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LETTER

The importance of who infects whom: the evolution of diversity in host resistance to infectious disease

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Abstract

Variation for resistance to infectious disease is ubiquitous and critical to host and parasite evolution and to disease impact, spread and control. However, the processes that generate and maintain this diversity are not understood. We examine how ecological feedbacks generate diversity in host defence focussing on when polymorphism can evolve without co-evolution of the parasite. Our key result is that when there is heritable variation in hosts in both their transmissibility and susceptibility along with costs to resistance, there is the possibility of the evolution of polymorphism. We argue that a wide range of behavioural or physiological mechanisms may lead to relationships between transmissibility and susceptibility that generate diversity. We illustrate this by showing that a tendency for higher contacts between related individuals leads to polymorphism. Only dimorphisms can evolve when infection is determined only by an individuals' susceptibility or when transmissibility and susceptibility are simply positively or negatively correlated.

Keywords

Defence, dimorphism, disease, diversity, ecology, genetic, immunity, polymorphism, resistance, variation.

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INTRODUCTION

Organisms are typically challenged by a variety of infectious agents that cause damage and reduce their fitness. Given this ubiquitous risk of infectious disease, hosts have evolved a wide range of defence mechanisms (Schmid-Hempel 2011) including avoidance of infection through behavioural and physiological mechanisms (Decaestecker *et al.* 2002), the control of the population growth rate and potentially clearance of the infectious organism through complex immune systems (Schmid-Hempel 2011) and tolerance mechanisms that reduce the harmful effects of infection (Kover & Schaal 2002; Raberg *et al.* 2007; Boots 2008). A striking feature of all these mechanisms is that host individuals within populations vary considerably in their degree of investment in defence (Bergelson *et al.* 2001; Frank 2002). This variation has long been recognised in human populations (Haldane 1949; Allison 1954), and modern genomic approaches have emphasised that there is considerable genetic diversity within human populations to many important infectious diseases (Casanova & Abel 2007). Heterogeneity in susceptibility has important implications not only for individuals but also for the epidemiology of the disease (Longini 1983; Lively 2010a), for the effective treatment and management of disease (Anderson & May 1991), for disease emergence (Lloyd-Smith *et al.* 2005) and of course for the evolutionary dynamics of disease (Schmid-Hempel 2011). As a consequence, there is considerable interest in understanding both the mechanistic basis of this variation in resistance and the evolutionary processes that determine how variation in defence is generated and maintained in host populations (Frank 1993; Antonovics & Thrall 1994; Ebert & Lorenzi 1994; Boots & Haraguchi 1999; Best *et al.* 2008, 2009; Boots *et al.* 2009; Schmid-Hempel 2011).

It is well understood that the evolution of defence alters the epidemiology, and in particular, the prevalence of the disease in the population and these eco-evolutionary feedbacks have the potential to generate diversity in hosts if defence is costly (see Boots *et al.* 2009). There is a substantial body of evidence for costs of both using defence mechanisms (Moret & Schmid-Hempel 2000; Graham *et al.* 2005) and the development and maintenance of defence in the absence of infection (Fuxa & Richter 1989; Boots & Begon 1993). These evolutionary costs of resistance have been shown theoretically to lead to the evolution and maintenance of diversity in resistance through epidemiological feedbacks (Antonovics & Thrall 1994; Bowers *et al.* 1994; Boots & Haraguchi 1999; Best *et al.* 2009). For example, Boots & Haraguchi (1999) used an evolutionary model with ecological feedbacks and a continuous trade-off relationship between avoidance resistance and host birth rate to show that dimorphic populations of highly resistant and susceptible types could evolve through branching from monomorphic populations (Boots & Haraguchi 1999). Intuitively this occurs because as a resistance allele spreads through a population, prevalence falls and therefore the selective advantage of resistance falls. This negative frequency dependence of resistance contrasts with the positive frequency dependence of an allele for a tolerance mechanism, which reduces the mortality of hosts and therefore lengthens the infectious period and increases the disease prevalence in the population (Roy & Kirchner 2000). The effect of ecological feedbacks on the evolution of host defence is therefore profound and differs depending on the type of defence mechanism that has evolved (Boots *et al.* 2009). However, in stark contrast to the variation observed in nature, models consistently predict the evolution of dimorphism between extreme types, rather than the polymorphism of many

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types (Boots & Haraguchi 1999; Best *et al.* 2009). It remains to be determined therefore whether ecological feedbacks on the evolution of resistance can generate and maintain polymorphism.

Herein, we develop a theoretical framework that allows us to understand the epidemiological mechanisms that lead to populations that are monomorphic, dimorphic and polymorphic in resistance. We show how dimorphism may result from fundamental biological processes and highlight a new mechanism that leads to the generation of polymorphism in host populations. Our approach is to examine community dynamics (CDs) to determine the maximum number of host types that can persist and then to carry out evolutionary analysis to show how many host types evolve from an initially monomorphic population. The results emphasise the importance of ecological feedbacks for evolutionary outcomes, show that polymorphism in resistance can be generated by host evolution alone and demonstrate that the ecological characteristics of the system, rather than the complexity of the trade-off, may limit diversity.

MODEL FRAMEWORK

We examine the evolution of resistance, and therefore, we assume that there is no diversity in the parasite population. The model framework considers n host types and represents the dynamics of susceptible hosts of type h, X_h, and infected hosts of type h, Y_h, with the following equations.

$$dX_h/dt = a_h X_h - q_h H X_h - b_h X_h - \Sigma_k \beta_{hk} X_h Y_k + \gamma_h Y_h \quad (1)$$

$$dY_h/dt = \Sigma_k \beta_{hk} X_h Y_k - \Gamma_h Y_h \quad (2)$$

where h, $k = 1,\ldots, n$, $H = \Sigma_h X_h + \Sigma_h Y_h$ and $\Gamma_h = \alpha_h + b_h + \gamma_h$.

Herein, for host type h, a_h represents the birth rate, b_h represents the natural death rate and q_h acts to reduce the birth rate due to density dependence. The terms α_h and γ_h represent the disease-induced mortality rate and recovery rate for hosts of type h, respectively. The parameter β_{hk} represents the transmission coefficient of infection for susceptible hosts of type h from infected hosts of type k.

We first determine analytically using the CDs framework the maximum number of types that can coexist (Bowers & Hodgkinson 2001). This is critical because when we subsequently use eqns (1) and (2) as the basis for evolutionary studies, the diversity that can evolve, through evolutionary branching or multiple branching events, can never be greater than that which could be supported under the CDs framework. Therefore, if the CDs framework produces restrictions to the number of coexisting types, then this imposes an upper limit on diversity that can arise through an evolutionary process. We then use evolutionary models to determine the pattern of diversity that can arise for the various different representations of the transmission properties.

RESULTS

We first consider the simplification, where $\beta_{hk} = \beta_h$. This simplification represents the situation where susceptibility to infection is host specific but transmissibility is the same for all (infected) hosts. This 'universal' resistance is equivalent to the system outlined by Boots & Haraguchi (1999) but for generality we additionally include the possibility of recovery from infection. We present a detailed CD analysis of this model in the SI (Supporting information), but extract the key results below so as to illustrate the approach used throughout the article.

When $\beta_{hk} = \beta_h$ we can simplify the equations that determine the equilibrium densities of eqns (1) and (2) (assuming $X_1 \ldots X_l \neq 0$ and defining $Y = \sum_k Y_k$ to (see SI for more details)

$$(a_h - q_h H - b_h - (\beta_h(\Gamma_h - \gamma_h)/\Gamma_h)Y) = 0 \quad h = 1, \ldots, l. \quad (3)$$

$$\Sigma_h(\beta_h/\Gamma_h)X_h - 1 = 0 \quad (4)$$

$$H - \Sigma_h X_h + Y = 0. \quad (5)$$

We wish to solve eqns (3–5) to find solutions $X_1,\ldots, X_h, Y, H$. In the SI, we systematically examine eqns (3–5) for different values of l to determine where there are consistent solutions. We show that generically, eqns (3–5) have a unique solution X_1, Y, H when $l = 1$ or a unique solution X_1, X_2, Y, H when $l = 2$ and there are no solutions for $l > 2$ as eqn (3) cannot be satisfied. These conditions are necessary and sufficient for equilibrium solutions (but not sufficient for feasibility and stability). The key insight from the CDs is that no more than two host types can coexist and that therefore the maximum level of diversity that can occur is dimorphism.

The results highlighted by the CDs can be examined in the full evolutionary model by undertaking an adaptive dynamic (AD) analysis (Geritz *et al.* 1998; we illustrate the AD analysis for this model below. Full details of the AD analysis for this and subsequent models are provided in the SI). For the general case [eqns (1) and (2)], it can be shown (23) that a proxy for the fitness of a rare mutant (with parameters denoted with subscript m) attempting to invade a resident (subscript r) is as follows:

$$S(a_m, \beta_{mr}, a_r, \beta_{rr}) = a_m - qH_r - b - \beta_{mr} Y_r \left(\frac{\alpha + b}{\alpha + b + \gamma}\right) \quad (6)$$

Initially, we apply the assumption that $\beta_{hk} = \beta_h$ and that there is a trade-off $a_h = f(\beta_h)$ such that decreased susceptibility to infection, lower β_h, is bought at a cost of decreased host birth rate, lower a_h (This trade-off is used throughout this study. Therefore, host type, h, has an associated value of susceptibility, β_h, and of host birth rate, a_h through the trade-off and these quantities change together). An evolutionary singular strategy, β^*, can be determined by setting the fitness gradient, $[\partial s/\partial \beta_m]_{\beta_m = \beta_r}$ equal to zero. The evolutionary behaviour at the singular point is determined by the following conditions (see SI):

Evolutionary stability (ES): $f''(\beta^*) < 0 \quad (7)$

Convergent stability (CS):

$$f''(\beta^*) < \frac{q(\alpha + b)(\alpha + b + \gamma)}{(\beta^*)^2(q(\alpha + b + \gamma) + \beta^*(\alpha + b))} = \Phi \quad (8)$$

Evolutionary branching occurs when a singular point is convergence stable (attracting) but evolutionarily unstable (invadable), and provided the resident and mutant types are mutually invadable at the singular point (which is guaranteed in evolutionary systems if the conditions for branching hold). In this model, evolutionary branching leading to dimorphism can occur for trade-offs that

satisfy $0 < f''(\beta^*) < \Phi$ [as here the system is not ES but is CS in eqns (7) and (8), respectively].

To examine whether further diversity can be generated, we consider a dimorphic resident population and examine whether branching can occur from either resident host type. After branching, the dimorphic population will follow a unique evolutionary trajectory until either it reaches a co-singular point (i.e. a singular point for both types) or the maximum/minimum limits of evolution. We can thus examine the success of a rare mutant attempting to invade a dimorphic resident population. It can be shown analytically [see equations (S15–S18) in the SI] by considering a rare mutant attempting to invade either of the resident strains that form the dimorphic population that further branching cannot occur (as the expressions for mutual invadability are zero). Simulation of the host evolution process for different trade-off curvatures is in agreement with the findings from the analysis of the community and ADs (see SI for the simulation procedure). Figure 1 shows how evolutionary attractors, repellors and branching points occur for specified trade-off shapes and emphasise that only one branching event is observed.

For universal resistance, our key novel result is that only two host types can coexist regardless of the complexity of the trade-off shape. For example, sigmoidal or more complex trade-offs between resistance and birth rate (Fig. 1d) have more inflection points with therefore more possible evolutionary singularities. These additional, local, singularities may in principle be stable attractors (and therefore evolutionary endpoints), repellors or branching points, and the increase in singularities may give the impression that increased diversity could be generated. However, the CDs analysis shows that only two types can coexist at any one time with universal resistance. In fact, the complex trade-offs shown in Fig. 1d indicate that branching can occur but that dimorphic populations may be reduced to a monomorphic population when one of the branched populations reaches a favourable region on the trade-off (and mutual invadability is lost). The simulations shown in Fig. 1 emphasise that different types can coexist, depending on initial conditions and trade-off shape, but only up to a maximum of two types. The lack of polymorphism is therefore not due to simple cost functions, but a result of the fundamental epidemiology of universal resistance.

Until now we have assumed that all host types have the same transmissibility. However, transmissibility and susceptibility may be correlated, most likely in a positive way such that types that are most likely to be infected are also most likely to infect. This relationship would be expected whenever a poor immune system allows infection with a higher load and/or subsequent faster growth, and this is the key determinant of transmissibility (Schmid-Hempel 2011; Lefevre *et al.* 2012). Figure 2 shows a series of transmission relationships in the form of 'heat' diagrams that illustrate these pos-

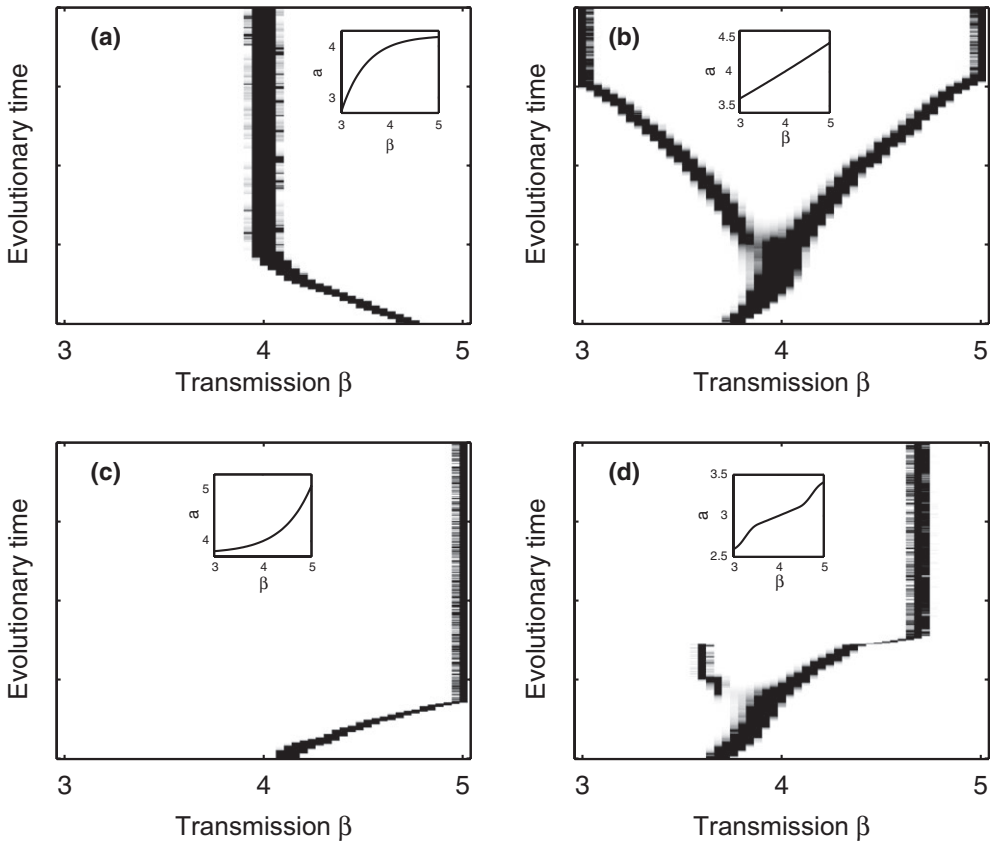

Figure 1 Simulations of the model where transmission, $\beta = \beta_{bk} = \beta_b$. In (a), the trade-off has strong accelerating costs, $a_b = f(\beta_b) = 4 - 0.21(\exp[-1.96(\beta_b - 4)] - 1)$ and the singular strategy is ES and CS and an evolutionary attractor. In (b), the trade-off has weak decelerating costs $a_b = f(\beta_b) = 4 - 5.58(\exp[0.073(\beta_b - 4)] - 1)$, the singular strategy is CS but not ES and is therefore an evolutionary branching point. Disruptive selection at the singular strategy leads to dimorphic types at the minimum and maximum levels of resistance. In (c), the trade-off has strong decelerating costs, $a_b = f(\beta_b) = 4 + 0.24(\exp[1.71(\beta_b - 4)] - 1)$ the singular strategy is neither ES or CS and is an evolutionary repellor. In (d), the trade-off takes a complicated form with several infection points leading to multiple singular strategies and a branching point at $\beta = 4$. The other parameters are $b = 1$, $q = 1$, $\alpha = 1$, $\gamma = 1$. For the simulation procedure, see the SI.

sible relationships. In Fig. 2a, all host types have the same transmissibility, while in Fig. 2b transmissibility and susceptibility are positively correlated while in Fig. 2c, for completeness, they are negatively correlated (this latter case relates to a situation where hosts that are less likely to be infected are more infectious in the relatively rare event that they become infected). Under the assumption that transmissibility and susceptibility are correlated, either positively or negatively, it is easy to show via community and ADs that there is still only the possibility of dimorphism (see SI, case 2). When they are positively correlated the parameter space in which dimorphism occurs is increased, while a negative correlation reduces the likelihood of branching, but there is still no chance of polymorphism. In both these cases and the case where all host types have the same transmissibility, overall resistance is 'universal' in the sense that one host type is most resistant and one is most susceptible no matter who infects it. As such, we have shown that epidemiological feedbacks in universal resistance only result in dimorphism.

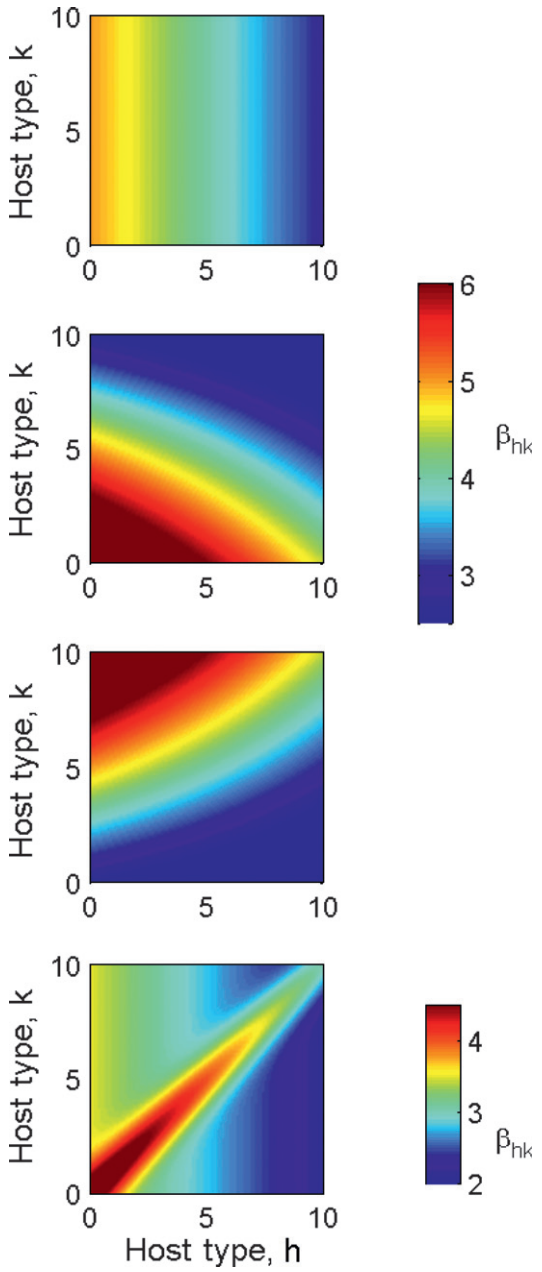

Figure 2 The value of the transmission coefficient (related to the level of host resistance) when infection occurs between a susceptible type h and an infectious type k. The panels (a–d) display 'heat' diagrams, where the value of β_{hk} is shown for a continuous combination of susceptible host types h against infectious types k (note that β_h is linked to the host type by the function $\beta_h = 5 - h/5$ and therefore as h increases from 0 to 10, β_h decreases from 5 to 3). In (a), $\beta_{hk} = \beta_h$ and all types have the same transmissibility so there is no dependency on k, (b) $\beta_{hk} = \beta_h\mu_k$ and transmissibility and susceptibility are positively correlated ($\mu_k = 0.5\beta_k - 1$), (c) $\beta_{hk} = \beta_h\mu_k$ and transmissibility and susceptibility are negatively correlated ($\mu_k = 3 - 0.5\beta_k$) and (d) β_{hk} is described by eqn (9) with $c = 0.3$ and $w = 0.05$.

We now consider the general case for host evolution where an individual's relative resistance depends both on its own genotype and also the genotype of the infected individual from which the challenge is occurring (i.e. the parameter β_{hk} is not simplified to $\beta_{hk} = \beta_h$). The CDs, ADs and simulations can be undertaken in a similar manner to the case above. We present the key results here and provide a full description of the results in the supporting information. The CDs analysis for the general transmission form, β_{hk}, indicates that the outcome is no longer restricted to at most two host types and instead any number of host types could potentially be supported (see SI, case 3). Mathematically, this occurs as it is no longer possible to make the simplification at eqns (3–5) yielding an approach involving only the total number of infected individuals (of any type) Y, as instead the host type-specific values are retained. Biologically, all that is required is that transmissibility differs among individuals but not in a way that correlates simply with their susceptibilities. As we discuss later, there are a wide range of different biological processes that may cause a complex relationship between the genotypic variation in transmissibility and susceptibility through effects on contact rates or the immune system.

Next, we give one concrete very general example that creates a more complex relationship between transmissibility and susceptibility by assuming that the contacts (which is a component of the transmission coefficient) are more likely between related individuals within a family (i.e. hosts of a similar type). We use an evolutionary model to examine whether in fact multi-type host polymorphisms can evolve by choosing a functional form for β_{hk} such that transmission depends on both host susceptibility, β_h, and the interaction between the susceptible, h, and infectious, k, host types such that transmissibility is greatest between similar host types. We define transmission, β_{hk}, as

$$\beta_{hk} = \beta_h\left[1 - c + c\exp\left(-\left(\frac{h-k}{w}\right)^2\right)\right] \quad (9)$$

Herein, c represents the 'strength' and w scales the 'range' of the interaction between host types (when $c > 0$ and $w > 0$). Figure 2d shows graphically the implications of this functional form. Individuals that are highly resistant are at more risk of being infected by other resistant types while susceptible individuals are at higher risk of being infected by other susceptible types.

Adaptive dynamics methods can be used to show that a monomorphic host population can branch but undertaking an AD analysis to examine whether further branching can occur is algebraically intractable. However, simulations of the host evolution process indicate that there is further branching after the initial branching event (Fig. 3). The simulation methods are supported by numerical calculations to produce pairwise invadability plots (PIPs) in regions close

to the resident types prior to each branching event (Fig. 3). These PIPs confirm that further branching would be expected as a result of ADs. Mutant types gain a small advantage by being slightly different to the resident population but will pay a cost through either increased susceptibility or decreased host birth rate (as these are linked through the trade-off). When the mutant evolves from a resident population that has low susceptibility, there is an advantage for the mutant to be more susceptible (paying less cost in terms of birth rate), and the low susceptibility of the resident population means overall infection levels will be low. When the mutant evolves from a resident population that has high susceptibility, there is an advantage for the mutant to reduce susceptibility as the overall infection levels will be high. This allows mutual invadability and therefore coexistence and underlies the evolutionary structure shown in Fig. 3. It is important to note that although the CDs indicate that an unrestricted number of hosts could evolve, the specific set-up in the simulation example indicates that a fixed number of types evolve and the degree of host polymorphism will depend on the details of the transmission expression and trade-off. In particular, as the transmission peak becomes tighter [which occurs as the parameter c increases and w decreases in eqn (9)], the region in which branching can occur increases [see SI eqns (S30–S33)] and the subsequent level of diversity that emerges also increases (determined from numerical simulations).

DISCUSSION

Using a combination of community and ADs analysis alongside numerical simulations we have developed a general theory of how and when epidemiological feedbacks may generate and maintain diversity in host resistance. We discuss in detail a concrete epidemiological mechanism that can generate polymorphism in resistance; the increased risk of infection from related hosts. In addition, the models show that the evolution of dimorphism between highly resistant and highly susceptible types is likely to be a common outcome resulting from fundamental characteristics of the ecology/epidemiology of the disease interaction. However, when the chance of infection depends not only on the resistance of the susceptible host type but also the transmissibility of the infected host type, the evolution of polymorphism may occur. Our key result, therefore, is that considerable diversity can evolve and be maintained due to the evolution of the host alone without reciprocal co-evolution in the parasite. Overall the work further emphasises the importance of ecological feedbacks in the evolution of hosts and parasites; trade-off shapes are critical to evolutionary outcomes, but the epidemiological interactions of particular systems are also crucial.

The most important new insight from our models is that substantial diversity in host resistance can evolve through multiple branching events under host evolution alone. For this to occur, infection of a particular host must depend on both its level of resistance (with associated costs to resistance) and the transmissibility of the host that is infecting it. It is important to emphasise that this heritable variation in both susceptibility and transmissibility could occur through a wide range of processes generated by specific recognition mechanisms and infection genetics or through host behaviour including the parasite manipulation of the host (Schmid-Hempel 2011). We discuss the processes that may be involved below, but in this article, we modelled in detail a specific example by showing that

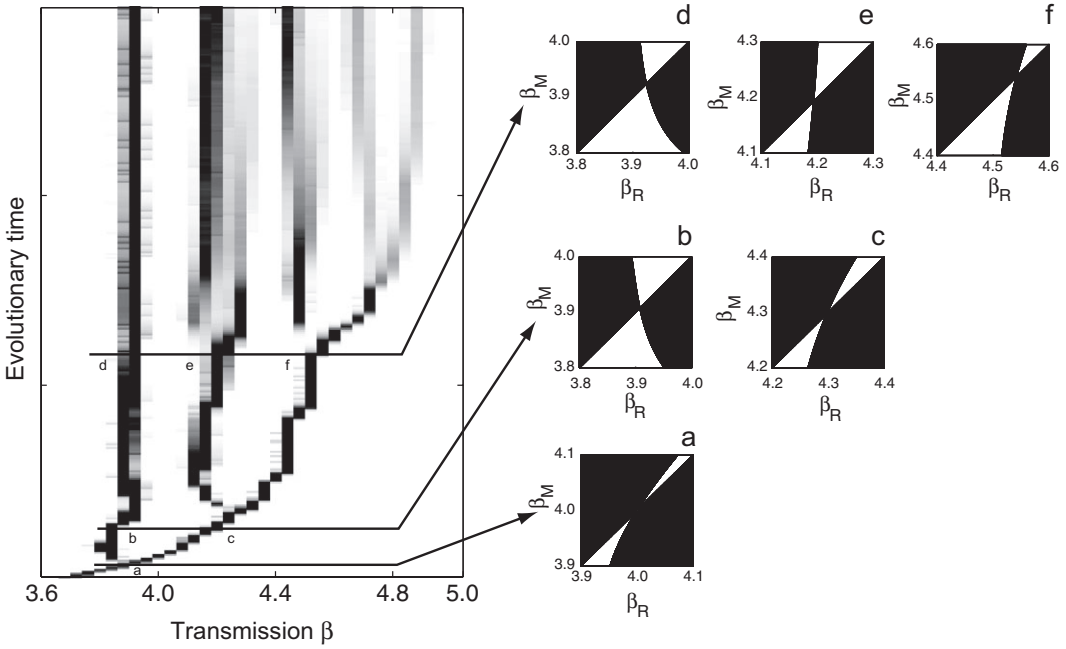

Figure 3 Simulations for the model represented by eqns (1) and (2), where β_{bk} is described by eqn (9) with $c = 0.3$ and $w = 0.05$ and a trade-off $a_b = f(\beta_b) = 4 - 0.84(\exp[-4.89(\beta_b - 4)] - 1)$. The main plot shows the evolution of host susceptibility, $\beta_b = \beta$ (which is linked directly to host type by the function $\beta_b = 5 - b/5$ and therefore enables calculation of the term β_{bk} for each host type). Local pairwise invadability plots (PIPs) are shown around the dominant types as indicated in the main figure panel. PIPs display the fitness profile for a mutant type (with parameter β_M) attempting to invade nearby resident type (with parameter β_R) in an environment composed of one or several resident types at equilibrium. Regions of the PIP in black indicate that the mutant fitness is positive and those in white that the mutant fitness is negative. In PIPs, (a), (c), (e) and (f) evolutionary branching can occur, while in (b) and (d), an evolutionary attractor occurs where types are attracted towards and remain at the singular strategy. The other parameters are the same as Fig. 1.

considerable diversity will evolve if infection risk is higher from related individuals. Very simply this will occur whenever contacts are higher within related social groups of animals and within human households (Shykoff & Schmid-Hempel 1991; Ezenwa 2004; Craft *et al.* 2008; Mossong *et al.* 2008); highly resistant individuals will on average interact more with other resistant individuals while susceptible host types will on average interact more with other susceptible types. Susceptible individuals are therefore more likely than resistant individuals to be challenged by infected individuals. This is the intuitive reason why this epidemiological feedback creates a selection pressure to evolve a different level of resistance: lower for resistant individuals and higher for susceptible ones. There has been a long running debate as to whether social organisms should invest more in immunity than generally solitary ones due to a higher perceived risk of infection due to sociality (Alexander 1974) although the evidence is equivocal (Wilson *et al.* 2003; Ezenwa 2004), and detailed theoretical studies (Wilson *et al.* 2003) have suggested that group living may not indeed lead to a greater individual risk. Our work has identified another way in which social and non-social organisms may differ as we predict that there will be more variation in resistance in social organisms if the social groups are related.

We have analysed one concrete example – the propensity to interact within social groups – of an epidemiological process that can lead to the evolution of polymorphism in host defence. However, it is important to emphasise that any process where transmissibility varies between individuals but not in a way that simply correlates (positively or negatively) with their susceptibilities may lead to polymorphism. Contacts and therefore the risk of transmission are affected by a wide range of host behaviours beyond the tendency to interact within social groups. For example, there has been recent interest in how particular individual males are implicated in transmission events due to aggressive or wide-ranging behaviour (Perkins *et al.* 2008). It is unlikely that the genetic variation in the behaviours that determine contacts is simply correlated with susceptibility and therefore our models suggest that a wide range of behaviours that impact disease transmission have the potential to generate polymorphism in host resistance. It also follows that given the complexity of transmission mechanisms and interactions with hosts on the one hand and the immune mechanisms involved in susceptibility on the other (Schmid-Hempel 2011), there is the potential for equally complex relationships between transmissibility and susceptibility in many disease interactions. Within host dynamical models of parasite and immune interactions have the potential to predict the relationships between transmissibility and susceptibility. Moreover, it is well known that there are super-spreaders in many disease interactions and considerable heterogeneity in the pattern of transmission (Lloyd-Smith *et al.* 2005). This has implications to disease emergence, but whatever the mechanism that underlies this, behavioural or physiological, if it has a genetic basis there is the potential for the generation of diversity in resistance in the hosts. This emphasises that a key insight of our models is that there is the potential for a wide range of mechanisms to generate diversity in host resistance. Whether diversity can be generated will depend on the characteristics of these complex relationships between transmissibility and susceptibility, and therefore, each example will require detailed modelling.

The second key result of our analysis is that evolution to dimorphism between relatively resistant and relatively susceptible types is predicted for a wide range of disease interactions. Two almost identical papers that examined a simple two type model of host resistance were the first to point out that coexistence was more likely between types that had very different levels of resistance (Antonovics & Thrall 1994; Bowers *et al.* 1994). Herein, we show when resistance is 'universal', such that the relative resistance of host types is independent of which type of host is challenging them, evolution leads to at most dimorphic populations. Even if there is genetic variation in transmissibility, there will still only be a maximum of two types if transmissibility and susceptibility are simply correlated. In general, resistant types might be expected to have low susceptibility and transmissibility when the resistant mechanism controls the growth rate of the parasite within the host, but even if low susceptibility is correlated with high transmissibility of infection, only dimorphism is predicted to occur. In our 'universal' resistance model, it is only possible to have a branching event when the population is monomorphic, leading to the evolution of dimorphism but not polymorphism, regardless of the complexity of the trade-off relationships. This is an important point as it tells us that complex trade-offs are not enough to generate diverse populations under universal resistance: the ecological interactions themselves define the level of diversity than can evolve. Furthermore, although our model framework does not include acquired immunity, related models (Boots & Bowers 2004) with explicit acquired immunity also predict the evolution of dimorphism as do equivalent co-evolutionary models (Best *et al.* 2009).

Another implication of our work is that considerable variation in host resistance can evolve without reciprocal evolution by the parasite. There is a body of theory that shows that co-evolutionary dynamics may generate temporal (Sasaki 2000; Lively 2010a,b) and static diversity (Sasaki 2000; Best *et al.* 2009, 2010) in disease interactions. However, our models show that only host evolution is necessary for the generation of static polymorphism. It is well known that variation may also be generated by local adaptation between hosts and parasites across spatially heterogeneous environments in what has been termed the 'coevolutionary mosaic' (Thompson 1994). Given that the likelihood of the generation of diversity due to host evolution will tend to be dependent on ecological parameters, heterogeneity in the environment may also result in an equivalent 'evolutionary mosaic'. The relative roles of host evolution, co-evolution and spatial heterogeneity in the generation of diversity in disease interactions need further theoretical and empirical work.

Our results should apply beyond our assumption of asexual to sexual populations. The evolutionary (Maynard Smith 1981) and convergence stability (Eshel 1983) of a continuous trait with additive genetics on a single locus or tightly linked loci in monomorphic populations of diploid, sexual populations with random mating are the same as in clonal populations (Kisdi & Geritz 1999). However, in diploid populations, phenotypically intermediate heterozygotes resulting from mating between individuals with the phenotypic characteristics from different branches may have implications to the generation of diversity. In multilocus systems without tight linkage branching into distinct genotypes may not occur, although increases in phenotypic variance will tend to be found (Abrams *et al.* 1993). However, during branching events in diploid populations with additive genetics, phenotypically intermediate heterozygotes between branches have low fitness resulting in selection against mating between types in the different branches (Geritz *et al.* 1998; Geritz & Kisdi 2000). Geritz & Kisdi (2000)

suggest that evolutionary branching does favour the evolution of partial assortative mating and selection against heterozygotes close to branching events may also select for dominance (Van Dooren 1999) that will tend to allow the predictions of clonal models to hold in diploid populations. Therefore, while it remains to test how different genetic assumptions affect the outcome of our models, the biological intuition of how epidemiological feedbacks generate our results suggest that these processes are likely to be widely applicable. The insights of our models may also have implications to wider studies on diversity both within species and in communities. Very generally, our models show that complex trade-off relationships do not necessarily lead to diversity and furthermore that dimorphism between extreme types may be common in antagonistic relationships. In addition, there is an established theory of the role of antagonistic trophic interactions in allowing the persistence of species classically in the context of an interaction between predation and competition (Chesson & Kuang 2008). Our models show how natural enemies may generate and maintain diversity in their host populations, and in principle, these processes, if there is assortative mating, may generate and maintain species diversity.

To conclude, part of the diversity in host defence that we see in nature may clearly be generated through spatial and temporal heterogeneity in the environment. However, it is well-established theoretically that co-evolutionary interactions may intrinsically generate diversity without this heterogeneity (Sasaki 2000; Lively 2010a,b), and recent empirical studies have shown how even in abiotic homogeneous environments coevolution may generate conditions that produce the coexistence of diverse host and parasite strains (Brockhurst *et al.* 2004). Our key result is that host evolution alone can generate and maintain considerable variation in resistance within populations. We show that this may result from uncorrelated variation in transmissibility and susceptibility due to processes such as the propensity for contacts to occur between related individuals. Furthermore, we have shown that dimorphisms, often between highly resistant and susceptible types, are predicted for universal resistance in a wide range of epidemiological contexts. The results do not depend fundamentally on the complexity of the trade-offs, but evolutionary dynamics are critically dependent on the ecological feedbacks of the evolution of resistance on disease prevalence. This is important because diversity in host parasite interactions is fundamental to the epidemiology and potentially control of disease and determines the rate of evolutionary responses.

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AUTHORSHIP

MB led the design of the paper with the contribution of all the authors, AW and AB led the evolutionary analyses and simulations with the contribution of all the authors, RB led the community dynamics with the contribution of all the authors and MB wrote the first draft of the manuscript, and all authors contributed to revisions.

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