

Evolutionary implications of host–pathogen specificity: fitness consequences of pathogen virulence traits

J.W. Kirchner¹ and B.A. Roy^{2*}

¹*Department of Earth and Planetary Science, University of California, Berkeley, CA 94720-4767, USA and* ²*Geobotanical Institute, Swiss Federal Institute of Technology (ETH), Zürichbergstrasse 38, CH-8044 Zürich, Switzerland*

ABSTRACT

Pathogens and parasites can be strong agents of selection and often exhibit genetic specificity for individual host strains. Here we use a simple host–pathogen model to explore the consequences of host–pathogen specificity for selection on pathogen infectiousness and lethality. Pathogens that can transmit themselves more readily from host to host should have a clear reproductive advantage, as should pathogens that are less lethal to their hosts (and thus can survive and reproduce longer). One would therefore expect that evolution should favour pathogens that are more infectious or less lethal, everything else being equal. These expectations are borne out when the genetic specificity of pathogen infection is low: selection favours pathogen strains with higher intrinsic fitness (reproduction rate times longevity in the host). However, at higher degrees of host–pathogen specificity, selection for these traits can be diminished, nullified or even reversed by host–pathogen feedback. This feedback produces stabilizing selection that can maintain polymorphism in pathogen traits, despite large intrinsic fitness differences among pathogen strains. When host–pathogen specificity is high enough that host–pathogen feedback regulates pathogen trait frequencies, greater infectiousness will be disadvantageous for pathogens, because it puts their preferred hosts at a competitive disadvantage with other host strains. Thus differences in specificity can reverse the direction of selection for pathogen virulence.

Keywords: frequency-dependent selection, infectiousness, life history, parasites, specificity, transmission, virulence.

INTRODUCTION

The evolution of virulence is a long-standing problem in evolutionary biology (for reviews, see Bull, 1994; Read, 1994; Ebert, 1998). Parasites and pathogens harm their hosts as a necessary byproduct of their growth, reproduction and transmission, but intuition suggests

* Address all correspondence to B.A. Roy, Department of Biology, 1210 University of Oregon, Eugene, OR 97403-1210, USA. e-mail: bit@darkwing.uoregon.edu

Consult the copyright statement on the inside front cover for non-commercial copying policies.

that they should not be too quick to kill the hosts on which they depend; theoretical and empirical studies have explored how such trade-offs shape the evolution of virulence (Anderson and May, 1982; May and Anderson, 1983a; Bull, 1994; Ebert, 1994, 1998; May and Nowak, 1995; Ebert and Hamilton, 1996; Frank, 1996a). The dependence of parasites on their hosts suggests that the evolution of virulence may also be affected by the degree of host–parasite specificity – that is, the degree to which individual parasite or pathogen strains infect some host strains more readily than others. We have shown elsewhere that selection on host life-history traits can be affected by host–pathogen specificity (Kirchner and Roy, 2001). Here, we explore how host–pathogen specificity can influence selection on pathogen virulence traits.

The term ‘virulence’ is potentially confusing, because different authors and disciplines use it in different ways (Bull, 1994; Jarosz and Davelos, 1995). For example, the plant pathology literature often equates virulence with the ability to cause infection, whereas the evolutionary literature uses the same term to refer to the increase in mortality or reduction in fitness caused by infection (Jarosz and Davelos, 1995). For our purposes, it is useful to distinguish between two components of pathogen virulence: a pathogen’s aggressiveness in transmitting itself from one host to another, which we term its ‘infectiousness’, and the severity of its impact on its host’s lifespan, which we term its ‘lethality’. Everything else being equal, a pathogen that is more infectious will transmit itself more rapidly from host to host, and one that is more lethal will kill its hosts more rapidly.

Any organism’s fitness is determined by its reproduction rate and its lifespan, and an obligate parasite’s lifespan is intimately linked to that of its host. Thus, one would intuitively expect that selection should favour pathogens with higher infectiousness and lower lethality. For pathogens whose infectiousness entails damage to their hosts, these two evolutionary objectives inherently conflict with each other; the evolutionary implications of this trade-off have been studied extensively (Anderson and May, 1982; Ebert, 1994, 1998; Ebert and Hamilton, 1996; Frank, 1996a) and will not be our main focus here. In particular, because our analysis does not encompass multiple infections on individual hosts, we will not address the consequences of intra-host competition for the evolution of virulence. Instead, we explore how selection for pathogen infectiousness and lethality depends on the degree of genetic specificity in the host–pathogen system (we will refer to pathogens and parasites interchangeably, as our analysis applies to both kinds of disease-causing organisms).

Infections typically exhibit some degree of genetic specificity, in which individual parasite strains infect some host strains more readily than others. We need to distinguish host–pathogen specificity from simple genetic variability in overall pathogen infectiousness or overall host susceptibility (Frank, 1996b). Host–pathogen specificity means that an individual pathogen strain will be more infectious to some host strains than others, and that other pathogen strains will exhibit different patterns of infectiousness across the different host strains. Note that this entails more than just variation in pathogens’ overall degree of infectiousness to all host strains. Instead, host–pathogen specificity means that the *relative* infectiousness of a pathogen to *different* host strains will vary from strain to strain in the pathogen. In a simple two-strain system, for example, one pathogen strain might infect host strain 1 more readily than host strain 2, while the other pathogen strain might infect host strain 2 more readily than host strain 1. Similarly, one pathogen strain might be twice as infectious as the other to host strain 1, but four times as infectious as the other to

host strain 2. In cases like these, the rate of disease transmission will be specific to each combination of host and pathogen strains, in a way that cannot be expressed as the simple product of each pathogen's overall infectiousness (to all host strains) and each host's overall susceptibility (to all pathogen strains).

Different host–pathogen systems exhibit different degrees of genetic specificity. For example, some soil-borne plant pathogens exhibit low specificity, readily infecting a wide range of host genotypes (Garrett, 1970; Weste, 1986; Borowicz and Juliano, 1991). In contrast, many plant species show quantitative differential susceptibility to wind-borne fungal pathogens (van der Plank, 1984; Roy and Bierzychudek, 1993; Clarke, 1997). Finally, there are examples of nearly absolute specificity, in which each pathogen genotype can specifically infect only the correspondingly susceptible host genotypes. Many fungal plant pathogens exhibit high degrees of genetic specificity, as do some viruses, bacteria and insects (Burdon, 1987; Weller *et al.*, 1991; Crute *et al.*, 1997). Biological mechanisms underlying host–pathogen specificity are discussed further by Kirchner and Roy (2001).

How does specificity evolve? Host–pathogen specificity can arise as a result of evolutionary constraints, when the traits that help a parasite to exploit one set of hosts make it less able to attack other hosts or, conversely, when the traits that help a host to resist one set of pathogens make it less able to resist others. Specialization can also be favoured by evolution when generalization requires plasticity and thus carries a cost (Via, 1990; van Tienderen, 1991; Thompson, 1994; Futuyma *et al.*, 1995). Even without such costs, specialization should evolve because parasites that show host preference will be more consistently exposed to selection on a particular host, and thus can adapt to evolving host defences faster than generalist parasites can (Kawecki, 1998).

Host–pathogen specificity is widespread in nature (Price, 1980; Burdon, 1987; Thompson and Burdon, 1992; Brooks and McLennan, 1993; Crute *et al.*, 1997), but little is known about its impact on the evolution of virulence. Here, we use a simple host–parasite model to explore how the fitness consequences of pathogen infectiousness and lethality are influenced by the genetic specificity of host–parasite interactions.

THE MODEL

Our analysis is based on a variant of the host–pathogen model developed by Kirchner and Roy (2001), which in turn was derived from Kirchner and Roy's (1999) extension of the classic model of May and Anderson (1983b). Our model contains two host strains and two pathogen strains; this is the simplest system that can illustrate the essential points. Our model can be generalized straightforwardly for more complex systems. For the sake of simplicity, our equations assume haploid genetics for the hosts and pathogens. Thus, the equations are formally equivalent to those for ecological competition between separate host and pathogen species and could be used in that context as well.

In our model, uninfected host populations are denoted X_i , where $i = 1 \dots 2$ denotes the host strain. Infected host populations are denoted Y_{ik} , where i denotes the host strain and $k = 1 \dots 2$ denotes the pathogen strain that it is infected with (we assume that multiple infections do not occur in a single individual). The pathogens cannot survive without hosts, so they need not be modelled explicitly; instead, their dynamics are represented by the infected host population. All of the host populations are expressed as fractions of the carrying capacity. A complete list of symbols can be found in Table 1.

Table 1. Table of symbols

Symbol	Definition	Defining equation (or first use)
i	subscript placeholder for host strains	(1)
k	subscript placeholder for pathogen strains	(1)
X_i	uninfected host population (as fraction of carrying capacity)	(1)
Y_{ik}	infected host population (as fraction of carrying capacity)	(2)
N	total host population (occupied fraction of carrying capacity)	(1)
a_i	host intrinsic reproduction rate	(1)
τ_i	mean lifespan of uninfected hosts	(1)
η	sterilization factor (fraction by which infection reduces host fecundity)	(1)
m_k	pathogen lethality (ratio by which infection accelerates host mortality)	(2)
t	time	(1)
s	specificity parameter	(3–7)
u_k	pathogen infectiousness	(3–7)
v_i	host vulnerability to infection	(3–7)
β_{ik}	pathogen transmission coefficient	(3–7)
β_0	host-to-host pathogen transmissibility	(3–7)
ω_k	pathogen fitness	(10)

Host mortality

Simple Lotka-Volterra expressions govern reproduction, infection and mortality in our model. We assume that uninfected hosts have a mean intrinsic lifespan of τ_i ; thus their mortality rate is X_i/τ_i . In the figures shown here, both host strains are assumed to have a lifespan of $\tau_1 = \tau_2 = 1$. Giving them a lifespan of 1 is equivalent to measuring time in units of the uninfected host lifespan (that is, non-dimensionalizing the time-scale by the host lifespan). We assume that infection accelerates mortality by a factor m_k that may vary between the pathogen strains (where $m_k = 1$ indicates that the pathogen has no lethal effect on the host and $m_k \gg 1$ indicates high pathogen lethality and a substantial reduction in host lifespan). Infected hosts thus have an average lifespan of τ_i/m_k and a mortality rate of $m_k Y_{ik}/\tau_i$. In Figs 1–3, infection by either pathogen strain shortens lifespan by a factor of $m_1 = m_2 = 5$; Figs 4–8 explore how differences in pathogen lethality (and thus in the value of m) affect pathogen fitness.

Host reproduction

In our model, uninfected hosts reproduce at a rate $a_i(1 - N)X_i$ (i.e. a per-capita rate of $a_i(1 - N)$), where a_i is the potential per capita reproduction rate in the absence of carrying capacity constraints and $(1 - N) = 1 - \sum_i X_i - \sum_i \sum_k Y_{ik}$ is the fraction of carrying capacity that is unoccupied (and thus available for new individuals to become established). In the figures shown here, both host strains have a potential reproduction rate of $a_1 = a_2 = 10$. That is, in the absence of carrying capacity constraints, healthy hosts could produce an average of 10 offspring in their lifetime. We assume that infected hosts can also reproduce,

but infection reduces their reproduction rate by a fraction η , compared to uninfected hosts ($0 \leq \eta \leq 1$). Thus the reproduction rate of infected hosts is $a_i(1 - N)(1 - \eta) \sum_k Y_{ik}$, where $\sum_k Y_{ik}$ is the total infected population of the i th host strain. For the results reported here, infection is non-sterilizing ($\eta = 0$); results for partially sterilizing ($\eta = 0.5$) and completely sterilizing ($\eta = 1$) infections are qualitatively similar. We assume that the pathogen is transmitted only horizontally, so that all hosts are born uninfected.

Infection

For simplicity, we assume that infection is permanent; hosts do not recover and do not acquire immunity, as is typical for many plant–pathogen systems (Agrios, 1988; Clay, 1991) and some animal diseases such as AIDS. The rate of pathogen transmission from an infected host to a healthy one will be the product of three things: the infected (and thus infectious) population Y_{ik} , the uninfected (and thus susceptible) population X_i and a transmission coefficient β_{ik} (explained in more detail below) that expresses the capacity of pathogen strain k to infect host strain i . New infections of host strain i by pathogen strain k will arise at a rate of $\beta_{ik} X_i \sum_i Y_{ik}$, where X_i is the population of uninfected (and therefore infectible) individuals in the i th host strain and $\sum_i Y_{ik}$ is the total population of hosts infected by pathogen strain k (from which infection can spread). The rate that hosts of the i th strain become infected will be the sum of the infection rates by each pathogen strain, or $\sum_k (\beta_{ik} X_i \sum_i Y_{ik})$. When the infection, reproduction and mortality expressions outlined above are combined together, the governing equation for the uninfected hosts becomes

$$\frac{dX_i}{dt} = a_i(1 - N) \left[X_i + (1 - \eta) \sum_k Y_{ik} \right] - \sum_k \left(\beta_{ik} X_i \sum_i Y_{ik} \right) - \frac{X_i}{\tau_i} \quad (1)$$

and the governing equation for the infected hosts becomes

$$\frac{dY_{ik}}{dt} = \beta_{ik} X_i \sum_i Y_{ik} - \frac{m_k Y_{ik}}{\tau_i} \quad (2)$$

Pathogen infectiousness, host vulnerability and host–pathogen specificity

Pathogen transmission is controlled by both host and pathogen characteristics, so the transmission coefficient β_{ik} can potentially differ for each combination of host and pathogen phenotypes. We express the individual β_{ik} values as a function of four components:

1. A constant coefficient β_0 that scales the overall transmissibility of pathogens from host to host. All of the simulations in this paper use a value of $\beta_0 = 15$.
2. A host-dependent coefficient v_i that allows the two hosts to have different degrees of vulnerability to pathogen attack (where $v_i = 1$ and $v_i > 1$ indicate normal and above-normal vulnerability, respectively). In all of the simulations in this paper, both host strains have equal vulnerability to infection: $v_1 = v_2 = 1$.
3. A pathogen-dependent coefficient u_k that allows the two pathogens to have different degrees of infectiousness (where $u_k = 1$ and $u_k > 1$ indicate normal and above-normal infectiousness, respectively).

4. A factor s that quantifies the degree of host–pathogen specificity ($-1 \leq s \leq 1$), where $s = 0$ indicates no specificity and $s = 1$ or $s = -1$ indicates absolute specificity (but with opposite pairings between the host and pathogen strains).

The transmission coefficients β_{ik} combine these four elements as follows:

$$\beta_{ik} = \begin{cases} \beta_0 v_i u_k (1 + s) & \text{for } i = k \\ \beta_0 v_i u_k (1 - s) & \text{for } i \neq k \end{cases} \quad (3)$$

The effects of host–pathogen specificity on pathogen transmission can be visualized through the matrix of transmission coefficients β_{ik} . If pathogen transmission is non-specific, the transmission matrix becomes one of the kind conventionally used in host–pathogen modelling studies:

$$\beta_{ik} = \beta_0 \begin{pmatrix} v_1 u_1 & v_1 u_2 \\ v_2 u_1 & v_2 u_2 \end{pmatrix} \quad (4)$$

It is important to note that not all possible transmission matrices are of this form. In matrices like (4), elements on the same row must share the same host vulnerability v_i and elements in the same column must share the same pathogen infectiousness u_k . Thus host–pathogen specificity of the type we wish to study is impossible in singular transmission matrices like (4).

If each pathogen is completely host-specific (such that each pathogen strain can infect only one host strain), or equivalently if host susceptibility is completely pathogen-specific (such that each host strain is vulnerable to only one pathogen strain), the transmission matrix becomes either

$$\beta_{ik} = \beta_0 \begin{pmatrix} 2v_1 u_1 & 0 \\ 0 & 2v_2 u_2 \end{pmatrix} \quad \text{or} \quad \beta_{ik} = \beta_0 \begin{pmatrix} 0 & 2v_1 u_2 \\ 2v_2 u_1 & 0 \end{pmatrix} \quad (5)$$

depending on which pathogen is specific to which host. The factor of 2 appears in (5) so that if $v_1 \approx v_2$ and $u_1 \approx u_2$, the overall infectiousness of pathogens and vulnerability of hosts (that is, the sums across each row or down each column) will be similar in the specialist matrices (5) as in the generalist matrix (4). Equations (4) and (5) represent the ‘generalist’ and ‘specialist’ extremes of a continuum of possible host–pathogen specialization; many host–pathogen systems lie somewhere between these end-members. This continuum of possible specialization is encompassed by the specificity coefficient s , which specifies the fraction of ‘specialist’ behaviour in the transmission matrix (Kirchner and Roy, 2001). That is, the β_{ik} matrix is the weighted average of the ‘generalist’ matrix (4) and the ‘specialist’ matrix (5), with weighting factors of $1 - s$ and s , respectively:

$$\beta_{ik} = (1 - s) \beta_0 \begin{pmatrix} v_1 u_1 & v_1 u_2 \\ v_2 u_1 & v_2 u_2 \end{pmatrix} + s \beta_0 \begin{pmatrix} 2v_1 u_1 & 0 \\ 0 & 2v_2 u_2 \end{pmatrix} = \beta_0 \begin{pmatrix} v_1 u_1 (1 + s) & v_1 u_2 (1 - s) \\ v_2 u_1 (1 - s) & v_2 u_2 (1 + s) \end{pmatrix} \quad (6)$$

As the specificity parameter varies from $s = 0$ (indicating no specificity) to $s = 1$ (indicating absolute specificity), the specificity matrix varies continuously from the purely ‘generalist’

matrix to the purely ‘specialist’ matrix. It can be seen by inspection that the linear combination of the generalist and specialist matrices, as in (6), is equivalent to the β_{ik} ’s as defined in (3). The specificity coefficient can also take on values down to $s = -1$, indicating increasing degrees of specificity but with the opposite orientation (such that pathogen strain 2 can more readily infect host strain 1 and pathogen strain 1 can more readily infect host strain 2). Thus one can also view the β_{ik} matrix as a weighted average of the two specialist matrices,

$$\beta_{ik} = \frac{1+s}{2} \beta_0 \begin{pmatrix} 2v_1u_1 & 0 \\ 0 & 2v_2u_2 \end{pmatrix} + \frac{1-s}{2} \beta_0 \begin{pmatrix} 0 & 2v_1u_2 \\ 2v_2u_1 & 0 \end{pmatrix} = \beta_0 \begin{pmatrix} v_1u_1(1+s) & v_1u_2(1-s) \\ v_2u_1(1-s) & v_2u_2(1+s) \end{pmatrix} \quad (7)$$

which is again formally equivalent to the β_{ik} ’s as defined in (3). Because we have given the two host strains the same vulnerability to infection ($v_1 = v_2$), changing the specificity parameter s does not alter the total transmissibility of each pathogen strain; that is, the sums along each column in the transmission matrix do not change. This allows us to distinguish the effects of changing host–pathogen specificity from the effects of changing overall pathogen transmissibility.

Why not just specify numerical values for the four transmission coefficients β_{ik} individually and be done with them? The purpose of the formalism above is to clarify the role of four conceptually distinct factors in determining pathogen transmission. Assuming one host strain has ‘normal’ vulnerability ($v = 1$) and one pathogen strain has ‘normal’ infectiousness ($u = 1$), there are four independent degrees of freedom in the transmission matrix: the overall transmissibility β_0 , the relative infectiousness of the two pathogen strains (u_2/u_1), the relative vulnerability of the two host strains (v_2/v_1) and the degree of host–pathogen specificity, s (an interaction between hosts and pathogens). By specifying these four factors, one can specify any set of values for the β_{ik} ’s, but in a way that allows each of the biological factors to be quantified separately.

The simulations shown below assume haploid genetics, as implied by equations (1) and (2). More complex genetic systems are, of course, possible, but the genetic details should only affect the disequilibrium dynamics of the system, not its equilibria (Barrett, 1988). We have repeated our simulations using a more complex genetic model, in which the phenotype is determined by a diploid diallelic locus with complete dominance. This diploid model has separate equations similar to (1) and (2) for each host and pathogen genotype (dominant, recessive and heterozygous), with random mating among them. The dynamics of the haploid and diploid models are almost indistinguishable and, as one would expect, their equilibria are exactly identical.

The model used in this paper consists of equations (1), (2) and (3), with the parameter values given above, except as noted. We simulate the model system’s time-dependent evolution (Figs 1, 3 and 4) by numerical integration and find its equilibria (Figs 2, 5, 6 and 8) using multidimensional Newton-Raphson methods. We derive analytically the invasion and fixation conditions for pathogen virulence traits (Figs 7, 8) in the Appendix. Because our primary focus is the evolutionary implications of host–pathogen specificity, rather than the evolution of infectiousness and lethality as quantitative traits, we do not allow these traits to change over time. Instead, we examine how host–pathogen specificity affects the outcome of competition between two pathogen strains with different (but fixed) levels of infectiousness or lethality. This approach emphasizes the selection mechanisms underlying

evolution and the specific consequences of individual traits, but does not explicitly simulate their quantitative evolution through time.

SELECTION ON PATHOGEN INFECTIOUSNESS UNDER HOST–PATHOGEN GENETIC SPECIFICITY

Infectiousness, or the ability to propagate from one host to another, is a key life-history component for a pathogen. Pathogens that can transmit themselves more readily from host to host have a clear reproductive advantage. One would therefore expect that selection should favour pathogens that are more infectious; furthermore, if less infectious pathogens are otherwise identical to their more infectious competitors, competitive exclusion should drive them to extinction. Here we test this proposition in our host–pathogen system, under different levels of host–pathogen specificity.

Dynamics of fixation and polymorphism

Figure 1 shows the behaviour of our host–pathogen model under two different levels of genetic specificity, assuming that both strains of hosts and pathogens are otherwise identical, except that the infectiousness of pathogen strain 2 is 20% greater than that of pathogen strain 1 ($u_1 = 1$ and $u_2 = 1.2$ in equation 3). As the left-hand column of Fig. 1 shows, when host–pathogen genetic specificity is as low as 5%, the model behaves as one would intuitively expect: pathogen strain 2 rapidly dominates the gene pool and strain 1 is rapidly driven to extinction (Fig. 1a). This creates a disadvantage for host strain 2, which is slightly more susceptible to pathogen strain 2 than host strain 1 is. Thus the extinction of pathogen strain 1 also entails the extinction of host strain 2 (Fig. 1b,c) and polymorphism is rapidly lost from both the host and pathogen populations.

At slightly higher levels of specificity, however, the model system's behaviour is strikingly different. Raising host–pathogen specificity from 5% to 15% replaces the competitive exclusion process in Fig. 1a–c with an oscillation that converges towards polymorphic equilibrium in both the pathogen and the host (Fig. 1d–f). Although pathogen strain 1 has a substantial competitive disadvantage compared to pathogen strain 2, both strains persist in the population at roughly equal average frequencies.

Closer examination of Fig. 1 shows how this occurs. Each pathogen strain exerts selection against the host strain that it preferentially exploits. As each pathogen strain becomes more successful, it depresses the population of the host strain on which it preferentially depends, thus limiting its further expansion. The strength of this host–pathogen negative feedback mechanism will depend on the fitness consequences of infection and the degree of host–pathogen specificity. If these are high enough, host–pathogen feedback can outweigh the intrinsic advantage that one pathogen strain has over the other and both strains will persist.

The feedback process that maintains polymorphism in this system is a form of frequency-dependent selection. The same feedback mechanism underlies pathogen-mediated frequency-dependent selection on host traits (Kirchner and Roy, 2001); our simulations illustrate how it can also create what may be considered 'host-mediated' frequency-dependent selection on pathogen traits. This form of selection is familiar to plant pathologists, who have documented the boom–bust cycles created by natural selection for pathogen strains that can overcome the resistance defences of the most common host

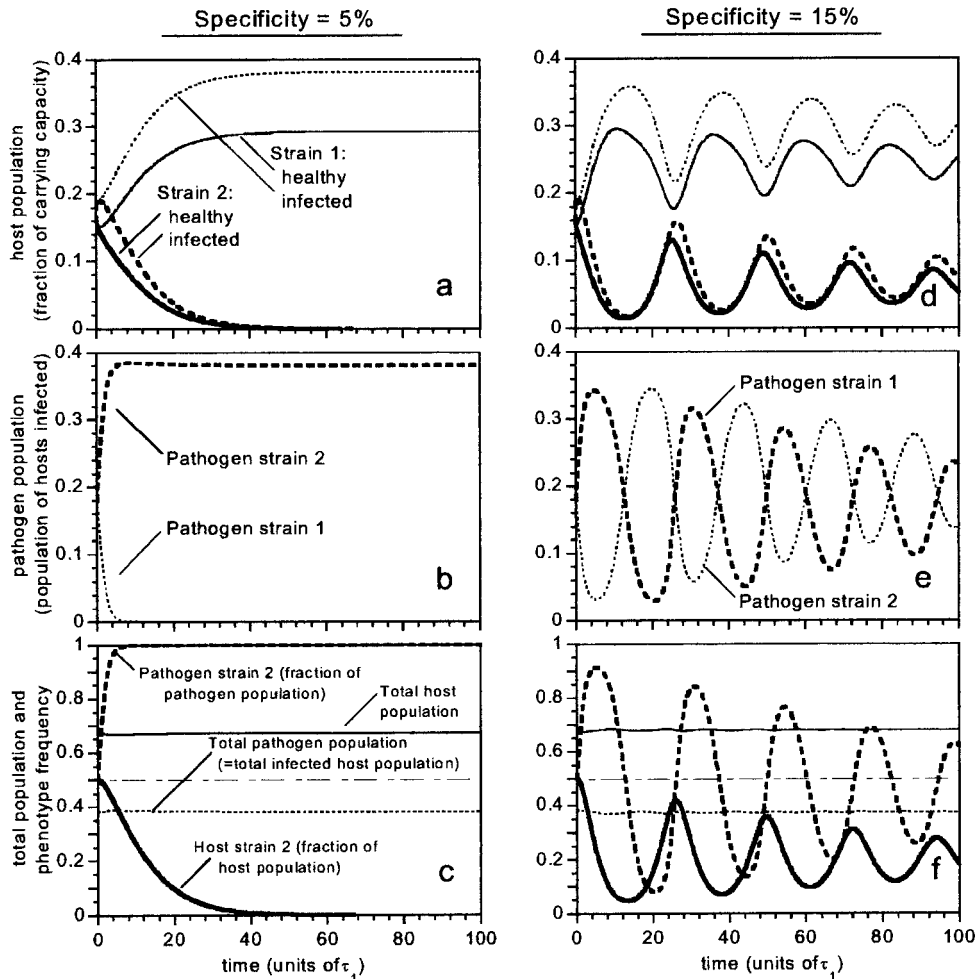


Fig. 1. Selection for increased pathogen infectiousness, illustrated by host and pathogen population trajectories through time at two different levels of host–pathogen specificity; in each case, pathogen strain 2’s infectiousness is 20% greater than that of pathogen strain 1 ($u_1 = 1$, $u_2 = 1.2$). Each of the three rows of panels depicts the behaviour of a different group of variables. The first row shows healthy and infected populations (solid and dotted lines, respectively) of host strains 1 and 2 (thin and thick lines, respectively). The second row shows the populations of pathogen strain 1 (thin dotted line) and pathogen strain 2 (thick dotted line). These are not the same as the populations of the infected host strains, because pathogen strain 1 can infect host strain 2 and vice versa. The third row shows the total populations of the hosts and pathogens (thin solid and thin dotted lines, respectively), the frequency of host strain 2 (thick solid line) and the frequency of pathogen strain 2 (thick dotted line); the horizontal dashed line indicates equal frequencies of strain 1 and strain 2. Model parameters are: $u_1 = 1$, $u_2 = 1.2$, $m_1 = m_2 = 5$, $v_1 = v_2 = 1$, $a_1 = a_2 = 10$, $\eta = 0$, $\beta_0 = 15$ and $\tau_1 = \tau_2 = 1$.

strains. Our analysis shows that the same selection mechanism can regulate selection on pathogens’ more general traits, such as their overall degree of infectiousness or their lethality to the host, when they exhibit sufficient host specificity.

Further increases in the specificity parameter s make the oscillation in the host and pathogen frequencies more symmetrical, decrease its amplitude and increase its frequency. The frequency of oscillation increases and the range of oscillation shrinks because, at higher host–pathogen specificity, changes in pathogen frequencies have larger effects on host fitness, leading to faster changes in host frequencies (and vice versa).

Figure 1 indicates two distinct modes of behaviour: rapid fixation of a single strain in both the host and pathogen populations when genetic specificity is low (the left-hand column of Fig. 1), and damped oscillations in strain frequencies that maintain polymorphism in both the host and pathogen populations when genetic specificity is higher (the right-hand column of Fig. 1). Note that, between these two distinct modes of behaviour, the overall infectiousness of the pathogens and the overall susceptibility of the hosts do not change; all that differs is the degree to which the host–pathogen interaction is specialized rather than generalized.

Equilibria

We can explore more comprehensively the effects of host–pathogen specificity on selection for pathogen infectiousness by mapping the equilibrium host and pathogen strain frequencies across the entire possible range of specificity (Fig. 2). We do this by solving equations (1) and (2) for the host and pathogen populations for which all the time derivatives become zero. Figure 2 shows the central tendency in the system’s behaviour at the two specificity values featured in Fig. 1 (shown as small open circles in Fig. 2), as well as all other values of host–pathogen specificity.

The two distinct modes of behaviour (fixation and polymorphism) that were observed in Fig. 1 are separated by a discontinuous shift in the equilibrium frequencies of the pathogen strains (Fig. 2a). Below this specificity threshold (which varies according to the difference in infectiousness between the two pathogen strains), the equilibrium frequencies of pathogen strain 2 and host strain 1 are exactly 100%. In this domain, host–pathogen specificity is too low (and thus the feedback between host and pathogen frequencies is too weak) to maintain polymorphism in the face of pathogen strain 2’s greater ability to transmit itself from host to host. Above the threshold specificity value, polymorphism is maintained, but the equilibrium frequency of pathogen strain 2 is less than 50%, even though it is nominally ‘fitter’ than pathogen strain 1. The greater its nominal fitness advantage, the smaller its frequency in the polymorphic equilibrium. This occurs because pathogen strain 2’s greater infectiousness magnifies its deleterious impact on its preferred host strain; above the specificity threshold, this indirect effect outweighs the direct benefit of increased infectiousness for the pathogen.

One would intuitively expect that, as host–pathogen specificity increases, host–pathogen feedback should gradually dilute pathogen strain 2’s fitness advantage; instead, it abruptly reverses it. The gradual shift that one would intuitively expect to see in the pathogen frequencies instead occurs in the host frequencies.

General model dynamics

Vector-field diagrams, such as those shown in Fig. 3, aid in visualizing the short-term dynamics of our model system. The arrows in Fig. 3 show how any combination of host and pathogen frequencies will change over a fixed interval of time; thus longer arrows

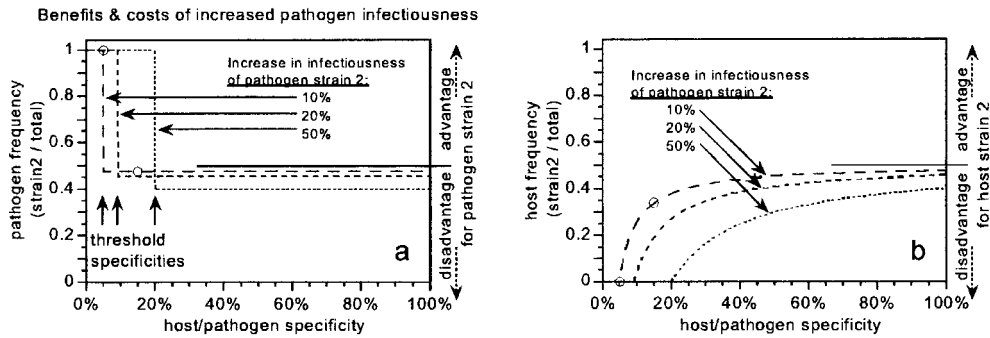


Fig. 2. Equilibrium frequencies in host and pathogen populations (expressed as the fraction of each population that strain 2 represents) as a function of host–pathogen specificity. Curves are shown for three different levels of infectiousness in pathogen strain 2: 10%, 20% and 50% greater than strain 1 (dashed line, small dashes and dotted line, respectively, corresponding to values of $u_2 = 1.1, 1.2$ and 1.5 in equation 3; other model parameters are as in Fig. 1). Small circles mark conditions corresponding to the two simulations in Fig. 1. (a) Frequency of strain 2 in the pathogen population. Note the abrupt transition in host strain frequency, corresponding to the shift in dynamic behaviour shown in Fig. 1. This transition occurs at a threshold specificity that varies with the degree of strain 2's infectiousness advantage. Above the threshold specificity value, strain 2 comprises less than 50% of the pathogen population, regardless of the size of its infectiousness advantage over strain 1 and regardless of the level of host–pathogen specificity. (b) Frequency of host strain 2 as a fraction of the total host population. Note that the abrupt transition in pathogen strain frequencies corresponds to more gradual change in host strain frequencies.

indicate faster changes in strain frequencies. These diagrams depict the system's dynamics under almost any initial conditions, not just individual trajectories from particular initial conditions (such as the trajectories in Fig. 1, which are shown in Fig. 3 as continuous lines). Below the specificity threshold, all possible initial conditions lead to loss of polymorphism, through the extinction of pathogen strain 1 and host strain 2 (Fig. 3a). In contrast, above the specificity threshold all possible trajectories preserve polymorphism; none of the flow lines in Fig. 3b,c intersect the system boundaries, which represent fixation. However, at specificity values near the specificity threshold, many cycling trajectories pass very close to the system boundary for long periods of time, increasing the risk of stochastic extinction. Cycles in this system occupy orbits that spiral towards equilibrium; external perturbations can change the amplitude of the system's oscillations by bumping the system from one orbit to another, but will not change its equilibrium point or its average strain frequencies.

Above the specificity threshold, stochastically induced extinction of either host strain implies extinction of one of the pathogen strains and vice versa. That is, if the system is driven onto one of the boundaries of Fig. 3b,c, the vector field will carry it into one of the corners representing fixation of one of the host strains and one of the pathogen strains. Persistent polymorphism can be restored after any of these dual-extinction events (that is, from any corner of the diagram), but this requires reintroducing the missing host and the missing pathogen together.

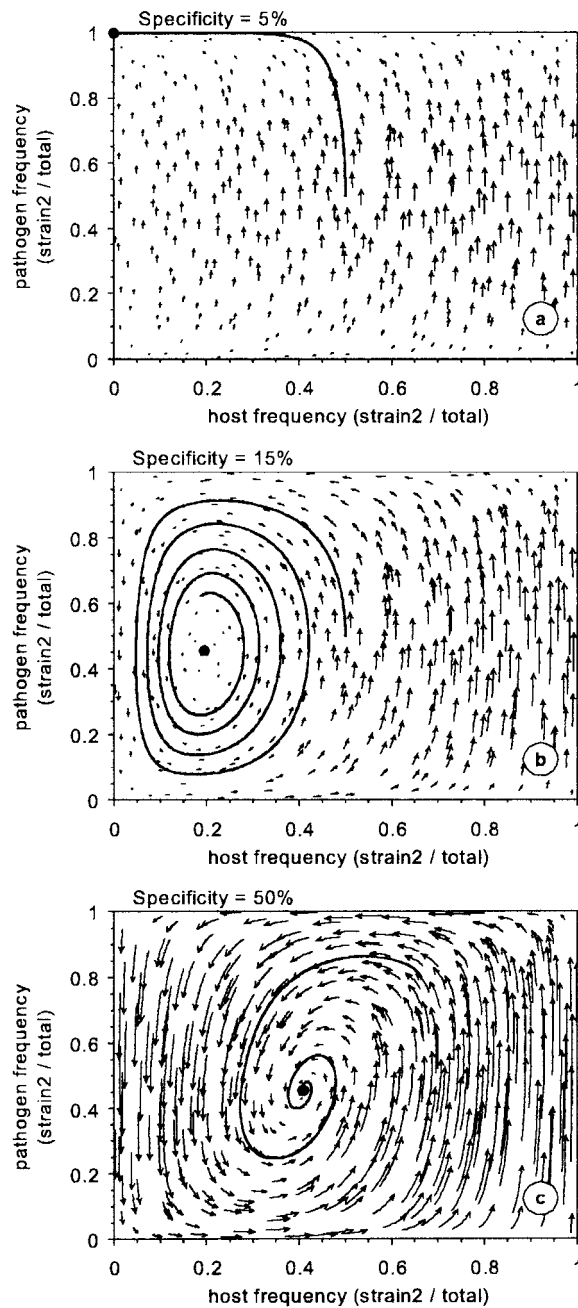


Fig. 3. Vector-field diagram of host and pathogen strain frequencies for model parameters corresponding to the simulations shown in Fig. 1 (20% higher infectiousness in pathogen strain 2) under host–pathogen specificity of 5%, 15% and 50% (panels a–c, respectively). The arrows depict changes in strain frequencies during equal intervals of time (here, 0.2 time units); longer arrows indicate faster changes in frequencies. The solid dots show the equilibrium strain frequencies. The solid lines show

SELECTION ON PATHOGEN LETHALITY UNDER HOST–PATHOGEN GENETIC SPECIFICITY

Obligate pathogens and parasites cannot survive without their hosts. Nevertheless, pathogen growth, reproduction and transmission necessarily entail damage to the host (and thus, in our terminology, some degree of lethality). Therefore, pathogens must find a balance between strategies that maximize their growth and reproduction rates and strategies that maximize their hosts' survival (and thus their own). Other studies have addressed how this trade-off shapes the evolution of lethality (Bull, 1994; Read, 1994; Ebert, 1998). We will instead ask how a pathogen's host-specificity affects selection on its lethality traits, everything else being equal. That is, will selection favour pathogen strains of greater or lesser lethality if they have the same overall infectiousness (but are more infectious on one host strain than another, as a consequence of host–pathogen specificity)?

Dynamics of fixation and polymorphism

Figure 4 shows the results of simulations in which both pathogen strains have equal overall infectiousness ($u_2 = u_1$), but pathogen strain 2 is 20% less lethal than pathogen strain 1, and thus hosts infected with pathogen strain 2 survive 20% longer than hosts infected with pathogen strain 1 ($m_1 = 5$, $m_2 = 4$). When host–pathogen specificity is relatively low, the less lethal pathogen strain becomes dominant and, as a consequence, its preferred host is driven to extinction (Fig. 4a–c). To understand why host strain 2 goes extinct, even though its preferred pathogen is less lethal, note that pathogen strain 2 benefits from its lower lethality (and thus greater longevity) when it infects either host; thus it has a selection advantage over pathogen strain 1. But host strain 2 benefits only to the extent that it is infected more often with the less lethal pathogen strain, and that is precisely its problem: it is more susceptible (than its competing host strain) to pathogen strain 2, which, by virtue of its greater longevity, comes to dominate the pathogen pool. This shift in pathogen strain frequencies outweighs any advantages for host strain 2 from pathogen strain 2's diminished lethality.

Under higher host–pathogen specificity, the model behaviour is qualitatively different (Fig. 4d–f). As pathogen strain 2 becomes more abundant, host strain 2 declines in frequency, as before. However, because the host and pathogen strains are more tightly coupled to each other, pathogen strain 2's competitive advantage is reduced as its preferred host strain becomes less common. The negative feedback between host and pathogen strain frequencies becomes stronger as host–pathogen specificity increases, transforming the model's behaviour from asymptotic fixation (Fig. 4a–c) to damped oscillations in which polymorphism is maintained (Fig. 4d–f).

the trajectories of the simulations in Fig. 1. The angular velocity of the system around the equilibrium point indicates the frequency of oscillation through time, which increases systematically with increasing specificity. The numbers of arrows, their starting positions and the length of time they represent are the same in all three panels; their apparent increase in density from (a) to (c) is a result of their increasing length, reflecting the system's increasing frequency of oscillation.

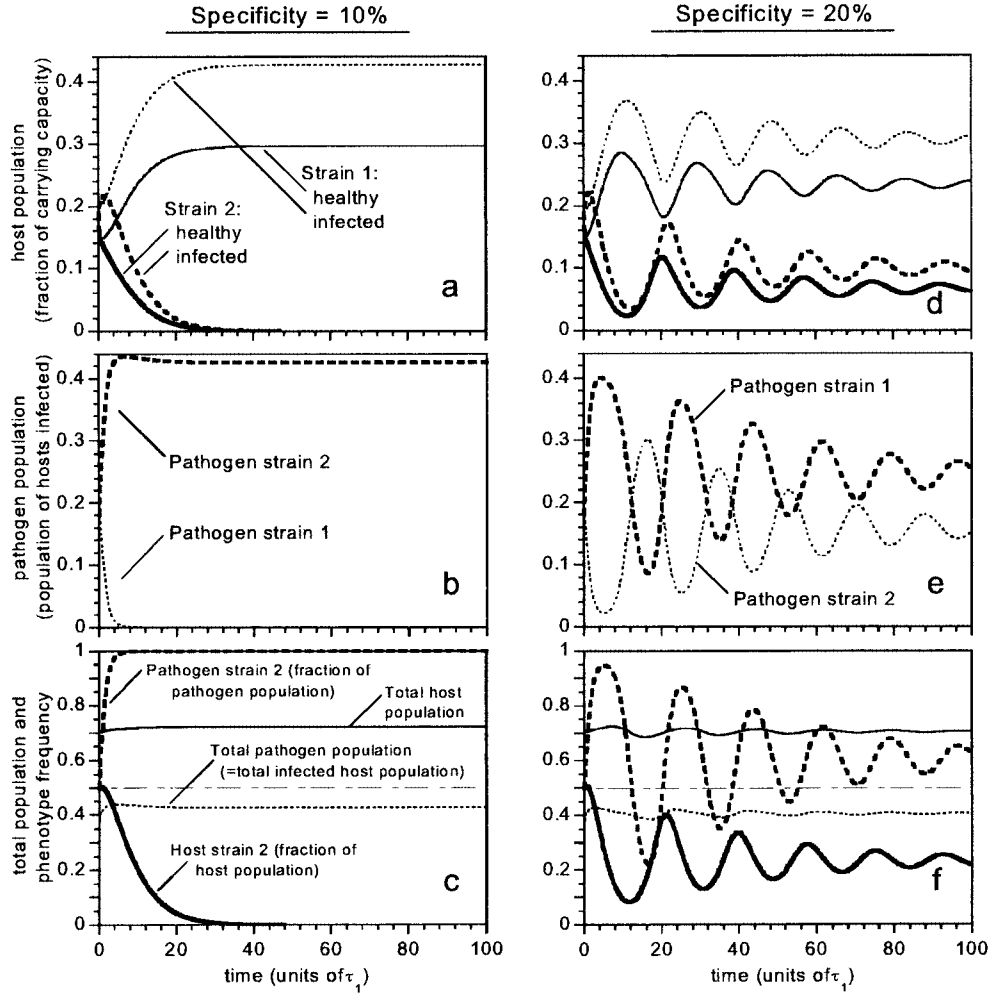


Fig. 4. Selection on pathogen lethality, illustrated by host and pathogen population trajectories through time at two different levels of host–pathogen specificity. In both cases, pathogen strain 2’s lethality is 20% less than that of pathogen strain 1. Note that when specificity is less than roughly 12%, the less lethal strain has a clear evolutionary advantage over the more lethal strain (panels a–c) and its preferred host strain is driven to extinction (see text). However, at higher levels of specificity, the advantage of the less lethal strain is greatly reduced and both host and pathogen strains co-exist. For a guide to the layout and symbols, see the caption to Fig. 1. Model parameters are: $u_1 = u_2 = 1$, $m_1 = 5$, $m_2 = 4$, $v_1 = v_2 = 1$, $a_1 = a_2 = 10$, $\eta = 0$, $\beta_0 = 15$ and $\tau_1 = \tau_2 = 1$.

Equilibria

Above the specificity threshold, the equilibrium frequency of pathogen strain 2 is substantially reduced, indicating that host-mediated frequency-dependent selection reduces the fitness advantage that pathogen strain 2 gains from its diminished lethality (Fig. 5a). Although the equilibrium frequencies of the pathogen strains shift abruptly at the

specificity threshold, the equilibrium frequencies of the host strains change more gradually (Fig. 5b). Over wide ranges of specificity, lower lethality in pathogen strain 2 corresponds to smaller equilibrium frequencies of host strain 2 (Fig. 5b) – that is, pathogen strain 2’s diminished lethality is disadvantageous for its preferred host strain. This is because strain 2’s diminished lethality creates larger and more persistent pools of infected hosts and thus a greater risk of infection for its preferred host strain. Qualitatively similar equilibrium frequencies – with small quantitative differences – are seen for completely sterilizing, partly sterilizing and non-sterilizing infections.

DISCUSSION

The results presented here show that host–pathogen specificity can affect the magnitude, and even the direction, of selection on pathogen traits. Most prior analyses of pathogen virulence and its effect on pathogen fitness have assumed that pathogens compete for a single, uniform host population – that is, individual pathogen strains have no host specificity. We have shown that at levels of host–pathogen specificity below the specificity threshold, selection acts as one would expect, with traits for increased infectiousness or decreased lethality becoming fixed. Above the specificity threshold, however, selection on lethality traits is weakened and selection on infectiousness is reversed: higher levels of infectiousness lead to lower equilibrium frequencies.

Host–pathogen specificity alters the pathogens’ selection regime by coupling them to the hosts on which they depend. When pathogens are not host-specific (and thus individual pathogen strains share the same host population), the impact of each pathogen strain on the host ‘feeds back’ to affect the fitness of all the pathogen strains equally. Because the pathogens’ effects on the host are shared among all the pathogen strains, they do not create fitness differences on which selection can act. The greater the degree of host–pathogen specificity, the more each pathogen strain’s impact on its preferred host ‘feeds back’ to affect

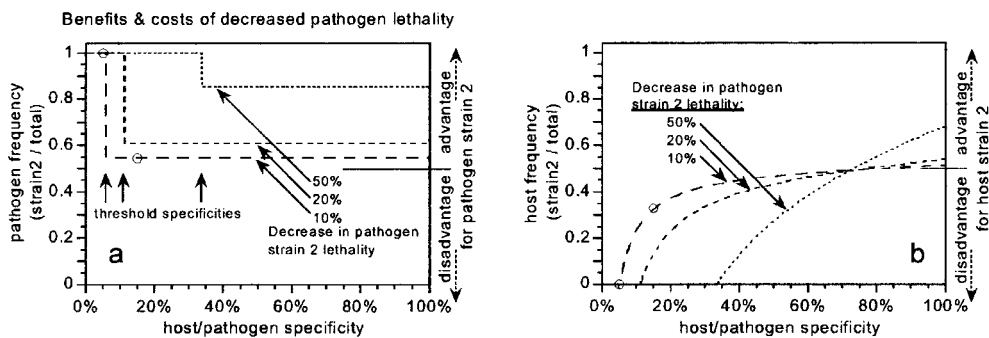


Fig. 5. Equilibrium frequencies in pathogen (a) and host (b) populations (expressed as the fraction of each population that strain 2 represents) as a function of host–pathogen specificity. Curves are shown for three different reductions in lethality for pathogen strain 2: 10%, 20% and 50% less than strain 1 (dashed line, small dashes and dotted line, respectively, corresponding to values of $m_2 = 4.5, 4$ and 2.5 ; other parameters as in Fig. 4). Small circles mark conditions corresponding to the two columns of Fig. 4. Over wide ranges of host–pathogen specificity, pathogen strain 2’s diminished lethality is disadvantageous for its preferred host strain (see text).

its individual fitness, rather than affecting the fitness of all strains alike. Host–pathogen specificity does not strengthen the feedback between the host and pathogen populations as a whole, but partitions it among the individual pathogen strains and their preferred hosts. Thus host–pathogen specificity makes it possible for host–pathogen feedback to affect selection on pathogen traits.

The consequences of this feedback can be illustrated by examining how a pathogen strain’s infectiousness affects its equilibrium frequency (and that of its preferred host) under different degrees of specificity (Fig. 6). In Fig. 6, pathogen strain 2’s infectiousness increases from left to right on the horizontal axis, while pathogen strain 1’s infectiousness remains constant (and all other host and pathogen parameters, including pathogen lethality, are equivalent). In the absence of host–pathogen specificity (dotted line), pathogen strain 2 would have an absolute fitness advantage whenever its infectiousness was higher than that of pathogen strain 1, because both strains would be competing for the same host pool. Zones of fixation are also observed under high host–pathogen specificity, when the two pathogen strains differ sufficiently in infectiousness that one or the other host strain is eliminated (note that the discontinuous ‘jumps’ to fixation in Fig. 6a match the corners in the host frequency curves in Fig. 6b). Between these zones of fixation, however, higher infectiousness confers a net disadvantage (Fig. 6a). This downward-sloping relationship arises because the direct benefits of greater infectiousness are outweighed by the consequences of depleting the preferred host strain. The zones of fixation correspond to conditions below the specificity threshold, where host–pathogen feedback is too weak to overcome the intrinsic fitness difference between the pathogen strains. The curves between the zones of fixation correspond to conditions above the specificity threshold – that is, conditions dominated by host–pathogen feedback. As the system crosses the specificity threshold, it jumps discontinuously between these two different selection regimes.

One can derive analytically the conditions that separate zones of fixation from domains

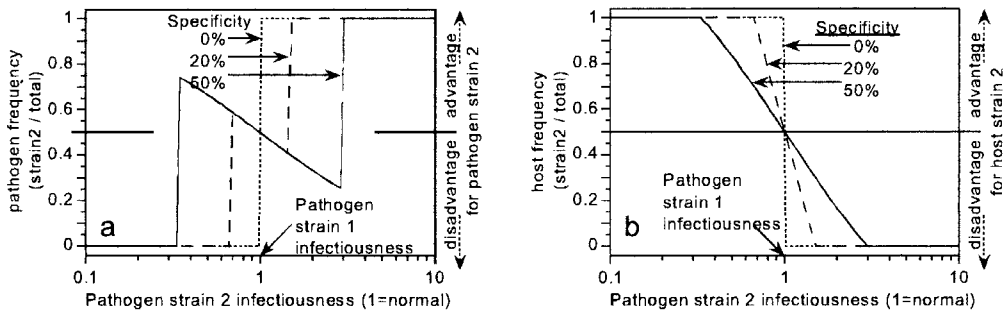


Fig. 6. Equilibrium frequencies of pathogen strain 2 (a) and host strain 2 (b) as a function of pathogen strain 2’s infectiousness, for three levels of host–pathogen specificity: 0% (dotted line), 20% (dashed line) and 50% (solid line). Pathogen strain 2’s infectiousness (horizontal axis) is u_2 in equation (3); pathogen strain 1’s infectiousness is held constant at $u_1 = 1$. Other parameters are the same as in Fig. 1. Where host-mediated frequency-dependent selection can act (that is, where hosts and pathogens are polymorphic), higher infectiousness is disadvantageous to pathogen strain 2, because it reduces the population of its preferred host strain. Under conditions that drive either host strain to extinction, higher infectiousness is advantageous because both pathogen strains are competing for the same uniform host pool.

in which pathogen strains with different infectiousness and/or lethality can co-exist (see Appendix). As one would expect, higher degrees of host–pathogen specificity lead to larger domains of co-existence, as shown in Fig. 7.

If pathogen strain frequencies are significantly affected by host–pathogen feedback, a pathogen strain’s intrinsic fitness (that is, its infectiousness times its longevity on the host) is not a good guide to its fate in competition with other strains. This can readily be visualized by plotting the equilibrium frequency of pathogen strain 2 as a function of both its infectiousness and its lethality, for several different levels of host–pathogen specificity (Fig. 8). The large dot in the centre of each panel denotes the lethality and infectiousness of the competing pathogen strain (strain 1). Through this point runs a diagonal line, representing conditions for which the two pathogen strains have equal intrinsic fitness. Because the two axes are logarithmic, this line corresponds to a constant ratio of infectiousness to lethality, or equivalently, a constant product of infectiousness times pathogen longevity. All points above and to the left of this line denote conditions where pathogen strain 2 has higher intrinsic fitness than pathogen strain 1. Conversely, points below and to the right of this line indicate lower intrinsic fitness for strain 2. When host–pathogen specificity is absent (Fig. 8a), the regions above and below this line correspond to regions of extinction and fixation for pathogen strain 2. That is, in the absence of any host–pathogen specificity, the outcome of competition between the two pathogen strains is determined entirely by their intrinsic fitnesses.

Much of the prior theoretical work on the evolution of virulence has focused on biological constraints that control the relationship between lethality and pathogen transmission and

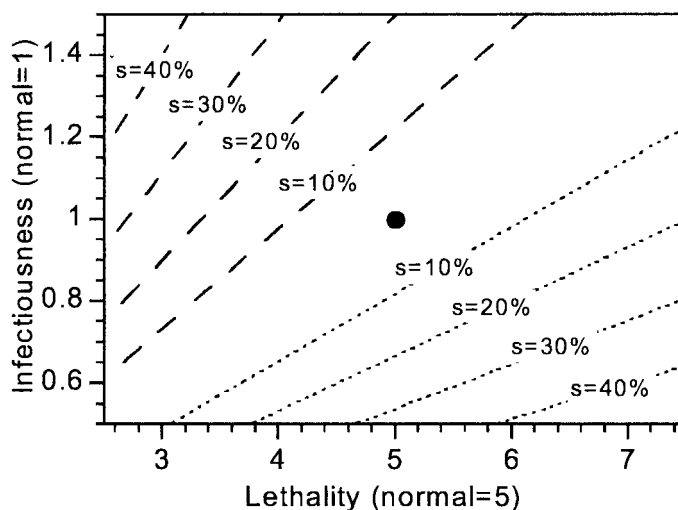


Fig. 7. Conditions under which pathogen strains can invade a model system dominated by a ‘normal’ pathogen strain ($u_1 = 1$, $m_1 = 5$) (dotted lines) and conditions under which they can drive the ‘normal’ strain to extinction (dashed lines). The solid dot in the centre of the figure indicates the infectiousness and lethality of the ‘normal’ pathogen strain. Pathogens below the dotted line (for a given level of specificity) cannot invade against the ‘normal’ pathogen strain. Pathogens above the dashed line (for a given level of specificity) will drive the ‘normal’ strain to extinction. Pathogens between the dotted and dashed lines will co-exist with the ‘normal’ strain. The domain of co-existence grows with the degree of host–pathogen specificity (see Appendix for derivation of invasion and fixation conditions).

thus the evolutionary trade-offs between these two characteristics (Anderson and May, 1982; Bull, 1994; Ebert, 1994; Lenski and May, 1994; Lipsitch *et al.*, 1995, 1996; Frank, 1996a). These kinds of trade-offs, and their evolutionary consequences, can be visualized through the two alternative evolutionary constraints labelled A–A' and B–B' in Fig. 8a. A pathogen's infectiousness and lethality might be biologically constrained to lie along line A–A', for which a given increase in lethality (and thus reduction in pathogen lifespan on the host) corresponds to a more-than-proportional increase in infectiousness. In this case, the pathogen's fitness is increased by moving in the direction of point A, thus raising its infectiousness and lethality. If, instead, the pathogen's biological constraints are different, and a given increase in lethality corresponds to a less-than-proportional increase in infectiousness (as indicated by the line marked B–B'), its fitness will be increased by moving in the direction of point B', reducing its infectiousness and lethality. In the absence of host–pathogen specificity, any change in infectiousness or lethality that increases a pathogen's

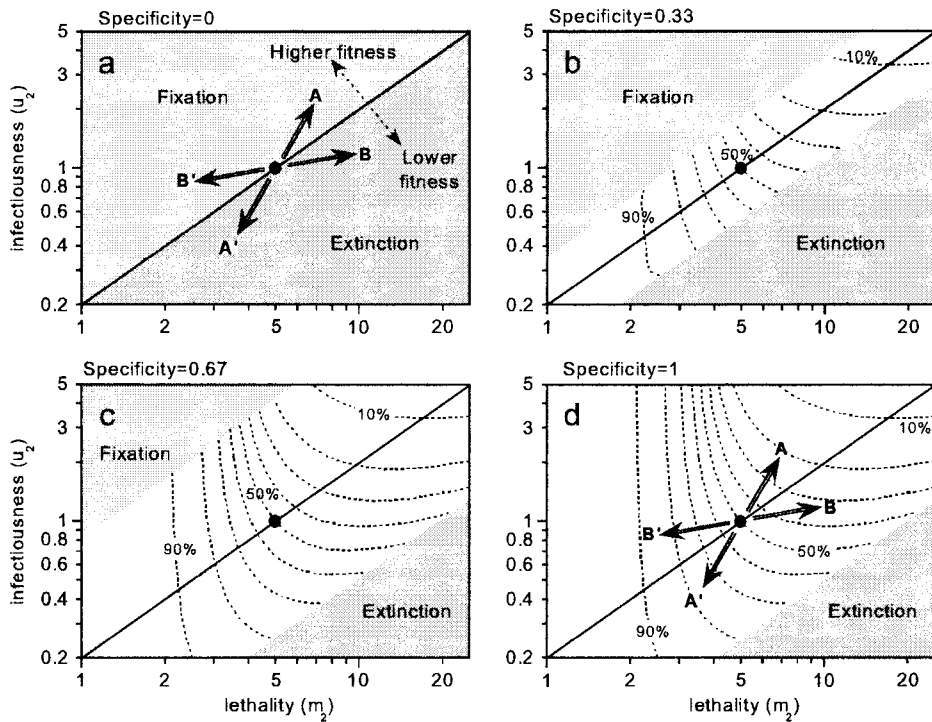


Fig. 8. Domains of competitive exclusion and stable polymorphism under different levels of host–pathogen specificity. Axes are the infectiousness (u_2) and lethality (m_2) of pathogen strain 2; pathogen strain 1's infectiousness and lethality are held constant at $u_1 = 1$ and $m_1 = 5$ throughout. The large dot in the centre of each panel is the point at which the two pathogen strains have the same infectiousness and lethality. The diagonal line through this point indicates conditions for which the two pathogen strains have equal intrinsic fitness. Shaded domains indicate conditions under which competitive exclusion will drive pathogen strain 2 to fixation (frequency = 1) or extinction (frequency = 0). Dotted contours indicate frequency of pathogen strain 2 in polymorphic equilibria. Lines A–A' and B–B' indicate possible trade-offs between pathogen lethality and infectiousness (see text).

intrinsic fitness (that is, its transmission rate times its longevity on the host) will give it an absolute fitness advantage and carry it to fixation at equilibrium.

Host–pathogen specificity complicates this simple relationship between intrinsic fitness and evolutionary success by coupling the fates of individual pathogen strains with the fates of their preferred hosts. For example, when specificity is absolute (Fig. 8d), a pathogen’s equilibrium frequency is no longer a step function determined by the pathogen’s characteristics alone; instead, it is a smoothly sloping surface, shaped by host–pathogen feedback. This feedback-dominated surface slopes downward as infectiousness increases, indicating that for host-specific pathogens, greater infectiousness (beyond the level required to sustain infection) is disadvantageous. Greater infectiousness is disadvantageous for host-specific pathogens, because it puts their preferred hosts at a competitive disadvantage with other host strains. As a result, the diagonal line that denotes equal intrinsic fitness between the two pathogen strains no longer denotes equal outcomes of selection between them. Instead, for the same intrinsic fitness, pathogen strain 2 can be near fixation or near extinction (lower left corner and upper right corner, respectively, of Fig. 8d). As before (Fig. 8a), moving in the direction of point B’ increases intrinsic fitness and increases the frequency of the pathogen strain. But moving in the direction of point A’ is also advantageous to the pathogen (in the sense that it increases its frequency), even though this entails a decrease in intrinsic fitness – that is, even though the decrease in lethality is accompanied by a more-than-proportional decrease in pathogen transmission.

Figures 8b and 8c illustrate the transition between competitive exclusion in the absence of host–pathogen specificity (Fig. 8a) and feedback-dominated stabilizing selection under absolute host–pathogen specificity (Fig. 8d). As host–pathogen specificity increases, the shape of the feedback-dominated selection surface remains constant, but the domain of feedback-dominated behaviour widens, and the domains of competitive exclusion retract like a pair of shutters. This occurs because at higher levels of specificity, individual host and pathogen strains are more tightly coupled, so host–pathogen feedback can override larger intrinsic fitness differences between the pathogen strains (corresponding to larger distances in the ‘northwest–southeast’ direction, perpendicular to the diagonal line denoting constant fitness). A vertical transect across Fig. 8b corresponds to a diagram such as Fig. 6a. In this three-dimensional view, one can see the generality of the pattern shown by Fig. 6a: domains of competitive exclusion are separated by a backward-sloping selection surface.

Considered together, these results show that host–pathogen genetic specificity can exert first-order control on selection for pathogen virulence traits. Our results suggest that empirical studies of the evolution of virulence may need to account for host–pathogen genetic specificity. Previous experiments have shown that the evolution of virulence can be shaped by pathogen life-history traits and by competition among pathogen strains (Herre, 1993; Ebert, 1994, 1998; Ewald, 1994; Taylor *et al.*, 1998), and have indicated that host variability in response to infection can constrain pathogen adaptation (Gupta and Hill, 1995; Imhoof and Schmid-Hempel, 1998). Our analysis has shown that the magnitude, and even the direction, of selection on virulence traits can depend on the degree of specificity between hosts and pathogens.

SUMMARY

Pathogens and parasites commonly exhibit genetic specificity, infecting some host strains more readily than others. We used a simple host–pathogen model to explore how host–

pathogen specificity affects selection on two pathogen life-history traits, infectiousness and lethality. When host–pathogen specificity is low, a pathogen strain with greater intrinsic fitness will out-compete a less fit strain, driving it to extinction (Figs 1a–c, 3a and 4a–c). However, at higher levels of host–pathogen specificity, stabilizing feedback between hosts and pathogens permits both pathogen strains to persist in the population, despite large intrinsic fitness differences between them (Figs 1d–f, 3b,c, 4d–f and 7). An abrupt specificity threshold separates the competitive exclusion domain from the domain of co-existence, where host–pathogen feedback dominates (Fig. 5). Above this threshold, host-mediated selection can reduce, nullify or even reverse the fitness consequences of pathogen infectiousness and lethality (Figs 1, 2, 4 and 5). Above the specificity threshold, maintaining polymorphism in the host requires maintaining polymorphism in the pathogen as well; elimination of either pathogen strain results in the extinction of one of the host strains and vice versa (Fig. 3). When host–pathogen specificity is high enough for host–pathogen feedback to regulate pathogen trait frequencies, selection will favour decreased pathogen infectiousness (Figs 6 and 8). Thus selection can favour either virulence or avirulence in pathogens, depending on the degree of specificity between pathogens and their hosts.

ACKNOWLEDGEMENTS

Our collaboration was supported by National Science Foundation grant EAR-9357931 to J.W.K. and Swiss National Fund grant 3100-046865.96 to B.A.R. We thank the reviewers for their comments.

REFERENCES

- Agrios, G.N. 1988. *Plant Pathology*. San Diego, CA: Academic Press.
- Anderson, R.M. and May, R.M. 1982. Coevolution of hosts and parasites. *Parasitology*, **85**: 411–426.
- Barrett, J.A. 1988. Frequency-dependent selection in plant–fungal interactions. *Phil. Trans. R. Soc. Lond. B*, **319**: 473–482.
- Borowicz, V.A. and Juliano, S.A. 1991. Specificity in host–fungus associations: do mutualists differ from antagonists? *Evol. Ecol.*, **5**: 385–392.
- Brooks, D.R. and McLennan, D.A. 1993. *Parascript*. Washington, DC: Smithsonian Institution Press.
- Bull, J.J. 1994. Virulence. *Evolution*, **48**: 1423–1437.
- Burdon, J.J. 1987. *Diseases and Plant Population Biology*. Cambridge: Cambridge University Press.
- Clarke, D.D. 1997. The genetic structure of natural pathosystems. In *The Gene-for-Gene Relationship in Plant–Parasite Interactions* (I.R. Crute, E.B. Holub and J.J. Burdon, eds), pp. 231–243. Wallingford, UK: CAB International.
- Clay, K. 1991. Parasitic castration of plants by fungi. *Trends Ecol. Evol.*, **6**: 162–166.
- Crute, I.R., Holub, E.B. and Burdon, J.J., eds. 1997. *The Gene-for-Gene Relationship in Plant–Parasite Interactions*. Wallingford, UK: CAB International.
- Ebert, D. 1994. Virulence and local adaptation of a horizontally transmitted parasite. *Science*, **265**: 1084–1086.
- Ebert, D. 1998. Experimental evolution of parasites. *Science*, **282**: 1432–1435.
- Ebert, D. and Hamilton, W.D. 1996. Sex against virulence: the coevolution of parasitic diseases. *Trends Ecol. Evol.*, **11**: 79–82.
- Ewald, P.W. 1994. *Evolution of Infectious Disease*. Oxford: Oxford University Press.

- Frank, S.A. 1996a. Models of parasite virulence. *Quart. Rev. Biol.*, **71**: 37–78.
- Frank, S.A. 1996b. Problems inferring the specificity of plant–pathogen genetics. *Evol. Ecol.*, **10**: 323–325.
- Futuyma, D.J., Keese, M.C. and Funk, D.J. 1995. Genetic constraints on macroevolution: the evolution of host affiliation in the leaf beetle genus *Ophraella*. *Evolution*, **49**: 797–809.
- Garrett, S.D. 1970. *Pathogenic Root-infecting Fungi*. Cambridge: Cambridge University Press.
- Gupta, S. and Hill, A.V.S. 1995. Dynamic interactions in malaria: host heterogeneity meets parasite polymorphism. *Proc. R. Soc. Lond. B*, **261**: 271–277.
- Herre, E.A. 1993. Population structure and the evolution of virulence in nematode parasites of fig wasps. *Science*, **259**: 1442–1446.
- Imhoof, B. and Schmid-Hempel, P. 1998. Patterns of local adaptation of a protozoan parasite to its bumblebee host. *Oikos*, **82**: 59–65.
- Jarosz, A.M. and Davelos, A.L. 1995. Effects of disease in wild populations and the evolution of pathogen aggressiveness. *New Phytol.*, **129**: 371–387.
- Kawecki, T.J. 1998. Red Queen meets Santa Rosalia: arms races and the evolution of host specialization in organisms with parasitic lifestyles. *Am. Nat.*, **152**: 635–651.
- Kirchner, J.W. and Roy, B.A. 1999. The evolutionary advantages of dying young: epidemiological implications of longevity in metapopulations. *Am. Nat.*, **154**: 140–159.
- Kirchner, J.W. and Roy, B.A. 2001. Evolutionary implications of host–pathogen specificity: the fitness consequences of host life history traits. *Evol. Ecol.*, **14**: 665–692.
- Lenski, R.E. and May, R.M. 1994. The evolution of virulence in parasites and pathogens: reconciliation between two competing hypotheses. *J. Theor. Biol.*, **169**: 253–265.
- Lipsitch, L., Herre, E.A. and Nowak, M.A. 1995. Host population structure and the evolution of virulence: a ‘law of diminishing returns’. *Evolution*, **49**: 743–748.
- Lipsitch, M., Siller, S. and Nowak, M.A. 1996. The evolution of virulence in pathogens with vertical and horizontal transmission. *Evolution*, **50**: 1729–1741.
- May, R.M. and Anderson, R.M. 1983a. Parasite–host coevolution. In *Coevolution* (D.J. Futuyma and M. Slatkin, eds), pp. 186–206. Sunderland, MA: Sinauer Associates.
- May, R.M. and Anderson, R.M. 1983b. Epidemiology and genetics in the coevolution of parasites and hosts. *Proc. R. Soc. Lond. B*, **219**: 281–313.
- May, R.M. and Nowak, M.A. 1995. Coinfection and the evolution of parasite virulence. *Proc. R. Soc. Lond. B*, **261**: 209–215.
- Price, P.W. 1980. *Evolutionary Biology of Parasites*. Princeton, NJ: Princeton University Press.
- Read, A.F. 1994. The evolution of virulence. *Trends Microbiol.*, **2**: 73–76.
- Roy, B.A. and Bierzychudek, P. 1993. The potential for rust infection to cause natural selection in apomictic *Arabis holboellii* (Brassicaceae). *Oecologia*, **95**: 533–541.
- Taylor, L.H., Mackinnon, M.J. and Read, A.F. 1998. Virulence of mixed-clone and single-clone infections of the rodent malaria *Plasmodium chabaudi*. *Evolution*, **52**: 583–591.
- Thompson, J.N. 1994. *The Coevolutionary Process*. Chicago, IL: University of Chicago Press.
- Thompson, J.N. and Burdon, J.J. 1992. Gene-for-gene coevolution between plants and parasites. *Nature*, **360**: 121–125.
- van der Plank, J.E. 1984. *Disease Resistance in Plants*. Orlando, FL: Academic Press.
- van Tienderen, P.H. 1991. Evolution of generalists and specialists in spatially heterogeneous environments. *Evolution*, **45**: 1317–1331.
- Via, S. 1990. Ecological genetics and host adaptation in herbivorous insects: the experimental study of evolution in natural and agricultural systems. *Annu. Rev. Entomol.*, **35**: 421–446.
- Weller, S.G., Ohm, H.W., Petterson, F.L., Foster, J.E. and Taylor, P.L. 1991. Genetics of resistance of CI 15160 durum wheat to biotype D of Hessian fly. *Crop Sci.*, **31**: 1163–1168.
- Weste, G. 1986. Vegetation changes associated with invasion by *Phytophthora cinnamoni* of defined plots in the Brisbane Ranges, Victoria (Australia), 1975–1985. *Austr. J. Bot.*, **34**: 633–648.

APPENDIX: THRESHOLD CONDITIONS FOR INVASION OF VIRULENCE TRAITS

Here we derive the conditions under which systems dominated by a single pathogen strain can be invaded by another pathogen strain with different infectiousness or lethality characteristics. If the two host strains are otherwise identical and only one pathogen strain (say, strain 1) is present, its preferred host strain will be driven to extinction and only the other host (strain 2) will persist. The equilibrium uninfected host population X_2^* will then be determined by the single-strain form of equation (2):

$$\frac{dY_{21}}{dt} = \beta_{21} X_2^* Y_{21} - \frac{m_1 Y_{21}}{\tau_2} = 0 \quad (8)$$

for which the solution is

$$X_2^* = \frac{m_1}{\beta_{21} \tau_2} \quad (9)$$

In a system dominated by pathogen strain 1 and host strain 2, the fitness of either pathogen strain will be the number of new hosts that can be infected during the average lifespan of an infected host, or

$$\omega_k = \beta_{2k} X_2^* \frac{\tau_2}{m_k} = \frac{\beta_{2k} m_1}{\beta_{21} m_1} \quad (10)$$

where $\beta_{2k} X_2^*$ is the per-capita transmission rate of pathogen strain k to new individuals of host strain 2, and τ_2/m_k is the average lifespan of hosts (in strain 2) infected with pathogen strain k . If pathogen strain 1 is in equilibrium, its fitness will be equal to 1; for pathogen strain 2 to invade this equilibrium system, its fitness must be greater than 1. Combining equations (10) and (3), we see that this criterion becomes

$$\omega_2 = \frac{\beta_{22} m_1}{\beta_{21} m_2} = \frac{\beta_0 v_2 u_2 (1+s) m_1}{\beta_0 v_2 u_1 (1-s) m_2} = \frac{u_2 m_1 (1+s)}{u_1 m_2 (1-s)} > 1 \quad (11)$$

or, equivalently, that the necessary host–pathogen specificity is $s > (u_1 m_2 - u_2 m_1)/(u_1 m_2 + u_2 m_1)$. Even if pathogen strain 2 is less infectious or more lethal than pathogen strain 1 (i.e. $u_2 < u_1$ or $m_2 > m_1$), it may nonetheless be able to invade if the degree of host–pathogen specificity (s) is sufficiently high.

A similar argument can be used to show that pathogen strain 2 can drive pathogen strain 1 to extinction (even if host strain 1 dominates the host population) when

$$\frac{u_2 m_1 (1-s)}{u_1 m_2 (1+s)} > 1 \quad (12)$$

Between these invasion and extinction thresholds, both pathogen strains can co-exist, provided that host strains can occasionally migrate into the system (because maintaining polymorphism in the pathogen population requires the presence of both host strains). Figure 7 shows the domains of co-existence and exclusion under different degrees of host–pathogen specificity. As one would expect from equations (11) and (12), higher degrees of host–pathogen specificity correspond to larger domains of co-existence.