The Implications of Coevolutionary Dynamics to Host-Parasite Interactions

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abstract: Due to the importance of infectious disease, there is a large body of theory on the evolution of either hosts or, more commonly, parasites. Here we present a fully coevolutionary model of a host-parasite system that includes ecological dynamics that feed back into the coevolutionary outcome, and we show that highly virulent parasites may evolve due to the coevolutionary process. Parasite evolution is very sensitive to evolution in the host, and virulence fluctuates substantially when mutation rates vary between host and parasite. Evolutionary branching in the host leads to parasites increasing their virulence, and small changes in host resistance drive large changes in parasite virulence. Evolutionary branching in one species does not cause branching in the other. Our work emphasizes the importance of considering coevolutionary dynamics and shows that certain highly virulent parasites may result from responses to host evolution.

Keywords: coevolution, host-parasite, resistance, virulence, adaptive dynamics.

Introduction

The importance of host-parasite interactions has led to much theory on the evolution of parasite virulence (Bremermann and Pickering 1983; Getz and Pickering 1983; May and Anderson 1983) and host resistance (Antonovics and Thrall 1994; Bowers et al. 1994; Boots and Haraguchi 1999). However, the long-term behavior of interactions between hosts and their parasites is likely to depend on the interplay of both species' evolutionary characteristics: the coevolutionary dynamics. Here, we develop a model of these coevolutionary dynamics and show that there are important implications to evolutionary outcomes and the degree of virulence with which parasites attack their hosts.

Modern theoretical studies on the evolution of parasites, in which virulence (increased host mortality) is assumed to be traded off against transmission, show that selection often leads to intermediate levels of virulence, as parasites seek to maximize the epidemiological R_0 (Bremermann and Pickering 1983; Getz and Pickering 1983; May and Anderson 1983). Provided that hosts are only infected by one parasite at any one time, a competitive exclusion principle dictates that evolution will favor the parasite strain with the maximal R_0 (Bremermann and Pickering 1983; Bremermann and Thieme 1989; Nowak and May 1994). However, when density dependence acts on host death rate, then disruptive selection may allow the evolution of coexisting parasite strains through a process of evolutionary branching (Pugliese 2002). Meanwhile, the recognition that the evolution of host defense mechanisms may itself affect the host-parasite interaction has led to the development of models focused on trade-offs between host resistance and other life-history traits (Antonovics and Thrall 1994; Bowers et al. 1994; Boots and Bowers 1999, 2004; Boots and Haraguchi 1999; Roy and Kirchner 2000; Miller et al. 2005, 2007). Coexistence of host strains is possible for many defense mechanisms: avoiding infection (avoidance), increased clearance (recovery), and reducing the within-host parasite growth rate (control; Miller et al. 2005). In contrast, tolerance of the damaging effects of parasite growth does not lead to the coexistence of host strains (Roy and Kirchner 2000). These evolutionary models allow us to gain insight into how ecological feedbacks shape selective pressures on the host or parasite, but in nature host and parasite often evolve together.

Models that examine the coevolution of quantitative traits in hosts and parasites are relatively few in number (van Baalen 1998; Dieckmann et al. 2002; Gandon et al. 2002; Koella and Boëte 2003; Restif and Koella 2003; Bonds 2006; see also Hochberg and van Baalen [1998], who use simulations to study coevolution focusing on spatial heterogeneities). These models tend to search for so-called coevolutionary stable states (CoESSs), which once attained cannot be invaded by other strategies/strains. For example, it can be shown that a single CoESS exists if host defense

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is through avoidance (Restif and Koella 2003), whereas with resistance through recovery there may be bistability such that resistance and virulence are either both low or both high (van Baalen 1998). However, this approach examines only the evolutionary stability (ES) of the outcomes, that is, their ability to be invaded once reached. The other important component of the evolutionary process is convergence stability (CS; Eshel 1983; Christiansen 1991). This is important because it determines whether through evolutionary time the population will move toward or away from a CoESS and whether evolutionary branching will occur. The impact of coevolution on ES and CS in general is now well understood (Dieckmann and Law 1996; Marrow et al. 1996). However, a recent general model of predator-prey coevolution has provided a theoretical framework to focus on the impact of trade-off shapes on coevolutionary dynamics (Kisdi 2006). These theoretical advances allow us to examine the importance of coevolutionary dynamics to the evolution of hosts and parasites.

Given that most natural systems will be coevolutionary, there is a clear need to assess whether the predicted dynamics from models in which only one of the two species evolves (purely evolutionary models) accurately match the outcomes of fully coevolutionary systems. Allied to this, there is considerable variation within both host defense and parasite transmission in natural systems, and it is important to understand whether this variation has coevolutionary consequences that may be missed by purely evolutionary studies. Here we consider the coevolution of hosts and parasites, assuming explicit trade-offs between host reproduction and resistance on the one hand and parasite virulence and transmission on the other. In particular, our aim is to determine how the trade-off shape influences the coevolutionary behavior. We consider whether the coevolutionary dynamics may be accurately predicted from frameworks that consider only the evolution of one species, paying particular attention to the impact of variation through evolutionary branching. We show that in a fully coevolutionary system outcomes very different from those predicted by purely evolutionary theory can occur, particularly when the host experiences evolutionary branching. This not only has important implications for our understanding of host-parasite interactions but also suggests that coevolutionary dynamics may need to be considered more generally.

Material and Methods

We employ the technique of adaptive dynamics, which determines the evolutionary outcome by assuming that rare individuals arise in an established population with small mutations from the resident strategy (Dieckmann and Law 1996; Marrow et al. 1996; Metz et al. 1996; Geritz et al. 1998). The success of a mutant, y, in an environment set by the resident population, x, depends on its invasion fitness, $s_x(y)$. A negative fitness results in the mutant dying out, whereas a positive fitness means that the mutant will increase in density and could coexist with or replace the resident strategy. Through a succession of mutations, the population's strategy will evolve in the direction of the local fitness gradient, $[\partial s_x(y)/\partial x]_{y=x}$, until the gradient is 0 and a "singularity" has been reached. At a singularity, the evolutionary behavior is determined by the combination of two properties—evolutionary stability (ES) and convergence stability (CS). ES concerns whether a singularity can be invaded by nearby mutants and is similar to the classical game theory evolutionarily stable strategy concept. CS, meanwhile, concerns whether the singularity is locally attracting—that is, whether populations will move toward or away from the singularity. If the singularity is neither ES nor CS, it is an evolutionary repellor (Metz et al. 1996), whereas if it is ES but not CS it exhibits "Garden of Eden" behavior (Nowak 1990): at the singularity it cannot be invaded, but all strategies near the singularity evolve away from it. If the singularity is ES and CS, then it is a continuously stable strategy (CSS; Metz et al. 1996; Geritz et al. 1998) and the end point of evolution. The phenomenon of evolutionary branching occurs if the singularity point is not ES but is CS. In this case, the population will evolve toward the singularity point but when close by will undergo disruptive selection that results in the coexistence of two distinct strategies.

The role of trade-offs in determining evolutionary behavior is well studied (Stearns 1992; Roff 2002). Trade-offs are fundamental in nature and reflect the fact that any gain in one life-history trait (e.g., host resistance) incurs a cost in another (e.g., birthrate). That such trade-offs exist is well documented (Boots and Begon 1993; Kraaijeveld et al. 2001), but their exact forms are rarely known. Many evolutionary models need to specify an explicit functional form for the trade-off before analysis of the system, but recent work has looked to develop a geometric theory of adaptive dynamics whereby the exact form need not be specified until a later stage (de Mazancourt and Dieckmann 2004; Rueffler et al. 2004; Bowers et al. 2005; Hoyle et al. 2008; Svennungsen and Kisdi 2009). These methods allow us to consider the full range of possible evolutionary outcomes and directly infer which trade-off shapes give rise to which outcomes.

The geometric theory of adaptive dynamics has mostly focused on the evolution of a single species. Kisdi (2006) has developed an extension of the theory that allows analysis of the coevolution of two interacting populations. The properties of ES generalize directly from an evolutionary to a coevolutionary system. However, in a coevolutionary

framework CS cannot be determined as easily because there the evolving populations may exert some effect on each other. Therefore, a further condition is derived by which we can guarantee the coevolutionary outcomes under certain trade-off shapes. We apply the methods of Kisdi (2006) to a host-parasite system. Where the analytic methods are unable to guarantee the long-term behavior, we use simulations and pairwise invasion plots (PIPs; Geritz et al. 1998) to determine the evolutionary outcomes.

We introduce a generic host-parasite model in which parameters can be adjusted to analyze different ecological scenarios (i.e., density dependence may act on either birth or death, and it is possible to switch between susceptible-infected [SI; infection with no recovery] and susceptible-infected-susceptible [SIS; infection with recovery] frameworks). We consider the density of susceptible, X, and infected, Y, hosts by the following system of differential equations:

$$\frac{dX}{dt} = [a - q(X + Y)]X - [b + p(X + Y)]X - \beta_X\beta_Y XY + \gamma Y, \quad (1a)$$

$$\frac{dY}{dt} = \beta_X\beta_Y XY - [b + p(X + Y)]Y - (\alpha + \gamma)Y. \quad (1b)$$

All births enter the susceptible class with a maximum birthrate, a, that can be reduced due to crowding through the density-dependence term, q. The natural death rate, b, can be increased due to crowding through the density-dependence term, p. Susceptibles can become infected via a mass-action transmission process in which the total transmission is a multiplicative function of the host's susceptibility, β_X, and the pathogen's transmission rate, β_Y. The parasite thus controls only its own level of transmission, while the host's strategy dictates whether an infection is successful. The pathogen induces additional mortality at rate α, and infected hosts can recover back to susceptibility at rate γ. If density dependence acts on birth, then we set $p = 0$ and $q > 0$; if it acts on death, then $p > 0$ and $q = 0$. For an SI framework we assume that there is no recovery, $\gamma = 0$, while for the SIS framework $\gamma > 0$.

We assume that certain parameters are linked through trade-offs. In general, host defense may be through avoidance (lowered susceptibility), clearance (increased recovery), or tolerance (lowered pathogen-induced mortality; Boots and Bowers 1999, 2004; Miller et al. 2005). Here, the host is assumed to benefit by reducing infection through avoidance of the pathogen (reducing β_X), but any such resistance incurs a cost to its birthrate (a corresponding reduction in a). Similarly, we assume that the parasite can increase its transmissibility (increase β_Y) but that to do so must cause greater virulence in the host (increase α). We express these trade-offs as $a = f(\beta_X)$ and $\alpha = g(\beta_Y)$.

Results: Analysis

Density-Dependent Birth

We first study a system with density dependence acting only on birthrate and assume that the resident strain of the host with parameters, (β_X, a), and the resident strain of the parasite, (β_Y, α), have reached a positive, stable equilibrium (X^*, Y^*). We then determine the invasion fitness of a mutant host, $(\bar{\beta}_X, \bar{a})$, and fitness of a mutant parasite, $(\bar{\beta}_Y, \bar{\alpha})$, attempting to invade the resident equilibrium (see appendix in the online edition of the *American Naturalist*):

$$s(\bar{\beta}_X, \bar{a}, \beta_X, a, \beta_Y, \alpha) = [\bar{a} - b - q(X^* + Y^*) - \bar{\beta}_X\beta_Y Y^*](\alpha + b + \gamma) + \gamma\bar{\beta}_X\beta_Y Y^*, \quad (2a)$$

$$r(\bar{\beta}_Y, \bar{\alpha}, \beta_X, a, \beta_Y, \alpha) = \beta_X\bar{\beta}_Y X^* - (\bar{\alpha} + b + \gamma). \quad (2b)$$

(Technically, expression [2a] is not host fitness. It is, however, sign equivalent to the mutant's growth rate and therefore acts as an accurate fitness proxy; see appendix.) Selection leads to each population moving toward a singular strategy. The conditions for ES remain the same in a coevolutionary context as for the evolution of a single species, and they concern whether a singular strategy may be invaded by nearby strategies. We apply a strict condition here that the single-species CS criteria must also still be obeyed. These conditions dictate whether selection directs each population toward or away from the singular strategy, assuming that the other species were not evolving and are now termed isoclinic stability (IS). Due to the effect each species' evolution has on the other, however, IS cannot guarantee convergence to the cosingular strategy. Instead, a further condition is required, termed absolute convergence (AC), which guarantees that the host and the parasite converge despite the cross-species effect. Note that the convergence conditions are sufficient but not necessary and that systems that are not absolutely convergent may still converge. See the appendix for the full derivations.

In this model, the coevolutionary singularity is ES if the benefits of increased resistance (to the host) and transmission (to the parasite) have accelerating costs. The AC condition is found to be redundant, provided that the IS conditions hold. The host and parasite, therefore, coevolve as they would in single-species evolution. The parasite's isoclinically stable conditions are found to be identical to the ES conditions, thus confirming that with density-dependent birth the parasite cannot branch.

For the parasite, if the costs of transmission are accelerating, it will evolve to its singular strategy since it is both ES and fully CS (and therefore a CSS). If the costs are decelerating, the singular strategy will be neither ES nor CS, and transmission will evolve to a maximum or minimum value. For the host, if the costs of resistance are accelerating, its singularity is a CSS. If costs weakly decelerate, it will exhibit evolutionary branching. Strongly decelerating costs mean that the host singularity is neither ES nor CS, and resistance will evolve away from the singularity. Including or excluding recovery from infection only makes small quantitative differences to the evolutionary outcomes.

With density dependence acting on the birthrate, the host is able to branch while the parasite is not, fitting with previous findings (Boots and Haraguchi 1999; Pugliese 2002). This result is connected to the work of Rueffler et al. (2006), who found that the number of factors that affect a mutant's fitness, called the feedback environment, determines the potential for evolutionary branching. In our model there are two factors, the uninfected and infected host densities, which permit branching. However, equation (2b) identifies that only the uninfected host density affects the mutant parasite's fitness, so that its feedback environment is reduced to 1, ruling out evolutionary branching.

Can Branching in the Host Force Branching in the Parasite? We investigate whether branching in the host could force the parasite to branch by considering the evolution of the parasite when there are two resident host strains: X_1 and X_2 with parameters (β_{X_1}, a_1) and (β_{X_2}, a_2), respectively. The modified framework is outlined in the appendix. The fitness of a mutant parasite in such an environment is

$$r(\bar{\beta}_Y, \bar{\alpha}, \beta_Y, \alpha) = (\beta_{X_1} X_1^* + \beta_{X_2} X_2^*)\bar{\beta}_Y - (\bar{\alpha} + b + \gamma). \quad (3)$$

The growth of the mutant parasite now depends on the resident equilibrium densities of both the first and the second host strains. However, we find that the branching of the host has no effect on the stability conditions of the parasite (compared to an environment with one host). In particular, there remains just one feedback to the parasite, so from the parasite's perspective the total host population acts as one. In particular, branching in the host population cannot induce branching in the parasite.

Can the Host Experience Subsequent Branching? We also consider whether a host can experience subsequent branching once it has branched. This is achieved by again assuming two hosts and one parasite (see appendix) and considering the fitness of mutant hosts. Using the coevolution techniques for dimorphic populations (Kisdi 2006), the fitnesses of the respective two mutant host strains are as follows (where N is the total population):

$$s^{(1)}(\bar{\beta}_{X_1}, \bar{a}_1, \beta_{X_1}, a_1, \beta_{X_2}, a_2) = [\bar{a}_1 - b - qN^* - \bar{\beta}_{X_1}\beta_Y(Y_1^* + Y_2^*)](\alpha + b + \gamma) + \gamma\bar{\beta}_{X_1}\beta_Y(Y_1^* + Y_2^*), \quad (4a)$$

$$s^{(2)}(\bar{\beta}_{X_2}, \bar{a}_2, \beta_{X_1}, a_1, \beta_{X_2}, a_2) = [\bar{a}_2 - b - qN^* - \bar{\beta}_{X_2}\beta_Y(Y_1^* + Y_2^*)](\alpha + b + \gamma) + \gamma\bar{\beta}_{X_2}\beta_Y(Y_1^* + Y_2^*). \quad (4b)$$

We find that further branching cannot occur in either strain. Thus, in a model with density dependence acting on births, a single host type may branch to form a dimorphic population, but subsequent branching cannot occur.

Density-Dependent Death

We now consider the model (eqq. [1]) in which density dependence acts on the death rate. The resulting fitness expressions for the host and the parasite are as follows:

$$s(\bar{\beta}_X, \bar{a}, \beta_X, a, \beta_Y, \alpha) = [\bar{a} - b - p(X^* + Y^*) - \bar{\beta}_X\beta_Y Y^*][\alpha + b + p(X^* + Y^*) + \gamma] + \gamma\bar{\beta}_X\beta_Y Y^*, \quad (5a)$$

$$r(\bar{\beta}_Y, \bar{\alpha}, \beta_X, a, \beta_Y, \alpha) = \beta_X\bar{\beta}_Y X^* - [\bar{\alpha} + b + p(X^* + Y^*) + \gamma]. \quad (5b)$$

There are now two feedbacks for both the host ($X^* + Y^*$ and $\beta_Y Y^*$) and the parasite ($X^* + Y^*$ and $\beta_X X^*$), and so branching is permitted for both species. The ES conditions again require accelerating costs of both resistance and transmission. We now find that the convergence conditions indeed allow both host and parasite to branch, depending on the trade-off curvatures. We also find that the convergence of both species is affected by the cross-terms, and we must consider both the IS and the AC conditions.

The results for a particular parameter setup are shown in figure 1, which shows how the ES, IS, and AC properties depend on the host's and parasite's trade-off curvatures. Inside the AC boundary (above and to the left on our plot), we can guarantee the evolutionary behavior. In region 1, both host and parasite are ES, IS, and AC, and the singular pair is a cocontinuously stable strategy (CoCSS). In region 2, the host has lost ES but remains IS and AC, so it will branch, and the parasite will head to its CSS. The reverse is true in region 3, where the parasite will branch and the host will head to its CSS. Outside the AC

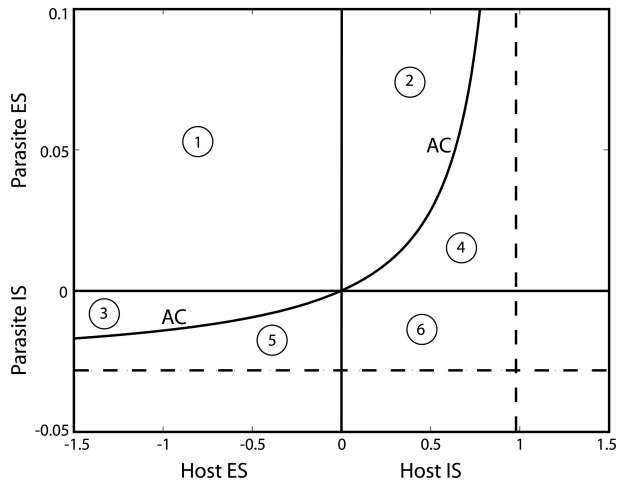

Figure 1: Stability properties of the singular pair $(\beta_X, a) = (1, 2)$ and $(\beta_Y, \alpha) = (2, 2)$ in the density-dependent death susceptible-infected-susceptible model. The axes refer to the curvature of each species' trade-off at the singularity. The solid lines mark the boundaries of evolutionary stability (ES), the dashed lines isoclinic stability (IS), and the curve absolute convergence (AC). The behavior for trade-off combinations in each of the numbered regions is analyzed through simulations and pairwise invasion plots in figures 2 and 3. The remaining parameter values are $\gamma = 0.5$, $q = 0$, $p = 0.5$, and $b = 0.5$.

boundary, regions 4–6, we cannot guarantee the convergence properties of the system analytically using this framework.

Can There Be Any Further Branching? We consider whether branching in either species affects the possibility of subsequent branching by adjusting the framework used with density dependence acting on births (as outlined in the appendix). Once we have two resident host strains, we find that the evolving parasite cannot branch. This can again be understood in the context of feedback environments. Both before and after host branching the potential feedbacks to the parasite are the susceptible host density (those available for infection) and the total host density (affecting density dependence). Before branching, both of these terms depend on the mutating parasite parameters (β_Y, α), giving a feedback dimension of two and thus allowing evolutionary branching. However, after branching has occurred the total host density becomes independent of the mutating parasite parameters, which reduces the feedback dimension to one and rules out evolutionary branching. The same is true of the reverse situation—a host cannot branch when interacting with two parasite strains. Moreover, neither the host nor the parasite can experience subsequent branching once split into two coexisting strains. All of these findings indicate that there can only be one branching event in our host-parasite framework.

Results: Simulations of the Coevolutionary Process

We generate numerical simulations of the coevolutionary process to confirm the analytical findings within the AC boundary (regions 1–3 in fig. 1) and to understand the coevolutionary behavior outside of the AC boundary (regions 4–6). The SIS model with density-dependent death is run for time sufficient to allow the populations to approach their equilibriums. We then allow either the host or parasite, with equal probability, to mutate by initializing a nearby strain (subject to the trade-off) at low density (see "Discussion" for details of the coevolutionary behavior when the host and parasite have different mutation rates). Repeating this process, we can follow the directional evolution of both species. We note that the simulations are not strictly mutation limited because new mutations can occur before the effect of previous mutations has been fully realized. However, previous studies have shown that simulation results correspond well to those from adaptive-dynamics theory when the dynamic attractor is an equilibrium point (Kisdi 1999; White and Bowers 2005; White et al. 2006). To help understand the behavior observed in the simulations and to be sure that they accurately reflect the dynamics, we also use PIPs, a tool that allows us to quickly spot the location of evolutionary singularities (see fig. 2 for a brief guide to their use, as well as Geritz et al. 1998).

Figure 3*A* shows the simulation of the coevolutionary behavior for trade-off shapes in region 1 of figure 1. As predicted by the theory, the host and parasite populations both evolve toward their CoCSSs (marked with thick dashed lines) and remain there. Figure 3*B* shows the coevolutionary process in region 2. Here the host is expected to branch, whereas the parasite should adopt its CoCSS. The simulations show that near its singularity the host branches into two strains, evolving to one of maximal resistance (i.e., low susceptibility) and one of minimal resistance. The parasite initially evolves to transmission levels below its CoCSS but then increases transmission significantly after the host has branched.

To understand why branching in the host leads to the evolution of high virulence, we plot PIPs, taking parameter values from the simulations at the marked points (fig. 3*B*). Before branching, the host and parasite PIPs show the expected shapes for branching and CSS singularity points, respectively (fig. 2; see also Geritz et al. 1998; Boots and Haraguchi 1999). Notice, though, that at the marked point the host strategy is above its coevolutionary singularity, altering the position of the parasite's strategy. When we plot the PIP for the parasite after the host has branched,

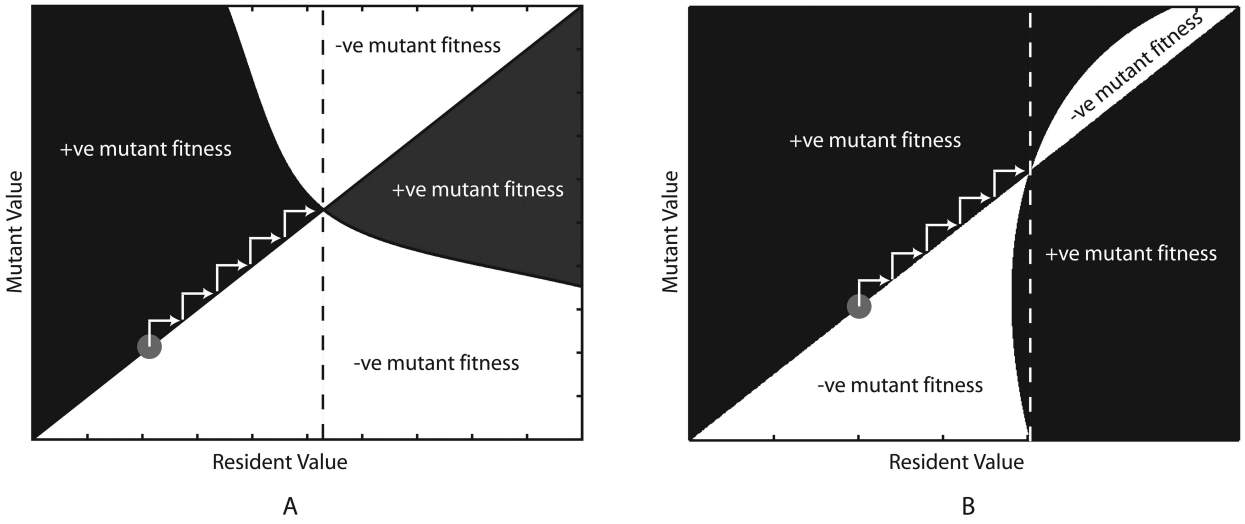

Figure 2: Guide to pairwise invasion plots. Mutant fitness is plotted as a function of the resident and mutant trait values. Shaded areas indicate where the mutant has positive fitness relative to the resident strategy, while unshaded areas are where the mutant has negative fitness. Given small mutations, selection will move the evolving population up or down the diagonal. *A*, Continuously stable strategy. Assume an initial resident population at the circle. Any mutants with lower trait values have negative fitness and die out, while mutants with higher trait values have positive fitness and will invade and replace the resident, as indicated by the arrows. A sequence of mutations/substitutions will increase the resident value until it reaches an evolutionary singularity (marked by a dashed line). Here, mutants with both lower and higher trait values will die out, and the population will remain at the singularity. *B*, Evolutionary branching. Again, from the initial strategy selection will drive the population up to the singularity. However, now mutants with both lower and higher trait values have positive fitness causing disruptive selection. Given clonal reproduction, this will lead to the establishment of two distinct resident strains.

the parasite CSS has shifted to a strategy of higher transmission. In the simulations, therefore, the parasite is attracted toward a shifted CSS of higher transmission and virulence. The cause of this increase in the parasite's transmission and virulence is a subtle one. After host branching, the overall susceptible host density increases. This increase in density has the consequence of increased death due to crowding (recall that density dependence is on death rate). Therefore, host life span is reduced, meaning that the parasite must increase transmission, and thus virulence, so that it can infect hosts before they die naturally. Further investigation shows that this general behavior is retained for a large range of parameter values. One further point from the PIPs is that, should the host's starting strategy be for very low resistance (high susceptibility), it may be beyond the second singularity (fig. 3*B*; thin dashed line) and evolve to minimal resistance.

Simulations from region 3 are shown in figure 3*C*. Here the host reaches its CSS, and the parasite subsequently branches. After the parasite has branched, the PIP indicates that the location of the host's CSS remains the same (although there are minor quantitative changes to the fitness landscape).

In figure 4*A* we move outside the AC boundary and show simulations from region 4 of figure 1. In the single-species cases, we expect the host to branch and the parasite to attain a CSS. The simulations show that the host does branch, but the parasite increases its transmission and virulence. The PIPs show that the parasite is maximizing both before and after the host has branched. The parasite's final strategy depends on which side of the singularity the initial host and parasite strains are located. The second host singularity is close to the branching point, and so for some initial conditions the host may minimize resistance. The results from region 5 in figure 4*B* are qualitatively similar to those of region 3 (fig. 3*C*). Note again that parasite branching has not altered the position of the host's strategy (whereas host branching did alter the parasite strategy; figs. 3*B*, 4*A*). The main difference between regions 3 and 5 is that in region 5 the parasite is far more sensitive. If the host deviates slightly from its CSS, then the parasite will maximize or minimize its transmission and virulence.

In region 6 in the monomorphic cases, both the host and parasite would be predicted to branch. Our analytic results suggested, however, that only one of the species may branch. Our simulations in figure 4*C* show the host branching, while the parasite first decreases and then increases its transmission. The PIPs show that the parasite initially minimizes but then maximizes after host branching. If the initial host susceptibility is high, it will cross

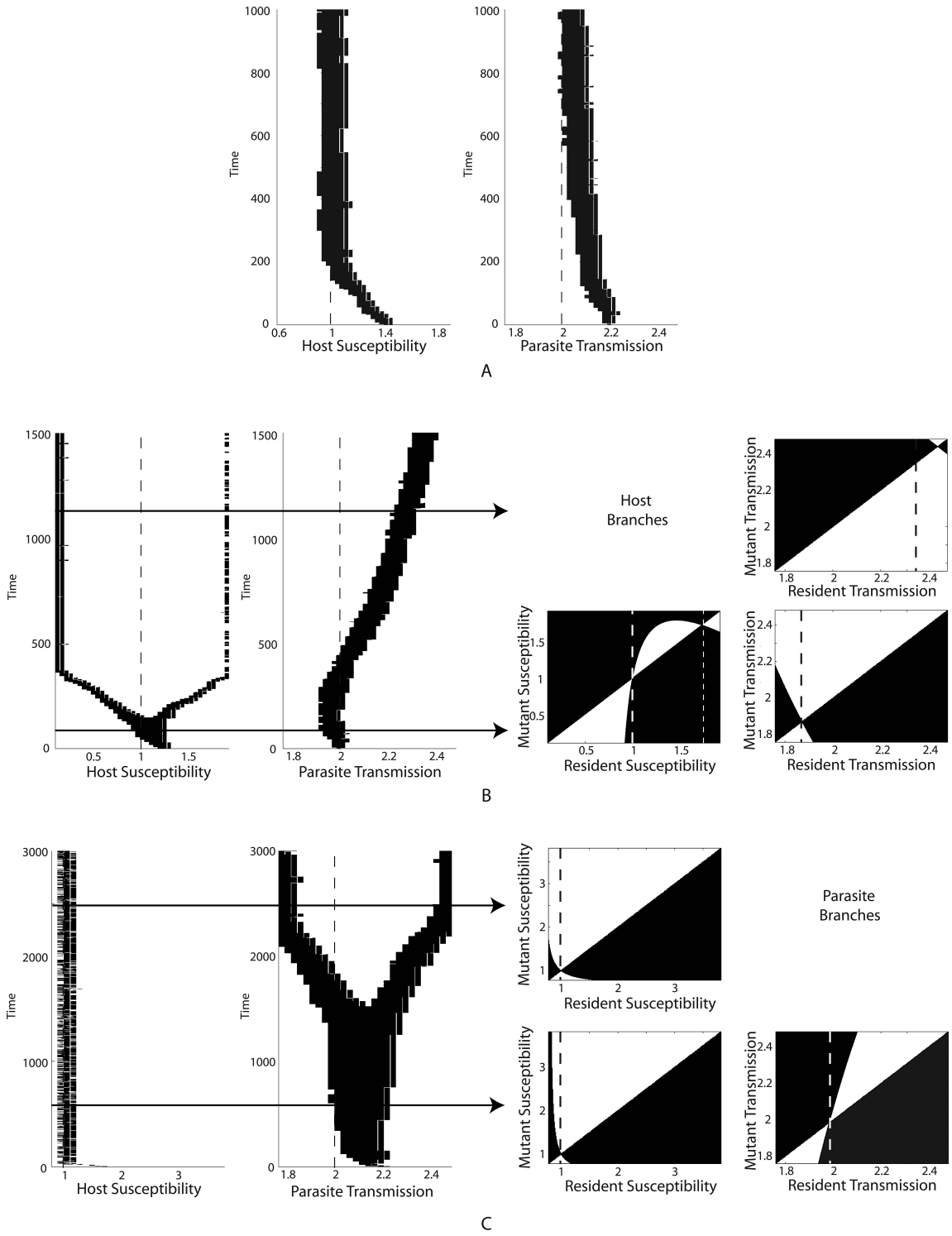

Figure 3: Simulations of the coevolutionary process in regions 1–3 (those within the absolute convergence boundary in fig. 1) and pairwise invasion plots (PIPs) for parameter values at the marked points. Host dynamics and PIPs are on the left, parasite dynamics and PIPs on the right. *A*, Results for region 1, with $f'' = -0.5$, $g'' = 0.1$; *B*, region 2, with $f'' = 0.25$, $g'' = 0.075$; and *C*, region 3, with $f'' = -1.5$, $g'' = -0.01$. Other parameters are as in figure 1. Thick dashed lines mark the principal singularities. The thin dashed line in the host PIP of *B* marks a secondary singularity.

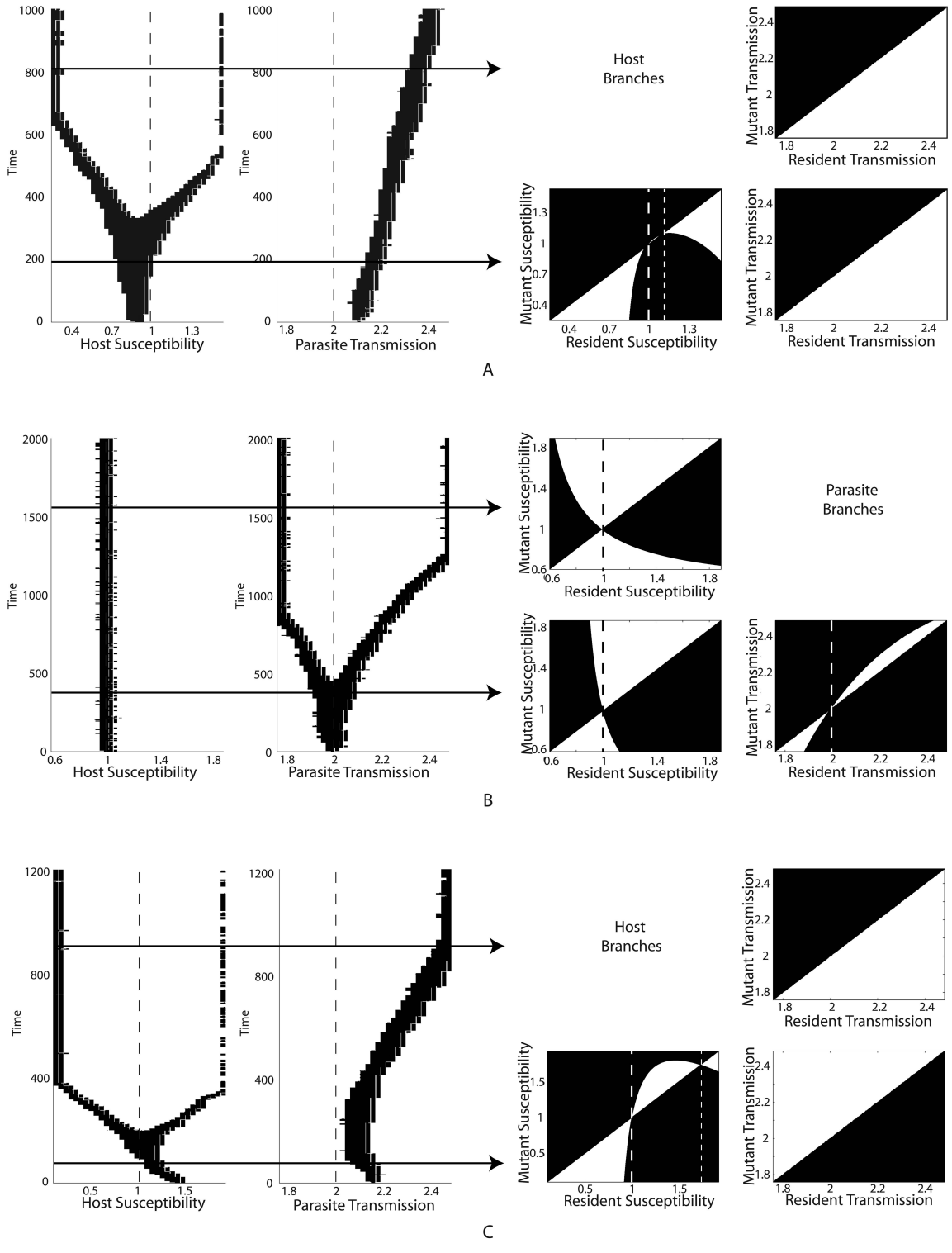

Figure 4: Simulations of the coevolutionary process in regions 4–6 (those outside the absolute convergence boundary in fig. 1) and pairwise invasion plots (PIPs) for parameter values at the marked points. Host dynamics and PIPs are on the left, parasite dynamics and PIPs on the right. *A*, Results for region 4, with $f'' = -0.8$, $g'' = 0.05$; *B*, region 5, with $f'' = -0.5$, $g'' = -0.02$; and *C*, region 6, with $f'' = 0.25$, $g'' = -0.02$. Other parameters are as in figure 1. Thick dashed lines mark the principal singularities. The thin dashed lines in the host PIPs of *A* and *C* mark secondary singularities.

the second singularity and minimize resistance. In this region we would expect that whichever population reaches its singularity first would be the one to branch. However, since the host must be near its singularity for the parasite's to occur within its trade-off range, it will almost certainly always be the host that branches.

We further highlight the sensitivity of the parasite in figure 5, choosing a combination of curvatures in region 1 and calculating the parasite CSS. Starting with a resident host slightly below its singular strategy ($\beta_X = 1$), the PIPs show that the parasite's transmission is maximized. As the resident host moves toward and then above its singular strategy, the parasite's CSS level tends to lower rates of transmission. As the resident host moves further above its singular strategy, the parasite's transmission is minimized. Thus, the location of the parasite's singularity point is very sensitive to the host strategy, and the parasite is often attracted to a coevolutionary singularity only after host convergence. If the host's trade-off has strong decelerating costs, it will repel to maximum or minimum resistance. As figure 5 suggests, if the host minimizes resistance, the parasite's CSS will reach minimal virulence. If the host maximizes resistance, the parasite will be forced to maximize virulence. We show a simulation of this latter case in figure 6*A*. Although the parasite should reach its CoCSS, the host's strategy of repelling to maximal resistance forces the parasite to increase its virulence through its CoCSS to the maximum level.

Although we have presumed equal mutation rates, due to its short life span and rapid reproduction it is likely that the parasite will mutate at a faster rate. Adjusting the respective rates of mutation accordingly allows the parasite to reach its temporarily stable level of virulence (given the current host strategy) before the host mutates again. A simulation of such an example is shown in figure 6*B* from region 1 (cf. fig. 3*A*). Both host and parasite do eventually attain their CoCSSs. However, during the coevolutionary process the parasite's virulence varies considerably as it quickly adapts to the slowly mutating host. Only once the host's strategy nears the cosingularity does the parasite also move to the predicted CoCSS (cf. the top two PIPs of fig. 5). Both host branching (regions 2 and 4) and parasite branching (regions 3 and 5) are still found to occur with the altered mutation rates.

Discussion

Most theory of antagonistic interactions has concentrated on the evolution of just one of the two species (e.g., Brem-

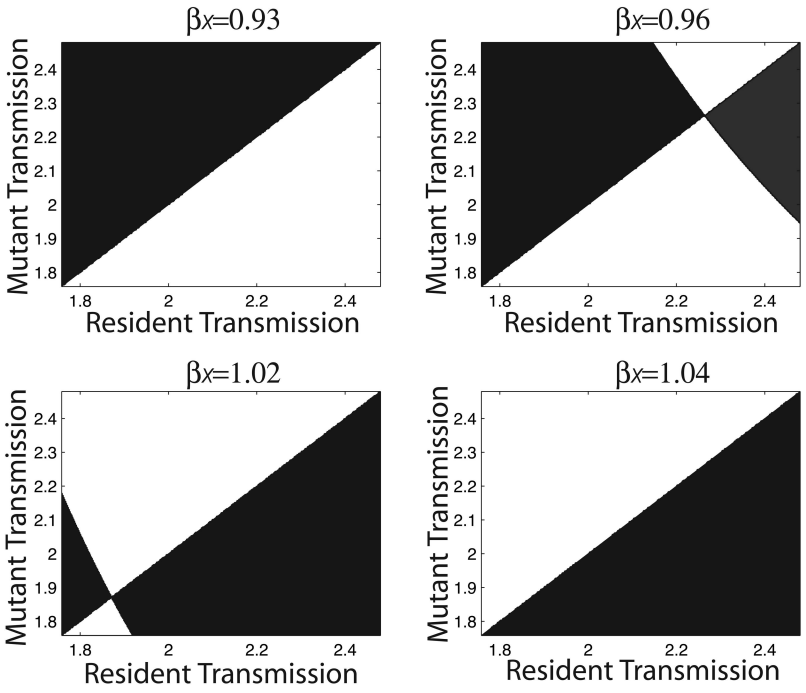

Figure 5: Pairwise invasion plots for the parasite in region 1 ($f'' = -0.5$, $g'' = 0.05$), highlighting its sensitivity to the host's mutating strategy. The host's singular strategy should occur at $\beta_X = 1$ and the parasite's at $\beta_Y = 2$. As the resident host moves from very slightly below its singular strategy to very slightly above it, the parasite's strategy moves from maximizing transmission, through reducing levels of transmission, and eventually to minimizing transmission (and therefore virulence).

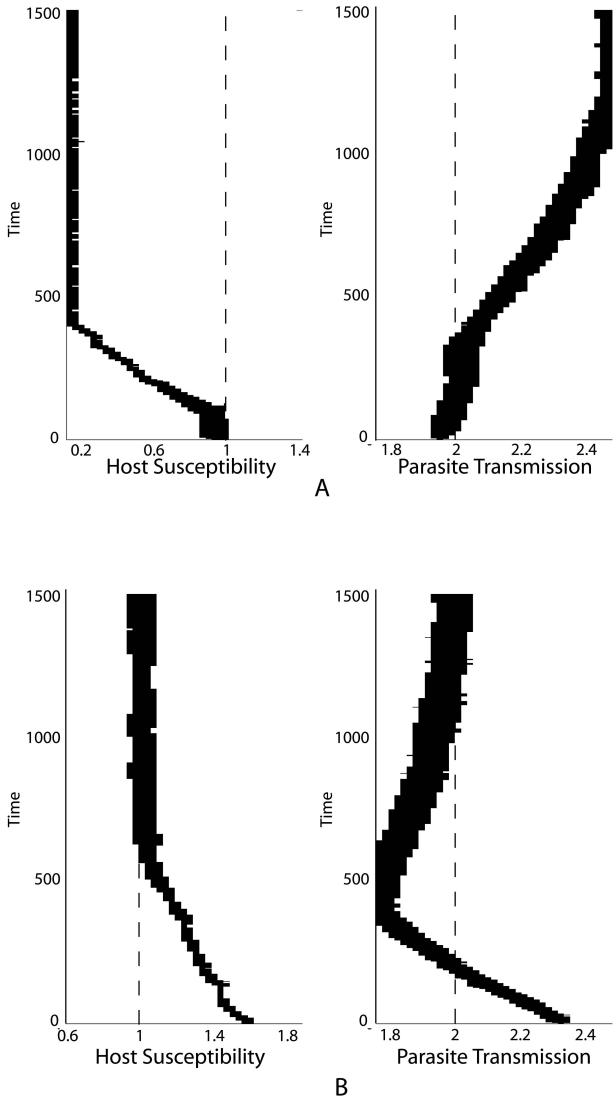

Figure 6: Further simulations of the coevolutionary process. *A*, Outcome when the host's singularity is a repellor and the parasite's is an attractor (i.e., to the right of region 4 in fig. 1: $f'' = 1.3$, $g'' = 0.1$). The repelling nature of the host forces the parasite to move through its cocontinuously stable strategy (CoCSS) and maximize virulence. *B*, Outcomes from region 1 ($f'' = -0.5$, $g'' = 0.1$) where mutation rates favor the parasite by 10 : 1. Both host and parasite eventually reach their CoCSSs, but the parasite varies considerably until the host nears the singularity.

ermann and Pickering 1983; Boots and Haraguchi 1999). However, it is obvious that the evolution of one species affects selection on the other, and it is therefore important to develop a fully coevolutionary framework to completely understand evolutionary outcomes. The coevolutionary model of host-parasite interactions developed here shows that (1) coevolutionary outcomes cannot always be predicted from the single-species evolutionary outcomes; (2) parasite evolution is highly sensitive to that of the host, often resulting in the evolution of highly virulent parasites; (3) differences in mutation rates lead to highly variable parasite virulence; (4) branching in one species does not induce branching in the other; and (5) relative shapes of trade-off relationships are crucial in determining the evolutionary outcome. These results are important to our understanding of not only host-parasite interactions but also coevolutionary dynamics more generally.

Our work highlights the importance of coevolutionary processes to host-parasite interactions. Given that interactions in nature are likely to be coupled, coevolutionary models must be considered in order to fully understand the long-term behavior of most if not all systems. Modern

evolutionary game theory has emphasized the importance of dynamic evolutionary behaviors (Eshel 1983; Christiansen 1991), and CS is just as important to the final evolutionary outcome as ES. CS determines whether the population evolves toward or away from a strategy, and therefore the outcome critically depends on this criterion. Importantly, unlike ES, CS of a species' strategy can be altered by the coevolution of an antagonistic species (Marrow et al. 1996; Kisdi 2006). It is important to stress that here the parasite is much more sensitive to host evolution than vice versa, emphasizing that there may be important asymmetries in coevolutionary outcomes due to ecological characteristics and that a fully coevolutionary model is the only way to predict them. It is clear from our work that we can only fully understand the evolution of parasites in the context of coevolution. We have shown that there are important implications of coevolutionary dynamics for the likelihood and nature of evolutionary branching and therefore the diversity of both the host and the parasite.

Perhaps our most important result is that the level of parasite virulence is highly dependent on the evolutionary dynamics of the host. In particular, evolution in the host can induce selection for highly virulent parasites that have much higher transmission and shorter infectious periods than predicted by purely evolutionary models. Such "fast," acute, and deadly parasites are of course a cause for great concern. Our work suggests that these parasites may arise in response to host evolution that maximizes resistance. Furthermore, these deadly parasites are likely to evolve in polymorphic host populations, in which a proportion of host individuals are infected easily as well as killed quickly. This results from a subtle feedback that may well be missed by purely evolutionary studies, with the implication that host evolutionary dynamics may largely determine the virulence of their parasites. It also follows from our models that any imposed changes in host resistance in agriculture (Campbell et al. 2002; Gurr and Rushton 2005) or medicine (Ridley 2002; de Clercq 2004) will affect parasite evolution and risk selecting for high virulence.

A key insight from our models is thus that the high virulence of some parasites may be the result of resistance evolution in the host. Clearly, understanding the processes that determine how deadly particular parasites are to their hosts is of crucial importance to wildlife, agriculture, and not least human health. In particular we are especially concerned about diseases with high virulence. These may sometimes be "spillover" parasites, such as Ebola in humans (Pedersen and Fenton 2007) and squirrel pox in the Eurasian red squirrel (Tompkins et al. 2003), in which the high virulence is manifested in an evolutionary dead-end host from which there is little transmission. However, high virulence may be an evolutionary response of the parasite. Generally, trade-offs with transmission can explain why parasites cause mortality as the parasite optimizes R_0 (May and Anderson 1983; Bremerman and Thieme 1989), but our work emphasizes that host resistance can drive much higher virulence than would optimize the parasite R_0 in the absence of host resistance. Previous studies have suggested that host heterogeneity may lead to either reduced (Regoes et al. 2000) or increased parasite virulence (Ganusov et al. 2002), depending on the nature of the heterogeneity. We have shown here that when there is polymorphism in avoidance resistance, there is selection for very high virulence. It is possible that this process may have led to the evolution of effectively obligate killers, such as the insect baculoviruses (Boots and Begon 1993; Dwyer et al. 1997), in which, in general, challenged hosts either do not become infectious or are killed. Comparative studies are needed to examine whether host variation does correlate with high parasite virulence.

Another important factor in determining the coevolutionary outcome is the respective rates of mutation, which can alter the CS of coevolutionary systems (Dieckmann and Law 1996; Marrow et al. 1996). We have shown that the effect of biased mutation rates is that the parasite's virulence varies considerably on its way to its CoCSS, while the host behaves the same as when the mutation rates were equal. (For particular mutation rates it may be possible to find evolutionary cycling [Dieckmann et al. 1995], but this has not been our main focus.) The sensitivity of the parasite to host evolution leads to significant transient changes in its virulence if it has a higher mutation rate. Coevolutionary processes such as this may therefore explain some of the variation in parasite virulence in nature. Whenever a parasite has a much higher mutation rate than its host, it undergoes rapid change because relatively slow changes in its host have large impacts on parasite virulence. Clearly, microparasites such as viruses and bacteria have much faster generation times than their vertebrate or even invertebrate hosts. This potential to evolve much faster than their hosts has in fact been one of the implicit justifications for modeling parasite evolution alone. However, in our coevolutionary models, we find that the slower host evolution leads to dramatic changes in parasite transmission and virulence. In particular, the parasite's evolutionary optimum is very sensitive to the current level of host resistance. The implication of this is that the virulence that we see is merely a transient state brought on by the evolution of new resistance mechanisms in the host until the host has itself reached its evolutionary optimum. This has obvious implications for the emergence of disease and the management of virulence (Dieckmann et al. 2002; Ebert and Bull 2003). If parasite virulence is indeed a moving target, managing disease in host populations becomes much more difficult.

Our work again emphasizes the importance of trade-

off shapes assumed between life-history parameters (de Mazancourt and Dieckmann 2004; Rueffler et al. 2004; Bowers et al. 2005; Hoyle et al. 2008), because small differences in trade-off shapes can lead to dramatically differing coevolutionary outcomes as the CS of the system changes. Using our methods, the range of trade-off shapes for which CS can be guaranteed is reduced in a coevolutionary system (Kisdi 2006), making it hard to make definite predictions concerning evolutionary branching. In general, we find that only one instance of evolutionary branching may occur and that coevolution cannot in itself cause branching when the evolutionary dynamics alone do not. This contrasts with previous coevolutionary predator-prey studies in which high levels of polymorphism can evolve through repeated branching from a single ancestor (Kisdi 1999; Weitz et al. 2005). These studies link traits to functional forms leading to asymmetric competition, and it is likely that more complex trade-off relationships would produce similar results in our framework. There has been considerable debate about the potential for evolutionary branching in nature (Butlin and Tregenza 2005) since it appears to be much easier in models than in real systems. The fact that the models deal with the evolution of only one species, whereas coevolution is the rule in real systems, may help to explain this discrepancy. It should also be noted that here the total transmission is decomposed into host susceptibility and parasite transmission in a straightforward multiplicative fashion and that more complex interactions between susceptibility and transmission may well lead to a greater chance of polymorphisms.

It is important to note that some of the key results from purely evolutionary models do hold in the fully coevolutionary framework. In particular, the finding that parasites cannot branch if density dependence acts on host birthrate but can if density dependence is on host death rate (Pugliese 2002) is shown to remain true when the parasite coevolves with its host. However, the convergence of the parasite is found to be very sensitive to the host strategy and requires the host to have evolved to its singularity before parasite branching. This sensitivity is accentuated further when both host and parasite could potentially branch, that is, when the coevolutionary response of the host may prevent parasite branching but as a consequence cause the evolution of a highly virulent parasite. There are therefore crucial implications of the coevolutionary process, and, given the sensitivity of the parasite to host evolution, we would argue that fully coevolutionary models are needed to understand the coevolution of hosts and parasites. Furthermore, faster mutation rates in the parasite make coevolutionary models even more important.

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