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Source: *The American Naturalist*, Vol. 181, No. S1, A Critical Look at Reciprocity in Ecology and Evolution (May 2013), pp. S58-S75
Published by: The University of Chicago Press for The American Society of Naturalists
Stable URL: http://www.jstor.org/stable/10.1086/669952
Accessed: 26/06/2013 11:08

Symposium

Navigating the Devious Course of Evolution: The Importance of Mechanistic Models for Identifying Eco-Evolutionary Dynamics in Nature

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abstract: In proposing his genetic feedback mechanism, David Pimentel was one of the first biologists to argue that the reciprocal interplay of ecological and evolutionary dynamics is an important process regulating population dynamics and ultimately affecting community composition. Although the past decade has seen an increase in research activity on these so-called eco-evolutionary dynamics, there remains a conspicuous lack of compelling natural examples of such feedback. Here we argue that this lack may be due to an inherent difficulty in detecting eco-evolutionary dynamics in nature. By examining models of virulence evolution, host resistance evolution, and antigenic evolution, we show that the influence of evolution on ecological dynamics can often be obscured by other ecological processes that yield similar dynamics. We then show, however, that mechanistic models can be used to navigate this, in Pimentel's words, "devious" course of evolution when effectively combined with empirical data. We argue that these models, improving upon Pimentel's original mathematical models, will therefore play an increasingly important role in identifying more subtle, but possibly ubiquitous, eco-evolutionary dynamics in nature. To highlight the importance of identifying these potentially subtle dynamics in nature, we end by considering our ability to anticipate the effect of population control strategies in the presence of these eco-evolutionary feedbacks.

Keywords: eco-evolutionary dynamics, host-pathogen dynamics, rapid evolution, virulence evolution, host resistance evolution, antigenic evolution.

Introduction

Research in the field of eco-evolutionary dynamics has become increasingly active over the past decade (Fussmann et al. 2007; Johnson and Stinchcombe 2007; Kokko and López-Sepulcre 2007; Post and Palkovacs 2009; Schoener 2011). Theoretical research has focused on the development and analysis of models to assess how feedback between ecological and evolutionary dynamics can impact population regulation and community composition (Abrams and Matsuda 1997; Abrams 2000, 2001; Jones et al. 2009; Vasseur et al. 2011). Empirical research has instead focused on identifying instances of eco-evolutionary dynamics in laboratory settings (Yoshida et al. 2003, 2004; Meyer et al. 2006; Nahum et al. 2011) and in the field (Hanski and Saccheri 2006; Pelletier et al. 2007; Palkovacs and Post 2008; Hanski 2011; Turcotte et al. 2011). Taken together, these research efforts have demonstrated that eco-evolutionary dynamics may be more important than generally appreciated. However, the field is still conspicuously lacking a set of examples that convincingly demonstrate the dynamic interplay between ecology and evolution in nature (Fussmann et al. 2007; Schoener 2011).

Although activity in this field has only recently flourished, the concept of eco-evolutionary dynamics is not new (see supplement introduction by D. Reznick [2013]). One of the field's earliest contributors, David Pimentel, proposed his "genetic feedback mechanism" in 1961, describing the process as one in which "density influences selection; selection influences genetic make-up; and in turn, genetic make-up influences density" (Pimentel 1961, p. 65). He argued that the reciprocal feedback between ecological and evolutionary dynamics would lead to population stabilization and that understanding this process would facilitate the design of more effective population control strategies (Pimentel 1968).

Pimentel aimed to illustrate the occurrence of his genetic feedback mechanism in nature with several empirical examples. His most frequently used example is the eco-evolutionary interaction between the purposefully released myxoma virus and its host, the highly invasive European rabbit in Australia (Fenner et al. 1952). Following its release as a biocontrol agent in 1951, the virus's virulence, as measured by mortality rates in laboratory rabbits, decreased from 99% to 60% (Fenner et al. 1953; Marshall and Fenner 1960). At the same time, the rabbit population

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Am. Nat. 2013. Vol. 181, pp. S58–S75.
DOI: 10.1086/669952

evolved higher levels of resistance (Fenner et al. 1953; Marshall and Fenner 1960). Both of these rapid evolutionary changes were driven by selection pressures arising from the species' ecological interactions (Marshall and Fenner 1960; Pimentel 1961; Levin and Pimentel 1981). These observed evolutionary changes, in turn, led to a stabilization of the rabbit population. This example, therefore, clearly illustrates Pimentel's genetic feedback mechanism in the field. However, it cannot fairly be presented as one that is entirely natural: the introduced strain of the virus was deliberately chosen for its high virulence. Whether selection would have been strong enough to bring about genetic changes in either the host or the virus population had the introduced virus been less virulent is an open question.

Pimentel's (1961, 1968) second natural example of eco-evolutionary dynamics focuses on the herbivorous Hessian fly and its host plant, wheat. The introduction in the 1940s of fly-resistant varieties of wheat led to a rapid decline in the then-expanding Hessian fly population in Kansas, demonstrating that a host population's genetic makeup can affect a parasite's ecological dynamics. However, this example does not demonstrate eco-evolutionary dynamics because the evolutionary changes that occurred in the wheat were not directly brought about by the ecological interaction between the fly and its host.

Pimentel's third example focuses on another exploitative interaction: the interaction between an oyster and its pathogen (Pimentel 1961). In the decades following a severe disease outbreak in Canadian waters, disease-resistant oysters were detected in previously infected regions. This nicely illustrates that ecological dynamics can drive rapid evolution. However, because the pathogen was never isolated, it remains unclear whether the subsequent increase in the oyster population following the disease outbreak was due to resistance evolution. Other processes, such as a decline in the number of oyster predators, favorable environmental conditions for oyster growth, or regulation of the pathogen population by other factors, could have been primarily responsible for the observed increase in the oyster population instead. This example, therefore, also does not convincingly demonstrate the occurrence of eco-evolutionary feedback in nature.

Along with these three examples, Pimentel aimed to provide support for his perspective using laboratory experiments. In his most detailed experiment, he convincingly showed that a housefly and its parasitoid wasp underwent eco-evolutionary dynamics (Pimentel 1968). The housefly developed resistance in response to a large population of virulent wasps, and the wasps evolved toward lower virulence. These genetic changes stabilized the population dynamics of both the host and the parasitoid. Ecological dynamics, therefore, brought about rapid evolution, and these evolutionary changes indeed had an appreciable effect on ecological dynamics. The stabilization of population sizes that Pimentel observed in this experiment further supported his perspective that eco-evolutionary dynamics generally result in "increased homeostasis within populations and the ecosystem" (Pimentel 1961, p. 76). Although theoretical studies since then have shown that eco-evolutionary dynamics do not necessarily result in population stabilization (Abrams 2000), Pimentel's wasp-housefly system is still one of the most convincing laboratory examples showing that the dynamic interplay between ecology and evolution can regulate population sizes. In comparison to this laboratory example, Pimentel's three natural examples provide tenuous evidence, at best, for the occurrence of eco-evolutionary dynamics.

The lack of convincing, well-documented natural examples persists today (Fussmann et al. 2007; Schoener 2011). For a field that has shown much growth in terms of theoretical and laboratory studies, the paucity of natural examples is particularly conspicuous. Does this lack reflect a real rarity of eco-evolutionary dynamics in nature? Here we argue that this is not necessarily the case. Rather, these dynamics may simply be difficult to identify in nature because the effect of evolution on ecological dynamics can be obscured by the presence of other ecological processes that might be in play. We argue this point using examples of eco-evolutionary dynamics from virulence evolution, host resistance evolution, and antigenic evolution. We first show that these three cases, as formulated through their accompanying models, indeed exhibit eco-evolutionary dynamics in the manner described by Pimentel. By comparing these models with ones that implement only ecological processes, we then illustrate the impact of eco-evolutionary feedback on population dynamics. However, these comparisons also show that the impact of eco-evolutionary processes on population dynamics may not differ qualitatively from those brought about by purely ecological processes. Even in cases when evolutionary feedback does qualitatively alter population dynamics, we argue that other ecological processes that display similar population dynamics can readily be invoked in the place of evolution. In other words, the presence of numerous ecological "factors will make the course [of evolution in influencing population dynamics] devious" (Pimentel 1961, p. 73). This suggests that we may chiefly be finding empirical support in dramatic natural examples such as the rabbit myxoma system because the less dramatic, but likely more ubiquitous, examples go unnoticed. Mechanistic models, however, are starting to be used to detect the presence of eco-evolutionary dynamics in nature, and we use our three examples to show how these models can help navigate evolution's devious, that is, potentially obscured or hidden, course. These examples demonstrate that an integration

of theoretical and empirical approaches may be necessary in identifying natural systems that undergo eco-evolutionary dynamics. Finally, we address Pimentel's (1968) comment that more effective control strategies could be devised by gaining a better understanding of the processes regulating population dynamics, including the process of eco-evolutionary feedback.

Because each of our three examples makes use of eco-evolutionary models, we attempt to first familiarize the reader with the structure of mathematical models that have been used to consider the dynamic interplay between ecology and evolution. We start with a brief review and critical appraisal of one of Pimentel's models and follow with current modeling approaches that we adopt in our examples.

An Evolution of Mathematical Eco-Evolutionary Models

To our knowledge, the first mathematical model that implemented eco-evolutionary dynamics was presented by Pimentel (1961). This model considered the interaction between an evolvable plant population and a genetically static herbivore population. Pimentel used a one-locus, two-allele model for the diploid plant population, with the proportion of *A* alleles in the population given by p and the proportion of *a* alleles given by q. The reproduction rates of the herbivore were assumed to depend on the plant genotypes on which the animals fed. With R_p being the number of offspring resulting from an herbivore feeding on an *AA* plant, R_{pq} being the number of offspring resulting from an herbivore feeding on an *Aa* plant, and R_q being the number of offspring resulting from an herbivore feeding on an *aa* plant, the change in the herbivore population, N, over time was given by $N_{t+1} = p^2R_pN_t + 2pqR_{pq}N_t + q^2R_qN_t$. This equation demonstrates that the plant population's genetic makeup influences herbivore density in the model.

Selection pressure on the plant population was assumed to consist of two components. One selection pressure originated from the "environment," independent of the herbivore population. This pressure was formulated in terms of survival probabilities with $(1 - S_p)$, $(1 - S_{pq})$, and $(1 - S_q)$ being the survival probabilities of plant genotypes *AA*, *Aa*, and *aa*, respectively, in the absence of the herbivore. The second selection pressure originated from the herbivore population alone, with survival probabilities of the plants given by $(1 - N/b)$, $(1 - N/c)$, and $(1 - N/d)$ on genotypes *AA*, *Aa*, and *aa*, respectively, where b, c, and d were chosen constants and N was the size or density of the herbivore population. Thus, by construction, herbivore density influenced selection in the plant population. Under these selection pressures, the proportion of all plants of genotype *AA* at the time of reproduction was therefore given as $p^2(1 - S_p)(1 - N/b)/G$, the proportion of plants of genotype *Aa* as $2pq(1 - S_{pq})(1 - N/c)/G$, and the proportion of plants of genotype *aa* as $q^2(1 - S_q)(1 - N/d)/G$, where G is the total number of plants surviving until reproduction. Assuming random mating of the plant population, the proportion of *A* alleles (and *a* alleles) in the next generation could be written as a function of these survival probabilities, showing that in this model, selection indeed influenced genetic makeup.

This model therefore exhibits eco-evolutionary feedbacks, with density influencing selection, selection influencing genetic makeup, and genetic makeup in turn influencing density (Pimentel 1961). However, the simplicity that makes this model an elegant proof-of-concept eco-evolutionary model suffers from two main limitations in terms of its applicability to natural systems. The first limitation of the model is that the dynamics of the herbivore population are to an unrealistic extent driven by the genetic makeup of the plants. Decades of ecological research indicate that factors other than the genetic characteristics of populations are also likely to influence population dynamics. These include abiotic environmental factors (e.g., rainfall and temperature variability) and biotic interactions (e.g., predation and intra- and interspecific competition), both of which can affect the birth and death rates of organisms and thereby regulate population sizes. In other words, although "evolution" can influence "ecology," "ecology" will also surely influence "ecology."

The second limitation of Pimentel's eco-evolutionary model is its phenomenological structure. This is most readily apparent in the two terms that provide the selection pressures on the plants. The products of these two terms, for example, $(1 - S_p)(1 - N/b)$, provide the survival probabilities for the plant genotypes immediately prior to reproduction and therefore quantify the genotypes' fitness values. Although this formulation may be amenable to parameterization in the case of laboratory experiments, a model with this phenomenological structure would be difficult to parameterize for a natural system, where empirically measured quantities usually reflect the combined effect of both types of selection pressures.

More recent eco-evolutionary models circumvent these above limitations. Specifically, dynamical systems models, now pervasive in the ecological modeling literature, can be used to mechanistically express the effect that certain ecological processes, both biotic and abiotic, can have on populations of interest (i.e., how "ecology" affects "ecology"). These ecological models can be augmented with models of evolution such that selection pressures also arise mechanistically rather than phenomenologically. To illustrate the structure of these eco-evolutionary models, we briefly review two simple approaches originally presented

by Abrams and Matsuda (1997) and refer to these approaches in the three examples we later provide. We note here that neither of these approaches uses an adaptive dynamics framework. This is because adaptive dynamics, although it considers the effect of ecological dynamics on the invasibility of mutant phenotypes (and therefore considers how density affects selection pressures), is not an appropriate approach for studying eco-evolutionary dynamics; the framework assumes a separation of timescales, with evolution occurring at timescales that are too long to feed back onto ecological dynamics (Champagnat et al. 2006).

The first approach is to treat the phenotype as a continuous quantitative trait whose mean changes dynamically with ecological dynamics. One takes an ecology-only model, assumes that one or more of the parameters of this model are affected by the phenotype under consideration, and based on fitness considerations, derives an equation for the evolutionary dynamics of the mean phenotype. This equation is simulated or mathematically analyzed alongside the equation governing the ecological dynamics. Using prey evolution in a predator-prey system for illustration, Abrams and Matsuda (1997) provide an example of this approach. The ecological dynamics are given by

$$\frac{dP}{dt} = b(g(CN)CN)P, \tag{1a}$$

$$\frac{dN}{dt} = [r(C) - f(N) - g(CN)CP]N. \tag{1b}$$

Here P is the predator density, and N is the prey density. The per capita reproduction rate of the predator, b, is assumed to increase with the amount of captured prey, given by the term $g(CN)CN$, where C quantifies the vulnerability of the prey, CN is the average prey availability, and $g(CN)$ is a function specifying how the capture rate depends on prey availability. The prey's per capita reproductive rate depends on the prey's intrinsic growth rate r (a function that is assumed to increase with prey vulnerability C), negative density dependence specified in the function f, reflecting competition for resources, and the rate at which prey are captured by predation, $g(CN)CP$. The evolutionary dynamics of mean prey vulnerability, the phenotype under consideration, can then be written as

$$\frac{dC}{dt} = V\left[\frac{dr}{dC} - g(CN)P\right], \tag{1c}$$

where V is additive genetic variance and the term in brackets is the selection gradient, which is appropriately defined as the derivative of fitness with respect to the evolving trait. The fitness of an organism is generally defined as its per capita reproduction rate, so the selection gradient in the above example is given by $(dr/dC) - g(CN)P$. We point the reader to Abrams and Matsuda (1997) for more details, including assumptions implicit in this quantitative genetics model formulation.

A second, alternative approach to modeling eco-evolutionary dynamics mechanistically is to partition out distinct phenotypic subpopulations, letting the subpopulations' sizes be governed by separate equations. The population of interest thereby evolves by virtue of changes in the relative frequencies of these subpopulations. Again, Abrams and Matsuda (1997) provide an illustrative predator-prey example:

$$\frac{dP}{dt} = b(g(C_1N_1 + C_2N_2) \times (C_1N_1 + C_2N_2))P, \tag{2a}$$

$$\frac{dN_1}{dt} = [r(C_1) - f(N_1 + N_2) - g(C_1N_1 + C_2N_2)C_1P]N_1, \tag{2b}$$

$$\frac{dN_2}{dt} = [r(C_2) - f(N_1 + N_2) - g(C_1N_1 + C_2N_2)C_2P]N_2, \tag{2c}$$

where P is again the size of the predator population and N_1 and N_2 are the sizes of the two prey subpopulations, each having their own discrete (and constant) vulnerability phenotype, C_1 and C_2, respectively. In equation (2), the sum $C_1N_1 + C_2N_2$ represents prey availability and plays the same role as CN did in equation (1). The two prey populations are governed by the same dynamics as in equation (1), with intrinsic growth rates, negative density dependence, and predation affecting their dynamics.

Both equations (1) and (2) consider the eco-evolutionary dynamics of prey evolution in a coupled predator-prey system. They are, therefore, similar to the type of interactions modeled by Pimentel, in which the phenotype of the resource is able to evolve in a coupled consumer-resource system. However, the two approaches outlined by Abrams and Matsuda (1997) have several advantages over Pimentel's formulation. First, they mechanistically incorporate processes that impact ecological dynamics other than the genetic makeup of the prey population. For example, the size of the predator population is modulated by prey density and foraging behavior, while the size of the prey population is modulated by consumption by the predator and density-dependent factors. The role of abiotic factors, although not explicitly incorporated into the models, could easily be considered by their effect, for example, on the strength of density dependence in the prey population. The inclusion of biotic and abiotic processes that

impact ecological dynamics thus addresses the first limitation of applying Pimentel's model formulation to natural systems. Second, the selection pressures on the evolving trait are defined in terms of ecological dynamics, either directly through the selection gradient in the case of the continuously evolving trait or implicitly through their effect on phenotypic frequencies in the case of population subdivision. This contrasts with Pimentel's more phenomenological treatment of selection pressures. Trade-offs associated with the evolving trait are also explicit: prey growth rates (r) are assumed to be higher when prey are more vulnerable. Taken together, the explicit mechanistic expression of ecological dynamics, selection pressures, and trade-offs addresses the second limitation of Pimentel's model.

Three Examples of Evolution's Influence on Ecological Dynamics

The additional ecological processes that can be incorporated into mechanistic eco-evolutionary models, though important, have the potential to obscure the impact of evolution on population dynamics in natural settings. We illustrate this with three examples of eco-evolutionary dynamics: the first brought about by virulence evolution, the second brought about by host resistance evolution, and the third brought about by antigenic evolution. However, when combined with empirical data, these same models are starting to be effectively used to identify the occurrence (and expected occurrence) of eco-evolutionary dynamics in nature as illustrated by recent studies.

Virulence Evolution

Our first example of eco-evolutionary dynamics in nature considers the evolving trait of pathogen virulence, commonly defined by the rate of disease-induced mortality. Virulence evolution is a widely studied topic in infectious disease, with theoretical treatments of the trait being based on trade-offs, an approach first introduced by Anderson and May (1982). Using none other than the rabbit myxoma virus system as their motivating example, Anderson and May suggested that, though high virulence threatens the long-term survival of the pathogen by harming the host, low virulence might increase the rate of recovery and consequently reduce the number of opportunities to infect new hosts (virulence-recovery trade-off) or decrease the transmission efficacy of the pathogen (virulence-transmission trade-off). If virulence is positively correlated with traits that are beneficial to pathogen reproduction, then it is possible that the level of virulence that maximizes fitness is at an intermediate value.

Although Anderson and May's work inspired an area of theoretical research that remains active to this day (Frank 1996; Dieckmann 2002; Day and Proulx 2004; Bolker et al. 2010), there are still few, if any, well-documented empirical examples of virulence evolution other than the rabbit myxoma virus system (Ebert and Bull 2003). Empirical support exists for a virulence-transmission trade-off, in particular in spore-transmitting (Agnew and Koella 1997; Jensen et al. 2006; de Roode et al. 2008) and vector-borne (Mackinnon and Read 1999, 2004; Ferguson et al. 2003; Chapuis et al. 2012) pathogens for which transmission proxies are relatively easy to quantify, as well as in human immunodeficiency virus (HIV; Fraser et al. 2007; for reviews, see Alizon et al. 2009 and Froissart et al. 2010). However, the functional form of the virulence-transmission trade-off, which is necessary to parameterize models, is difficult to determine from these data (Ebert and Bull 2003; Alizon et al. 2009; Froissart et al. 2010).

Despite the lack of empirical data on the form of virulence-related trade-offs, it remains the most popular and well-characterized theoretical approach for modeling the evolutionary dynamics of virulence (Day and Proulx 2004; Bolker et al. 2010). We therefore consider an eco-evolutionary model for virulence evolution under the assumption of a virulence-transmission trade-off. We use a simple variation of a quantitative genetics model developed and analyzed by Bolker et al. (2010) to simulate the dynamics of an emerging pathogen. The model is given by

$$\frac{dS}{dt} = B - \beta(\alpha)SI - \mu S, \tag{3a}$$

$$\frac{dI}{dt} = \beta(\alpha)SI - (\mu + \alpha)I, \tag{3b}$$

where S and I are the susceptible and infected host populations, respectively, B is a constant birth rate, μ is the per capita death rate, α is the disease-induced mortality rate (virulence), and β is the transmission rate. The model does not have a recovered class—infected individuals die either from natural causes (at rate μ) or from the disease itself (at rate α). The transmission-virulence trade-off is modeled by assuming that transmission increases with virulence according to $\beta(\alpha) = c\alpha^{1/\gamma}$, where c is a positive constant and $\gamma > 1$ controls the extent of the transmission-virulence trade-off. A large value of γ implies a rapid saturation of transmission benefit from virulence, while a γ close to 1 implies that transmission increases close to linearly with virulence. With these ecological dynamics, the evolutionary dynamics of virulence are given by

$$\frac{d\alpha}{dt} = V\left(S\frac{d\beta}{d\alpha} - 1\right) = V\left(S\frac{c}{\gamma}\alpha^{(1/\gamma)-1} - 1\right), \tag{3c}$$

where, as described above, V is the additive (or, in this

case, clonal) genetic variance and the expression in parentheses is the selection gradient.

By definition, equation (3) specifies a model with eco-evolutionary dynamics. The expression for the rate of change of virulence (eq. [3c]) reflects how ecology, or, more specifically, population density, influences evolution: at high susceptible host densities, there is selection for increased virulence, while at low susceptible densities, there is selection for reduced virulence (fig. 1*a*). Changes in mean virulence levels feed back to change the density of susceptible hosts. This feedback occurs both directly, through a change in the rate at which susceptible hosts are infected (fig. 1*b*), and indirectly, through a change in the transition rates into and out of the infected host class (fig. 1*c*). The latter leads to changes in the number of infected hosts, which in turn affect the rate at which susceptible hosts become infected. Evolution, therefore, influences ecology, completing the eco-evolutionary feedback loop.

This eco-evolutionary interplay can result in epidemiological dynamics that quantitatively differ from those arising from an ecology-only model in which virulence cannot evolve. As an example, we consider the invasion dynamics of a highly virulent virus (such as the myxoma virus) into a naive host population (fig. 1*d*–1*f*). Virulence evolution leads to two main differences. The first difference is a more rapid initial increase in infected hosts (fig. 1*e*). This occurs because evolutionary changes in virulence levels act to maximize the growth rate of infected hosts (eq. [3c]). In this case, a lower level of virulence is optimal for the initial density of susceptible hosts; virulence, therefore, decreases (fig. 1*f*) and the per capita growth rate of infected hosts ($(dI/dt)/I$) rapidly increases. Then, through eco-evolutionary feedback, this change in virulence, by its influence on the exponential increase in the number of infected hosts, leads to a decrease in the number of susceptible hosts. Once appreciable, the lower number of susceptible hosts results in virulence evolving a second time, again toward lower levels (fig. 1*f*). This leads to a second difference: once the disease is endemic in the population, the density of susceptible hosts when virulence can evolve is lower than when it cannot (fig. 1*d*). This is because equilibrium virulence maximizes the pathogen's basic reproduction number R_0 (Day and Proulx 2004), and because the fraction of susceptible hosts at equilibrium is given by $1/R_0$, the ability for virulence to evolve will always result in a lower equilibrium number of susceptible hosts.

Although figure 1*d*, 1*e* shows that models with and without virulence evolution yield different epidemic dynamics, it is not the case that if presented with time series of infected individuals, one could easily identify the occurrence of eco-evolutionary feedbacks in the case when they are present. The more rapid rise in cases and the lower equilibrium susceptible host density are both consistent with a higher value for R_0. An alternative ecology-only model with a higher R_0—either through a higher transmission coefficient β or a lower virulence α—would yield similar dynamics (fig. 1*d*–1*f*). Epidemic dynamics under eco-evolutionary feedback may, therefore, look quantitatively similar to those arising from a purely ecological process. Furthermore, under both ecology-only and eco-evolutionary scenarios, the number of infected individuals increases initially at an exponential rate and then levels off to an endemic equilibrium due to an ecological factor: resource limitation, that is, depletion of susceptible hosts. Compared to the role this ecological factor plays in the dynamics, the role of evolution can easily be overlooked.

Although evolution's effect might be more subtle, mechanistic mathematical models can be used to address the impact virulence evolution might have on disease dynamics. For example, a model similar to the one given by equation (3) was used by Bolker and coauthors to investigate whether the high virulence observed in emerging pathogens was due to the inherently higher virulence of novel pathogens or whether it could instead be the result of a transient increase in virulence driven by eco-evolutionary dynamics (Bolker et al. 2010). The authors were able to partially parameterize their model using independent estimates from emerging pathogens, including severe acute respiratory syndrome (SARS), HIV, West Nile virus, and myxoma virus. This parameterization included empirical data on pathogen virulence, basic reproduction numbers, shapes of transmission-virulence trade-off curves, and levels of genetic variation. Combining these data with their model, they found that virulence could transiently double in pathogens with moderate levels of genetic variation, high transmissibility, and high virulence at equilibrium. Equally important, they found that virulence eco-evolutionary dynamics were unlikely to occur under alternative parameterizations. Their work therefore helps to identify natural systems in which eco-evolutionary dynamics might occur, as well as ones in which their presence is unlikely.

Host Resistance Evolution

Our second example of eco-evolutionary dynamics is one that considers the evolving trait of host resistance. The topic of resistance evolution has received a large amount of empirical as well as theoretical consideration over the past several decades, focusing not only on host-pathogen systems (Antonovics and Thrall 1994; Bowers et al. 1994; Boots and Haraguchi 1999; Gandon et al. 2002; Restif and Koella 2004; Miller et al. 2005; Laine 2006; Boots et al. 2009) but also on herbivore-plant systems (Pimentel 1961; Simms and Rausher 1987; Fritz and Simms 1992; Fineblum

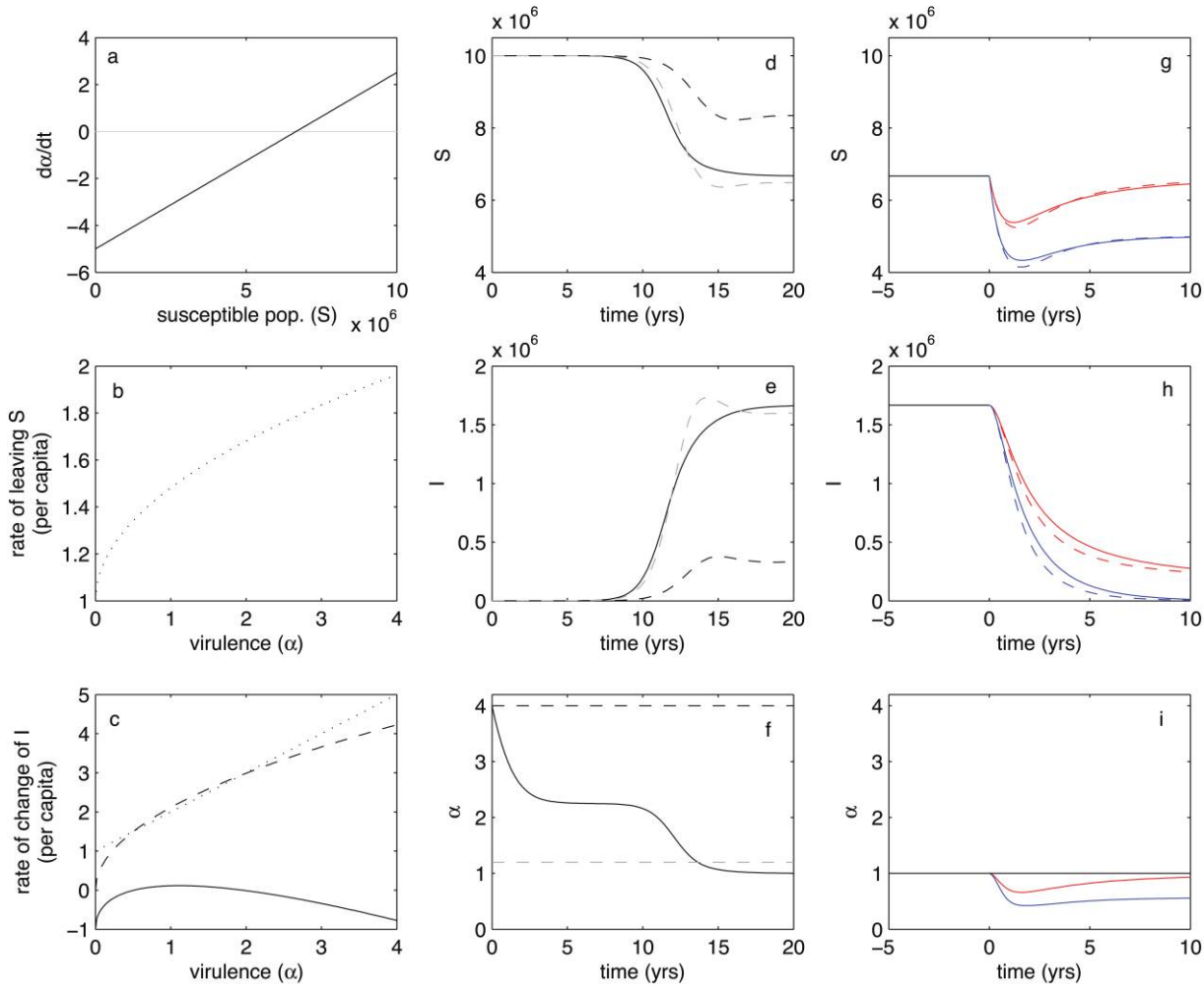

Figure 1: Eco-evolutionary dynamics with virulence evolution. *a*, Ecology influences evolution: the rate of change of virulence ($d\alpha/dt$) depends on the number of susceptible hosts S (solid line). The relationship is linear, given by equation (3c). The gray line shows where the level of virulence stays constant ($d\alpha/dt = 0$). Virulence α will increase from its current level (assumed to be 1.06 year^{-1}) if the number of susceptible hosts is above 6.8×10^6 and decrease if the number of susceptible hosts is below this value. *b*, *c*, Evolution influences ecology. *b*, The per capita rate at which hosts leave the susceptible class ($\beta(\alpha)I + \mu$) depends on the pathogen's virulence α. For this plot, we fix the number of infected hosts I at 1.6×10^6. *c*, The per capita rate of change of infected hosts ($(dI/dt)/I$; solid line) also depends on the pathogen's virulence α. This per capita rate is given by the difference in the per capita rate at which hosts enter the infected class ($\beta(\alpha)S$; dashed line) and the per capita rate at which hosts leave the infected class ($\mu + \alpha$; dotted line), both of which depend on virulence α. For this plot, we fix the number of susceptible hosts S at 6.8×10^6. *d–f*, Disease dynamics arising from eco-evolutionary interactions (solid lines) compared to those arising from ecology-only models: (i) with the same initial conditions and parameterization as the eco-evolutionary model but without the possibility for virulence evolution (dashed black lines) and (ii) parameterized to mimic infection dynamics of the eco-evolutionary model (dashed gray lines). *d*, The number of susceptible hosts S over time. *e*, The number of infected hosts I over time. *f*, Virulence levels α over time. Initial conditions for the simulations shown in *d–f* are $S(0) = 1.0 \times 10^7$, $I(0) = 1$, and $\alpha(0) = 4$ year^{-1}, with the exception of the mimicking ecology-only dynamics, which have $\alpha(0) = 1.2$ year^{-1}. These mimicking dynamics have $c = 3.1 \times 10^{-7}$. *g–i*, Effects of a vaccination strategy in an eco-evolutionary system with virulence evolution (solid lines) and in an ecology-only system (dashed lines). Red lines show a vaccination strategy that is below the eradication threshold, with $p = 0.3$. Blue lines show a vaccination strategy that is above the eradication threshold, with $p = 0.5$. The vaccination strategy starts at time 0, when the disease is endemic in the population, with $S(0) = 6.7 \times 10^6$, $I(0) = 1.7 \times 10^6$, and $\alpha(0) = 1$. *g*, The number of susceptible hosts over time. *h*, The number of infected hosts over time. *i*, Virulence levels over time. Epidemiological and evolutionary parameter values for all subplots unless otherwise stated are $B = 10^7$ year^{-1}, $c = 3 \times 10^7$, $\gamma = 2$, and $\mu = 1$ year^{-1}. Variance $V = 5$ for the eco-evolutionary simulations, while we set $V = 0$ for the ecology-only simulations, resulting in no virulence evolution.

and Rausher 2002) and predator-prey systems (Abrams 2000). Many of the empirical examples consider how ecological interactions have shaped the selection pressures for resistance evolution to occur but assume that evolution acts on slower timescales than ecological dynamics such that a reciprocal feedback is not considered. Similarly, the majority of the theoretical research on resistance evolution assumes this separation of timescales (Bowers et al. 1994; Boots and Haraguchi 1999; Miller et al. 2005), with adaptive dynamics approaches frequently being used to predict evolutionary outcomes.

Resistance evolution in host-pathogen systems can occur through a variety of different mechanisms. These include avoidance of infection, a more rapid recovery to infection, and tolerance (Boots and Bowers 1999). Each of these mechanisms affects population dynamics differently, with avoidance evolution impacting the pathogen's transmission rate, recovery evolution impacting the rate at which infected individuals clear the pathogen, and tolerance evolution impacting the rate of disease-induced mortality. The occurrence and direction of resistance evolution can therefore depend on the particular mechanism by which resistance is assumed to act (Boots and Bowers 1999). Here we consider the dynamics of resistance evolution where resistance to a pathogen is through avoidance of infection. The model we use is again a simple variant of one already existing in the literature and studied in detail by Duffy and colleagues in a number of articles (Duffy and Sivars-Becker 2007; Duffy and Hall 2008; Duffy et al. 2009). The model's ecological dynamics of susceptible and infected hosts are given by

$$\frac{dS}{dt} = B - \mu S - \beta SI, \tag{4a}$$

$$\frac{dI}{dt} = \beta SI - (\mu + \alpha)I, \tag{4b}$$

where B is the constant birth rate into the host population, μ is the background mortality rate of hosts, β is the transmission rate, and α is the disease-induced mortality rate. As in Duffy and Sivars-Becker (2007), the evolving trait of host resistance is interpreted in terms of the transmission rate β, with higher levels of host resistance corresponding to lower values of β. As in the previous example of pathogen virulence, host resistance is assumed to be a quantitative trait. Fitness of hosts is maximized by maximizing the growth rate of susceptible hosts. With these assumptions, the evolutionary dynamics of host resistance are given by

$$\frac{d\beta}{dt} = -VI, \tag{4c}$$

where V is the host's genetic variance.

Equation (4) satisfies Pimentel's definition of an eco-evolutionary system. Ecology influences evolution via equation (4c): the rate of host resistance evolution depends on the density of infected hosts, with host resistance evolving more rapidly when a higher number of infected individuals are present (fig. 2*a*). However, unlike in the previous example of virulence evolution, the model given by equation (4) does not assume a trade-off. This is why higher host resistance always has a fitness advantage, reflected in $d\beta/dt$ always being negative (fig. 2*a*). Evolution also has a reciprocal influence on ecology in this system. Specifically, higher levels of host resistance (lower β) always increase the growth rate of susceptible hosts by lowering the per capita rate at which they become infected (fig. 2*b*) and always lower the growth rate of infected hosts (fig. 2*c*) by making transmission occur less frequently (while not affecting the rate at which infected hosts recover or die from the disease).

We now consider how the dynamics of the system might be different if host resistance could not evolve. This question has been previously addressed by Duffy and Hall (2008) with a slightly more complicated version of this model, and we reproduce their results here with the model specified by equation (4). Parameterized with initial conditions for an epidemic to occur, figure 2*d*–2*f* shows total host population sizes, infected population sizes, and mean transmission rates, respectively, over time with and without evolution in play. Compared to the dynamics arising from the ecology-only model, host population sizes stay relatively constant when eco-evolutionary dynamics are in play (fig. 2*d*). The reason for this relatively constant total host population size can be understood by looking at the magnitudes of the epidemics: the epidemic arising in the eco-evolutionary system is much smaller than the one arising in the system without host resistance evolution (fig. 2*e*). This leads to less disease-induced mortality and, consequently, a less variable population size for the eco-evolutionary system. The reason for the smaller epidemic size in the eco-evolutionary system is directly due to host resistance evolution (fig. 2*f*), which rapidly occurs as the number of infected hosts increases (fig. 2*e*). In fact, host resistance evolves to such a high level that the reproductive rate of the pathogen falls below 1, resulting in the termination of the epidemic (fig. 2*e*). In the model without resistance evolution, the pathogen instead is able to become endemic, with births replenishing the susceptible population.

Figure 2*d*–2*f* clearly shows that the interplay between ecology and evolution results in a qualitative difference in epidemic dynamics: epidemics terminate in the eco-evolutionary system, whereas the disease becomes endemic in the ecology-only system. Although one can argue that the role of evolution in this natural system should therefore

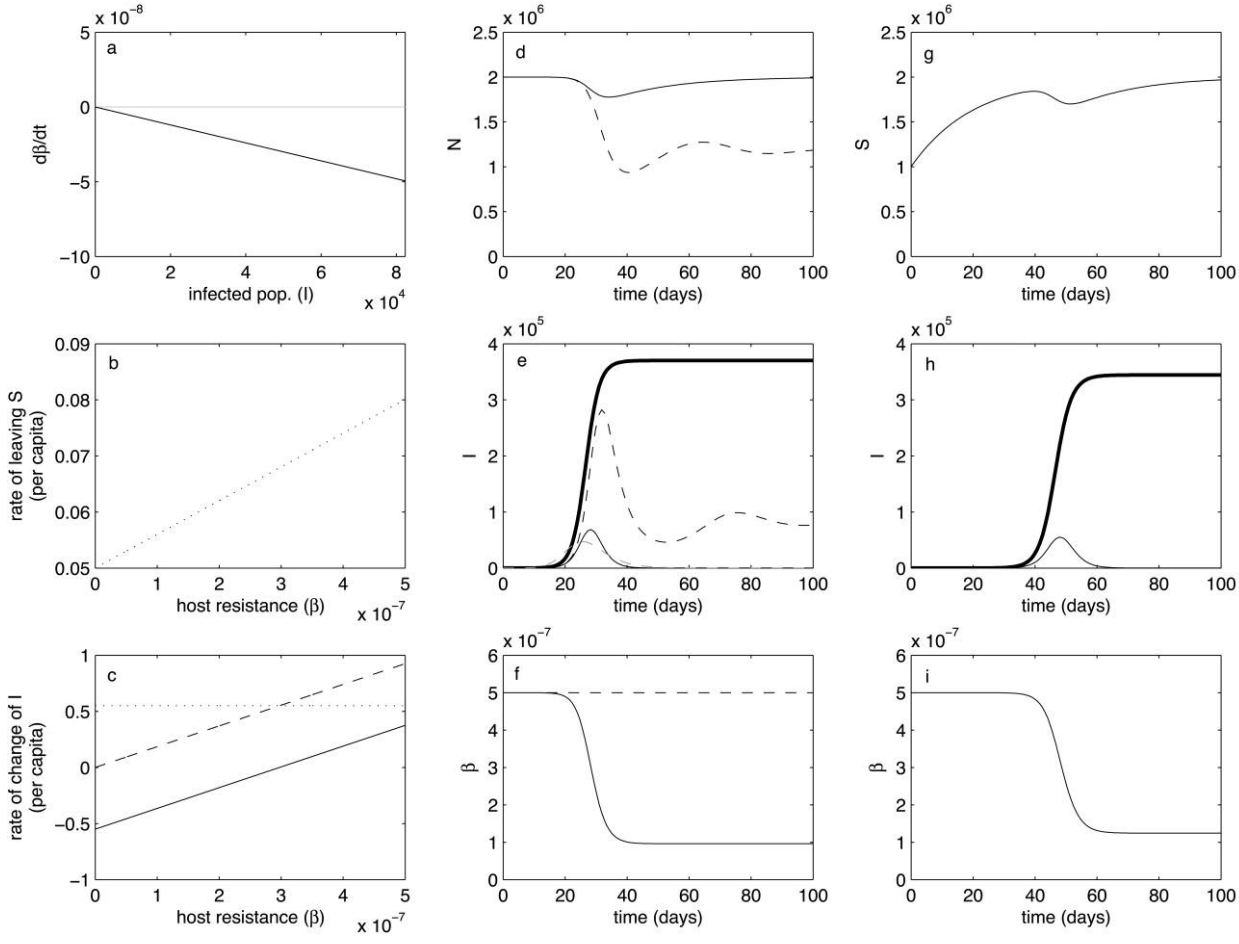

Figure 2: Eco-evolutionary dynamics with host resistance evolution. *a*, Ecology influences evolution: the rate of change of host resistance ($d\beta/dt$) depends on the number of infected hosts I (solid line). The relationship is linear, given by equation (4c). The gray line shows where the level of host resistance would stay constant ($d\beta/dt = 0$). Host resistance will always increase from its current level but will evolve more rapidly (toward smaller β) when there are a large number of infected hosts present. *b*, *c*, Evolution influences ecology. *b*, The per capita rate at which hosts leave the susceptible class ($\beta I + \mu$) depends on host resistance, parameterized in terms of the transmission rate β. For this plot, the number of infected hosts I is assumed to be 6.0×10^4. *c*, The per capita rate of change of infected hosts ($(dI/dt)/I$; solid line) depends on the level of host resistance, which is inversely related to β. This per capita rate is given by the difference in the per capita rate at which hosts enter the infected class (βS; dashed line) and the per capita rate at which hosts leave the infected class ($\mu + \alpha$; dotted line). Only the former depends on host resistance, parameterized by β. For this plot, the number of susceptible hosts S is assumed to be 1.8×10^6. *d–f*, Disease dynamics arising from eco-evolutionary interactions (solid lines) compared to those arising from ecology-only models: (i) with the same initial conditions and parameterization as the eco-evolutionary model but without the possibility for resistance evolution (dashed black lines) and (ii) parameterized to mimic infection dynamics of the eco-evolutionary model (dashed gray line). *d*, The size of the population N over time, where N is given by the sum of susceptible hosts S and infected hosts I. *e*, The number of infected hosts I over time. The bold black line shows cumulative disease incidence for the eco-evolutionary epidemic. *f*, Host resistance, parameterized by β, over time. Evolution toward lower β reflects the evolution of host resistance. Initial conditions for the simulations shown in *d–f* are $S(0) = 2.0 \times 10^6$, $I(0) = 1$, and $\beta(0) = 5 \times 10^{-7}$ day^{-1}, with the exception of the mimicking ecology-only dynamics, which have $\beta(0) = 7.37 \times 10^{-7}$ day^{-1}. These mimicking dynamics have $B = 26{,}000$ day^{-1}. *g–i*, Effects of a mass vaccination strategy in an eco-evolutionary system with host resistance evolution. Vaccination of 50% of the population occurs at time 0. Immediately following vaccination, $S(0) = 6.7 \times 10^6$, $I(0) = 1.7 \times 10^6$, and $\beta(0) = 5 \times 10^{-7}$ day^{-1}. *g*, The number of susceptible hosts over time. *h*, The number of infected hosts over time. The bold black line shows cumulative disease incidence for the epidemic. *i*, Host resistance evolution over time. Epidemiological and evolutionary parameter values for all subplots unless otherwise stated are $B = 10^5$ day^{-1}, $\alpha = 0.5$ day^{-1}, and $\mu = 0.05$ day^{-1}. Variance $V = 6.0 \times 10^{-13}$ for the eco-evolutionary simulations, while we set $V = 0$ for the ecology-only simulations, resulting in no host-resistance evolution.

be easy to identify, there are many ecological processes that could instead be invoked that would similarly lead to the termination of an epidemic (Duffy and Sivars-Becker 2007; Duffy et al. 2009). Two of the most likely explanations are a decrease in the number of susceptible hosts over time and transmission rates that decline over time due to ecological factors. The former would arise if susceptible hosts were not replenished sufficiently fast; for example, an ecology-only model with a lower birth rate B but a higher transmission rate produces quantitatively similar dynamics to the eco-evolutionary model (fig. 2*d*). The latter could arise if the transmission rate β were dependent upon external environmental conditions such as temperature changes that occurred over an epidemic season. Thus, even though the result of evolution in this example is clearly toward greater host resistance and smaller epidemics, the role of evolution in shaping ecological dynamics could easily be overlooked in nature, where resource limitation and seasonal abiotic variation may produce the same effect and are known to commonly occur.

Akin to the example of virulence eco-evolutionary dynamics, mechanistic models have also started to be used to assess the occurrence of resistance eco-evolutionary dynamics in nature. Most notably, Duffy et al. (2009) have illustrated how these types of eco-evolutionary models can be statistically interfaced with epidemic data. By analyzing infection data from *Daphnia dentifera*, an aquatic crustacean host, in the presence of its yeast pathogen, the authors sought to determine whether the termination of five observed yeast epidemics were more likely to be due to seasonality (affecting the transmission rate) or to rapid resistance evolution in the *Daphnia* host. By sequentially considering three alternative discrete-time models, they found that rapid evolution of host resistance was a more likely explanation for the observed infection data than temperature-driven changes in transmission rates alone. Their analysis, however, could not reject the possibility that resistance evolution and temperature changes acted together to curb the yeast epidemics. A second study illustrating the use of mechanistic models in finding subtle eco-evolutionary dynamics in nature is one by Elderd et al. (2008), who investigated the causes of seasonal outbreaks in gypsy moth populations by studying their interactions with a viral pathogen. They found that a model where heterogeneity in host resistance, or infectious risk, was allowed to evolve yielded dynamics that were both qualitatively and quantitatively more consistent with observed data than an ecology-only model.

Antigenic Evolution

Our third and final example of eco-evolutionary dynamics considers antigenic evolution. Pathogens exhibiting antigenic variation fall broadly into two categories: those, such as cholera and dengue, that consist of antigenically distinct, cocirculating strains that persist in a population over time and those for which antigenic variants appear de novo. The majority of pathogens in this latter category are RNA viruses with high mutation rates (Grenfell et al. 2004; Moya et al. 2004; Holmes and Grenfell 2009), with influenza viruses providing one of the most well-documented examples (Earn et al. 2002; Nelson and Holmes 2007). As well as being a topic of intense theoretical interest to disease ecologists (Gog and Grenfell 2002; Ferguson et al. 2003; Koelle et al. 2006, 2011; Boni 2008), antigenic evolution is also a prime example of eco-evolutionary feedback driven by frequency-dependent selection.

Antigenic evolution is naturally described in the context of Pimentel's genetic feedback mechanism. In a multivariant system, hosts infected with distinct antigenic variants compete for resources: susceptible hosts. However, these susceptible hosts are not common to all variants. While naive hosts are susceptible to all variants, some hosts can recover from and have full immunity against one antigenic variant while being partially or fully susceptible to another. In a manner akin to niche differentiation, different variants may therefore have access to different but overlapping subsets of resources, with the amount of overlap determined by the level of cross-immunity between variants. Epidemiological dynamics then dictate that these resources change in response to changes in variant frequency. A variant that becomes abundant necessarily depletes its susceptible host population. This decline in hosts susceptible to the abundant variant decreases the variant's growth rate and correspondingly increases the relative fitness of more rare variants.

Here we explicitly illustrate how this feedback mechanism operates in a theoretical model of antigenic evolution by considering a status-based model (Gog and Grenfell 2002) with two antigenic variants (or strains):

$$\frac{dS_1}{dt} = \mu(N - S_1) - \beta\frac{S_1}{N}I_1 - \sigma\beta\frac{S_1}{N}I_2, \tag{5a}$$

$$\frac{dI_1}{dt} = \beta\frac{S_1}{N}I_1 - (\nu + \mu)I_1, \tag{5b}$$

$$\frac{dS_2}{dt} = \mu(N - S_2) - \beta\frac{S_2}{N}I_2 - \sigma\beta\frac{S_2}{N}I_1, \tag{5c}$$

$$\frac{dI_2}{dt} = \beta\frac{S_2}{N}I_2 - (\nu + \mu)I_2, \tag{5d}$$

where S_i and I_i are the populations of hosts susceptible and infected with strain i, respectively, where $i \in \{1, 2\}$. The parameter μ is the birth and death rate, β is the transmission rate, σ is the probability that infection with

one variant confers full immunity to the other variant, and ν is the recovery rate. N is the size of the total population, which is assumed to be constant.

Unlike the previous two examples, the above model does not consider the evolvable phenotype as a quantitative trait. Instead, as in the second approach outlined by Abrams and Matsuda (1997), the system's evolutionary dynamics occur by changes in phenotypic frequencies, in this case, strain frequencies. Modeling antigenic evolution in this way is more common because antigenic strains are frequently considered discrete classes of a pathogen that do not fall along a continuum of some quantitative trait. To compare the relative fitness of one strain against another, we first define a strain's effective reproduction number as

$$R_i = R_0 \frac{S_i}{N}, \tag{5e}$$

where the basic reproduction number R_0 is defined as the ratio $\beta/(\nu + \mu)$. This effective reproduction number is simply a rescaling of our usual measure for pathogen fitness, the per capita growth rate of individuals infected (in this case, with strain i). With this characterization of absolute fitness, and assuming that one of the strains (say, strain 1) is endemic in the population, the selective advantage of a mutant species (say, strain 2), should it arise, increases linearly with the size of its susceptible host population (fig. 3*a*) so that

$$s = R_2 - R_1 = R_0 \frac{S_2}{N} - 1. \tag{5f}$$

From this equation, we can see how ecology, in this case the number of hosts susceptible to the mutant variant, would influence evolution through modulating selection pressures. Once a mutant variant arises, its relative frequency in the population, $p_2 = I_2/(I_1 + I_2)$, will impact epidemiological dynamics. Specifically, a higher relative frequency of the mutant variant leads to a higher total incidence rate (fig. 3*b*). Evolution, described by changes in phenotype frequencies, thus affects ecological dynamics.

As in the previous two examples, we again consider whether there are appreciable differences that arise in epidemic dynamics between systems with and without evolutionary feedback. We first extend the above model to reflect more realistic viral dynamics by including multiple strains, seasonal changes in the transmission rate, and waning immunity to any particular strain and track viral strain structure over time using a previously published "phylodynamic" model for influenza A/H3N2 (Koelle et al. 2010). Simulations of this eco-evolutionary model result in disease dynamics that show a transient rise in the number of infected hosts during the invasion of a new variant, with otherwise seasonal, but somewhat variable, epidemics (fig. 3*c*). The fraction of hosts susceptible to each dominant mutant variant is shown in figure 3*d* and, in conjunction with figure 3*a*, indicates how the selection pressures for new variants change over time. Invariably, when a new variant arises, it has a higher selective advantage than the resident variant. It therefore generates more infections than the resident variant, driving the resident variant to extinction. Although these disease dynamics are generated by an antigenic evolution model that incorporates eco-evolutionary feedback, their general pattern is also consistent with a susceptible-infected-recovered-susceptible (SIRS) model with some interannual variation in seasonal forcing (Greene et al. 2004; fig. 3*e*). In this case, movement of recovered (and immune) individuals back to the susceptible class in the SIRS model could reflect waning of immunity rather than pathogen evolution per se, and we can therefore interpret this latter model as an ecology-only model. Interannual variation in seasonal forcing, brought about by abiotic phenomena such as El Niño/Southern Oscillation (ENSO), North Atlantic Oscillation, or other smaller-scaled climate effects, is known to play a role in the transmission dynamics of many pathogens (Pascual et al. 2000; Rodó et al. 2002; Koelle et al. 2005; Baeza et al. 2011), including influenza (Viboud et al. 2004).

Presented with these two possible explanations of the same epidemic dynamics, how can we identify whether eco-evolutionary dynamics are involved? Here our approach to this question differs from our earlier two examples, in which we argued that independent parameterization of models or their statistical interface with epidemiological data could shed light on whether the dynamics arose from the interplay between ecology and evolution. In this example, we suggest that the answer can instead lie in patterns present in the systems' evolutionary dynamics, specifically the pathogen's genetic diversity over time and in the shape of its phylogeny. In the ecology-only SIRS model, once a pathogen is endemic in a population, its standing genetic diversity will be relatively stable (fig. 3*f*) as long as the epidemiological dynamics do not have substantial population bottlenecks. Consistent with this pattern, a phylogeny inferred from the model simulation shown in figure 3*e* shows sustained levels of genetic diversity through time (fig. 4*a*). These evolutionary dynamics are representative of diseases that are known to be antigenically stable, such as measles (Grenfell et al. 2004). In contrast, in the case where antigenic variants arise via de novo mutations, pairwise genetic diversity is more variable and lower on average (fig. 3*f*). Overall genetic diversity is maintained at a lower level than in the ecology-only SIRS case because new variants arise and sweep through the population before the previous variant

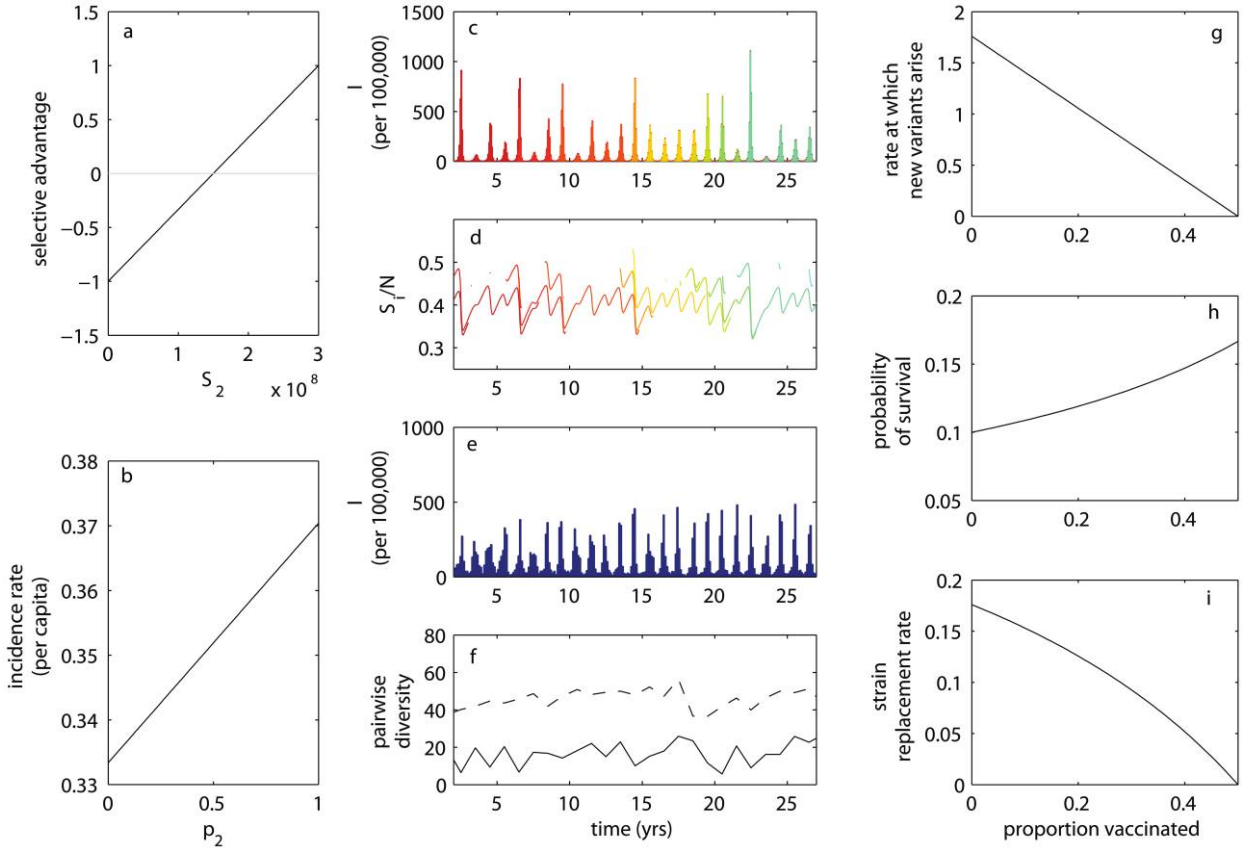

Figure 3: The eco-evolutionary dynamics of antigenic evolution. *a*, Ecology influences evolution: the selective advantage of a mutant strain (strain 2) depends on the number of susceptible hosts available to it, S_2 (solid line). The gray line shows where the mutant's selective advantage is zero. *b*, Evolution influences ecology: the per capita daily incidence rate of infected hosts, given by $\beta(S_1/N)I_1 + \beta(S_2/N)I_2$, depends on the frequency of the mutant strain, p_2. This can be seen by rewriting the total incidence rate as $[\beta(S_1/N)(I_1/I_1 + I_2) + \beta(S_2/N)(I_2/I_1 + I_2)](I_1 + I_2)$. Substituting p_2 for $(I_2/(I_1 + I_2))$ and $(1-p_2)$ for $(I_1/(I_1 + I_2))$, the per capita incidence rate of infected hosts becomes $\beta[(S_1/N)(1 - p_2) + (S_2/N)(p_2)]$. Here we have fixed the value of S_1 at 1.5×10^8 and the value of S_2 at 1.67×10^8. *c*, *d*, Epidemiological dynamics arising from a phylodynamic SIRS model with punctuated immune escape and seasonality, described in Koelle et al. (2010). Colors correspond to distinct antigenic strains. *c*, The number of infected hosts (per 100,000) over time. *d*, The fraction of hosts susceptible to infection by each antigenic strain. *e*, The number of infected hosts (per 100,000) over time for an ecology-only SIRS model driven by seasonality and the multivariate ENSO index, per Greene et al. (2004). The average duration of immunity is assumed to be 4 years with otherwise identical parameters to those used in subplot *c*. *f*, Pairwise genetic diversity for the eco-evolutionary model, whose epidemiological dynamics are shown in *c*, *d* (solid line), and for the ecology-only SIRS model, whose epidemiological dynamics are shown in *e* (dashed line). *g*, The rate at which new strains arise through de novo mutation as a function of the proportion of births vaccinated. The rate is given by mI_1, where the resident strain I_1 is at its equilibrium number in the vaccinated population and the rate at which new antigenic strains arise is assumed to be 10^{-4} strains per year. *h*, The probability that a new strain survives stochastic extinction, given by $1 - 1/(R_0(S_2/N))$. *i*, The rate, per year, at which strains turn over in the population, given by the product of the curves shown in subplots *g* and *h*. Parameter values for all subplots are life span $1/\mu = 70$ years, duration of infection $1/\nu = 3$ days, $R_0 = 2$, $\beta = R_0(\mu + \nu)$, cross-immunity between antigenic strains $\sigma = 0.8$, and population size $N = 3 \times 10^8$.

has accumulated many mutations or reached a stable level of genetic diversity. These diversity patterns are also evident in the model's simulated phylogeny, showing "ladder-like" evolutionary dynamics (fig. 4*b*). This ladder-like structure of the phylogeny is a hallmark of antigenically evolving viruses such as influenza A/H3N2 (Grenfell et al. 2004; fig. 4*c*).

As with the previous examples, we have a case where similar epidemic dynamics can be reasonably explained in terms of either an eco-evolutionary model or an ecology-only model. However, here we have shown that the evolutionary dynamics (characterized by patterns of genetic diversity and viral phylogenies) generated by these two candidate models are fundamentally different. By comparing the evolutionary dynamics arising from these phylodynamic models against those that can be inferred from

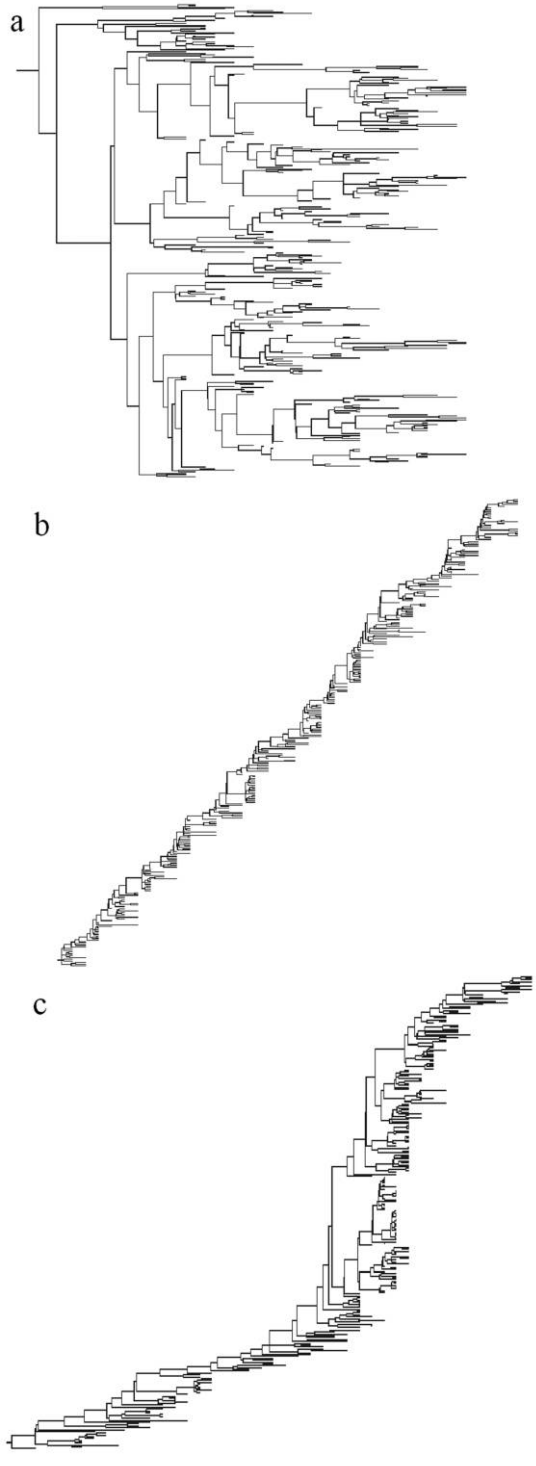

Figure 4: Viral phylogenies: *a*, Phylogeny reconstructed from viral sequences simulated by the ecology-only SIRS model driven by seasonality and the multivariate ENSO index. *b*, Phylogeny reconstructed from viral sequences simulated by the eco-evolutionary SIRS model with antigenic evolution. *c*, Phylogeny inferred from influenza A/H3N2's hemagglutinin protein. Dates of sequences in all subplots span 30 years.

viral sequence data, the occurrence of eco-evolutionary dynamics can therefore be more readily identified in nature. This example therefore not only illustrates the utility of using mechanistic models to assess competing explanatory theories but also highlights the effect of eco-evolutionary dynamics on an alternative source of data: a population's genetic makeup. With advances in sequencing technologies, this source of data is likely to become increasingly important for identifying the occurrence of eco-evolutionary dynamics in nature.

Implications of Eco-Evolutionary Dynamics for Population Control

In the above three examples, we argued, in agreement with Pimentel, that the course of evolution in influencing ecology in natural eco-evolutionary systems may indeed be obscured by other ecological processes, be they abiotic or biotic. If this is the case, is it necessarily important to isolate the true underlying mechanism? Here we return to our three examples to illustrate how knowing the underlying process generating the observed dynamics is indeed important in an applied context, namely, in the design of vaccination strategies.

In our first example of virulence evolution, we consider the introduction of a continuous vaccination strategy into a population where the disease is endemic. With a fraction of births p into the population becoming vaccinated, the dynamics of susceptible hosts become $dS/dt = B(1 - p) - \beta(\alpha)SI - \mu S$, where $B(1 - p)$ is the lower rate of susceptible replenishment due to vaccination. In the absence of evolution, the infected population decreases more rapidly than if the dynamics of the system were eco-evolutionary (fig. 1*h*). This is because virulence levels of the pathogen evolve to maximize pathogen fitness (fig. 2*i*). The direction in which virulence will evolve following the initiation of the vaccination strategy will always be toward lower virulence in this example. This is because vaccination will have the (possibly transient) effect of lowering the number of susceptible hosts, and optimal virulence levels are lower when the number of susceptible hosts is lower (fig. 2*a*). With this example, we can consider two vaccination rates leading to qualitatively different epidemiological and evolutionary dynamics. When vaccination rates are below the eradication threshold, both the susceptible host population and virulence will return to prevaccination equilibrium levels after a transient decrease, while the density of infected hosts experiences a permanent decrease (fig. 2*g*–2*i*). When vaccination rates are above the eradication threshold, the decreases in the susceptible host population and virulence persist as the pathogen is eliminated from the population (fig. 2*g*–2*i*). Although the vaccination strategies we consider yield slower declines of the

infected population when eco-evolutionary dynamics are in play (compared to when only ecological dynamics are present), these strategies also result in at least a transient decrease in pathogen virulence. This latter result is consistent with a previous theoretical study in which a vaccine that induces infection-blocking immunity is expected to cause pathogen evolution toward lower virulence (Gandon et al. 2001). However, this and other theoretical studies have also found that vaccination may induce an increase in virulence, depending on the target of vaccination (Gandon et al. 2001) and on the form of the trade-off curve (Medlock et al. 2009). These studies, as well as the one provided here, show that eco-evolutionary dynamics alter both the ecological and evolutionary expectations of the effect of a vaccination strategy. Identifying the occurrence of eco-evolutionary dynamics in nature when virulence can evolve is therefore important from a public health perspective. The differences in evolutionary outcomes (toward higher or lower virulence) between these studies also indicate that understanding the details of the eco-evolutionary system is important for correctly predicting dynamical outcomes, rather than just recognizing the existence of the dynamic interplay.

In our second example of host resistance evolution, we instead consider a mass vaccination strategy in which a fraction of the population is vaccinated at a single point in time. In this case, we can imagine that a public health official believes that previous seasons' epidemics terminated from a depletion of susceptible hosts—a purely ecological cause. Under this impression, the official predicts that mass vaccinating the population above a critical vaccination threshold of $p = 1 - 1/R_0$ at the beginning of the season would stave off this year's epidemic. However, if the termination of the epidemic was brought about by host resistance evolution, this mass vaccination strategy would not have this desired effect. Instead, susceptible hosts would be replenished through births (fig. 2*g*), and the epidemic would simply be delayed from previous years (fig. 2*h*). As in previous years, resistance would evolve over the time course of the epidemic (fig. 2*i*), such that differences in cumulative incidence would be negligible (fig. 2*h* vs. fig. 2*e*). Recognizing that the termination of observed epidemics could be a consequence of eco-evolutionary dynamics is therefore again important from a public health perspective.

In our third and final example of antigenic evolution, we again assume a continuous vaccination strategy, with a fraction p of incoming births becoming vaccinated. We assume the vaccine provides full protection against the resident variant and partial protection against the mutant variant. This strategy leads to a modification of the susceptible dynamics in equation (5a), (5c):

$$\frac{dS_1}{dt} = \mu((1 - p)N - S_1) - \beta\frac{S_1}{N}I_1 - \sigma\beta\frac{S_1}{N}I_2, \quad (6a)$$

$$\frac{dS_2}{dt} = \mu((1 - \sigma p)N - S_2) - \beta\frac{S_2}{N}I_2 - \sigma\beta\frac{S_2}{N}I_1, \quad (6b)$$

while leaving the equation for the dynamics of infected hosts as before. Vaccination impacts antigenic evolution in two ways. First, by reducing the total number of infected individuals, vaccination decreases the rate at which new mutant variants arise (fig. 3*g*). Second, vaccination increases the equilibrium number of hosts susceptible to the mutant variant, thereby increasing the probability that a new variant survives stochastic extinction should it occur (fig. 3*h*). The overall effect of vaccination on the rate at which antigenic variants emerge and replace one another is the product of these two factors (fig. 3*i*). For our parameterization, this calculation indicates that the benefit of vaccination extends beyond simply decreasing the number of currently infected hosts; vaccination has the additional effect of reducing the rate of antigenic evolution. This result is echoed in a recent study that found that a broad-spectrum influenza vaccine could potentially decrease the rate of antigenic evolution as well as decrease disease incidence (Arinaminpathy et al. 2012). Because peaks in incidence occur in years with strain turnover (fig. 3*c*), recognizing the interplay between ecology and evolution in the case of antigenically evolving viruses therefore enables us to anticipate changes in the disease's interannual variability brought about by vaccination, an effect that would not be present if the epidemiological dynamics were driven by climatic factors.

Discussion

The interplay of ecological and evolutionary dynamics has been called the "Newest Synthesis" in Schoener's (2011) recent review of the topic. Although this interplay was recognized by Pimentel 50 years ago (Pimentel 1961, 1968), its importance is still largely an open question because there are still few examples that convincingly demonstrate the occurrence of eco-evolutionary dynamics in nature. Here we have argued that this lack of convincing natural examples does not necessarily reflect the absence of these dynamics in nature. Rather, the role of evolution in influencing ecological dynamics in natural eco-evolutionary systems is likely obscured by the ubiquity of ecological processes that concomitantly affect these dynamics. Our ability to arrive at convincing natural examples of eco-evolutionary dynamics may therefore be hampered by our inability to detect natural systems that exhibit it.

Although this point may initially seem discouraging, we also argued that mechanistic models will prove instru-

mental in isolating examples in which eco-evolutionary dynamics are likely to occur and cases in which the role of eco-evolutionary feedback can be statistically supported over ecology-only models. We further highlighted several recent research studies that have been able to successfully isolate eco-evolutionary dynamics in natural host-pathogen systems, despite the role of evolution being partially obscured by the impact of other ecological processes. We know of one other study outside of host-pathogen systems that has done the same: Shertzer et al.'s (2002) work on identifying eco-evolutionary dynamics in a laboratory predator-prey system. The publication dates of these studies attest to the novelty of this approach in the field of eco-evolutionary dynamics and indicate that this research program is well under way.

A particularly instructive example of how mechanistic models can be used to illuminate the impact of evolutionary forces on ecological dynamics comes from a predator-prey laboratory system studied by Yoshida et al. (2007). In their study, the authors found that population densities of rotifer predator and algae prey grown in chemostats exhibited no statistical signs of trophic interaction between the two species, despite this predator-prey system being well established and studied. Algal populations remained relatively constant, while rotifer population density cycled. Here is a system, then, where the ecological data do not display any evidence of ecological interaction, let alone eco-evolutionary dynamics. The researchers use a mathematical model to demonstrate how such population dynamics can be generated with two phenotypically distinct prey subpopulations, each experiencing predator-prey oscillations and fluctuating in frequency but whose sum remains relatively constant. The constancy of this sum, arising from rapid evolutionary dynamics, illustrates that population dynamics can be "cryptic." The eco-evolutionary underpinnings of such a system, with its constant population size and an inapparent ecological interaction between the two organisms, would be nearly impossible to detect in a less studied natural system.

While Yoshida et al.'s (2007) study highlights the importance of theoretical approaches for identifying hidden interplays of ecological and evolutionary dynamics, other approaches, not considered in the examples above, are also worth mentioning. One is the Geber method, which can be used to determine whether evolutionary dynamics are rapid enough to affect ecological dynamics, a requisite for eco-evolutionary feedback (Hairston et al. 2005; Ellner et al. 2011). In systems where the ecological impact on evolutionary variables is well understood, such an approach can be applied to assess the role of evolution on ecology, thereby closing the feedback loop. In this case, mechanistic models will still be useful for understanding the implications of this dynamic interplay and to correctly anticipate the effects of changes (including those brought about by control strategies) on dynamics.

Assessing whether eco-evolutionary dynamics or pure ecological dynamics occur in a system is a special case of a general model selection problem: choosing between alternative plausible processes that produce quantitatively similar patterns. The field of eco-evolutionary dynamics may therefore benefit from approaches successfully applied to this problem in related fields. In particular, theoretical ecologists have used mechanistic models to select between alternative ecological processes that give rise to population cycles (Kendall et al. 1999) and a range of other ecological dynamics (Turchin 2003). A more recent example comes from disease ecology where researchers used a novel statistical inference method to assess the likelihood of alternative mechanistic models (King et al. 2008). All of these examples illustrate effective approaches for model selection that interface mechanistic models with empirical data. Although the identification of eco-evolutionary dynamics involves evolutionary dynamics in addition to ecological dynamics, to the extent to which these methodologies apply to general dynamical systems models, they are transferable to the field of eco-evolutionary dynamics.

Finally, we remark that when Pimentel first proposed his genetic feedback mechanism, it was as a hypothesis to explain the observed stability of population sizes, an important question for ecologists at that time. Since then, more mechanistic models have demonstrated that eco-evolutionary feedbacks need not always lead to more stable population dynamics; they can be destabilizing (Abrams 2000) and even chaotic (Ferrière and Gatto 1993). The interest in eco-evolutionary dynamics remains, however, and a more fundamental question still needs to be answered: How relevant are eco-evolutionary dynamics to our understanding of the natural world? Here we have argued that through a synthesis of theoretical approaches and empirical research, the set of convincing examples from nature will expand and with it our ability to understand, predict, and control our environments. To this end, mechanistic models will prove instrumental in identifying the presence of eco-evolutionary dynamics.

Acknowledgments

We thank S. Ellner, D. N. Reznick, and two anonymous reviewers for their helpful comments and D. N. Reznick for the opportunity to speak at the eco-evolutionary dynamics symposium at the 2011 Evolution meeting. This work was funded by National Science Foundation grant NSF-EF-08-27416 and by a James S. McDonnell Foundation grant to K.K.

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Symposium Editor: David N. Reznick