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# THE COEVOLUTIONARY IMPLICATIONS OF HOST TOLERANCE

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**Host tolerance to infectious disease, whereby hosts do not directly "fight" parasites but instead ameliorate the damage caused, is an important defense mechanism in both plants and animals. Because tolerance to parasite virulence may lead to higher prevalence of disease in a population, evolutionary theory tells us that while the spread of resistance genes will result in negative frequency dependence and the potential for diversification, the evolution of tolerance is instead likely to result in fixation. However, our understanding of the broader implications of tolerance is limited by a lack of fully coevolutionary theory. Here we examine the coevolution of tolerance across a comprehensive range of classic coevolutionary host–parasite frameworks, including equivalents of gene-for-gene and matching allele and evolutionary invasion models. Our models show that the coevolution of host tolerance and parasite virulence does not lead to the generation and maintenance of diversity through either static polymorphisms or through "Red-queen" cycles. Coevolution of tolerance may however lead to multiple stable states leading to sudden shifts in parasite impacts on host health. More broadly, we emphasize that tolerance may change host–parasite interactions from antagonistic to a form of "apparent commensalism," but may also lead to the evolution of parasites that are highly virulent in nontolerant hosts.**

**KEY WORDS:** **Coevolution, defense, gene-for-gene, host–pathogen, matching alleles, tolerance.**

The distinction between *resistance* and *tolerance* defense mechanisms has long been recognized in the plant-herbivore/pathogen literature (Simms and Triplett 1994; Tiffin and Rausher 1999; Stowe et al. 2000) but is now gaining increasing recognition as an important component of animal disease interactions (Råberg et al. 2007, 2009; Ayres and Schneider 2008; Boots 2008; Read et al. 2008; Medzhitov et al. 2012, Adelman et al. 2013). In the theoretical literature, the dichotomy of these two forms of defense has been explored extensively by elucidating the impact of the evolution of defense on epidemiological parameters that feed back into selection on the host (Boots et al. 2009). Resistance mechanisms, such as avoidance of infection or faster recovery once infected, reduce the fitness of the parasite. The evolution of increased resistance therefore leads to a reduction in disease prevalence, meaning that selection on resistance alleles is negatively frequency dependent. As a consequence if there are life-history costs to high defense (Boots and Begon 1993; Boots 2011) there is the potential for diversification and the coexistence of host strains (Antonovics and Thrall 1994; Bowers et al. 1994; Boots and Bowers 1999; Boots and Haraguchi 1999; Boots et al. 2012). In contrast, tolerance mechanisms either do not impact on (if they reduce the fecundity effects of the parasite; (Best et al. 2008), or more generally may increase, the fitness of the parasite due to an increase in the infectious period brought about by reduced disease-induced mortality (Boots and Bowers 1999; Roy and Kirchner 2000; Miller et al. 2005). As a consequence tolerance may increase disease prevalence within the population leading to positive frequency dependence such that tolerance alleles have an advantage when






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common (because this is when the prevalence of the disease is higher). As such while epidemiological feedbacks to the evolution of host resistance may promote diversity, those of tolerance will tend to fix it in populations (Roy and Kirchner 2000).

Clearly, host–parasite interactions are fundamentally coevolutionary, with hosts and parasites adapting in response to changes in the other. In specific coevolutionary models, both Best et al. (2008) and Carval and Ferriere (2010) showed that coevolution is not in itself enough to generate diversity in host tolerance, while Restif and Koella (2003) found that the coevolution of tolerance can reverse the classic result of parasites evolving higher virulence against shorter lived hosts. More broadly, Miller et al. (2006) examined the impact of the evolution of mortality tolerance, once it has become fixed, on the evolution of parasite virulence. They showed that the evolution of the parasite may lead to a "tragedy of tolerance" whereby although individual risk of death in hosts is lower, more individuals within a tolerant population may die of disease (Miller et al. 2006). Furthermore, tolerance can often lead to the evolution of parasites that are highly virulent to nontolerant hosts leading to catastrophic epidemics (Miller et al. 2006). These insights have important implications to the control and management of disease, not least because many disease treatments may act as tolerance mechanisms—if they reduce symptoms—but their robustness to a fully dynamical coevolutionary model of both host and parasite have not been tested. This has led to criticism of the evolutionary theory of tolerance in particular as being either host or parasite centric, with calls for greater study of fully coevolutionary models (Little et al. 2010). Furthermore there is no theory on the impact of tolerance to the predictions of the classic gene-for-gene (GFG) and matching allele (MA) host–parasite coevolutionary theoretical frameworks.

Classic GFG and MA host–parasite models of resistance have ignored epidemiological feedbacks and instead focused on how different forms of specificity between hosts and parasites, arising from particular genetic mechanisms, lead to cycles in host–parasite genotypes (Flor 1956; Burdon 1987; Thompson and Burdon 1992; Sasaki 2000; Agrawal and Lively 2002). Empirical evidence for GFG interactions has tended to come from plant–pathogen interactions (Flor 1956; Burdon 1987; Thompson and Burdon 1992) while MA has been implicated in invertebrate disease (Dybdahl and Lively 1996; Luijckx et al. 2013). The key insight of these GFG and MA models is that temporal diversity can occur through "Red Queen" cycling of gene frequencies, particularly in MA models and when there are costs to wider infectivity in parasites and resistance in hosts in GFG models (Jayakar 1970; Sasaki 2000; Agrawal and Lively 2002). These cycles occur due to the specificity assumptions of the models where particular host types are preferentially infected by particular parasite strains, resulting in negative frequency dependence. The models have until now assumed that host defense is through resistance, but tolerance has been proposed to "slow the Red Queen" by eliminating this negative frequency dependence (Råberg et al. 2007, 2009). However, this coevolutionary insight has also not yet been thoroughly examined theoretically (Little et al. 2010). There is therefore a clear need to better understand the coevolutionary dynamics of host tolerance and parasite virulence.

As we have summarized, the vast majority of coevolutionary theory of resistance has been developed within either an explicitly genetic (GFG/MA) or evolutionary invasion (ecological feedbacks) framework (though we note recent advances by Day and Gandon 2007 to combine elements of each framework). These have shown how negative frequency dependence in the evolution of resistance can lead to diversity, in the form of cycles in the GFG/MA models and static polymorphisms in the evolutionary invasion models (also see Best et al. 2010 for an example of cycles in an evolutionary invasion model). Here we develop a general theory of host–parasite coevolution using a comprehensive range of classic baseline coevolutionary frameworks. However, rather than host resistance, our focus is on host tolerance, namely a reduction in the level of disease-induced mortality (classically defined as "virulence" in the evolutionary ecology literature). For generality, we develop models both within the multiallelic GFG/MA—following Sasaki (2000)—and the evolutionary invasion—following Best et al. (2009a,b, 2010)—frameworks. Our focus is on the potential for the generation of diversity due to the coevolutionary process, either through cycles or through the coexistence of strains.

# Methods

## TOLERANCE GFG MODEL

Taking a GFG framework similar to Sasaki (2000), we initially assume the outcome of the interaction is governed by a single locus in the host and in the parasite. At its locus the host may have an allele conferring either tolerance (T) or intolerance (t), while the parasite may have an allele conferring either virulence (V) or avirulence (v) (we note here that we are defining "virulence" as disease-induced mortality, not infectivity as is often the case in classic GFG models. We are therefore assuming virulence causes a fitness loss to parasites, not a fitness gain.). We assume random encounters between hosts and parasites, and implicitly assume that all encounters result in infection (note that this is unlike classic GFG models where infection only occurs between certain combinations of host and parasite genotypes as a result of host resistance). The fitnesses of each host and parasite type are then adjusted by the interactions as follows.

### *Hosts*

t—an intolerant host incurs a fitness loss ($\alpha_H$) from interactions with all parasite types.

T—a tolerant host only incurs a fitness loss from virulent parasites ($\alpha_H p_\tau$) but pays a cost of investment ($c$).

### *Parasites*

v—an avirulent parasite incurs a fitness loss only from interactions with intolerant hosts ($\alpha_P(1-q_\tau)$).

V—a virulent parasite incurs a fitness loss ($\alpha_P$) from interactions with all host types, but receives a benefit of investment ($b$).

The fitness losses to the host ($\alpha_H$) and parasite ($\alpha_P$) we define as "virulence" (in line with evolution of virulence theory, but, as above, it is important to distinguish this from the use of virulence as infectivity in classic GFG models). Note that we assume that virulence not only damages the host but also the parasite due to the reduction in the infectious period. The cost to the host of investing in tolerance ($c$) is assumed to be to a general life-history trait related to reproductive rate that acts to reduce the prevalence of this host strain in future generations. The benefit to the parasite of virulence ($b$) we assume to be some increase to the parasite's growth rate (as is classically assumed in evolution of virulence theory) that acts to increase the prevalence of this strain in future generations (although we do not define $b$ as transmission, there is a clear link between the two as a higher value of $b$ implies a more successful parasite). However, we emphasize that there are no explicit epidemiological or ecological dynamics in this GFG model.

The fitness of each strain, denoted $s$ for hosts and $r$ for parasites, is given by the exponential of the sum of the virulence and cost/benefit terms as given above, that is, $s(T) = exp\{-\alpha_H p_\tau - c\}$, $r(V) = exp\{-\alpha_p + b\}$, etc. (cf. Sasaki 2000). The frequencies of the tolerant ($q_\tau$) and virulent ($p_\tau$) strains will then obey the following discrete dynamics,

$$q_{\tau+1} = \frac{s(T)q_\tau}{s(T)q_\tau + s(t)(1-q_\tau)}$$
$$p_{\tau+1} = \frac{r(V)p_\tau}{r(V)p_\tau + r(v)(1-p_\tau)}. \quad (1)$$

We will also extend the system to a multilocus setup by denoting each host and parasite strain by $t$ and $v$ where, for example, $t = \{t_1, t_2, t_3, \ldots, t_n\}$ is a binary list of the states of each of the $N$ loci. Similarly to Sasaki (2000), we assume that tolerance at each loci is in fact partial, such that each extra tolerance allele reduces the probability of damage by a multiplicative factor $\sigma < 1$, rather than preventing it entirely. A matrix giving the virulence experienced by the host and parasite for the $N = 2$ case is shown in Table 1a (in our results below we take $N = 5$). The lowest virulence is experienced by a fully tolerant host interacting with a completely avirulent parasite, while any fully intolerant host or any fully virulent parasite always incurs maximum virulence. The dynamics of the strains given by (1) are numerically integrated for 5000 time steps. All strains are initially present, with one strain dominating, and there are no explicit mutations.

**Table 1. Matrices of virulence for the (a) gene-for-gene and (b) matching allele models, for two-locus models.**

(a)

| | vv | vV | Vv | VV |
|---|---|---|---|---|
| tt | $\alpha_i$ | $\alpha_i$ | $\alpha_i$ | $\alpha_i$ |
| tT | $\sigma\alpha_i$ | $\alpha_i$ | $\sigma\alpha_i$ | $\alpha_i$ |
| Tt | $\sigma\alpha_i$ | $\sigma\alpha_i$ | $\alpha_i$ | $\alpha_i$ |
| TT | $\sigma^2\alpha_i$ | $\sigma\alpha_i$ | $\sigma\alpha_i$ | $\alpha_i$ |

(b)

| | vv | vV | Vv | VV |
|---|---|---|---|---|
| tt | $\sigma^2\alpha_i$ | $\sigma\alpha_i$ | $\sigma\alpha_i$ | $\alpha_i$ |
| tT | $\sigma\alpha_i$ | $\sigma^2\alpha_i$ | $\alpha_i$ | $\sigma\alpha_i$ |
| Tt | $\sigma\alpha_i$ | $\alpha_i$ | $\sigma^2\alpha_i$ | $\sigma\alpha_i$ |
| TT | $\alpha_i$ | $\sigma\alpha_i$ | $\sigma\alpha_i$ | $\sigma^2\alpha_i$ |

## MA TOLERANCE MODEL

We also develop a similar genetic model within the MA framework. Here, if the host and parasite alleles match at a particular loci, tolerance is induced. In the single-locus model, the interactions are therefore as follows (we note that the terms "intolerant/tolerant" and "virulent/avirulent" are less meaningful in this model, but we keep the "t/T" and "v/V" labeling for continuity):

### *Hosts*

t—incurs a fitness loss ($\alpha_H p_\tau$) from interactions with parasite type V.

T—incurs a fitness loss ($\alpha_H(1-p_\tau)$) from interactions with parasite type v.

### *Parasites*

v—incurs a fitness loss $\alpha_P q_\tau$ from interactions with host type T.

V—incurs a fitness loss $\alpha_P(1-q_\tau)$ from interactions with host type t.

We assume no costs or benefits to investment in the MA model, as there is no direct benefit of investing in more genes (unlike the GFG model, where, e.g., more tolerance genes give protection against a larger range of parasite strains). In the multilocus model, we again assume that tolerance is partial such that each extra MA reduce the probability of damage, as shown in Table 1b for the case $N = 2$.

## UNIVERSAL TOLERANCE MODEL

In our second set of models we take an evolutionary invasion approach (Geritz et al. 1998). In this case we assume a somewhat simpler genetic structure but incorporate explicit epidemiological/ecological feedbacks to evolution through an SIS framework.

Similarly to Best et al. (2009a,b), we initially assume hosts and parasite share control of the key trait, here virulence, through a multiplicative function, with virulence therefore depending on "universal" levels of investment, rather than the specific strategies adopted by host and parasite (see Best et al. 2010 and model 4). The population dynamics of susceptible and infected hosts are governed by the following pair of ODEs:

$$\frac{dS}{dt} = a(h)S - qSN - bS - \beta(p)SI + \gamma I$$
$$\frac{dI}{dt} = \beta(p)SI - (\alpha(h, p) + b + \gamma). \quad (2)$$

Susceptible hosts reproduce at birth rate $a$ (for analytical tractability we assume that infected hosts are sterilized, but our results are robust to the inclusion of reproduction from infected), which is reduced through crowding by a factor $q$. All hosts have a background mortality rate $b$. Transmission is a mass-action process with coefficient $\beta$. Virulence (disease-induced mortality) is made up of a combination of host investment in tolerance, $h$, and parasite investment in virulence, $p$, with $\alpha(h, p) = h \times p$. Finally, infected hosts are able to recover at rate $\gamma$.

We assume that hosts and parasites are able to evolve their respective share of the virulence term by small mutational steps. However, we also assume that there are trade-offs such that for both host and parasite, reducing virulence is costly elsewhere in their life history. In particular, we assume that the cost to the host is a reduced birth rate, $a(h)$, and the cost to the parasite is a reduced transmission rate, $\beta(p)$. Following the framework of evolutionary invasion analysis ("adaptive dynamics"; Geritz et al. 1998), we assume rare mutations with small phenotypic variation arise that attempt to invade a resident that is at its equilibrium. The success of the mutant depends on its invasion fitness, defined as the initial growth rate of a mutant in an environment set by the resident. Following a similar method to Best et al. (2009a,b), the respective fitnesses for the host and parasite can be calculated as

$$s = (a(h_m) - qN - b - \beta I^*)(\alpha(h_m p) + b + \gamma) + \gamma\beta I^*$$
$$r = \beta(p_m)I^* - (\alpha(h, p_m) + b + \gamma), \quad (3)$$

where subscript $m$ denotes a mutant trait. (In fact, as in Best et al. 2009a,b, the host expression here is a sign-equivalent "fitness proxy") The host and parasite then evolve along their respective fitness gradients, $[\partial s/\partial h_m]_{h_m=h}$ and $[\partial r/\partial p_m]_{p_m=p}$, forming a co-evolutionary trajectory, until a "co-evolutionary singular point" is reached where these two gradients are zero. The outcome at such a coevolutionary endpoint depends on second-order terms, namely evolutionary stability (is the point a fitness optimum for either/both species?), convergence stability (is the point locally attracting?), and mutual invadibility (can nearby types invade each other when rare?) (see Geritz et al. 1998). We will particularly focus on where these conditions lead to coevolutionary outcomes of long-term attractors of coevolution (continuously stable strategies; CSSs—an attracting fitness maximum), or to diversity either through branching points (an attracting fitness minimum with mutual invadibility) and evolutionary cycles.

### TOLERANCE RANGE MODEL

We also develop a related "tolerance range" model (cf. Best et al. 2010), where the virulence function no longer depends on "universal" rates of investment by host and parasite, buts on the specific strategies of the host and parasite. As such, the virulence function is expressed as

$$\alpha(h, p) = \alpha_0(p)(1 - (1 + \exp(p - h))^{-1}). \quad (4)$$

We assume that $\alpha_0'(p) < 0$. This means that parasites may vary from "specialists" (low $p$), which are extremely virulent on the most intolerant hosts (high $\alpha_0(p)$) but avirulent to on other hosts, to "generalists" (high $p$), with low virulence (low $\alpha_0(p)$) against most hosts. This system automatically includes costs for the parasite. As in model 3, we impose a cost such that high tolerance (high $h$) is bought at a reduced birth rate (low $a$). We will consider cases both where transmission is not involved in the trade-off (i.e., transmission is constant) and where there is a three-way link between virulence, range, and transmission. The model is then analyzed in the same way as model 3.

## Results

### GFG MODEL

The steady states of the single-locus model and their stability are easily determined analytically to be:

- $(q, p) = \left(\frac{b}{\alpha_P}, 1 - \frac{c}{\alpha_H}\right)$—unstable (saddle);
- $(q, p) = (0, 0)$—unstable;
- $(q, p) = (1, 1)$—unstable;
- $(q, p) = (0, 1)$—stable;
- $(q, p) = (1, 0)$—stable provided $c < \alpha_H$ and $\beta < \alpha_P$.

As such, stable polymorphisms of intolerant and tolerant types at the internal equilibrium can never exist (there is also no possibility of evolutionary cycling—see the phase plane Fig. 1). Instead there is bistability, with the system either evolving to where virulence is incurred by all hosts (but the parasite benefits through greater transmission) or to where tolerance is successful and there is no virulence in the population (but the host has paid a cost). If the costs of tolerance or benefits of virulence are too high, then the system will always evolve to a state of virulence. We plot a sample "phase plane" for this system in Figure 1. The two stable equilibria appear in the top-left and bottom-right of the plot (filled circles). The boundary of attraction between these two equilibria is shown by dashed lines. For the parameters used here,

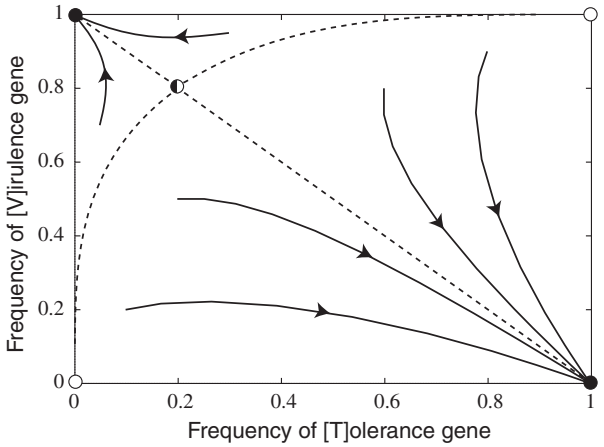


**Figure 1. Single-locus GFG model produces bistability. Example dynamics of the single-locus genetic model. Circles denote equilibria of the system (filled = stable, half-filled = saddle, empty = unstable). The dashed line marks the boundary of attraction between the two stable equilibria, with solid lines giving example trajectories. $\alpha_i = 1$, $b = 0.2$, $c = 0.2$.**

most initial conditions will result in no virulence in the system (i.e., the host has the tolerance gene and the parasite the avirulence gene).

Results from numerical simulations of the multilocus model ($N = 5$) are shown in Figure 2A–C, where we have initially assumed that the dominant genotypes, respectively, have no tolerance or virulence genes. This shows the number of tolerance (Fig. 2A) and virulence (Fig. 2B) genes invested in after 5000 time steps for varying $c$ (the cost to the host of each tolerance gene) and $b$ (the benefit to the parasite of each virulence gene). There is a clear effect of costs to the host, such that fewer tolerance genes are invested in as costs increase (left to right), and of benefits to the parasite, such that more virulence genes are invested in as benefits increase (bottom to top). The combination of these trends to the overall virulence can be seen in Figure 2C, which shows that full virulence (no tolerance) occurs only where both the costs and benefits are high, and minimal virulence (full tolerance) where there are no costs or benefits. For most cost/benefit combinations, intermediate levels of investment are adopted, but we note that only certain combinations appear to occur (in particular, three or four tolerance genes, and one or two virulence genes make up a very small part of parameter space), leading to a stable, single level of investment by both host and parasite at intermediate levels of virulence for most cost/benefit combinations.

We also show results from simulations when the initial dominant genotypes are randomly selected in Figure 2D–F. Although the broad behavior for investment by hosts and parasites described above still holds, particularly in the overall virulence experienced by hosts and parasites (Fig. 2F), there is considerably more variation. This suggests that there is multiple stability in the system, such that there is again uniform investment at intermediate levels, but that the precise outcome depends on the initial setup of the population. We found the final distribution of genotypes to be highly dependent on the initial distribution of strains, with those strains with an early advantage tending to shape the future course of evolution. Interestingly, with random starting conditions extreme investment by either host or parasite is much less likely, meaning virulence is rarely maximized or minimized.

We found none of our multilocus simulations resulted in "Red Queen" cycles in genotype frequencies. Instead, the host and parasite strains tend to arrange themselves to minimize virulence (as far as the costs/benefits allow), resulting in "apparent commensalism." This means that there are also rarely any static polymorphisms, that is, long-term coexistence of specific strains, in our simulations, with "matching" host and parasite strains dominating. Static diversity of hosts and parasites at identical levels of investment does arise when there is a "mismatch" between the investment by hosts and parasites, with that diversity made up of types that result in the same level of virulence (i.e., hosts with genotypes 00100 and 00001 would be equally fit against a parasite with genotype 11010). In extremely rare cases, we see diversity at different levels of investment. This occurs only at specific levels of cost or benefit where the trade-offs roughly balance between two levels of investment (9 and 11 of the 676 cost-benefit structures in the fixed and random starts, respectively, resulted in such host diversity, and 5 and 10 in parasite diversity).

## MA MODEL

The MA model produced very similar results to its GFG counterpart. In the single-locus model, there is again an unstable (saddle) internal equilibrium, with all trajectories now resulting in tolerance (t-v or T-V depending on the initial conditions). Investigations of the multilocus model show that the final coevolutionary outcome is highly dependent on the starting conditions, but we again find "apparent commensalism" with both species arranging their genotypes to match such that virulence is kept very low. We again found no cycling, but we did find more evidence of static polymorphisms within both species, because multiple partially matching strains will have equal fitness. Those genotypes that initially dominate (due to the chosen starting conditions) shape the future course of evolution, with matching, or partially matching, genotypes from the other species quickly being selected for.

## UNIVERSAL TOLERANCE

We initially consider evolutionary invasion models that assume tolerance is shared through a multiplicative function, such that different host and parasite strains are "universally" more or less

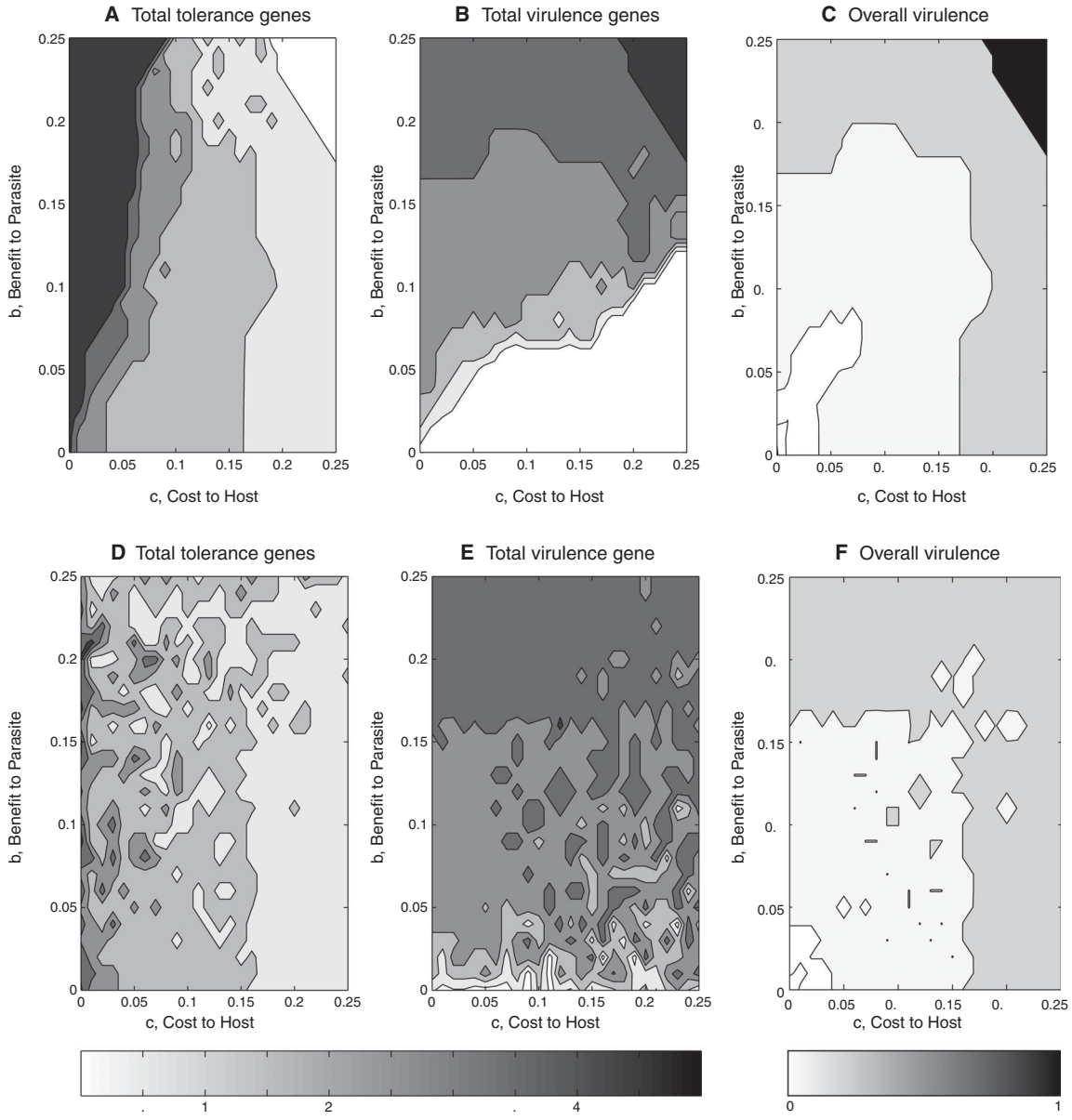


**Figure 2.** **Multilocus GFG model shows strong effects of costs and evidence of multiple stable strategies. Simulation results from the five-locus GFG model for a single simulation run for each cost and benefit combination. Panes A–C (top row) show results where the initially dominant population had no tolerance or virulence genes, and panes D–F (bottom row) where the initially dominant population genotypes were randomly selected. Panes A and D show (average) host investment, panes B and E (average) parasite investment, and panes C and F the overall effect on (average) virulence. In A, B, D, and E darker shadings imply a greater level of investment with contours marking each extra gene. In C and F, darker shadings indicate higher virulence, with each contour marking an exponential step in the virulence (i.e., $\sigma^c$, where *c* is the contour).**

tolerant than others. There is therefore no specificity between host types and parasite strains. Figure 3 shows how the possible coevolutionary behaviors at a fixed endpoint of coevolution, where there is intermediate investment by both host and parasite, depend on the curvatures of the respective trade-offs (negative curvature implies costs "accelerate," positive curvatures costs "decelerate," and zero curvature yields a linear trade-off). We have focused on the region of the space where the stability conditions intersect. The dotted region shows those combinations that produce a long-term attractor for both species at this intermediate level of investment (a CSS). Everywhere else, besides the numbered regions, this intermediate point is a repeller. This leads to bistability (although the ending points may not be stable, but rather limits of evolution) such that the host and parasite will maximize or minimize virulence depending on the initial conditions. In region 1, the host strategy is a CSS but the parasite strategy is an attracting

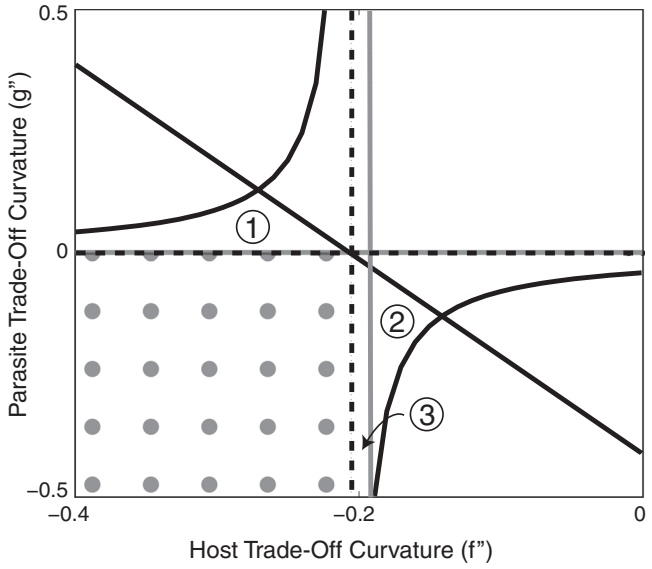


**Figure 3. Universal tolerance model shows strong effects of trade-off shapes but no possibility of evolutionary branching. Classification of evolutionary behavior in the evolutionary ecology model for varying host and parasite trade-off curvatures at a fixed singular point. The gray lines mark the boundaries of evolutionary stability (vertical line for the host; horizontal line for the parasite), the dashed black lines the single-species evolution boundaries of convergence stability, and the solid black lines the trace and determinant conditions governing coevolutionary convergence. The dotted region marks a co-CSS. Region 1 produces parasite "entrapment" by the host, and region 2 host "entrapment" by the parasite. Region 3 produce an achievable Garden of Eden. Elsewhere the system produces a coevolutionary repeller. Parameter values: $b = 0.5$, $q = 0.2$, $\gamma = 0.5$, $a = 2$, $\beta = 2$, $h = 1$, $p = 1$.**

fitness minimum (evolutionarily unstable but convergence stable). However, evolutionary branching will not occur here as the parasite does not have mutual invadibility (Geritz et al. 1998; Best et al. 2008) and the parasite will remain "trapped" at this fitness minimum. The same occurs for the host in region 2—the parasite is at its CSS but the host will converge to a fitness minimum but be unable to branch due to the parasite's entrapment. In region 3 the host's strategy when it evolves alone is a "Garden of Eden," an unattainable fitness maximum. However, in the coevolutionary model the parasite's counteradaptation allows the host to successfully reach this fitness maximum. Overall we emphasize that no evolutionary branching of either hosts or parasites can occur, confirming the results of a previous coevolutionary model (Best et al. 2008). Therefore there will be no static polymorphisms in either population. Numerical investigation also found no evidence of evolutionary cycles through a Hopf bifurcation (the mathematical condition denoting the onset of cycles; see Strogatz 1994) at the boundary of convergence stability.

Using host and parasite trade-offs that result in the system reaching a long-term attractor (co-CSS), in Figure 4, we show how the respective host and parasite strategies, $\alpha_H$ and $\alpha_P$, vary with host life span. In Figure 4A, we show the purely evolutionary responses for the host (gray line) against a fixed parasite ($\alpha_P = 1$) and for the parasite (black line) against a fixed host ($\alpha_H = 1$). The host has little tolerance (i.e., high $\alpha_H$) at short life spans as the cost of reduced reproduction is not worth paying. However, as life span increases and hosts spend a greater proportion of their lifetime infected, there is a greater advantage to tolerance. The parasite invests in greater transmission, and therefore has higher virulence, at short life spans as there is a need to infect quickly before the hosts die. However, as life span increases so does the infectious period and there is less benefit to fast transmission.

In Figure 4B, we show the host (gray line) and parasite (black line) responses when the two species coevolve, as well as the actual virulence, $\alpha = \alpha_H \alpha_P$ (dashed line). The host response is almost identical to the trends predicted by the evolutionary models, however, the parasite's strategy is substantially different from its purely evolutionary response, increasing its investment with increasing life span. As the host increases its tolerance at high life spans, the parasite is able to increase its transmission rate without raising the level of actual virulence; thus the tolerance in the host has reduced the cost of investing for the parasite. We note that these results match those of a similar coevolutionary study by Restif and Koella (2003). Interestingly, the actual virulence in the coevolutionary model, which combines both parasite and host strategies, is almost identical to when the parasite evolved alone, suggesting the parasite will always be selected to invest up to a set level of reduced infectious period. This result matches with the findings of Miller et al. (2006), where it was shown that if a tolerance mechanism causing a constant reduction in virulence has become fixed, the parasite is always selected to increase investment due to the reduced costs. As such the dynamic process of coevolution has little effect on the outcomes in the evolution of tolerance, with a two-stage process of host evolution followed by parasite evolution resulting in equivalent predictions.

## TOLERANCE RANGE

In our "tolerance range" model (cf. Best et al. 2010), we assume that the degree of virulence is jointly controlled by both the host and parasite, depending on specific combinations of host and parasite strains. If there is simply a trade-off in the host between $a$ and $h$ and in the parasite between $\alpha_0$ and $p$, then the parasite will always evolve to the generalist, low-virulence type as there is no benefit to incurring high virulence against any hosts. The host then evolves to the most intolerant type as this maximizes reproduction while virulence is minimal due to the parasite's strategy. If we assume that there is a further trade-off in the parasite to transmission, then intermediate CSS strategies may evolve

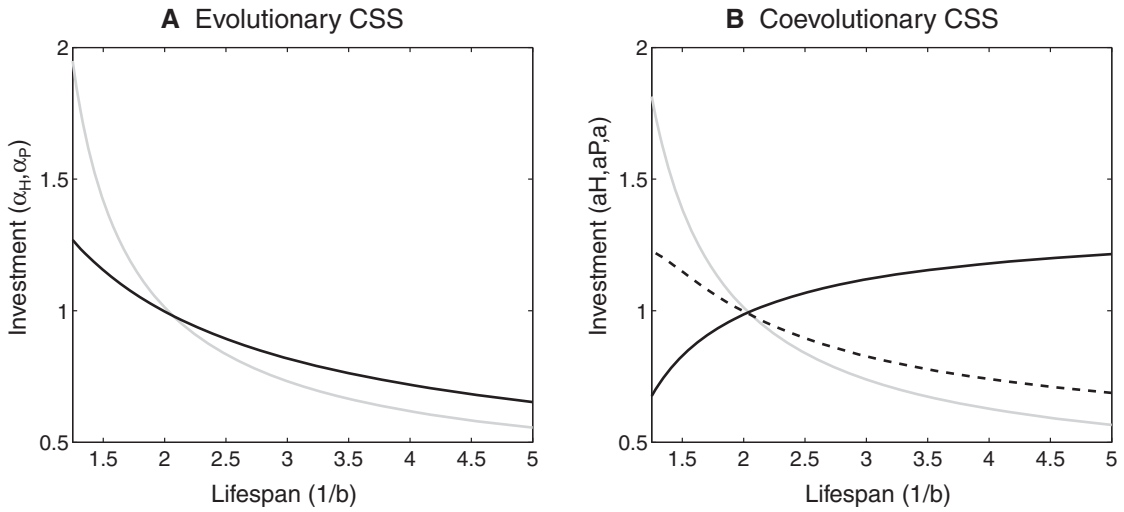


**Figure 4. Coevolution in the universal tolerance model alters the parasite strategy to invest in greater transmission at long life spans. Plots showing the variation in CSS investment by hosts (thin line) and parasites (thick line) in (A) a purely evolutionary model and (B) the fully coevolutionary model. In (B), the dashed line shows the combined effect on overall virulence. The trade-offs used were $a(h) = 2.1 - 0.3(1 - (h - 0.5)/1.5)/(1 + 3.33(h - 0.5)/1.5)$ and $\beta(p) = 2.8 - 1.37(1 - (p - 0.5)/1.5)/(1 + 0.43(p - 0.5)/1.5)$. Parameter values as of Figure 3.**

because now there is a benefit to the parasite incurring virulence. However, we still find that there can be no evolutionary branching in either species. Numerical investigations also found no evidence of evolutionary cycles. An equivalent model of the coevolution of resistance range (Best et al. 2010) shows both the evolution of trait diversity and cycles.

## Discussion

There is now a body of theory on the evolution of host tolerance mechanisms to disease (Boots and Bowers, 1999; Roy and Kirchner 2000; Restif and Koella 2003, 2004; Miller et al. 2005; Best et al. 2008, 2009b; Boots et al. 2009; Carval and Ferriere 2010), but the relevance of these results without considering the coevolution of the parasite has been questioned (Little et al. 2010). Here we developed a comprehensive range of mathematical models to examine the coevolution of host tolerance and parasite virulence across a range of classic host–parasite coevolutionary modeling frameworks. Our key result is that diversity, whether it is through "Red Queen" cycles or static polymorphisms, rarely occurs when defense is through tolerance. As such, by considering a wide range of fully coevolutionary theoretical frameworks, we have shown the broad applicability of these insights of the evolutionary theory. Beyond this, we generally predict intermediate investment in both the host and parasite but multiply stable (often extreme) states are common, raising the potential for dramatic shifts in the impact of the infectious disease.

Although evidence of tolerance to disease in animal and plant hosts continues to grow (Simms and Triplett 1994; Stowe 2000; Råberg et al. 2007, 2009; Ayres and Schneider 2008; Boots 2008; Read et al. 2008; Medzhitov et al. 2012, Adelman et al. 2013), few studies have investigated whether there are costs to this tolerance. We therefore have little information on where any costs are likely to be manifested. Generally, we would expect from theory that qualitative conclusions concerning the evolution of defense are independent of where the costs are incurred (Bowers et al. 1999), although we have previously identified that the evolution of sterility tolerance is sensitive to where costs act (Best et al. 2009b). It is therefore important that there is more empirical work on the nature of costs to tolerance in disease interactions. Similarly, there is little clear evidence from empirical studies of how specific the genetic interaction for tolerance is in particular systems. One study found evidence of a GFG like interaction for tolerance to bacterial wilt in *Arabidopsis* conferred by a single R-gene (Van der Linden et al. 2013), but such specificities might also be effectively modeled by a tolerance range function. Overall, however, our results have emphasized that whatever the model structure, the coevolutionary interaction of hosts and parasites is not in itself enough to generate diversity in host tolerance.

Understanding the processes that generate and maintain diversity in host–parasite systems has been the focus of much theoretical study. "Red Queen" evolutionary cycles are a well-known phenomenon in MA and GFG models (Jayakar 1970; Sasaki 2000; Agrawal and Lively 2002), while static polymorphisms can be generated through ecological interactions (Tellier and Brown 2007a,b, 2009; Best et al. 2009a, 2010; Boots et al. unpubl. ms.). Studies on the evolution of host tolerance, without the coevolution of its parasite, have previously found that static diversity through

evolutionary branching cannot occur (Boots and Bowers 1999; Miller et al. 2005; but see Best et al. 2008). Here, we have shown that in a fully coevolutionary framework, diversity of hosts and parasites does not occur when the host evolves tolerance, either through transient cycles or long-term coexistence and therefore we confirm these previous findings (Best et al. 2008). There is increasing experimental evidence that tolerance mechanisms are a key component of host defenses in a range of host–parasite systems (Råberg et al. 2007, 2009; Ayres and Schneider 2008; Boots 2008; Read et al. 2008; Medzhitov et al. 2012), and there is evidence of variation in tolerance (Råberg et al. 2007), which conflicts with the predictions from purely evolutionary theoretical studies (Roy and Kirchner 2000; Miller et al. 2005). Although we have shown here that the coevolution of the parasite is not in itself enough to lead to the maintenance of diversity in tolerance mechanisms, in a previous study we identified two scenarios in which static diversity in host tolerance could emerge and be maintained (Best et al. 2008). The first required trade-offs in the host not just between tolerance and a life-history characteristic (typically reproduction), but additionally in resistance, and experimental studies do indeed suggest that there may be trade-offs between tolerance and resistance mechanisms (Råberg et al. 2007; Ayres and Schneider 2008). The second scenario required that tolerance be targeted at the sterilizing effects of disease, rather than the mortality effects (Best et al. 2008, 2009b). This is important because it is often unclear from experimental studies where tolerance mechanisms occur. Overall, the theory tells us that further empirical and theoretical work is needed to understand the processes that generate and maintain diversity in tolerance. A combination of theory and empirical work is likely to be needed to understand the specific processes underpinning this diversity in particular host–parasite systems.

We might have expected to find that diversity in tolerance would occur where there is some specificity between host and pathogen strains (cf. Best et al. 2010). However, our models showed here that diversity was not predicted when this specificity was incorporated in to our evolutionary ecology model. In the GFG and MA models, where a stricter specificity is assumed, we found rare instances of static diversity, but this was generally only between genotypes with identical levels of investment. As such there is genotypic diversity but not trait diversity. Overall, we note that theory does not completely rule out the generation and maintenance of diversity in host tolerance (Best et al. 2008), but it does predict that such diversity will be more limited compared to resistance mechanisms. This prediction should be tested by comparative studies as more data becomes available.

Given that both the host and parasite benefit from reduced virulence, it is intuitive that our GFG and MA models revealed a strong degree of "apparent commensalism" (Miller et al. 2006). For any set level of investment, combinations of host and parasite strains that minimize virulence will naturally dominate. An interesting insight from the evolutionary ecology model is that the parasite is much more sensitive to the coevolution of host tolerance than vice versa, a result also seen in coevolutionary studies of resistance (Best et al. 2009a). When the parasite evolves alone, we have confirmed the classic result that the parasite should decrease virulence with increasing host life span, but found that when the host coevolves this pattern reverses (which confirms the results of Restif and Koella 2003). This is because of the investment in tolerance by the host, which allows the parasite to gain "free" infections. These results have clear links to those of Miller et al. (2006), who found that host–parasite interactions may appear commensal when the parasite is able to respond to host evolution in a two-stage evolutionary process, as the parasite has adapted its strategy based on the reduced costs of investment caused by host tolerance.

Although the coevolution of tolerance and virulence is unlikely to result in cycles or coexistence, we do find multiply stable evolutionary endpoints. As such, the level of disease-induced mortality is likely to be highly sensitive to any small changes to the ecological or genetic background and populations may experience large shifts in virulence as the system moves from one attractor to another. In evolutionary ecology models, bistability caused by evolutionary repellers is a common outcome when the costs to increased defense or infectivity are strongly decelerating. It is hard to assess whether bistability is more or less "likely" when comparing resistance and tolerance evolution as we cannot ensure that the parameter values covered by the trade-offs are identical, but our results show that bistability can occur in tolerance evolution for a wide range of trade-off shapes, including linear and even accelerating costs. In GFG and MA models, the existence of multiply stabile states appears to be rarely examined, but again our results suggest that this may be a common outcome in the coevolution of tolerance.

In summary, we have provided a broad coevolutionary perspective on the evolution of tolerance by confirming and extending theoretical results on the evolution and coevolution of host tolerance with a range of mathematical models. In particular, we have highlighted that, even when the parasite coevolves, either static or temporal diversity is far less likely to evolve when the host presents tolerance rather than resistance to disease.

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