of wild-type VSV when both are grown together[55]. However, when D51 is grown on its own, it quickly becomes extinct because local host cells activate their antiviral defences.

There are other types of extracellular public goods in phages that could potentially be exploited by cheats. Several kinds of phage that infect Bacillus bacteria use small signalling molecules to ensure that they only lyse their hosts once there is a sufficient density of phages around. This 'arbitrium' quorum sensing system provides a public benefit by allowing neighbouring phages to time their life cycle optimally[56]. Many kinds of phage encode proteins that deactivate bacterial CRISPR defence systems, providing a benefit to neighbouring phages by creating a pool of susceptible bacterial hosts[57–59]. Phages that don't encode anti-CRISPR proteins are only able to grow in the presence of 'cooperator' phages that do encode such proteins, indicating that suppressing CRISPR is an extracellular public good, and so cheats could potentially exist that exploit this function [60].

Virulence:

In parasites such as viruses, slow growth is another potentially cooperative trait, because it avoids hosts being overexploited, allowing for more transmission opportunities in the long run[61]. Faster-growing parasite strains can be seen as cheats, because they can outcompete slower growing strains in the short-term, but also exhaust the local supply of hosts[62,63]. Examples of virulence cheats in viruses include the fast-growing 'rapacious' phages, which burst their bacterial hosts especially quickly, and have been described in a number of different phage species[63–65].

Where else could viral cheats be found?

We have yet to find cheats in many cases where coinfec-

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tion is common, and so they might be expected. Defective interfering genomes have not been identified in lentiviruses such as HIV, even though HIV produces non-interfering defective genomes, and coinfection seems to be relatively common[27,66]. Phages also seem to not have defective interfering genomes, although they do have other kinds of cheat, and they can produce defective genomes[29,52].

One advantage of an evolutionary definition of cheating is that we can make predictions even when we do not yet understand all of the biological details. For example, using experiments such as in Fig. 3, Turner & Chao determined that PhiH2 is a cheat of Phi6, without fully understanding the mechanisms by which it gains an advantage[52,67]. Such experiments allows us to place newly discovered viral entities within an existing framework, and to draw common links between otherwise disparate parts of the virosphere. For example, virophages and many satellite viruses are cheats, even though they differ substantially in the mechanistic details in how they exploit the cooperation of their hosts[49,68,69]. Focussing on unifying evolutionary features of viruses, rather than on mechanistic details, could be one way to help bring 'order to the viral universe'[70].

Why don't cheats take over?

Given the potential benefits of cheating, what stops cheats from spreading to fixation after they have arisen and started to spread? Do cheats inevitably win, or can cooperation be maintained, and if so, how?

One common feature of cheating is that the relative fitness of cheats decreases as they become more common – termed negative frequency dependence[71]. Because cheats spread by exploiting cooperators, they experience the greatest fitness advantages when rare, when most other individuals they interact with are cooperators. In contrast, as cheats become more common, they interact with other cheats more frequently than with cooperators, and so their fitness advantage decreases. Consequently, cheating can be self-limiting, and even cheats that have substantial fitness advantages when rare, may end up coexisting with cooperators rather than driving cooperators extinct.

Another possibility is that cooperators adapt to the presence of cheats, in a way that limits their spread[72–74]. In Vesicular Stomatitis Virus (VSV), wild-type cooperators can evolve a form of resistance to cheats, by changing the recognition sequence for the replicase enzyme, so that it still replicates the wild-type cooperator, but no longer replicates the defective interfering cheat genome[75]. Alternatively, viruses could manipulate population structure in ways that prevent cheats from spreading, such as by decreasing the number of viral genomes that collectively transmit to new cells (smaller collective infectious units)[76,77], or by excluding additional viral genomes from infecting the same host cell (superinfection exclusion)[78–82].

Not cheats

Cheating is a special form of parasitism, where it is a social trait that is being exploited. Consequently, while cheats are a type of parasite, not all parasite are cheats. For example, cuckoos are both cheats and parasites of their host species, whereas viruses and other pathogens are parasites, but not usually cheats, of their host cell. This distinction matters because we expect different evolutionary pressures and population dynamics when parasites are not cheats[1].

Viruses vs Other Life-Forms

Is cheating in viruses the same as cheating elsewhere in the living world (Fig. 2)? We argue that while it is clearly analogous, viral biology leads to important differences. These include:

(1) The high mutation rate and simple genome of viruses means that mutations to cheating can happen relatively easily. For example, defective interfering genomes regularly emerge de novo in viral infections[83].

(2) The short-term advantages of cheating in viruses can be exceptionally high. Viral cheats can achieve more than a 1,000-fold replicative advantage over cooperators, which is orders of magnitude higher than the fitness advantages seen in cuckoos, non-producing bacteria, or other cheats[13,18,21].

(3) The fitness advantage of cheats is often transient at a local scale. Cheats can emerge easily, and then spread rapidly, for example within a host, but then show poor or even non-existent transmission to new hosts[31,77].

Taken together, these three features mean that cheating is both common and transient in many viruses. Viral cheats are therefore special in the extent to which they are characterised by 'boom and bust' dynamics. Cooperative viruses will consequently be selected to evolve mechanisms to either avoid generating cheats, and/or reduce exploitation by cheats.

Not all viral cheats are transient. We can place viral cheats

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on a continuum between 'short-sighted' and 'long-sighted' cheats[84]. Defective interfering genomes are short-sighted cheats, that arise and spread transiently, mostly within but not between hosts, with boom and bust dynamics. Satellite viruses are long-sighted cheats that spread both within and between hosts, allowing persistence over long evolutionary timescales. Long-sighted cheats are more similar to forms of cheating observed in animals, such as cuckoos[1,18].

Unlike other organisms, many viruses gain at least two different kinds of mechanistic advantage from cheating. One advantage is that viral cheats avoid a costly trait, such as producing a gene product. This is analogous to how cheats in other organisms avoid costly cooperative behaviours, such as feeding offspring, collecting acorns, or producing siderophores. However, in contrast to other organisms, many viral cheats also have much shorter genomes than cooperators, and these shorter genome gives them an additional replication advantage over cooperators[85,86]. Hence, in viruses, there appears to be both a cost to cooperation, and a cost to possessing a cooperative gene. This second cost might be unique to viruses, because cooperative genes are a significant fraction of the genome, and a smaller genome can lead to substantially faster replication.

Why Should Evolutionary Biologists Care?

Viruses are excellent model organisms for studying cheating. Cheats may be both more common and easier to find in viruses than in other organisms. The relatively small genomes and short generation times of viruses mean that it is often easy to link genotype with phenotype, allowing us to identify cheats relatively easily, and to follow evolutionary dynamics over time. The large amounts of clinical and environmental genomic data allow the ecological and coevolutionary dynamics of cheating to be studied in nature[7]. These studies can then be complemented with manipulative laboratory experiments that are more feasible in viruses than in other organisms[87,88].

Cheating in viruses raises novel evolutionary problems. Have viral genomes evolved to make it harder for cheats to arise through mutation, such as by linking cooperative genes with essential private functions, that cannot be cheated[89]? For example, in polioviruses, defective genomes that lack sections of the replicase gene are unable to be incorporated into virions, and so 'replicase-cheats' do not evolve, although cheats that lack capsid proteins do evolve[90]. Another potential example is in Flock House Virus, where successful cheats contain two large deletions in the genome. This appears to be because there are several regions in the middle of the genome that perform essential functions that cannot be complemented by coinfecting with another genome, and so cheats with deletions spanning these regions cannot replicate[91].

On the other side of the coin, could some viruses have evolved to produce cheats 'adaptively', to decrease the effects of virulence by reducing the overall viral load[36,92,93]? This strategy may make more sense in viruses than in other organisms, because viral mutation rates mean that viral infections tend to be genetically diverse. Consequently, evolving a slower replication rate may be selected against, as any strain that did this would be out-competed by faster-replicating strains within the same host, whereas producing cheats could slow the growth of all strains within a host.

Why Should Virologists Care?

Cooperative traits such as replicating the viral genome, building a capsid to transmit progeny genomes, and suppressing host immune responses, are fundamental to the epidemiology and success of viruses. Consequently, understanding how viral cheats disrupt cooperation could allow us to better understand viral dynamics. How important a role does cheating play in natural viral infections? What kind of mechanisms have viruses evolved to counter cheating? Can we make use of our evolutionary understanding of cheating to better control viral populations? Could cheating help to explain the evolution of genome segmentation, multipartite viruses, or other puzzling aspects of viral biology[54,94–97]?

Fundamental Virology

An understanding of cheat-cooperator dynamics can inform how we conceptualise viral populations. Viral cheats appear to be very common, but also have strongly negative consequences for viral infections. Selection on individual viral genomes can have detrimental effects for other viral variants and to the infection as a whole. This challenges the idea that viruses should be defined at the group or 'quasispecies' level - the potential for conflict is likely to prevent adaptations that are solely for the benefit of the group of viruses[98,99]. Therefore, we should not necessarily expect viral populations to evolve as coherent groups, nor to be adapted towards any collective goal.

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Applied Virology

From an applied perspective, cheating can be exploited as a mechanism to disrupt viral infections, and social evolution could inform how we approach this. Therapeutic interfering particles (TIPs) are synthetic viruses designed to exploit wild-type virus cooperation, and to suppress viral infections by acting as a cheat, mimicking defective interfering genomes[100,101]. Social evolution theory could be helpful for designing effective TIPs, because it asks the same or analogous questions to those being posed in therapeutic interfering particle research. For example, compare "when do TIPs suppress wild-type viruses?", "can TIPs be maintained in the population?", and "can TIPs revert to being fully infectious viruses?", with "when do cheats win?", "when does frequency dependent selection maintain cheats and cooperators at equilibrium?", and "can cooperation be regained?".

A social evolution perspective could also help us determine how to use TIPs effectively, by focusing on the evolutionary dynamics of natural viral cheats. Before using a synthetic cheat to control a viral infection, we would first want to know what kinds of cheat affect the virus naturally, and how the virus responds to them. Are some viruses more susceptible than others to being exploited by cheats? Which viral cheats are able to spread between hosts, and why? In what ways do viruses evolve resistance to cheats, and can cheats coevolve in response? These are all pressing questions about the natural history of viral cheats, which also have clear applications in informing how TIPs could be used safely and effectively.

Where Next?

The study of viral cheats offers amazing opportunities to both evolutionary biology and virology. However, the biggest obstacle in this field is that most of the existing empirical work has been done in the laboratory, either in tissue culture or model hosts. To move forward, we need to understand the role that cheats play in the epidemiological and evolutionary dynamics of viruses in their natural environment, which includes humans, crops, and livestock. Fortunately, exactly the right kind of data is now being collected, as next-generation sequencing technology is increasingly being used to monitor viral outbreaks and to chart the enormous unexplored diversity of viruses[102–106]. The next steps will involve harnessing this rapidly advancing technology in order to test and expand evolutionary theory about viral cheats.

ACKNOWLEDGEMENTS

For useful comments and discussion, we would like to thank Rafael Sanjuán, Ashleigh Griffin, Helen Leggett, and John Bruce. A.L. was supported by funding from the Clarendon Fund, St. John's College, Oxford, and the BBSRC (grant number BB/M011224/1). This draft makes use of the Henriques Lab preprint template.

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