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The Evolution of Costly Resistance in Host-Parasite Systems

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ABSTRACT: Pairwise invadability analysis is used to examine the evolutionary dynamics of host resistance to microparasitic infection. A continuum of strains of the host differs in susceptibility to infection, with less susceptible strains paying a cost resulting in a lower intrinsic growth rate. With a combination of analytical and graphical pairwise invadability analysis, we show that the evolutionary outcome depends crucially on the shape of the constraint function between resistance and its assumed cost in intrinsic growth rates. When resistance is increasingly costly, a single evolutionarily stable strategy is predicted. Alternatively, with decreasingly costly resistance, we find that the hosts tend to be maximally resistant or not at all resistant. There are conditions under which dimorphism of both these types exists but intermediate resistances do not occur. Independently of the trade-off function used, we are always more likely to get resistant strains of the host when the carrying capacity of the host is high. The pathogenicity of the parasite is also important in determining the likelihood and degree of resistance.

Keywords: evolution, parasite, trade-offs, polymorphisms, resistance, strain.

Interest in the importance of parasites (including pathogens) to their host populations was stimulated by a number of theoretical studies, most notably those of Anderson and May (1979, 1981). Once relatively neglected in the ecological literature, this theoretical background has led to a proliferation of both theoretical and empirical studies of the roles of various parasites in diverse taxa (e.g., Levin and Pimentel 1981; Dwyer et al. 1990; Sait et al. 1994). Interest has been fueled further by the need to manage disease in animal and human populations (Anderson and May 1991) and by the use of diseases as control agents for pests (Payne 1988). Hosts are likely to vary in their relative resistance to parasites, and hence their evolution is also likely to be influenced by the parasite interaction, especially when the host "pays" a cost in another component of fitness for increased resistance (Boots and Begon 1993). An understanding of these evolutionary dynamics is clearly necessary both to understand the role of pathogens in ecological communities and to manage effectively disease in various applied contexts.

The question of evolution in host-parasite interactions has received some theoretical attention. In systems where the genetic basis of resistance to the pathogen is well understood, genetically explicit gene-for-gene models have been applied successfully (Levin 1983). Other models have tended to ignore explicit genetics and either to examine the evolution of the pathogen alone (Levin and Pimentel 1981; Frank 1992) or to have been coevolutionary (Lewis 1981; May and Anderson 1983; Beck 1984; Frank 1994). These models concentrate on trade-offs between transmission and virulence in the parasite or the coevolution between strains of the host and parasite that show strain-specific susceptibility or virulence.

Recently, two similar studies (Antonovics and Thrall 1994; Bowers et al. 1994) have considered the evolution of susceptibility in a host—with no acquired immunity—to a directly transmitted microparasite (pathogen) by using models analogous to two host/one pathogen models where the host species are replaced by a susceptible and a resistant strain of a single host. The basis of these studies is that the resistant strain pays a cost in its other life-history traits. This can be justified by evolutionary theory (Stearns 1992), since in the absence of such costs the resistant alleles would increase in the presence of disease and we would not find polymorphism in disease resistance (Gillespie 1975; Parker 1992). There are also empirical data (Boots and Begon 1993) that support the existence of costs, although demonstrating costs has often proved difficult (Fritz and Simms 1992).

Our main motivation in these studies was to investigate the conditions for stable polymorphism in host disease resistance in the presence of a genetically uniform pathogen. It was shown that coexistence of the two strains was more likely when the difference in resistance was large rather than small and that coexistence was possible over

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a wide range of costs, including situations where the costs were small. However, these models only consider two strains and, therefore, strictly "polymorphism" in this case is dimorphism. Both models found that resistance is most likely to evolve in productive hosts (those with the characteristics of many pest species), and Bowers et al. (1994) also showed that with highly pathogenic pathogens, the "susceptible" strain may exclude the "resistant" strain because its higher growth rate is more effective against the pathogen than reduced transmissibility.

By not allowing any strains of intermediate resistance, the models may bias the chance of coexistence. Resistance to pathogens is often a quantitative trait, with resistance to attack a graded response (Briese and Podgwaite 1985) and, therefore, more realistically modeled by considering a number of strains that vary in their resistance to the pathogen. When resistance is involved in a trade-off with other life-history traits, there will be a series of possible strains defined by the shape of the trade-off curve between the resistance and other life-history traits. This article will consider a multistrain model of host evolution in response to a genetically uniform microparasite. The approach is evolutionary, which is pragmatic in that it allows us to examine in detail one part of the coevolutionary process between hosts and their parasites, although there are natural systems where the parasite is believed to be genetically uniform (Antonovics and Thrall 1994). In addition, the approach has direct application to understanding the effect on pest species evolution of the inundative use of single strains of pathogens as biological pesticides. The evolutionary consequences of specific trade-off formulations will be considered and trade-off curves will be predicted from mechanisms of resistance.

The Model

We adopt a simple biological framework that corresponds broadly to those used by Antonovics and Thrall (1994) and Bowers et al. (1994), which allows us to make direct comparison to their work and to apply our results generally to a broad range of natural systems. We assume that the pathogen is a microparasite, and we do not, therefore, explicitly model pathogen numbers (Anderson and May 1981). The probability of healthy hosts becoming diseased is dependent on the density of infected hosts, corresponding to diseases where transmission is through random contact. We do not model frequency-dependent transmission and do not, therefore, explicitly examine sexually transmitted and vector-borne diseases. However, Antonovics and Thrall (1994) showed that the evolutionary outcomes of diseases characterized by frequency-dependent transmission were often comparable with those of density-dependent transmission. We assume no acquired immunity to infection and no recovery from infection and that infected individuals do not reproduce. In this way we focus, as did the previous models, on one possible route to disease resistance, avoidance of infection by reduced susceptibility to the disease. The model is, therefore, most applicable to invertebrate and plant diseases and less appropriate for vertebrate diseases characterized by such factors as acquired immunity. However, the general conclusions from this simple model may prove to be applicable to these more complex situations and will certainly provide a basis for comparison. One important group to which these models directly apply is the characteristically obligatory lethal larval diseases of insects, a group in which there is considerable interest because of their use as biological pesticides (Payne 1988).

We have a number of strains of a host that differ in their susceptibility to a directly transmitted pathogen. The model is haploid, but the results may also be applicable to diploid systems (Maynard Smith 1981; May and Anderson 1983; Frank 1994). The disease is invariably lethal (there is no recovery once an individual is infected), and infected individuals do not reproduce. We further assume that susceptibility to the pathogen is involved in a trade-off with other aspects of the host's biology that affect fitness (life-history traits). In this case we assume that relatively resistant host strains pay the price of reduced intrinsic rate of increase. The form that this trade-off takes will be explicitly modeled.

The system we have can be described in the following equations:

$$\frac{dX_i}{dt} = r_i X_i - q\left(\sum_{i=0}^{n} X_i + Y\right)X_i - \beta_i X_i Y, \tag{1}$$

$$\frac{dY}{dt} = \sum_{i=0}^{n} \beta_i X_i Y - \Gamma Y, \tag{2}$$

where X_i is the density and r_i is the intrinsic rate of increase of the ith healthy strain; β_i is the rate at which the pathogen is transmitted to the ith strain. The differences in r values between the strains depend on differences in birth rate. The strains share a common natural mortality rate that, along with disease-induced mortality (pathogenicity), gives rise to a single overall death rate of infected individuals, Γ. Density-dependent reduction in the population growth rate depends on the total density of all the strains and the infected individuals. There is a single coefficient determining susceptibility to crowding, q, which corresponds to r/K, where K is the carrying capacity. We assume that diseased individuals of all the strains transmit the

parasite equally and that the strains therefore share one single infected class of density, Y.

Analysis

We assume that resistance to the pathogen involves a cost such that a higher transmission rate, β (higher susceptibility), is associated with a higher intrinsic growth rate, r. The analytical study of the outcomes found with nonlinear trade-off functions (fig. 1) is difficult unless the value of the candidate evolutionarily stable strategy (ESS) can be determined numerically. Pairwise invadability plots provide a convenient and powerful graphical method of determining evolutionary outcomes (Metz et al. 1996; Geritz et al. 1997, 1998). The pairwise invadability plot (PIP) displays graphically the sign of the growth rate of a rare mutant (s_m) in an equilibrium population of a wild-type strategist. If this growth rate is positive, then the mutant will invade the resident strategist.

In figure 2, possible mutant transmission rates are on the vertical axis, while those of the resident strategy are on the horizontal axis and regions where the growth rate of the invading species is positive are shaded. On the main diagonal, the resident and mutant strains have the same phenotype, and therefore the marginal growth rate of the mutants is 0 ($s_m = 0$) by definition. The intersection of another curve where again the marginal growth rate of the mutant is 0 ($s_m = 0$) with the diagonal corresponds to what has been termed evolutionary singular (Metz et al. 1996; Geritz et al. 1997, 1998), which is a point at which a number of evolutionary outcomes are possible. At this point the marginal growth rate function attains either a local maximum or a local minimum and is therefore potentially an equilibrium point or an evolutionary repeller. It has been shown (Metz et al. 1996; Geritz et al. 1997) that there are eight possible configurations to the PIP at such points, and from these local configurations different evolutionary outcomes can be predicted. The eight possible configurations arise from combinations of four distinct evolutionary properties that, although not independent of each other, can arise in various combinations. Specifically, the potential equilibrium point may (or may not) when resident resist invasion by all other strains when they are rare (ESS); the potential equilibrium point may (or may not) be able to invade all other phenotypes when it itself is rare; resident phenotypes not at the potential equilibrium point may (or may not) be invaded by mutants closer to the potential equilibrium point (convergence stable; Christiansen 1991); and mutual invadability near to the potential equilibrium point may or may not be possible. Among the eight possible configurations, three main groups can be identified, leading to three evolutionary outcomes: points that lack convergence stability and therefore act as evolutionary repellers; points that are both evolutionarily and convergence stable ("continuously stable strategies" [CSH]; Eshel 1982) and therefore are the final outcome of evolution; and points that are convergence stable but not evolutionarily stable that, if evolution by local mutation is assumed, are approached through time by a monomorphic population and, once reached, a process of evolutionary branching (Metz et al. 1996; Geritz et al. 1997) occurs.

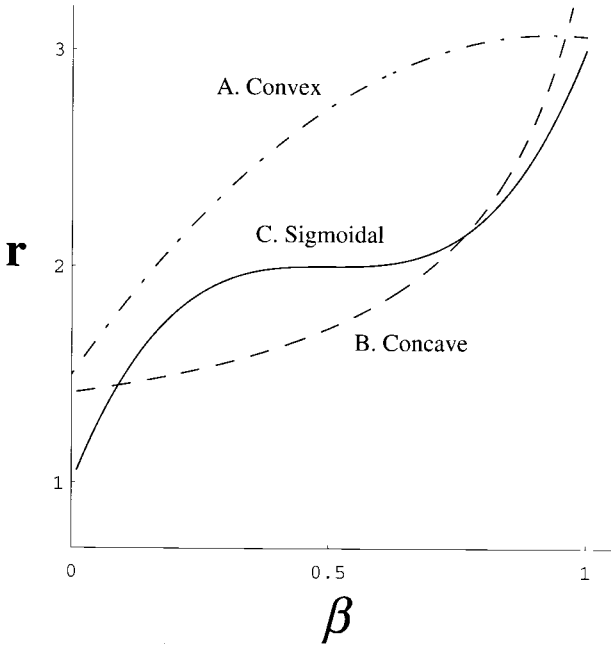

Figure 1: Host intrinsic growth (r) against pathogen transmission rate (β) illustrating the shapes of the (A) convex, (B) concave, and (C) sigmoidal trade-off curves referred to in the text.

Interpretation of pairwise invadability plots is simplified by examining three of the evolutionary characteristics individually. First, if a phenotype cannot be invaded when resident at the point (ESS) and the point is therefore an evolutionary trap, the vertical axis through the point will not be shaded (indicated by the line on fig. 2*B*). The horizontal axis determines whether a strain at the point can itself invade other strains when it is rare (indicated by the line on fig. 2*C*). If the horizontal axis is darkly shaded, the strain is able to invade all other strains when rare. Finally, whether the point is convergence stable (Eshel 1983) in that resident populations of nearby phenotypes can be invaded by mutants that are closer to the equilibrium point, is indicated by a shaded region immediately to the left of the diagonal, below the equilibrium point (residents lower than the point are invaded by those higher

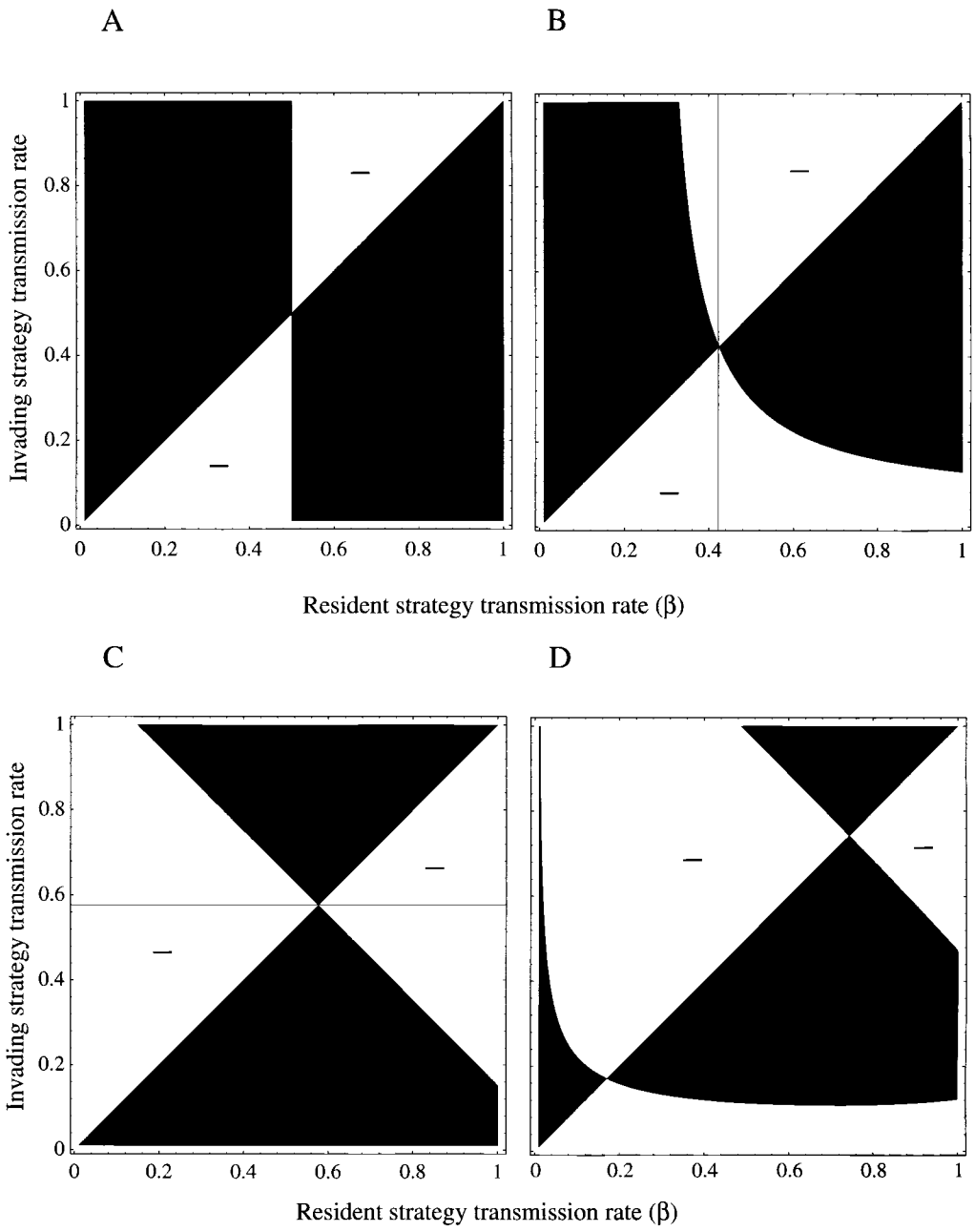

Figure 2: Pairwise invadability plots (PIP) where the transmission rates of invading phenotypes are on the vertical axis and those of the resident phenotypes are on the horizontal axis. The marginal growth rate of the invading mutant is positive in the shaded regions and negative in the unshaded regions. *A*, Linear trade-off function between r and β, such that $r = 2^*\beta + 0.012$, $q = 0.003$, $\Gamma = 1$. *B*, Convex trade-off such that $r = 1/[-2^*(\beta + 0.2)] + 2$ when $q = 0.05$ and $\Gamma = 15$. *C*, Concave trade-off such that $r = 1/[-1^*(\beta - 1.2)] + 0.01$; where $q = 0.05$ and $\Gamma = 0.05$. *D*, PIP from a sigmoidal trade-off curve such that $q = 0.003$; $\Gamma = 15$; $r = [2^*(\beta - 0.5)]3 - [2^*(-0.5)]3$.

and closer to it) and to the right of the diagonal above the equilibrium point (residents higher than the strategy are invaded by those lower and closer to it). Fundamentally, the convergence stability criteria determine whether a monomorphic population close to the point will move toward it, and the classical ESS condition determines whether a population at the singular strategy will stay there. In addition a singular strategy that can invade other residents when it is rare is more easily attained.

For simplicity, let us first assume that the trade-off is linear, such that

$$r_i = \mathrm{A}\beta_i + \mathrm{B}, \tag{3}$$

where A and B are constants. Then if $\mathrm{A}q - \mathrm{B}$ is negative, then we have a candidate ESS (β_c) at

$$\beta_c = -\frac{\Gamma}{\mathrm{A} - \frac{\mathrm{B}}{q}}. \tag{4}$$

Otherwise we get monomorphism of the most susceptible morph ($\beta_{\max}$). We can show analytically (appendix) that β_c is not what is usually termed evolutionarily stable (ESS) and will not, therefore, resist invasion when it is resident. We can also show that mutants closer to β_c than the resident phenotype can invade and that β_c can therefore be termed "convergent stable" (Eshel 1983). Since β_c is convergent stable, it is an evolutionary attractor and will tend to be approached in evolutionary time even though it is not evolutionarily stable. This emphasizes the point that evolutionary stability (whether a point is an evolutionary trap in that, once established, it cannot be invaded) and convergence (whether a point is approached in evolutionary time) are distinct properties that can occur in any combination. It should be noted that the marginal growth rate of strains near to β_c is close to 0, which means that β_c is close to "neutrally stable" and therefore β_c is approached very slowly. We can see that a high q, which corresponds to strong self-limitation in the host, will tend to make the evolution of resistance unlikely, since $\mathrm{A}q - \mathrm{B}$ is less likely to be negative. When the costs to resistance approach are minimal ($\mathrm{A} \to 0$), β_c approaches the lowest transmission rate at which the pathogen can be supported in the host population ($\beta_c \to \Gamma/K$, where K is the carrying capacity r/q). The PIP for the linear trade-off case (fig. 2*A*) confirms the analytical results showing the point to be convergent stable but not an ESS. The analysis is taken further by the PIP in that we can see that the point is evolutionarily attainable, in that a strategy at this point can invade other strategies when it is itself rare. Geritz et al. (1998) point out that, generally when there is such a linear relationship, once the point is reached, further mutations are neutral and, therefore, in this case no evolutionary branching can occur. Although not a true ESS, this point will in the end be the final outcome of the evolutionary process.

It is extremely unlikely that an exactly linear trade-off would occur in nature, and therefore we need to consider nonlinear trade-offs. Let us introduce nonlinearity such that

$$r_i = \frac{1}{\mathrm{A}(\beta_i - \mathrm{B})} + \mathrm{C}, \tag{5}$$

where A, B, and C are constants (fig. 1), the sign of which determines whether the curve is convex (fig. 1,*A*) or concave (fig. 1,*B*). The shape of the convex constraint curve (fig. 1,*A*) itself fixes a minimum β, while, in contrast, the concave curve (fig. 1,*B*) fixes a maximum β. However, it should be emphasized that in both cases possible strains are assumed to lie on the curve, and therefore the maximum and minimum β (and the corresponding intrinsic growth rates) are fixed arbitrarily in any case.

If we first assume that resistance is to some degree increasingly costly, producing a convex trade-off curve such that $\mathrm{A} < 0$, $\mathrm{B} < 0$, and $\mathrm{C} > 0$ (fig. 1,*A*), the PIP (fig. 2*B*) shows that the internal equilibrium point is an ESS (*vertical axis unshaded*), can itself invade all other strategies when it is rare (*horizontal axis shaded*), and is convergent stable. With these three conditions fulfilled, we can be confident that this point will be rapidly reached as the final outcome of evolution. Figure 3 shows how the ESS transmission rate depends on the infected death rate and the host's susceptibility to crowding. If q is low, corresponding to a host with a low susceptibility to crowding, the transmission rate is also low, corresponding to higher resistance (fig. 3*A*). Higher resistance (low β) will also occur when Γ is low (fig. 3*B*) and, therefore, more resistance is likely to develop in response to a less pathogenic pathogen.

If higher resistance is relatively less costly, we will have a concave trade-off curve such that $\mathrm{A} < 0$, $\mathrm{B} > 0$, and $\mathrm{C} > 0$ (fig. 1,*B*). In this case, we generally have no internal equilibrium (fig. 2*C*). The point is not an ESS, is not convergent stable, and is not attainable and, therefore, acts as an evolutionary repeller. If we assume that variation for resistance or evolution by global mutation is present, we get monomorphism of either the most or the least resistant strains or dimorphism of these two. The outcome is again parameter dependent, since as we increase Γ, we get, respectively, the most resistant morph alone or dimorphism between the most resistant and the most susceptible morphs followed by the most susceptible morph alone (fig. 3*C*). This same pattern of monomorphism giving way to dimorphism followed by monomorphism also occurs as we increase q. If we assume that evolution occurs by local

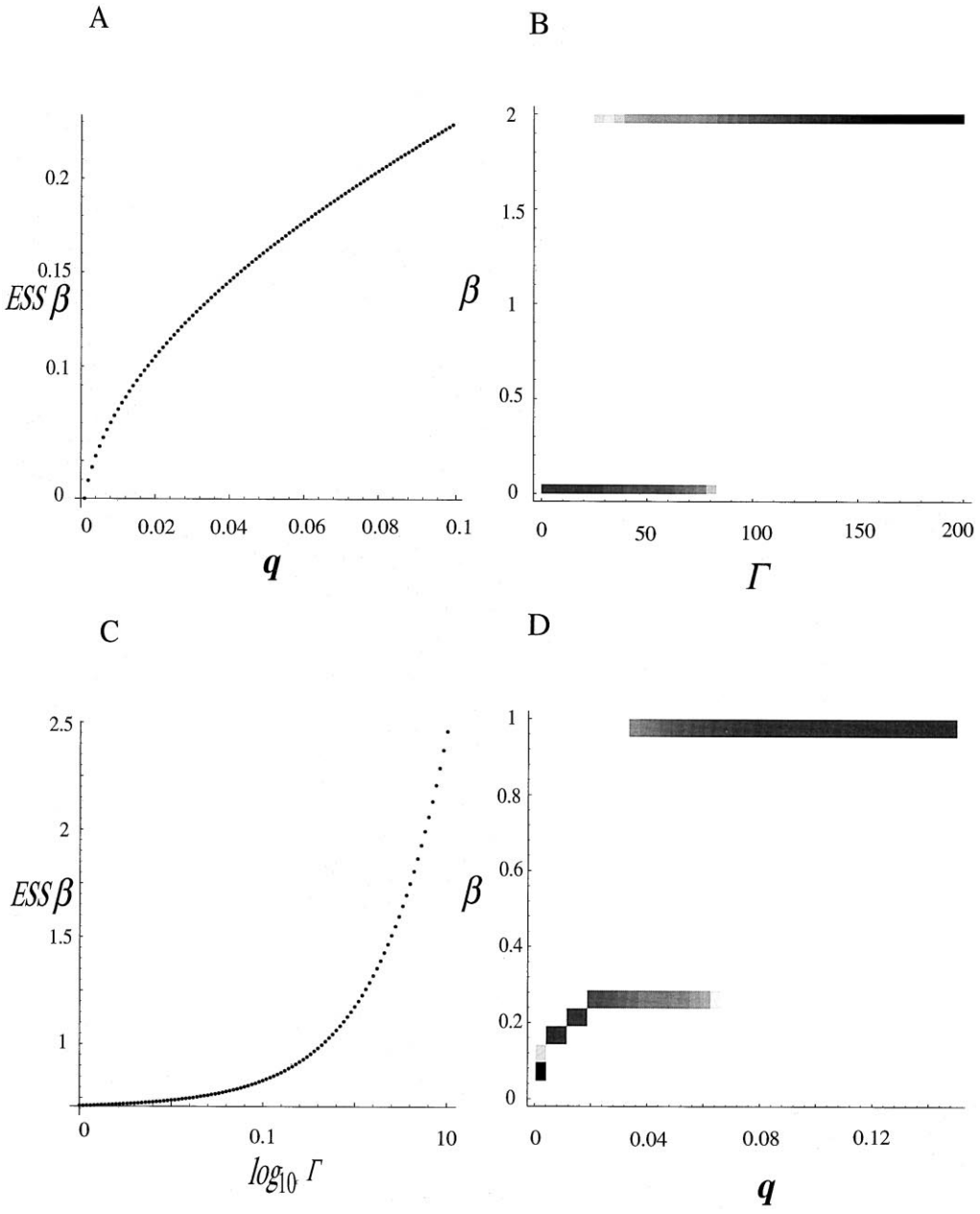

Figure 3: Values of evolutionarily stable (*ESS*) transmission rates against (*A*) q and (*B*) $\log_{10}\Gamma$, where the trade-off curve is convex such that $r = 1/[-2.0(\beta + 0.2)] + 2.5$, and in *A*, $\Gamma = 1$, while in *B*, $q = 0.05$. Density plots showing the equilibrium transmission rates (β) for a range of Γ (*C*) and q (*D*). The relative darkness of the shading indicates the relative population densities of the host. *C*, Trade-off function is concave, such that $r = 1/[-2.0^*(\beta - 2.2)] + 0.01$. *D*, Trade-off function is sigmoidal, such that $r = [2^*(\beta - 0.5)]3 - [2^*(-0.5)]3$.

mutation from an initial strain, we get the same pattern, except that in the previously dimorphic region we get monomorphism of either the most or least resistant morph, depending on which side of the evolutionary repeller the initial strain is found (fig. 4*A*, *B*).

There is, however, a distinct region with a concave constraint function in which the internal singular point is not an ESS but is convergence stable (appendix). In general, as we move from a concave to a convex trade-off curve, we have a "knife-edge" change from an evolutionary trap (ESS) to a phenotype that does not resist invasion by rare mutants at linearity, but there is a further region of weak

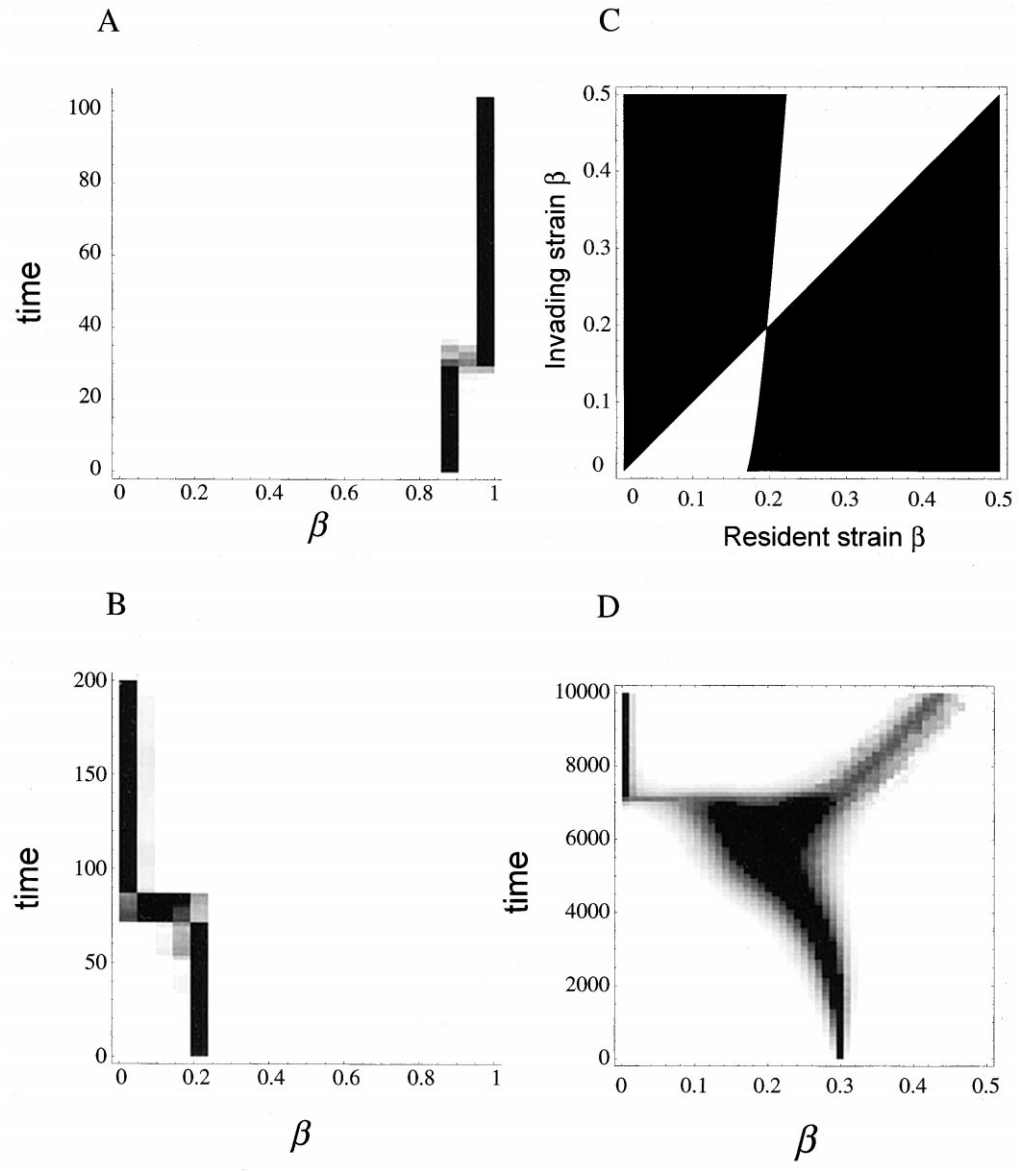

Figure 4: Density plots under the assumption of local mutation. *A*, *B*, Point (candidate ESS) is neither evolutionarily nor continuously stable, while *C* shows the PIP, when the point is continuously but not evolutionarily stable, which results in the density plot (*D*). *A*, *B*, Parameters are the same as in figure 2*B*, while in *C* and *D*, $\Gamma = 1.5$, $q = 0.001$ and $r = \beta^{1.007} + 0.01$.

concavity where the point is still convergent stable (table 1). In mutation-limited evolution, where small evolutionary steps are assumed, it has been shown (Geritz et al. 1997) that evolutionary branching of a previously monomorphic population occurs at singularities that are convergent stable but lack evolutionary stability (apart from in the case of exact linearity). Figure 4*D* illustrates this branching process in this model when the PIP (fig. 4*C*) shows the singular point to be convergent stable but not an evolutionary trap (ESS).

Discussion

Clearly, whether we expect an evolutionarily stable transmission rate, dimorphism at the extreme maximal, and minimally obtainable transmission rates depends critically on the shape of the trade-off curves found in nature. It is difficult and resource intensive to measure the shape of trade-off curves, generally involving selection or breeding designs in different environments (Stearns 1992). However, detailed knowledge of the mechanism of resistance

Table 1: Summary of the evolutionary characteristics of the potential equilibrium points with a trade-off function $f(x)$

	Convex	Concave	
	$f''(x^*) < 0$	$0 < f''(x^*) < \frac{q\Gamma}{(x^*)^2(q+x^*)}$	$f''(x^*) > \frac{q\Gamma}{(x^*)^2(q+x^*)}$
Unbeatable (ESS)	✓	X	X
Continuous (CSS)	✓	✓	X

Note: ✓ = yes; X = no.

in a particular host-parasite interaction may allow us to conjecture the shape of the trade-off curve.

For example, a primary form of defense against pathogens in insects is passive barriers such as the gut wall and the cuticle (Dunn et al. 1994), which effectively exclude the pathogen (Jouvanaz et al. 1996). We can assume a model in which the resistance of the insect increases in proportion to the thickness of components of the gut wall that provide a passive barrier to the entry of pathogens. A thicker gut requires more energy to produce and, therefore, will reduce the intrinsic reproductive rate. The energetic costs are likely, however, to be related to the costs of producing the entire volume of the gut wall. Clearly the volume and the thickness of the gut wall scale differently, and this can easily be shown to lead to a convex trade-off between β and r (fig. 1,*A*), with resistance becoming increasingly more costly. Since many insect pathogens are ingested, we might expect this form of trade-off curve to be common whenever the gut wall provides the major source of resistance. If infection often occurs via the cuticle, as in many fungal infections (Goettel et al. 1995), similar arguments would apply, and we might expect a similar shape to the trade-off curve.

Resistance through defense mechanisms that are costly to produce but, once produced, increase resistance over a large range at little additional cost would lead to resistance becoming increasingly less costly (a concave trade-off). However, it is unlikely that a mechanism occurs where resistance continues to become increasingly less costly indefinitely. More realistically, we might expect to reach a maximal efficiency, after which resistance again becomes increasingly costly, leading to a sigmoidal trade-off curve such as that shown in figure 1,*C*. However, PIP (fig. 2*D*) and simulation show that essentially the same results are found as with the simpler concave function. The minimum resistance level is a singular strategy fixed just after the costs to resistance again become high. The size of this ESS is not strongly affected by the size of Γ or q, but, rather, whether the ESS is reached, dimorphism occurs, or the most susceptible morph is found alone is dependent on the parameter values (fig. 3*D*). The sigmoidal shape effectively fixes the maximum resistance level internally.

We have shown that when polymorphism occurs, it is likely to be dimorphism between the two extreme strains: the most resistant and the most susceptible. This confirms the inference from previous work (Antonovics and Thrall 1994; Bowers et al. 1994) that dimorphism between two very similar strains is unlikely. Empirical data in natural and agricultural plant systems also suggest that variation is of an extreme nature (Kennedy and Barbour 1992; Parker 1992). There remains the possibility of internal dimorphism due to evolutionary branching when the trade-off curve is nearly linear and concave; however, simulations suggest that the final outcome in this case is also dimorphism of extreme types (fig. 4*D*). Internal polymorphism in the host with respect to quantitative resistance is, therefore, unlikely to be maintained by the host-pathogen interaction without changes in the pathogen.

However, dimorphism can only occur when the costs to resistance are decreasingly expensive at higher levels of resistance. In this case the hosts can also be maximally resistant or not at all, but intermediate resistances do not occur. In contrast, an evolutionarily stable, continuous, and attainable transmission rate will be favored in the host in response to a pathogen, when the resistance mechanism becomes increasingly more expensive. With a simple model, we have shown that resistance determined by the thickness of the gut wall of an insect, for example, may produce constraints of this form and therefore favor monomorphism in the host. This type of analysis can be applied to other systems where the mechanism of resistance is understood but the measurement of the constraint curve is impracticable.

If a natural population is dimorphic, the introduction of the pathogen as a biological pesticide may remove all the susceptible hosts quickly, leading to an apparently dramatic increase in the resistance of the population. Such populations would fail to fit standard dose-response models used to assess the resistance status of a population, such as probit analysis (Finney 1971). Failure of a population to fit dose-response models should lead to an examination of the pattern of resistance within the population, to determine whether the population is dimorphic.

Independent of the trade-off function used, we are always more likely to get resistant strains of the host when q, the relative resistance to crowding, is low. This is a

characteristic of pest species, the very species that may be subject to the use of pathogens as biological control agents. Furthermore, resistance to crowding (q), along with the intrinsic growth rate (r), determines the carrying capacity. As well as scaling the size of K, q can be viewed as a population's recovery rate, in that when q is low, the carrying capacity is large relative to r. Therefore, at low q, the population recovers to the carrying capacity more slowly from low densities. We have shown here that species with this low recovery rate would be expected to develop more resistance to their parasites.

We have confirmed the previous inference (Bowers at al. 1994) that the pathogenicity of the parasite is also crucial in determining the chance of evolving resistance. This shows that the costs are such that in response to a highly pathogenic strain of parasite, a susceptible host strain's higher reproductive rate is more beneficial than a resistant host strains avoidance of infection with the parasite. The host's evolutionary response to the parasite, therefore, may lie in characters other than those concerned directly with the transmission of the disease. This occurs since the density of infected individuals is higher when the parasite's pathogenicity is low, and therefore there is greater pressure to avoid infection. Highly pathogenic strains that may be desirable for inundative use as biological pesticides, since they reduce the time infected pests are still able to cause economic damage, may also, therefore, not cause as much resistance (in transmissibility) in their hosts as strains of intermediate pathogenicity. In classical biological control, however, pathogens of intermediate pathogenicity would still be favored due to their greater reduction of the host population size (Anderson and May 1981).

The multistrain approach used here has confirmed many of the conclusions of previous models (Antonovics and Thrall 1994; Bowers et al. 1994) that had limited themselves to considering two strains of the host. In addition, we have been able to show that a series of outcomes are possible, including monomorphism of either the most or the least resistant strains, dimorphism of these strains, or the evolution of an evolutionarily stable level of resistance to the pathogen. None of this information can be obtained from simpler two-strain models in which the only outcomes possible are monomorphism and "polymorphism." In particular, we have shown that dimorphism will only occur when the constraints are such that resistance becomes decreasingly costly. Future work needs to extend the work to increase the range of trade-offs and thereby consider other types of resistance such as reduced pathogenicity and increased recovery rates. Any such models will by necessity be complicated by the need for a multistrained infectious class in contrast to the single shared infectious class in this model.

Acknowledgments

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APPENDIX

Invadability and Stability Analysis

Let us consider the dynamics of a population that consists of a single susceptible class with intrinsic growth rate r and transmission rate β and an infected class. The dynamics of these are

$$\frac{dN}{dt} = rN - q(N + Y)N - \beta YN, \tag{A1}$$

$$\frac{dY}{dt} = \beta YN - \Gamma Y. \tag{A2}$$

If $r/q > \Gamma/\beta$ (the carrying capacity of the host is greater than the threshold density of the pathogen), the steady state $(N^*, Y^*) = [\Gamma/\beta,(r - q\Gamma/\beta)/(\beta + q)]$ is relevant and stable. Let us consider a mutant with different growth and transmission rates invading this infected steady state. If the density of the mutant n is much lower than that of the wild type, its dynamics are

$$\frac{dn}{dt} = [r_m - q(N^* + Y^*) - \beta_m Y^*]n, \tag{A3}$$

where r_m is the intrinsic growth rate of the mutant and β_m is its transmission rate. The marginal growth rate of a rare mutant against the wild-type population with (N^*, Y^*) is

$$\begin{aligned}\phi(\beta_m, r_m|\beta, r) &= r_m - q(N^* + Y^*) - \beta_m Y^* \\ &= r_m - r - \frac{(\beta_m - \beta)(r - q\Gamma/\beta)}{q + \beta}.\end{aligned} \tag{A4}$$

If equations (A4) are positive, the mutant will invade the wild population.

Let us consider a general trade-off function between the intrinsic growth rate and transmissibility, such that $r = \mathrm{f}(\beta)$. We denote a candidate ESS as x^* and the marginal growth rate of the mutant as $\phi(y|x)$, where x is the wild strain and y, the mutant strain. Then x^* satisfies

$$\frac{\partial \phi}{\partial y}(x^*|x^*) = \mathrm{f}'(x^*) - \frac{1}{q + x^*}\left[\mathrm{f}(x^*) - \frac{q\Gamma}{x^*}\right] = 0. \tag{A5}$$

Then the candidate ESS is the solution of equation (A5). If x^* is a local ESS, it satisfies $\phi(y|x^*) < \phi(x^*|x^*)$ for any y close to x^* ($|y - x^*| = 0\,[\varepsilon]$). In our model, this condition is approximately written as

$$\frac{\partial^2 \phi}{\partial y^2}(x^*|x^*) = \mathrm{f}''(x^*) < 0. \tag{A6}$$

Therefore, whether x^* is an ESS or not is determined by the sign of the second-order differential equation of $\mathrm{f}(x)$ at $x = x^*$. Furthermore, if x^* is locally convergent stable, it satisfies $\phi(y|x) < \phi(x|x) = 0$ if $x^* - \varepsilon < y < x < x^*$ and if $x^* < x < y < x^* + \varepsilon$ (Eshel 1983), where ε corresponds to a small deviation. That is, if a wild-type x is nearer the ESS strain x^* than the mutant one, y, it cannot be invaded. From the proof given by Eshel (1983), this condition is also approximately written as follows:

$$\left(\frac{\partial^2 \phi}{\partial y^2} + \frac{\partial^2 \phi}{\partial y \partial x}\right)(x^*|x^*) = \mathrm{f}''(x^*) - \frac{q\Gamma}{(x^*)^2(q + x^*)} < 0. \tag{A7}$$

In the case of a linear trade-off interaction between r and b, $r(\beta) = \mathrm{A}\beta + \mathrm{B}$, where A and B are positive constants, we have a candidate of ESS that satisfies equation (A5),

$$\beta_c = \frac{q\Gamma}{(\mathrm{B} - \mathrm{A}q)}. \tag{A8}$$

If a mutant with β_c is a local ESS, it must also satisfy condition (A6). However, $\mathrm{f}''(x^*)$is always 0 for any β_c. Therefore, β_c cannot be a true ESS. However, we can show that the β_c satisfies the local convergence stable condition. From equations (A7) and (A8),

$$\left(\frac{\partial^2 \phi}{\partial \beta_m^2} + \frac{\partial^2 \phi}{\partial \beta_m \partial \beta}\right)(\beta_c|\beta_c) = -\frac{q\Gamma}{(q + \beta_c)\beta_c^2}, \tag{A9}$$

which is always negative for positive q, Γ, and β_c.

We can also see from equation (A7) that when x^* is an ESS, it is also necessarily convergent stable and therefore a continuously stable strategy (CSS). Also, there is a region such that

$$0 < f''(x^*) < \frac{q\Gamma}{(x^*)^2(q + x^*)}; \tag{A10}$$

here x^* is not an ESS but is convergent stable.

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