

## Review Article

# Cooperative Virus-Virus Interactions: An Evolutionary Perspective

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Despite extensive evidence of virus-virus interactions, not much is known about their biological significance. Importantly, virus-virus interactions could have evolved as a form of cooperation or simply be a by-product of other processes. Here, we review and discuss different types of virus-virus interactions from the point of view of social evolution, which provides a well-established framework for interpreting the fitness costs and benefits of such traits. We also classify interactions according to their mechanisms of action and speculate on their evolutionary implications. As in any other biological system, the evolutionary stability of viral cooperation critically requires cheaters to be excluded from cooperative interactions. We discuss how cheater viruses exploit cooperative traits and how viral populations are able to counteract this maladaptive process.

## 1. Introduction

Viruses exhibit a wide range of direct and host-mediated interactions, some of which have been known for decades. Most of these interactions take place in cells coinfecting with different viral variants or species. For instance, genetic complementation occurs when two or more viral mutants carrying deleterious mutations at different loci share their gene products to compensate for these defects, thus restoring normal functions [1, 2]. Another well-known example is pseudotyping, which takes place when two different viruses coinfect a cell and produce virions carrying the genome from one virus but some structural proteins from the other virus [3–7]. Two additional examples are provided by embedded viruses, which are retroviruses that fully integrate their genome into the genome of another virus [8–10], and by heterologous transactivation, which occurs when a virus expresses transcription factors that activate promoters of another virus [11, 12]. Negative interactions are also common among coinfecting viruses. In addition to the obvious phenomenon of direct competition for host resources, viruses exhibit mechanisms to inhibit foreign infections, with superinfection exclusion (SIE), a mechanism by which a virus that is infecting a host is able to block other infections, being particularly important [13–17]. Some plant

viruses are also able to promote host-wide protection, a process called cross-protection [18, 19].

Viruses can also establish more indirect interactions, which are determined by the characteristics of the environment or the host, particularly the immune system. There are many examples of environmental and immunological interactions between different viruses, some of the most important being altering host susceptibility, modifying or suppressing interferon (IFN) response, or altering immune cell activation [20]. For instance, human immunodeficiency virus (HIV) is able to increase human cytomegalovirus (HCMV) replication in various tissues as a result of lymphocyte activation [21], and humans infected with herpes simplex virus (HSV) are more susceptible to HIV infections and more contagious due to an increased expression of the receptor CCR5 [22, 23]. Innate immunity can also promote negative interaction between viruses [24, 25]. Cooperative and competitive interactions mediated by cross-reactive innate immunity appear to be particularly frequent among respiratory viruses [26].

Most of these well-known interactions involve viruses from different species. Cases of embedding, transactivation, or pseudotyping or the interactions between HIV and HSV may occur as a by-product of a normal process in the infection cycle of the other virus. Less attention was traditionally

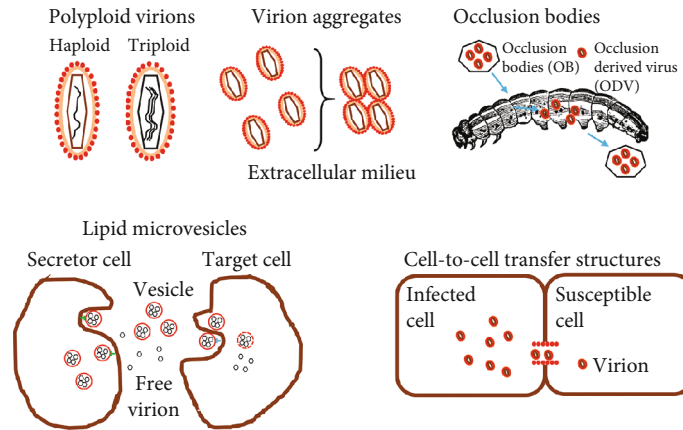


FIGURE 1: Different types of collective transmission in viruses. Polyploid virions: polyploid virions containing more than one copy of the viral genome. Virion aggregates: aggregates of virions in the extracellular milieu. Occlusion bodies: baculovirus occlusion bodies for interhost transmission. Lipid microvesicles: extracellular vesicles containing multiple virions. Cell-to-cell transfer structures: cell-to-cell transmission mediated by cellular or virus-induced structures that promote group transmission of multiple virions.

paid to cases of interactions between viruses of the same species (with the exception of genetic complementation), in which the ability of a viral particle to achieve a successful infection is promoted or hampered by the presence of other viral particles. However, several research lines have emerged in recent years showing this kind of viral interactions in various processes including evasion of host immunity [24] and regulation of virulence [27]. Inclusive fitness theory is a well-established theoretical framework for studying these interactions, which was initially developed to explain the evolution of altruism in higher organisms but allows viral interactions to be formally analyzed in terms of fitness costs and benefits. For a trait to be considered social, its evolution should be determined, at least partially, by the effect it produces on individuals different from the actor.

## 2. Viral Coinfection Mechanisms That Facilitate Interactions

The most common scenario for virus-virus of interactions takes place when multiple infectious particles are present in the same host cell, that is, when there is a high multiplicity of infection (MOI), defined as the number of viral genomes that initiates an infection. Animal viruses typically produce a large number of infectious particles per infected cell, usually ranging from 100 to 1000 [28–30]. In the simplest form of viral spread, these particles diffuse in a viscous medium [31] until they reach a neighbor cell, producing infection foci that create a high local MOI. However, the amount of genomes that are actually transmitted from cell to cell is variable and depends, among other factors, on adsorption efficiency. Bacteriophages can exhibit extremely high adsorption efficiencies [32, 33] that, together with their environmental ubiquity, should promote coinfection and, in turn, select for mechanisms that regulate coinfection levels.

A more specialized form of viral spread is cell-to-cell transmission, which should also favor coinfection. Plant viruses can achieve elevated MOIs by delivering multiple viral particles via plasmodesmata [34, 35] (Figure 1). How-

ever, the amount of genomes that are transmitted from cell to cell is variable [36, 37]. Animal viruses also exhibit several mechanisms for cell-to-cell transmission such as the formation of actin tails [38], the exploitation of structures like filopodia [39], and tunneling nanotubes [40], as well as the induction of syncytia [41–44] or cell synapses [45, 46].

High MOIs can also be achieved when viral spread occurs through collective infectious units (CIUs, Figure 1). This term describes a wide range of virus-promoted structures that allow cotransmission and delivery of multiple viral genomes in a single host cell [47]. CIUs are found in many different types of viruses, although they have been best characterized in animal viruses. For example, some viruses can form “polyploid” virions containing more than one genome copy [48–52]. CIUs can also be formed when virions aggregate in the extracellular milieu, as has been shown, for instance, for vesicular stomatitis virus (VSV) in saliva [53, 54] or HIV in semen [55, 56]. Occlusion bodies (OBs) of baculoviruses are composed of polyhedrin protein crystals harboring tens of nucleocapsids [57, 58]. A well-described type of CIUs is extracellular vesicles containing multiple viral particles, which have been described in noroviruses [59]; picornaviruses such as coxsackieviruses [60], polioviruses [61], and hepatitis A virus (HAV) [62]; rotaviruses [59]; and marseilleviruses [63]. Despite the great diversity of structures involved in CIU formation, a common theme is the simultaneous delivery of multiple genomes to the same host or cell. CIU-mediated elevation of MOI can be advantageous in different ways, since it could promote cooperative interactions between potentially identical viral genomes (homotypic) or between different genetic variants of a virus (heterotypic).

**2.1. “Mass” Effects.** Everything else being equal, if  $K$  virions infect a single cell instead of  $K$  different cells, there should be a direct  $K$ -fold reduction in the amount of viral progeny produced per cell. For mechanisms promoting coinfection to be beneficial in terms of fitness, they must therefore compensate for this cost by increasing the viral progeny per cell

TABLE 1: Summary of possible fitness advantages of coinfection due to mass effects.

Fitness advantage	Virus	Normalized benefits per capita	Reference
Acceleration of the infection cycle	Poliovirus	Yes	61
	Marseillevirus	No	63
	Influenza A virus	Yes (depending on the MOI and cell type)	70-72
	Human immunodeficiency virus	No	55
Increased per-cell yield	Influenza A virus	Yes (depending on the MOI and cell type)	69-72
	Vaccinia virus	Yes	73
	Vesicular stomatitis virus	Yes	68
Increased infectivity	Infectious bursal disease virus	Yes	51
	Human immunodeficiency virus	No	55
	Vaccinia virus	Yes	73
	Influenza A virus	Depends on segment encapsidation	70

by at least the same factor; or promote some other fitness advantage such as faster infection or greater environmental stability (Table 1). This question has been addressed both theoretically and experimentally, and although there are several possible mechanisms that may confer an evolutionary advantage to CIUs, there is no general answer that applies to all viruses [64].

A general feature of viruses is that there exists a positive feedback between the number of replication templates and the number of virally encoded proteins, since viral genomes code for replication-promoting proteins [65]. Consequently, there should be a disproportionate increase in short-term replication efficiency as the copy number of the viral founder genomes within a cell increases. Several lines of evidence support this idea, such as the fact that increased MOI leads to a direct increase in viral gene expression levels in herpesviruses [66]. In polioviruses, phosphatidylserine vesicles, which promote the *en bloc* transmission of multiple virions, increase the rate of viral replication [61], and a similar result was described for noroviruses and rotaviruses [59]. Marseillevirus vesicles have also been shown to accelerate the infection cycle [63], but in this case, the authors speculated that the main reason might be a difference in the mechanism of entry, rather than an effect of coinfection per se.

In addition to simply accelerating the release of viral progeny in infected cells with a high MOI, cooperative replication may increase the viral yield per cell. This could take place if viral progeny production is not limited by cellular resource availability, but by the time an infected cell is productive since viral entry (Figure 2). Apoptosis is triggered in infected cells upon recognition of pathogen-associated molecular patterns such as, for instance, double-stranded RNA [67]. This antiviral response imposes a time window for viruses to produce and release progeny. Increased per-cell yield has been demonstrated for VSV [68], influenza A virus (IAV) [69–72], infectious bursal disease virus (IBDV) [51], and vaccinia virus [73].

Finally, coinfection could also reduce the fraction of abortive infections. When a single virion initiates infection, nucleic acid or protein degradation (spontaneous or driven by cellular mechanisms) may take place before the key steps of viral gene expression or replication can occur. This sto-

chasticity results in abortive infections and contributes to explain why most viral particles fail to yield productive infections (Figure 2). The ratio of productive infections per particle has been shown to increase with the MOI in vaccinia virus [73] and with cell-to-cell transmission in HIV-1 [74], albeit the latter could be due to the use of a different transmission pathway. Polyploid virions of IBDV also show enhanced infectivity [51], but since this is a segmented virus, such increase could be explained by a higher likelihood of transmission of each genome segment.

Despite the fitness benefit that cotransmission mechanisms may provide (Figure 2), the critical question is whether these advantages increase the per-capita yield of viral genomes, compared to single infections. As argued above,  $K$  individually infected cells have the potential to yield  $K$  times more viral progeny than a single cell coinfecting with  $K$  particles. Therefore, viruses in coinfecting cells should overcome this  $K$ -fold cost. To our knowledge, this has only been demonstrated in VSV [68] and vaccinia virus [73]. Coinfection could increase the per-cell viral yield, accelerate the replication cycle [61], or increase infectivity by a factor greater than  $K$ . In [59], the authors compared infections with equivalent numbers of free virions and vesicle-cloaked virions, but as they performed *in vivo* infections, it is not easy to determine which cellular-level benefits these vesicles afforded.

There are also connections between the benefits of coinfection and the immune response. IFN is released from infected cells and activates an antiviral state in neighboring cells [75, 76], but the onset of this process takes several hours, at least in cell cultures. Some viruses present specific antiapoptotic proteins that block IFN-activated apoptotic pathways [77, 78], whereas others such as VSV block IFN production [79]. In this context, an increased infection rate or per-cell yield may be critical for infection progression. The fitness advantage of VSV virion aggregates has been shown to correlate with the ability of host cells to mount an effective antiviral innate immune response [68], and similar results have been obtained for IAV [71, 72].

**2.2. Diversity-Based Interactions.** Viruses are the genetic systems exhibiting the highest mutation rates, particularly RNA

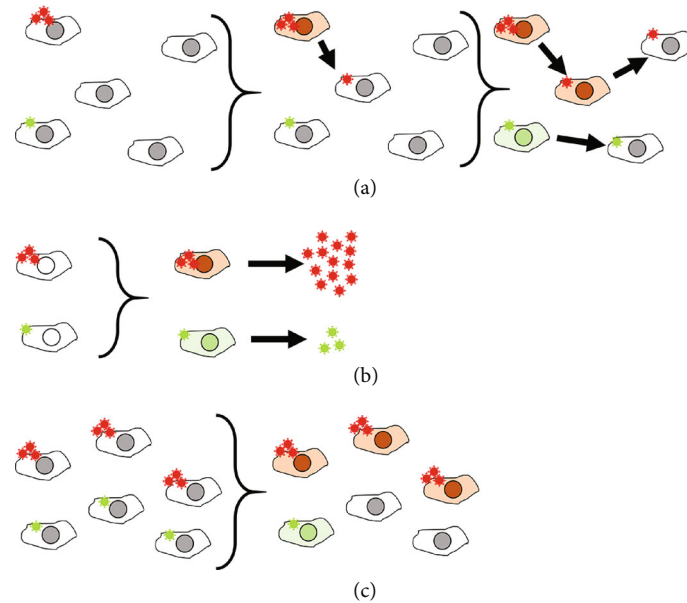


FIGURE 2: Fitness advantages of coinfection in terms of mass effects. (a) Coinfected cells present a faster replication cycle compared to single infected cell. (b) Coinfected cells produce a higher number in infectious particles (increased per-cell yield). (c) Coinfections are more likely to produce successful infections (increased infectivity).

viruses [80]. This, together with other mechanisms such as recombination, creates highly diverse and rapidly evolving populations at the cost of frequently suffering detrimental or lethal mutations [81]. Coinfection has been speculated to play an important role in determining viral diversity. Genetic complementation among two coinfecting genomes carrying different deleterious mutations may rescue both and allow them to perform successful infections equivalent to a nonmutated virus (Figure 3). However, buffering deleterious effects implies that such mutations will tend to increase their population frequency. Deterministic [82] and stochastic [83] simulations have shown that genetic complementation transiently alleviates the impact of deleterious mutations but does not change mean population fitness over the long term. This is because, at equilibrium, complementation will reduce the average fitness effect of mutations but will similarly increase the frequency of these mutations in the population.

On the other hand, we can speculate that genetic complementation could promote evolvability by increasing cryptic genetic variation. In a context of high MOI and CIU-mediated transmission, genetic complementation might allow deleterious mutations to be maintained in the population and, potentially, some of these mutations could become advantageous in a different context, such as, for instance, in a new host. This could be the case described in [84], where the authors found Asian-type IAV variants in pigs, suggesting that these variants were deleterious but remained at a certain frequency in the original host, potentially due to complementation, and were subsequently amplified in the alternate host where they provided a fitness advantage to the virus.

A potential direct benefit of transmitting genetically diverse viral populations among hosts could take place when

viruses must infect different cell types. An often successful strategy in heterogeneous environments is a generalist phenotype that trades off fitness compared to specialists in every specific environment but increases overall performance [85]. We hypothesize that collective viral dispersal could alleviate such trade-offs by allowing different specialist variants to be jointly transmitted (Figure 3). In baculoviruses, OBs carry multiple infectious particles and are essential for host-to-host transmission, as evidenced by the fact that variants carrying a deletion of the polyhedrin gene are unable to infect new hosts. However, OBs containing a mixture of wild-type and polyhedrin-defective variants are efficiently transmitted and can generate more productive and severe infections than genetically homogeneous OBs [86]. This observation suggests that polyhedrin-defective mutants are better adapted to intrahost dissemination, whereas nonmutated genomes provide interhost transmissibility. Both variants could benefit from this interaction, since the enhanced severity of the infection caused by the polyhedrin-defective mutant could potentially favor transmission. Thus, collective viral transmission via OBs could promote a stable coexistence between complementary specialists. The conditions required for such coexistence include functional complementary, synergistic advantages, and a positive assortment of specialists [87]. Further experiments are required to analyze whether this type of interactions in baculoviruses and potentially other viruses exhibits negative frequency-dependent selection, which is another process promoting stable coexistence.

In a similar vein, it has recently been speculated that high-MOI regimes might be at the origin of segmentation in viruses [88], as each segment functions as a defective genome incapable of performing a successful infection alone. For a set of genomes that are constantly cotransmitted, the



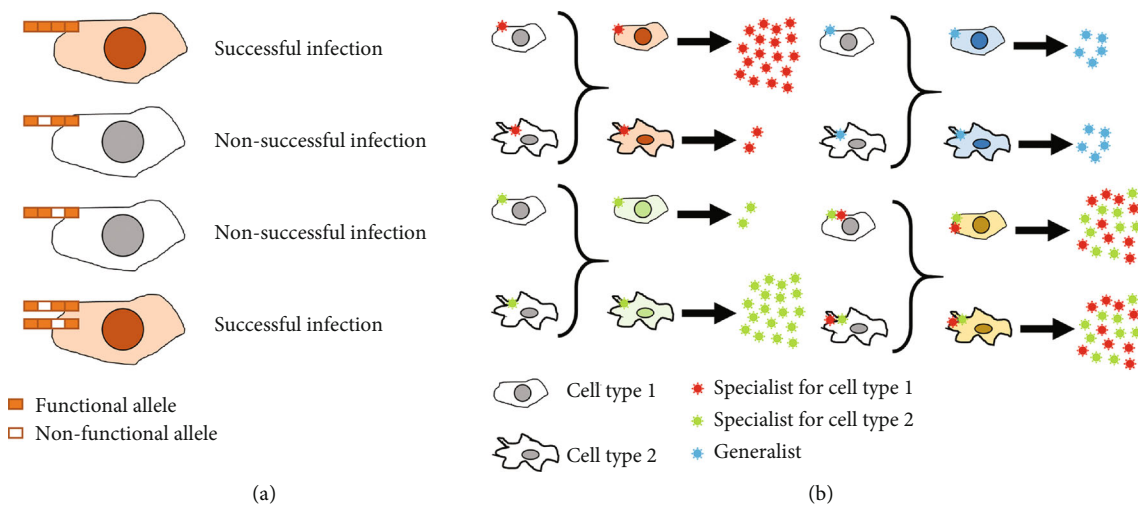


FIGURE 3: Potential fitness advantages produced by coinfection of cells with different virus variants (diversity-driven interactions). (a) Coinfection can rescue lethal mutants by means of genetic complementation. (b) Genetic complementation can promote the cotransmission of different specialists that are overall fitter than a generalist.

selection pressure to keep the entire genome as a unit should be reduced, which may lead to some of them retaining only a subset of all functional genes. Eventually, these genomes might experience long deletions and become segments of the original genome. This was experimentally addressed by passing foot-and-mouth disease virus (FMDV) at high MOIs for many viral generations, which resulted in the emergence of different mutants that could reciprocally complement their genetic defects [89].

### 3. Interactions Mediated by Sequential Infections

Superinfection occurs when a given host or cell is sequentially infected with the same virus or different viruses. As mentioned in Introduction, many viruses possess mechanism to avoid superinfection [13–17]. Intuitively, SIE can be thought of as a trait that helps viruses avoid competition for cellular resources from other incoming viruses. However, it has also been suggested that SIE may function as a cooperative trait. In vaccinia virus, repulsion of virions from the surface of already infected cells was shown to accelerate the propagation of the infection by helping the excluded virions to reach uninfected susceptible cells in the neighborhood [90]. In other cases, SIE may also simply be a passive process, that is, a by-product of infection progression, as the case of *Sonchus* yellow web nucleorhabdovirus indicates [91].

A seemingly cooperative interaction mediated by sequential infection was demonstrated in bacteriophages. Some phages inhibit the bacterial CRISPR system using anti-CRISPR proteins (Acr), but Acr function is often not sufficient to ensure successful infection, as the CRISPR system is not fully blocked. Still, infection with Acr-encoding phages can induce a transient “immunosuppressed” state in the bacterial cell, in which CRISPR function is partially disabled. As a result, a second Acr phage infecting the same

cell may encounter more permissive conditions for infection [92, 93]. This might not be considered superinfection, since primary infections are unsuccessful. In fact, it has been suggested that the phages performing the first abortive infection function as altruistic cooperators.

### 4. Interactions Established between Viruses Infecting Different Cells

Recent work has revealed virus-virus interactions mediated by signals released from infected cells, which are sensed by other infected cells and influence infection outcome. The VSV matrix protein (M protein) inhibits overall host gene expression by binding to nuclear pores and blocking the export of mRNA from the nucleus to the cytoplasm [94]. Such blockade is potentially costly for the virus, for instance, by inducing premature apoptosis, but has the obvious benefit of preventing an antiviral innate immune response. However, this benefit is perceived not only by viruses in the infected cell (autocrine effects) but also by viruses infecting neighbor cells (paracrine effects). Thus, IFN blockade can be considered as a social trait, since it modifies the fitness of other members of the viral population. Importantly, a mutant virus that does not block IFN production can take advantage from the blockade exerted by the normal virus without paying the associated costs. Conversely, the IFN-blocking virus could be suppressed by the presence of an IFN-inducing mutant in the neighborhood. Such costly cooperation has been modeled in the classical evolutionary literature using Hamilton’s rule, which states that the cooperative trait will be favored by selection depending on the direct costs/benefits experienced by the actor, the indirect benefits experienced by other members of the population, and the genetic relatedness between the interacting individuals (Box 1) [95–97]. It was shown that IFN blockade in VSV obeys these principles and, specifically, that the fitness

2 × 2 general payoff matrix for interactions between two phenotypes: C: cooperators and D: cheaters. Detailed analysis of these models can be found in [95–97, 108, 112, 113].

	C	D
C	$f_{C C}$	$f_{C D}$
D	$f_{D C}$	$f_{D D}$

Fitness of cooperators interacting with cooperators:  $f_{C|C}$   
 Fitness of cooperators interacting with cheaters:  $f_{C|D}$   
 Fitness of cheaters interacting with cooperators:  $f_{D|C}$   
 Fitness of cheaters interacting with cheaters:  $f_{D|D}$   
 Fraction of cooperators:  $p = C/(C + D)$   
 Total fitness of cooperators:  $f_C = f_{C|C}p + f_{C|D}(1 - p)$   
 Total fitness of cheaters:  $f_D = f_{D|C}p + f_{D|D}(1 - p)$   
 Mean population fitness after cooperation:  $\bar{f} = f_C p + f_D(1 - p)$

Box 1: Social games between two actors.

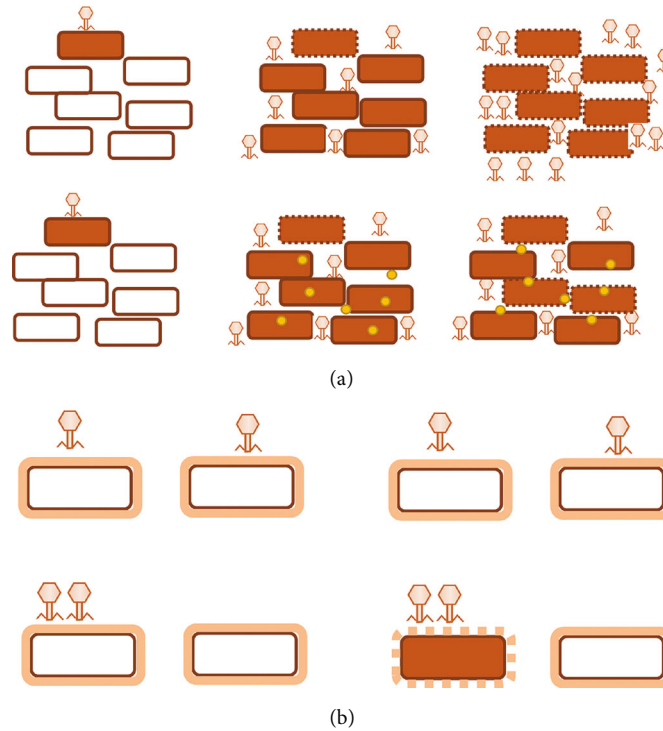


FIGURE 4: Social interaction of phages. (a) Induced lysogeny increases the fitness of the population, avoiding extinction of the host bacteria. (b) Cooperative depolymerization of bacterial exopolysaccharides allow infections.

benefit of this trait correlates with genetic relatedness which, in viruses, depends essentially on the spatial structure of the population [24]. In structured infections where VSV virus spread took place in foci, the wild-type IFN blocking virus was vastly superior to a mutant defective for this trait, whereas this advantage was lost in unstructured infections in which the two virus variants were spatially mixed.

Intercellular virus-virus interactions have also been demonstrated in bacteriophages. In recent years, a regulatory system similar to quorum sensing, called Arbitrium, has

been described in some temperate *Bacillus* phages such as phi3T or SPBeta. Arbitrium controls lysis versus lysogeny decisions, as well lysogen reactivation [98]. The system comprises at least three genes: a signal peptide (*aimP*), a receptor for that peptide that functions as a transcription factor (*aimR*), and a regulator (*aimX*) that inhibits the expression of prolysogenic genes. When the fraction of infected bacterial hosts is low, there is little signal peptide in the medium, since the peptide is produced by lysogens. In this scenario, *aimR* promotes the expression of *aimX*, which blocks lysogeny genes. This leads to an acute infection phase, with

Cooperators pay a fitness cost ( $c$ ), while cheaters do not. Any individual interacting with a cooperator obtains a fitness benefit ( $b$ ), with  $b > c$ .

	C	D
C	$b-c$	$-c$
D	$b$	$0$

$$f_C = p(b-c) + (1-p)(-c) = pb - c$$

$$f_D = pb$$

$$f_C - f_D = pb - c - pb = -c$$

Cooperation is not stable in a PD scenario, although the mean population fitness is maximal in a cooperator-only population:  $p = 1$  leads to  $\bar{f} = f_{C|C} = b - c$ .

Box 2: Prisoner's dilemma.

The cost of cheaters interacting with cheaters ( $d$ ) is greater than the cost paid by cooperators ( $d > c$ ).

	C	D
C	$b-c$	$-c$
D	$b$	$-d$

$$f_C = p(b-c) + (1-p)(-c) = pb - c$$

$$f_D = pb + (1-p)(-d) = pb + pd - d$$

$$f_C - f_D = pb - c - pb - pd + d = d - pd - c$$

A stable equilibrium point arises at  $p = (d - c)/d$ . For cooperation to be stable, the mean population fitness after cooperation must be greater than 0. This is achieved when:  $(pb - c) \times p + (pb + pd - d) \times (1 - p) > 0$ , being  $p = (d - c)/d$ .

Box 3: Snowdrift.

abundant lysis, therefore promoting the accumulation of infectious particles in the medium and, consequently, increasing the fraction of infected hosts. As the density of lysogens increases, so does the concentration of the signal peptide in the medium, which blocks *aimR*, promoting lysogeny. In this way, phages display a communication system to regulate virulence and promote prudent exploitation of the host (Figure 4). However, it is possible for more rapacious variants to emerge and outcompete prudent phages by infecting and lysing as many hosts as possible, leading to the dilemma of parasite prudence, which is actually a particular case of a more general dilemma often referred to as *yield* versus *rate*. Exploiting resources quickly confers a short-term advantage and prevents others from using them but usually reduces efficiency over the long term by exhausting resources [99, 100]. Further investigation is required to analyze what kind of social games is promoted by the Arbitrium system.

Depolymerases may also mediate intercellular virus-virus interactions in phages. These enzymes are typically located on bacteriophage tails and promote infection by disrupting bacterial exopolysaccharides and exposing phage receptors [101–105]. Diffusible depolymerases that are dissociated from tails or remain associated to broken tails could function as classical public goods since they can potentially benefit many members of the local phage population, regardless the specific phage that produced them [104]. It has been suggested that certain synergistic interactions between different phage species at the level of host entry might be mediated by depolymerases [105], although the experimental support for this type of interaction is scarce (Figure 4).

### 5. Viral Cheating

Just as cooperation is widespread in nature, so are cheaters, defined as individuals that reap the benefits of cooperation

without contributing to such benefits. If cooperation entails a cost (for instance, producing a capsid), cheaters may experience higher fitness than cooperators because they do not pay such a cost, potentially jeopardizing the maintenance of cooperative traits in the population (the so-called tragedy of the commons). Box 2 illustrates some well-studied cooperative interactions from a game theory point of view. A classical scenario is the Prisoner's dilemma (PD), in which (i) cooperative traits bear a cost for the actor ( $-c$ ) and a greater benefit for the receptor ( $b > c$ ); (ii) the payoff of interactions between cooperators is the sum of both terms ( $f_{C|C} = b - c$ ); (iii) the payoff of cheaters interacting with cooperators is simply the positive effect they receive from cooperators ( $f_{D|C} = b$ ); (iv) the payoff of cooperators interacting with cheaters equals the cost of cooperating ( $f_{C|D} = -c$ ); and (v) the payoff of cheaters interacting with cheaters is zero since there is no interaction ( $f_{D|D} = 0$ ). Thus, the fitness of cooperators is lower than that of cheaters regardless of the probability of encountering a cooperator or a cheater ( $f_{D|C} > f_{C|C}$  and  $f_{D|D} > f_{C|D}$ ). The overall fitness difference between cooperators and cheaters is  $f_C - f_D = -c$ , which means that cooperation should always go extinct despite the fact that mean population fitness would be maximal if all individuals were cooperators (Box 3).

Viruses and genetic systems in general have to accomplish a balance between two key processes, namely, gene expression and replication. During coinfections, a PD social game may occur if the gene products of one virus can be exploited by the other virus [106, 107]. If this is the case, a virus variant that reduces transcription and prioritizes replication may be capable of producing progeny genomes faster than a counterpart that invests more in transcription. However, a cell coinfecting with only such cheaters would produce little progeny [81]. PD is fulfilled in this scenario since infections with only

A fraction ( $r$ ) of cooperators interact preferentially with cooperators.

	C	D
C	$(b-c)(1+r)$	$br-c$
D	$b-cr$	$0$

$$f_c = p(b-c)(1+r) + (1-p)(br-c) = pb + rb - pcr - c$$

$$f_D = p(b-cr) = pb - pcr$$

$$f_c - f_D = pb + rb - pcr - c - (pb - pcr) = rb - c$$

Cooperation may evolve if  $r > c/b$ , which is the condition of the well-known Hamilton rule.

Box 4: Kin selection.

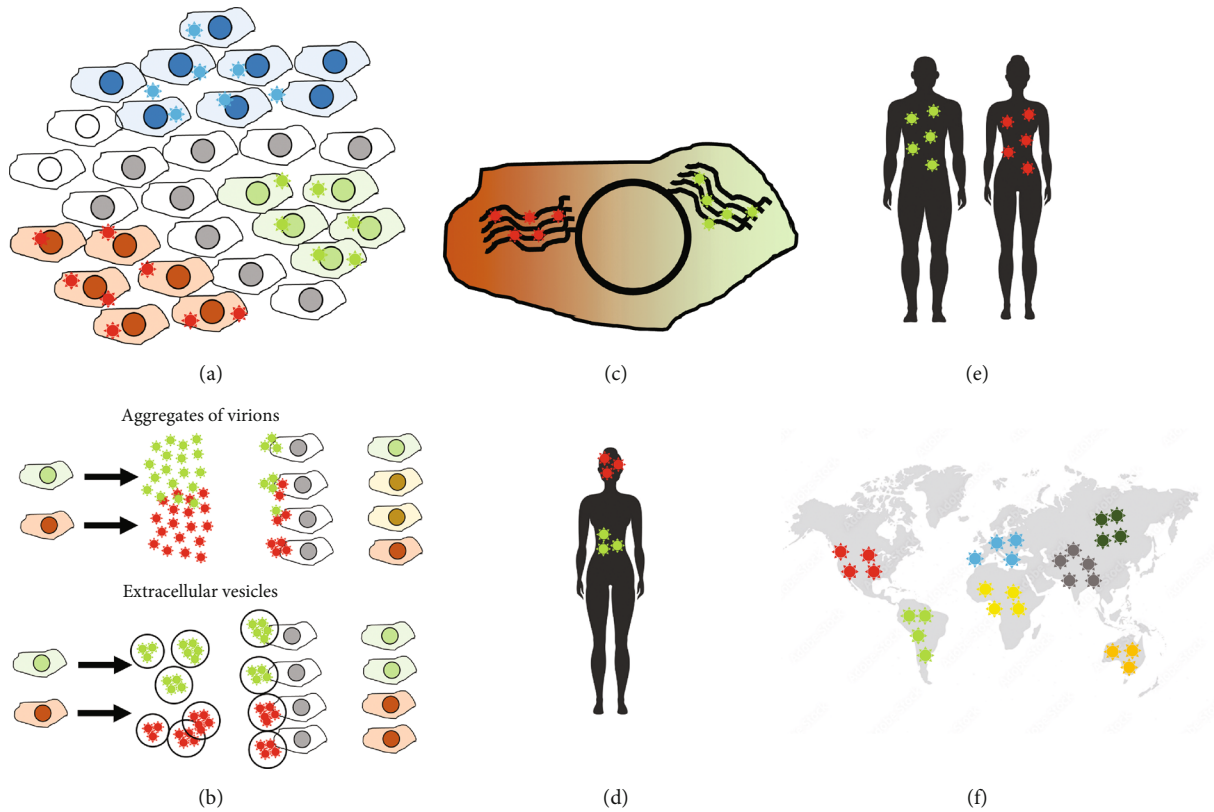


FIGURE 5: Levels of population structure in viruses. (a) Growth in foci segregates variants due to limited diffusion and superinfection exclusion. (b) CIUs such as extracellular vesicles cause segregation, in contrast to other types of CIUs such as aggregates of virions. (c) Subcellular replication centers. (d) Tissue and organ segregation. (e) Host segregation. (f) Host population segregation.

cooperators are the fittest, but coinfections between cooperators and cheaters are always dominated by cheaters.

A different scenario arises when the fitness payoffs of the interaction between cheaters (due to an extremely low propensity for transcription) decrease so much that it is even lower than those of single infections (no interaction). Here, a fundamental modification of the payoff matrix occurs, since now, the interaction between cheaters is no longer neutral ( $f_{D|D} = -d < -c$ ). A new social game called Snowdrift (SD) emerges, in which the optimal strategy is no longer to always be a cheater [108]. Since  $f_{D|C} > f_{C|C}$ , but  $f_{C|D} > f_{D|D}$ , selection is frequency-dependent and a stable equilibrium between cooperators and cheaters is possible (Box 4). This model describes a very well-known type of cheaters, namely, defective interfering particles (DIPs). DIPs are viruses that

have lost a large fraction of the viral genome, such that they are unable to complete an infectious cycle except if a normal or “helper” virus is present in the same cell [109–111]. It has been shown that a nonlinear trade-off between replication and transcription can also generate a SD game between cheater and cooperator viruses [112].

Generally speaking, cooperators can outcompete cheaters if they are more likely to interact with other cooperators than cheaters are (Box 1). Hamilton’s rule states that cooperative traits will be favored by selection if  $r > c/b$ , where  $r$  is the genetic relatedness between interactors for the relevant trait in question, that is, the probability that the benefits of cooperation are received by individuals who share the cooperative trait [95–97]. In the absence of complex phenotype recognition mechanisms such as memory and



learning, viruses have to rely on spatial population structure as the main process that promotes genetic relatedness and thus prevents the spread of cheaters.

Viruses exhibit spatial population structure at different levels, ranging from subcellular replication centers to tissues, organs, hosts, or host populations (Figure 5). For instance, infections in solid tissues usually progresses as foci founded by one or a few particles. This creates a region in which each cell is infected by genetically related viruses and where coinfection is likely due to the high local MOI (Figure 5). Concerning CIUs, some allow greater levels of genetic relatedness than others. For instance, extracellular vesicles or occlusion bodies promote the cotransmission of genomes originating from the same infected cell, limiting interactions to “sibling” genomes. Direct cell-to-cell transmission also preserves genetic relatedness in a similar way. In contrast, other CIUs such as virion aggregates generate mixtures of virions from different cells. Increased genetic relatedness should promote the evolution of cooperation between similar variants, but it may also have a negative effect on diversity-driven cooperation.

## 6. Conclusions

The evolution of cooperation is a widely explored topic in the evolutionary biology literature [113]. In the last two decades, the attention has focused on the social interactions displayed by microorganisms, mainly bacteria but more recently also viruses [114, 115]. Cooperative interactions have been shown to have an important effect on viral evolution, such as, for instance, on the evolution of innate immunity evasion [24], but also on infection outcomes in animal [86] and plant viruses [116, 117]. Moreover, the fact that DIPs are found naturally in human patients [118, 119] provides evidence that cooperative interactions take place in nature and have a practical relevance. Although still poorly explored, social evolution could also offer a new perspective on other important traits such as viral tropism and the regulation of virulence. Concerning collective viral transmission, unresolved questions remain, such as whether there is a general fitness benefit for this transmission mode, which should be associated to elevating the MOI, or whether CIUs have evolved in different viruses in response to specific selective pressures. It is noteworthy that extracellular vesicles, which are a well-studied type of CIU vehicle, are used by different viral families such as *Reoviridae* [59], *Caliciviridae* [59], *Picornaviridae* [60], and *Marseilleviridae* [63]. Further research from an evolutionary approach is required to shed light on these unresolved questions.

## Conflicts of Interest

The authors declare no conflict of interest.

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