Evolution of Host Defense against Multiple Enemy Populations

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ABSTRACT: Natural and managed populations are embedded within complex ecological communities, where they face multiple enemies. Experimental studies have shown that the evolution of host defense mechanisms to a focal enemy is impacted by the surrounding enemy community. Theoretically, the evolution of host defenses against a single enemy population, typically parasites, has been widely studied, but only recently has the impact of community interactions on host-parasite evolution been looked at. In this article, we theoretically examine the evolutionary behavior of a host population that must allocate defenses between two enemy populations, parasites and predators, with defense against one enemy constraining defense against the other. We show that in simpler models the composition of the enemy community plays the key role in determining the defense strategy of the hosts, with the hosts building up defenses against the enemy population posing a larger threat. However, this simple driver is shown to break down when there is significant recovery and reproduction from infected hosts. Additionally, we find that most host diversity is likely to occur when there is a combined high risk of infection and predation, in common with experimental studies. Our results therefore provide vital insight into the ecological feedbacks that drive the evolution of host defense against multiple enemy populations.

Keywords: host-parasite, defense evolution, predator-prey, community complexity, adaptive dynamics.

Introduction

Many ecological populations are faced with a wide range of natural enemies. Often, adaptations to one enemy will also confer an advantage against others, for example, a behavioral change may reduce encounters with multiple enemies (Moore 2002). However, given limited resources, we may often expect improved defense against one enemy to constrain defense against another. Such a trade-off has been demonstrated experimentally in a number of systems, for example, in bacteria against phage and protists (Friman and Buckling 2012), in a plant against two herbivores (Stinchcombe and Rausher 2001), and in flies against parasitic wasps and birds (Craig et al. 2007). Given these examples of antagonistic community interactions, it is important to understand the factors that impact the evolution of host defense strategies against their different enemies.

From a theoretical perspective, we now have a considerable understanding of how the underlying ecology can drive the evolution of host defenses against a single natural enemy. A key example is the evolution of costly host defense against parasites (see the review by Boots et al. 2009). If we consider the direct impacts of additional natural enemies, we may expect it to primarily lead to increased host mortality. Miller et al. (2007) explored how varying mortality rates impact a range of host defense mechanisms, finding that higher mortality rates generally lead to less investment in defense against disease, as such shorter-lived hosts are less likely to become infected, although the results are complicated when models include acquired immunity (Miller et al. 2007; Best and Hoyle 2013). However, considering increased mortality alone does not account for the dynamic feedbacks that result from the inclusion of a second enemy. We may also expect infected hosts to be preferentially targeted by additional enemies, with empirical evidence from red grouse (Hudson et al. 1992) and snowshoe hare (Murray et al. 1997) populations, such that infected hosts have higher mortality. Theoretically, it has been shown that sterilizing diseases that incur higher parasite-induced mortality (virulence) should select for lower host resistance due to the reduction in disease prevalence (Boots and Haraguchi 1999), while van Baalen (1998) found that resistance through increased clearance is maximized at intermediate rates of virulence. It is also well known that disruptive selection leading to the coexistence of host strains (known as evolutionary branching) can occur when host defense is through resistance but not when defense is through tolerance (Boots and Bowers 1999; Roy and Kirchner 2000; Miller et al. 2005; but see Best et al. 2008), and Bruns et al. (2014) found that polymorphisms occurred in long-lived hosts for more costly and more extreme resistance levels compared with short-lived hosts. Although these studies give us an indication of host defense against parasites, they do not consider the evolution of host defense when there is an additional enemy present.

Another well-studied exploiter-victim interaction is predator-prey systems, with the focus often on the potential

for Red Queen coevolutionary cycles (Dieckmann et al. 1995; Marrow et al. 1992) or on the occurrence of diversity through evolutionary branching (Day et al. 2002; Abrams 2003; Geritz et al. 2007; Hoyle and Bowers 2007; Landi et al. 2013). Landi et al. (2013) found that prey branching leading to dimorphism is induced when prey are highly sensitive to competition, as this increases the advantage of branching into prey with distinct traits. More generally, it has been found that the evolution of antipredator defense in the prey can promote the coexistence of two prey species with different traits and a predator population (Yamauchi and Yamamura 2005). However, the effects of additional species interactions have also not been included in these studies.

Recently, there has been a growing interest in the dynamic effects of predation on host and parasite evolution (Morozov and Adamson 2011; Hoyle et al. 2012; Morozov and Best 2012; Kisdi et al. 2013; Toor and Best 2015). Specifically to host evolution, Toor and Best (2015) showed that given a trade-off between host investment in defense against infection and birth rate, host investment in defense against disease is maximized at intermediate predation rates, that is, intermediate additional mortality, where there is both a high risk and a cost of infection, with this effect being heightened when there is strong selective predation on infected hosts (in contrast to Miller et al. [2007], who looked at host defense against parasites alone and found that defense is highest when mortality is high). Meanwhile, Hoyle et al. (2012) showed how the presence of a predator can lead the host to evolve such that there is deterministic eradication of the disease, which cannot occur in a standard host-parasite model. Both of these studies also showed that the presence of a predator population increases the parameter range leading to evolutionary branching in host resistance (Hoyle et al. 2012; Toor and Best 2015). Although these studies have provided useful insight into host-parasite evolution in the presence of a predator population, they

still do not directly address the question of what happens when host species must allocate resources between defenses against the two different enemies.

In this article, we focus on a host population facing two enemies, parasites and predators. We assume that by increasing defense against one enemy, the host constrains their defenses against the other. Using an evolutionary invasion approach (adaptive dynamics; Geritz et al. 1998), we look at the evolutionary behavior of the host population with the aim of determining when the hosts are more likely to defend themselves against the infection or predation.

Model

We modify a classic host-parasite model by including an additional predator population (Hoyle et al. 2012; Toor and Best 2015). The model is given by the following ordinary differential equations

$$\frac{dS}{dt} = a(S + fI) - qH(S + fI) - bS - \beta SI + \gamma I - cSP, \quad (1)$$

$$\frac{dI}{dt} = \beta SI - (\alpha + b + \gamma)I - c\phi IP, \quad (2)$$

$$\frac{dP}{dt} = \theta cP(S + \phi I) - dP, \quad (3)$$

where S, I, and P are the densities of susceptible hosts, infected hosts, and predators, respectively, with $H = S + I$. The parameters are defined in table 1. In this model, once a host is infected it moves from the susceptible class to the infected class. If the infected host recovers, it moves back into the susceptible class, as it can be reinfected by the parasite again (susceptible-infected-susceptible [SIS] model). Using a Holling type I response, we assume that there is no limitation on predation (in previous work we have found the evolutionary behavior to qualitatively hold for type II

Table 1: Parameter definitions and values used

Parameter	Definition	Default value
β	Transmission rate	Varies
a	Prey birth rate	2
α	Parasite-induced death rate/virulence	1.3
ϕ	Increase/decrease in the predation rate suffered by infected individuals	3
θ	Conversion of predation into births of new predators	1
γ	Recovery rate	.2
q	Rate of density-dependent competition, acting on births	.5
b	Natural prey death rate	.2
d	Predator death rate	.3
f	Infected fecundity (proportion of infected individuals able to reproduce)	1
Γ	1/infectious period, $\alpha + b + \gamma$	.6
c	Predation rate	Varies

and III responses provided that the population dynamics remain as equilibria; Toor and Best 2015). We also assume that the predator is immune to infection in this system.

Additionally, we include a trade-off, $c(\beta)$, between the predation rate (c) and the transmission rate (β) in our model, given by the following (similar form to that previously used by Hoyle et al. [2012] and Toor and Best [2015]):

$$c(\beta) = c(\beta^*) - \frac{c'(\beta^*)^2}{c''(\beta^*)}\left(1 - e^{\frac{c''(\beta^*)(\beta-1)}{c'(\beta^*)}}\right) \quad (4)$$

(see the trade-off curve in fig. A1; figs. A1, A2 are available online). Note: Here we use primes to denote derivatives; for example,

$$c'(\beta^*) = \frac{\partial c}{\partial \beta}\bigg|_{\beta=\beta^*},$$

and (β^*, c^*) is the equilibrium point. For our results, we set the equilibrium point, gradient, and curvature of the trade-off curve as $(\beta^*, c^*) = (1.15, 0.08)$, $c'(\beta^*) = -0.2$, and $c''(\beta^*) = 1$, respectively. Given that $c''(\beta^*) > 0$, the trade-off curve is a decreasing function (concave curve) with resistance becoming increasingly costly. The mutant strains vary in their strategies along this trade-off, such that higher host defense against one enemy corresponds to lower defense against the other. If $c''(\beta^*) < 0$, the curve switches to one with decelerating costs (convex curve).

In this case ($c''(\beta^*) > 0$), when the hosts increase defense against one enemy (the parasite or the predator), they constrain their defense against the other. As the hosts increase their resistance against the infection they lower their resistance against predation (β decreases and c increases), whereas as the hosts increase their resistance against predation they lower their resistance against the infection (c decreases and β increases). For example, evolving toward low c will lead to β increasing, as the hosts are defending themselves against predation rather than infection. There is good experimental evidence that such a trade-off exists (Stinchcombe and Rausher 2001; Nuismer and Thompson 2006; Craig et al. 2007; Edeline et al. 2008; Gomez et al. 2009; Siepielski and Benkman 2009; Friman and Buckling 2012). We also consider the addition of another trade-off in the host in which their birth rate is lowered when defense against both parasites and predators is high (see app. A; apps. A, B are available online).

We use the evolutionary invasion framework of adaptive dynamics (Geritz et al. 1998) to determine the evolution of host defense. This means that we introduce small, rare mutant strains to a resident strain at equilibrium. For this model, the fitness of a mutant host invading a resident equilibrium is given by the following fitness equation (see app. B for the computation of the fitness equation):

$$s(\hat{c}, \hat{\beta}; c, \beta) = (a - qH - b - \hat{\beta}I - \hat{c}P)(\Gamma + \hat{c}\phi P) \\ + \hat{\beta}I(af - qfH + \gamma). \quad (5)$$

Note: Here we use $\hat{c}$ and $\hat{\beta}$ to denote the mutant strain traits and assume that only the resident's density is affecting the mutant, given the rarity of the mutant. The fitness is equivalent to the mutant's growth rate while rare. When $s > 0$, the mutant population has positive fitness and can invade the resident population, and when $s < 0$, the mutant population has negative fitness and cannot invade the resident population.

We start by looking at the evolutionary outcome of the system by looking for "singular strategies" that the population will evolve toward and stay at. These points are known as continuously stable strategy (CSS) points and occur when the gradient of the fitness equation is 0:

$$\frac{\partial s}{\partial \hat{\beta}}\bigg|_{\hat{\beta}=\beta} = 0.$$

CSS points are evolutionarily stable (ES, meaning the population will stay at this point once reached, as no nearby mutants can invade) and convergence stable (CS, meaning the population will converge to this point when close to it). The ES and CS properties are met when certain second-order conditions are satisfied (see eqq. [8], [9]). We use the composition of the enemy communities (by obtaining the ratio of infected hosts to predators) to gain a better understanding of the mechanisms behind the evolutionary behavior of the host population. We vary the parameters in our model to determine when the hosts are more likely to defend themselves against the infection or predation while focusing on the region where the susceptible and infected hosts coexist with the predator population (note: there are regions where the parasite, predator, or both are excluded from the system). We then move on to look at the diversity that can be produced by looking at the possibility of the population branching into coexisting host populations with different defense strategies.

Results

Proportion of Infected Hosts to Predators

We begin by simplifying the model to assume that there is no recovery ($\gamma = 0$) and that the infected hosts are sterile ($f = 0$), such that the gradient of the fitness equation (eq. [5]) is simply

$$\frac{\partial s}{\partial \hat{\beta}}\bigg|_{\hat{\beta}=\beta} = -\mu_I P\left(\frac{I}{P} + c'(\beta)\right), \quad (6)$$

where $\mu_I = \Gamma + c\phi P$ (rate at which infected hosts leave the infected compartment), and

$$c'(\beta) = \left.\frac{\partial c}{\partial \hat{\beta}}\right|_{\hat{\beta}=\beta}$$

(here $c'(\beta)<0$). From equation (6), we see that at a CSS point $I/P = -c'(\beta)$, so any change in the ratio of the enemy populations will move the host population toward selection for lower or higher values of β. For example, if an environmental change leads to a larger infected population and a smaller predator population—that is, $I_{new}>P_{new}$—then the gradient will become negative, leading to higher host resistance to the disease (lowering β). Clearly, in this case the proportion of infected hosts to predators plays the key role in determining the direction of evolution of host defense against the infection or predation.

Considering the full model (where $\gamma>0$ and $f>0$), the gradient of the fitness equation (eq. [5]) is now given by

$$\left.\frac{\partial s}{\partial \hat{\beta}}\right|_{\hat{\beta}=\beta} = P(\phi\rho_S-\mu_I)\left(\frac{I}{P}\frac{\rho_I-\mu_I}{\phi\rho_S-\mu_I}+c'(\beta)\right),\quad (7)$$

where $\rho_S = a-qH-b-\beta I-cP$ (contribution from susceptible hosts to the growth rate of the host population) and $\rho_I = af-qfH+\gamma$ (contribution from infected hosts to the growth rate of the host population). Now, since $\rho_S \leq 0$ and $\rho_I \geq 0$ at equilibrium, the driver of selection is clearly no longer as simple as the ratio of infected hosts to predators, as now the growth rates also play a role. For example, if an environmental change leads to $P_{new}>I_{new}$, we also need to know what happens to the growth terms ρ_S, ρ_I, and μ_I. In fact, given the signs of the ρ_S and ρ_I terms at equilibrium, even if $P_{new}>I_{new}$, the gradient may become negative, leading to higher defense against infection.

In general, therefore, we find that the hosts increase their defenses to either the infection or the predation depending on the composition of the enemy populations (i.e., the ratio of infected hosts to predators present in the population). The hosts tend to evolve defense mechanisms against parasites or predators depending on which enemy has a higher population density, as this relates to whether they are more likely to be infected by a parasite or preyed on by a predator, although this may not always be the single driving factor of the host's evolutionary behavior, as additionally the growth rates may play a role in determining the evolutionary behavior of host defense.

Note: Unless stated otherwise, we assume that $\gamma>0$ and $f>0$ throughout the following sections.

Predation Rate Suffered by Infected Individuals (ϕ)

We first consider how the degree of selective predation on infected hosts (ϕ) impacts host investment in defense mechanisms. As ϕ increases, there is an increasing risk of mortality through predation while infected. For $\phi>1$, the pred-

ators are selectively preying on infected hosts, so as ϕ increases (provided that there is a sufficient amount of infected hosts available for the predators to consume) the predator population grows and removes the infected hosts from the population, thereby lowering the risk of infection for the susceptible hosts. For high virulence (α), as ϕ increases the ratio of infected hosts to predators decreases, because the infected hosts are being removed through predation (see the solid line in fig. 1). Hence, the predators pose a greater threat to the host population, which leads to the hosts increasing their resistance to the predators while consequently becoming more susceptible to infection (β increases, as shown by the dashed line in figure 1 for high α and fig. 2). The parameters for the prey birth rate (a) and the conversion of predation into births of new predators (θ) behave similarly to ϕ, as an increase in these parameters also leads to the host population increasing their defenses against predation.

This result changes for low virulence (α) values. In this case, as ϕ increases the hosts initially increase their defenses against predation and then switch to increase their defenses against infection (see the dashed line in fig. 1 for low α and fig. 2). Since α is small, the ratio of infected hosts to predators is no longer the single factor determining the evolution of host defense (note: here $\rho_I-\mu_I$ changes from positive to negative; see eq. [7]). As ϕ increases, it becomes increasingly risky to become infected, as the host is more likely to be preyed on once infected, so the hosts switch to defending themselves against infection, even though the predator is the main enemy. Hence, for less virulent diseases, as ϕ increases we find that the hosts increase their defenses against predation and then switch to increase defenses against infection.

Virulence (α)

We find that the hosts increase their defenses against infection as virulence (α) increases (note: this holds for all values of $0 \leq f \leq 1$). Here the predators have fewer infected hosts to prey on because the parasite is removing infected hosts quickly from the population, so the predator population decreases and the ratio of infected hosts to predators increases. The infected population is also decreasing as α increases, but it is still larger than the predator population. Hence, due to the increased parasite-induced mortality, the parasite poses a greater threat to the host population, so the hosts correspondingly increase their resistance to the parasite (fig. 2).

We find that this also holds when the predators are selectively preying on the susceptible hosts; this shows that increasing α has a highly detrimental effect on the predator population, as the predators do not have enough susceptible hosts to maintain their population density. Hence,

High virulence ($\alpha = 0.8$) Low virulence ($\alpha = 0.1$)
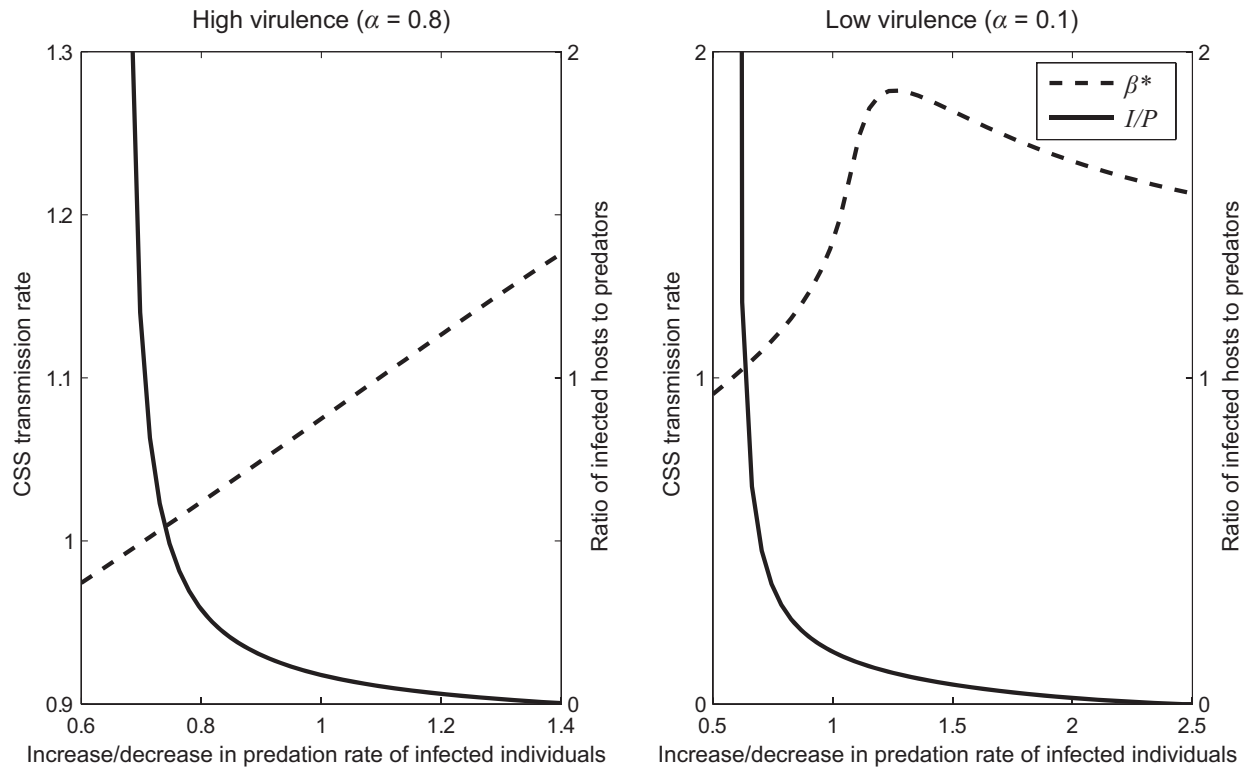
Figure 1: Continuously stable strategy (CSS) transmission rate (β^*) and ratio of infected hosts to predators (I/P) for varying values of predation rate of infected hosts (ϕ), where $d = 0.22$, $\beta = 1$, and $c = 0.1$ and other parameters are as in table 1 (note: the results hold for higher ϕ values using all of the parameter values given in table 1). As ϕ increases, the ratio of infected hosts to predators decreases (solid line) and β^* increases (dashed line), reflecting a decrease in host defense against the infection and an increase in host defense against predation. For lower virulence levels ($\alpha = 0.1$), β^* increases and then decreases, reflecting a decrease followed by an increase in host defense against the infection as it becomes increasingly costly to be infected due to the growing risk of predation once infected.

for varying values of ϕ we find that the hosts continually increase resistance to the disease as α increases, regardless of whether the predators selectively prey on the susceptible hosts, the infected hosts, or both equally. The parameters for the rate of density-dependent competition acting on births (q), natural prey death rate (b), and predator death rate (d) behave similarly to α. Increases in q and b lead to a smaller host population, so the predator population declines as they have less prey to consume, causing the hosts to increase their defenses against the infection as it poses a larger threat. An increase in d leads to a decline in the predator population, so the hosts once again focus on defense against the infection rather than predation.

Recovery Rate (γ)

As the recovery rate (γ) increases, the infected hosts are recovering and returning to the susceptible class at a quicker rate. For γ, we see that the results change depending on whether the predators selectively prey on the susceptible

hosts, the infected hosts, or both equally. For values of ϕ close to 1, the predators are being less selective when deciding which prey to consume, so both the susceptible and the infected hosts are being preyed on. As γ increases, the number of infected hosts decreases, as the infected hosts are recovering from the disease and reentering the susceptible class, lowering the risk of infection. This causes a reduction in the ratio of infected hosts to predators, so the hosts increase their defenses to the predators as they face a higher risk of predation rather than infection (fig. 3).

For higher values of ϕ, as γ increases the hosts increase resistance to the predators first and to the infection second (β increases and then decreases, as shown in fig. 3). Initially as γ increases there are fewer infected prey, leading the hosts to increase their defenses against predation. However, the ratio of infected hosts to predators begins to increase because the predators are more reliant on the infected population and have fewer infected hosts to consume as more of them are recovering, so the predator population decreases. As the pool of susceptible hosts increases, this eventually leads to an increase in the number of infected prey be-
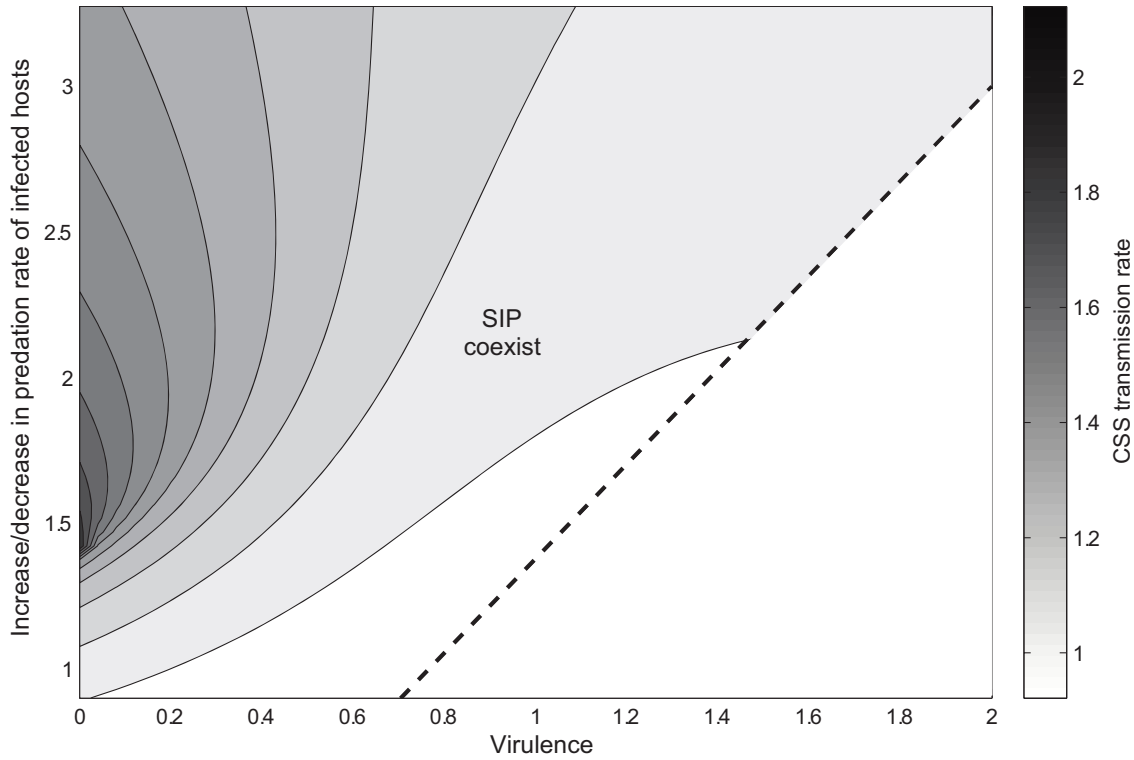
Figure 2: Continuously stable strategy (CSS) transmission rate (β^*) for varying values of virulence (α) and predation rate of infected hosts (ϕ), using the parameter values given in table 1. The susceptible and infected hosts coexist with the predator population in the region to the left of the dashed line (SIP; the predator or both the predator and the parasite population have been excluded in the white region). As α increases, β^* decreases, as the hosts increase their defenses against the parasite.

cause there are more susceptible hosts for the infected hosts to infect. The hosts then switch their defense strategy and focus on increasing their defenses against the infection for large values of γ. For low ϕ, this increase in γ does not lead to an increase in the susceptible pool because the predators are being less selective and are also preying on the susceptible host population (rather than selectively preying on infected hosts, which is the case when ϕ is large). Hence, as γ increases the hosts increase their defenses against the predators when ϕ is low and against the infection when ϕ is high.

Infected Fecundity (f)

As the infected fecundity (f) approaches 0, there is a smaller proportion of infected individuals that are able to reproduce, and when $f = 0$, the infected population is completely sterile. The infected hosts reach a small density only as f approaches 0, so it takes a longer time for the predator population to grow as there are fewer prey for them to consume, but when f is large the predator population has more infected hosts to consume, so the predator population grows and the infected population decreases, leading to the preda-
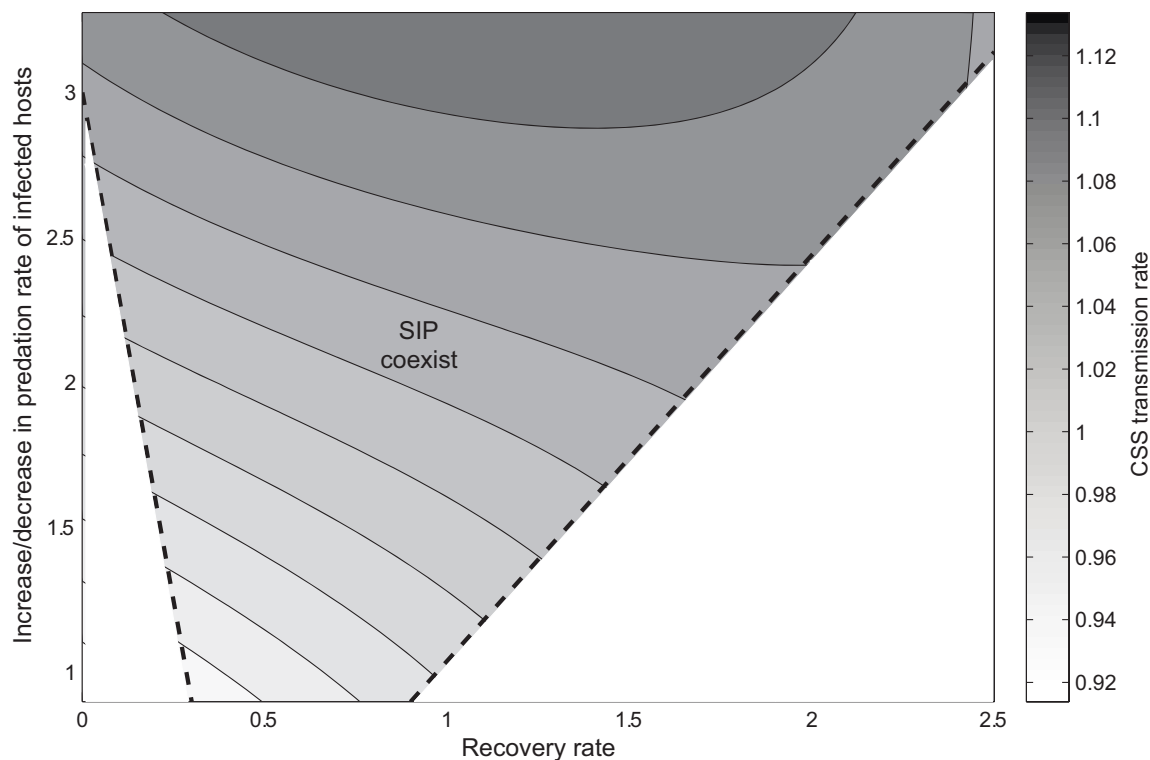
tors posing a greater threat to the susceptible host population. This decrease in the ratio of infected hosts to predators as f increases is shown in figure 4 (solid line). Hence, as f increases the hosts increase their resistance to the predators, becoming more susceptible to the infection, so β increases, as shown in figure 4 (dashed line).

Branching Region

Next, we looked at the possibility of two populations coexisting through the occurrence of disruptive selection (branching) in the system. Figure 5 shows the regions where various evolutionary outcomes can occur at a fixed "singular point." Above each curve lies the region that satisfies the relevant ES (eq. [8]) or CS (eq. [9]) condition.

$$\frac{\partial^2 s}{\partial \hat{\beta}^2}\bigg|_{\hat{\beta}=\beta} < 0, \tag{8}$$

$$\left[\frac{\partial^2 s}{\partial \hat{\beta}^2} + \frac{\partial^2 s}{\partial \hat{\beta}\partial \beta}\right]\bigg|_{\hat{\beta}=\beta} < 0 \tag{9}$$

Figure 3: Continuously stable strategy (CSS) transmission rate (β^*) for varying values of recovery rate (γ) and predation rate of infected hosts (ϕ), using the parameter values given in table 1. The susceptible and infected hosts coexist with the predator population in the region between the two dashed lines (SIP; the predator population has been excluded for low γ and the parasite population has been excluded for high γ in the white regions). As γ increases, β^* increases, as the hosts lower their defenses against the infection and increase their defenses against the predators. For high values of ϕ, the hosts alter their evolutionary behavior to increase their defenses against predation and then infection as γ increases (β^* increases and then decreases).

Above both lines represents an attractor (CSS), above the CS line and below the ES line represents a branching point, below the CS line represents a repeller, and above the ES line and below the CS line represents a Garden of Eden point (a locally repelling fitness maximum; i.e., these are points that the population will not evolve toward, but populations at these points will stay there). The branching region occurs where it is CS and not ES. Along the Y-axis is the curvature of the trade-off at the singular point that determines the behavior at the evolutionary singularity (the slope of the trade-off curve determines whether the point is an evolutionary singularity). Figure 5 shows a numerical simulation where the host population converges to a point and then undergoes disruptive selection and branches into two coexisting populations with varying defense strategies. Here we get two specialist host populations: one host population evolves low defenses against the disease (population evolving toward high β) with high defenses against predation, and the other evolves high defenses against the disease (population evolving toward low β) with low defenses against predation.

Figure 6 shows the branching region for varying values of ϕ. The ES and CS conditions are plotted only for the parameter space where all three species coexist. For low d values the infection is excluded, and for high d values the predators are excluded. We find that as ϕ increases the size of the branching region (i.e., the range of trade-off curvatures that give branching) decreases. Branching is more likely for lower values of ϕ because the hosts are more likely to defend themselves against the disease or predators, as both are posing a threat to the susceptible population. This leads to more diversity in the population, as some hosts will evolve defenses against the disease and others against predation. However, for high ϕ branching is less likely, as the hosts are likely to defend themselves against the predators due to the high risk of predation. In this case, less diversity occurs in the system, as the hosts clearly face a high risk of predation, making it more beneficial to evolve defenses against the predators. Hence, branching is more likely to occur when both enemy populations are present and posing relatively balanced simulta-
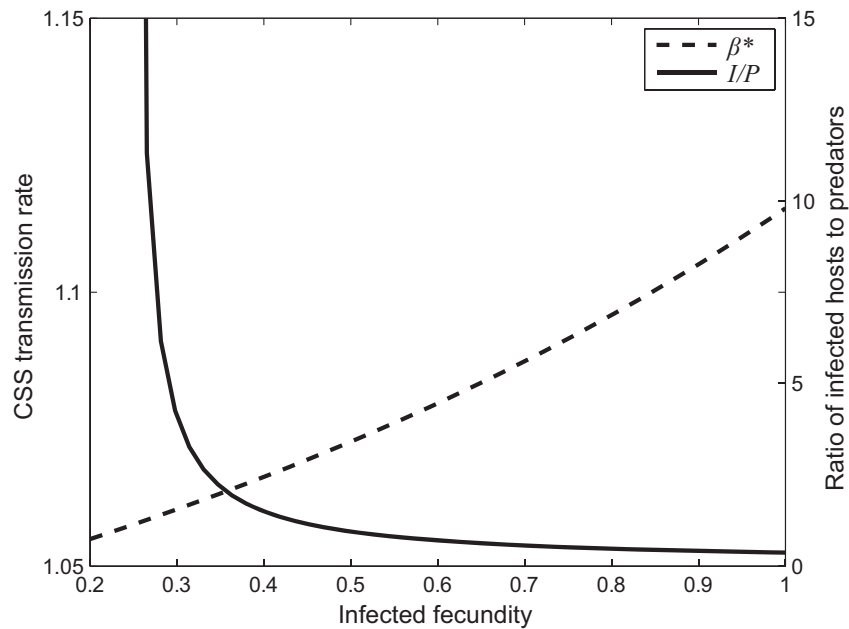
Figure 4: Continuously stable strategy (CSS) transmission rate (β^*) and ratio of infected hosts to predators (I/P) for varying values of infected fecundity (f), using the parameter values given in table 1. As f increases, the ratio of infected hosts to predators decreases (solid line) and β^* increases (dashed line), reflecting a decrease in host defense against the infection.

neous risks of infection and predation, whereas branching is less likely to occur when one enemy strongly dominates the enemy community composition. We found that as the parameters ϕ, a, and θ increase the size of the branching region increases, and as the parameters α, γ, q, and b increase the size of the branching region decreases.

Discussion

We have shown how ecological feedbacks drive the evolution of host defense against multiple enemies. In particular, we have shown that investment in defense against parasites and predators varies depending on the composition of the enemy community, as this relates to the relative risk of infection or predation. In general, we have found, quite intuitively, that when environmental change leads to a higher proportion of infected hosts relative to predators, the hosts increase their defenses to infection, whereas when there are a higher proportion of predators, the hosts increase their defenses to predation. Thus, the proportion of infected hosts to predators forms a simple ecological driver for the evolutionary behavior of many host populations. However, we found that this driver is modified to include the relative growth rates of susceptible and infected hosts when there is significant recovery or reproduction from infected hosts, highlighting the important distinction between parasites that do or do not act as "functional predators" (Boots 2004).

It would be easy to dismiss these results as being rather trivial. That host defense is directed against the most threatening enemy, whether that threat is determined solely by relative abundance or in combination with host growth rates, appears straightforward. However, we have in fact uncovered this simple driver as being responsible for the seemingly nonintuitive trends that emerge across environmental gradients—trends that can be understood only when we consider these broader ecological feedbacks. For example, we have shown that higher recovery rates from infection lead to increased defense against parasites (if predators selectively prey on infected hosts)—a seemingly counterintuitive result, as we might presume that high recovery would reduce selection for resistance to disease. However, our analytic evaluation of the fitness gradient shows that in this case the predator density decreases faster than the infected host density, making the infection the bigger threat. Therefore, we emphasise the vital role that ecological feedbacks play in antagonistic evolution within communities.

A crucial question, of course, is whether the predictions from our theoretical model are observed in experimental or empirical studies. One particularly relevant study is that of Friman and Buckling (2012), who not only studied host (bacteria) evolution against two enemies (phage and protists) but also recorded population densities across the evolutionary timescale, a rarity among experimental studies. They showed that when *Pseudomonas fluorescens* bacteria
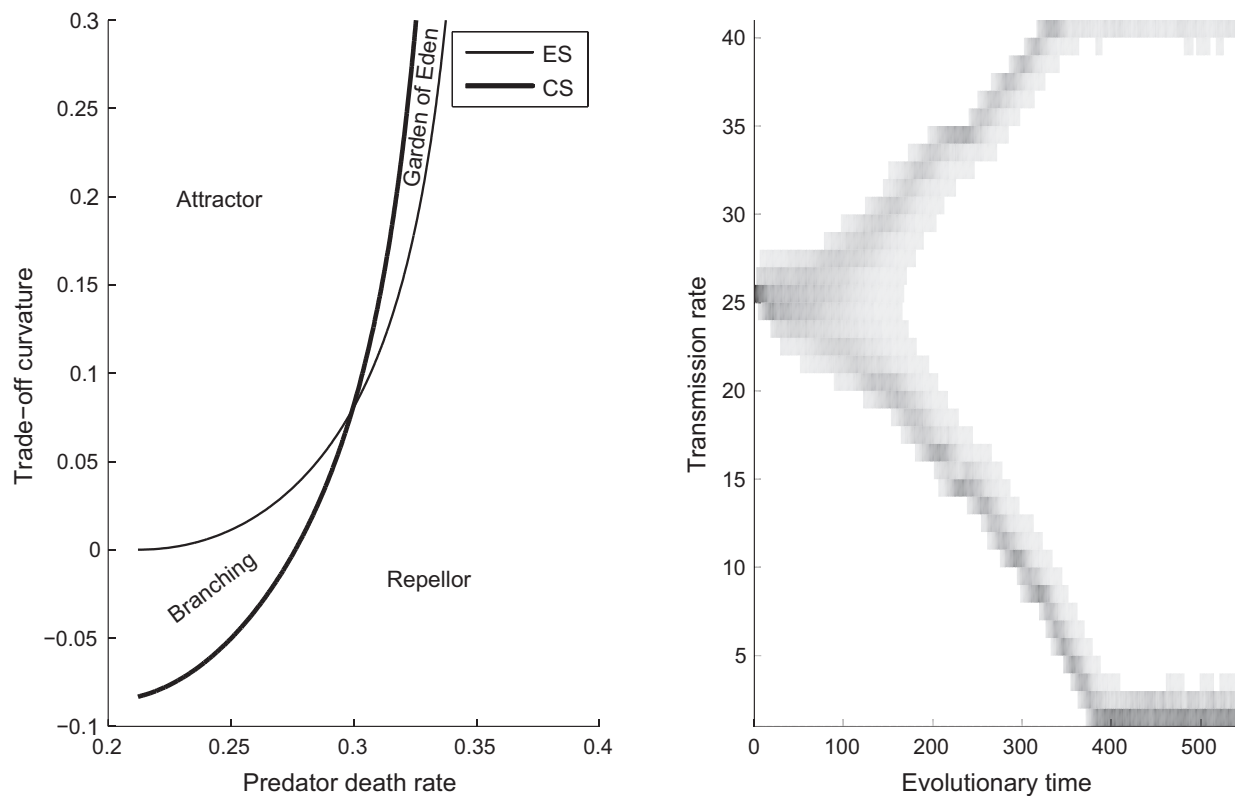
Figure 5: Various regions for differing evolutionary outcomes, where parameters are as in table 1. Above each curve lies the region that satisfies the relevant evolutionarily stable (ES) or convergence stable (CS) condition. The numerical simulation shows a host population branching into two coexisting populations, where $\beta_{min} = 0.5$, $\beta_{max} = 1.5$, $c''(\beta^*) = -0.05$, and $d = 0.25$ and other parameters are as in table 1.

were exposed to both enemies, the host population evolved into two coexisting specialist populations, one with high defense against phage and one with high defense against protists. Similarly, we have predicted that such coexistence can arise through evolutionary branching, specifically when neither of the enemies is dominant (meaning that selection is not biased toward a particular enemy), and the trade-off is roughly linear. The population data from Friman and Buckling (2012) appear to agree with this, since the densities of the two enemies remained relatively balanced over the evolutionary time period. We would predict that repeating the experiments with one enemy at a higher initial density, either through direct control or manipulation of the environmental conditions, would be more likely to result in a monomorphic specialist or "biased generalist" dominating in the bacteria with defenses aimed at the larger enemy population. Such evolution toward a host with defense mechanisms aimed at the enemy posing a larger threat is evident in other empirical studies. Using a 50-year-long time series on *Perca fluviatilis* perch (host) and *Esox lucius* pike (predator), Edeline et al. (2008) found that without a perch-specific pathogen, the pike's preference for small

perch had driven the perch to evolve toward a large body size. However, after introduction of the pathogen, which is more successful in large perch, selection had driven the perch to evolve toward a small body size. Not only does this demonstrate an indirect trade-off between defense against different enemies, but it appears that selection depends on the relative threat from each enemy, aligning with our results. Similarly, Craig et al. (2007) showed that the evolution of gall size in *Eurosta solidaginis* flies is driven by the composition of the enemy community, as small galls are more prone to infection and large galls are more likely to suffer predation. Consequently, given a higher chance of infection the flies evolved toward large galls, and given a higher chance of predation the flies evolved toward small galls. This would be expected from our results, as the flies are evolving their defense mechanisms on the basis of whether there is a higher risk of infection or predation. Furthermore, experimental work by Rigby and Jokela (2000) found that as *Lymnaea stagnalis* freshwater snails increased investment in predator avoidance behavior (as a result of being exposed to the predator more often), they lowered their immune defenses against potential pathogens, indi-
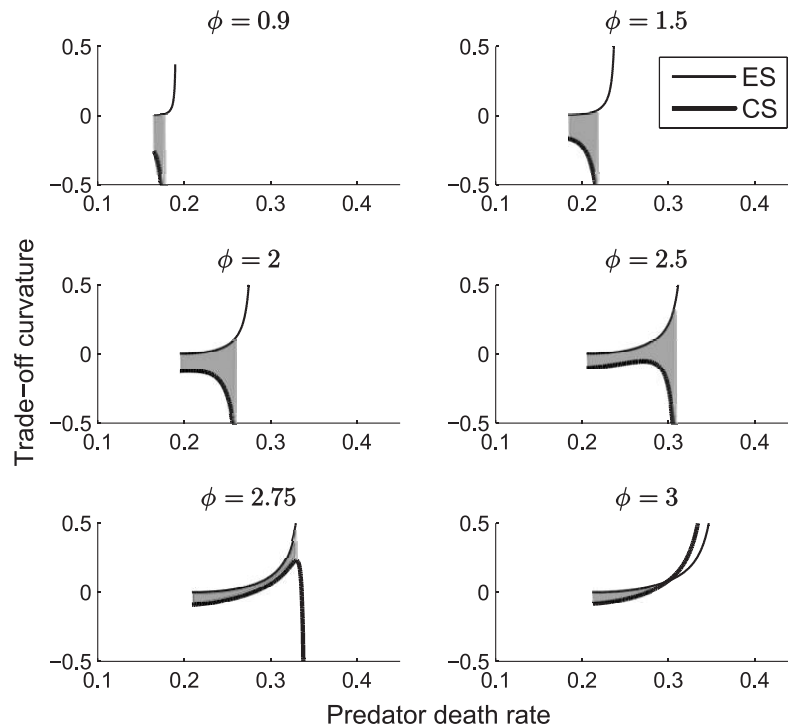
Figure 6: Branching region (shaded region) for varying values of predator death rate (d) and predation rate of infected hosts (ϕ), where $(\beta^*, c^*) = (1.15, 0.08)$ and other parameters are as in table 1. The trade-off curvature ($c''(\beta^*)$) is plotted on the Y-axis. The evolutionarily stable (ES) and convergence stable (CS) conditions are plotted for the region where all three populations coexist (for low d values the infection is excluded, and for high d values the predators are excluded).

cating a trade-off between defenses against predators and parasites with evolution seemingly driven by the relative exposure of hosts to the two enemies. These observable traits reveal the crucial effects that community dynamics can have on driving the evolution of host defenses.

It is important to note that the type of coexistence we have shown after branching is between hosts whose defense strategies focus on different enemies. This differs from previous theoretical examples of branching in host defense against parasitism where the trade-off is between defense and general life-history traits (Boots and Haraguchi 1999; Miller et al. 2005; Hoyle et al. 2012; Toor and Best 2015). We believe we are the first theoretical study to demonstrate branching to coexistence of this nature. Branching was most likely when selection against one particular enemy was not too strong. For example, diversity was less common when there was high virulence (since this favors high defense against parasitism) or strong selective predation (since this favors high defense against predation). Interestingly, the experimental study of Friman and Buckling (2012) noted that, in addition to the trade-off between host defense strategies, there appeared to be further costs to life-history traits. We have found here that further costs can still

give rise to the coexistence of hosts with varying traits (see app. A), but we emphasise that these additional costs are not necessary for branching in our model, as the trade-off between defense mechanisms alone is sufficient to generate the negative frequency dependence required for coexistence.

The role played by community interactions in antagonistic evolution is receiving increasing attention within both mathematical modeling and experimental evolution fields. Clearly, the development of evolutionary theory relies on both of these disciplines working collectively, and we believe that there are many exciting opportunities for development of this field. Experimental and empirical studies that consider evolution within complex communities must overcome many practical difficulties in maintaining and sampling from such systems. Only a few such studies of evolution against multiple enemies exist (Rigby and Jokela 2000; Craig et al. 2007; Edeline et al. 2008; Friman and Buckling 2012). A key insight of our work is that the relative population densities of enemies are a significant determinant of the host's evolutionary behavior. While there are undoubtedly practical issues to overcome to record population data during experimental evolution, where this is possible (such as in Friman and Buckling 2012) these data

may provide crucial insights into the observed traits. Indeed, recording these data may allow for experimental tests of our findings here, specifically to determine how well the relative population densities of two enemies can explain patterns of investment along environmental gradients.

Theoretical studies in this emerging field have investigated both parasite and host evolution in the presence of a (dynamic) immune predator. For parasite evolution, the additional feedbacks from the predator can lead to branching and coexistence of multiple parasite strains (Morozov and Best 2012), which is prevented due to a competitive exclusion principle when there is no predator (Bremermann and Pickering 1983; Bremermann and Thieme 1989; but see Best and Hoyle 2013 for other counterexamples), as well as cyclic fluctuations of parasite virulence and predator densities (Kisdi et al. 2013). Predation of hosts therefore appears to make diversity (both temporal and static) of parasites more likely. For the host, it has been shown that defense against parasitism is greatest at intermediate predation rates (Toor and Best 2015), as this combines high risk and cost of infection, and that hosts can drive their parasite to extinction if the predator is present (Hoyle et al. 2012). There are many potential developments to come in our theoretical understanding in this field. One example is to consider the coevolution of the host population with the enemy populations, since the parasite and predator populations will certainly adapt in response to the host. There is much existing work on host-parasite coevolution (van Baalen 1998; Restif and Koella 2003; Best et al. 2009, 2010; Boots et al. 2014), showing, for example, how the degree of static diversity that can arise in hosts and parasites depends on the nature of the infection interaction (Best et al. 2009, 2010; Boots et al. 2014). The work mentioned above suggests that predation is likely to play an important role here. The existing theoretical work has also focused on host defense through resistance (specifically avoidance, lowered transmission rate), and it would be interesting to explore how predation might impact the dichotomy between resistance (which causes negative frequency dependence) and tolerance (which causes positive frequency dependence; Roy and Kirchner 2000; Miller et al. 2005; Best et al. 2008). Crucially, we would emphasize that improvements in our understanding of antagonistic evolution in complex communities requires further work both within and between experimental evolution and mathematical modeling.

Acknowledgments

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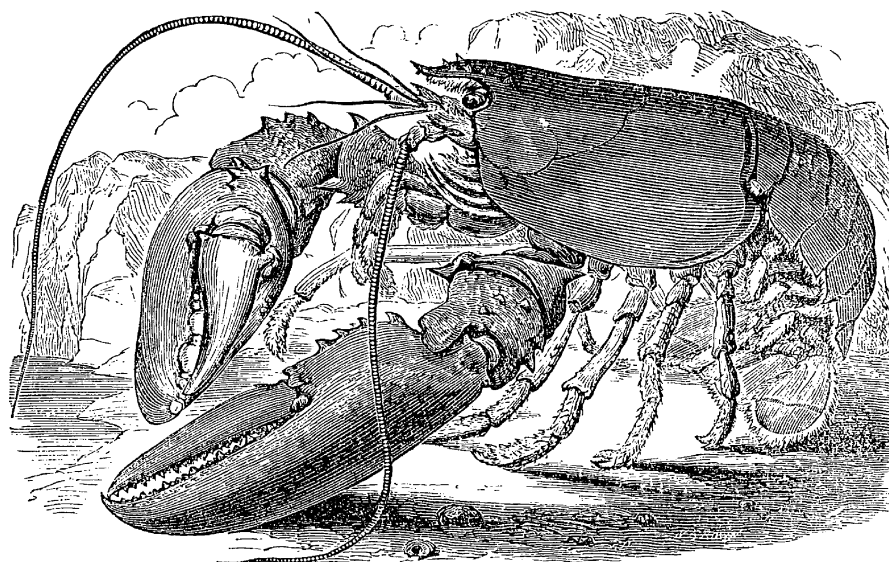
"It is not pleasant for the epicure to learn that the lobster . . . is essentially a scavenger; but in a list of scavengers this and other crustaceans, notwithstanding their exhibition of true predaceous habits, cannot be omitted. They eagerly feed upon the dead organic materials which they find at the bottom of the ocean." From "A Few Words about Scavengers" by Sanborn Tenney (*The American Naturalist*, 1877, 11:129–135).