Infect while the iron is scarce: nutrient-explicit phage-bacteria games

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Abstract

Marine microbial primary production is influenced by the availability and uptake of essential nutrients, including iron. Although marine microbes have evolved mechanisms to scavenge sub-nanomolar concentrations of iron, recent observations suggest that viruses may co-opt these very same mechanisms to facilitate infection. The “Ferrojan Horse Hypothesis” proposes that viruses incorporate iron atoms into their tail fiber proteins to adsorb to target host receptors. Here, we propose an evolutionary game theoretic approach to consider the joint strategies of hosts and viruses in environments with limited nutrients (like iron). We analyze the bimatrix game and find that evolutionarily stable strategies depend on the stability and quality of nutrient conditions. For example, in highly stable iron conditions, virus pressure does not change host uptake strategies. However, when iron levels are dynamic, virus pressure can lead to fluctuations in the extent to which hosts invest in metabolic machinery that increases both iron uptake and susceptibility to viral infection. Altogether, this evolutionary game model provides further evidence that viral infection and nutrient dynamics jointly shape the fate of microbial populations.

Keywords Game theory · Viral ecology · Siderophores · Marine ecology

Introduction

Photosynthetic marine plankton account for approximately half of global annual carbon fixation [1]. Trace metals, including iron, are necessary for the function of molecular machinery which perform important metabolic processes such as photosynthesis and nitrogen fixation [2, 3]. However, concentrations of iron in the open ocean surface are sub-nanomolar [4]. Furthermore, due to iron’s low solubility in water and the relatively high concentration of weakly iron-binding organic molecules dissolved in seawater, iron in seawater is largely confined to the particulate phase, either as ferricydrite minerals or bound to organic particles [2, 5, 6].

Neither of these forms of iron are readily available for uptake by bacteria, rendering iron a scarce resource for photosynthetic picoplankton [7, 8]. Iron limitation has been implicated as the cause of high-nutrient low-chlorophyll zones (HNLCs), including the equatorial Pacific and Southern Oceans [9, 10]. In these zones, the quantity of phytoplankton biomass is lower than would be expected given the concentration of nitrogen, a typically limiting macronutrient in marine ecosystems, indicating limitation induced by exceedingly low concentrations of other micronutrients, like iron. Iron amendment experiments (such as those reported in [11–13]) have found that added iron can increase primary productivity in these regions. In contrast, other iron amendment mesoscale experiments have found no release from iron limitation [14], or, interestingly, in the case of the 1995 IronEx II experiment, possible competition for the added iron between diatoms and heterotrophic bacteria [15].

Microbes in host–pathogen, soil, and marine systems have adapted to respond to local iron conditions through the evolution of siderophores [16–18]. Siderophores are small molecules with much higher iron-binding affinity than ambient dissolved organic matter [19]. Iron, once bound by a siderophore, remains in the dissolved size class. Bacterioplankton can take up the iron–siderophore complex with a corresponding siderophore-uptake receptor. Notably, siderophores
can be freely excreted into the environment. Extracellular excretion poses challenges for understanding the benefits of siderophore production for cellular fitness [20–23]. Studies on the fitness benefits of siderophores have often focused on dynamics of “cheating” phenotypes, cells which express siderophore uptake receptors without taking the metabolic cost of producing siderophores (e.g., [21–23]). Field studies in the marine environment reveal a large diversity of siderophore molecular structures, which support the hypothesis of siderophore production as a competitive adaptation [4, 19]. However, there may also be costs associated with siderophore production and uptake. Specifically, siderophore surface receptors may also provide a port of entry for viral infection [24]. Some siphoviruses of E. coli have been found to use ferrichrome (a siderophore) uptake protein FhuA as a receptor [25]. The T4 Myovirus of E. coli uses outer membrane protein OmpC, a different receptor protein which also has metal-binding properties [26]. However, the receptors used by marine viruses remain largely elusive. Comparing the amino acid sequences of tail fiber proteins from marine virus genomes to those of viruses with known receptors is one way to explore the possible catalogue of marine virus receptors. Via a comparative approach, Bonnain et al. [24] found dual histidine residues in marine viral tail fiber sequences homologous to those of E. coli phage T4. Structural studies of the T4 tail fiber protein show a small number of iron ions bound to those dual histidine residues [26]. A more recent study of environmental metagenomes and metatranscriptomes from the TARA oceans expedition [27] found extensive evidence of putative iron-binding residues in phage tail amino acid sequences, with dual histidine residues homologous to T4 and other markers of putative iron binding in 87% of viral tail proteins. These findings underscore the Ferrojan Horse Hypothesis, according to which abundant viruses of marine picoplankton [28, 29] incorporate iron into their tail fiber proteins to facilitate infection via siderophore uptake receptors. As a result, siderophore-producing cells in severely iron-limited conditions, such as cells in HNLCs, may experience a tension between the benefits of increasing local nutrient availability and increased risk of viral infection [30].

The Ferrojan Horse Hypothesis poses an interesting eco-evolutionary dynamics question: under what ecological circumstances is it evolutionarily advantageous for plankton to produce and take up siderophores? More specifically, does pressure from viral infection have an impact on the evolutionary dynamics of siderophore production? Previous studies modeling the eco-evolutionary benefits of siderophore utilization [21, 31] have focused on siderophores as a public or private good without incorporating feedback due to viral infection. Here, we propose a bimatrix replicator dynamics model of host–virus interactions coupled to an exogenous resource (in this case, iron). In doing so, we assess the ways in which conflicting pressures between resource limitation and viral infection can influence host uptake strategies. As we show, when resource levels are variable, viral infection can drive oscillatory dynamics involving multiple virus types (including some that incorporate iron into their tails) and multiple host types (including some that produce siderophores). These oscillatory dynamics may provide a mechanism of virus–host coexistence mediated by a tension between resource uptake and protection against infection.

**Results**

**Evolutionary game theory of ferrojan horse hypothesis**

**Replicator dynamics for bimatrix games**

We first construct a non-resource-explicit bimatrix game in which hosts interact solely with viruses (Fig. 1). In this game, each individual utilizes one of two phenotypic strategies. Host strategies include producing siderophores (Production) or not (non-Production). Virus strategies include iron-tail fiber incorporation (Ferrojan) or not (non-Ferrojan). The payoff matrix is:

\[
P = \begin{bmatrix} a & b \\ c & d \end{bmatrix}
\]

We use a bimatrix convention for payoffs: e.g., if a producer host (P) encounters a Ferrojan virus (F), the payoff (average fitness) to the host will be \( a \) while that to virus will be \( b \). Table 1 summarizes the relative fitness of all strategy combinations in terms of payoff parameters. Using the “battle of the sexes” model as described in [32], the replicator dynamics for this phage-host system are:

\[
x = x(1-x)(a-c)y + (b-d)(1-y)
\]

\[
y = y(1-y)((a - \beta)x + (\gamma - \delta)(1-x))
\]

where \( x \) represents the proportion of producer hosts and \( y \) represents the proportion of Ferrojan viruses. In Appendix Section "No feedback model" we derive this model from fitness calculations, solve the equilibria, and calculate their corresponding eigenvalues (see Table 2). Importantly, this model does not contain a host–host interaction. (The host strategy fitness payoff is only dependent on the frequencies of the two viral strategies.) We specify the model this way to focus entirely on the direct impact of changing viral strategy profiles on host evolutionary dynamics. Later in this manuscript, we extend the model to include indirect effects of host–host interactions.
This system contains five equilibria, only one of which is a mixed strategy equilibrium, where both viral types and both host types stay at nonzero frequency. The mixed strategy equilibrium will only exist in $x \in [0, 1]$ and $y \in [0, 1]$ if the sign of $(a - c)$ is the opposite of the sign of $(b - d)$, and if the sign of $(a - \beta)$ is the opposite of the sign of $(\gamma - \delta)$. The mixed strategy equilibrium can either be a saddle or the center of neutral periodic orbits depending on conditions described in Appendix Section "Stability analysis". Due to symmetries in the eigenvalues, there can only be either one or two stable exterior fixed points as long as $a - c, b - d, a - \beta, \gamma - \delta$ are nonzero. When $\sgn(a - c) = \sgn(b - d)$ or $\sgn(\gamma - \delta) = \sgn(a - \beta)$, there will only be one stable exterior fixed point. Otherwise, the system will have bistable exterior fixed points and a defined mixed strategy equilibrium.

In ecological terms, simultaneous existence of both viral and host types is only possible in this model when Ferrojan

![Table 1](image)

| Parameter | Interpretation |
|-----------|----------------|
| $a - c$   | Relative fitness of producer host when infected by a Ferrojan virus |
| $b - d$   | Relative fitness of producer host when infected by a non-Ferrojan virus |
| $a - \beta$ | Relative fitness of a Ferrojan virus infecting a producer host |
| $\gamma - \delta$ | Relative fitness of a Ferrojan virus infecting a non-producer host |
viruses have a fitness advantage infecting only one host type, and producer hosts have a fitness advantage amidst a population of only one viral type. If these conditions do not hold, then there will be a pure evolutionarily stable strategy (ESS) for hosts and viruses. A pure ESS occurs when one host type and one virus type reach fixation and exclude invasion by other types. Next, we interpret this model in the context of two stable iron conditions: complete iron starvation and replete iron bioavailability. Because this model does not specify a host–environment feedback, we define these two conditions by establishing inequalities in the payoff matrices which correspond to the selection pressures associated with a given environment.

Stability analysis of bimatrix model for ferrojan horse hypothesis

First, we consider a scenario where the only bioavailable iron is iron ligated to a host’s siderophores. Under this assumption, producing siderophores will be necessary for host growth, and therefore, a population of only non-productors cannot grow. We represent this scenario by imposing the constraint that producers always have a fitness advantage over non-productors. Using the expression for the payoff matrices in Eq. 1, this means that the fitness of a producer host encountering a Ferrojan virus (a) will be higher than the non-producer host encountering the same virus type (c) and similar for non-Ferrojan viruses. This is equivalent to the conditions \( a - c < 0, b - d > 0 \). Using the signs of these two quantities and the information in Table 2, the feasible and stable equilibria will be either \( x = 1, y = 0 \) or \( x = 1, y = 0 \). The dynamics will approach one or the other depending on the signs of the relative fitness differences of viruses infecting producer hosts, i.e., whether \( \alpha - \beta \) is positive or not. If \( \alpha - \beta \) is positive, the only evolutionarily stable strategy (ESS) is producer hosts and the system will converge to one in which all viruses have iron tails. If \( \alpha - \beta \) is negative, then the ESS for hosts remains the same but will be the opposite for viruses. If the two virus strategies have neutral fitness \( (\alpha - \beta = 0) \), then any combination of viral strategies will be evolutionarily stable. A simulation of the \( \alpha - \beta > 0 \) case is demonstrated in both phase space and time-evolution in Fig. 2, left panel.

Second, consider the scenario in which bioavailable iron is entirely replete. In this scenario, producing siderophores constitutes a fitness disadvantage. This is equivalent to the case where \( a - c > 0, b - d < 0 \). As in the last scenario, the only ESS for hosts is \( x = 0 \) (no siderophore producers). The ESS for viruses will be no iron-tail incorporation if \( \gamma - \delta < 0 \), all iron-tail incorporation if \( \gamma - \delta > 0 \) (simulated in Fig. 2 right panel), or any combination of strategies in the case \( \gamma - \delta = 0 \). In both of these cases, we consider scenarios in which \( \text{sgn}(a - c) = \text{sgn}(b - d) \), such that there can only be one ESS for hosts (see Table 2).

Bimatrix replicator dynamics with resource coupling

Next, we consider the outcomes of the bimatrix game given a dynamical iron resource. To do this, we introduce an environmental condition state variable, \( n \), along the lines of Weitz et al. [23] and Tilman et al. [33]. The variable \( n \) takes values between 0 and 1, where \( n = 0 \) represents an environmental condition where iron is limiting to host growth and siderophores must be produced to alleviate the limitation. We emphasize that the environmental state \( n = 0 \) does not refer to a complete depletion of the concentration of iron. Rather, it indicates that iron limitation has its strongest negative effect on host fitness in the absence of siderophore production. In contrast, if \( n = 1 \), iron is sufficiently bioavailable that the benefits of siderophore production have saturated and producing additional siderophores provides no additional benefit to host fitness. The environmental state impacts the host–virus dynamics via two separate payoff matrices, one for the \( n = 0 \) case and one for the \( n = 1 \) case.

\[
P_{n=0} : P \begin{bmatrix} F \end{bmatrix} N - F = a, \alpha, b, \beta \\
N - P \begin{bmatrix} c, \gamma, d, \delta \end{bmatrix}
\]

(4)

\[
P_{n=1} : P \begin{bmatrix} F \end{bmatrix} N - F = a', \alpha', b', \beta' \\
N - P \begin{bmatrix} c', \gamma', d', \delta' \end{bmatrix}
\]

(5)

The payoffs at any given intermediate value of \( n \) are the linear interpolation of the \( n = 0 \) and \( n = 1 \) payoffs [23]. In this model, the payoffs for host and viral strategies will be a function of these two payoff matrices proportional to the current resource state. Specifically,
Although more general properties of the model will be analyzed, to investigate the biological question of viral impact on host siderophore evolution, we present some assumptions about model parameters below:

**Host payoff conditions** We assume that during iron limitation \((n = 0)\), producing siderophores is a higher-fitness strategy than not producing siderophores. Conversely, we also assume that under no iron stress \((n = 1)\), not producing siderophores is a higher-fitness strategy. These assumptions are expressed in terms of model parameters in Table 3.

**Virus payoff conditions** To interpret this model, we also make assumptions about the fitness of viral strategies under differing iron limitation conditions. First, we assume that both host types express siderophore receptors, as well as the iron-replete nutrient condition and the corresponding payoff matrix.

Open points indicate the initial conditions of each simulation; closed points indicate the equilibrium conditions.

### Table 3 Parameter constraints for host payoff matrices for environmental feedback-coupled bimatrix game

| Condition | Interpretation |
|-----------|----------------|
| \(a - c > 0\) | Producing siderophores is advantageous in iron-starved environments |
| \(b - d > 0\) | Producing siderophores is advantageous in iron-replete environments |
| \(d' - c' < 0\) | Producing siderophores is deleterious in iron-starved environments |
| \(b' - d' < 0\) | Producing siderophores is deleterious in iron-replete environments |

\[ P(n) : \begin{array}{c}
F \\
N - F
\end{array} = \begin{array}{c}
P + (a - a)n, \alpha + (\alpha' - \alpha)n, \beta + (\beta' - \beta)n \\
N - P + (c - c)n, \gamma + (\gamma' - \gamma)n, \delta + (\delta' - \delta)n
\end{array} \]
receptor for non-Ferrojan viruses, at comparable levels. Consequently, we assume that the fitness of a given viral strategy is independent of the host type the virus infects. While an argument could be made that possible differences in receptor expression between the two host types or increased viral susceptibility due to the metabolic tax of siderophore production could lead to differential virus susceptibility, we leave results for these types of parameterizations to the Appendix. Under an iron-stressed condition, we assume that Ferrojan viruses have a fitness advantage due to the increased pressure to uptake iron via siderophore receptors. Conversely, in the iron-replete condition, we assume that siderophore-ligated iron outcompetes Ferrojan viruses for host uptake receptors, leading non-Ferrojan viruses to have a fitness advantage. Plaque experiments on cultures of E. coli grown with iron bound by the siderophore enterobactin show an inverse relationship between iron-enterobactin concentration and infection by phage H8, which uses siderophore-uptake receptors [34]. We describe these assumptions in terms of parameter values in Table 4.

Environmental feedback model In our environmental feedback model, the replicator dynamics for viruses and hosts is coupled to a differential equation describing the relative change in environmental state. Using these parameter and model attributes, we propose the following dynamical system:

\[
\dot{x} = x(1-x)((\alpha - c) + ((\alpha' - c') - (\alpha - c))n)y + [(b - d) + ((b' - d') - (b - d))n](1 - y)) \\
\dot{y} = y(1-y)((\alpha - \beta) + ((\alpha' - \beta') - (\alpha - \beta))n)x + [(y - \delta) + ((y' - \delta') - (y - \delta))n](1 - x)) \\
\dot{n} = n(1-n)[-1 + \theta_x x - \theta_y y]
\]

The formulation of \(\dot{n}\) belongs to a general class of environment-feedback models presented in Weitz et al. [23] and Tilman et al. [33]. The environment is assumed to change logistically over time, as we assume iron stress increases in a manner similar to the underlying uptake kinetics [20]. The logistic formulation also normalizes the environment condition to lie between 0 and 1, representing iron stress and replete states, respectively. In this model, siderophore-producing hosts increase the availability of iron (via the intrinsic rate of logistic growth at a rate \(\theta_x\)). In contrast, the presence of ferrojan viruses decreases the availability of iron. We note that ligand-binding kinetics occurring between siderophores and iron in seawater are typically modeled using logistic-like Michaelis Menten enzyme kinetics [20]. Lastly for this model, we assume Ferrojan viruses exacerbate the intrinsic decay of the environmental state by a factor \(\theta_y\). Our justification for proposing this mechanism is that Ferrojan viral particles sequester iron that otherwise might be available in dissolved lysate [35, 36]. A recent study of unimatrix resource-coupled game theory by [33] suggests that using density-dependent resource models may induce limit cycles in otherwise bistable dynamical regimes. While their findings have not yet been extended to the bimatrix case, we note that extending the present model to include density-dependent dynamics may be of interest.

### Classes of model behaviors

#### Summary of behavior categories

Using the parameter conditions summarized in Table 3, we identify four classes of model behaviors for this system: (1) attraction to a single exterior fixed point, (2) neutral 2-dimensional orbits, (3) neutral 3-dimensional orbits, (4) attraction to a heteroclinic network (Fig. 3). We interpret these dynamical behaviors as the following ecological situations: (1) resource crash, (2) dominating phenotypes, (3) phenotypic oscillations, (4) phenotypic jumping.

#### Resource crash

First, consider the case where host siderophore production is insufficient to generate a ‘replete’ iron state. This is equivalent to \(\theta_x \leq 1\). Further, we assume that virus iron incorporation diverts iron from the available pool, i.e., \(\theta_y > 0\). With these parameters, \(\theta_x x - (1 + \theta_y y) < 0\) for all \(x, y \in [0, 1]\), meaning \(\dot{n}\) will be negative in the entire state space. Any dynamics will then immediately go to the stable exterior fixed point where \(n = 0, x = 1\) (because we enforce that producer hosts have an advantage in iron-starved conditions, see Table 3), and either \(y = 0\) or \(y = 1\) depending on which viral phenotype has higher average fitness infecting producer hosts.

Ecologically, the parameter \(\theta_x\) represents the degree to which producing siderophores improves local iron bioavailability, \(\theta_y\) represents iron incorporation into the tail fibers of Ferrojan viruses, and the \(-1\) term indicates that iron limitation becomes more severe over time in the absence of siderophore production. Therefore, \(\theta_x\) would only be less than 1 if a population of entirely producer hosts could not produce

| Table 4 Parameter constraints for virus payoff matrices for environmental feedback-coupled bimatrix game |
| Condition | Interpretation |
| \(\alpha - \beta > 0\) | Ferrojan viruses are more fit in iron-starved environments |
| \(\gamma - \delta > 0\) | Ferrojan viruses are less fit when abundant siderophores compete for receptors |
| \(\alpha' - \beta' < 0\) | Ferrojan viruses are more fit in iron-starved environments |
| \(\gamma' - \delta' < 0\) | Ferrojan viruses are less fit when abundant siderophores compete for receptors |
siderophores fast enough to improve local iron bioavailability, resulting in persistent iron starvation.

**Dominating phenotypes**

We define a ‘dominating strategy’ as a host or virus phenotype, which has a fitness advantage in all environments. For example, Ferrojan viruses would be a dominating strategy for viruses if $\alpha - \beta, \gamma - \delta, \alpha' - \beta', \gamma' - \delta' > 0$. That is, if a Ferrojan virus has a fitness advantage over non-Ferrojan viruses infecting both producer and non-producer hosts in iron-replete or iron-deplete conditions. In the case of a dominating strategy for either viruses or hosts, one of the boundary planes of the state space will become attracting. Dynamics will always tend to that plane, and once that plane is reached, then the dynamics of the remaining two state variables will either be neutral orbits about an internal equilibrium, or that equilibrium will be a saddle and two of the corners of that plane will constitute bistable fixed points. We predict this behavior by solving for the constant of motion in terms of $x$ and $n$ for both the $y = 0$ and $y = 1$ planes (see Eq. 31). We extend this finding and can identify a unique constant of motion for all fixed values of $y$, which will always exist given the ecological parameter constraints in Table 3 (see Eq. 52). We can solve a similar constant of motion for the hosts in terms of $n$ and $y$. The fixed point at the center of these closed orbits, however, is always unstable if there is a dominating viral phenotype and will be unstable for some values of $x \in [0, 1]$ otherwise (see Eq. 60). We also note that these periodic oscillations can still occur even without a dominating strategy, as long as there is an unstable internal fixed point, explained in further detail in Appendix section "Heteroclinic networks".

**Fig. 3** Phase diagrams and time evolutions for environmental feedback model exemplifying four classes of model behavior. Left panel is a phase diagram of the time evolution in center panels. Payoff matrices and resource-related parameters are listed in right panels. Each row corresponds to one of the classes of model behaviors. Open circle in phase diagram represents initial conditions; closed circle represents the state at the end of simulations (200 generations).

Payoff | Payoff
--- | ---
$n = 0$ | $n = 1$

\[
\begin{bmatrix}
3.2, 5 & 5.2, 2 & 3.2, 5 & 2.4, 5 \\
2.4, 5 & 4.2, 4 & 5.2 & 4.4 \\
\end{bmatrix}
\]

$\theta_x = 1.5, \theta_y = 1$

\[
\begin{bmatrix}
4.3 & 4.2 & 1.4 & 1.2 \\
3.2 & 2.1 & 2.3 & 2.1 \\
\end{bmatrix}
\]

$\theta_x = 2.5, \theta_y = 1$

\[
\begin{bmatrix}
4.3 & 4.2 & 1.5, 2 & 1.5, 3 \\
3.5, 3 & 3.5, 2 & 2.2 & 2.3 \\
\end{bmatrix}
\]

$\theta_x = 2.5, \theta_y = 0.5$

\[
\begin{bmatrix}
2.4 & 2.3 & 3.1 & 2.3 \\
1.4 & 1.3 & 4.1 & 4.1, 3 \\
\end{bmatrix}
\]

$\theta_x = 4, \theta_y = 1$
Using the assumptions in Table 3, producer hosts only have an advantage in iron limitation conditions and not in iron-replete conditions. Therefore, we assume no dominating strategy for hosts. Similarly, under the assumptions in Table 4, the Ferrojan strategy is only advantageous under iron limitation and not in iron-replete conditions. However, in the case these assumptions are relaxed, we can assume, for example, that Ferrojan viruses always have a fitness advantage regardless of the extent of iron limitation. In this case, our model predicts that the Ferrojan phenotype will rapidly reach fixation, after which the degree of iron limitation and proportion of producer hosts in the population will undergo neutrally stable periodic oscillations. This prediction contrasts with the bimatrix model with no environmental feedback, which predicts that a fixed viral phenotype cannot coexist with a host population of both producer and non-producers.

Population oscillations

Neutral oscillations in environment quality as well as the frequency of phenotypes in both hosts and viruses can also occur in this model. Neutral 3D oscillations can only occur when there is a neutrally stable internal fixed point. Such a fixed point is feasible when there is some \( \hat{n} \) such that:

\[
\dot{\hat{n}} = \frac{a - c}{(a - c) - (d' - c')}
\]

(10)

\[
= \frac{b - d}{(b - d) - (b' - d')}
\]

(11)

\[
= \frac{a - \beta}{(a - \beta) - (a' - \beta')}
\]

(12)

\[
= \frac{\gamma - \delta}{(\gamma - \delta) - (\gamma' - \delta')}
\]

(13)

If \( \hat{n} \) is in the range \( 0 \leq \hat{n} \leq 1 \), then when \( n = \hat{n} \), there will be no flow in the \( x \) or \( y \) directions. Further, \( \dot{n} = 0 \) when:

\[
\dot{x} = \frac{1 + \theta_{x,y}}{\theta_x}
\]

(14)

When \( x > \frac{1 + \theta_{x,y}}{\theta_x} \), the flow will be toward \( n = 1 \), and toward \( n = 0 \) when \( x < \frac{1 + \theta_{x,y}}{\theta_x} \). The intersection of the \( n = \hat{n} \) plane and the \( x = \frac{1 + \theta_{x,y}}{\theta_x} \) plane can be used to separate the state space into quadrants. In Appendix Section 3D neutral orbits neutral orbits, we calculate the directions of flow with respect to these quadrants and demonstrate orbits. Additionally, we find under these conditions that all exterior fixed points are repelling while the interior fixed point is neutrally stable. The stability of fixed points is consistent with our finding of closed 3-dimensional periodic orbits.

While the oscillating-phenotypes outcome is interesting from a dynamical standpoint, due to a requirement of exact symmetries in the payoff matrices between nutrient states, we recognize this as a marginal case. Neutral oscillations in a similar nutrient-explicit bimatrix game theoretic model are also described in [37].

Characterizing heteroclinic networks

Phenotypic jumping

Using the payoff structure from Table 3, we find that all exterior fixed points will be unstable with either one or two positive eigenvalues if the resource crash is avoided, i.e., \( \theta_x > 1 \) (see Appendix Section "Heteroclinic networks" for full demonstration). Heteroclinic cycles occur when the dynamics move in a repeating sequence from one unstable exterior fixed point to another and are known to be common in replicator dynamical systems [38]. We identified heteroclinic cycles in this model using the characteristic matrix method developed by [39] (see Appendix Section "Heteroclinic networks"). Heteroclinic cycles can be characterized by the eigenvalues associated with each exterior fixed point in the cycle [40]. Heteroclinic networks occur when the heteroclinic cycles in a system are connected via positive transverse eigenvalues [40]. In this model, heteroclinic cycles are guaranteed to exist when all three assumptions listed in Fig. 5 are met. Additionally, heteroclinic cycles are guaranteed to form a heteroclinic network as long as any of the Ferrojan virus marginal fitness are positive. In terms of parameters, if any of \( a - \beta, \gamma - \delta, a' - \beta', \gamma' - \delta' \) are positive, there will be a heteroclinic network.

Heteroclinic cycles will appear as rapid transitions between the neighborhoods of external fixed points, where they linger for increasingly long times (see Fig. 3 bottom center for example). In ecological terms, we can interpret this as rapid sweeps of either host or viral phenotype, or a rapid shift in iron limitation. Because each exterior fixed point is unstable, eventually small deviations will cause a new sweep to happen, and the system will ‘jump’ to a new state. The sequence of these ‘jumps’ is dependent on viral payoff structure, and multiple possible sequences can exist for one particular set of payoffs (see Fig. 4).

To illustrate the interpretation of heteroclinic cycles, we provide two concrete examples of heteroclinic cycles belonging to the heteroclinic network demonstrated in Fig. 3 as represented by panels (a) and (e) in Fig. 4. In cycle (a), consider a system that starts with an initial condition under extreme iron stress with no
siderophore-producing hosts and no Ferrojan viruses (the completely unfilled node). While the concentration of siderophore-bound iron is still low, Ferrojan viruses have a fitness advantage over non-Ferrojan viruses and sweep the population. Once this occurs, siderophore-producing hosts sweep the host population, after which iron bioavailability improves. Upon improved iron conditions, non-producer hosts sweep the host population, and competition with siderophores for uptake causes Ferrojan viruses to be outcompeted by non-Ferrojan viruses. However, with a population of all non-producer hosts, iron stress is reintroduced and the cycle repeats. Cycle (e) (the attracting cycle in this system, as shown in Fig. 3) tells a slightly different eco-evolutionary story. Here, start again in a condition under extreme iron stress with no Ferrojan viruses or siderophore-producing hosts. First, siderophore-producing hosts sweep the host population. Then, Ferrojan viruses sweep the viral population, while iron stress is still high. Siderophore-producing hosts increase iron bioavailability and relieve iron stress, after which Ferrojan viruses are
outcompeted by non-Ferrojan viruses. Then, under low iron stress, non-producer hosts sweep producers, after which iron bioavailability declines and the cycle restarts. Using the intuition that cycles with the largest ratio of contracting-to-expanding eigenvalues will ultimately be attracting dovetails with our ecological interpretations, as the eigenvalues in the $x$ and $y$ directions associated with each exterior fixed point simplify to the relative fitness of host and virus phenotypes at the local environmental state (see Appendix Section "Heteroclinic networks").

**Discussion**

Viral infection [28] and demand for iron [2] are both important aspects of marine microbial ecology. The Ferrojan Horse Hypothesis offers a potential mechanistic linkage between these two factors. Here we used a bimatrix game theoretic model to assess the eco-evolutionary impacts of the Ferrojan Horse Hypothesis on host siderophore use. In a nutrient-implicit model, we found that viral infection does not impact the global evolutionary dynamics of the hosts. Instead, the host phenotype which performs better in a given iron condition always reaches fixation, regardless of its susceptibility to viral infection. We then coupled this model to an explicit environmental feedback. Under varying environmental states, the host and environmental eco-evolutionary dynamics of this model strongly depend on viral strategies. If a single viral phenotype has a fitness advantage under all conditions, the model predicts oscillatory dynamics for both host phenotype and environmental state. Under different viral fitness conditions, dynamics attract to a heteroclinic network, which implies intermittent rapid switching between extreme host phenotype, virus phenotype, and environmental states. All of these findings diverge from the expectation under a constant-environmental model, which predicts a single, pure host ESS.

This model contains some simplifying assumptions. Notably the bimatrix game formulation considers frequency-dependent but not density-dependent effects. As a consequence, the absolute concentration of iron is not modeled. In related work considering games with environmental feedback, Tilman et al. [33] show how alternative, density-implicit environmental state models can alter system dynamics by inducing limit cycles. Extending the present model to a density-dependent context is a priority for future research; it is possible that emergent limit cycles may exist for different viral strategies. Under varying environmental states, the host and environmental eco-evolutionary dynamics of this model strongly depend on viral strategies. If a single viral phenotype has a fitness advantage under all conditions, the model predicts oscillatory dynamics for both host phenotype and environmental state. Under different viral fitness conditions, dynamics attract to a heteroclinic network, which implies intermittent rapid switching between extreme host phenotype, virus phenotype, and environmental states. All of these findings diverge from the expectation under a constant-environmental model, which predicts a single, pure host ESS.

In closing, via our resource-coupled bimatrix replicator dynamics modeling approach, we find viral infection can have a substantive impact on host adaptation to iron scarcity under variable resource conditions. Further, viral phenotypes as well as their impacts on host adaptation propagate to affect the dynamics of the resource itself. Our model suggests that the Ferrojan Horse Hypothesis warrants further investigation in marine environments, as viruses may have yet to be understood impacts on iron dynamics on microbial communities [48]. Understanding viral impacts on marine microbial communities is necessary to disentangle bottom-up and top-down drivers of global primary production. Incorporating viruses into models of microbe-iron feedbacks may also help improve predictions of iron amendments and their consequences for carbon drawdown in an ecosystem context.

**Appendix**

**No feedback model**

**Derivation of the bimatrix replicator dynamic model**

To build the bimatrix replicator model with no environmental feedback, begin with the payoff matrix:

$$
P = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

$$\mathcal{N} - \mathcal{F} = \begin{bmatrix} \alpha & b \\ \beta & d \end{bmatrix}$$

The average fitness ($r$) of each strategy for both hosts and viruses can be determined by the payoff matrix and the frequencies of each strategy. Denote the frequency of producer hosts as $x$ and the frequency of Ferrojan viruses...
as \( y \), where the frequency of non-producer hosts are \( 1 - x \), and of non-Ferrojan viruses are \( 1 - y \). The fitness values are:

\[
\begin{align*}
  r_p &= ay + b(1 - y) \\
  r_{N-P} &= cy + d(1 - y) \\
  r_F &= ax + \gamma(1 - x) \\
  r_{N-F} &= \beta x + \delta(1 - x)
\end{align*}
\]  

(15) (16) (17) (18)

The nullclines of Eqs. 21 and 22 are:

Identifying fixed points

The dynamics for the prevalence of host and viral strategies becomes:

\[
\begin{align*}
  \dot{x} &= x(r_p - (r_p)x + r_{N-P}(1 - x)) \\
  \dot{y} &= y(r_F - (r_F)x + r_{N-F}(1 - y))
\end{align*}
\]

(19) (20)

where the subscripts \( P, N-P, F, N-F \) denote producer hosts, non-producer hosts, Ferrojan viruses, and non-Ferrojan viruses, respectively. The change in frequency of a strategy increases proportionally to the difference between that strategy’s fitness and the entire population’s average fitness. The fitness values for bimatrix game are:

\[
\frac{\text{fitness of producer hosts}}{\text{fitness of non-producer hosts}} = \frac{1}{1 - \text{fitness of producer hosts}}
\]

Table 5 Fixed points of bimatrix game

| \( x^* \) | \( y^* \) |
|---------|---------|
| 1       | 0       |
| 1       | 1       |
| 0       | 1       |
| 0       | 0       |

Table 6 External eigenvalues for bimatrix game

| \( x^* \) | \( y^* \) | \( \lambda_1 \) | \( \lambda_2 \) |
|---------|---------|-------------|-------------|
| 1       | 0       | \(-b-d\)   | \(\alpha - \beta\) |
| 1       | 1       | \(-c\)     | \(-\alpha - \beta\) |
| 0       | 1       | \(a-c\)    | \(-\gamma - \delta\) |
| 0       | 0       | \(b-d\)    | \(\gamma - \delta\) |

Stability analysis

We linearize the system about each of the fixed points to determine their local stability. The Jacobian is:

\[
J = \begin{bmatrix}
(1 - 2x)((a - c)y + (b - d)(1 - y)) & x(1 - x)((a - b) - (b - d)) \\
(1 - 2y)((a - \beta) - (y - \delta)) & (1 - 2y)((a - \beta)x + (y - \delta)(1 - x))
\end{bmatrix}
\]

For the external fixed points, the off-diagonals of the Jacobian simplify to 0, so the eigenvalues correspond to the diagonal elements. The eigenvalues for each boundary fixed point are listed in Table 6.

For the interior fixed point, we solve:

\[
\begin{bmatrix}
0 & \frac{0}{(a - c)(b - d)(a - \beta)(y - \delta)} \\
\frac{0}{(a - c)(b - d)(a - \beta)(y - \delta)} & 0
\end{bmatrix}
\]

For this fixed point, the eigenvalues are:

\[
\lambda_{int} = \pm \sqrt{\frac{(a - c)(b - d)(a - \beta)(y - \delta)}{(a - c)(b - d)(a - \beta)(y - \delta)}}
\]

(27)

If the quantity inside this radical is positive, the internal equilibrium will be a saddle, but if it is negative, the eigenvalues will be imaginary and stability must be further investigated. For this case, we identify closed neutral orbits by solving for a time-invariant feature of this system. To do this, we begin with \( \frac{dx}{dy} \):

\[
\begin{align*}
  \frac{dx}{dy} &= \frac{x(1 - x)}{(a - \beta)x + (y - \delta)(1 - x)} \\
  \frac{dy}{dx} &= \frac{(a - c)y + (b - d)(1 - y)}{y(1 - y)}
\end{align*}
\]

(28)

(29)

(30)

Table 6 External eigenvalues for bimatrix game

| \( x^* \) | \( y^* \) | \( \lambda_1 \) | \( \lambda_2 \) |
|---------|---------|-------------|-------------|
| 1       | 0       | \(-b-d\)   | \(\alpha - \beta\) |
| 1       | 1       | \(-c\)     | \(-\alpha - \beta\) |
| 0       | 1       | \(a-c\)    | \(-\gamma - \delta\) |
| 0       | 0       | \(b-d\)    | \(\gamma - \delta\) |
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Solving with partial fractions yields

\[
\begin{align*}
\text{Const} & = -(a - \beta) \ln(1 - x) + (\gamma - \delta) \ln(x) \\
& - (a - c) \ln(1 - y) + (b - d) \ln(y)
\end{align*}
\] (31)

We confirm this Hamiltonian is time-independent, in that

\[
\frac{\partial H}{\partial t} = 0.
\]

Conditions for neutral stability

First, for there to be an internal fixed point with neutral stability, that fixed point must be feasible, i.e., reside in \(x, y \in [0, 1]\). Using the expressions for \(x, y\) in Table 5, the following conditions are necessary for the fixed points to be feasible:

\[
\text{sgn}(a - c) \neq \text{sgn}(b - d) \text{ AND } \text{sgn}(a - \beta) \neq \text{sgn}(\gamma - \delta)
\] (32)

When this condition is imposed, the numerator in the radical for the expression of the eigenvalues associated with this fixed point is necessarily nonnegative. Therefore, for neither eigenvalue to have a positive real part, the denominator must be negative, so either

\[
(a - c) < (b - d) \text{ OR } (a - \beta) < (\gamma - \delta)
\] (33)

We conclude that this system will exhibit neutral periodic oscillations along a constant energy surface if both Eqs. 32 and 33 are true.

Feedback model

Derivation of the bimatrix replicator model with environmental feedback

For the feedback model, we construct two payoff matrices, one to represent a replete environment, and one to represent a depleted environment. For intermediate environmental conditions, we assume the payoff matrix is a linear interpolation of these two matrices. Therefore, the payoff matrix becomes a function of environmental condition, which is expressed as:

\[
P(n) : \begin{array}{c}
P \quad \text{F} \\
N - P \quad \text{N-F}
\end{array}
\]

Then, we use the same derivation as in the no-feedback model to define dynamics for \(x\) and \(y\) in terms of \(n\). These are the new fitness:

\[
\begin{align*}
r_F &= (a + (a' - a)n)x + (\gamma + (\gamma' - \gamma)n)(1 - x) \\
r_{N,F} &= (\beta + (\beta' - \beta)n)x + (\delta + (\delta' - \delta)n)(1 - x)
\end{align*}
\] (36)

Using these fitness gives the following dynamics:

\[
\begin{align*}
\dot{x} &= x(1 - x)[((a - c) + ((a' - c') - (a - c))n)y + ((b - d) + ((b' - d') - (b - d))n)(1 - y)] \\
\dot{y} &= y(1 - y)[((\alpha - \beta) + ((\alpha' - \beta') - (\alpha - \beta))n)x + ((\gamma - \delta) + ((\gamma' - \delta') - (\gamma - \delta))n)(1 - x)]
\end{align*}
\] (38)

Now, dynamics must be established for \(n\). We use a logistic decay term to restrict \(n\) to \([0, 1]\). Then, we increase \(n\) proportional to the fraction of producer hosts and decrease \(n\) relative to the fraction of Ferrojan viruses. This results in the following dynamics for \(n\):

\[
n = n(1 - n)(-1 + \theta_x x - \theta_y y)
\] (40)

We assume that producer hosts will always have a fitness advantage regardless of which type of virus they encounter when there is no bioavailable iron. We further assume that non-producer hosts will always have a fitness advantage in an environment replete with iron. We represent these effects with the parameter constraints in Table 7.

Dynamical behaviors

Resource crash demonstration

Here we demonstrate the resource crash dynamical outcome. Start with the environmental dynamics:

\[
n = n(1 - n)(-1 + \theta_x x - \theta_y y)
\] (41)

Because \(n \in [0, 1]\), both the \(n\) and \(1 - n\) terms will always be positive. When \(\theta_x \leq 1, \theta_y x \leq 1 \forall x \in [0, 1]\). Therefore, the \((-1 + \theta_x x - \theta_y y)\) term will always be negative, and \(\dot{n}\) will

| Table 7 Parameter constraints for payoff matrices for environmental feedback-coupled bimatrix game |
| --- |
| Condition | Interpretation |
| \(a - c > 0\) | Producing siderophores is always advantageous in iron-starved environments |
| \(b - d > 0\) | Producing siderophores is always deleterious in iron-replete environments |
| \(a' - c' < 0\) | Producing siderophores is always deleterious in iron-replete environments |
| \(b' - d' < 0\) | Producing siderophores is always deleterious in iron-replete environments |
always be negative, meaning dynamics will always go to 
$n = 0$. In this model, when $n = 0$, producing is a dominant 
strategy for hosts, and so dynamics will also go to $x = 1$. 
The edge $x = 1, n = 0$ is flow invariant. Trajectories go 
toward $y = 1$ if Ferrojan viruses have a fitness advantage on 
producer hosts in a scarce environment (i.e., $\alpha - \beta > 0$), or 
y $= 0$ in the opposite case.

**Solving for conserved quantities in 2D**

We find a conserved quantity in this system similar to the 
no-feedback game. We demonstrate these for any fixed 
value of $y$ or $x$ on an $x - n$ or $y - n$ plane, respectively. First, 
select some fixed value of $\hat{y}$. Then calculate $\frac{dx}{dn}$.

\[
\frac{dx}{dn} = \frac{x(1 - x)((a' - c')n + (a - c)(1 - n))\hat{y} + ((b' - d')n + (b - d)(1 - n))(1 - \hat{y})}{n(1 - n)}
\]

We can integrate this function using partial fractions. The 
result is:

**Constr** \[= (a - c)\hat{y} + (b - d)(1 - \hat{y})ln(n) - ((a' - c')\hat{y} + (b' - d')(1 - \hat{y})ln(1 - n)) - (1 + \theta_{y}x)ln(x)
\]

We confirm that $\frac{dx}{dn} = 0$. Now analyze the stability of 
the interior fixed point of this plane. We calculate this fixed 
point in terms of $\hat{y}$:

\[
\hat{n} = n(1 - n)(1 - 1 + \theta_{y}x - \theta_{y}\hat{y})
\]

\[
0 = -1 + \theta_{y}x - \theta_{y}\hat{y}
\]

The payoff structure we enforce for this model includes 
$(a - c) > 0 > (a' - c')$ and $(b - d) > 0 > (b' - d')$. Therefore, 
we can conclude for all $\hat{y} \in [0, 1]$ the $x$ and $n$ dynamics 
can be described as neutral periodic oscillations about a 
closed surface. This conclusion is important for choices 
of $\hat{y}$ where $\hat{y} = 0$, i.e., $\hat{y} = 0, 1$. For other selections of $\hat{y}$, 
the dynamics of $y$ will prevent the system from staying on a 
neutral 2D $x - n$ orbit. We also note that the equilibrium 
coordinate $x^*$ will be in the domain for all selections of $\hat{y}$ as 
long as $\theta_{x} > 1 + \theta_{y}$. In biological terms, there can be neutral 
oscillations between host types and environmental iron 
conditions for any fixed frequency of Ferrojan viruses if a 
population of only producer hosts can still improve iron conditions 
with a population of entirely Ferrojan viruses.

In a similar manner to the orbits we just solved, we can 
solve orbits for some fixed value of $\hat{x}$ on the $y - n$ plane. We find:

\[
\frac{dy}{dn} = \frac{y(1 - y)((a' - \beta')n + (a - \beta)(1 - n))\hat{x} + ((y' - \delta')n + (y - \delta)(1 - n))(1 - \hat{x})}{n(1 - n)}
\]

\[
x^* = \frac{1 + \theta_{y}\hat{y}}{\theta_{x}}
\]

\[
\hat{x} = x(1 - x)((a - c) + ((a' - c') - (a - c))n)\hat{y} + ((b - d) + ((b' - d') - (b - d))n)(1 - \hat{y})
\]

\[
0 = ((a - c) + ((a' - c') - (a - c))n)\hat{y} + ((b - d) + ((b' - d') - (b - d))n)(1 - \hat{y})
\]

\[
n^* = \frac{(b - d)(1 - \hat{y}) + (a - c)\hat{y}}{((a - c) - (a' - c'))\hat{y} + ((b - d) - (b' - d'))(1 - \hat{y})}
\]

If $y$ is held constant at $\hat{y}$, we can evaluate a Jacobian using 
$\hat{x}$ and $\hat{n}$ at this fixed point and determine its eigenvalues. The 
expression for the eigenvalues becomes:

\[
\lambda = \pm \sqrt{n^* (1 - n^*) \theta_x x^*(1 - x^*) f(\hat{y})}
\]

\[
f(\hat{y}) = (((a' - c') - (a - c))\hat{y} + ((b' - d') - (b - d))(1 - \hat{y})
\]

As long as $x^*, n^* \in [0, 1]$, one of the eigenvalues will 
have a positive real part unless:

\[
((a' - c') - (a - c))\hat{y} + ((b' - d') - (b - d))(1 - \hat{y}) \leq 0
\]
with eigenvalues:
\[ \lambda = \pm \sqrt{-n^*(1-n^*)y^*(1-y^*)\theta_1g(\tilde{x})} \]  
(57)

\[ g(\tilde{x}) = ((\alpha' - \beta') - (\alpha - \beta))\tilde{x} + ((\gamma' - \delta') - (\gamma - \delta))(1 - \tilde{x}) \]  
(58)

For this fixed point to be neutrally stable, the expression \( g(\tilde{x}) \geq 0 \). With \( y^*, n^* \in [0, 1] \), we write a condition for \( \tilde{x} \) which is equivalent to \( g(\tilde{x}) \geq 0 \).

\[ \tilde{x} \geq \frac{(\gamma - \delta) - (\gamma' - \delta') - (\gamma - \delta')(1 - \tilde{x})}{((\gamma - \delta) - (\gamma' - \delta')) + ((\alpha' - \beta') - (\alpha - \beta))} \]  
(59)

When this inequality is true, the dynamics of \( y - n \) for any \( \tilde{x} \) will be neutral periodic orbits. Further, we can examine this condition in more detail. First, in the case where \( \text{sgn}((\gamma - \delta) - (\gamma' - \delta')) = \text{sgn}((\alpha - \beta) - (\alpha' - \beta')) \),

\[ x^* = \frac{(1 - \tilde{x}) - (\gamma - \delta)}{(1 - \tilde{x}) + ((\gamma' - \delta') - (\gamma - \delta))} \]  
(60)

\[ y^* = \frac{(b - d) + ((b' - d') - (b - d))\tilde{n}}{(b - d) + ((b' - d') - (b - d))\tilde{n} - ((\alpha - c) + ((\alpha' - \beta') - (\alpha - \beta))\tilde{\alpha})} \]  
(61)

the condition will be equivalent to \( \tilde{x} > 1 \), which means there will be no neutral orbits for any selection of \( \tilde{x} \) in the domain of \( x \). If either \( \text{sgn}((\gamma - \delta) - (\gamma' - \delta')) \) or \( \text{sgn}((\alpha - \beta) - (\alpha' - \beta')) \) is undefined, the fixed point for \( n^* \) will be undefined, so there will be no neutral oscillations. Finally, if \( \text{sgn}((\gamma - \delta) - (\gamma' - \delta')) \neq \text{sgn}((\alpha - \beta) - (\alpha' - \beta')) \), there will some values of \( \tilde{x} \) for which neutral oscillations are possible. We can additionally constrain this value, because the

\[ \tilde{n} \geq \frac{((\alpha - c) + (b - d) + (\alpha - \beta) + (\gamma - \delta))}{((\alpha - c) + (b - d) + (\alpha - \beta) + (\gamma - \delta)) - ((\alpha' - \beta') - (\alpha' - \beta'))} \]  
(62)

\[ y \text{- coordinate of the fixed point must also be in the domain of } y \text{. Leveraging the expression for } y^*, \text{ we find:} \]

\[ \tilde{x} \geq \max \left( \frac{1}{\tilde{\delta}_x}, \frac{(\gamma - \delta) - (\gamma' - \delta')}{{((\gamma - \delta) - (\gamma' - \delta')) + ((\alpha' - \beta') - (\alpha - \beta))}} \right) \]  
(63)

3D neutral orbits

Identifying internal equilibrium

We derive the nullclines of the entire model to understand the interior fixed points.

\[ x \text{ nullclines:} \]

\[ x = 0, 1 \]  
(64)
\[ y = \frac{(b - d) + ((b' - d') - (b - d))n}{((b - d) + ((b' - d') - (b - d))n) - ((a - c) + ((a' - c') - (a - c))n) \quad (68) \]

\[ y \text{ nullclines:} \quad y = 0, 1 \quad (69) \]

\[ x = \frac{(\gamma - \delta) + ((\gamma' - \delta') - (\gamma - \delta))n}{((\gamma - \delta) + ((\gamma' - \delta') - (\gamma - \delta))n) - ((a - \beta) + ((a' - \beta') - (a - \beta))n) \quad (70) \]

\[ n \text{ nullclines:} \quad n = 0, 1 \quad (71) \]

\[ x = \frac{1 + \theta_y y}{\theta_x} \quad (72) \]

Solving the intersection of the nullclines, the interior fixed points can be described by the solutions to this quadratic equation of \( n \):

\[ 0 = (\theta_x - 1 - \theta_y)h_1(n)h_2(n) + (1 + \theta_y)h_1(n)h_3(n) - (\theta_x - 1)h_2(n)h_4(n) - h_1(n)h_4(n) \]

\[ h_1(n) = (b - d) + ((b' - d') - (b - d))n \]

\[ h_2(n) = (\gamma - \delta) + ((\gamma' - \delta') - (\gamma - \delta))n \]

\[ h_3(n) = (a - \beta) + ((a' - \beta') - (a - \beta))n \]

\[ h_4(n) = (a - c) + ((a' - c') - (a - c))n \]

The system will have either 0, 1, or 2 interior fixed points for any given payoff structure. Next, we determine the Jacobian evaluated at these fixed points:

\[
J_{\text{int}} = \begin{bmatrix}
0 & x^*(1 - x^*)(h_4(n^*) - h_1(n^*)) \\
 y^*(1 - y^*)(h_3(n^*) - h_2(n^*)) & 0 \\
\theta_y n^*(1 - n^*) & -\theta_x n^*(1 - n^*)
\end{bmatrix}
\]

\[ x^*(1 - x^*)((a' - c') - (a - c))y^* + ((b' - d') - (b - d))(1 - y^*) \]

\[ y^*(1 - y^*)((a' - \beta') - (a - \beta))x^* + ((y' - \delta') - (\gamma - \delta))(1 - x^*) \]

We evaluate the trace and determinant of this matrix:

\[ \text{Tr}(J_{\text{int}}) = 0 \quad (74) \]

\[ \text{Det}(J_{\text{int}}) = x^*(1 - x^*)y^*(1 - y^*)n^*(1 - n^*)((\theta_x h_3(n^*) - h_1(n^*)) - h_2(n^*) - h_4(n^*)) \]

\[ + ((\gamma' - \delta') - (\gamma - \delta))(1 - x^*) - \theta_y h_2(n^*)h_4(n^*)((a' - c') - (a - c))y^* + ((b' - d') - (b - d))(1 - y^*)) \quad (75) \]

\[ \text{Demonstration of orbital flow about null-planes} \]

Under some parameterizations, it is possible that both \( x \) and \( y \) can be invariant for some particular value of \( n, \hat{n} \). This occurs when:

\[ \hat{n} = \frac{a - c}{(a - c) - (a' - c')} \quad (76) \]

\[ \frac{b - d}{(b - d) - (b' - d')} \quad (77) \]
If $\hat{n}$ exists, when $n = \hat{n}$, there will be no flow in the $x$ or $y$ directions. There is a corresponding plane describing when $\hat{n} = 0$, which has the following definition:

$$0 = -1 - \theta_{y}y + \theta_{x}x$$

(80)

$$x = \frac{1 + \theta_{y}y}{\theta_{x}}$$

(81)

Now consider $\hat{n}$ for values of $x$. If $x > \frac{1+\theta_{y}y}{\theta_{x}}$, here $\hat{n} > 0$. For values of $x$ such that $x < \frac{1+\theta_{y}y}{\theta_{x}}$, $\hat{n} < 0$. Substituting the equality for the $n$ nullcline into $\dot{x}$:

$$\dot{x} = x(1-x)((a-c) + ((a'-c') - (a-c))y + ((b-d) + ((b'-d') - (b-d))n(1-y))$$

(82)

The first term in this product will be positive for all $y$. The second term will be positive for all $y$ as long as $\theta_{x} > 1 + \theta_{y}$. Under that condition, the sign of $\dot{x}$ will only depend on the third term. When $n < \hat{n}$, this term will be positive for all $y$ and negative for all $y$ when $n > \hat{n}$. We represent the directions of the flow diagrammatically in Fig. 6. This field suggests clockwise orbits such as observed when the model is simulated under the parameter conditions described in the main text (see Fig. 7).

### Heteroclinic networks

#### Stability analysis of exterior fixed points

We also analyze the stability of the exterior fixed points. For any of the exterior fixed points, the Jacobian becomes diagonal, and so the eigenvalues can be read off of the matrix. The eigenvalues for each exterior fixed point are summarized in

$$\dot{x} = \left(\frac{1 + \theta_{y}y}{\theta_{x}}\right)\left(\frac{\theta_{x} - (1 + \theta_{y}y)}{\theta_{x}}\right)[((a-c) + ((a'-c') - (a-c))n)y + ((b-d) + ((b'-d') - (b-d))n(1-y)]$$

(83)
Table 8. All of these fixed points have at least one positive eigenvalue using parameter constraints that avoid resource crash dynamics. All fixed points also have at least one negative eigenvalue if $\theta_x > 1 + \theta_y$, regardless of viral pay-off parameters. In this case, all exterior fixed points exhibit saddle stability, which leads us to investigate the existence of heteroclinic cycles.

### Solving characteristic matrix

Hofbauer’s [39] strategy for characterizing heteroclinic cycles in replicator dynamics involved a transformation of the equations into a finite number of half-spaces and evaluating the eigenvalues at their intersections. Our model can be redefined in terms of half-spaces in $\mathbb{R}^3$.  

\[
\begin{align*}
    z_1 &= x \\
    z_2 &= 1 - x
\end{align*}
\]  

(84)  

(85)
We can read the stability of each exterior fixed point in the directions of its adjacent fixed points off of this matrix. If there are any such set of vertices that form a closed loop with each other, this is a heteroclinic cycle. In the case such that are more than one closed loops, then multiple possible heteroclinic cycles emerge, and this is called a heteroclinic network. If each row had exactly one positive and one negative value, then the system would have a simple heteroclinic cycle [39]. Using the dynamics demonstrated in Fig. 3, we will work through an example characterizing this heteroclinic cycle.

We use the payoffs:

$$\begin{align*}
P &= \begin{bmatrix} 4(1-n) + n, 3(1-n) + 2n & 4(1-n) + n, 4(1-n) + n \end{bmatrix} \\
N &= \begin{bmatrix} 4(1-n) + n, 3(1-n) + 2n & 4(1-n) + n, 4(1-n) + n \end{bmatrix}
\end{align*}$$

and the environmental restoration parameters $\theta_0 = 4, \theta_1 = 1$. Plugging these in to $C$, the resultant characteristic matrix is:

$$\begin{align*}
\begin{bmatrix} x & y & z \\ 0 & 0 & 1 \end{bmatrix} &= \begin{bmatrix} (x, y, z, x_{0-1}, x_{1-0}, y_{0-1}, y_{1-0}, n_{0-1}, n_{1-0}) \end{bmatrix}
\end{align*}$$

$$\begin{align*}
\begin{bmatrix} x & y & z \\ 0 & 0 & 1 \end{bmatrix} &= \begin{bmatrix} 2 & 0 & -3 & 0 & -1 & 0 \\ -1.1 & 0 & 2 & 0 & 0 & 1 \\
0 & 1 & 0 & 3 & -2 & 0 \\
-1 & 0 & 0 & -2 & 0 & 2 \\
0 & -2 & -1 & 0 & 3 & 0 \\
1 & 0 & 1 & 0 & 0 & -3 \\
0 & -1 & 0 & 1 & 2 & 0 \\
0 & 1 & 0 & -1 & 0 & -2 \\
\end{bmatrix}
\end{align*}$$

Each row of this matrix has at least one positive value and one negative value, and four of the rows have more than one positive value. This means that a heteroclinic network exists. To identify a cycle, start at any given point and follow the directions indicated by the positive eigenvalues. This network is comprised of the following cycles:

$$\begin{align*}
\begin{bmatrix} x & y & z \\ 0 & 0 & 1 \end{bmatrix} &= \begin{bmatrix} (x, y, z, x_{0-1}, x_{1-0}, y_{0-1}, y_{1-0}, n_{0-1}, n_{1-0}) \end{bmatrix}
\end{align*}$$

$$\begin{align*}
\begin{bmatrix} x & y & z \\ 0 & 0 & 1 \end{bmatrix} &= \begin{bmatrix} 2 & 0 & -3 & 0 & -1 & 0 \\ -1.1 & 0 & 2 & 0 & 0 & 1 \\
0 & 1 & 0 & 3 & -2 & 0 \\
-1 & 0 & 0 & -2 & 0 & 2 \\
0 & -2 & -1 & 0 & 3 & 0 \\
1 & 0 & 1 & 0 & 0 & -3 \\
0 & -1 & 0 & 1 & 2 & 0 \\
0 & 1 & 0 & -1 & 0 & -2 \\
\end{bmatrix}
\end{align*}$$
Now we investigate the relative stability properties of each of these cycles. Because all of these cycles contain at least one positive transverse eigenvalue (there are 2 positive values for some row in $C$ for at least one vertex in each cycle), none of these cycles will be asymptotically stable.

Brannath in [40] describes heteroclinic cycles as essentially asymptotically stable if, aside from some cusp shaped region of initial conditions with small Lebesgue measure, trajectories are attracted to the cycle. For this heteroclinic network, we use the two necessary and sufficient conditions for essential asymptotic stability from [38] 4.11:

$$\prod_{j=1}^{k} \min(e_j, e_j - t_j) > \prod_{j=1}^{k} e_j$$

$$t_j < e_j, j = 1, \ldots, k$$

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where $e_j$ is the eigenvalue in the direction of the cycle leaving the fixed point $j$ (expanding eigenvalue), $c_j$ is the absolute value of the eigenvalue in the direction of the cycle arriving at fixed point $j$ (contracting eigenvalue), and $t_j$ is the eigenvalue in the direction away from the cycle (transverse eigenvalue). $t_j$ can take on positive or negative values. We can calculate these stability criteria for any cycle in the heteroclinic network. Take $\Gamma_1$ as an example. These eigenvalues are:

| Point   | $-c$ | $e$ | $t$ |
|---------|------|-----|-----|
| (0,0,0) | -1   | 2   | -3  |
| (1,0,0) | -2   | 3   | -1  |
| (1,0,1) | -3   | 1.1 | 1   |
| (0,0,1) | -1.1 | 1   | 2   |

We find $t_{(0,0,1)} > e_{(0,0,1)}$ and conclude $\Gamma_1$ is unstable. Because all heteroclinic cycles in the network are connected by at least one fixed point, there will only be one cycle for which there is no $t_j > e_j$. For these payoffs, that cycle is $\Gamma_2$. We then conclude that any trajectory which is attracted to this heteroclinic network will be attracted to $\Gamma_2$. Also notice for $\Gamma_1$ that $\prod c = \prod e$. This will be the case for all heteroclinic networks in our model because of the symmetrical nature of the eigenvalues. This means that no heteroclinic cycle in our model will be essentially asymptotically stable. Simulations find that without an unstable interior fixed point to drive dynamics towards the exterior of the state space,
they dynamics tend to the neutrally stable periodic orbits on the $y = 0$, $I$ planes (see Fig. 8). This result demonstrates that the neutral 2D orbit outcome (in which one viral type reaches fixation) can occur for parameter regimes outside of a dominating strategy for a particular viral phenotype.

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Author contributions DM and JSW conceived the work, DM performed analysis, and DM and JSW wrote and edited the manuscript.

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Data availability All numerical integrations of ODEs were carried out via the fourth-order Runge–Kutta method as implemented by function ode45 in MATLAB v 2017a. Heteroclinic networks were visualized using R v 3.5.2’s [49] igraph v 1.2.2 [50] package. Scripts are available at https://doi.org/10.5281/zenodo.4750365

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

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