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Alternating lysis and lysogeny is a winning strategy in bacteriophages due to Parrondo's paradox

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Temperate bacteriophages lyse or lysogenize host cells depending on various parameters of infection, a key one being the ratio of the number of free viruses to the number of host cells. However, the effect of different propensities of phages for lysis and lysogeny on phage fitness remains an open problem. We explore a nonlinear dynamic evolution model of competition between two phages, one of which is disadvantaged in both the lytic and lysogenic phases. We show that the disadvantaged phage can win the competition by alternating between the lytic and lysogenic phases, each of which individually is a "loser." This counterintuitive result is analogous to Parrondo's paradox in game theory, whereby individually losing strategies combine to produce a winning outcome. The results suggest that evolution of phages optimizes the ratio between the lysis and lysogeny propensities rather than the phage burst size in any individual phase. These findings are likely to broadly apply to the evolution of host–parasite interactions.

bacteriophages | lysis | lysogeny | game theory | Parrondo's paradox

Significance

Bacteriophages, the most widespread reproducing biological entity on Earth, employ two strategies of virus–host interaction: lysis of the host cell and lysogeny whereby the virus genome integrates into the host genome and propagates vertically with it. We present a population model that reveals an effect known as Parrondo's paradox in game theory: Alternating between lysis and lysogeny is a winning strategy for a bacteriophage, even when each strategy individually is at a disadvantage compared with a competing bacteriophage. Thus, evolution of bacteriophages appears to optimize the ratio between the lysis and lysogeny propensities rather than the phage burst size in any individual phase. This phenomenon is likely to be relevant for understanding evolution of other host–parasites systems.

Bacteriophages outnumber all other reproducing biological entities in the biosphere combined, reaching an estimated instantaneous total of about 10^{31} virus across all biomes (1, 2). Bacteriophages attain this hyperastronomical abundance using two basic strategies of infection that are traditionally classified as lytic and temperate. Lytic phages enter host cells and immediately take over the cellular machinery to produce progeny virions, followed by a programmed burst of the cell (lysis), which releases progeny virions into the environment where they can initiate subsequent rounds of infection (3). In contrast, temperate phages "decide" to follow the lytic or lysogenic strategy at the onset of infection. Under the lysogenic strategy, the phage genome stably integrates into the host genome, becoming a prophage that is inherited by the daughter cells during cell division and thus, propagates vertically with the host, without lysis of host cells. Phage lambda, one of the best-studied models of genetics and molecular biology, is a classic example of lysogeny. Upon sensing an appropriate signal, such as DNA damage, a prophage decides to end lysogeny and reproduce through the lytic pathway (4, 5). Given that an estimated 10^{23} infections of bacteria by bacteriophages occur on Earth every second (6), with profound effects on the global ecology as well as human health (1, 7, 8), the evolutionary processes that shape phage replication strategies are of fundamental biological interest and importance.

The ability of temperate phages to decide between lysis or lysogeny has drawn considerable attention of theorists, resulting in the development of models aiming to quantify the conditions in which one strategy prevails over the other, or in other words, deciphering the rules of phage lysis vs. lysogeny decisions. Temperate viruses that choose lysogeny are constrained by cellular binary fission, whereas lytic replication can produce large bursts of progeny virions from a single cell. A foundational theoretical study asked the question simply. Why be temperate (9)? The potential benefits of a nonlytic strategy are realized when the host cell density is too low to support lytic growth that would otherwise cause collapse of one or both populations. Furthermore, under these conditions, the frequency of encounters of the phage particles that are released upon host lysis with uninfected host cells is low, such that vertical propagation with the host becomes advantageous for the virus. In essence and put as simply as possible, lysogeny is advantageous in hard times (9). Several recent formal model analyses agree that lysogeny is favored at low host cell density (10–12). However, somewhat paradoxically, lysogeny appears to be the dominant behavior at very high host cell density as well (13, 14). The mechanisms driving viruses toward lysogeny at both low and high host cell densities are not well understood, but differential cellular growth rates, viral adsorption rates, and the structure of the host–phage interaction network all appear to contribute (14, 15). Collectively, these studies underscore the importance of density-dependent dynamics for infection outcomes.

The paradigm for the decisions temperate phages make on the lytic vs. lysogenic pathway upon infection is phage lambda. Seminal work on lambda has demonstrated

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that lysogeny is favored at high virus/host ratios, when multiple lambda virions coinfect the same cell (16). The standard interpretation of these findings is that the coinfection rate is a proxy for host cell density, which drives lambda toward lysogeny at high coinfection rates: that is, low density (17). The genetic circuitry underlying lambda's lysogenic response has been meticulously dissected over decades of research (5, 18, 19), and additional mechanistic determinants have been identified in later studies (20–24). Directed evolution of lambda yields mutants with different thresholds for switching from lysogeny to lysis (induction), and such heterogeneity has been observed in numerous lambda-like phages (25–27). Moreover, the vast genomic diversity of phages implies a commensurately diverse repertoire of lysis–lysogeny circuits, and indeed, experiments with phages unrelated to lambda have revealed a variety of ways evolution constructed these genetic switches (28–30). In general, how the different propensities for lysis or lysogeny impact phage fitness at different host cell densities (virus/host ratios) and in particular, when in competition with other phages remains an open problem.

Inspired by the previous theoretical and experimental studies, we developed a population evolution model to investigate the competition between two phages that differ in their rates of establishing lysogeny based on the ratio of the number of free virions to the number of host cells. In this model, the first phage (P_1) has a higher mortality rate, a lower burst size, and a lower infection rate during both lysis and lysogeny compared with the second competing phage (P_2). From a game-theoretic perspective, P_1 is burdened by two losing strategies. Unexpectedly, analysis of our model shows that, by alternating between these two losing strategies, P_1 outcompetes P_2 within a large domain of the parameter space. This counterintuitive result is analogous to a phenomenon known as Parrondo's paradox in game theory (31). Parrondo's paradox was first conceptualized as an abstraction of flashing Brownian ratchets (32, 33), wherein diffusive particles exhibit unexpected drift when exposed to alternating periodic potentials. The sustained interest in the paradox has since fostered a synergistic interdisciplinary effort. Indeed, manifestations of Parrondo's paradox have been studied in various biological systems, such as nomadic and colonial lifestyles (34), activity and dormancy in predator–prey systems (35), and unicellular and multicellular phases in organismal life history (36). The fact that the paradox can occur when the game sequence is completely or partially random appears compatible with the inherent stochasticity in biological systems as manifested, for example, in environmental or demographic noise (37).

Here, we examine the evolution of different strategies of bacteriophage–host interaction within the framework of Parrondo's paradox. The analysis of the model developed in this work suggests that alternating between lysis and lysogeny is intrinsically beneficial for a phage within a broad range of model parameters. This conclusion has implications for understanding the evolution of parasite–host interactions in diverse biological contexts.

Results

Alternating between Losing Lysis and Lysogeny Strategies Results in a Winning Outcome for a Phage. We designed a population model to investigate the outcomes of infection between two competing phages that differ in their rates of adsorption, mortality, burst size (number of progeny virions per infection), and principally, their propensities for lysis or lysogeny. To realistically capture the propensity for a phage to switch between lysis and lysogeny, each of these propensities is not represented by a constant but rather, by a probability function $\mu_i\left(\frac{V_i}{H+L_1+L_2}\right)$, where $\frac{V_i}{H+L_1+L_2}$ represents the ratio of the number of free phage virions to the number of host cells (i.e., multiplicity of infection [MOI]) (Eq. **2** in *Materials and Methods* has details). A detailed list of all parameters of the model, their descriptions, initial conditions, and units are given in *SI Appendix*, Table S1. In all competitions, the first phage (P_1) is temperate and set at a complete disadvantage to the second phage (P_2), regardless of whether P_1 replicates via the lytic or lysogenic pathway. Specifically, compared with P_2, P_1 is penalized with a smaller burst size (ρ_1), lower infection rate (f_1), and higher mortality rate (d_1 for free virions and d'_1 for infected cells and lysogens) than that of P_2.

In the first competition, the lysis–lysogeny probability function (μ_1 and μ_2) was set to zero for both phages, such that all cells are lysogenized upon infection by either phage. We define the total density of each phage to be the sum $P_i = I_i + L_i + V_i$. As expected, the density of P_2 is higher throughout the competition than that of P_1, including number of infected cells ($I_2 > I_1$), lysogens ($L_2 > L_1$), and free virions ($V_2 > V_1$) (Fig. 1 *A* and *C*). Therefore, from a game-theoretic perspective, for P_1, to lysogenize host cells is a losing strategy in the competition with P_2 (denoted losing result I). Equivalently, P_2 can be regarded as enjoying a relative winning outcome because each compartment of P_2 maintains a higher density than the corresponding compartment of P_1 throughout the competition. It should be noted that such win–loss assessments are relative between the phages. Under the present conditions, pure lysogeny eventually leads to the extinction of both phages, which is attributable to the low initial density of lysogenized hosts compared with uninfected hosts and the insufficient number of infectious virions available to initiate subsequent rounds of infection (Fig. 1 *A* and *C*). Although this outcome can be considered absolutely losing in the broader context, the relative competitive advantage enjoyed by P_2 nonetheless manifests as a longer survival duration compared with P_1.

A different outcome is obtained if both phages instead enter the lytic pathway upon infecting a susceptible host cell, which is set by fixing the lower bound α_i and range β_i of the probability function $(\alpha_i, \beta_i) = (1, 0)$ for $i = 1, 2$. In this competition, P_2 infects all susceptible hosts, exhibits Lotka–Volterra-like fluctuations in density, and drives P_1 to extinction without itself suffering the same fate (losing result II in Fig. 1 *A* and *C*). Clearly, P_1 loses in the competition. Thus, neither the purely lytic nor the purely lysogenic pathways of infection are viable strategies for P_1. We note, in addition, that when each phage infects the host alone, the qualitative trends are similar to the present case of simultaneous competition (*SI Appendix*, Fig. S1). In these scenarios, the overall density of P_1 also remains lower than that of P_2, likewise indicating that P_1 is disadvantaged when adopting a purely lytic and/or a purely lysogenic strategy.

We next explored the outcome of a competition between two types of phages that can alternate between strategies. Here, both phages were temperate and could switch between the lytic and lysogenic pathways as determined by the probability function set with parameters $(\alpha_i, \beta_i) = (0, 1)$ for $i = 1, 2$. By alternating between the lytic and lysogenic phases, P_1 overtakes P_2 in density around $t = 50$ and reaches the environmental carrying capacity by $t = 300$, in the process driving P_2 to extinction and easily winning the competition (winning result I in

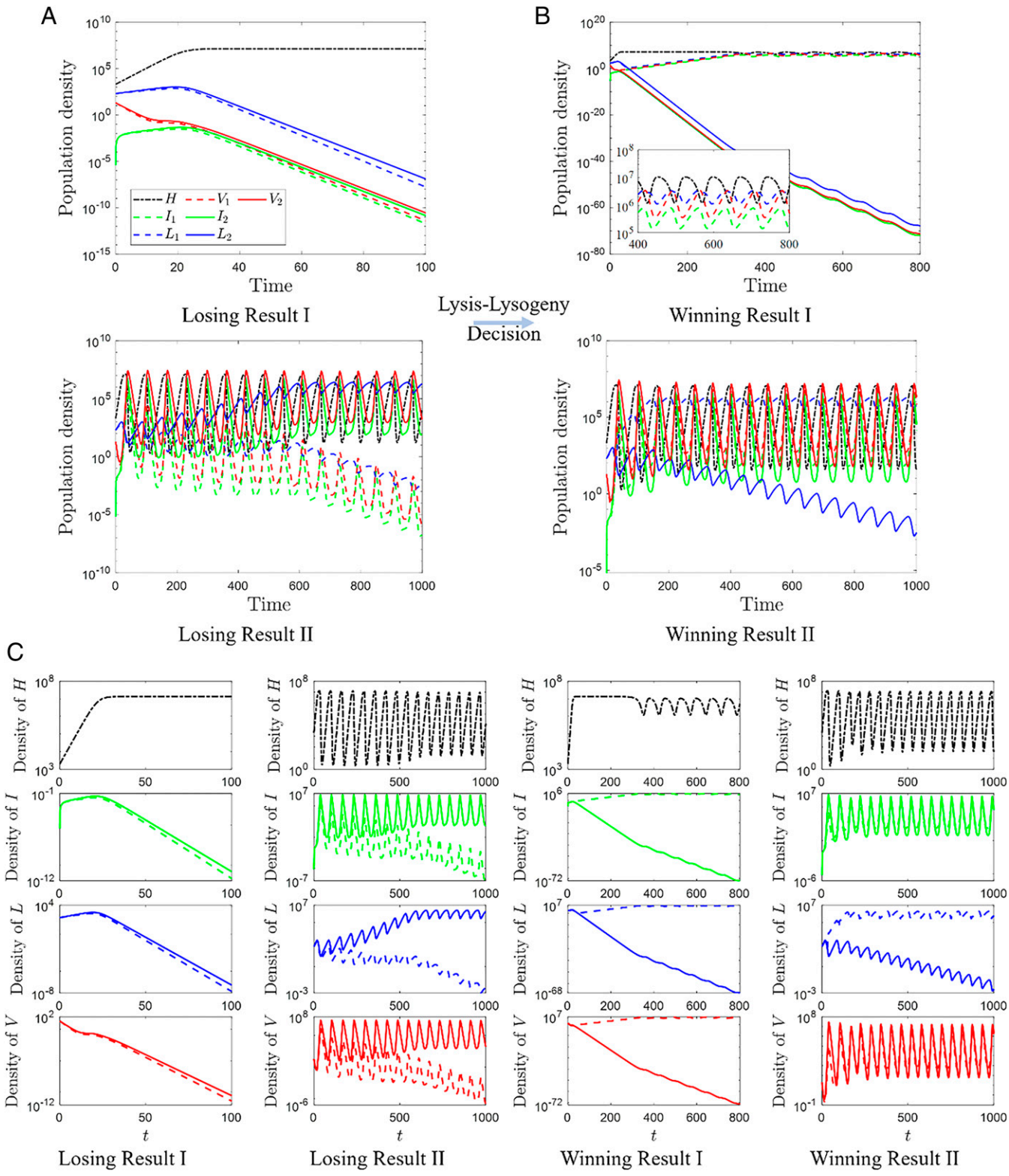

Fig. 1. Observation of Parrondo's paradox in a model competition between two bacteriophages. (*A*) In a competition for hosts between two phages, one of which is at a disadvantage (P_1) relative to the other (P_2), P_1 is driven to extinction if both phages adopt a purely lysogenic strategy [losing result I, $(\alpha_i, \beta_i) = (0, 0)$ for $i = 1, 2$] or purely lytic strategy [losing result II, $(\alpha_i, \beta_i) = (1, 0)$ for $i = 1, 2$]. (*B*) From a game-theoretic perspective, a "winning" outcome for P_1 is obtained when both phages alternate between the lytic and lysogenic phases $(\alpha_i, \beta_i) = (0, 1)$ for $i = 1, 2$. A second winning outcome occurs if the competitor adopts a purely lytic strategy $(\alpha_2, \beta_2) = (1, 0)$ and P_1 infections are biased toward lysis $(\alpha_1, \beta_1) = (0.8, 0.2)$. A zoomed-in version of the dynamics of P_1 and H in winning result I is given in the *Inset*. (*C*) Population dynamics for all compartments across all competitions. Parameter values are listed in *SI Appendix*, Table S1 unless stated otherwise.

Fig. 1 *B* and *C*; a clearer illustration of the dynamics of P_1 and H is in Fig. 1 *B*, *Inset*). This winning outcome occurs despite both lytic and lysogenic strategies individually being losing strategies for P_1 (Fig. 1*A*). We thus find that switching between lysis and lysogeny is critical for a disadvantaged phage to outcompete an advantaged phage under these conditions.

The next experiment featured a purely lytic phage opponent to determine if and when a winning outcome could be achieved

by P_1. Specifically, P_2 is set to replicate through a purely lytic pathway by fixing $(\alpha_2, \beta_2) = (1, 0)$, which was originally a winning strategy for P_2 (Fig. 1*A*). For a fair comparison, the lysis–lysogeny probability parameters (α_1, β_1) for P_1 were set as $(0.8, 0.2)$, so that most but not all infections by P_1 resulted in lysis of the host cell. Under these circumstances, L_1 overtakes L_2 around $t = 100$, but I_i and V_i maintain similar density for the two phages (winning result II in Fig. 1 *B* and *C*). The clear decline of L_2 illustrates the importance of the availability of the lysogenic pathway for a phage to be competitive under large-amplitude population fluctuations. As the total density of P_1 rapidly exceeds that of P_2, the experiment outcome is a clear win for P_1. Thus, we conclude that, by alternating between the lytic and lysogenic pathways, a disadvantaged phage can outcompete a phage with more favorable individual life history traits. Conceptually, this counterintuitive result arises from the differing optimalities of the lysis and lysogeny strategies in a fluctuating environment, which is indeed analogous to Parrondo's paradox, as further discussed below.

In the experiment (winning result I in Fig. 1*B*), infections by P_1 drove P_2 to extinction, even though both phages alternated between lysis and lysogeny. We next examined competition outcomes for a range of lysis–lysogeny decisions by P_1 when P_2 also switched between the two pathways. Here, P_2 is a temperate phage $[(\alpha_2, \beta_2) = (0, 1)]$ that can lyse or lysogenize host cells as determined by the probability function. When the probability function is adjusted such that at least part of P_1 infections result in lysis $[(\alpha_1, \beta_1) = (0.1, 0.9)]$, the decline of P_2 becomes slower, but nevertheless, the hosts are mainly infected by P_1 (Fig. 2*A*). Adjustment of the probability function to $(\alpha_1, \beta_1) = (0.5, 0.5)$ results in an even slower decline of P_2, and host density fluctuations are amplified, with H regularly declining past 10^4 amidst the oscillations (Fig. 2*B*). Finally, if the probability function is inverted such that most of the P_1 infections result in lysis $[(\alpha_1, \beta_1) = (0.9, 0.1)]$, the extinction of P_2 is substantially delayed (Fig. 2*C*). It is hence apparent that the extinction of the competitor is tightly coupled to the lysis–lysogeny decisions made by P_1. In all cases, regardless of the exact probability function parameters, when both phages switch between the lytic and lysogenic pathways, P_1 still reaches a much higher density than P_2, although individually, the lysis and lysogeny strategies were losing for P_1 (Fig. 1*A*). Collectively, these results emphasize the role of the lysis–lysogeny switch as a key life history trait mediating between-phage competition for host cells.

Combinations of Model Parameters. Comprehensive simulations were performed to determine the range of parameters that support winning outcomes for P_1. The experiment outcomes were evaluated by time-averaging the density of each competitor $(I_i + L_i + V_i)$ after the model has reached steady-state conditions (between $t = 2,700$ and $t = 3,000$). Because an all-vs.-all parameter comparison is impractical to examine, we present the results of this systematic survey by considering three qualitatively categorized sets of parameters: environmental conditions, the lysis–lysogeny switch function, and phage life history traits. By exploring parameter space and evaluating the outcome of the competition, we can determine the range of conditions over which Parrondo's paradox manifests.

We first investigated the space of environmental parameters, namely, carrying capacity K, growth rate r, and host cell mortality rate d_h. The carrying capacity K limits the total number of cells in the environment, including both uninfected hosts and lysogens emerging upon infection by either phage. By alternating between strategies, P_1 dominates in the vast majority of cases, except at small values of K (10^7 cells/mL) (Fig. 3*A*). This suggests that the total density of cells $(H + L_1 + L_2)$ and their growth rate affect the ability of a disadvantaged temperate phage to outcompete the advantaged phage (14, 15). A similar situation occurs in the space of K and d_h: P_1 outcompetes P_2 in a large domain of the parameter space, except for the region with small values of K and high mortality rates of host cells d_h $(0.4h^{-1})$ (Fig. 3*B*). Overall, P_1 outcompetes P_2 when there are many susceptible host cells in the environment, that is, at high carrying capacity, fast growth rate, and slow mortality rate of host cells (Fig. 3 *A* and *B*).

Given the central role of the lysis–lysogeny probability function (Eq. **2**) in determining the outcome of the competition, the effect of the switching threshold and width parameters of this function was evaluated across a wide range of values. A high switching threshold (θ_i) causes a phage to switch from lysis to lysogeny at a relatively high MOI. The parameter χ_i is the switching width, whereby a small value of χ_i results in a quick transition to lysogeny with the decline in MOI. P_1 wins the competition when few free virions are required to signal the transition to lysogeny (Fig. 3*C*) and when the transition is slow (Fig. 3*D*). Collectively, these results indicate that a disadvantaged phage can win the competition by optimizing the key parameters involved in the switch between lysis and lysogeny.

We next examined the life history traits that are traditionally analyzed in models of viral fitness evolution, including the mortality rate (d_i and d_i'), burst size (ρ_i), infection rate (f_i), induction rate (γ_i), and the proportion of infected cells that can replicate (η_i). Evidently, P_1 can easily reach higher density with a lower mortality rate (Fig. 3 *E* and *F*), larger burst size (Fig. 3*G*), or more rapid infection rate (Fig. 3*H*). The induction rate

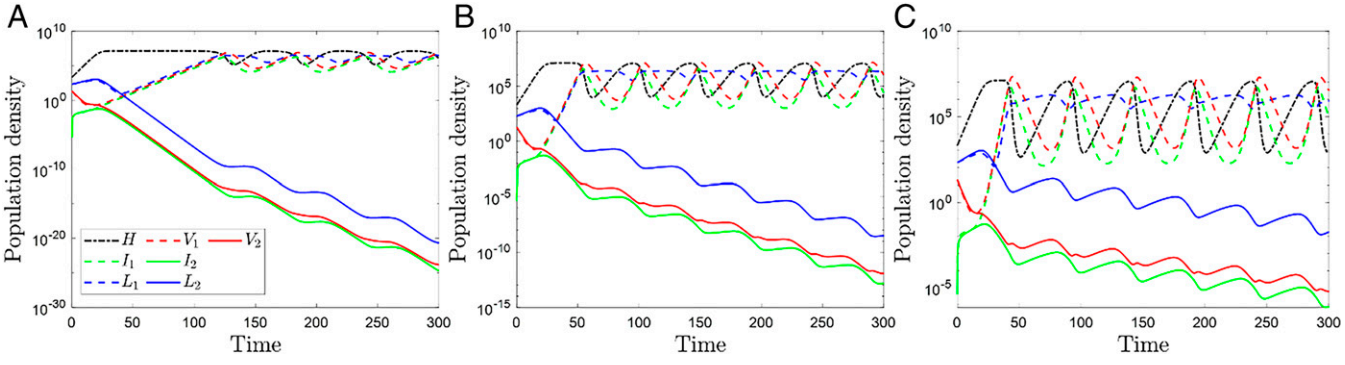

Fig. 2. Long-term competition between two phages that alternate between the lytic and lysogenic pathways. Population dynamics during competition for hosts between phages are shown. The fraction of P_1 infections that follow the lytic pathway increased from (*A*) 10% at switching probability function parameters $(\alpha_1, \beta_1) = (0.1, 0.9)$ to (*B*) 50% at $(\alpha_1, \beta_1) = (0.5, 0.5)$ and (*C*) 90% at $(\alpha_1, \beta_1) = (0.9, 0.1)$. All other parameter values are listed in *SI Appendix*, Table S1.

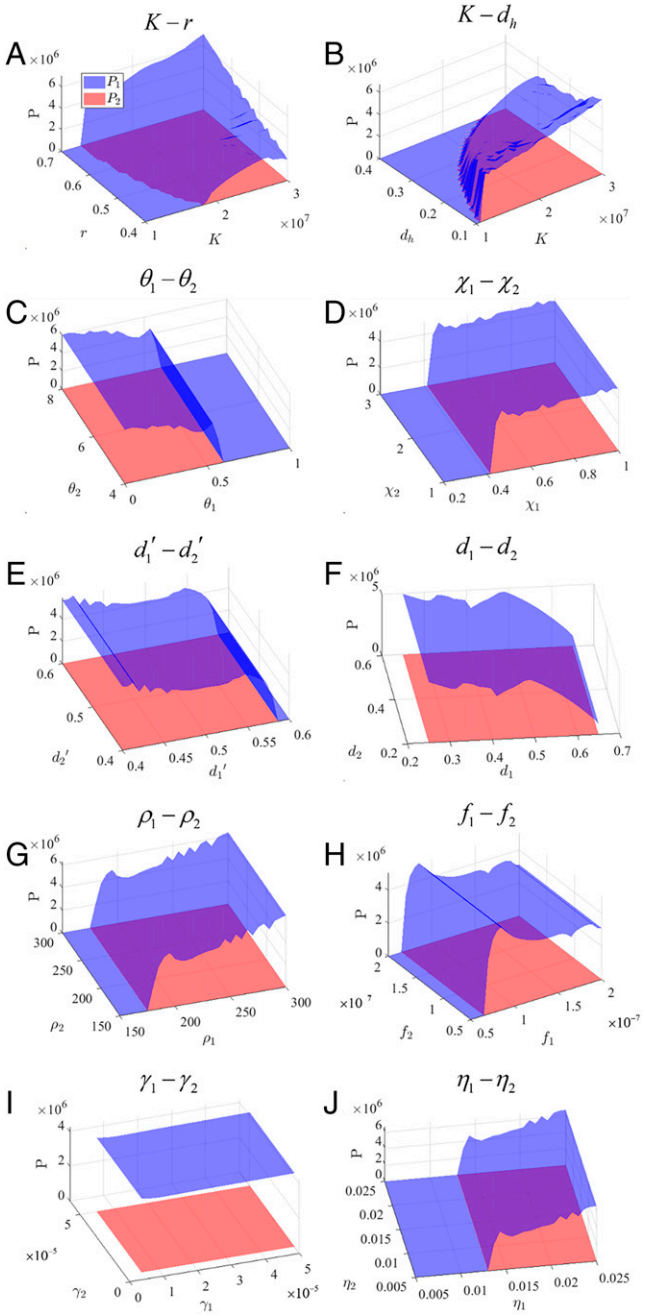

Fig. 3. The regions of parameter space yielding Parrondo's paradox in a competition between two phages. Outcomes are evaluated by time-averaging the total density of each competitor at steady state $t \in [2,700, 3,000]$, which contains at least one full cycle of oscillation. (*A* and *B*) The change in environment carrying capacity K is compared against the growth rate r or mortality rate of the host cell d_h. (*C*–*J*) Comparison of switching thresholds θ_i or switching intervals χ_i, mortality rates d'_i and d_i, burst size ρ_i, infection rate f_i, induction rate γ_i, and the portion of infected cells to replicate η_i are shown. Parameter values are from *SI Appendix*, Table S1 unless indicated otherwise.

appears to exert no obvious effect on the competition outcome, such that P_1 always maintains a higher density than P_2 (Fig. 3*I*). Lastly, P_1 can reach a higher density than P_2 when the proportion of infected cells able to replicate is large but becomes extinct with smaller η_1 (Fig. 3*J*). Across all the parameters tested, few appear to substantially increase the total density of P_2 compared with that of P_1. Our simulation results predict that Parrondo's paradox is likely to emerge in the parameter space established in Fig. 3, specifically within the regions where the disadvantaged P_1 phage achieves larger density than its competitor. Furthermore, the life traits of P_2 appear to have a lesser impact on the outcome of the competition compared with those of P_1.

The two parameters that had the greatest effect on the outcome of the competition in our initial experiments (Figs. 1 and 2) were α_i and β_i, which set the lower and upper bounds of the probability of a phage to enter the lytic pathway, respectively. Moreover, the probability function that models the phage lysis–lysogeny switch (Eq. **2**) had been demonstrated to substantially impact the outcome of the competition (Fig. 2). Motivated by this observation, we further assessed the impact of lysis–lysogeny decisions on the outcome of the competition, in particular by examining the time-averaged population density of the host and two phages at steady state, between $t = 2,700$ and $t = 3,000$ (Fig. 4). The lower switching bound α_1 and the upper bound $\alpha_1 + \beta_1$ were constrained in the region $0 < \alpha_1 \leq \alpha_1 + \beta_1 \leq 1$, as both phages become extinct when α_i and β_i are equal to 0 (Fig. 1*A*). In the presence of P_1 alone, there are more free progeny virions than lysogens at large values of α_1 (Fig. 4*A*), and V_1 becomes more abundant as α_1 is increased. The population densities H and L_1 are greater than V_1 only at small values of α_1, largely independent of β_1. In a competition between two temperate phages, V_1 is greater than V_2 across the entire range of α_1 and β_1 values (Fig. 4*B*). The densities of P_1 and H are similar to the values observed in the experiment without a competitor, indicating that the temperate phage P_2 is outcompeted by P_1, and indeed, P_2 goes extinct throughout the parameter space (Fig. 4*B*). If the competing phage is purely lytic, the densities of L_1 and I_1 are close to those of L_2 and I_2, respectively (especially at larger values of α_1), while V_1 cannot outcompete V_2 across the entire range of α_1 and β_1 (Fig. 4*C*). The small size of the domain of the parameter space, in which the densities of P_1 and P_2 are close, is attributable to two principal constraints. 1) There have to be enough P_1 progeny virions to initiate subsequent rounds of infection, and 2) the progeny must be able to produce new lysogens at low host cell density to avoid extinction. Thus, lysogeny enables a temperate phage to reach a similar density as a purely lytic phage, even if the lytic competitor possesses superior life history traits.

Discussion

We demonstrate here that a phage with inferior life history traits can outcompete a phage with superior traits over a broad set of conditions by switching between the lytic and lysogenic pathways at an optimal frequency. Neither the lytic nor the lysogenic strategy of the disadvantaged phage is competitive on its own, yet a winning outcome is achieved by alternating between the two strategies (Fig. 1). This counterintuitive phenomenon is analogous to the game-theoretic Parrondo's paradox, in which alternating between two losing strategies can yield winning outcomes. This effect is manifested at different levels of biological organization (37), such as the alternation between unicellular and multicellular phases in organismal life history (36), between phases of activity and dormancy in predator and prey (35), or between nomadic and colonial lifestyles (34).

Several studies have examined the conditions under which lysogeny is more favorable than lysis for phages. In particular, vacillations of the host cell population density caused by environmental downturns and/or other factors lead to extended periods of low host availability that is insufficient to support lytic infection (9). Lysogenizing host cells under these conditions allays the risk of population collapse (10). However, as the host cell population recovers, this strategy of leveraging

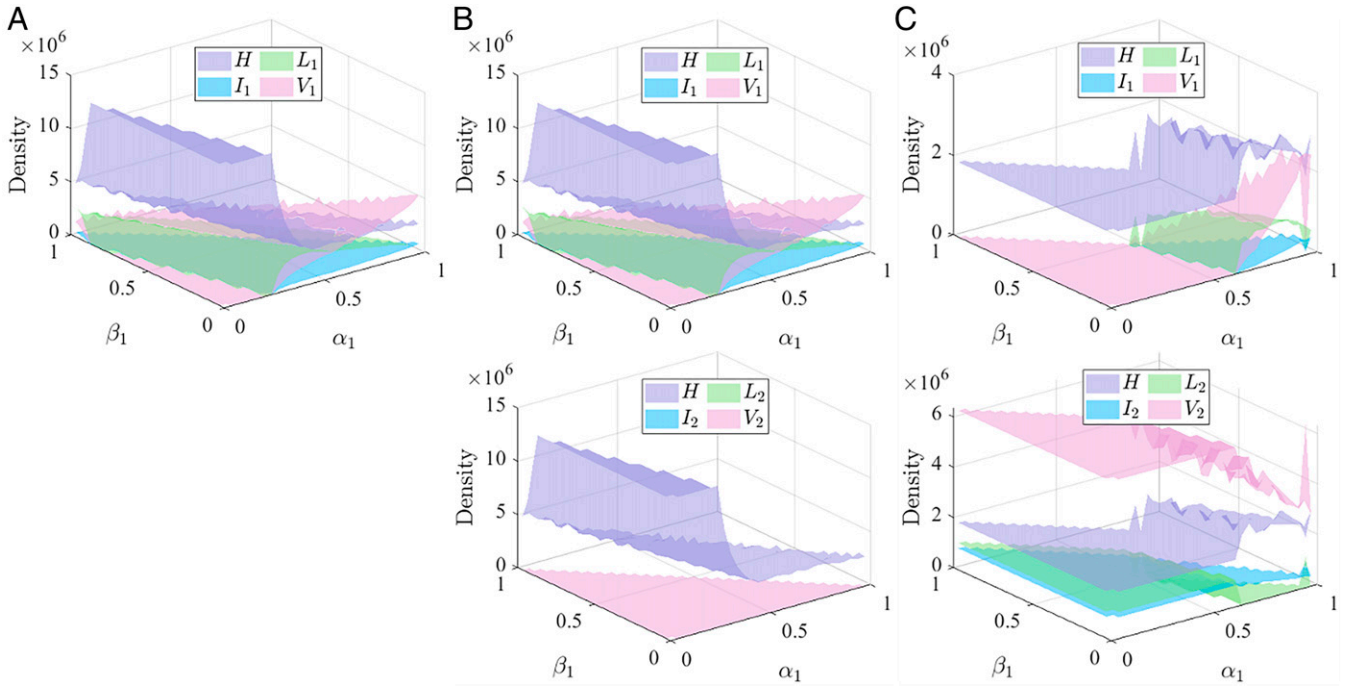

Fig. 4. Population dynamics during competition between phages under different lysis–lysogeny probabilities. The outcomes are evaluated by averaging the density of each compartment at steady state $t \in [2,700, 3,000]$ that contains at least one full cycle of oscillation. (*A*) Mean density of each compartment in the presence of P_1 alone. (*B*) Mean density of P_1 (*Upper*) and P_2 (*Lower*) when both phages compete, with $(\alpha_2, \beta_2) = (0, 1)$. (*C*) Mean density of P_1 (*Upper*) and P_2 (*Lower*) when both phages compete, with $(\alpha_2, \beta_2) = (1, 0)$. Parameter values are from *SI Appendix*, Table S1 unless indicated otherwise.

binary cellular fission for vertical transmission becomes inferior to horizontal transmission: that is, lytic reproduction (12, 38).

The parameters of infection that dictate the outcome of the competition between two phages infecting the same host population remain poorly understood. The ubiquity and biological importance of intervirus competition are perhaps best reflected by the broadly distributed and diverse superinfection exclusion mechanisms that prevent secondary infections of lysogens by other phages (39–41). Mathematical models predict that temperate phages can invade microbial populations in the presence of a competing lytic virus, so long as they confer at least a minimal level of superinfection immunity (38). In our computational experiments, the disadvantaged phage indeed confers superinfection immunity to the host cell during lysogeny. With the decrease of the probability to lysogenize, the amplitude of host density fluctuations increases, and the phage with superior traits is slowly driven to extinction (Fig. 2). Notably, we identified multiple regions of the parameter space where the two phages can compete and the disadvantaged phage that alternates between lysis and lysogeny reaches a higher overall density than the competing phage that enjoys advantage under each individual strategy (Figs. 3 and 4).

Our analysis identifies the conditions in which a disadvantaged phage can not only coexist with, but outcompete, a phage with superior life history traits by cycling between two losing strategies. Parrondo's paradox appears to apply to large regions of the parameter space, with propensities for lysis or lysogeny being the primary parameters of infection that determine this winning outcome (Fig. 2). It should be emphasized, however, that many combinations of parameters favor a pure lytic or pure lysogenic strategy. There exists much room for further exploration of the switching mechanism investigated in this work. In particular, the present model includes the assumptions that phages only infect susceptible cells (abortive infection is disregarded) and that superinfection is excluded. Exploration of a model devoid of these assumptions could lead to a more realistic picture of phage–host interactions affecting the lysis–lysogeny decision. Further, incorporation of different modes of sensing the host cell state by infecting phages might yield further insight into Parrondo's paradox manifestations in host–phage interactions. Indeed, it has been shown that, in many groups of phages, the lysis–lysogeny decision is regulated by interphage communication via small molecules secreted by infected cells (28, 42). Investigation of such more complex regimes of interaction between phages can be a productive direction for further modeling.

On closer examination, the advantage of alternating modes of interaction with the host by a virus does not appear truly paradoxical, being tightly linked with the oscillations of the host population that are well known from the classic Lotka–Volterra-type prey–predator models (13, 43, 44). Indeed, once the host cell density drops due to cell lysis by the virus, the latter switches to lysogeny, but when the host population recovers, switching to lysis becomes advantageous. Combined with superinfection exclusion, such a biphasic lifestyle seems to be optimal for viruses under a broad range of infection and environmental parameters. Analysis of the model described here shows that the advantage of such flexibility is large enough to overcome inferiority in each of the individual strategies.

Lysogeny probably evolved as an adaptation to host population oscillations caused by the virus itself or by other environmental factors. Given that such oscillations are a generic feature of population dynamics, there exists a tantalizing possibility that Parrondo's paradox could be a common, if not universal, phenomenon in host–parasite interactions.

Materials and Methods

Dynamic Evolution Model of Lysis–Lysogeny. Our dynamic evolution model includes two phages (P_1 and P_2) competing for a sensitive host cell (H). After infection by a virion (V), the host cell (H) becomes either a lytically infected cell (I) or a lysogen (L) (12). Subscripts on all variables described refer to phages P_1 or P_2. Host cells lysogenized by a phage are immune to infection by the

competitor phage (i.e., P_1 prevents superinfection of the host cell from P_2 and vice versa). The growth rates of the host cell and the lysogenic virus are assumed to follow the logistic model, with environment carrying capacity K and maximum growth rate r. A susceptible host cell can be infected by the two phages at different rates f. Lytic infections occur with a probability $\mu\left(\frac{V}{H+L_1+L_2}\right)$, and lysogenic infections occur with a probability $1-\mu\left(\frac{V}{H+L_1+L_2}\right)$. The respective probabilities are dependent on the ratio of the number of free viruses to the combined number of susceptible host cells and lysogens since phages can be adsorbed by the lysogens. A phage in the lysogenic phase can be induced at the rate γ. There is only a portion of infected cells (η) that can replicate. The number of free virions produced from host cell lysis is the phage burst size ρ. Free virions are inactivated at the rate d, the mortality rate of uninfected cells is given by d_h, and the mortality rate of infected cells and lysogens is given by d'. Thus, the model is captured by the following differential equations:

$$
\begin{aligned}
\frac{dH}{dt} &= r\left[1-\frac{H+I_1+L_1+I_2+L_2}{K}\right]H - f_1HV_1 - f_2HV_2 - d_hH,\\
\frac{dI_1}{dt} &= \mu_1\left(\frac{V_1}{H+L_1+L_2}\right)f_1HV_1 - \eta_1I_1 + \gamma_1L_1 - d_1'I_1,\\
\frac{dL_1}{dt} &= r\left[1-\frac{H+I_1+L_1+I_2+L_2}{K}\right]L_1 + \left[1-\mu_1\left(\frac{V_1}{H+L_1+L_2}\right)\right]\\
&\quad f_1HV_1 - \gamma_1L_1 - d_1'L_1,\\
\frac{dV_1}{dt} &= \rho_1\eta_1I_1 - f_1HV_1 - d_1V_1,\\
\frac{dI_2}{dt} &= \mu_2\left(\frac{V_2}{H+L_1+L_2}\right)f_2HV_2 - \eta_2I_2 + \gamma_2L_2 - d_2'I_2,\\
\frac{dL_2}{dt} &= r\left[1-\frac{H+I_1+L_1+I_2+L_2}{K}\right]L_2 + \left[1-\mu_2\left(\frac{V_2}{H+L_1+L_2}\right)\right]\\
&\quad f_2HV_2 - \gamma_2L_2 - d_2'L_2,\\
\frac{dV_2}{dt} &= \rho_2\eta_2I_2 - f_2HV_2 - d_2V_2.
\end{aligned}
\qquad [1]
$$

The interactions among these compartments are shown in *SI Appendix*, Fig. S2, and the initial values for each compartment and parameters are detailed in *SI Appendix*, Table S1. Values for each phage parameter were collected from recent analyses of phage lysis–lysogeny decisions (12, 45–49).

Parameter Functions. The probability function $\mu_i\left(\frac{V_i}{H+L_1+L_2}\right)$ for host cell lysis is given below:

$$
\mu_i\left(\frac{V_i}{H+L_1+L_2}\right) = \begin{cases} \alpha_i+\beta_i\left[1+\exp\left(-\frac{\frac{V_i}{H+L_1+L_2}-\theta_i}{\chi_i}\right)\right]^{-1} & \frac{V_i}{H+L_1+L_2} \le \theta_i+n\chi_i \\ \alpha_i+\beta_i\left[1+\exp\left(\frac{\frac{V_i}{H+L_1+L_2}-(\theta_i+2n\chi_i)}{\chi_i}\right)\right]^{-1} & \frac{V_i}{H+L_1+L_2} > \theta_i+n\chi_i \end{cases}, \; i=1,2, \qquad [2]
$$

where $n=2$, α_i is the lower bound, and β_i is the range determining the upper bound ($\alpha_i+\frac{\beta_i}{1+e^{-n}}$). θ_i is the switching threshold $\mu_i(\theta_i)=\alpha_i+\beta_i/2$. χ_i determines the shape of the function, whereby sharper switching occurs at smaller χ_i. $\theta_i+n\chi_i$ is the turning point of this function.

Data Availability. The source code used in this work can be accessed at Open Science Framework (https://osf.io/vth96/?view_only=c61c0a312ef04624acbeb41d071e70df). All other data are included in the manuscript and/or *SI Appendix*.

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