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*Review*

# The role of ecological feedbacks in the evolution of host defence: what does theory tell us?

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Hosts have evolved a diverse range of defence mechanisms in response to challenge by infectious organisms (parasites and pathogens). Whether defence is through avoidance of infection, control of the growth of the parasite once infected, clearance of the infection, tolerance to the disease caused by infection or innate and/or acquired immunity, it will have important implications for the population ecology (epidemiology) of the host–parasite interaction. As a consequence, it is important to understand the evolutionary dynamics of defence in the light of the ecological feedbacks that are intrinsic to the interaction. Here, we review the theoretical models that examine how these feedbacks influence the nature and extent of the defence that will evolve. We begin by briefly comparing different evolutionary modelling approaches and discuss in detail the modern game theoretical approach (adaptive dynamics) that allows ecological feedbacks to be taken into account. Next, we discuss a number of models of host defence in detail and, in particular, make a distinction between 'resistance' and 'tolerance'. Finally, we discuss coevolutionary models and the potential use of models that include genetic and game theoretical approaches. Our aim is to review theoretical approaches that investigate the evolution of defence and to explain how the type of defence and the costs associated with its acquisition are important in determining the level of defence that evolves.

**Keywords:** defence; evolution; theory; parasites; resistance; tolerance

## 1. INTRODUCTION

The ubiquity of infectious organisms (parasites and pathogens) in nature and the damage that they cause to their hosts has led to the evolution of a diverse range of host defence mechanisms, from simple mechanical barriers through to complex immune systems. As emphasized throughout the different contributions to this special issue, these defence mechanisms need to be understood in the context of evolutionary theory. In particular, defence is a fundamental part of the life history of the host and is costly to acquire. Evolutionary theory allows us to examine the factors that lead to different levels of investment in different forms of defence. As a consequence of the continued importance of parasites (broadly defined here to include microparasites and pathogens, including viruses and bacteria) to agriculture and human health (Keeling *et al.* 2001; Lloyd-Smith *et al.* 2005), and the growing recognition of the role of parasites in structuring natural communities (Hudson *et al.* 1998; Haydon *et al.* 2006), there is a well-developed theory on the evolution of hosts. This theory includes models that focus on genetic interactions (Thompson & Burdon 1992; Agrawal & Lively 2002), and those that consider explicitly the ecological dynamics of the host–parasite (pathogen) interaction. In this review, we focus on this latter class of model and examine what theory tells us about the potential role of ecological feedbacks in the evolution of host defences (the way life-history parameters evolve will feedback on species density—known as an ecological feedback). In particular, we focus on modern game theoretical models (that use the techniques of adaptive dynamics).

So why should ecological feedbacks be important to the evolution of defence against infectious organisms? Essentially, the type and degree of defence invested in by hosts will affect the prevalence of the parasite in the population. Since this prevalence alters the chance that an individual will be challenged and infected, it therefore partly defines the selection pressure for defence. For example, consider a mutation that not only reduces the chance that an individual becomes infected but also includes a cost such that birth rate is reduced. If the chance of infection is high enough such that the cost is worth paying, this trait will spread through the population. Clearly, however, as the frequency of this trait increases in the population, less infection will occur and therefore prevalence decreases. As such, there is less selection for the trait as it spreads in the population. This frequency-dependent selection emerges from the feedback of the ecological dynamics to the evolutionary ones. Any defence mechanism that reduces the prevalence of the parasite (e.g. avoiding

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Table 1. The outcome of interactions for a single locus (1) and two loci (1 or 2) set-up between a host with susceptible (S) or resistant (R) alleles and a parasite with avirulent (A) and virulent (V) alleles, indicating whether infection (inf) or no infection (no inf) will occur under a gene-for-gene model framework and a matching-alleles model framework.

| parasite genotype | host genotype | | | |
|---|---|---|---|---|
| *gene-for-gene model* | | | | |
| *1 locus* | $1_S$ | $1_R$ | | |
| $1_A$ | inf | no inf | | |
| $1_V$ | inf | inf | | |
| *2 loci* | $1_S\,2_S$ | $1_R\,2_S$ | $1_S\,2_R$ | $1_R\,2_R$ |
| $1_A\,2_A$ | inf | no inf | no inf | no inf |
| $1_V\,2_A$ | inf | inf | no inf | no inf |
| $1_A\,2_V$ | inf | no inf | inf | no inf |
| $1_V\,2_V$ | inf | inf | inf | inf |
| *matching-alleles model* | | | | |
| *1 locus* | $1_S$ | $1_R$ | | |
| $1_A$ | inf | no inf | | |
| $1_V$ | no inf | inf | | |
| *2 loci* | $1_S\,2_S$ | $1_R\,2_S$ | $1_S\,2_R$ | $1_R\,2_R$ |
| $1_A\,2_A$ | inf | no inf | no inf | no inf |
| $1_V\,2_A$ | no inf | inf | no inf | no inf |
| $1_A\,2_V$ | no inf | no inf | inf | no inf |
| $1_V\,2_V$ | no inf | no inf | no inf | inf |

infection in the first place, recovering more rapidly from infection or controlling the growth rate of the parasite within the host) has this type of feedback. Since these defences reduce the parasite's prevalence, they also reduce its fitness and are therefore classified as forms of 'resistance' (Roy & Kirchner 2000; Restif & Koella 2004; Miller *et al*. 2005; Råberg *et al*. 2007). By contrast, a defence mechanism that ameliorates the damage that a parasite causes to its host, such that it reduces an individual's disease-induced mortality, will lengthen the infectious period of the parasite. As such, this type of mechanism increases parasite prevalence as it spreads through the host population. This is a type of 'tolerance' (Roy & Kirchner 2000; Restif & Koella 2004; Miller *et al*. 2005; Råberg *et al*. 2007) that increases the parasite's fitness, and since the ecological feedback is very different from those occurring with resistance mechanisms, it leads to very different evolutionary outcomes. As ecological scenarios become more complex with, for example, multiple infections, different transmission modes or long-lasting acquired immunity, the ecological feedbacks may in turn become very complex, such that they are hard to understand intuitively. It is here that models become useful. They can make predictions in these complex situations and also guide our intuition in understanding how ecological interactions underpin these predictions.

The purpose of this paper is to review the theoretical studies that have examined the evolution of defence. We start by giving an overview of the different modelling approaches and provide insight into how these can be applied to different questions. Next, we give a detailed introduction to the modern game theoretical approach (also called adaptive dynamics or evolutionary invasion analysis), which allows ecological feedbacks to be included in evolutionary models. (Note that we use this terminology as we wish to highlight that there are similarities between game theory and adaptive dynamics, particularly in terms of determining whether a strategy can be invaded by other strategies. We also acknowledge that the techniques are not analogous and differ, for example, in terms of local and global stability properties and the mutation/invasion evolutionary dynamics.) We then review theoretical findings on the evolution of defence and conclude with a discussion of future directions for evolutionary theory of host defence.

## 2. APPROACHES TO EVOLUTIONARY MODELLING

There are a number of different approaches to modelling evolutionary dynamics. Here, we introduce briefly locus-based and quantitative genetic (QG) approaches and then discuss in detail the game theoretical (adaptive dynamics) approach. Our aim is to introduce how each approach can be used to understand the evolution of host defence and to outline the different assumptions on which they are based. More general reviews on evolutionary modelling techniques can be found, among other places, in Abrams (2001) and Fussman *et al*. (2007).

### (a) *Locus-based models*

There has been a long tradition of using an approach based on the interaction of genes in hosts and parasites (normally termed gene-for-gene models) in plant–pathogen interactions (Flor 1956; Burdon 1987; Thompson & Burdon 1992). Recently, this approach has been developed and applied more widely to invertebrate diseases, in 'matching-alleles' models (see Grosberg & Hart 2000; Agrawal & Lively 2002). In all these models, the outcome of the interaction between hosts and parasites depends entirely upon the host's genes for resistance and the parasite's genes for infection. The purely genetic structure of these model systems has advantages in that it allows comparison with experimental data. However, such frameworks do not link phenotype to ecological (life-history) parameters and, as such, they do not include explicit ecological feedbacks. Such feedbacks in which phenotypic evolution influences the population ecology that in turn influences further evolution have been shown to be important in determining evolutionary behaviour, but this is not captured in locus-based models. Most models consider two possible alleles at two loci for the host and the parasite. In gene-for-gene models, the parasite has two possible alleles, a widely infectious allele (traditionally termed virulent, V) and a narrowly infectious allele (termed avirulent, A). (Note that the concept of virulence used here differs markedly from the concept often used in game theoretic approaches to understand parasite evolution, where virulence is defined as the increase in host mortality due to infection.) There are corresponding host alleles termed susceptible, S, and resistant, R. Hosts carrying the susceptible allele can be infected by any parasite type but those carrying the resistant allele can only be infected if there is a virulent allele at that loci. In matching-alleles models, the parasite must exactly match the host's genotype in order to infect. This is summarized in table 1.




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In gene-for-gene models, there is an advantage for parasites that carry the virulent allele as it can then infect a wider range of host genotypes. Similarly, there is an advantage for hosts that carry the resistant allele. If there are no costs to virulence or resistance, then these two alleles will evolve to fixation. If there is a cost to resistance and virulence, then the allele frequencies will cycle and therefore diversity of host and parasite types is maintained. The cycle occurs since, when the virulent type dominates, the resistant type is ineffective and yet incurs a cost, and therefore selection tends to increase the frequency of the susceptible allele. This in turn means that the parasite can infect the host without incurring the cost of the virulent allele and so the frequency of avirulent alleles increases. It is then of benefit for the host to pay the cost of resistance to limit infection, and then in turn for the parasite to pay the cost of the virulent allele. The cycle then repeats. Thus, the costs to resistance and virulence in the gene-for-gene system can be thought of as a form of frequency-dependent selection and the system oscillates between specialist and generalist hosts and parasites. This cycling behaviour is even more pronounced in the matching-alleles model, which can be considered as one in which all parasite types specialize on a single host type (note that the costs to resistant and virulent alleles are not relevant here). The cycle occurs due to a similar process as that outlined for the gene-for-gene model since the host can evade infection by possessing alleles that do not match the parasites. Model systems that lie somewhere between the gene-for-gene and matching-alleles systems can also be constructed; these tend to generate cycles and promote variation in host and parasite genotypes (for a full description, see Agrawal & Lively 2002).

### (b) *Quantitative genetic models*

The classic gene-for-gene and matching-alleles models assume that relatively few loci are important in determining whether infection takes place. Extensions of the classic theory to include multi-locus gene-for-gene frameworks (Sasaki 2000) found that small costs to resistance (and virulence) promote cycles in allele frequency (as in the classic gene-for-gene set-up). When the costs of virulence increase, provided the host has the resistance allele at a sufficient number of loci, the cycles disappear and, instead, the host maintains a static polymorphism against a single completely avirulent parasite strain (Sasaki 2000). By further extending the number of loci that contribute to host defence, the frameworks effectively become QG models. These models are based on the assumption of sexual reproduction and follow the evolution of a phenotypic trait. They represent genetic systems where a large number of loci make a small additive contribution to a trait. Genetic variation in these models is not modelled as an explicit mutation process but maintained by including the additive genetic variance of each trait. QG theory (Lande 1976) then follows the change in the mean value of a phenotypic trait under selection. By assuming that the trait distribution is unimodal, symmetric and narrow compared with the distribution of the fitness function, the expression for the change in the mean trait value, $\Delta z^*$, can be written as

$$\Delta z^* = \frac{V_A}{W^*}\frac{\partial W}{\partial z}\bigg|_{z=z^*}, \tag{2.1}$$

where $V_A$ is the additive genetic variance of the trait; $W^*$ is the mean fitness; and $[\partial W/\partial z]_{z=z^*}$ is the fitness gradient evaluated where the trait is equal to the mean trait value of the population (see Hochberg & Holt 1995; Abrams 2001). The simplification assumes that the distribution of trait values remains unimodal under selection, which fits well with observations from genetic models with random mating, weak selection and many independent loci having an additive effect on the trait (Abrams 2001). The approach has been used most commonly to examine the evolution of phenotypic quantities for interacting species (Taper & Case 1985 and references in Abrams 2001) and to examine the evolution of host defence in a host–parasitoid system (Hochberg & Holt 1995). Here, the population dynamics were represented by a modified version of the classical Nicholson–Bailey difference equations for host and parasitoid abundance (that included host self-regulation and aggregated parasitoid searching). Host defence occurred through a refuge from parasitoid attack or by an immunological response that arrested parasitoid development. The paper showed that host refuge evolution allowed the populations to maintain a stable equilibrium with host abundance not depressed substantially below its carrying capacity for a wide range of conditions. The evolution of host defence depended on the relative benefit of increasing defence compared with the cost in terms of the reduction in growth rate, and these costs were scaled by the ability of the parasitoid to counter the defence.

### (c) *Modern game theoretical approaches (adaptive dynamics)*

The game theoretical 'adaptive dynamics' approach shares many similarities with the QGs approach. Both assume that there are many genes which have a small additive effect and that the direction of evolution depends on the fitness gradient. However, QGs assumes that 'mutations' (genetic variation) arise implicitly due to a probability distribution and therefore many strains are maintained at low density (since there is a distribution of traits around the population mean). In general, the evolutionary outcome depends a great deal on the nature of this trait probability distribution. By contrast, under adaptive dynamics, stochastic mutations arise explicitly and a more restricted set of strains occurs (therefore strain variation is due to mutation invasion and survival processes, rather than the QG assumption of a fixed distribution). Commonly, adaptive dynamics employs an asexual modelling approach and examines the invasion of new rare mutants into a monomorphic resident population. The ecological time scale is assumed to be much faster than the evolutionary time scale, and therefore mutant strains attempt to invade resident populations at their dynamic attractor (this means the population densities have time to 'settle down' before a new mutant type can attempt to

Box 1

The model of host defence developed by Boots & Haraguchi (1999) can be represented by the following equations:

$$\frac{dS_i}{dt} = r_i S_i - qS_i \sum_i (S_i + I_i) - \beta_i S_i \sum_i I_i \qquad \frac{dI_i}{dt} = \beta_i S_i \sum_i I_i - (\alpha + b) I_i. \tag{B 1}$$

Here, $S$ is the density of the susceptible population; $I$ is the density of the infected population; and the dynamics are shown for the $i$th host strain. The parameters are growth rate, $r$ (equal to birth minus death), which is modified due to density dependence through the crowding parameter $q$. Hosts die at natural rate, $b$, and at an additional rate due to infection, $\alpha$. The transmission rate of infection is $\beta$. They investigated the evolution of host resistance and considered a trade-off between host growth rate, $r$, and transmission rate $\beta$. From equation (B1), it is possible to determine the fitness of a rare mutant type ($i=y$) attempting to invade an established resident population ($i=x$) at equilibrium ($S_x$, $I_x$),

$$s_x(y) = r_y - q(S_x + I_x) - \beta_y I_x = r_y - q\left(\frac{\alpha + b}{\beta_x} + \frac{\beta_x - q(\alpha + b)}{\beta_x(\beta_x + q)}\right) - \beta_y\left(\frac{\beta_x - q(\alpha + b)}{\beta_x(\beta_x + q)}\right). \tag{B 2}$$

Whenever $s_x(y) > 0$, the mutant type, $y$, can invade and whenever $s_x(y) < 0$ it cannot. The invasion boundary $s_x(y) = 0$ and the boundary $s_y(x) = 0$ are used to produce a trade-off invasion plot (TIP). Here, $s_y(x)$ is the fitness of type $x$ attempting to invade a type $y$ resident. A TIP plots the invasion boundaries $s_x(y) = f_1 = 0$ and $s_y(x) = f_2 = 0$ in parameter space and the position of the trade-off curve in relation to the invasion boundaries determines the evolutionary dynamics (Bowers *et al.* 2005; Hoyle *et al.* 2008).The invasion boundaries for the model represented by equation (B 1) are

$$r_y = f_1(\beta_y) = r_x \frac{q + \beta_y}{q + \beta_x} - \frac{(\beta_y - \beta_x) q(\alpha + b)}{\beta_x(q + \beta_x)}; \qquad r_y = f_2(\beta_y) = r_x \frac{q + \beta_y}{q + \beta_x} - \frac{(\beta_y - \beta_x) q(\alpha + b)}{\beta_y(q + \beta_x)}. \tag{B 3}$$

These invasion boundaries are plotted on the TIP and, if ($\beta_x$, $r_x$) is an evolutionary singular point, the invasion boundaries can be used to partition the parameter region in terms of the possible evolutionary behaviour (figure 1). In the region between $f_1$ and $f_2$ in figure 1, the evolutionary behaviour is partitioned by the dashed line (which is the line with the mean curvature of $f_1$ and $f_2$ at the singular point ($\beta_x$, $r_x$)). From this TIP, it is clear that all trade-offs with accelerating costs (those which curve below $f_1$) will produce evolutionary attractors. Trade-offs with decelerating costs (and above the dashed line) will produce evolutionary repellors and therefore lead to the evolution of extreme values. Trade-offs with weakly decelerating costs (between the dashed line and $f_1$) will produce evolutionary branching points and hence dimorphism or polymorphisms evolve. Simulations of the model (equation (B1)) indicate how the transmission coefficient, $\beta$, evolves for the different types of evolutionary behaviour. The lines in the simulations represent the way in which $\beta$ evolves if new mutations are introduced at low density into an established population. For trade-off shapes that lead to a repellor, $\beta$ evolves away from $\beta_x$, and for an attractor $\beta$ evolves towards and remains at $\beta_x$. For trade-offs that lead to branching, the population evolves towards $\beta_x$, and when close by undergoes disruptive selection, which leads to evolution of distinct types.

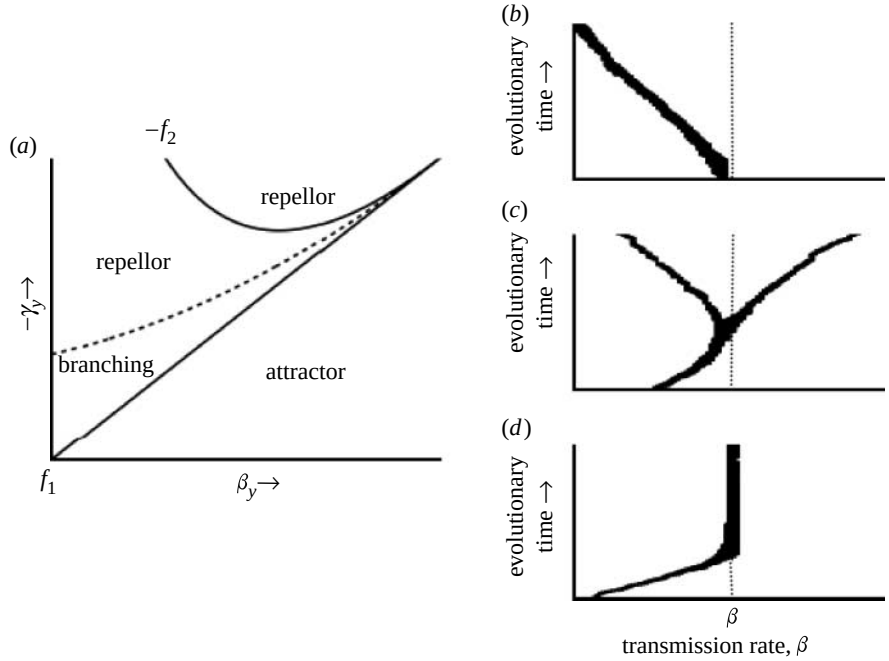


Figure 1. (*a*) The TIP for the model system described in Boots & Haraguchi (1999). For different trade-off shapes (cost structures), the evolutionary behaviour can exhibit a (*b*) repellor, (*c*) branching point or (*d*) an attractor. Simulations of the evolutionary process for the model show how the transmission coefficient $\beta$ evolves under the different types of evolutionary behaviour. For more details on TIPs and simulating adaptive dynamic processes, see Bowers *et al.* (2005).

invade). Evolution can be directed towards a fitness minimum where disruptive selection can lead to evolutionary branching and the evolution of distinct strains away from the fitness minimum (see Dieckmann & Law 1996; Metz *et al.* 1996; Geritz *et al.* 1998; Abrams 2001). By contrast, QG models may have equal

ecological and evolutionary time scales, such that evolutionary changes occur at rates similar to changes in the densities of hosts and parasites. Although disruptive selection is possible, the population is likely to remain at the fitness minimum because it is limited by the trait distribution, which remains unimodal due to sex and recombination each generation.

The key expression in the analysis of adaptive dynamics is the fitness function of the mutant strategy, which is calculated as the *per capita* growth rate of a mutant strategy, $y$, in an environment determined by the resident population, $x$, and denoted by $s_x(y)$. If $s_x(y)$ is negative, the mutant dies out; if $s_x(y)$ is positive, it will spread. Successful mutants can replace the existing resident type and in so doing change the environment. The feedback between evolution reshaping the environment and the environment determining which types can evolve is therefore very clear. Given that mutations are small, the population will evolve in the direction of the local fitness gradient, $[\partial s_x(y)/\partial x]_{y=x}$ (if a nearby type has a greater fitness than the current type, it will be favoured and we therefore evolve up gradients of the fitness function). The population continues to evolve until it reaches an evolutionary fixed point, $x^*$, for which the fitness gradient is zero. Fixed points under the QG model framework (equation (2.1)) also occur when the fitness gradient is zero. In fact, the canonical equation of the adaptive dynamics framework that considers the evolution of the trait value explicitly uses an expression that is analogous to equation (2.1). Adaptive dynamics determines the behaviour at the evolutionary fixed point by examining the second derivatives of the fitness function (precisely, from combinations of the associated second-order partial derivatives of the fitness function with respect to the mutant and resident strategies). The fixed point can be classified in terms of two properties: convergence stability (CS) and evolutionary stability (ES). If the fixed point is CS, then types away from the fixed point will evolve towards it, while, if the fixed point is ES, then it cannot be invaded by nearby types. Combinations of these properties lead to different evolutionary outcomes. For instance, if $x^*$ is not CS and not ES, it is an evolutionary repellor and types will evolve away from it. If it is not CS but is ES, it is again an evolutionary repellor, with the exception of at $x^*$ at which it cannot be invaded (known as 'Garden of Eden' evolutionary behaviour). If $x^*$ is CS and ES, then it is an evolutionary attractor. The phenomenon of evolutionary branching occurs when $x^*$ is CS but not ES. In this case, we get evolution towards $x^*$ but when the population is close by it undergoes disruptive selection and two distinct strategies coexist either side of $x^*$ (see box 1).

## 3. APPLICATION OF MODELS OF THE EVOLUTION OF DEFENCE

There are a number of theoretical studies investigating the evolution of resistance to pathogens that take into account ecological feedbacks and frequency dependence (Antonovics & Thrall 1994; Bowers *et al.* 1994; Boots & Bowers 1999, 2003, 2004; Boots & Haraguchi 1999; Roy & Kirchner 2000; Restif & Koella 2003, 2004; Miller *et al.* 2005). All of these models assume that defence incurs a cost such that the host has a reduced fitness in the absence of disease. The existence of these costs is supported by both theoretical arguments (Stearns 1992) and empirical evidence (Boots & Begon 1993; Biere & Antonovics 1996; Kraaijeveld & Godfray 1997; Rolff & Siva-Jothy 2003; Siva-Jothy *et al.* 2005). The models have made a number of important predictions, notably, as mentioned before, that tolerance has unique evolutionary dynamics, since, as it spreads through the host population, it leads to increased prevalence of the pathogen (Roy & Kirchner 2000). By contrast, other forms of resistance reduce disease incidence as they spread, leading to the possibility of polymorphism (Antonovics & Thrall 1994; Bowers *et al.* 1994; Boots & Bowers 1999, 2004; Boots & Haraguchi 1999). We now describe a number of these modelling papers in detail before outlining future directions for the theory. A summary of the types of defence considered and evolutionary framework of each of the main papers discussed is given in table 2.

In 1994, two papers (Antonovics & Thrall 1994; Bowers *et al.* 1994) appeared in the same volume of *Proceedings of the Royal Society B*, which examined with almost identical models (and the convergent evolution of the same graphical presentation of their results) competition between a costly resistant strain and a susceptible one. The resistant strain was less likely to become infected, but had a lower birth rate or was more susceptible to crowding. The models considered the interaction of the two strains and plotted the outcome (susceptible wins, resistant wins or coexistence) in a reciprocal invasion plot that fixes the most susceptible strain and looks at whether different resistant strains can invade. Both studies made similar conclusions: the evolution of resistance depended on the cost structure, but this was asymmetric such that coexistence was likely between highly susceptible and highly resistant strains. Furthermore, very susceptible strains could coexist with very resistant ones even if the resistant ones did not pay very large costs.

These two papers considered only the interaction of two strains of the host. Boots & Haraguchi (1999) extended this work to a multi-strain context and in so doing produced an adaptive dynamical model of the evolutionary dynamics of host resistance to microparasitic infection. A continuum of strains of the host differed in their susceptibility to infection, with less susceptible strains paying a cost in terms of a lower intrinsic growth rate. Using a combination of analysis and graphical pairwise invasibility plots (from adaptive dynamics), they showed that the evolutionary outcome depends crucially on the shape of the constraint function between resistance and its assumed cost in terms of intrinsic growth rates. When resistance is increasingly costly (has accelerating costs), a single evolutionarily stable strategy (ESS) is predicted. Alternatively, with decreasingly costly resistance (decelerating costs), they found that the host tends to be either maximally or minimally resistant, or evolutionary branching occurs leading to dimorphism of both these types. This and

Table 2. A breakdown of the features of the principal papers assessed in this review.

| | defences | costs | framework | key results |
|---|---|---|---|---|
| Antonovics & Thrall (1994) | avoidance | reproduction, crowding | SI two-strain | highly susceptible strains can coexist with highly resistant strains |
| Bonds (2006) | sterility tolerance | maintenance | SI coevolutionary | reproduction falls upon infection when parasite 'steals' host resources |
| Boots & Bowers (1999) | avoidance, recovery, mortality tolerance | reproduction, crowding | SIS evolutionary | polymorphism possible in avoidance and recovery |
| Boots & Bowers (2004) | acquired immunity, avoidance, recovery, mortality tolerance | reproduction, crowding | SIRS evolutionary | acquired immunity has little impact on innate mechanisms; coexistence less likely for acquired immunity than innate mechanisms |
| Boots & Haraguchi (1999) | avoidance | growth rate | SI evolutionary | branching for weakly decelerating costs |
| Bowers *et al.* (1994) | avoidance | reproduction, crowding | SI two-strain | highly susceptible strains can coexist with highly resistant strains |
| Gandon *et al.* (2002) | sterility tolerance | maintenance | SI coevolutionary | reproduction increases upon infection |
| Miller *et al.* (2005) | control, mortality tolerance | reproduction | SIS evolutionary | tolerance should always evolve to fixation; polymorphism in control strains is possible under a weakly decelerating trade-off |
| Miller *et al.* (2006) | mortality tolerance | reproduction | SIS evolutionary | tolerance may lead to the evolution of either more or less virulent pathogens (with correspondingly higher or lower transmission rates) |
| Miller *et al.* (2007) | avoidance, recovery, mortality tolerance, acquired immunity | reproduction | SIRS evolutionary | acquired immunity reduces the optimal avoidance, recovery and tolerance in longer lived populations; bistability in the optimal duration of acquired immunity in shorter lived hosts |
| Restif & Koella (2003) | avoidance, mortality tolerance | mortality | SIS coevolutionary | defence maximized at intermediate parasite replication rates |
| Restif & Koella (2004) | recovery, sterility tolerance | reproduction | SIS evolutionary | mixed strategies can evolve; tolerance dominates resistance for high parasite $R_0$ |
| Roy & Kirchner (2000) | avoidance, mortality tolerance | reproduction | SI two-strain | tolerance genes will generally evolve to fixation; incomplete avoidance may lead to polymorphism; complete avoidance can never become fixed |
| van Baalen (1998) | recovery | reproduction | SIS coevolutionary | bistability in evolutionary outcomes: either highly virulent pathogens and hosts that recover quickly or avirulent pathogens and slow host recovery |

subsequent more general work (de Mazancourt & Dieckmann 2004; Bowers *et al.* 2005; Hoyle *et al.* 2008) emphasizes the importance of the shape of the trade-off (i.e. the functional relationship between the level of resistance/tolerance and its cost in terms of other life-history traits) in determining the evolutionary outcome. We emphasize this in box 1 by using the method of trade-off invasion plots (TIPs; Bowers *et al.* 2005) to illustrate the evolutionary behaviour in the Boots & Haraguchi (1999) model. It is important to emphasize that, in general, many of the outcomes of evolutionary models depend on the assumptions that are made concerning the shapes of trade-off curves (Hoyle *et al.* 2008), but we often have little idea about these relationships apart from what we can infer from mechanisms (Boots & Haraguchi 1999).

Defence mechanisms in hosts include not only avoiding becoming infected, but also recovering more quickly after infection or surviving longer once infected. Antonovics & Thrall (1994), Bowers *et al.* (1994) and Boots & Haraguchi (1999) examined only avoidance resistance and also considered an interaction where there was no recovery or reproduction from infected hosts. These models are essentially 'predator–prey' with which many of the evolutionary outcomes are shared, but it can be argued that the link between infected individuals to the susceptible class through recovery or reproduction defines a parasite ecologically. Boots & Bowers (1999) extended Bowers *et al.* (1994) to examine the evolution of costly host resistance to directly transmitted microparasites with three distinct defence mechanisms: avoidance (reduction in the

transmission rate); recovery (increase in the clearance rate); and tolerance (reduction in the death rate due to infection (virulence)). Again, when polymorphism occurred, it was between very dissimilar strains and defence was always more likely to occur in hosts with high intrinsic productivity. In general, polymorphism cannot occur when defence evolves as a tolerance mechanism, due to intrinsic positive frequency dependence such that prevalence increases as tolerance spreads through a population (Roy & Kirchner 2000). It is important to understand that such tolerance mechanisms are not an evolutionary defence for the host if there is no recovery or reproduction from infected hosts (as assumed in Bowers *et al.* 1994). In this case, the infected hosts are an evolutionary dead end, and therefore any reduction in the disease effects has no effect on host fitness. It is also important to note that tolerance is defined here as the reduction in the disease-induced death rate, and, as such, corresponds to a lengthened infectious period and increased parasite fitness. This is distinct from a mechanism that reduces the damage to host fecundity; this form of defence does not increase the parasite's fitness and does not show the same evolutionary dynamics.

Boots & Bowers (2004) further developed these models to examine the evolutionary dynamics of different forms of defence against parasites in the presence of acquired immunity. In their general model, defence could be achieved through the innate mechanisms of avoidance of infection, tolerance (as defined above), through recovery from infection or through remaining immune to infection, acquired immunity. They assumed that each of these mechanisms is costly to the host and found that the evolutionary dynamics of innate immunity in hosts that also have acquired immunity are quantitatively the same as in hosts that only possess innate immunity. However, compared with resistance through avoidance or recovery, there is less likely to be polymorphism in the length of acquired immunity within populations. Further modelling showed that long-lived organisms that can recover at intermediate rates, faced with fast transmitting pathogens that cause intermediate pathogenicity (the disease-induced mortality of infected individuals), are most likely to evolve long-lived acquired immunity. This work emphasized that whether acquired immunity is beneficial depends on the characteristics of the disease, and therefore organisms may be selected to only develop acquired immunity to some of the diseases that they encounter.

Miller *et al.* (2005) emphasized that a reduction in the disease-induced mortality that a host may suffer can arise because the host either (i) *tolerates* pathogen damage or (ii) *controls* the pathogen by inhibiting its growth. Their model assumed a free-living microparasite, allowing the two types of defence to be clearly delineated. The results emphasized that polymorphism of tolerant genotypes is impossible; by contrast, the evolution of control could lead to disruptive selection, and ultimately to dimorphism of extreme strains. Although the free-living framework used made the distinction between tolerance and control explicit, the distinction applies equally to directly transmitted parasites. Owing to the evolutionary differences exhibited, it is important to design experiments that distinguish between these two forms of host defence (one tolerance and the other resistance; Råberg *et al.* 2007).

Restif & Koella (2004) examined the concurrent evolution of resistance and tolerance. Resistance (through increased recovery) and a form of tolerance against sterility are assumed to be independent evolving traits that cause a combined cost to birth rate. They considered only evolutionarily stable strategies, and therefore no conclusions can be made regarding disruptive selection and polymorphisms. If the combined costs are additive and linear, there are never any mixed strategies; only fully tolerant or fully resistant populations can evolve and there may also be bistability. For more complex trade-offs, mixed strategies can evolve. A key result is that investment in tolerance is only relatively high when hosts are faced with parasites with a high $R_0$. This can be understood through another form of ecological feedback as tolerant hosts transmit the infection to less tolerant ones and therefore bias competition. Again, it should be noted that this form of tolerance against sterility effects does not increase the parasite's fitness, and therefore has different feedbacks compared with tolerance of mortality effects of the parasite.

### (a) *Coevolutionary models*

The models discussed in §2 consider the evolution of host defence against a fixed parasite strain (they are evolutionary models as only the host is evolving). However, the interaction between hosts and parasites is commonly a coevolutionary process. Parasites as well as hosts evolve, but there are a significant number of technical and conceptual issues with modelling coevolutionary scenarios and there are therefore currently relatively few models. One issue is that key parameters such as transmission rates are influenced by the evolution of both the host and the parasite. van Baalen (1998) neatly overcame this issue by examining the evolution of the parasite as a transmission–virulence trade-off and of host defence through recovery rate. In this way, transmission and virulence are parasite-determined traits while recovery rate is a host-determined trait. Under these circumstances, hosts tend to either lose resistance completely or invest in very high levels. When there is zero defence, parasites are common but avirulent, while, at high defence, parasites are rare but virulent.

Restif & Koella (2003) modelled the more general situation where both the host and the parasite influence the key parameters; transmission rate is determined by both the host and the parasite. The model considers two circumstances where the host can resist (avoid) or tolerate the parasite. They find the coevolutionarily stable strategy (Co-ESS) by assuming the parasite has reached its ESS replication rate, and then use this to find the host's ESS. They show that resistance is maximal at an intermediate parasite replication rate, as is tolerance (in fact, there is no investment in tolerance if the parasite has either too low or too high a replication rate). Miller *et al.* (2006) investigated the evolution of parasites once host tolerance had become fixed in the population. They also assumed that the virulence experienced by an infected host is determined

by both the host and the parasite. A variety of tolerance mechanisms were considered—parasites were shown to evolve either higher or lower within-host growth rates depending on the nature (and degree) of tolerance. For example, if tolerance reduces virulence by a constant factor, the parasite is always selected to increase its growth rate. Alternatively, if tolerance reduces virulence in a nonlinear manner such that it is less effective at reducing the damage caused by higher growth rates, this may select for either faster or slower replicating parasites. If the host is able to completely tolerate pathogen damage up to a certain replication rate, this may result in 'apparent commensalism', whereby infection causes no apparent virulence but the original evolution of tolerance has been costly. In this case, if the level of tolerance that evolves is sufficiently high, the pathogen may actually evolve a higher replication and transmission rate. Thus, although tolerance does not reduce parasite fitness and cannot therefore lead to antagonistic coevolution in the same manner as other forms of resistance (Råberg *et al.* 2007), it may yet prompt the evolution of more virulent and transmissible parasites. Indeed, subsequent evolution of the parasite may erode much of the benefit of tolerance, with potentially serious implications for non-tolerant populations coming into contact with the intrinsically more virulent parasite.

### (b) *Life history and defence*

It is commonly thought that longer lived organisms should invest more in costly resistance and tolerance mechanisms. However, if hosts benefit from acquired immunity, the situation is often more complex. For example, if costs only manifest during the infected state, longer lived hosts may invest relatively less in avoidance than their shorter lived counterparts (van Boven & Weissing 2004). This is due to a reduction in prevalence in longer lived populations, as hosts who do survive infection reduce the supply of susceptible hosts (assuming some form of population density dependence) and therefore the infection rate. Such epidemiological feedbacks may also occur where the cost is constitutive. Using an adaptive dynamics approach, Miller *et al.* (2007) showed how, in the absence of acquired immunity, longer lived populations generally evolve greater resistance and tolerance; if hosts have acquired immunity, these investments may either increase or decrease with increasing lifespan. Where the trait evolving is the *duration* of acquired immunity, the optimal investment always increases with lifespan. However, due to bistability, shorter lived hosts may commonly not evolve this form of resistance. By contrast, as host lifespan increases, the optimal investment in the *probability* of acquiring immunity initially increases and then decreases.

The detrimental effects to a host of parasitic attack may not only be limited to an increased mortality, but may also cause a loss of fecundity. The evolutionary response of hosts in such systems has been investigated by Gandon *et al.* (2002), where investment in reproduction and survival evolve in response to parasitism, and also by Bonds (2006), who extended this by presuming that the parasite had 'stolen' some generic host resources to aid its own transmission. In some sense, then, these studies are considering a trade-off between tolerance of mortality and tolerance of sterility. Gandon *et al.* (2002) predicted that the host will increase reproduction upon infection while Bonds (2006) predicted that fecundity will fall. Strictly speaking, the outcomes predicted by both of these models are not responses to direct sterilizing effects of the parasite, but rather due to the reallocation of resources to negate the increased mortality rate.

## 4. FUTURE DIRECTIONS

We have described a number of models that have examined the evolution of host defence given ecological feedbacks. There is a fundamental difference between defence mechanisms that reduce parasite 'fitness' and disease prevalence (resistance) and those that increase these (tolerance). However, it is important to carefully define tolerance and resistance in any particular situation if we are going to apply the results of these models. Host characteristics such as lifespan and birth rates in addition to epidemiological characteristics such as the overall transmission rates or virulence of the parasites each select for different levels of defence. The models show us how sometimes the effects of these characteristics can be somewhat counter-intuitive as a result of the complexity of the ecological feedbacks in host–parasite systems. We have only begun to include even very general complexities such as multiple infections into these theoretical models. As we develop more complex models, we become increasingly dependent on information on the relationship between, for example, different defence mechanisms and a better understanding of the costs of defence themselves. In many evolutionary models, the elephant in the room is that the outcomes depend on the assumptions of where costs act and what the nature of the relationship between costs and benefits really are. We still lack these detailed data in most systems. There is still therefore a long way to go before we have a complete theory of the evolutionary ecology of host defence.

The majority of the papers discussed in this review consider the evolution of the host in isolation. As informative as this approach is, we would often expect hosts and parasites to coevolve, constantly adapting to the other's evolving strategy. Those coevolutionary models that have been considered here focus only on Co-ESS outcomes and therefore ignore the effects of CS, including the potential for disruptive selection and polymorphisms. A recent predator–prey model has provided the theoretical tools to study fully coevolutionary ecological models in an adaptive dynamics framework (Kisdi 2006). Combining these analytical tools with numerical simulations, we are now able to study the dynamics of fully coevolutionary host–parasite systems. In particular, we can consider how the potential for polymorphisms is affected, and the consequences of coevolution on the long-term investment in host defence as well as parasite virulence.

Recent advances in evolutionary theory that have focused on parasite evolution allow many of the advantages of adaptive dynamics and QGs to be combined (Day & Proulx 2004; Day & Gandon 2005, 2007). These approaches follow both susceptible

and infected densities and also the frequency of strains. Moreover, under this approach, the ecological and evolutionary time scales are not separated, the population need not be at its dynamics attractor and the transient evolutionary dynamics can be followed. The results show that transient evolutionary dynamics may differ from predictions of evolutionary equilibria. The approach also allows predictions of the rate of evolution that will be of critical importance in assessing, say, the spread of a drug-resistant parasite strain. Adapting these approaches to understand the evolution of host defence will provide new insight into the interplay between ecological and evolutionary feedbacks. More importantly, however, a breakthrough can be gained by applying these methods to understand the transient coevolutionary dynamics of host and parasite systems. This breakthrough is now within reach.

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