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Cheating Viruses and Game Theory

The theory of games can explain how viruses evolve when they compete against one another in a test of evolutionary fitness

Paul E. Turner

The 19th-century circus showman P. T. Barnum is reputed to have coined the phrase "There's a sucker born every minute"—although Barnum denied the saying was his, and it has been variously attributed by biographers. In any event, whoever did voice this cynical view of human gullibility could not have predicted that the terms "cheaters" and "suckers" would describe individuals in the world of microorganisms as well. However, my colleagues and I have been studying interactions between viruses, and it seems that strategies for taking advantage of the other fellow are just another way for the viruses, too, to make a "living."

The temptation to cheat appears to be a universal fact of life. In the struggle to survive and reproduce that drives evolution, selfish individuals may be favored over cooperators because they are more energy efficient. By definition, cheaters expend relatively little energy in a task because they specialize in taking advantage of others—"suckers"—whose efforts they co-opt to their own advantage. In certain animal species some males exert tremendous energy maintaining and defending territories to attract females. Meanwhile, the population may contain subordinate "sneaker" males that are uninterested in territory but linger at the boundaries and specialize in surreptitious copulations. This strategy is very successful for maintaining a subpopulation of sneakers, but it's unlikely that the population will evolve to contain only cheaters because territorial males are most attractive to female mates.

In general, cheaters are highly successful when they are rare because they frequently encounter suckers. The benefits of cheating wane as more individuals in the population opt to cheat. In the parlance of evolutionary biology, the success of cheaters should be governed by *frequency-dependent selection*. That is, some cost should be associated with a cheating strategy so that selfish individuals are at an advantage when they are rare, but disadvantaged when they are common.

Game theory is a useful approach for mathematically predicting which strategy, if any, will dominate such a contest. Social scientists use game theory to predict which behaviors will spread through a population, especially in contests involving classic strategies such as "hawk" versus "dove," and "cooperator" versus "cheater." One of the most intriguing results of this approach is a mathematical proof demonstrating that cheating can take over a population, even though deceit can be considered an irrational behavior because it is punishable.

My colleagues and I have applied game theory to the experimental evolution of viruses in the laboratory. This is a field that is relatively new, but is proving to be powerful for testing fundamental questions in evolutionary biology. It's an approach with many advantages: Viruses are easy to culture. They have rapid generation times and large population sizes. In addition, an array of modern tools makes them easy subjects for manipulation and study. Although the experiments are conducted in the laboratory, evolution proceeds by natural selection because the laboratory habitat dictates which genetic variants are favored to contribute their genes to the next generation. This is very different from artificial selection, such as dog breeding, where the experimenter determines the variants that will reproduce. Perhaps most important, microorganisms can be stored in a freezer indefinitely, creating a "fossil record" that permits direct comparisons between the genetic makeup of an ancestral population and that of its evolved descendants. Our experiments suggest that yes, perhaps at this moment, there may be cheaters among the viruses vying for survival within and near your own cells. But in the long run, such crimes don't always pay.

Viruses in Conflict

We experience viruses mainly through the symptoms, such as fever and fatigue, that signal that our body is defending against an invader's attempt to commandeer the normal activities of the body's cells. Viruses are parasites that rely on the genetic machinery of a host organism to make copies of themselves. At any particular moment an infected individual can harbor several species of viruses or even genetic variants (genotypes) of the same species. So the host serves as an ecosystem for potential interactions between the viruses. These interactions may be indirect—for example, when the host's immune system takes action against one species of virus, while simultaneously affecting other viruses. A host's fever may be a generalized response to a specific infection, but the high tem-

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Figure 1. Cheaters often win in the simulations used in game theory, a branch of mathematics that analyzes competitive interactions between individuals. Regrettably too common among human beings, cheating has also been found among many other animal species and, perhaps surprisingly, among viruses. The cheating viruses were discovered in laboratory experiments by the author. In *Le Tricheur* ("The Cheat"), the 17th-century French painter Georges de La Tour depicts a card game with at least one deceitful player.

perature can impair the growth of all viruses within the body.

When viruses interact directly, their effects on each other are more difficult to detect because they take place within an individual cell. When a virus enters a cell, it hijacks the host's metabolism, instructing it to make the bits and pieces needed to assemble other viral particles. When more than one virus infects a cell, the metabolic products are freely accessible to any of the co-infecting viruses. In a process called *complementation,* one virus provides a useful product that cannot be made by another virus. If the viruses provide each other with useful resources, the interaction is of mutual benefit. Consider the co-infection of a cell by two mutant viruses, which differ by having inactivated genes at different locations in the genome. The common resource pool allows the viruses to use each other's protein products. The co-infection rescues the mutants, allowing them to reproduce when they couldn't otherwise do so.

Such mutually beneficial interactions between viruses are either rare or extremely difficult to detect. More often, viruses seem to experience a conflict of interest over the resource pool. When this happens one virus can selfishly usurp resources to the detriment of other virus species or genotypes.

In a form of complementation known as *phenotypic mixing,* a virus acquires certain observable (phenotypic) traits from another virus. This phenomenon frequently involves a conflict over proteins used to create the viral *capsid,* a shell that protects the genetic material of the virus. Phenotypic mixing allows a virus to acquire capsid proteins from the resource pool of a different virus. This is critical because some proteins on the capsid dictate whether a virus can attach to a particular host cell and thrive.

An interaction between two plant viruses illustrates how this strategy can be important in the transmission of a virus. Luteoviruses infect nearly all the crops that people grow for food or fiber. These viruses can easily travel between plants by hitching a ride with the tiny plant-sucking insects called aphids. Umbraviruses also infect crop plants, but they are unable to hook up with the aphid vector. This situation changes if luteoviruses and umbraviruses happen to co-infect the same plant. The umbraviruses steal some of the capsid proteins from the luteovirus resource pool, attach themselves to the aphids and so move on to new host plants. Meanwhile, the hapless luteoviruses experience a net loss in the capsid proteins they need to assemble their progeny.

Complementation can also be a factor in conflicts when one virus usurps an enzyme needed for replication from another virus. The best known examples involve an ordinary virus and a defective form, typically a virus with a "shortened" genome, one that lacks one or more essential genes. This phenomenon was first described in laboratory experiments involving polioviruses. When these viruses are grown at high densities there is strong selection pressure for them to lose genes (become defective) because shortened viruses replicate much faster than viruses with genomes of normal length.

Figure 2. Cheating as an evolutionary strategy can be studied by measuring the reproductive success of animals that engage in covert copulations or fertilizations, such as these bluegill sunfish *(Lepomis macrochirus)*. Here a male bluegill *(right)* gains access to a nesting female *(center)* by mimicking her appearance, and so cuckolds a so-called "parental" male *(left)* who courts the female and cares for the offspring. Both breeding tactics used by the males are successful, and so neither can displace the other in the population. Cheating viruses use tactics very different from the mimicking male fish, but it is possible to conduct experiments that show how cheating affects their reproductive success and thus the viruses' evolutionary fitness. (Image courtesy of Brian D. Neff, University of Western Ontario.)

The defective viruses interfere with the reproductive success of the ordinary viruses by using their gene products, so that the ordinary viruses take on the role of helpers. Because viruses reproduce exponentially, even a slight advantage in replication rate can result in drastic differences in the relative success of the viruses. The problem faced by the "defective-interfering" viruses is that they are entirely dependent on helper viruses to provide key proteins.

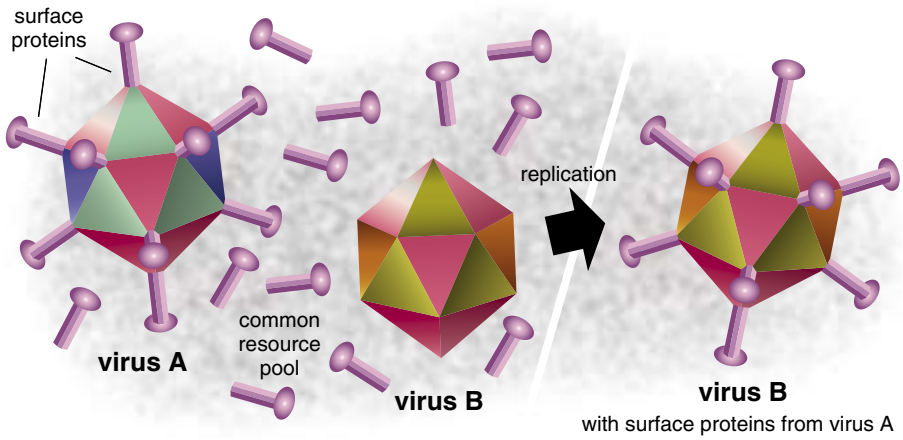


Figure 3. Viruses compete for resources when they co-infect the same cell. In some instances, one virus may provide a useful product for another virus, a phenomenon called complementation. In this hypothetical example, virus A carries a gene that codes for a valuable surface protein—for example, one that allows it to infect other cell types. Although virus B lacks the gene for this protein, it can steal the protein from the common resource pool inside the host cell. Virus B gains the use of the protein, whereas the offspring of virus A now experience a shortage of the protein. A form of complementation called phenotypic mixing takes place when one virus acquires observable (phenotypic) traits from another virus, as shown here. Complementation may be involved when viruses cheat.

If the replication advantage of the defective-interfering viruses drives the helpers to extinction, both strains will die.

Most virologists view defective-interfering viruses as an unfortunate nuisance, one that may compromise their research goals—as when, for example, such a virus contaminates the purity of a commercial vaccine. To a microbial ecologist, however, the defective-interfering viruses are especially intriguing because they are parasites on parasites, or hyper-parasites, something rarely seen elsewhere in biology.

This naturally raises the question of whether defective-interfering viruses are merely laboratory artifacts. Some recent evidence suggests that a related phenomenon may not be uncommon outside the laboratory. Natural hyperparasitism is seen among viruses that infect farm animals and crops. The majority of the defective viruses identified from these systems are *satellite* viruses; they are usually unrelated to their helpers. By contrast, defective-interfering viruses have recognizable genetic similarities to the helpers from which they evolved by losing certain genes. Defective-interfering viruses may be rare in nature because the helper viruses appear to evolve a resistance to being parasitized by closely related viruses. For some reason satellite viruses are more easily able to circumvent any resistance put up by the helpers.

Defective viruses are not known to play a widespread role in human disease. A notable exception is the hepatitis delta virus, a satellite virus associated with its helper, the hepatitis-B virus. Together these two viruses cause unusually severe liver damage in cases of chronic active hepatitis. It is not clear why defective viruses are not commonly implicated in human disease, but it is conceivable that other examples have yet to be discovered by the medical community.

Although hyperparasitic viruses may evolve readily, they can easily wind up as evolutionary dead ends because of their strict reliance on helper viruses. It would be a daunting task to study the relative success of parasitic viruses in nature because there are so many uncontrolled variables in field studies. However, virus interactions can be examined under controlled laboratory conditions in experiments that measure relative growth rates. This approach can be augmented with mathematical models that explore how eas-

ily parasitic viruses arise and whether they can persist. As it happens, game theorists have had a long-standing interest in the success of parasites and other cheaters, so there are many mathematical models to choose from.

Cheaters Sometimes Prosper

To understand how game theory might be applied to virus interactions, consider a game involving cooperators and cheaters, known as the "prisoner's dilemma." This scenario, which has been used to explore philosophical, political, economic and biological questions for half a century, involves two felons who are separately interrogated about a crime they committed. In one version of the game, an understanding between the prisoners is assumed: They can cooperate in denying the crime in the hope that they'll both be let off the hook. The interrogator, however, offers two choices to each prisoner. If both stay silent (cooperate), each will receive a light one-year jail sentence. If both confess, each goes to prison for 10 years. However, if one confesses—in other words, cheats—the cooperator will receive a 20-year sentence while the cheater goes free. So what's a prisoner to do?

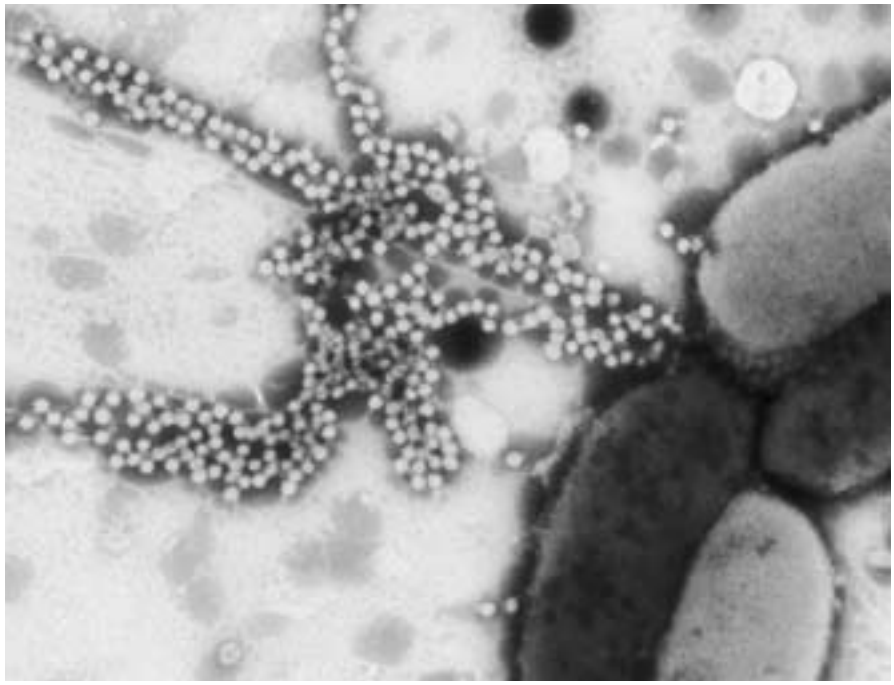
Game theory holds that in such a dilemma, it always pays the individual to cheat because cheating, even though it risks a long sentence, offers the only possibility of obtaining the best payoff—freedom. The result is intriguing because it explains how a potential, but uncertain, reward can drive individuals to behave in a way that is collectively irrational: When both prisoners follow their individual interests, both lose.

When the differing strategies are associated with different underlying genetics, game theory can be applied to the study of evolution. Popularized by the late British biologist John Maynard Smith, evolutionary game theory comes into play when an individual's reproductive success, or *fitness*, is frequency dependent. Consider a predator that preferentially feeds on the most common type of organism in a prey population because these individuals provide an easy "search image." Prey types with a rare appearance, perhaps sporting an uncommon fur color, will have a higher fitness because they escape the predator's notice. This advantage will wane as their type becomes more common in the population and therefore more obvious to the predator.

Evolutionary game theory weighs the costs and benefits in terms of fitness associated with different strategies, and so predicts the evolutionary fate of the different types. This is done by creating a 2×2 matrix that contains all pairwise interactions between two different strategies. Each entry within the matrix consists of the fitness payoff to one strategist when it interacts with the other. The matrix reveals the relative success of the strategies in the contest so long as the mathematical fitness values can be calculated. When a population evolves to contain only individuals with a single strategy, it is defined as an "evolutionary stable strategy." If two strategies are unable to displace one another, as hinted at

	cooperator	cheater
cooperator	reward	sucker's payoff
cheater	temptation to cheat	punishment

Figure 4. Payoff matrix for a contest between a "cheater" and a "cooperator" shows the outcome of each pairwise interaction for one individual *(left side of matrix)* who encounters another *(top of matrix)*. A cooperator who meets another cooperator is rewarded, whereas a cooperator who meets a cheater receives the "sucker's payoff," typically a loss of some useful resource. A cheater gains this valuable resource when interacting with a cooperator and so is tempted to cheat. When a cheater meets another cheater, nothing is gained, and the two are usually punished in some way. The relative success of cheaters and cooperators can be determined if the respective costs and benefits can be quantified for each of the interactions. When these strategies are associated with different underlying genetics, the payoff matrix can predict whether one tactic will displace another over the course of evolution.



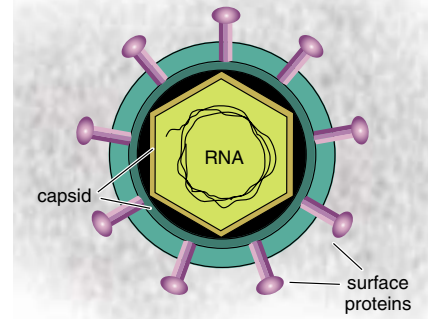
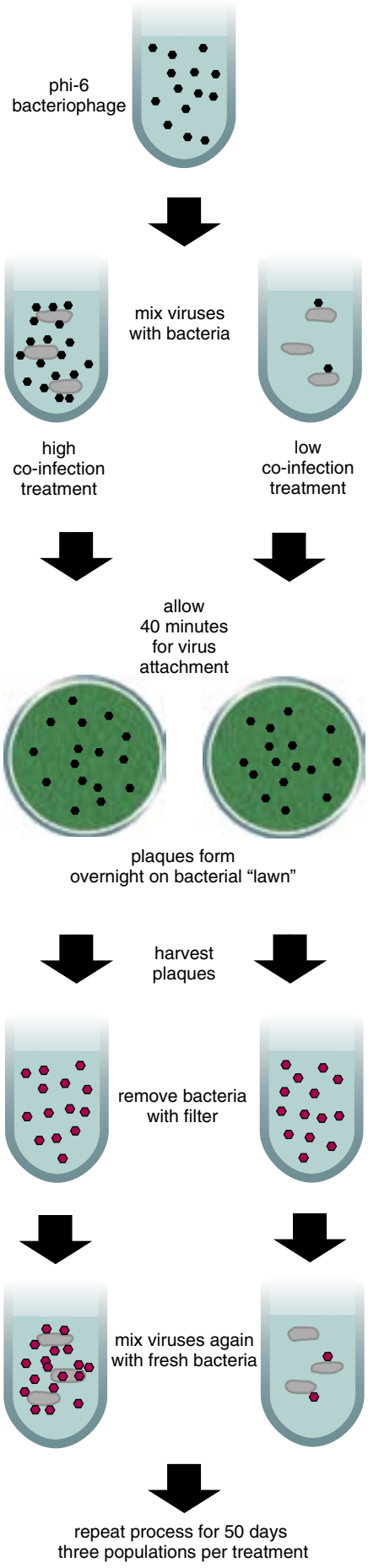


Figure 5. Viral particles of the bacteriophage phi-6 *(left, small circles)*, which grow on *Pseudomonas phaseolicola* bacteria *(larger lozenge shapes)* in the laboratory, are the subjects of experiments in evolutionary game theory. Each phi-6 particle *(above)* consists of the genetic material RNA, which is housed in a protein shell (or capsid) and a lipid membrane. The phi-6 bacteriophages may compete against one another for the capsid proteins in the common resource pool inside the bacterial host. (Electron micrograph courtesy of Dennis Bamford, University of Helsinki.)



in the predator-prey example above, both strategies will coexist indefinitely; this is defined as a "mixed evolutionary stable strategy."

In the prisoner's dilemma, evolutionary game theory suggests that cheaters should take over the population—selfishness turns out to be the evolutionary stable strategy. The result is striking because it is somewhat counter to Darwin's theory of evolution by natural selection. Darwinism holds that differential performance allows the fittest individuals to produce more offspring, which steers the population to become better adapted to its environment over time. The prisoner's dilemma indicates that cheaters can successfully displace cooperators, while simultaneously *lowering* the average fitness of the population. The prisoner's dilemma is very easy to prove mathematically, but it took laboratory experiments on viruses to demonstrate that the strategy may take place in a biological population.

Experiments in Evolution

My colleague Lin Chao, of the University of California, San Diego, and I designed a series of experiments to explore the evolution of behavioral interactions between viruses. In this case, the players in our experimental game were bacteriophages, or "phages," viruses that infect bacteria. Phages are not typically thought to exhibit behavior, but they have proved to be very useful to test models of conflicting behavioral strategies in evolutionary game theory. Such tests would be difficult if not impossible to do with higher organisms.

We employed the services of a phage called phi-6, an RNA virus (one that has RNA instead of DNA as its genetic material) in the family *Cystoviridae*, which attacks legume-infecting bacteria. In the laboratory, the virus is typically grown on *Pseudomonas phaseolicola* bacteria, which are easily cultured on agar plates. By combining the phage and bacterial populations in different ratios it is simple to control whether a virus will infect a bacterial cell on its own or co-infect the same cell with other viruses.

Chao and I created six laboratory populations of phi-6 growing on the *P. phaseolicola* bacteria. Three populations were allowed to evolve at phage-host ratios that resulted in strictly single infections. The other three populations were grown at ratios that allowed co-infection with an average of about two or three viruses entering each bacterium. We let the viruses grow for 50 days, which corresponds to about 250 generations of phage evolution. By comparison, a similar experiment using a human population would take 5,000 years (assuming about 20 years per generation).

After 250 viral generations had elapsed, the evolved populations were each placed into an agar-plate "arena" to compete against the revived ancestor that had been stored in the freezer. This allowed us to gauge changes in viral fitness, which we defined by measuring the growth rate of the virus on the bacteria. If both viruses grew equally well, the fitness of an evolved virus relative to its ancestor was said to equal one. However, if evolution had either improved or worsened the virus's ability to grow, then the fitness was respectively either greater or less than one.

A conspicuous result of the study was that the viruses cultured in the co-infecting populations had much higher fitnesses during co-infection, than during single infections. This result is consistent with the possibility that evolution under co-infection had selected for cheater viruses—genotypes that could efficiently use the products of other viruses in the resource pool, but that were less efficient on their own. The evolved viruses also had the ability to infect the bacteria and replicate on their own, indicating that the cheaters were not simply defective-interfering viruses that had lost key genes. Because the ancestral virus did not show any fitness advantage during co-infection with other virus genotypes, we defined the ancestral strategy as cooperation.

Figure 6. Different strains of phi-6 bacteriophages *(dots)* can be created in the laboratory by controlling the number of bacteriophage particles that can co-infect a single bacterial cell *(lozenges)*. Three populations were grown on a bacterial "lawn" at phage-bacterium ratios that allowed at least two or three bacteriophages to enter each host cell *(left protocol)*, whereas three other populations were allowed to evolve in ratios where no more than one phage entered a bacterial cell *(right protocol)*. After 50 days, or 250 phage generations, each population was allowed to compete against an ancestral strain *(see Figure 7)*.

Game-Theory Solutions

The evolution of cheater viruses containing a full set of genes provided a unique opportunity to examine wheth-

er the phage was caught in the prisoner's dilemma. We needed to confirm two key predictions. First, the fitness of the cheaters relative to the ancestral cooperator had to be frequency dependent—sensitive to the ratio between cheaters and cooperators—because the model predicts that cheaters will show their greatest fitness advantage when they are rare relative to the cooperators. Second, the cheaters had to displace the ancestral cooperators completely and take over the population. If these two criteria were met, and the takeover by cheaters resulted in a decline in the average fitness of the population, then the results would be consistent with the prisoner's dilemma.

We set up a series of competitions between an evolved cheater and the ancestral cooperator. To test for frequency-dependent fitness, the two strains were represented at different initial frequencies (ranging from 0.1 to 0.9) for each competition and the numbers were sufficiently high to allow co-infection. After allowing the strains to compete for five generations, we found that, indeed, the fitness of the cheater decreased sharply as its initial frequency increased. In other words, when cheaters were rare, they generally were involved in co-infections with cooperators (rather than with other cheaters), and so they gained a large fitness advantage through their ability to usurp the components in the resource pool. However, when the cheaters were common, they tended to co-infect cells with other cheaters and so could not profit from their selfish behavior.

The same experiment also supported the second prediction: The cheaters must takeover the population. The fitness of the evolved cheaters relative to the ancestral cooperator was always greater than one at all of the initial ratios. This global advantage predicts that the evolved cheater will always displace the ancestral cooperator. The strong competitive advantage allows the cheaters to increase their numbers rapidly when they are initially rare. Even though the cost of cheating increases as the number of cheaters increases, the cooperators that interacted with the cheaters always had the lowest fitness in the system. For this reason, nothing could prevent the cheaters from taking over the population. Our study was the first to demonstrate the evolution of irrational, selfish behavior in a biological system *(see "Estimating the Payoffs," next page)*.

Interactions between selfish defective-interfering viruses and cooperative helper viruses can also be explained using game theory. Imagine a population composed entirely of cooperative helpers growing in an environment where co-infection is common. If a mutant defective-interfering virus enters the population, it has a very large fitness advantage because it is surrounded by cooperators that provide essential gene products. So defective-interfering

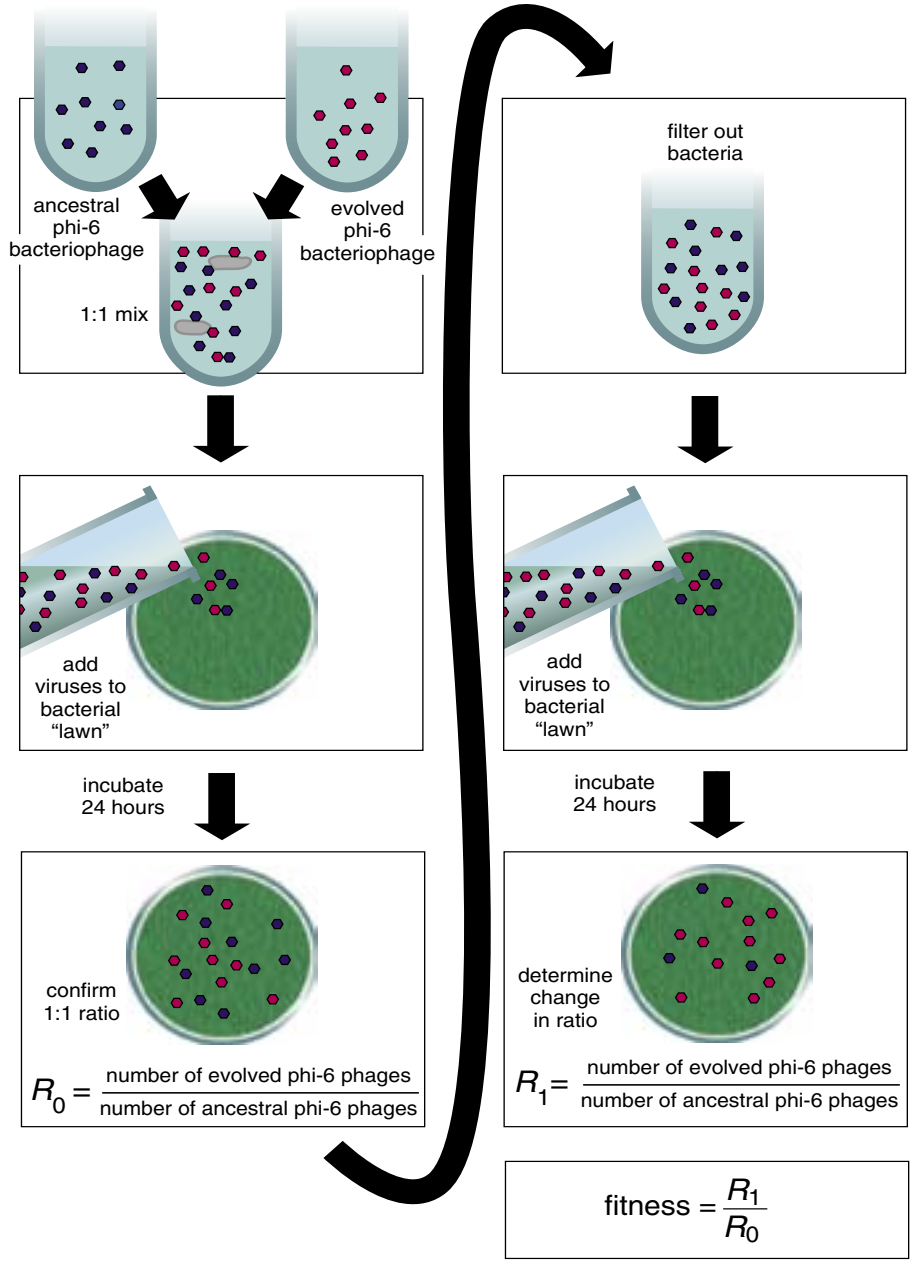
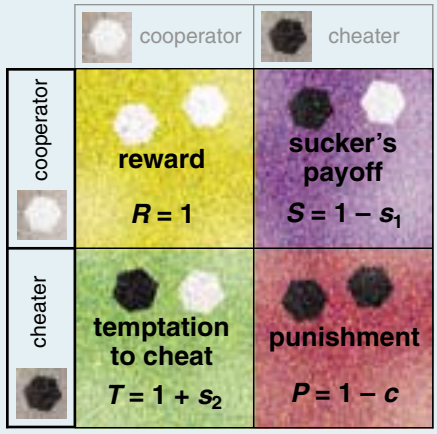


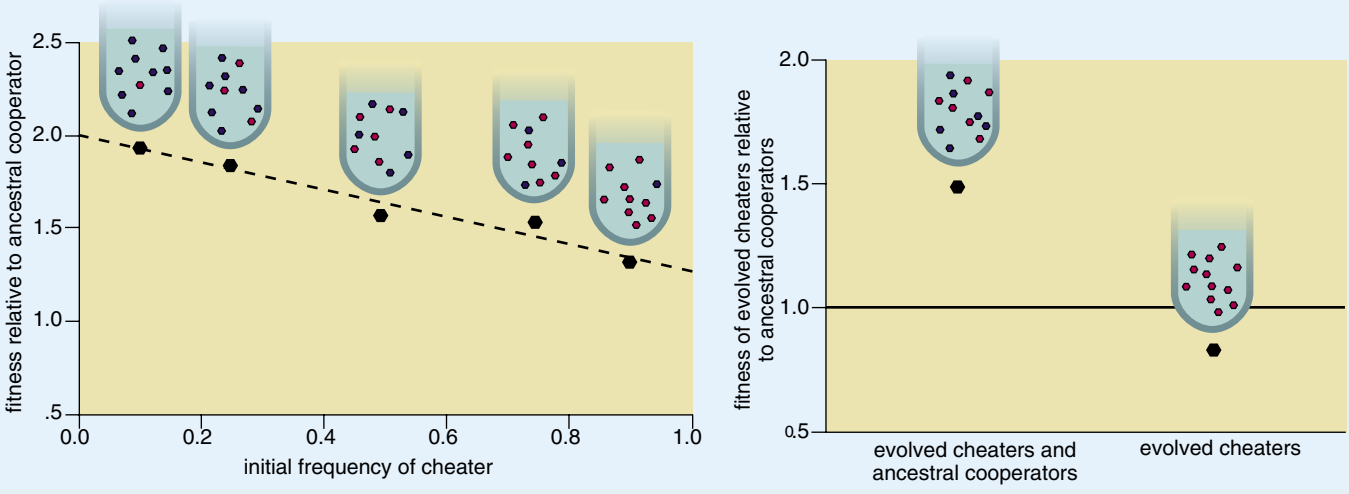
Figure 7. The fitness of an evolved strain of phi-6 bacteriophages relative to the ancestral phi-6 bacteriophages can be determined by having the two strains compete for bacterial hosts. The ability of the two populations to establish themselves and reproduce on a bacterial "lawn" is first established by confirming that they maintain a 1:1 ratio after a 24-hour incubation period *(left column)*. When the phages are again counted after a second 24-hour incubation period, the change in the ratios of the populations (R_1 vs. R_0) is a measure of their ability to compete against each other. In the author's experiments, bacteriophages that evolved under conditions of high co-infection had a higher fitness during co-infection than during single infections. This result is consistent with the possibility that evolution had selected for "cheating" bacteriophages—strains that could usurp the products of other bacteriophages ("cooperators") from the resource pool, but were less efficient on their own. The evolutionary costs and benefits of the interactions between cheaters and cooperators can be calculated with further experiments *(see* "Estimating the Payoffs," *next page).*

Estimating the Payoffs

Experiments between cheating and cooperating viruses allow scientists to estimate the fitness payoffs for each of the strategies in a 2×2 matrix *(right)*. In the prisoner's dilemma, when two cooperators interact the reward is defined as $R = 1$. When a cheater meets a cooperator, the temptation to cheat, T, must exceed the reward for cooperating by some value, say s_2, so that $T = 1 + s_2$. So the fitness of the cheater relative to the cooperator is T/R, when the cheaters are rare. The value of s_2 can be determined from experimental data. My colleagues and I set the equation, $T/R = (1 + s_2)/1$, equal to the left y-intercept of the regression line for the data *(see graph below, left)*. The y-intercept represents the case where a cheater is very rare and therefore guaranteed of interacting with cooperators. So an individual cheater receives the maximum benefit: $T/R = (1 + s_2)/1 = 1.99$, and $s_2 = 0.99$.

When two cheaters meet, there is a loss of fitness, and the punishment for cheating is defined as $P = 1 - c$. A cooperator also loses fitness when interacting with a cheater and receives the "sucker's payoff," $S = 1 - s_1$. Here we set $P/S = (1 - c)/(1 - s_1)$ equal to the right y-intercept of the regression line, which represents the case when there is the greatest frequency of cheaters. Because our results found that the right y-intercept was a number greater than one, P had to be a value greater than S. However, the ratio cannot be solved because of two unknown variables, c and s_1. We needed to devise an additional experiment to directly estimate P or S. We did this by measuring the growth rates of the cheaters and cooperators when co-infecting cells on their own. This experiment mimics the situation when the cheater viruses take over the virus population. We found that the growth rate of the cheaters was 83 percent of the cooperators' growth rate. So $P = 1 - c = 0.83$. We substitute the value $c = 0.17$ in the equation for P/S. It was then trivial to estimate the parameter s_1, so we could fill in the payoff matrix. Because the cheater ultimately replaces the cooperator, while lowering the fitness of the population *(see graph below, right)*, the results are consistent with the prisoner's dilemma.





viruses become increasingly common in the population. However, as the selfish individuals increase in relative frequency, their fitness will decline because there are fewer cooperators present. If the defective-interfering viruses take over, their fitness falls to zero because they cannot reproduce on their own. In this case, the strategy of the defective-interfering viruses can only persist through a mixed evolutionary stable strategy involving a helper virus. Evolutionary game theorists call this the "chicken game."

It is still not clear how the selfish phi-6 genotypes can so efficiently sequester products from the resource pool to the detriment of their cooperative ancestor. Evidence from other experiments with phi-6 suggest that complementation may be involved. When the ancestral phi-6 strain is allowed to co-infect the same cell with various less fit mutants of the virus, a greater-than-expected number of mutants appear among the offspring. This suggests that complementation can take place passively whenever multiple phi-6 genotypes co-infect the same cell. The evolution of cheating viruses may occur because their prolonged exposure to co-infection results in a strong selection for the virus to become more efficient at complementation—a trait that was already present in the ancestor. This idea assumes that complementation is not always entirely passive and so can be improved through selection. One possibility is that the cheaters may be poor at producing capsid proteins, which could explain their low productivity when they infect cells on their own. However, they may be very efficient at stealing entry into capsids produced by cooperators during co-infection. It may be that cheaters have evolved mechanisms that recognize attachment and entry into viral capsids.

Outside the Laboratory

Laboratory studies of cheating viruses and bacteria may seem esoteric, but

they have much to offer for understanding the ecology and evolution of microorganisms in nature and in medical and commercial settings. Very little is known about the interactions between microorganisms in the wild. In fact, the vast majority of microbial species in nature have yet to be described. Cheating has been observed in laboratory experiments among viruses, bacteria and slime molds, and it seems likely that we will discover cheaters in natural communities of these microorganisms as well.

Human beings have a long history of using bacteria and yeasts for the production and flavoring of foods and beverages, including cheese, bread, wine and beer. More recently, we have purposefully cultured microorganisms to create vaccines, which are often weakened or inactivated microbes that are administered to elicit an immune response. Vaccines are widely available for combating infectious diseases such as polio, measles and mumps, and there are now efforts to develop vaccines for other diseases such as AIDS and malaria. Similar strategies are used in agriculture, where vaccines are administered to prevent diseases in livestock, and crops are sprayed with viruses or bacteria to combat plant diseases or to target insects that destroy crops. The research described in this article suggests that industrial producers of microorganisms should be wary of contamination by cheaters, which may compromise the desired tastes of foods and beverages, or the effectiveness of vaccines and biological pesticides.

On the other hand, cheating viruses and bacteria may provide desirable and exciting new avenues for the application of microorganisms. For example, scientists are now trying to determine whether defective HIV strains can interfere with the ability of ordinary HIV to replicate and spread within the body and so prevent or delay the onset of AIDS in HIV-infected individuals.

Biologists still need to determine the conditions that promote or hinder the growth of microbial cheaters. Mathematical models such as evolutionary game theory will be valuable for predicting their long-term success. As we continue to discover the intriguing interactions between microorganisms that foster the evolution of cheating strategies, we will in turn provide opportunities for exchanges between scientists interested in evolutionary biology and those working in basic and applied aspects of microbiology.

A Dilemma?

Following our study, other scientists suggested that certain populations of yeast and bacteria may also evolve according to the prisoner's dilemma. Some yeast cells forgo the production of a sugar-digesting enzyme, opting to steal sugar that was digested by cooperators. And certain bacterial mutants cheat by ignoring a chemical signal to stop growing, while others in the population enter a stationary phase. But not everyone agrees that the prisoner's dilemma is the best way to describe interactions between microorganisms. Microbes obviously lack the complex behavior of "higher" life forms, and so it's been suggested that mathematical models that are not based on animal behavior may be more accurate to describe these phenomena.

An alternative interpretation involves "producers" and "scroungers." A producer expends energy generating opportunities to exploit resources that are essential to survival and reproduction, whereas a scrounger takes advantage of these opportunities, usurping the resources that producers extract from the environment. In this view, the ancestral phi-6 phage is the producer, whereas the descendant viruses that evolved under co-infection are scroungers. The limited resources could be replication enzymes or other proteins essential for the production of progeny. When scroungers are rare, they frequently encounter producers, so they have many opportunities to grab the resources. The scroungers have an advantage and should increase when they are rare.

The producer/scrounger analogy assumes there is a cost associated with scrounging. This may be simply the increased competition between scroungers when they become common. If the cost of scrounging is not too great, the scrounging strategy will replace the producer strategy in the population. However, if each producer retains a sizable fraction of the resources it creates, despite a high frequency of scroungers, the producers will increase when they are rare and drive the two strategies into a mixed equilibrium in the population.

The cooperator/cheater and the producer/scrounger conflicts obviously have many similarities—most notably, both analogies deal with the parasitism of one virus by another. One difference may be that scroungers broadly excel at indirectly competing for rare resources, whereas cheaters narrowly specialize in directly competing with their particular helper virus. So, examining frequency-dependent fitness relative to a variety of viral genotypes might resolve whether one conflict is a better descriptor than the other. In either case, there's always a cheater and a sucker involved. A showman aware of these viruses and their prodigious rate of replication might have quipped instead, "There's a sucker born every microsecond."

Bibliography

Denehy, J. J., and P. E. Turner. 2004. Reduced fecundity is the cost of cheating in RNA virus Φ6. *Proceedings of the Royal Society: Biological Sciences* 271:2275–2282.

Froissart, R., C. Wilke, R. Montville, S. Remold, L. Chao and P. E. Turner. 2004. Co-infection weakens selection against epistatic mutations in RNA viruses. *Genetics* 168:9–19.

Giraldeau, L.-A., and T. Caraco. 2000. An introduction to producer-scrounger games. In *Social Foraging Theory*, ed. L.-A. Giraldeau and T. Caraco. Princeton, N.J.: University Press, pp. 151–173.

Lopez-Ferber, M., O. Simon, T. Williams and P. Caballero. 2003. Defective or effective? Mutualistic interactions between virus genotypes. *Proceedings of the Royal Society: Biological Sciences* 270:2249–2257.

Maynard Smith, J. 1982. *Evolution and the Theory of Games*. Cambridge, U.K.: Cambridge University Press.

Nowak, M. A., and K. Sigmund. 1999. Phagelift for game theory. *Nature* 398:367–368.

Roux, L., A. E. Simon and J. J. Holland. 1991. Effects of defective interfering particles on viral replication and pathogenesis *in vitro* and *in vivo*. *Advances in Virus Research* 40:181–211.

Travisano, M., and G. J. Velicer. 2004. Strategies for microbial cheater control. *Trends in Microbiology* 12:72–78.

Turner, P. E., and L. Chao. 1998. Sex and the evolution of intrahost competition in RNA virus Φ6. *Genetics* 150:523–532.

Turner, P. E., and L. Chao. 1999. Prisoner's dilemma in an RNA virus. *Nature* 398:441–443.

Turner, P. E., and L. Chao. 2003. Escape from prisoner's dilemma in RNA phage Φ6. *American Naturalist* 161:497–505.

Vogt, P. K., and A. O. Jackson. 1999. Satellites and defective viral RNAs. *Current Topics in Microbiology and Immunology 239*. New York: Springer-Verlag.

Wilke, C. O., and I. S. Novella. 2003. Phenotypic mixing and hiding may contribute to memory in viral quasispecies. *BMC Microbiology* 3:11.

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