Theoretical models for the evolution and ecological dynamics of host-parasite systems

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Summary

Natural organisms are infected by many different parasites, and as a consequence, hosts have evolved a wide range of defences to cope with them. Resistance may be conferred through mechanisms that reduce susceptibility to infection ('avoidance') or increase the rate of clearance ('recovery'). Other forms of resistance reduce the deleterious effects of infection ('tolerance'), or inhibit the parasite's growth ('control'). In addition to these innate forms, hosts may also benefit from immunological memory ('acquired immunity'). The evolution of resistance is expected to be costly in terms of other life history traits. In the presence of such 'trade-offs', the host population may evolve towards an evolutionarily stable strategy (ESS) that balances the costs and benefits of resistance. Another possibility is that a process of evolutionary branching occurs, leading to polymorphism of distinct strategies. Parasites also show adaptation to their hosts and have generally not evolved to be avirulent. Again, this is the result of trade-offs between virulence and other aspects of life history. Often, a higher transmission rate is attained at the cost of increased virulence.

This thesis uses a mathematical modelling approach to examine host-parasite interactions. The first part considers the evolutionary dynamics of quantitative host resistance and parasite traits, employing fitness expressions constructed using the techniques of adaptive dynamics. The second part examines the population dynamics of host-parasite interactions; in particular, how different assumptions about the nature of the transmission process may affect the dynamics.

Contents

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Declaration

This dissertation summarizes the research I have conducted since January 2003, under the supervision of Dr. Michael Boots and Dr. Andrew White.

Chapter 2 forms the basis of a manuscript published in the *Journal of Theoretical Biology* 236 (2005), pp. 198-207. Chapter 4 forms the basis of a manuscript published in *Evolution* 60:5 (2006), pp. 945-956.

Chapters 3 and 6 are currently being written up as manuscripts.

Chapter 5 is the result of collaborative research with Dr. Jonathan Ryder and Dr. Rob Knell. It forms the basis for a manuscript that has recently been submitted for review. I contributed to the model design and performed the analysis.

1. Introduction

1-1. Biological Outline: Host-Parasite interactions

1-1-1. Classification of resistance mechanisms

Nature shows countless examples of parasitic organisms. Faced with this array of natural enemies, hosts have evolved many diverse forms of defence that can be functionally classified. Defence against parasites (resistance) may evolve through mechanisms that reduce the probability of infection (avoidance; Boots and Bowers 1999). Avoidance may be conferred by numerous mechanisms, such as a behavioural change for example. It may also manifest through physiological barriers; in insects, parasites must first penetrate the gut wall before they can successfully infect the host (Dunn et al. 1994; Boots and Haraguchi 1999). In addition to these first line defences, a more efficient immune system will also confer resistance to parasites (Medzhitov and Janeway 1997; Zuk and Stoehr 2002; Schmid-Hempel 2003, 2005). This may manifest as an increased rate of recovery (van Baalen 1998; Boots and Bowers 1999; Restif and Koella 2004), or better control of the parasite once an infection has developed (Sheldon and Verhulst 1996). Resistance may also be conferred by a more efficient immunological memory (acquired immunity; Boots and Bowers 2004).

Tolerance mechanisms that reduce the deleterious effects of infection (virulence) may also be classed as a form of resistance (Boots and Bowers 1999). Plant tolerance of herbivores in particular has been widely documented (Strauss and Agrawal 1999; Stowe et al. 2000), and pathogen tolerance has also been observed in some plant species (Simms and Triplett 1994; Kover and Schaal 2002). There is also evidence for tolerance in insects; the bumblebee, *Bombus terrestris*, has been shown to evolve tolerance in response to a trypanosome intestinal parasite (Imhoof and Schmid-Hempel 1998). Importantly, the mechanisms conferring resistance may act in more than one way. In the rabbit-myxomatosis system, the evolution of genetic resistance initially correlates with an increased survival time, while higher levels of resistance also increase the chance of recovery (Ross and Sanders 1984; Williams et al. 1990).

1-1-2. Costs of resistance

The evolution of resistance is generally expected to incur a cost (Sheldon and Verhulst 1996). Costs have been identified in both plant-herbivore (Mauricio et al. 1997; Tiffin and Rausher 1999) and plant-pathogen interactions (Simms and Triplett 1994). Costs have also been identified in vertebrates, where a reduction in reproductive effort may reduce the likelihood of contracting a sexually transmitted disease, but also the number of offspring (Zuk and Stoehr 2002). In terms of the host's immune response, there may be evolutionary costs that arise due to negative genetic covariances. Here resistance is traded-off at the genetic level with another fitness-related trait such as growth or reproduction (antagonistic pleiotropy; Stearns 1992). Evolutionary costs have been demonstrated experimentally by, for example, Boots and Begon (1993) and Kraaijeveld and Godfray (1997).

1-1-3. Parasite evolution

This tension between cost and benefits of resistance is only half the story, however, as parasites also show adaptation to their hosts. When initially introduced to Australian rabbits in 1950, the myxomatosis virus was extremely virulent, with nearly 100% mortality of infected rabbits. The following ten years then witnessed a gradual decline in virulence (Fenner and Ratcliffe 1965). In contrast, in a horizontally transmitted microparasitic disease of the planktonic crustacean, *Daphnia*, increasing geographic distance between host and parasite origin correlated with a decrease in spore production and also virulence (Ebert 1994). This contradicted the conventional hypothesis that parasites should evolve to be benign. Indeed, virulence may often be an unavoidable consequence of pathogen replication in order to transmit to new hosts (Anderson and May 1982; Lipsitch and Moxon 1997; Mackinnon and Read 1999; Messenger et al. 1999). Multiple infections within a single host in particular are thought to select for more virulent parasites. In nematodes infecting fig wasps, increased horizontal transmission was correlated with higher virulence, and this was explained by within-host competition (Herre 1993; Bull 1994). That the mode of transmission also influences virulence evolution is widely recognised. Pathogens

transmitted via free-living infective stages (TB, smallpox) or through insect vectors (malaria) generally have much higher virulence compared to those requiring direct host-to-host contact (Ewald 1993).

1-1-4. Male-biased parasitism

There is convincing evidence that parasitism may often be biased towards males. This may often be due to differences in behaviour; males tend to have larger home ranges and higher activity levels, which may increase the likelihood of infection (Poulin 1996; Perkins et al. 2003). Sexual size dimorphism is common in mammals, with males usually being the larger sex, and this is associated with increased parasitism - possibly because a larger body size makes an easier target for parasites (Moore and Wilson 2002). In this context, two recent studies of the yellow-necked mouse, *Apodemus flavicollis*, identified a small proportion of the population (large, sexually mature males) as the key agents chiefly responsible for spreading the disease (Perkins et al. 2003; Ferrari et al. 2004). Male-biased parasitism may also be due to differences in immune investment. From an evolutionary perspective, this is likely to be a consequence of life history differences. Males gain fitness mainly through mating success, and females mainly through longevity, a phenomenon known as Bateman's principle (Bateman 1948; Trivers 1972; Clutton-Brock 1988; Rolff 2002). In some cases, the trade-off between immune function and mating may be explicit. Androgenic hormones that increase mating success (i.e. testosterone in vertebrates) are thought to have an immunosuppressive effect (Folstad and Karter 1992; Moore and Wilson 2002); in insects, the juvenile hormone may also reduce phenoloxidase activity after mating (Rolff and Siva-Jothy 2002).

1-2. Theoretical models

1-2-1. The evolution of host resistance

Theoretical models typically model costs as a lower intrinsic growth rate or higher susceptibility to crowding. Under this assumption, avoidance (reduced susceptibility

to infection) evolves over a wide range of costs (Antonovics and Thrall 1994; Bowers et al. 1994), and in some circumstances may result in polymorphism. This is because avoidance reduces the force of infection acting upon susceptible hosts (the transmission rate multiplied by the density of infecteds) and therefore the advantage of resistance (negative feedback; Antonovics and Thrall 1994; Roy and Kirchner 2000). Polymorphism becomes increasingly likely as the degree of difference between susceptible and resistant strains increases (Boots and Bowers 1999); this would seem to agree with observations of plant populations (Burdon 1987; Alexander et al. 1993). In this context, the structure of the trade-off is particularly important for determining the evolutionary outcome; polymorphism is only predicted to evolve under a decelerating trade-off, where the cost increases less than linearly with the benefit of resistance (Boots and Haraguchi 1999).

Crucially, in the model of Boots and Haraguchi (1999), the level of resistance a host manifested also determined its uninfected carrying capacity. Boot and Bowers (2003) later showed this to be a necessary condition for the coexistence of different avoidance strategies. Mutual invadability (polymorphism) is impossible under the assumption of a constant carrying capacity, because here an invader's fitness can be expressed as a separable function of two terms, one depending on the resident strain, and the other on the invader (Boots and Bowers 2003). This leads to a competitive exclusion principle, whereby the host evolves to minimize the basic depression ratio (D_0), defined as the number of host individuals, per capita infected, by which an endemically infected population is depressed below its carrying capacity (Bowers 2001). Analysis of the basic predator-prey model has further revealed that polymorphism is only possible given an emergent carrying capacity (i.e. one defined implicitly by the host's birth rate and susceptibility to crowding) (Bowers et al. 2003). Thus, the negative feedbacks associated with avoidance allow for polymorphism only under certain ecological conditions. In populations where the carrying capacity is effectively fixed by environmental factors, therefore, polymorphism in avoidance should not evolve (Boots and Bowers 2003).

The evolution of higher recovery rates is qualitatively similar to avoidance, in terms of the dynamics. A faster recovery rate reduces the duration of infection, which incurs negative feedback and may select for polymorphism (Boots and Bowers 1999). Interestingly, the recovery rate evolves to maximize the force of infection (van Baalen 1998). This is an example of the 'pessimization principle,' whereby the optimal strategy is the one that creates (and can survive in) the worst possible environment (Mylius and Diekmann 1995). In contrast, the evolution of tolerance is associated with positive feedback, since as the density of tolerant individuals increases, so does the prevalence of infection (Roy and Kirchner 2000). As tolerance spreads, it becomes increasingly beneficial, and is therefore predicted to be monomorphic within populations (Roy and Kirchner 2000; Boots and Bowers 2004).

Clearly, resistance only ever evolves where its benefits exceed its costs (Boots and Bowers 1999, 2004; Boots and Haraguchi 1999). Since, by definition, resistance reduces the fitness loss due to parasitism, the evolution of one form may therefore reduce selection for others (Simms and Triplett 1994; Mauricio et al. 1997; Kover and Schaal 2002). In plant-herbivore interactions, tolerance is often negatively correlated with other forms of resistance (Fineblum and Rausher 1995). Population genetics models also suggest that avoidance and tolerance are mutually exclusive, unless there is genetic covariance between the traits and unequal costs (Tiffin 2000). The evolution of avoidance may reduce selection for recovery, as the latter is only selected in response to highly transmissible pathogens; similarly, avoidance is favoured at low recovery rates (Boots and Bowers 1999). In contrast, the evolution of tolerance may actually increase selection for avoidance or recovery, because these mechanisms are increasingly favoured as virulence decreases (Boots and Bowers 1999). The evolutionary dynamics of innate resistance (avoidance, recovery, tolerance) are quantitatively the same whether or not the host also benefits from acquired immunity (Boots and Bowers 2004). Acquired immunity itself (evolving as reduced rate of loss of immunity) is selected in response to high transmission rates, high virulence and intermediate rates of recovery, and has a limited potential for polymorphism.

Restif and Koella (2004) examined the concurrent evolution of recovery and tolerance as distinct strategies. Tolerance was favoured at low virulence and high transmission rates of infection. In contrast, high virulence and low transmission selected for relatively greater recovery. Crucially, the optimal defence strategy depended on the cost structure. Accelerating costs favoured mixed strategies, where the host balanced investments between the two defences to minimize the total cost. With linear costs, either mixed or pure strategies could evolve. Polymorphism of pure strategies was also possible, and in some cases the outcome was dependent on the initial conditions (evolutionary bistability).

1-2-2. The evolution of parasites

Theoretical models often assume a trade-off between parasite transmission and virulence. The dominant paradigm is that parasites achieve transmission through within-host replication, with virulence seen as an unavoidable consequence. If transmission is modelled as an increasing saturating function of virulence, this selects for an intermediate level of virulence (van Baalen and Sabelis 1995; Frank 1996; Restif and Koella 2003). However, many pathogens transmit via free-living infective stages, capable of surviving for long periods of time outside the host (Anderson and May 1981). This partially decouples transmission from the lifespan of infected hosts, and therefore selects for higher virulence (Day 2002b). If free-living particles are released upon death of the infected host (e.g. as in the nuclear polyhedrosis and granulosis viruses), this potentially selects for even higher virulence (Day 2002b). Obligately killing parasites in particular may be expected to evolve very high virulence (Ebert and Weisser 1997). Furthermore, some free-living pathogens, such as the bacteria *Bacillus anthracis*, produce toxic substances that have no clear connection to within-host replication (Prescott et al. 1999; Mock and Fouet 2001). Recent theory has shown that such toxicity effects may actually confer a selective advantage, particularly in, although not limited to, obligate killers (Day 2002b).

If hosts may be simultaneously infected by more than one pathogen strain (multiple infection), this generally selects for higher virulence, where more

exploitative parasites have a competitive advantage within infected hosts (Bremermann and Pickering 1983; Frank 1992a, 1994, 1996; May and Nowak 1994, 1995; Nowak and May 1994; van Baalen and Sabelis 1995; Mosquera and Adler 1998). Here the evolution of virulence is mediated by the intensity of within-host competition; as such, reducing the probability of infection may therefore select for lower virulence (Ebert and Mangin 1997).

Heterogeneities in the host population have implications for virulence evolution. In this context, Gandon (2004) modelled the evolution of multi-host parasites. An extreme bias towards within-type transmission allowed polymorphism of different virulence strategies, each specialized to exploit a particular host, while increasing the relative amount of between-type transmission favoured more generalist strategies. Regoes et al. (2000) also investigated the evolution of virulence in a heterogeneous host population. The study showed that a decelerating trade-off between virulence on the two hosts (i.e. where a decrease in virulence in one host caused a less than proportionate increase in virulence on the other host) favoured polymorphism.

Parasites also exhibit different modes of transmission. This has important implications because different forms of transmission may lead to fundamentally different dynamics (Antonovics et al. 1995). In non-sexually transmitted diseases (ordinary infectious diseases, or OIDs), the rate of new infections tends to increase with the density of infecteds (density-dependent transmission; McCallum et al. 2001; Begon et al. 2002). On the other hand, in sexually transmitted diseases (STDs), the number of partners remains roughly constant as density increases and transmission therefore depends on the proportion of infected hosts (frequency-dependent transmission; Getz and Pickering 1983; Antonovics et al. 1995; McCallum et al. 2001; Begon et al. 2002). However, these two assumptions (density- and frequency-dependent transmission) represent extremes on a continuum, and in reality the transmission dynamics will often fall somewhere in between (see review by Ryder et al. 2005). Moreover, individual pathogens may often have more than one transmission mode (Lockhart et al. 1996; Thrall and Antonovics 1997).

1-2-3. Host-parasite coevolution

Coevolution has mainly been studied using population genetics models, which examine the interactions between resistance and infectivity alleles (Flor 1971; Burdon 1987). Matching genotype models assume a one-to-one correspondence between host and parasite genotypes, such that hosts possessing a resistance gene may only be infected by parasites with the corresponding virulence gene, or alternatively, that hosts only express resistance against a perfectly matched parasite genotype (Sasaki 2002). In real systems, however, the relationship between host and parasite genotypes is highly asymmetric: some parasite genotypes may be able to infect multiple hosts, and some host genotypes exhibit resistance to a wide range of parasites (Sasaki 2002). As such, natural systems are more realistically modelled using multi-locus gene-for-gene (GFG) interactions. Multi-locus GFG models generally predict the evolution of high degrees of resistance and virulence, with frequency-dependent selection favouring new gene combinations. This potentially leads to polymorphisms in both host and pathogen genotypes, and sustained cycles in the genotype frequencies (Frank 1992b; Sasaki 2002).

Gene-for-gene models are highly characteristic of the evolutionary arms races observed in many plant-pathogen systems (Burdon 1987). However, they fail to capture an important aspect of host-parasite interactions: that resistance will rarely be an all-or-nothing affair. This is particularly relevant in the context of the host's immune response: given that investing in immunity is costly, hosts will evolve different degrees of resistance to their parasites (van Baalen 1998). In turn, the host's investment in resistance affects the evolution of quantitative parasite traits (e.g. virulence, transmissibility) (Frank 1996). Epidemiological models including this complexity have been proposed by a number of authors. Restif and Koella (2003) showed that the optimal parasite virulence is often independent of the level of avoidance. This depends, however, on how the host's susceptibility and parasite's replication rate combine to determine transmission; in some cases, avoidance may select for increased virulence. In contrast, if hosts may be simultaneously infected by more than one parasite strain, avoidance may select for lower virulence (Gandon et al.

2002a). The evolution of tolerance is predicted to select for increased replication rates and potentially higher virulence (Restif and Koella 2003), as is resistance conferred through control of the parasite (Gandon and Michalakis 2000). The evolution of higher recovery rates also selects for increased parasite virulence; a faster recovery reduces the benefit of lower virulence in terms of prolonging the infectious period (van Baalen 1998). In some cases there are two locally stable outcomes: an internal optimum characterised by relatively high recovery and virulence, and zero investment in recovery with relatively low virulence (van Baalen 1998).

The evolution of parasites in response to host resistance is analogous to the selection imposed by imperfect vaccination strategies (Gandon et al. 2001, 2002b, 2003). This relates in particular to the evolution of malaria in response to partial vaccines acting at different parts of the infection process (Mackinnon 2005). Vaccines that reduce the toxicity due to pathogen replication are predicted to select for increased replication (Gandon et al. 2001), unless there is a separate metabolic cost of toxin production that the vaccine is able to maintain (Gandon et al. 2002b). Anti-growth vaccines reducing both virulence and transmission rate also generally select for higher replication rates (Gandon et al. 2003). Here the increase is likely to be less severe wherever there is a strong anti-infection component, as the lower probability of infection in vaccinated hosts reduces selection for higher replication. Furthermore, if superinfection by other parasite strains is possible, the infection-blocking component selects for lower parasite replication by decreasing the level of competition among strains. These theoretical predictions have recently gained some empirical support. Using the mouse-malaria model, *Plasmodium Chabaudi*, the evolution of virulence was investigated in both immunized and non-immunized mice: parasite lines in immune mice evolved higher virulence (Mackinnon and Read 2004).

Theoretically, population genetics models may incorporate the epidemiological details of the host-parasite interaction (e.g. May and Anderson 1983). However, such models are very complicated, which presents difficulties in their analysis. Gandon et al. (2002a) examined the coevolution of host avoidance and parasite virulence, with the simplifying assumption that resistance was complete (i.e.

hosts expressing resistance to a given parasite genotype cannot be infected). In the absence of superinfection, optimal virulence was shown to be independent of the level of avoidance. With superinfection, the evolution of virulence depended on the mutation rate at the infectivity locus: at low mutation rates, there were effectively two different parasite populations and virulence evolved independently in each; with a higher mutation rate, avoidance selected for a lower level of (monomorphic) virulence. Encouragingly, this agreed with the prediction of the epidemiological model without population genetics (Gandon et al. 2002a).

1-2-4. Population dynamics: stable points, cycles and chaos

Persistent long-term population cycles occur in many insect-pathogen systems (Baltensweiler 1964; Varley et al. 1973). There have been several theoretical models proposed to explain these dynamics. The continuous host-microparasite model of Anderson and May (1981) has the potential to exhibit long-term periodic cycles, if transmission occurs via free-living stages. The inclusion of density-dependence in the birth rate provides a stabilizing mechanism that increases dynamics stability and reduces the likelihood of cycles (Bowers et al. 1993; Dwyer 1994; White et al. 1996). However, cycles tend to occur in species with discrete, non-overlapping generations, where the pathogen typically kills the insect at the larval stage before it can reproduce. A discrete, seasonal formulation may therefore more accurately describe such systems, although this introduces greater complexity to the models. The basic discrete model is inherently less stable and predicts divergent oscillations, due to the time delay in the pathogen's response to changes in host density (Briggs and Godfray 1996; Bonsall et al. 1999). Mechanisms that allow the pathogen to respond more quickly, or control the host's growth by other means, will therefore increase stability (Bonsall 2004). For example, if the pathogen is able to pass through several infectious bouts per season, this reduces the time delay and may result in stable cycles (Briggs and Godfray 1996). Host density-dependence may also allow cycles, by preventing the divergent oscillations that normally ensue following low pathogen density. If infectious particles are able to survive between seasons, either in a

protected reservoir or through vertical transmission, this may also result in cycles (Briggs and Godfray 1996; Bonsall et al. 1999).

It is now believed that sublethal or covert infection may be responsible for the endemic persistence of many pathogens (Boots et al. 2003; Burden et al. 2003). Sublethal infection is assumed to reduce fecundity and/or increase development time, but to have no other overt symptoms. The general consensus is that sublethal infection is destabilizing, as the sublethal class is unable to infect and regulate the host (Boots and Norman 2000; Bonsall et al. 2005). Covert infection is similar to sublethal, although it may also spontaneously convert into overt infection and is also transmitted vertically. Covert infection is generally stabilizing, although this depends on the complex interplay of parameters - in some circumstances, covert infection may be destabilizing (Boots et al. 2003; Bonsall et al. 2005). Intermediate rates of conversion to the overt state are stabilizing, while high or low rates are destabilizing (Boots et al. 2003). Interestingly, the degree of stabilization is much greater in highly pathogenic diseases (Boots et al. 2003). If covert infection confers immunity to the overt stage this also stabilizes the dynamics (Bonsall et al. 2005).

1-3. Theoretical approach

1-3-1. Epidemiological models

In a seminal paper, Anderson and May (1981) developed models to describe the population dynamics of microparasites and their invertebrate hosts. The basic model assumes that transmission occurs through direct contact between an uninfected (susceptible) and an infected host (Fig. 1.1). Once infected, individuals suffer an increased mortality rate (virulence) and recover at a constant rate. The model can be adapted to include morbidity, vertical transmission, density-dependent birth rates, and transmission via free-living infective stages.

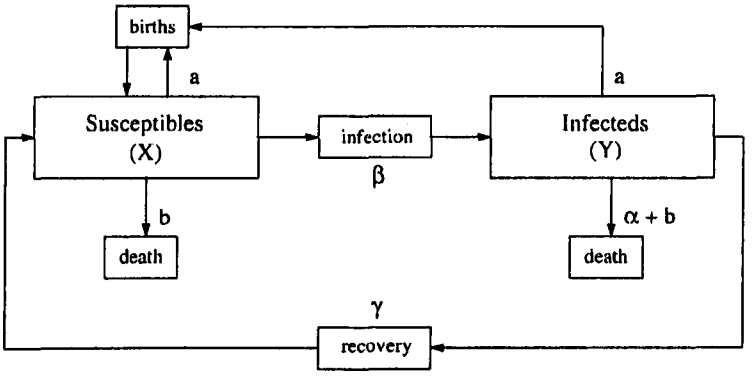

Figure 1.1. Compartmental representation of the basic susceptible-infected-susceptible model for a host-microparasite interaction (reproduced from Anderson and May 1981).

Holt and Pickering (1985) showed how the Anderson and May model could be extended to include two competing hosts interacting with a shared pathogen. Their model identified three possible dynamical outcomes: competitive dominance (where one host eliminates the other), mutual infected coexistence, and contingent competition (where either host may eliminate the other, depending on initial conditions). Coexistence was only possible if transmission within species was stronger than transmission between species. This model did not include density-dependence, and if unregulated by the pathogen, the population would therefore grow to infinity. The addition of self-regulation allows coexistence under a wider range of conditions (Begon et al. 1992). The model was later applied as an evolutionary algorithm, with the two hosts representing different haploid genotypes. This is the common methodology used to investigate the evolution of host populations (Antonovics and Thrall 1994; Bowers et al. 1994; Boots and Bowers 1999, 2004; Boots and Haraguchi 1999; Bowers 1999, 2001; van Boven and Weissing 2004). Similarly, host-pathogen-pathogen models have been applied to study the evolution of parasites (van Baalen and Sabelis 1995; Frank 1996; Restif and Koella 2003).

1-3-2. ESS theory and adaptive dynamics

The theory of evolutionarily stable strategies (Maynard Smith and Price 1973; Maynard Smith 1982) states that a particular phenotype, when adopted by a large

enough proportion of the population (i.e. when 'resident'), may be sufficiently advantageous such that it resists invasion by all other possible phenotypes. Such a phenotype is called an evolutionarily stable strategy, or ESS. The phenotypic approach is particularly useful in that genetic considerations may be circumvented to some extent. However, the ESS-definition does not specify whether the singular strategy will actually become established in the first place (Eshel 1983). This has led to an alternative definition of evolutionary stability: a singular strategy is called 'convergence stable' (CS) if nearby residents may be invaded by those closer to it (Christiansen 1991).

Evolutionary and convergence stability are independent stability properties that may occur in any combination (Eshel 1983; Christiansen 1991). Recognition of this fact has led to the theory of adaptive dynamics (Metz et al. 1996; Geritz et al. 1998), which assumes that the most common individuals (the 'residents') will necessarily determine the environment. As selection operates and the composition of the population changes, so therefore will the fitness of a putative invader. This indicates a dynamic feedback, where the fitness of a particular phenotype depends not only on its own life history parameters, but on those of the resident as well. Adaptive dynamics incorporates basic trade-off theory (Stearns 1992) to construct fitness expressions that determine the position and nature of singular points of evolution. Mutation is assumed to occur locally, near to the resident strategy, and evolutionary processes to occur over a sufficiently long time period such that the population always reaches its dynamic attractor before a new mutation occurs. A full treatment of the techniques of adaptive dynamics is given in Geritz et al. (1998), but I present here a basic outline.

Assume that a particular phenotype, x, is resident (i.e. the population is composed entirely of individuals with phenotype x). Let $r(x,E_x)$ represent the marginal fitness (the long-term population growth rate) of phenotype x in the environment determined by it, E_x. Assuming phenotype x is initially at its population dynamic attractor, its marginal fitness is given as (Geritz et al. 1998):

$$S_x(x) = r(x, E_x) = 0 \tag{1.1}$$

Let y denote a mutant strategy, initially rare, attempting to invade this resident population. Assuming the initial mutant density is negligible, the mutant's fitness can be expressed as (Geritz et al. 1998):

$$S_x(y) = r(y, E_x) \tag{1.2}$$

If $S_x(y) < 0$ then the mutant cannot invade and will become extinct. If $S_x(y) > 0$ and $S_y(x) < 0$ then the mutant can invade and replace the resident phenotype, x. If $S_x(y) > 0$ and $S_y(x) > 0$ then the mutant can invade the resident, but the resident can also invade the mutant; this leads to a dimorphism, as discussed later. Assuming local mutation then, a linear approximation of the mutant's fitness is (Geritz et al. 1998):

$$S_x(y) = S_x(x) + D(x)(y - x) \tag{1.3}$$

Here $D(x)$ gives the local fitness gradient:

$$D(x) = [\partial S_x(y) / \partial y]_{y=x} \tag{1.4}$$

From (1.1) the first term in (1.3) is always zero. An initially monomorphic population will therefore evolve in the direction of the local fitness gradient (1.4). If $D(x) > 0$ then only mutants with $y > x$ can invade, while if $D(x) < 0$ then only mutants with $y < x$ can invade. The mutation-selection process continues until a singular point is reached, where:

$$D(x) = 0 \tag{1.5}$$

By evaluating the second order partial derivatives of $D(x)$ with respect to x and y, the nature of the singular point can be determined. The condition for a singular point to be an ESS is (Geritz et al. 1998):

$$\frac{\partial^2 S_x(y)}{\partial y^2} < 0 \qquad (1.6)$$

The condition for convergence stability is (Geritz et al. 1998):

$$\frac{\partial^2 S_x(y)}{\partial x^2} - \frac{\partial^2 S_x(y)}{\partial y^2} > 0 \qquad (1.7)$$

Combinations of the ESS and CS properties lead to the classification of four types of singular point (Table 1.1). First, a singular point that is both evolutionarily and convergent stable is called an evolutionary 'attractor' because it resists local invasion and local mutation also proceeds towards it (Bowers and White 2002; Bowers et al. 2005). In contrast, an evolutionary 'repellor' is neither evolutionarily nor convergence stable (Bowers and White 2002; Bowers et al. 2005). A singular point that is convergence stable (CS) but lacks evolutionary stability (non-ESS) is an evolutionary branching point (Geritz et al. 1998; Bowers et al. 2005). Here, disruptive selection near to the singular point leads to coexistence of more than one distinct strategy. This may lead to further branching, and ultimately an evolutionarily stable coalition may evolve. Finally, a singular strategy that is evolutionarily but not convergence stable (ESS and non-CS) corresponds to a 'Garden of Eden' point (Bowers et al. 2005). There may also be more than one locally stable strategy, a phenomenon known as evolutionary bistability, where the outcome is dependent on the initial resident.

Table 1.1. Classification of the singular point in terms of the evolutionary properties

Evolutionarily stable (ESS)	Convergence stable (CS)	Type of singular point
×	×	Repellor
×	√	Branching point
√	×	Garden of Eden
√	√	Attractor

The evolution of a monomorphic population is often determined using pairwise invadability plots (PIP; Metz et al. 1996; Geritz et al. 1998; Boots and Haraguchi 1999). These display graphically the sign of the marginal fitness of possible mutant invaders, y, against the range of residents, x (Fig. 1.2). Here, regions of positive fitness ($S_x(y) > 0$) are shaded, while regions of negative fitness ($S_x(y) < 0$) are left unshaded. Along the main diagonal, resident and mutant strategies have identical phenotypes and the mutant therefore has a marginal fitness of zero.

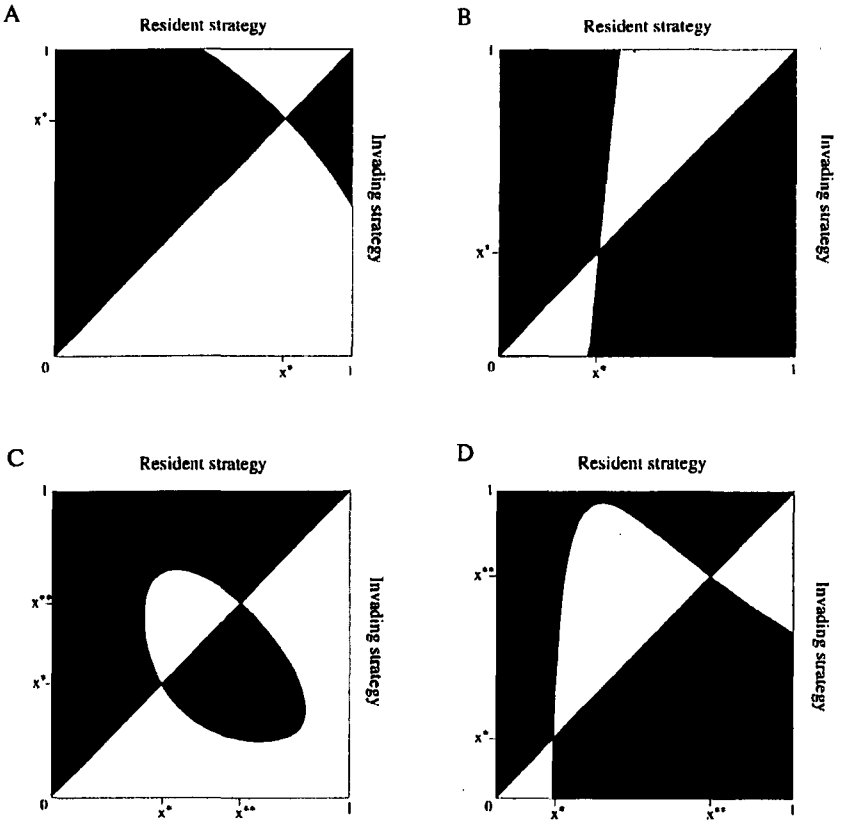

Figure 1.2. Pairwise invadability plots. (A) x^* is an attractor (ESS, CS); (B) x^* is an evolutionary branching point (CS, non-ESS); (C) (Bistability) x^* is an attractor, x^{**} is a repellor (non-CS, non-ESS), and the maximum strategy ($x = 1$) is also locally stable; (D) (Bistability) x^* is a branching point, x^{**} is a repellor, and the maximum strategy ($x = 1$) is also locally stable.

Singular points of evolution occur where the main diagonal intersects another zero fitness boundary. The evolutionary properties of the singular point can then be assessed by the way in which the neighbouring parameter space is partitioned. If a point is convergence stable (CS) then, when below the singular strategy, local mutants above the main diagonal have positive fitness, as do local mutants below the main diagonal when above the singular strategy (Figs. 1.2A, B). If a singular point is evolutionarily stable (ESS) then the vertical line through the point lies entirely in a region of negative fitness (Fig. 1.2A).

1-4. Thesis outline

This dissertation provides an investigation into the evolution and population dynamics of host-parasite interactions. The theoretical approach is to apply compartmental models that describe the epidemiology of host-parasite interactions combined with the techniques of adaptive dynamics. Chapters 2 and 3 investigate the evolution of host resistance traits assuming a uniform pathogen. Chapter 2 utilizes a free-living model to contrast two similar but qualitatively different forms of resistance (tolerance and control). In particular, the conditions promoting polymorphism in control strategies are examined. Chapter 3 looks at how the host's lifespan influences the evolution of resistance. Innate (avoidance, recovery, tolerance) and acquired immunity are investigated as separate traits. Chapter 4 investigates how the evolution of host tolerance may select the parasite, and the effect this has on the wider epidemiology. Chapter 5 considers a novel form of transmission function allowing varying degrees of density-dependent and frequency-dependent transmission, and how this affects the dynamics. Chapter 6 examines the population dynamics of a host-microparasite interaction under the assumption of male-biased parasitism. The stability of the equilibrium is compared to that occurring with unbiased parasitism, and an uninfected population.

2. The evolution of tolerance and control

2-1. Introduction

There are a variety of different biological mechanisms that may reduce pathogen virulence. These are generally grouped under the heading 'tolerance' (Simms and Triplett 1994; Boots and Bowers 1999, 2004; Roy and Kirchner 2000; Restif and Koella 2003, 2004; van Boven and Weissing 2004). Pure tolerance, however, is unique in that it reduces the deleterious effects to the infected host, but does not reduce the fitness of the pathogen. Applying a host-host-microparasite model, Boots and Bowers (1999) showed that tolerance is more likely to evolve when the host has a high intrinsic growth rate and/or a low susceptibility to crowding, suggesting that populations with larger carrying capacities are more likely to become tolerant. Boots and Bowers (2004) then extended this model, allowing recovered hosts to acquire temporary immunity to the disease. The probability of a tolerant host invading and becoming fixed in the population was shown to be inversely proportional to the duration of acquired immunity, suggesting tolerance may be selected against in the presence of other forms of resistance.

Roy and Kirchner (2000) have shown that, since tolerance increases the lifespan of infected hosts, it also increases disease prevalence, by providing more opportunities for transmission. Tolerance is therefore associated with a form of positive feedback that increases its own benefits. This implies that stable polymorphisms of strains with different degrees of tolerance is not deterministically possible, although stochastic effects might allow multiple strains to be maintained. Boots and Bowers (2004) also predict that polymorphism in tolerant strains will not occur for directly transmitted infection, and indicate there may be bistability in the evolutionary outcomes, where the level of tolerance that evolves depends on the initial resident strategy.

Previous theoretical work on the evolution of tolerance has generally assumed that pathogens are directly transmitted through contact between an infected and a susceptible host. However, in the life cycles of many microparasites, transmission occurs via free-living infective stages (Anderson and May 1981). In the insect

baculoviruses, host tissue is converted into millions of occlusion bodies, which are then released into the environment upon host death or shed continually during the infection through the faeces. Transmission then occurs upon ingestion by a susceptible host (Cory and Myers 2003).

In this chapter, the evolutionary dynamics of tolerance are investigated, where infection occurs through contact with free-living infective particles. Particles are released from diseased hosts at a constant rate during the period of infection (until the host either dies or recovers). Different forms of the production rate of infective particles are investigated, and their biological relevance discussed. I distinguish between two forms of host resistance, designated 'tolerance' and 'control'. Tolerance mechanisms reduce virulence but have no effect on the parasite's replication/growth within the infected host. The production rate of infective particles is therefore modelled as being independent of the level of tolerance. Control reduces virulence by limiting the parasite's replication/growth within an infected host (this assumes that virulence correlates with the rate at which host tissue is converted to pathogen particles), and their production rate is assumed to be an increasing function of virulence. In particular, a reduction in virulence conferred by control of the parasite is shown to allow a wider spectrum of evolutionary outcomes compared to when reduced virulence is due to tolerance. The implications of free-living stages, per se, to the evolution of resistance are also examined. For simplicity, I assume a haploid host. In line with previous theoretical work, tolerance and control both are both associated with a pleiotropic fitness cost, in terms of a reduced intrinsic growth rate.

2-2. A host-host-pathogen model

I consider the dynamics of two host genotypes (susceptible and resistant) and a shared free-living pathogen. The model structure is adapted from model G of Anderson and May (1981). I assume the system reaches an endemic equilibrium for a susceptible host, and consider a competing resistant strain attempting to invade this stationary state. This follows the common methodology used in host-host-pathogen models for directly transmitted infection (Antonovics and Thrall 1994; Bowers et al.

1994; Boots and Bowers 1999, 2004; Boots and Haraguchi 1999; Bowers 1999, 2001). Let X_i and Y_i denote the respective densities of uninfected and infected hosts of strain i, and Z denote the density of infective particles in the external environment. The dynamics are then described by the differential equations:

$$\frac{dX_S}{dt} = r_S(X_S + Y_S) - qH(X_S + Y_S) - \beta X_S Z + (\gamma + b)Y_S \tag{2.1}$$

$$\frac{dY_S}{dt} = \beta X_S Z - (\alpha_S + \gamma + b)Y_S \tag{2.2}$$

$$\frac{dZ}{dt} = \lambda_S Y_S + \lambda_R Y_R - \mu Z \tag{2.3}$$

$$\frac{dX_R}{dt} = r_R(X_R + Y_R) - qH(X_R + Y_R) - \beta X_R Z + (\gamma + b)Y_R \tag{2.4}$$

$$\frac{dY_R}{dt} = \beta X_R Z - (\alpha_R + \gamma + b)Y_R \tag{2.5}$$

The total host density is given by $H = X_S + Y_S + X_R + Y_R$ and the subscripts S and R denote the susceptible and resistant strains respectively (resistance may manifest as either tolerance or control). Here r_i gives the intrinsic growth rate of host strain i, equal to an implicit birth rate, a_i, minus the disease-independent death rate, b. The quantity q measures susceptibility to crowding and represents density-dependence acting on the birth rate of the host. Hosts become infected through contact with infective particles. The transmission rate of infection, the recovery rate, and the virulence (disease-induced mortality) are denoted β, γ and α_i respectively. Once infected, hosts produce free-living particles at a rate λ_i, until they either die or recover. These infective particles persist in the external environment with a background mortality rate μ. Equation (2.3) therefore differs from model G of Anderson and May (1981), in that there is no loss of infective particles due to consumption by susceptible or infected hosts. It has been shown by Dwyer (1994)

that such losses are likely to be negligible relative to other parameters. Loss of infective particles therefore occurs only through their natural decay rate μ.

I assume a uniform pathogen with a fixed level of potential virulence that is only fully expressed in susceptible hosts. The actual level of virulence experienced is the potential virulence that is not compensated for by a resistance mechanism. In tolerant hosts, resistance reduces virulence but this does not affect the growth of the pathogen. Control limits viral replication in infected hosts, reducing both virulence and the production of free-living particles. Both forms of resistance incur a cost in terms of a lower intrinsic growth rate of the host. The assumptions are therefore:

Tolerance: $\alpha_R < \alpha_S, \quad r_R < r_S, \quad \lambda_R = \lambda_S = \omega$ (2.6)

Control: $\alpha_R < \alpha_S, \quad r_R < r_S, \quad \phi\alpha_R = \lambda_R < \lambda_S = \phi\alpha_S$ (2.7)

Susceptible and tolerant hosts therefore produce infective particles at a constant rate measured by the parameter ω. In the control scenario, the production rate is an increasing function of virulence. Note the level of virulence experienced by susceptible hosts is always constant whichever form of resistance is being considered ($\omega = \phi\alpha_S$). All parameters are assumed to be positive.

It is assumed that diseased hosts produce free-living particles constantly throughout the period of infection. However, infective particles may sometimes be released into the environment only upon death of an infected host. Such obligately killing parasites must kill the host in order to transmit infection (Ebert and Weisser 1997). As shown by Anderson and May (1981), if the host releases a total of Λ infective particles upon death, and the infected lifespan is given by $1/(\alpha + \gamma + b)$, this is equivalent to producing infective particles at a constant rate:

$$\lambda = \Lambda(\alpha + \gamma + b) \tag{2.8}$$

Assuming the disease-independent and recovery rates are constant, this yields a positive relationship between virulence α and the production rate λ, which is

qualitatively the same as that in (2.7). In this case tolerance of an obligately killing parasite also confers an element of control (because the lower virulence increases host lifespan and reduces the average rate of production).

2-3. Analysis

2-3-1. Equilibrium states

There are six equilibrium solutions of equations (2.1)-(2.5). Taking the variables in the order (X_S, Y_S, Z, X_R, Y_R) the equilibria are:

$$(0, 0, 0, 0, 0) \tag{2.9}$$

$$(K_S, 0, 0, 0, 0) \tag{2.10}$$

$$(0, 0, 0, K_R, 0) \tag{2.11}$$

$$(X_S^*, Y_S^*, Z_S^*, 0, 0) \tag{2.12}$$

$$(0, 0, Z_R^*, X_R^*, Y_R^*) \tag{2.13}$$

$$(X_S^+, Y_S^+, Z^+, X_R^+, Y_R^+) \tag{2.14}$$

The trivial equilibrium (2.9) is always unstable for positive parameters. The third equilibrium (2.11) corresponds to the resistant carrying capacity, $K_R = r_R/q$. This equilibrium is always unstable, due to the susceptible strain's higher intrinsic growth rate in the absence of infection ($r_R < r_S$). The second equilibrium (2.10) corresponds to the susceptible carrying capacity in the absence of infection, $K_S = r_S/q$. The condition for the pathogen to invade this equilibrium is given as:

$$K_S > H_{T,S} = \frac{\mu(\alpha_S + \gamma + b)}{\lambda_S \beta} \tag{2.15}$$

Here $H_{T,S}$ is the threshold density required to support the pathogen (Anderson and May 1981). If (2.15) is not satisfied then the uninfected equilibrium (2.10) is stable and the parasite will go extinct. This result can be understood in terms of the basic

reproductive rate of the parasite, R_0, which gives the expected number of infections caused during the lifespan of a single infected host (Anderson and May 1981, 1982; van Baalen and Sabelis 1995; Frank 1996). For this model, the basic reproductive rate is:

$$R_0 = \frac{\beta \lambda_S H}{\mu(\alpha_S + \gamma + b)} \tag{2.16}$$

The threshold density is therefore related to the basic reproductive rate according to the equation (Anderson and May 1981):

$$\frac{H_{T,S}}{H} = \frac{1}{R_0} \tag{2.17}$$

Here the total host density, H, is simply the uninfected density, $X_S = K_S$. The condition for the pathogen to invade (2.15) can therefore be expressed as:

$$R_0 > 1 \tag{2.18}$$

This is the standard result for pathogen persistence in models of infectious disease (Anderson and May 1981, 1982). The fourth (2.12) and fifth (2.13) equilibria respectively correspond to the susceptible or resistant strain supporting the pathogen alone. The final equilibrium (2.14) corresponds to a dimorphic equilibrium where a susceptible and a resistant strain jointly support the pathogen. Throughout this study, I assume that condition (2.18) is always satisfied, and that the host is always capable of supporting the pathogen. The first three equilibria are therefore always unstable, and I need only consider the stability criteria with respect to the infected states (2.12)-(2.14). By applying an invadability analysis, the specific conditions for a resistant mutant strain to invade the resident susceptible equilibrium are established. These conditions are determined using a traditional Jacobian analysis, but I first present a more intuitive, biologically motivated derivation.

Consider then an initially rare mutant of the resistant strain, attempting to invade the susceptible equilibrium (2.12). To successfully invade, the resistant mutant must have a positive growth rate. This means that the net contribution of a single resistant individual must be greater than zero. On average, a single resistant mutant will remain uninfected for a period T_X, during which time it makes a contribution ρ_X to the total population, and will be infected for an average time T_Y, making a contribution ρ_Y. Letting I_R denote the overall contribution, this gives:

$$I_R = \rho_X T_X + \rho_Y T_Y \tag{2.19}$$

This term must be greater than zero for the genotype to invade. From equations (2.1)-(2.5) the uninfected contribution is:

$$\rho_X = r_R - q(X_S^* + Y_S^*) \tag{2.20}$$

Similarly, the contribution while infected is:

$$\rho_Y = r_R - q(X_S^* + Y_S^*) - \alpha_R \tag{2.21}$$

The average period an individual stays uninfected is determined by the natural mortality rate (b) and the probability of becoming infected through contact with an infective particle. Since there are Z_S^* such particles, the probability of an infection is βZ_S^*, which gives:

$$T_X = 1/(b + \beta Z_S) \tag{2.22}$$

The probability of dying while uninfected is bT_X. The only other possibility is to become infected and then either die or recover, with probability $(\alpha_R + \gamma + b)T_Y$. Logically, this gives:

$$bT_X + (\alpha_R + \gamma + b)T_Y = 1 \tag{2.23}$$

Note that successive periods of infection and recovery are possible, but this only serves to scale the results by a positive common factor. Also, infected individuals cannot prosper unless uninfected individuals do. It is therefore sufficient to consider only a single cycle, where an initially uninfected individual either remains so, or becomes infected and then either dies or recovers (Boots and Bowers 1999).

Combining equations (2.22) and (2.23):

$$T_Y = \frac{\beta Z_S^*}{(b+\beta Z_S^*)(\alpha_R+\gamma+b)} \tag{2.24}$$

Substituting the terms into (2.19) gives the expression for the growth rate I_R of the resistant strain:

$$I_R = \{r_R - q(X_S^* + Y_S^*)\} \times \frac{1}{(b+\beta Z_S^*)} + \{r_R - q(X_S^* + Y_S^*) - \alpha_R\} \times \frac{\beta Z_S^*}{(b+\beta Z_S^*)(\alpha_R+\gamma+b)} \tag{2.25}$$

To invade the susceptible equilibrium, I_R must be greater than zero. Eliminating a positive common factor, the condition for the resistant strain to invade is:

$$I_R = r_R - q(X_S^* + Y_S^*) - \frac{\beta Z_S^*}{(\alpha_R+\gamma+b)}\{\alpha_R - (r_R - q(X_S^* + Y_S^*))\} > 0 \tag{2.26}$$

If this condition is not satisfied then the susceptible equilibrium (2.12) resists invasion and a resistant mutant will be eliminated. By symmetry, the condition for a susceptible strain to invade the resistant equilibrium (2.13) is:

$$I_S = r_S - q(X_R^* + Y_R^*) - \frac{\beta Z_R^*}{(\alpha_S+\gamma+b)}\{\alpha_S - (r_S - q(X_R^* + Y_R^*))\} > 0 \tag{2.27}$$

The equilibria can now be classified according to these two invasion criteria. When only condition (2.26) holds, the resistant strain can invade the susceptible equilibrium but the resistant equilibrium resists invasion by the susceptible strain. In this case the susceptible strain is eliminated and equilibrium (2.13) is stable. Conversely, when only condition (2.27) holds, the susceptible equilibrium (2.12) is stable and the resistant strain is eliminated. If both (2.26) and (2.27) hold, then neither strain is favoured and the only stable equilibrium is the dimorphic state (2.14). The remaining situation occurs when neither condition holds, in which case both single equilibria ((2.12) and (2.13)) are locally stable, and the outcome is contingent on the initial conditions. Within the evolutionary context, this scenario favours the susceptible strain that is initially confronted with the parasite.

2-3-2. Jacobian Analysis

Taking the variables in the order (X_S, Y_S, Z, X_R, Y_R) the associated Jacobian matrix evaluated at the susceptible equilibrium (2.12) has the form:

$$J = \begin{pmatrix} A & B \\ O & C \end{pmatrix} \tag{2.28}$$

Here A, B, C are sub-matrices of size 3×3, 3×2 and 2×2 respectively, and O is the 2×3 zero matrix. Due to the linear independence of A and C, the stability conditions for J can be determined from two separate problems: a cubic equation corresponding to stability with respect to the pathogen (derived from A) and a quadratic corresponding to stability with respect to invasion by the resistant strain (derived from C). The stability conditions pertaining to A are satisfied if the susceptible strain is capable of supporting the pathogen. Since (2.18) is assumed to be satisfied, it therefore remains to consider the stability of C.

$$C = \begin{pmatrix} r_R - q(X_S^* + Y_S^*) - \beta Z_S^* & r_R - q(X_S^* + Y_S^*) + (\gamma + b) \\ \beta Z_S^* & -(\alpha_R + \gamma + b) \end{pmatrix} \tag{2.29}$$

The matrix C has trace, τ, and determinant, Δ, given by:

$$\tau(C) = r_R - q(X_S^* + Y_S^*) - \beta Z_S^* - (\alpha_R + \gamma + b) \tag{2.30}$$

$$\begin{aligned}\Delta(C) = &\{r_R - q(X_S^* + Y_S^*) - \beta Z_S^*\}\{-(\alpha_R + \gamma + b)\} \\ &-\{\beta Z_S^*\}\{r_R - q(X_S^* + Y_S^*) + (\gamma + b)\}\end{aligned} \tag{2.31}$$

The determinant (2.31) will certainly be negative unless the first term $\{r_R - q(X_S^* + Y_S^*) - \beta Z_S^*\}$ is less than zero (if this term is greater than zero then the final term $\{r_R - q(X_S^* + Y_S^*) + (\gamma + b)\}$ is necessarily greater than zero and the determinant must be negative). If this first term is less than zero, we can see from (2.30) that the trace must also be negative. The equilibrium (2.12) is therefore stable, if and only if the determinant is greater than zero. If the determinant is negative, then the equilibrium is unstable and a resistant mutant characterized by (α_R, r_R) can invade. The condition for a stable equilibrium is therefore:

$$\begin{aligned}&\{r_R - q(X_S^* + Y_S^*) - \beta Z_S^*\}\{-(\alpha_R + \gamma + b)\} \\ &-\{\beta Z_S^*\}\{r_R - q(X_S^* + Y_S^*) + (\gamma + b)\} > 0\end{aligned} \tag{2.32}$$

Reversing the sign of this inequality gives the condition for a resistant mutant strain to invade. Some algebraic manipulation allows this condition to be expressed as:

$$I_R = r_R - q(X_S^* + Y_S^*) - \frac{\beta Z_S^*}{(\alpha_R + \gamma + b)}\{\alpha_R - (r_R - q(X_S^* + Y_S^*))\} > 0 \tag{2.33}$$

Condition (2.33) is identical to the earlier result (2.26) for invasion fitness.

2-4. Results

2-4-1. Reciprocal invasion plots

The dynamics are illustrated using Reciprocal Invasion Plots (Antonovics and Thrall 1994; Bowers et al. 1994; Boots and Bowers 1999, 2004). I assume a fixed resident (susceptible) strain characterised by (α_S, r_S) and a range of possible resistant mutants (α_R, r_R). The susceptible strain is then paired with each resistant genotype and the invasion criteria (2.26) and (2.27) evaluated in each case. Using this method, the relative costs and benefits that favour control or tolerance (for a given level susceptible host) can be determined.

I begin by investigating the dynamics when resistance evolves as tolerance. Figure 2.1A partitions the (α_R, r_R) parameter space into regions where I_S and I_R are positive and negative. The solid lines therefore correspond to equality in (2.26) and (2.27). Importantly, there is no polymorphism: either the susceptible or the tolerant strain is eliminated. There is a limited region where the outcome is contingent on initial conditions, but this also results in monomorphism. This appears to be the general case: polymorphism was not observed for any parameter combinations. The addition of free-living stages therefore does not alter the prediction for a directly transmitted microparasite, which states that polymorphism is unlikely to evolve through tolerance (Boots and Bowers 1999, 2004; Roy and Kirchner 2000).

When instead resistance evolves as control, polymorphism is observed over a significant region of parameter space (Fig. 2.1B). It is most likely to occur between dissimilar strains, where the resistant strain has a much smaller virulence. The region of polymorphism becomes increasingly narrow as the degree of similarity between the resistant and susceptible strain increases. Note that the only difference between the two diagrams lies in the position of the $I_S = 0$ line. In Figure 2.1A this lies below the $I_R = 0$ line, whereas in Figure 2.1B it lies above it.

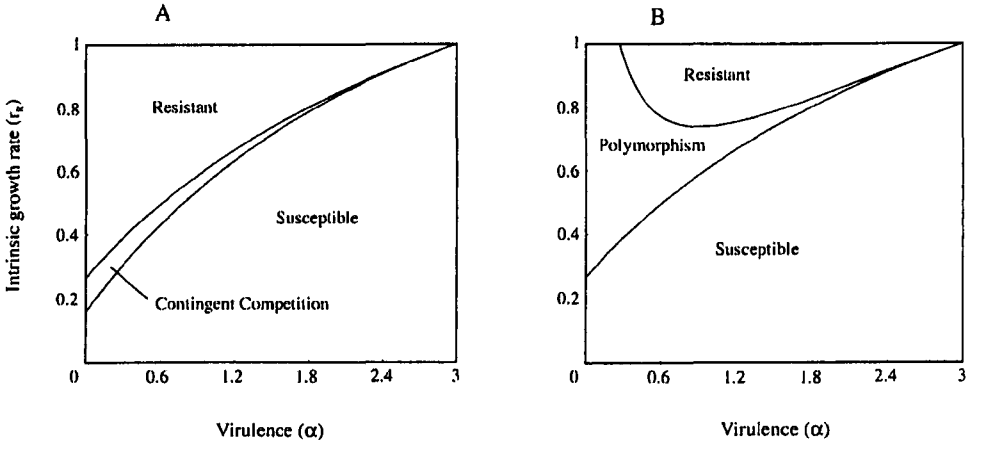

Figure 2.1. Outcomes in trade-off space when a resistant mutant characterized by (α_R, r_R) attempts to invade a resident susceptible strain. The susceptible strain has intrinsic growth rate $r_S = 1$ and experiences a level of virulence $\alpha_S = 3$. Resistance evolves as either: (A) tolerance, or (B) control. Other parameters are: $q = 0.1$, $\beta = 0.25$, $\gamma = 1.5$, $b = 0.5$, $\mu = 1$, $\omega = 10$ (tolerance) and $\phi = 10/3$ (control).

Examination of the resistant equilibrium (2.13) reveals that a lower value of λ_R (due to control) increases the total host density $X_R^* + Y_R^*$, and reduces the density of infective particles Z_R^*. A putative susceptible invader therefore faces an increased level of resource competition, but a reduction in the force of infection. The overall effect on I_S may theoretically be either positive or negative. However, the results indicate that I_S should increase under control (as compared to tolerance with the same parameters). Faced with a controlling rather than a tolerant competitor, the susceptible strain experiences a reduced force of infection that outweighs the increase in resource competition. Graphically, this shifts the $I_S = 0$ line upwards, reducing the region of parameter space where the susceptible strain is eliminated and precluding contingent competition as an outcome. Interpreted biologically, the presence of a control strain reduces the density of infective particles, the opportunities for new infections, and hence the selective pressure for resistance.

2-4-2. Adaptive Dynamics

In the preceding analysis, the susceptible strain was assumed to be resident and putative invaders had higher resistance (reduced virulence) and a lower growth rate. If a resistant strain is able to invade, it either eliminates the susceptible strain or coexists with it in a dimorphism. However, after an initial invasion has taken place, further mutations may arise to challenge the new equilibrium. There may indeed be many evolutionary steps before the final equilibrium is reached. To determine the ultimate outcome of evolution, it is necessary to embed the single step algorithm (2.1)-(2.5) within an adaptive dynamical framework. Applying the techniques of adaptive dynamics (Metz et al. 1996; Geritz et al. 1998), it can be determined whether the evolutionary behaviour outlined for the susceptible-resistant analysis can occur as a result of many evolutionary steps. In particular, I can investigate whether polymorphism is able to evolve from an initially monomorphic resident.

The invasion exponent (2.26) gives the fitness of a resistant mutant in the environment determined by the susceptible strain. Generally, the resident strain is not necessarily 'susceptible,' but may have any level of resistance and associated growth rate (assuming a particular trade-off). Nearby mutants may be either more or less resistant and are also subject to the trade-off constraint. In the general case, the invasion exponent for a given mutant (α_M, r_M) attempting to invade a resident strain (α_E, r_E) at equilibrium is:

$$I_M = r_M - q(X_E^* + Y_E^*) - \frac{\beta Z_E^*}{(\alpha_M + \gamma + b)}\{\alpha_M - (r_M - q(X_E^* + Y_E^*))\} > 0 \qquad (2.34)$$

This is identical to the invasion exponent (2.26), except that the subscripts M and E are now used to identify the mutant and the resident strains, respectively.

I now assume explicit trade-offs between virulence (α) and growth rate (r), such that a given level of resistance is associated with a specified cost. When resistance evolves as control, this implies an additional relationship between growth

and the production rate (λ). Attention is restricted to non-linear trade-off curves (Fig. 2.2).

With a decelerating trade-off, the cost (the reduction in growth rate) of a given increment of resistance becomes less as the investment in resistance increases (i.e. there are increasing benefits of resistance). Given a particular cost structure, I generate a corresponding Pairwise Invadability Plot (PIP), from which the evolutionary dynamics can be determined. I assume a weakly decelerating trade-off (Fig. 2.2) and compare the pairwise plots when resistance evolves as control (Fig. 2.3A) and tolerance (Fig. 2.3B). The virulence of the resident strategy is given on the horizontal axis and the mutant's virulence on the vertical axis. Where the region contains a plus (+) sign this indicates the mutant strain has a positive fitness and may invade the resident equilibrium. A minus (-) sign indicates the fitness is negative and that the mutant will be eliminated.

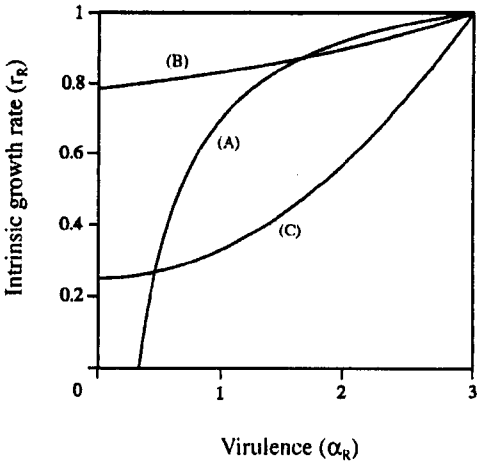

Figure 2.2. Non-linear trade-off curves. There is a cost of resistance (reduced virulence) in terms of a lower intrinsic growth rate. Resistance evolves from the initial susceptible strain defined by $\alpha_S = 3$ and $r_S = 1$. The examples shown are: (A) accelerating costs, (B) mildly decelerating costs, and (C) strongly decelerating costs.

In Figure 2.3A, resistance evolves as control; the intersection at $\alpha^* = 0.39$ indicates a singular strategy at which the local fitness gradient is zero. At resident values of α below this singular point, mutants with bigger α have positive fitness (indicated by the positive (+) region to the left of α^* and directly above the main diagonal). Similarly, given a resident above the singular point, mutants with smaller α have negative fitness (hence the (-) region to the right of α^* and below the main diagonal). Directional selection therefore moves towards the singular strategy at $\alpha^* = 0.39$ and the fixed point is convergence stable (CS). However, the singular strategy does not itself resist invasion by mutants with larger or smaller virulence (the vertical through α^* lies entirely in a positive (+) region). Once the fixed point is reached (or very near to it) disruptive selection will occur. Here the resident can be invaded by strains on either side of the singular point, and a process of evolutionary branching ensues. This leads ultimately to a dimorphic equilibrium composed of two sub-populations, one highly resistant ($\alpha^* = 0$) and the other highly susceptible ($\alpha^* = 3$).

This is seen in evolutionary time by simulating the mutation-selection process and tracking the resident strategy (Fig. 2.3C). In Figure 2.3B, resistance evolves as tolerance under the same trade-off. There is no internal strategy at which the fitness gradient is zero and the optimal fitness occurs at the minimum value. The evolutionary process converges at $\alpha = 0$ (Fig. 2.3D).

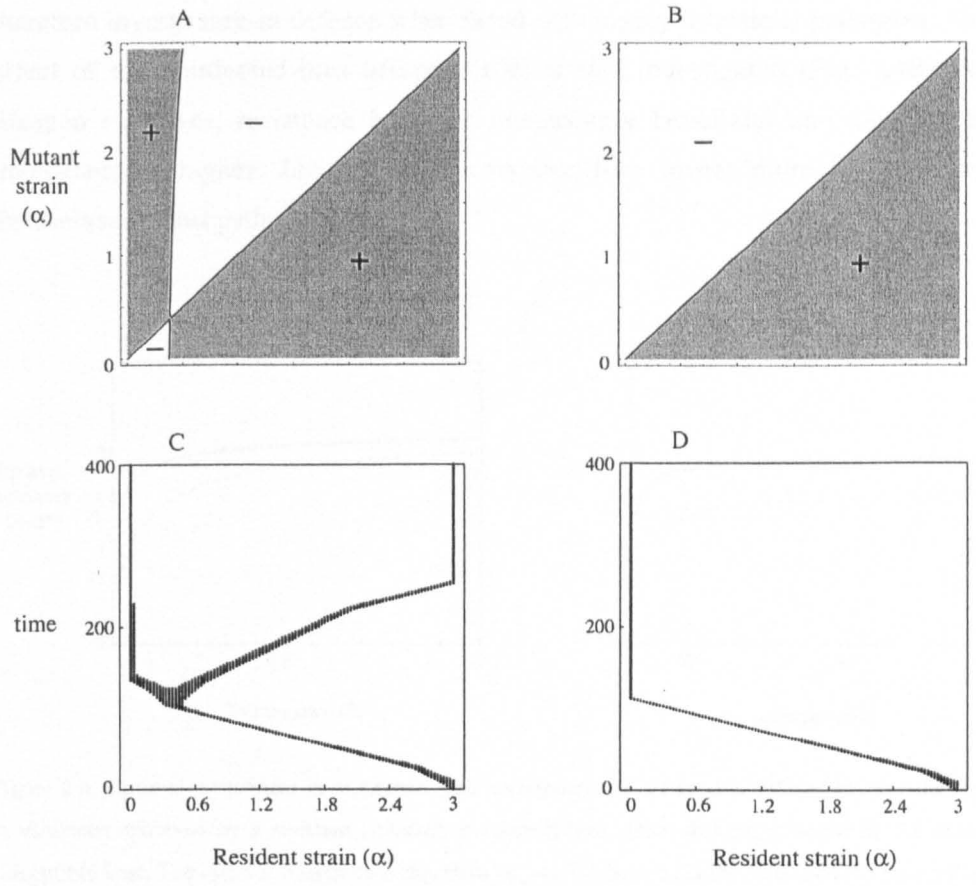

Figure 2.3. Pairwise invadability plots (PIPs) when resistance evolves as: (A) control, and (B) tolerance. In both cases, there is a decelerating trade-off, such that $r = 0.5 + 2/(7 - \alpha)$. Other parameters are: $q = 0.1$, $\beta = 0.25$, $\gamma = 1.5$, $b = 0.5$, $\mu = 1$, $\omega = 10$ and $\phi = 10/3$. The corresponding time plots are (C) control, and (D) tolerance.

When resistance incurs accelerating costs, dimorphism is not observed, whether resistance evolves as control or tolerance. Using the method of pairwise invadability plots, singular strategies were determined that were both convergence and evolutionarily stable (CS and ESS). It can therefore be seen how the optimal investment in resistance differs with control and tolerance under an accelerating trade-off. The optimal investment in resistance is defined to be the difference in virulence between optimally resistant (ESS) and susceptible hosts. The optimal strategies are plotted as a function of the transmission rate (Fig. 2.4A). As

transmission increases, the investment in both types of resistance increases. Hosts therefore invest more in defence when faced with highly infectious pathogens. The effect of the uninfected host lifespan ($1/b$) is also investigated (Fig. 2.4B). As lifespan increases, resistance becomes increasingly beneficial and the optimal investment is higher. Longer-lived hosts therefore invest more in defending themselves against pathogens.

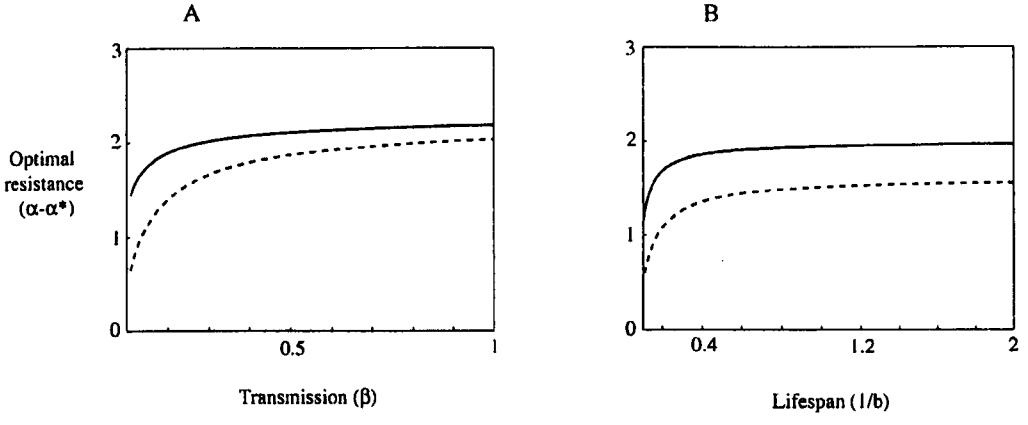

Figure 2.4. Optimal investment in resistance. The investment in resistance is defined as the reduction in virulence achieved by a resistant (tolerant or control) host, from that experienced by the initial susceptible host. The optimal resistance is therefore $(\alpha_S - \alpha^*)$ where α_S is the virulence experienced by the susceptible strain and α^* is the optimal virulence. The solid line corresponds to the optimal strategy when resistance evolves as tolerance, and the dotted line to the optimal investment in control. In both cases there are accelerating costs of resistance such that $r = 72/62 - 1/[2(\alpha + 0.1)]$ and the optimal strategy is evolutionarily stable (an ESS). The susceptible host is defined by $\alpha_S = 3$. In (A) there is a constant natural mortality rate $b = 0.5$; in (B) there is a constant transmission rate $\beta = 0.25$. Other parameters are: $q = 0.1$, $\gamma = 1.5$, $\phi = 10/3$, $\omega = 10$ and $\mu = 1$. Note that $\phi\alpha_S = \omega$ to allow comparison between tolerance and control (susceptible strains are defined by $\lambda_S = 10$ in each case).

Looking at Figures 2.4A and 2.4B, the optimal investment in tolerance is always greater than the investment in control. This is because control also reduces the prevalence of infective particles, the force of infection, and the selective pressure for further resistance. However, as transmission rate increases, the difference between the investments becomes smaller (Fig. 2.4A). There is stronger pressure on the host to reduce the force of infection, and mechanisms conferring reduced transmission

increase their benefits at a faster rate. Despite the cost of resistance, it is still worth allocating more resources to controlling the pathogen. By contrast, in response to greater host longevity, the two defences increase their benefits equally. As the average lifespan increases, the difference between the optimal allocations remains roughly constant (Fig. 2.4B).

2-5. Discussion

It has been shown that different forms of virulence-reducing resistance lead to different evolutionary outcomes. As a general rule, tolerance will result in monomorphism. However, the evolution of control may lead to dimorphism of extreme strains. Dimorphism is achieved when two distinct strategies are able to invade each other, and this is only likely when resistance evolves as control. Tolerance does not restrict the growth of the pathogen: on average, the longer-lived infected hosts produce more free-living infective particles, increasing the force of infection, βZ_R^*, and hence the selective pressure for further tolerance. This acts as a form of positive feedback (Roy and Kirchner 2000), such that tolerant hosts are better able to resist invasion by susceptible genotypes. The evolutionary dynamics of tolerance to a free-living pathogen are therefore analogous to those observed for a directly transmitted microparasite (Boots and Bowers 1999).

A control strategy reduces virulence, not through 'tolerating' the deleterious effects of disease, but rather by limiting pathogen growth. Since the within-host replication of the pathogen is likely to correlate with tissue damage (Bremermann and Pickering 1983), resistance mechanisms that control the virus will also reduce virulence. The evolution of a control genotype corresponds to lower viral productivity, reducing the force of infection and hence the selective pressure for more resistance. This negative feedback may allow a susceptible host to invade a more resistant one, promoting dimorphism of extreme strains. The free-living model employed here makes the mechanism of control explicit, since pathogen growth is correlated with the production rate of infective stages. The analysis, however, is not strictly limited to indirectly transmitted pathogens. There is often assumed to be a

positive relationship between transmission rate and virulence (Anderson and May 1982; Bremermann and Pickering 1983; Lenski and May 1994; van Baalen and Sabelis 1995; Restif and Koella 2003, 2004). There is also evidence in the rabbit-myxomatosis system that virulence may be negatively correlated with the recovery rate (Anderson and May 1982; May and Anderson 1983). Virulence-reducing mechanisms may therefore also reduce the transmission rate or increase recovery. These may be classed as 'control' and may be a likely response to directly transmitted microparasites.

There is some theoretical evidence that tolerance and avoidance (reduced susceptibility becoming infected) may not be mutually exclusive adaptive traits. Tiffin (2000) showed that intermediate investments in both traits could evolve, if the costs of resistance are unequal. Restif and Koella (2004) modelled the simultaneous evolution of tolerance and higher recovery rate as distinct traits and found that, when investment in either trait incurs accelerating costs, the host may split its investment between the two defences. These provide a parallel to my study, given that control may be viewed as a composite form of resistance combining the components of avoidance (through a lower density of infective particles) and tolerance; here, investment in one component of defence necessitated a given investment in the other (since there is a fixed relationship between virulence and the production rate of infective particles). However, Roy and Kirchner (2000) showed that a single gene conferring avoidance and tolerance can be maintained or become fixed in a population. It is clearly important, therefore, to distinguish whether resistance is conferred by one or more defence mechanisms. Where resistance is due to a single control trait, it may be easier to predict the evolutionary outcome, particularly if the trade-off could be determined. It would also be interesting to investigate the consequences of decelerating trade-offs in Restif and Koella's model, since decelerating costs of avoidance may also allow branching (Boots and Haraguchi 1999). Extrapolating from previous results, polymorphism should be less likely when the overall bias is towards higher investment in tolerance (Roy and Kirchner 2000).

When tolerance and control are equally costly, and the costs are accelerating, hosts will invest relatively less in control (Fig. 2.4). This is due to the added benefit of control in terms of reducing the force of infection, which also reduces the selective pressure for resistance (Boots and Bowers 1999). A weakly decelerating trade-off has been shown to promote maximal investment in tolerance (Figs. 2.3B, 2.3D), although different trade-offs (accelerating or strongly decelerating) may select for intermediate or even zero investment in tolerance.

Tolerance is most likely to evolve in response to high transmission rates and low virulence (Boots and Bowers 1999; Restif and Koella 2003). Restif and Koella (2003) also predicted only locally stable investments in tolerance, such that a highly susceptible host with high fecundity was capable of invading the local ESS and driving the pathogen to extinction. In this model, only host genotypes capable of supporting the pathogen were considered. This effectively fixes an upper limit on the level of virulence, which also implies a maximum growth rate, due to the trade-off. Pathogen extinction through invasion by a susceptible mutant with high birth rate was therefore assumed to be impossible. Nevertheless, it is worth noting that convergence towards the branching point (Fig. 2.3C) may be dependent on initial conditions: if the initial virulence in susceptible hosts is sufficiently high, evolution proceeds towards a monomorphic strategy with high fecundity and high virulence. Whether dimorphism is actually attained as the result of selection may therefore be contingent on the level of susceptibility exhibited by the resident genotype, although in real systems there will be constraints imposed by the morphology.

The dynamics in a free-living host-microparasite system can exhibit population cycles where those for a comparable directly transmitted system cannot (Anderson and May 1981; Bowers et al. 1993; Dwyer 1994; White et al. 1996). The invasion analysis performed in this study assumes stable equilibrium behaviour. However, when the underlying dynamics are non-equilibrium the invasion exponents ((2.26) and (2.27)) are not valid and need to be replaced by the largest Lyapunov exponent (Metz et al. 1992). Understanding how the introduction of population cycles would affect the results may form the basis of future work.

The chief aim in this chapter was to investigate the evolutionary dynamics of tolerance and control as distinct defence strategies in response to pathogenic infection. The two forms of resistance have been shown to attain different evolutionary optima. Control has been shown to promote a wider range of evolutionary outcomes, in particular dimorphism of extreme strains. This may go some way to explaining the high level of polymorphisms observed in nature.

3. Lifespan and the evolution of resistance

3-1. Introduction

There is widespread interest in how life history traits affect the evolution of resistance characteristics (Zuk and Stoehr 2002; Schmid-Hempel 2003; Schmid-Hempel and Ebert 2003). The level of resistance an organism evolves depends on the epidemiology of the particular host-parasite interaction, which in turn depends itself on the life histories of hosts and parasites (Zuk and Stoehr 2002). One aspect of life history that has attracted a great deal of recent attention in this context is the host's lifespan. Shorter-lived populations are generally expected to invest relatively less in costly resistance (Medzhitov and Janeway 1997; Rinkevich 1999; Zuk and Stoehr 2002). This is based on the idea that, since fitness is correlated with reproduction and survival, shorter-lived organisms will have a lower mortality cost of parasitism. However, selection for resistance is dependent on both epidemiological and demographic processes. Demographic turnover is lower in long-lived populations and this may lead to unexpected patterns of selection. In particular, analysis of the basic susceptible-infected-removed (SIR) model has revealed that, under certain conditions, there may be a non-monotonic relationship between lifespan and the optimal immune investment (van Boven and Weissing 2004). There can also be bistability in the evolutionary outcomes, where the level of resistance that actually evolves depends on the initial conditions of the system (van Baalen 1998; Boots and Bowers 1999; Restif and Koella 2003; van Boven and Weissing 2004),

It is therefore important to recognize that the evolution of resistance traits occurs within an adaptive context, which encompasses a dynamic ecological feedback loop. The life histories of the host and pathogen determine the population dynamics, which in turn determine the evolutionarily stable resistance and the evolution of life history characteristics (Frank 1996; van Baalen 1998; Day and Burns 2003; van Boven and Weissing 2004). In this chapter, I develop fitness expressions that depend on both resident and mutant strategies, therefore incorporating the feedbacks between life history traits and population dynamics. These expressions are used to determine the evolutionarily stable strategy (ESS; Maynard Smith and Price 1973) that cannot be invaded by any other genotype, and also whether this strategy is

attainable. Using this theoretical approach, I investigate the conditions under which longer-lived host populations evolve more or less resistance to their parasites, examining a variety of different forms of resistance. Particular emphasis is given to how acquired immunity affects the dynamics. The evolution of acquired immunity itself is also considered.

3-2. Models and Analysis

3-2-1. Susceptible-infected-susceptible (model I)

This describes a susceptible-infected-susceptible (SIS) interaction for a directly transmitted microparasite. Infected individuals are able to recover but then immediately return to being susceptible and may be subsequently re-infected. The dynamics are described by the following differential equations:

$$\frac{dS}{dt} = aH - qH^2 - bS - \beta SI + \gamma I \qquad (3.1)$$

$$\frac{dI}{dt} = \beta SI - (\alpha + \gamma + b)I \qquad (3.2)$$

Here S is the density of susceptible individuals, I is the density of infecteds, and $H = S + I$ is the total population density. The parameter a represents the birth rate, and b the natural death rate. The host population is assumed to experience intra-specific crowding that limits its growth. For simplicity, this density-dependent crowding is assumed to act directly to reduce the birth rate, and is measured by the parameter q which is related to the carrying capacity, K, by the relationship $K = (a - b)/q$. Susceptibles become infected through contact with infected hosts, at a rate determined by the transmission efficiency, β. Infected hosts have an increased death rate (virulence, α) due to pathogen replication and/or toxicity. Infected hosts are still able to reproduce, and recover at a rate γ.

3-2-2. Susceptible-infected-removed-susceptible (model II)

The second model corresponds to a susceptible-infected-removed-susceptible (SIRS) interaction, where infected hosts acquire immunity to the disease upon recovery. While immune, hosts do not become infected or transmit the disease to susceptibles. Immunity is lost at a constant rate, δ, whereupon individuals revert to being susceptible. The dynamics are described by the equations:

$$\frac{dS}{dt} = aH - qH^2 - bS - \beta SI + \delta R \tag{3.3}$$

$$\frac{dI}{dt} = \beta SI - (\alpha + \gamma + b)I \tag{3.4}$$

$$\frac{dR}{dt} = \gamma I - (\delta + b)R \tag{3.5}$$

3-2-3. Susceptible-infected-removed (model III)

The third model gives an alternative formulation including recovery to an immune class. I assume that upon recovery a proportion, ν, of recovered hosts acquire permanent immunity, while the remaining proportion, $1-\nu$, immediately return to being susceptible. The dynamics are described by the equations:

$$\frac{dS}{dt} = aH - qH^2 - bS - \beta SI + (1-\nu)\gamma I \tag{3.6}$$

$$\frac{dI}{dt} = \beta SI - (\alpha + \gamma + b)I \tag{3.7}$$

$$\frac{dR}{dt} = \nu\gamma I - bR \tag{3.8}$$

Note that in models II and III, the total population density is given by $H = S + I + R$. The evolution of resistance is investigated through the alternative mechanisms of avoidance, recovery, tolerance or acquired immunity (Boots and Bowers 2004). Avoidance reduces the probability of becoming infected, and resistant hosts therefore have a lower transmission rate (β). Recovery increases the rate of clearance (γ),

while tolerance reduces virulence (α) but does not affect the transmission rate. Finally, acquired immunity evolves as either a lower rate of loss of immunity (δ), or a higher probability of acquiring immunity (ν). The different forms are summarised as follows (where x denotes the host's investment in resistance):

Avoidance:	$\beta = \beta_1(1-x)^h + \beta_0$	(3.9)
Recovery:	$\gamma = \gamma_1 x^h + \gamma_0$	(3.10)
Tolerance:	$\alpha = \alpha_1(1-x)^h + \alpha_0$	(3.11)
Immunity (model II):	$\delta = \delta_1(1-x)^h + \delta_0$	(3.12)
Immunity (model III):	$\nu = \nu_1 x^h + \nu_0$	(3.13)

I consider explicit trade-offs such that a given level of resistance corresponds to a given reduction in the intrinsic birth rate of the host:

$$a = a_0(1-cx) \tag{3.14}$$

This trade-off is such that the benefit from an increase in resistance is bought at an ever-increasing cost in terms of a reduction in the birth rate (a trade-off with accelerating costs). In the absence of any resistance, the intrinsic birth rate is given by a_0. The parameter c provides a measure of the cost (to avoid negative birth rates, it is assumed that $0 \leq (1-cx) \leq 1$).

I begin by examining the evolution of avoidance (3.9), recovery (3.10) and tolerance (3.10) for the basic SIS interaction (model I). Acquired immunity is then added as described by (3.12) and (3.13), and the evolutionary dynamics considered. Since the natural death rate is b, the average lifespan of uninfected (susceptible) hosts is taken as $1/b$. The method is to examine how the level of investment in resistance (x^*) that evolves is affected by changes in lifespan ($1/b$). This is achieved using the method of adaptive dynamics as described below.

3-2-4. Invasion analysis

I derive the condition for a rare mutant strain to invade and replace an established resident host. I make the initial assumption that all host strains are capable of supporting the parasite in endemic equilibrium. This requires that host births exceed deaths ($a > b$) and that the carrying capacity exceeds a threshold density $K \geq H_T = (\alpha + \gamma + b)/\beta$. The analysis is presented in detail for model II and summarised for the other models.

Consider the stable endemic equilibrium (S^*, I^*, R^*) in model II with resident host strategy, x, and associated total density $H^* = S^* + I^* + R^*$. Suppose a mutant strain characterised by x_m evolves at an initially low density (in the following the subscript m denotes the mutant parameters). For this mutant strain to invade, its marginal growth rate must be positive. This means the average contribution per mutant individual to the population must be greater than zero. Assume the mutant is initially in the susceptible state, and remains uninfected for an average time period T_S, and let T_I and T_R denote the average times spent in the infected and recovered states. The average contributions while in the respective states are denoted ρ_S, ρ_I and ρ_R. From the arguments given in Boots and Bowers (2004), the following identities can be derived:

$$\rho_S = a_m - b - qH^* \tag{3.15}$$

$$\rho_I = a_m - b - qH^* - \alpha_m \tag{3.16}$$

$$\rho_R = a_m - b - qH^* \tag{3.17}$$

$$T_S = \frac{1}{(b + \beta_m I^*)} \tag{3.18}$$

$$T_I = \frac{\beta_m I^*}{(b + \beta_m I^*)(\alpha_m + \gamma_m + b)} \tag{3.19}$$

$$T_R = \frac{\gamma_m \beta_m I^*}{(b+\delta_m)(b+\beta_m I^*)(\alpha_m+\gamma_m+b)} \tag{3.20}$$

Let $\phi(x_m/x)$ denote the marginal growth rate of the rare mutant strain, x_m, in the resident population, x. This is equal to the sum of the average time periods (3.18)-(3.20), weighted by the corresponding contributions (3.15)-(3.17):

$$\phi(x_m/x) = \rho_S T_S + \rho_I T_I + \rho_R T_R \tag{3.21}$$

Substituting in the values for (3.15)-(3.20) and eliminating the positive common factor, $1/(b+\beta_m I^*)$, the marginal growth rate of a rare mutant strain is given as:

$$\phi(x_m/x) = a_m - b - qH^* + \frac{\beta_m I^*(a_m - b - qH^* - \alpha_m)}{(\alpha_m+\gamma_m+b)} + \ldots$$
$$\ldots + \frac{\gamma_m \beta_m I^*(a_m - b - qH^*)}{(\delta_m+b)(\alpha_m+\gamma_m+b)} > 0 \tag{3.22}$$

Provided (3.22) is satisfied, a rare mutant strain characterised by x_m can invade the resident strain x. Otherwise, the mutant strain has a negative growth rate and will become extinct. Two points need to be mentioned. Firstly, successive periods of infection are possible (assuming the rates of recovery, γ_m, and loss of immunity, δ_m, are non-zero). Taking this into account scales (3.22) by a positive constant and can therefore be ignored. Secondly, invasions by infected or recovered individuals may also occur. It can be shown, however, that infecteds or recovered cannot prosper unless susceptibles do. Equation (3.22) therefore sufficiently determines the growth rate of a rare mutant strain and can be taken as the invasion criterion (or fitness function). Using the same technique, the invasion criterion for model I is obtained as:

$$\phi(x_m/x) = a_m - b - qH^* + \frac{\beta_m I^*}{(\alpha_m+\gamma_m+b)}(a_m - b - qH^* - \alpha_m) > 0 \tag{3.23}$$

Similarly the invasion criterion for model III is:

$$\phi(x_m/x) = a_m - b - qH^* + \frac{\beta_m I^*(a_m - b - qH^* - \alpha_m)}{(\alpha_m + \gamma_m + b)} + \ldots$$

$$\ldots + \frac{\nu_m \gamma_m \beta_m I^*(a_m - b - qH^*)}{b(\alpha_m + \gamma_m + b)} > 0 \qquad (3.24)$$

Adaptive dynamics are now used to determine the evolutionary behaviour and the level of investment in resistance that evolves. Explicit trade-off functions are employed such that a given investment in resistance (3.9)-(3.13) is associated with a given reduction in birth rate (3.14). This trade-off is incorporated into the fitness functions (3.22)-(3.24). The theory of adaptive dynamics (Metz et al. 1996; Geritz et al. 1998) states that the population will evolve in the direction of the local fitness gradient, $[\partial\phi/\partial x_m]_{x=x_m}$, and that singular points of evolution occur where this fitness gradient is equal to zero:

$$[\partial\phi/\partial x_m]_{x=x_m} = 0 \qquad (3.25)$$

As discussed in chapter 1, evolutionary singular points may exhibit a number of evolutionary properties. Here the attention is limited to two particular properties. I determine whether the singular point is an ESS (if, when resident, it resists invasion by all other strains), and also whether it is convergence stable (if local evolution proceeds towards it). The optimal strategy is assumed to be the continuously stable strategy (CSS; Geritz et al. 1998) that is both evolutionarily and convergence stable. Such a strategy corresponds to a local maximum. An evolutionary repellor on the other hand, is neither evolutionarily nor convergence stable (non-ESS, non-CS) and therefore corresponds to a local fitness minimum. All the singular points analysed in this model were found to be either CSS attractors or evolutionary repellors. As will be shown, in some cases, this leads to the interesting phenomenon of evolutionary bistability. The evolutionary properties of the singular points was checked using pairwise invadability plots, and by numerical simulations of the mutation-selection process.

3-3. Results

3-3-1. Avoidance (model I)

When resistance evolves as reduced transmission rate (avoidance), the relationship between host lifespan ($1/b$) and the optimal investment, x^*, is dependent on the virulence, α. This is illustrated in Figure 3.1A, showing the level of investment that evolves as a function of lifespan. For intermediate or high virulence ($\alpha = 2, 2.75$), the optimal strategy, x^*, is an increasing saturating function of lifespan. At lower virulence ($\alpha = 1.75$), resistance initially increases and then decreases marginally. This predicts longer-lived hosts to evolve more avoidance, although this is not always the case; in response to low virulence ($\alpha = 1.67$), longer-lived hosts may evolve less avoidance than shorter-lived ones. In this case, the optimal avoidance, x^*, is non-monotonic, but mainly decreasing with lifespan. Over a range of intermediate lifespans ($10 < 1/b < 43$) there is bistability in the evolutionary outcomes: there evolves either a locally stable level of avoidance ($x^* > 0$), or no avoidance ($x^* = 0$), the outcome being determined by the initial conditions. If the initial level of avoidance is above a particular threshold (determined by the position of an evolutionary repellor; see Fig 3.1A) then avoidance evolves to the stable positive level of avoidance. If the initial level of avoidance is below the threshold then the population evolves to zero avoidance. Hosts with sufficiently high lifespan ($1/b \geq 43$) will evolve zero avoidance. This evolutionary behaviour only occurs over a small range of low virulences (α), between the regions where avoidance is worthwhile at all lifespans ($x^* > 0$ at $\alpha = 1.7$), and is never worthwhile ($x^* = 0$ for $\alpha \leq 1.5$).

That avoidance should generally increase with lifespan can be explained by the higher prevalence of infection in longer-lived populations (Fig. 3.1B). Longer-lived susceptibles encounter more parasites, while longer-lived infecteds have more opportunities to infect susceptibles. Provided virulence (α) is not too low, the higher prevalence in longer-lived populations increases the selection for avoidance (Fig. 3.1A). Importantly, there is also a negative relationship between virulence and disease prevalence (Fig. 3.1B). Lower mortality of infected hosts increases the

average infectious period, $1/(\alpha + \gamma + b)$, and therefore increases the opportunities for transmission. Assuming virulence (α) and the death rate (b) are low, a given level of avoidance may only marginally reduce the prevalence of infection. Consequently, longer-lived populations may evolve relatively less avoidance, but only if the pathogenic effect on fitness (virulence) is relatively small.

3-3-2. Recovery (model I)

The evolutionary dynamics when resistance evolves as recovery (increased rate of clearance) are illustrated in Figure 3.1C. At intermediate to high virulences ($\alpha = 1.75$, 2.75), the optimal recovery rate is an initially increasing then saturating function of lifespan. At low virulence ($\alpha = 1.25$), the optimal investment, x^*, initially increases with lifespan and then decreases towards a positive asymptote. As with avoidance, the prevalence of infection increases monotonically with lifespan. Longer-lived populations have higher disease prevalences and this generally increases the selection for resistance. At low virulence, disease prevalence is even higher such that recovered hosts are highly likely to be re-infected. Consequently, longer-lived populations may sometimes evolve marginally lower recovery rates in response to parasitism. Note, however, that there is no bistability in evolutionary outcomes.

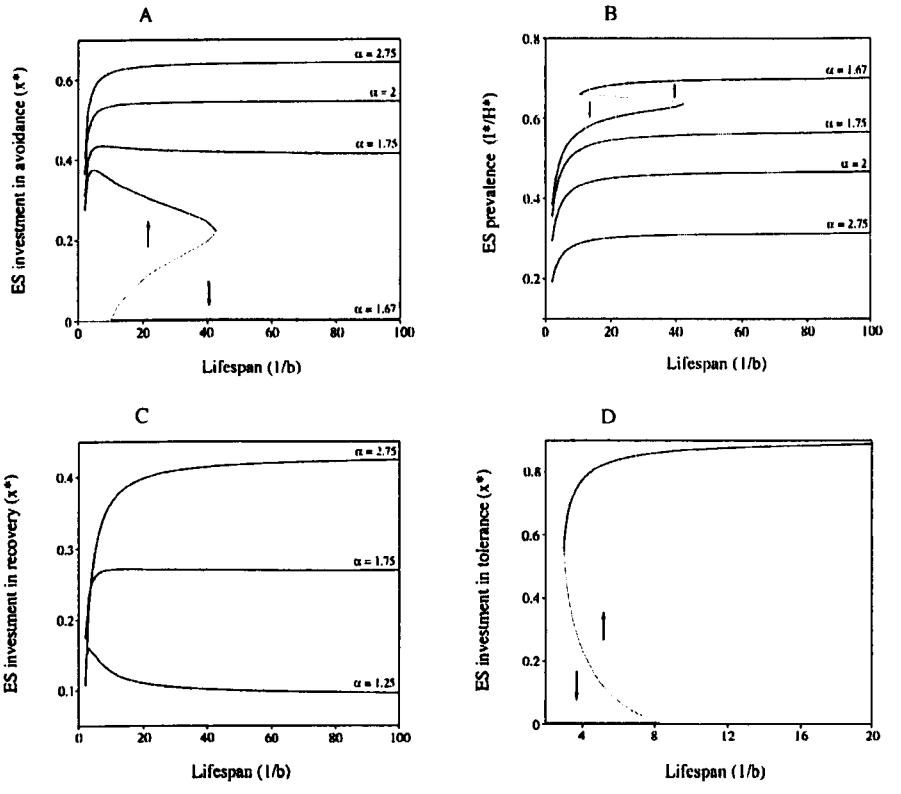

Figure 3.1. (A) Evolutionarily stable investment in avoidance, and (B) corresponding prevalence of infection, as a function of host lifespan. Parameters are $\gamma = 0.25$, $\beta_1 = \beta_0 = 1$ and $h = 2$. (C) Evolutionarily stable investment in recovery as a function of host lifespan; parameters are $\beta = 1.5$, $\gamma_1 = 2.5$, $\gamma_0 = 0.1$ and $h = 0.9$. (D) Evolutionarily stable investment in tolerance as a function of host lifespan. Parameters are $\beta = 1$, $\gamma = 0.25$, $\alpha_1 = 1.5$, $\alpha_0 = 1$ and $h = 1.5$. In all figures the black lines correspond to evolutionary attractors (CSSs) and the grey lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. Other parameters are $a = 1.5$, $q = 0.1$ and $c = 0.25$.

3-3-3. Tolerance (model I)

The evolutionary dynamics of tolerance are illustrated in Figure 3.1D. Very short-lived hosts do not invest in any tolerance. As lifespan increases, there is a range of bistable strategies, where the host either evolves no tolerance ($x^* = 0$), or some positive level, $x^* > 0$, that increases with lifespan. As lifespan further increases, the positive ES tolerance increases and the local optimum at $x^* = 0$ vanishes. Once again,

disease prevalence was found to increase with lifespan. Longer-lived populations invest more heavily in tolerance in response to these higher prevalences.

3-3-4. Avoidance (model II)

If there is a sufficiently high rate of loss of immunity ($\delta = 5$), optimal avoidance increases and saturates with lifespan (Fig. 3.2A). With longer lasting immunity ($\delta = 0.5$), the optimal investment initially increases with lifespan and then marginally decreases towards a positive asymptote (Fig. 3.2A). For lower rates of loss of immunity ($\delta = 0.325$), investment tends to fall with lifespan and over an intermediate range there is bistability (a positive optimum, $x^* > 0$, and the zero strategy, $x^* = 0$). Furthermore, above a threshold lifespan ($1/b \geq 50$) hosts do not evolve any avoidance (Fig. 3.2A). Comparing the three examples, it is notable that hosts invest relatively less in avoidance (at any lifespan), as the length of immunity ($1/\delta$) increases.

These results can again be explained by the epidemiology. At moderate or high rates of loss of immunity (δ), the prevalence of infection always increases with lifespan (Fig. 3.2B). Interestingly, disease prevalence is almost the same for a moderate rate of loss ($\delta = 0.5$) as for a high rate ($\delta = 5$). In the former case, however, a greater proportion of the population is immune to infection (Fig. 3.2C), reducing the selection for avoidance. This lower level of avoidance balances the reduction in the susceptible population due to the immune class, leading to a similar level of prevalence.

Provided the rate of loss of immunity (δ) is not too small, longer-lived populations will exhibit higher prevalences, and consequently evolve relatively greater avoidance.

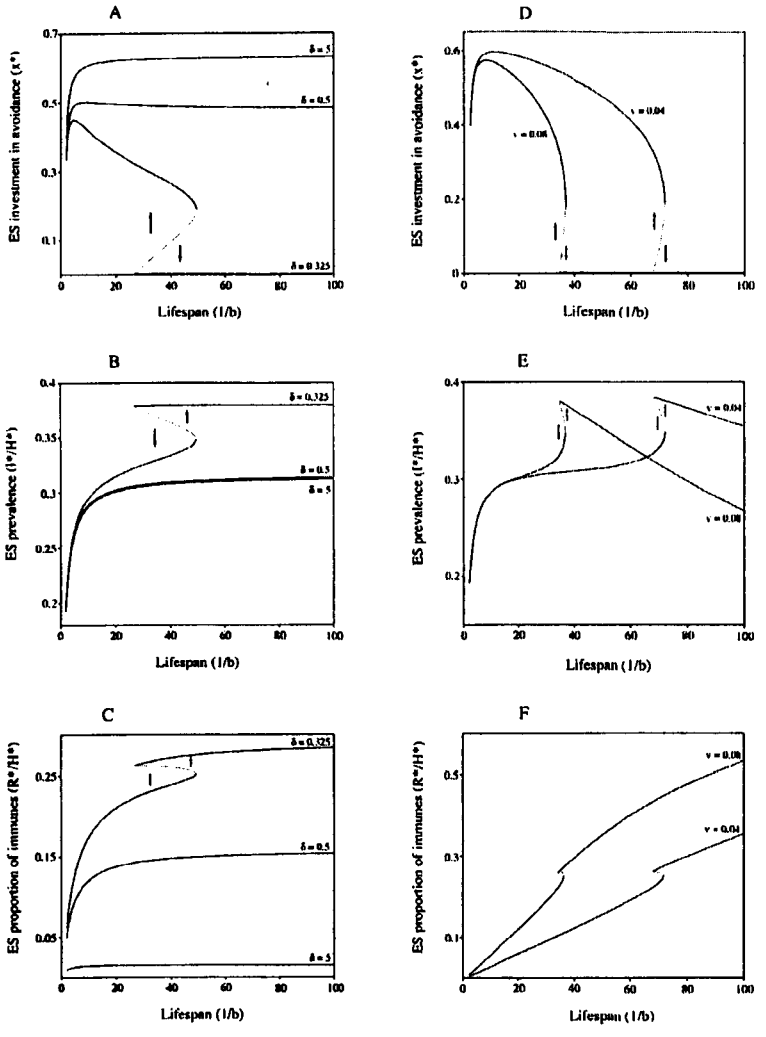

Figure 3.2. (A), (D) Evolutionarily stable investment in avoidance; (B), (E) corresponding prevalence of infection; and (C), (F) proportion of immune individuals, as a function of host lifespan. In all figures the black lines correspond to evolutionary attractors (CSSs) and the grey lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. In (A)-(C) recovered hosts lose immunity at a constant rate, δ (model II); in (D)-(F) the probability of acquiring immunity upon recovery is ν (model III). Other parameters are $a = 1.5$, $q = 0.1$, $c = 0.25$, $\alpha = 2.75$, $\gamma = 0.25$, $\beta_1 = \beta_0 = 1$ and $h = 2$.

Even at low rates of loss ($\delta = 0.325$), prevalence generally increases with lifespan, although it is constant when the host does not invest in any resistance (Fig. 3.2B). The proportion of immunes always increases with lifespan and with the duration of immunity (Fig. 3.2C). Longer-lived hosts are more likely to become infected, and to

recover from infection before (natural) death. They will also live longer while immune. If immunity is sufficiently durable, it may therefore be more advantageous to invest in reproduction rather than resistance, as this outweighs the advantage of avoiding infection in the first place (i.e. avoiding virulence).

3-3-5. Avoidance (model III)

Next I examine the situation where the proportion, ν, of hosts that acquire permanent immunity varies (model III). Here the optimal avoidance is always maximal for an intermediate lifespan; as lifespan increases from low values, the ES avoidance initially increases and then decreases (Fig. 3.2D). There always exists a narrow region of bistability, and a threshold lifespan above which hosts do not evolve any avoidance. As expected, at higher probabilities of acquiring immunity (ν), hosts always invest relatively less in avoidance (Fig. 3.2D). The proportion of immunes always increases with lifespan and with the probability of becoming immune, ν (Fig. 3.2F). Moving from low to intermediate lifespan, the prevalence of infection also increases (Fig. 3.2E). Longer-lived species have higher prevalences and a higher proportion of immunes; for sufficiently high lifespan, this always reduces selection for avoidance.

This contrasts with variation in waning immunity (model II), where optimal avoidance may be monotonic ($\delta = 5$ in Fig. 3.2A), non-monotonic but reach a positive asymptote ($\delta = 0.5$ in Fig. 3.2A), or non-monotonic and zero for sufficiently high lifespan ($\delta = 0.325$ in Fig. 3.2A). The relative importance of the immune class and its attendant density-dependent effects are more important when immunity is permanent (model III), as selection for avoidance always decreases at higher lifespan. Furthermore, where the host does not evolve any avoidance, prevalence is seen to decreases with increasing lifespan (Fig. 3.2E). In model II, immunity always wanes eventually (at rate δ), and the effects are weaker. Note also that the non-monotonic response described for both models is quantitatively dependent on the host's recovery rate (γ). As γ decreases, a lower rate of loss of immunity (or higher probability of

acquiring immunity) is required for selection for avoidance to decrease due to the relative importance of the immune class.

3-3-6. Recovery (model II)

I examine the evolutionary dynamics of recovery, assuming immunity wanes at a constant rate, δ (model II). At high rates of loss immunity ($\delta = 5$), the results are similar to that of the SIS interaction: optimal investment increases and saturates with lifespan, as recovered hosts quickly lose their immunity and prevalence increases monotonically with lifespan (Figs. 3.3A-3.3C). At intermediate rates of loss of immunity ($\delta = 0.25$), the optimal recovery initially increases with lifespan, then decreases towards a positive asymptote. When immunity wanes very slowly ($\delta = 0.01$), the ES recovery is again non-monotonic with lifespan but shows a stronger decrease. Here the proportion of immunes is much greater, and in long-lived species comprises the majority of the population (Fig. 3.3C). This reduces the proportion of susceptibles, and (due to the density-dependent effects) may also reduce their absolute density. This indirectly reduces the prevalence of infection (Fig. 3.3B), and therefore the selection for recovery (Fig. 3.3A).

3-3-7. Recovery (model III)

I now assume that a proportion (ν) of recovered hosts acquire permanent immunity (model III). The optimal recovery, x^*, initially increases and then decreases with higher lifespan, tending towards the zero asymptote; recovery is always maximal for an intermediate lifespan (Fig. 3.3D). At lower probabilities of acquiring immunity ($\nu = 0.5$), there is a stronger initial increase, but investments always tend to zero for sufficiently long lifespans. Again, the dynamics are explained by density-dependent effects and by the relative importance of immunes.

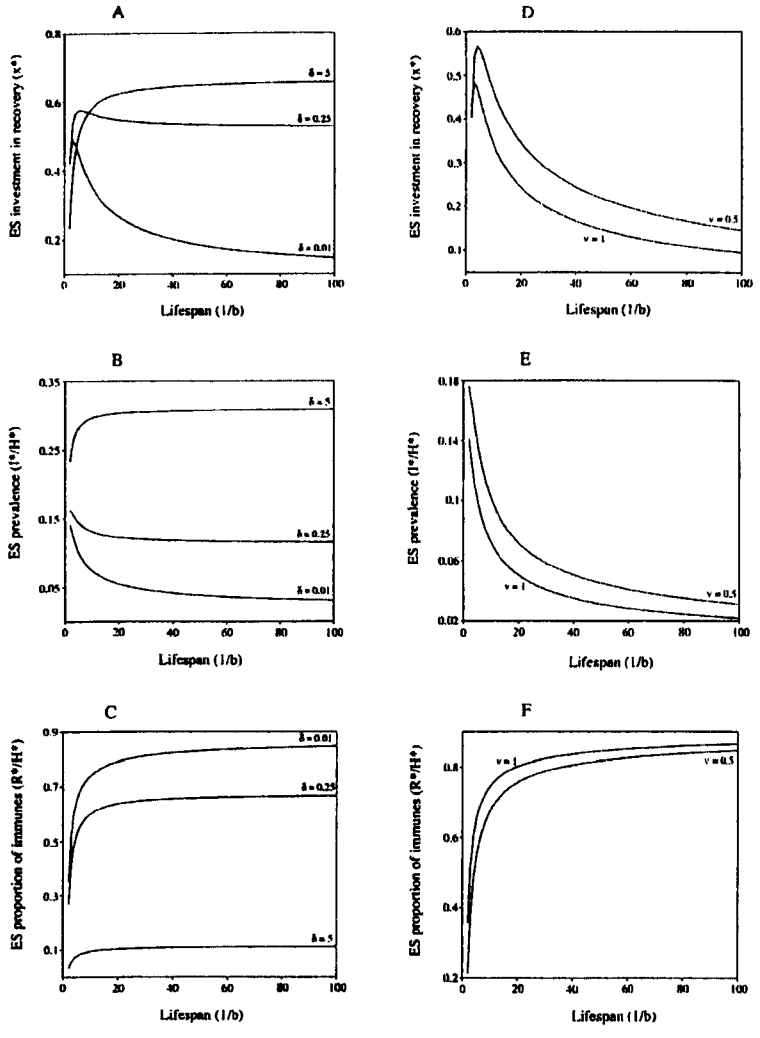

Figure 3.3. (A), (D) Evolutionarily stable investment in recovery; (B), (E) corresponding prevalence of infection; and (C), (F) proportion of immune individuals, as a function of host lifespan. In all figures the black lines correspond to evolutionary attractors (CSSs) and the grey lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. In (A)-(C) recovered hosts lose immunity at a constant rate, δ (model II); in (D)-(F) the probability of acquiring immunity upon recovery is ν (model III). Other parameters are $a = 1.5$, $q = 0.1$, $c = 0.25$, $\alpha = 2.75$, $\beta = 2$, $\gamma_1 = 2.5$, $\gamma_0 = 0.1$ and $h = 0.9$.

As shown in Figure 3.3E, the prevalence of infection decreases monotonically as lifespan is increased (at lower values of ν, prevalence may initially increase, but always decreases at higher lifespan). The proportion of immunes always increases with lifespan (Fig. 3.3F). At sufficiently high lifespan, this long-lived immune

population induces a higher level of density-dependent crowding. Disease prevalence is therefore lower and longer-lived populations invest less in recovery (Fig. 3.3D). The immune class has a greater effect in model (III) due to the fact that immunity is permanent: even at very low ν, prevalence and the selection for recovery always decrease for sufficiently high lifespan.

At low lifespan (models I, II) and/or high rate of loss of immunity (model II), the optimal recovery rate is much higher than in the absence of acquired immunity (compare Figs. 3.1C with 3.3A, 3.3D). The added benefit of becoming immune increases selection for recovery. Provided the overall proportion of immune hosts remains relatively low, individuals may therefore evolve higher recovery rates if they also have acquired immunity.

3-3-8. Tolerance (model II)

Next, I consider the evolution of tolerance when hosts lose immunity at constant rate (model II). Provided the rate of loss of immunity (δ) is sufficiently high, the optimal investment increases and saturates with lifespan (Fig. 3.4A). Below a certain lifespan ($1/b \leq 3$), host do not invest in any tolerance. For higher lifespans, hosts may evolve a positive level of tolerance, $x^* > 0$. However, for part of the range there is bistability whereby either a positive level of tolerance or zero tolerance will evolve; this is dependent on the initial level of tolerance. Disease prevalence and the proportion of individuals with immunity both increase with lifespan (Figs. 3.4B, 3.4C). Here the increases in prevalence dominate resulting in the selection for increases in tolerance mechanisms, since the immune class is too small to significantly influence the dynamics.

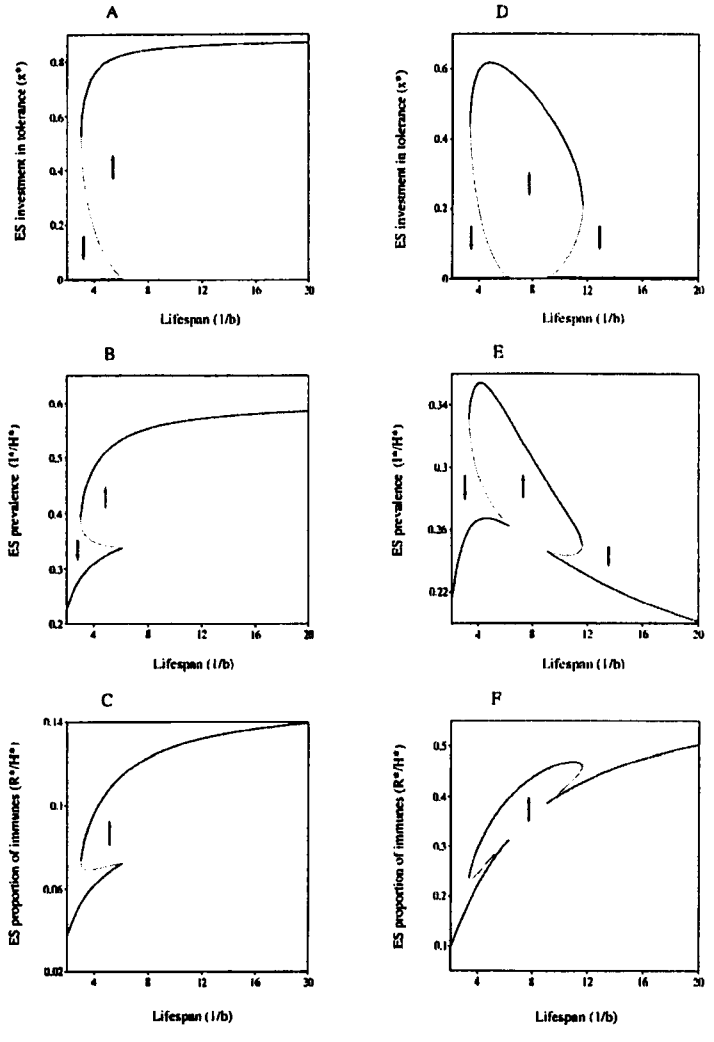

Figure 3.4. (A), (D) Evolutionarily stable investment in tolerance; (B), (E) corresponding prevalence of infection; and (C), (F) proportion of immune individuals, as a function of host lifespan. In all figures the black lines correspond to evolutionary attractors (CSSs) and the grey lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. In (A)-(C) the rate of loss of immunity is $\delta = 1$ (model II); while in (D)-(F) $\delta = 0.05$. Other parameters are $a = 1.5$, $q = 0.1$, $c = 0.25$, $\beta = 1$, $\gamma = 0.25$, $\alpha_I = 1.5$, $\alpha_0 = 1$ and $h = 1.5$.

At lower rates of loss of immunity (δ), neither very long-lived nor very short-lived hosts invest in any tolerance (Fig. 3.4D). At intermediate lifespans, there is a locally stable level of tolerance, $x^* > 0$, which is globally stable over a reduced range; otherwise, there also exists a locally stable investment at $x^* = 0$. The level of

investment ($x^* > 0$) initially increases and then decreases with lifespan, which is again due to the effect of the immune class. Initially, prevalence increases with lifespan, and there are relatively few hosts with immunity (Figs. 3.4E, 3.4F). As lifespan further increases, the proportion of immunes also increases, and prevalence correspondingly begins to decrease (Figs. 3.4D, 3.4E). There is therefore a clear positive relationship between disease prevalence and the optimal investment in tolerance. At high lifespan, the large immune class increases the density-dependent effects, reducing the proportion of susceptibles and therefore disease prevalence. If there is a sufficiently low rate of loss of immunity, longer-lived populations may therefore evolve relatively less tolerance (Fig. 3.4D). However, as with avoidance, the decrease in investments occurring at high lifespans is quantitatively dependent on the recovery rate, γ. If there is a lower rate of clearance, then lower rates of loss of immunity (δ) and/or higher host lifespans are required for tolerance to decrease.

3-3-9. Tolerance (model III)

Varying the proportion, ν, of hosts that acquire permanent immunity (model III), produces qualitatively similar evolutionary dynamics to those in Figures 3.4D-3.4F. Even at very low probabilities of acquiring immunity (ν), tolerance is always non-monotonic with lifespan and falls to zero for sufficiently long-lived hosts.

3-3-10. Acquired immunity (model II)

I now examine the evolution of acquired immunity itself, in terms of a reduced rate of loss of immunity, δ, or a higher probability, ν, of gaining acquired immunity. If immunity increases the duration of the immune period (model II), then very short-lived hosts do not invest in resistance at all (Fig. 3.5A). Above this threshold, there is bistability with an intermediate ES level of immunity, x^*, that rapidly attains a very high level and an alternate ES strategy at $x = 0$ (zero investment). The proportion of immunes increases with lifespan, and is relatively small where the host does not invest in any resistance (Fig. 3.5C) and disease prevalence increases monotonically with lifespan (Fig. 3.5B). When the host does invest in acquired immunity, the

immune class is very large at higher lifespan (Fig. 3.5C), and density-dependent effects cause prevalence to fall (Fig. 3.5B). At lower lifespan, the prevalence of infection is too high and the proportion of immunes too few, for it to be worthwhile investing in maintaining immunity. As lifespan increases, the benefits of increased immunity (in terms of a higher proportion of immunes and reduced prevalence) are greater. For sufficiently high lifespan, then, longer-lived populations always evolve greater immunity.

3-3-11. Acquired immunity (model III)

The situation is very different for the evolution of acquiring immunity (model III). Here, the ES level of immunity, x^*, increases initially and then decreases at higher lifespan (as lifespan tends to infinity, x^* asymptotes towards zero) (Fig. 3.5D). This contrast is due to differences in the effect of the immune class on the epidemiology, and therefore selection for immunity. As lifespan increases, the proportion of the individuals with acquired immunity increases, becoming very large at high lifespan (Fig. 3.5F). In contrast, disease prevalence decreases with increasing lifespan to low levels (Fig. 3.5E). Density-dependence from the long-lived immune class reduces the proportion of susceptibles and therefore the prevalence of infection. This reduces the selection for immunity as lifespan increases. The initial increase in immunity (Fig. 3.5D) is explained by the fact that, although disease prevalence in the population is decreasing, at the level of the individual, longer-lived hosts still have a greater number of encounters with infected hosts. If the immune class and the corresponding density-dependent effects are relatively small, moderately long-lived populations may therefore evolve greater immunity.

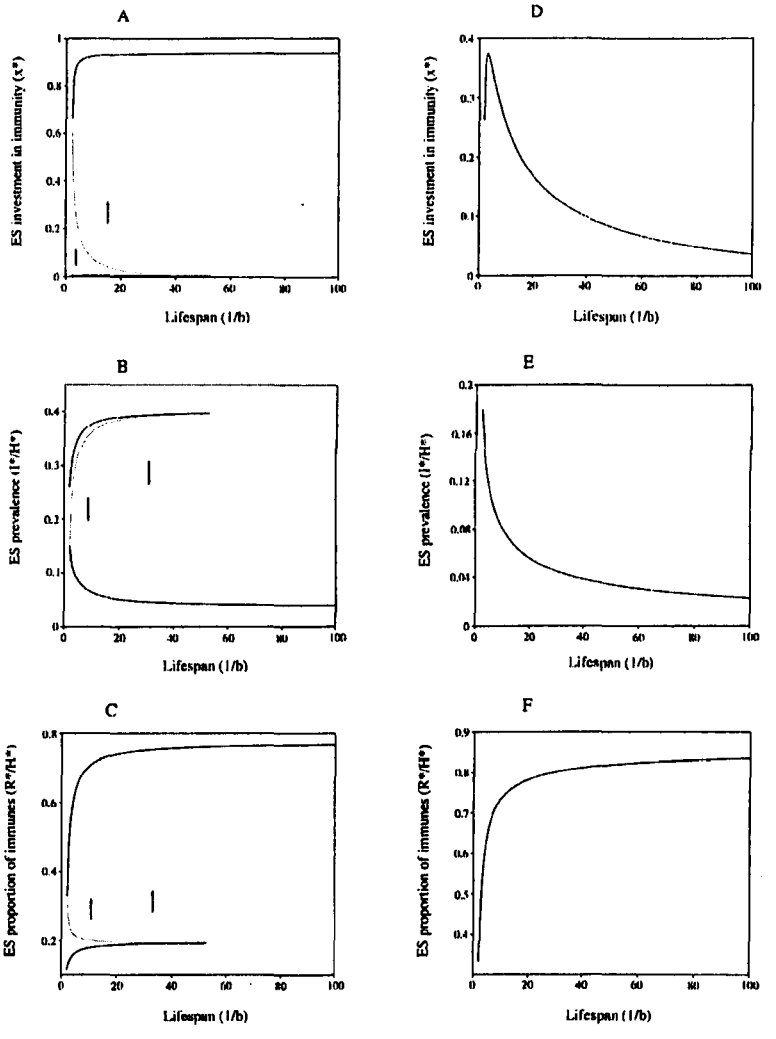

Figure 3.5. (A), (D) Evolutionarily stable investment in acquired immunity; (B), (E) corresponding prevalence of infection; and (C), (F) proportion of immune individuals, as a function of host lifespan. In all figures the black lines correspond to evolutionary attractors (CSSs) and the grey lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. In (A)-(C) $\delta_1 = 5$, $\delta_0 = 0.1$ and $h = 2$ (model II); in (D)-(F) $\nu_1 = 0.9$, $\nu_0 = 0.1$ and $h = 0.9$ (model III). Other parameters are $a = 1.5$, $q = 0.1$, $c = 0.25$, $\alpha = \gamma = 2.5$ and $\beta = 2.5$.

3-4. Discussion

Longer-lived species relying only on innate resistance to defend against parasites generally invest more in resistance. This increased investment occurs whether resistance reduces the probability of infection, increases the recovery rate, or reduces virulence. Longer-lived individuals are more likely to become infected, and therefore tend to have higher disease prevalence. This increases the selection for costly defences that avoid infection or tolerate pathogen damage. In the examples given, infected hosts were able to recover from infection but it can be shown these results hold even if the disease is invariably fatal. In contrast, if hosts benefit from immunological memory and therefore acquire immunity, the optimal investment in innate resistance may often be maximal for an intermediate lifespan. If immunity is permanent (the classic susceptible-infected-removed dynamic), the optimal immunity is always maximal for an intermediate lifespan. If immunity wanes over time, longer-lived individuals may invest more in innate defences, but this is not always the case: depending on the epidemiology, hosts of intermediate lifespan may again invest in relatively more resistance. These effects occur because longer-lived individuals are more likely to recover from infection, and may therefore invest relatively less in mechanisms that reduce transmission. Populations of longer-lived hosts have a higher proportion of immune individuals and, due to intra-specific crowding, a lower prevalence of infection. Selection for mechanisms that reduce virulence or increase recovery may therefore also be lower in such longer-lived species.

There is often bistability in the evolutionary outcomes. Where resistance reduces the probability of infection (avoidance), it is longer-lived individuals that show this bistability, either evolving resistance, or no resistance at all. This bistability is due to the existence of a local fitness minimum, or evolutionary 'repellor' (Metz et al. 1996; Geritz et al. 1998), occurring between two locally stable strategies (CSSs). An important implication of this is that if long-lived individuals are initially susceptible to a novel parasite, with local mutation, they will not evolve any resistance. However, if global mutations occur, even an initially susceptible population may evolve resistance. There may therefore be dramatic shifts in the level

of avoidance, when a highly resistant morph invades and eliminates an initially susceptible population. This type of bistability is also seen in the evolution of tolerance, although here it may occur in both short-lived and long-lived species. In this case, assuming local mutation, only hosts of intermediate lifespan will evolve tolerance to a novel pathogen. It is important to note, however, that this only occurs if acquired immunity is long lasting.

The evolution of acquired immunity depends on whether immunity is permanent or temporary. When the resistance mechanism operates by allowing the probability of gaining permanent immunity to evolve, then as lifespan increases, the optimal investment rises to a maximum and then falls towards zero (Fig. 3.5D). If, instead, resistance increases the length of the immune period, then optimal investment always increases with lifespan, although bistability at short and intermediate lifespan may possibly lead to zero investment. Given local mutation, shorter-lived species may therefore not evolve any acquired immunity, while longer-lived species are predicted to invest heavily (Fig. 3.5A). Acquired immunity is also most likely to evolve in response to high transmission rates and intermediate rates of recovery (Boots and Bowers 2004). These results suggest that acquired immunity should only evolve in the face of very strong selective pressure, where prevalence is high and the benefits of immunity are large (i.e. organisms have a considerable chance of recovering and also live long enough to benefit from immunity).

The possession of an acquired immune system has important implications, since longer-lived individuals may invest in relatively more, or relatively less innate resistance, if they have acquired immunity. Given that innate and acquired immunity are costly to maintain, hosts may be expected to balance the investment between the two defences in each in order to minimize the total cost. It is well known that different forms of resistance may be traded-off (Mallon et al. 2003). In particular, investment in specific forms of defence may be negatively correlated with investment in non-specific defences (Frank 2000), where the optimal allocation between the two forms will depend on the prevalence of infection (Moret 2003). As shown here, it also

crucially depends on the lifespan of the host, because this selects for innate and acquired immunity differentially.

It is well established that population density may affect the evolution of resistance characteristics (Svensson et al. 2001; van Boven and Weissing 2004). It has been shown here that increased crowding due to a long-lived immune class may indirectly reduce disease prevalence and therefore the selection for innate or (model III) acquired immunity. The evolutionary dynamics of resistance were also investigated omitting the density-dependent effects: this assumes a constant birth rate (i.e. the parameter $q = 0$ in the previous models). In this case, when resistance evolved as increased recovery or reduced virulence (tolerance) the optimal investment always increased with lifespan. However, the optimal investment in reduced transmission (avoidance) was maximal at intermediate lifespan. Density-dependence alone therefore cannot explain the reduction in avoidance occurring in longer-lived populations. The optimal avoidance is lower in long-lived individuals because these are highly likely to become infected anyway, but have a sufficiently high chance of recovering (and therefore acquiring long lasting immunity). This outweighs the advantage of investing in costly avoidance.

This model assumed purely constitutive costs of resistance. More resistant hosts therefore always have a reduced birth rate (whether infected, susceptible or immune). Evolutionary costs are strictly constitutive in that they are genetically determined and can change only through natural selection (Schmid-Hempel 2003, 2005). Energetic or physiological costs of resistance may also be constitutive, where the organism is forced to expend valuable resources to maintain its immune system in a state of readiness (Schmid-Hempel 2003, 2005). However, there are also likely to be 'induced' costs associated with activating and/or maintaining an immune response (Zuk and Stoehr 2002). The selective pressures may be very different under the assumption of induced costs. For example, Day and Burns (2003) showed that longer-lived hosts should invest relatively less in recovering from infection when there is no acquired immunity. In contrast, in assuming constitutive costs, longer-lived individuals generally evolve higher recovery rates if they lack acquired immunity

(Fig. 3.1C). Recent theoretical work has investigated when organisms should switch between constitutive and inducible forms of defence. Assuming constitutive defences act more rapidly, hosts should invest in these whenever parasites are highly virulent and transmissible, although pathogens that grow quickly within the host may favour a mixed response (Shudo and Iwasa 2001). It would be interesting to see how lifespan affects this response.

The results suggest that in long-lived species, the presence of a long-lasting acquired immune system may reduce selection for less specific, innate resistance. This is more likely if the species is particularly prone to intra-specific crowding, although internal or external (behavioural) mechanisms that reduce the probability of infection may be selected against even in the absence of such density-dependence. Both invertebrates and vertebrates have innate immunity, and vertebrates also benefit from a highly specific acquired immune system (Medzhitov and Janeway 1997). Invertebrates are generally thought to have no acquired immunity as such (Medzhitov and Janeway 1997; Rinkevich 1999; Zuk and Stoehr 2002), although there is increasing evidence for immunological memory in many insects (reviewed by Schmid-Hempel (2005)). My results may therefore apply to both vertebrate and invertebrate systems, although it is important to note that longer-lived species in particular are likely to be exposed to many different pathogens. Acquired immunity is antigen-specific and is activated by signals from the innate immune system (Medzhitov and Janeway 1997; Menezes and Jared 2002). As the diversity of parasites increases, the value of a given defence option therefore becomes less effective and may be selected against (Jokela et al. 2000). As a result, acquired immunity may only select for less innate resistance in long-lived organisms if these have relatively few parasites.

This chapter has investigated how lifespan affects the evolution of resistance, and the related implications of having an acquired immune system. The selective pressures affecting optimal allocation to resistance have been shown to depend on a variety of epidemiological and ecological factors, in particular, the effects of density-dependence and the immune class.

4. The evolution of virulence in response to tolerance

4-1. Introduction

In chapter 2, I distinguished between tolerance and control as different forms of resistance. The important distinction between these two forms is that control achieves a reduction in virulence by inhibiting the growth of the parasite within infected hosts, whereas tolerance mechanisms merely reduce the damage caused by parasite growth. The evolutionary dynamics of tolerance and control were shown to have marked differences in terms of the level of resistance that evolves. This has important implications because the evolution of the host may also select the parasite. This has been considered in a number of contexts before (van Baalen 1998; Gandon and Mickalakis 2000; Gandon et al. 2001, 2002b, 2003; Gandon et al. 2002a; Restif and Koella 2003). Epidemiological models have tended to assume that virulence is proportional to the within-host parasite replication rate (Read and Harvey 1993; Ebert 1998; Mackinnon and Read 1999; Ebert and Bull 2003; Gandon et al. 2003). Under this assumption, control of the parasite's growth rate by the host has been shown to select for more exploitative parasites (Gandon and Mickalakis 2000). This chapter focuses instead on how tolerance, once fixed in the host population, will act to select the parasite.

I classify three generic types of tolerance mechanism and consider the implications in terms of the parasite's evolution. The approach is to examine the evolution of parasite growth (or replication) rate within the host, assuming that this relates to transmission and causes virulence. An explicit account of the epidemiological feedbacks in the system is taken, and the consequences of tolerance evolution in terms of disease prevalence and mortality at the level of the population are considered. I develop a formal model that examines the evolution of parasites in response to tolerance with different characteristics and show that higher or lower parasite growth rates can be selected, depending on the nature of the tolerance mechanism. Roy and Kirchner (2000) have shown that tolerance will tend to become fixed in populations, with no possibility of polymorphism. I therefore assume that selection acts on the parasite after the evolution of tolerance. This is a realistic simplifying assumption for tolerance mechanisms, but less so for resistance through

avoidance, recovery or control of the parasite, where a full coevolutionary model may be more appropriate. In line with recent trade-off theory (Stearns 1992), the evolution of tolerance is assumed to be costly in terms of a reduction in the host's intrinsic growth rate.

4-2. The Model

The following equations describe a host-pathogen interaction for a directly transmitted microparasite, where X denotes the density of uninfected individuals, Y denotes the density of infected individuals, and $H = X + Y$ gives the total host density:

$$\frac{dX}{dt} = rH - qH^2 - \beta XY + (\gamma + b)Y \tag{4.1}$$

$$\frac{dY}{dt} = \beta XY - (\alpha + \gamma + b)Y \tag{4.2}$$

Here r is the intrinsic growth rate of the host genotype, equal to the birth rate (a) minus the natural death rate (b). Density-dependence is assumed to act directly on the birth rate, where the parameter q measures the host population's susceptibility to crowding. The transmission rate of infection, the recovery rate, and the virulence are denoted by β, γ and α respectively. All parameters are assumed to be positive.

I assume that virulence (α) is determined by the parasite's within-host replication rate (ε). In the 'wild type' host that has not evolved any tolerance, the relationship between increased death rate and parasite growth rate takes the form $\alpha = \varepsilon v_W$. The parameter v_W scales the damage that within-host growth causes the host, and may be interpreted as the 'intrinsic' virulence of the parasite.

Tolerance mechanisms reduce the damage caused for a given rate of replication. With type I (complete) tolerance, I assume the host is able to completely tolerate a given rate of parasite replication, ρ, below which it suffers no damage.

Above this level, virulence increases at the same constant rate that occurs in non-tolerant hosts, such that $\alpha = 0$ for $\varepsilon \leq \rho$, and $\alpha = \alpha(\varepsilon) = (\varepsilon - \rho)v_W$ for $\varepsilon \geq \rho$ (Fig. 4.1A). Type II (constant) tolerance reduces virulence by a constant factor across the range of parasite growth rates, such that $\alpha = \alpha(\varepsilon) = \varepsilon v_T$ where $v_T < v_W$ (Fig. 4.1B). Type III (saturating) tolerance causes virulence to increase at a non-linear rate. This form is able to ameliorate host damage well at lower rates of replication, but is less effective at higher rates, which swamp the tolerance mechanism. I assume the relationship $\alpha = \alpha(\varepsilon) = v_W m(\varepsilon/m)^a$, where $a \geq 1$ and there is a maximum rate of replication (m) attainable by the pathogen (Fig. 4.1C). For all three forms, tolerant host genotypes pay a cost in terms of a reduction in their intrinsic growth rate (r is a decreasing function of tolerance).

In line with previous work, transmission is assumed to be a bounded increasing function of parasite replication rate (Anderson and May 1982; van Baalen and Sabelis 1995; Restif and Koella 2003):

$$\beta = \beta(\varepsilon) = \frac{K\varepsilon}{\varepsilon + \eta} \tag{4.3}$$

Transmission and virulence are therefore traded-off from the point of view of the parasite. The parameter K gives the upper bound of the transmission rate, and η measures the rate at which transmission approaches this upper bound as ε increases (smaller values of η correspond to faster rates of saturation). Tolerance reduces the virulence that a particular growth rate causes but does not affect the transmission rate.

I investigate how the parasite is selected in response to the different forms of tolerance, compared to a wild host. The evolutionarily stable (ES) parasite replication rate ε^* (Figs. 4.1, 4.2) and the corresponding level of virulence α (Fig. 4.3) are determined.

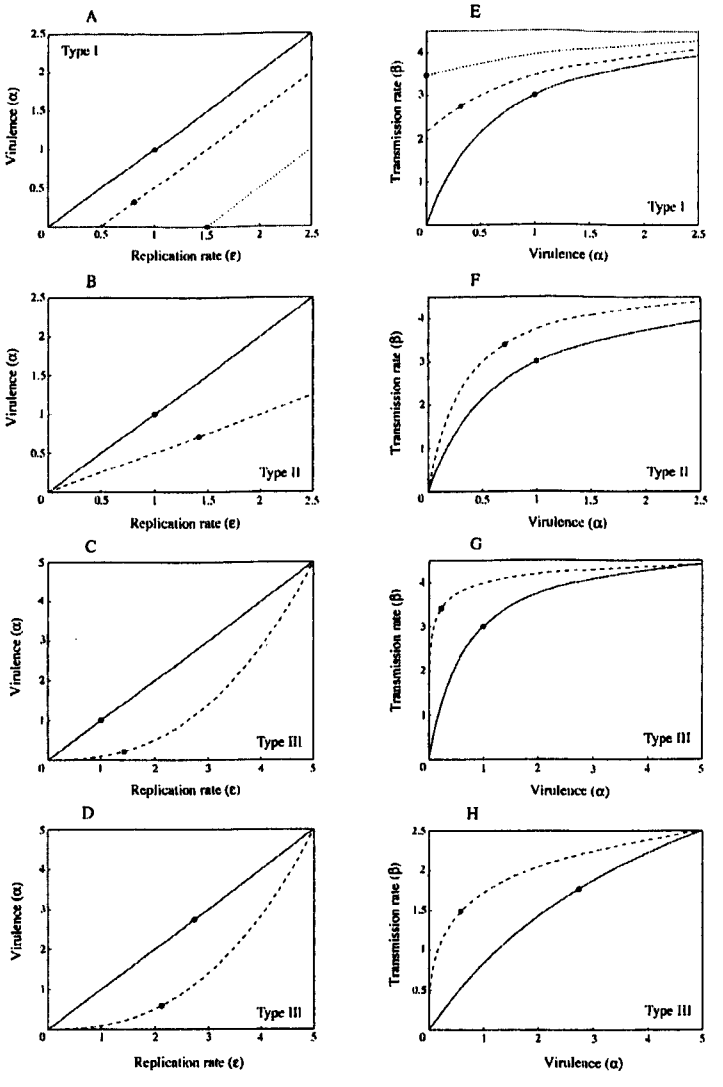

Figure 4.1. Responses for different forms of the tolerance mechanism. The left-hand panels plot virulence (α) as a function of the replication rate (ε); the right-hand panels give the corresponding transmission rate (β) as a function of virulence. The solid lines give the trajectories when the host genotype is wild. Filled circles denote the ES replication rate, virulence and transmission. Type I: (A), (E) the tolerant host is characterized by $\rho = 0.5$ (dashed line), $\rho = 1.5$ (dotted line). Type II: (B), (F) the tolerant host is characterized by $v_T = 0.5$ (dashed line). Type III: (C), (D), (G), (H) the tolerant host is characterized by $a = 2.5$ (dashed line). In all cases $\eta = 2/3$, except in (D), (H) where there is a higher rate of saturation, $\eta = 5$. Other parameters are: $\gamma = 1$, $b = 0.5$, $K = 5$, $v_W = 1$ and $m = 5$ (type III).

I then consider the epidemiology when a tolerant host replaces the wild type in two scenarios: one in which the parasite replication rate remains fixed (at the wild type rate ε_W^*) and one in which the replication rate evolves to its new optimum (ε_T^*). The epidemiology is described by the prevalence of infection (Fig. 4.4), the total number of hosts dying from infection αY^* (Fig. 4.5), and the relative number of hosts dying from infection $\alpha Y^*/H^*$ (Fig. 4.6). This last gives the average mortality due to infection (virulence, α) scaled by the probability that a given individual becomes infected (prevalence, Y^*/H^*).

4-3. Analysis and Results

The evolutionarily stable (ES) parasite strategies are summarized in Table 4.1 and are derived below.

Table 4.1. ES pathogen replication rates for different forms of tolerance

	ES pathogen replication rate ($\varepsilon = \varepsilon^*$)
Wild host	$\sqrt{\eta(\gamma+b)/v_W}$
Type I (complete)	$\sqrt{\eta(\gamma+b-\rho v_W)/v_W}$ if $\rho < \rho_c = \sqrt{\eta(\gamma+b)/v_W + \eta^2/4} - \eta/2$ ρ if $\rho \geq \rho_C$
Type II (constant)	$\sqrt{\eta(\gamma+b)/v_T}$
Type III (saturating)	The optimal strategy, $\varepsilon = \varepsilon^*$, is given by solution of: $\varepsilon(\varepsilon+\eta)av_W(\varepsilon/m)^{a-1} - \eta v_W m(\varepsilon/m)^a = \eta(\gamma+b)$

In the absence of infection, the host population (X) grows until it reaches its carrying capacity, $C = r/q$. This uninfected equilibrium will be invaded by a parasite strain with replication rate ε, if and only if the parasite's reproductive ratio (R_0) is greater than unity. The reproductive ratio is given as (Anderson and May 1981, 1982; van Baalen and Sabelis 1995; Frank 1996):

$$R_0 = \frac{\beta(\varepsilon)C}{\alpha(\varepsilon)+\gamma+b} \tag{4.4}$$

Throughout the analysis it is assumed that $R_0 > 1$ for all parasite strains. The host-parasite interaction with replication rate ε_1 (strain 1) will therefore attain a positive stable equilibrium (X_1^*, Y_1^*), found by equating the right hand side of equations (4.1) and (4.2) to zero. In particular:

$$X_1^* = \frac{(\alpha(\varepsilon_1)+\gamma+b)}{\beta(\varepsilon_1)} \tag{4.5}$$

The evolutionary dynamics of the parasite are determined using invasion analysis, examining whether a parasite strain with a different replication rate ε_2 (strain 2) can invade the resident equilibrium set by strain 1. From equation (4.2), parasite strain 2 can invade if and only if:

$$\beta(\varepsilon_2)X_1^* - (\alpha(\varepsilon_2)+\gamma+b) > 0 \tag{4.6}$$

By direct substitution of X_1^* (using equation (4.5)) into equation (4.6), strain 2 can invade if and only if:

$$\frac{\beta(\varepsilon_2)}{\alpha(\varepsilon_2)+\gamma+b} > \frac{\beta(\varepsilon_1)}{\alpha(\varepsilon_1)+\gamma+b} \tag{4.7}$$

It is clear from equation (4.7) that mutual invadability cannot occur and therefore any strain satisfying (4.7) will replace the resident. Define:

$$S(\varepsilon) = \frac{\beta(\varepsilon)}{\alpha(\varepsilon)+\gamma+b} \tag{4.8}$$

The parasite therefore evolves to maximise $S(\varepsilon)$ and the unique global maximum of $S(\varepsilon)$ is the evolutionarily stable (ES) parasite strategy ε^*. First assume a 'wild type'

host that has not evolved any tolerance. Substituting the functional form for $\alpha(\varepsilon)$ and $\beta(\varepsilon)$ for the wild type host, that has not evolved any tolerance, into (4.8) implies the following:

$$S(\varepsilon) = \frac{\varepsilon K}{(\varepsilon + \eta)(\varepsilon v_W + \gamma + b)} \tag{4.9}$$

Solving $\frac{dS(\varepsilon)}{d\varepsilon} = 0$ gives the ES parasite strategy:

$$\varepsilon_W^* = \sqrt{\eta(\gamma + b)/v_W} \tag{4.10}$$

The corresponding ES virulence is:

$$\alpha_W^* = \varepsilon_W^* v_W = \sqrt{v_W \eta(\gamma + b)} \tag{4.11}$$

The optimal replication rate therefore increases with the recovery rate γ, and the natural death rate b (Lenski and May 1994; van Baalen and Sabelis 1995; Ebert and Mangin 1997; Restif and Koella 2003). Higher rates of loss from the infected class decrease the average duration of infection and therefore diminish the benefit of reduced virulence (van Baalen 1998).

4-3-1. Type I (complete) tolerance

When the tolerance mechanism is complete (type I), the evolution of the parasite depends crucially on the extent to which the host can completely tolerate the parasite's growth rate. The optimal parasite strategy against the tolerant host (ε_T^*) is given as:

$$\varepsilon_T^* = \begin{cases} \sqrt{\eta(\gamma + b - \rho v_W)/v_W} & \text{if} \quad \rho < \rho_c = \sqrt{\eta(\gamma + b)/v_W + \eta^2/4} - \eta/2 \\ \rho & \text{if} \quad \rho \geq \rho_c \end{cases} \tag{4.12}$$

These results are now proved. First consider the case $\varepsilon \leq \rho$, which implies that $\alpha = 0$. From (4.8):

$$S(\varepsilon) = \frac{\varepsilon K}{(\varepsilon+\eta)(\gamma+b)} \quad \Rightarrow \quad \frac{dS(\varepsilon)}{d\varepsilon} = \frac{\eta K}{(\varepsilon+\eta)^2(\gamma+b)} > 0 \tag{4.13}$$

Since $dS(\varepsilon)/d\varepsilon$ is always positive it implies that $S(\varepsilon)$ is an increasing function and so is maximised when $\varepsilon = \rho$. Now consider $\varepsilon > \rho$, where:

$$S(\varepsilon) = \frac{\varepsilon K}{(\varepsilon+\eta)((\varepsilon-\rho)v_W + \gamma + b)} \tag{4.14}$$

This is maximised at ε_T^* (by solving $\frac{dS(\varepsilon)}{d\varepsilon} = 0$) where:

$$\varepsilon_T^* = \sqrt{\eta(\gamma + b - \rho v_W)/v_W} \tag{4.15}$$

Here the condition for the host to have positive density ($X^* > 0$) ensures that ε_T^* is positive. The parasite will evolve to ε_T^* provided $\rho < \varepsilon_T^*$. This requires that:

$$\rho < \rho_C = \sqrt{\eta(\gamma+b)/v_W + \eta^2/4} - \eta/2 \tag{4.16}$$

Substituting for ε_W^* from (4.10) into (4.16) it can be shown that:

$$(\rho_C + \eta/2)^2 = (\varepsilon_w^*)^2 + \eta^2/4 \quad \Rightarrow \quad (\rho_C)^2 + \eta\rho_C = (\varepsilon_w^*)^2 \tag{4.17}$$

Since all parameters are positive this implies $\rho_C < \varepsilon_W^*$. Therefore, if the maximum growth rate the host can completely tolerate is significantly less than that of the ES wild type parasite (such that $\rho \leq \rho_c$), then tolerance selects for reduced parasite replication ($\varepsilon_T^* < \varepsilon_W^*$), with positive but reduced rates of transmission and virulence

(Figs. 4.1A, 4.1E). If $\rho_c < \rho < \varepsilon_W^*$ then a form of apparent commensalism evolves where the ES replication rate falls to the maximum value for which virulence is zero ($\varepsilon_T^* = \rho$). This also corresponds to a reduction in the parasite's transmission rate. If $\rho > \varepsilon_W^*$, again the parasite evolves to the maximum replication rate for which virulence is zero ($\varepsilon_T^* = \rho$) but this is now higher than that of the wild type (Fig. 4.1A). The transmission rate will also be correspondingly higher (Fig. 4.1E).

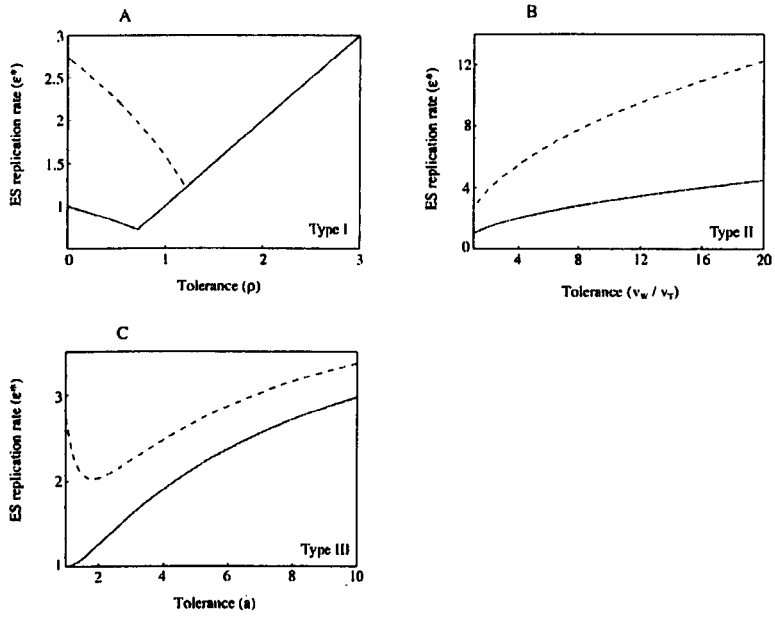

Figure 4.2. ES pathogen replication rate (ε_T^*) as a function of the level of tolerance. The rate at which transmission saturates is varied, such that $\eta = 2/3$, (solid line), $\eta = 5$ (dashed line). Other parameters are: $\gamma = 1$, $b = 0.5$, $K = 5$, $v_W = 1$ and $m = 5$ (type III).

The relationship between tolerance ρ and the ES replication rate ε_T^* is illustrated in Figure 4.2A. The level of virulence (α) experienced by infected hosts is always reduced when a tolerant genotype becomes fixed in the population (Figs. 4.3A, 4.3D).

The evolution of type I tolerance is likely to increase disease prevalence (Figs. 4.4A, 4.4D). This is due, in part, to the lower death rate of infected hosts, which also increases the opportunities for disease transmission (Roy and Kirchner 2000). The reduction in virulence associated with the evolution of tolerance may also reduce the

number of hosts dying from infection αY^* (Fig. 4.5A). However, a reduction in virulence due to tolerance may sometimes result in greater total mortality, particularly if the level of tolerance is low (Fig. 4.5D). This counter-intuitive result can be explained by the following consideration. If the wild type virulence (which is proportional to the parameter η) is relatively low, then the initial prevalence of infection will tend to be high (Fig. 4.4A). The evolution of tolerance therefore generates a relatively small increase in prevalence compared to the reduction in virulence experienced by infected hosts. Thus, the number of infected mortalities is likely to decrease as tolerance increases (Fig. 4.5A). If, however, wild-type virulence is high, initial prevalence will be low and tolerance induces a relatively large increase in prevalence compared to the reduction in virulence (Fig. 4.4D). As a result, there may often be more infected mortalities in response to low tolerance. Mortality always decreases at high tolerance (Fig. 4.5D), where the reduction in virulence is sufficiently large to outweigh the increase in prevalence. If the parasite is selected, the described changes in the epidemiology occur at lower levels of tolerance, due to the evolutionary decrease in virulence. Prevalence increases more rapidly (Figs. 4.4A, 4.4D), and absolute mortality increases at lower levels of tolerance (Fig. 4.5D). When the host evolves complete (type I) tolerance, relative infected mortality is generally lower (Figs. 4.6A, 4.6D). If tolerance also selects the pathogen, there is a greater reduction in virulence (Figs. 4.3A, 4.3D), and also relative mortality. Even in cases where the absolute mortality increases in response to low tolerance (Fig. 4.5D), the relative mortality is still reduced (Fig. 4.6D).

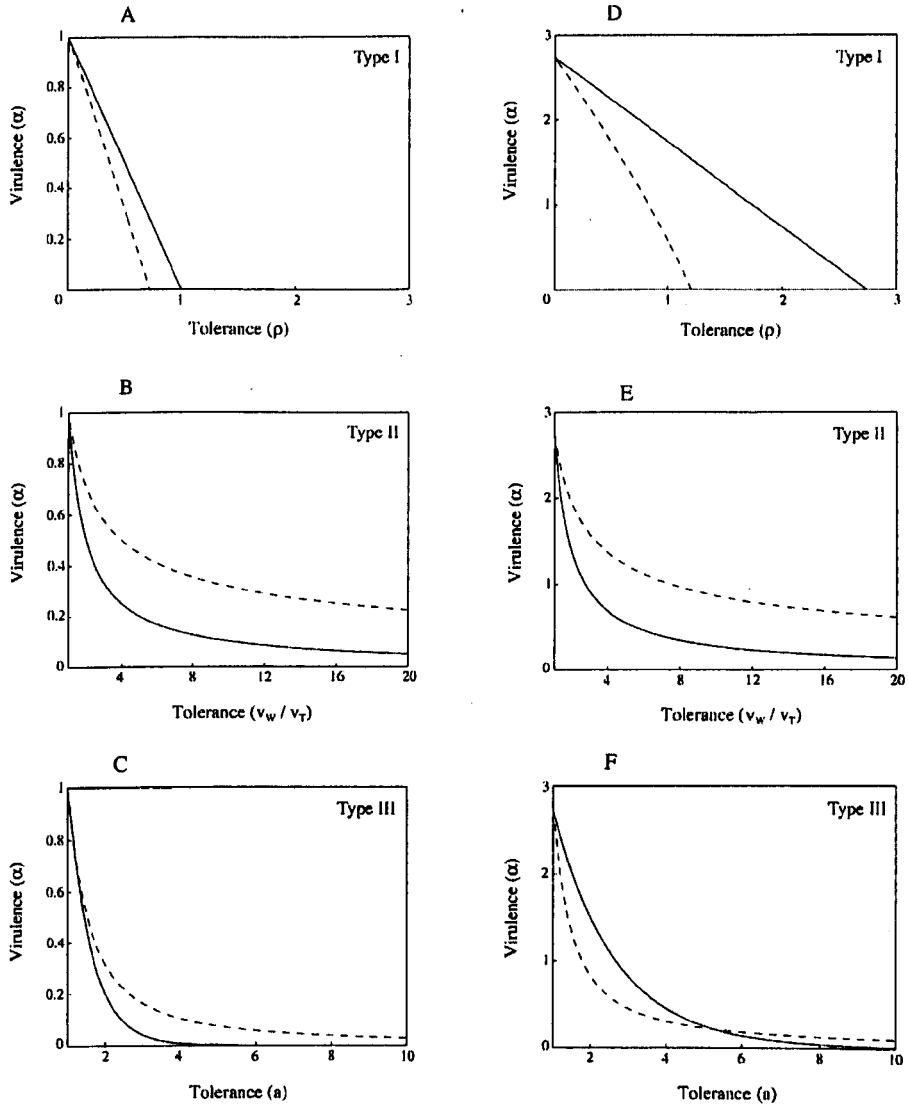

Figure 4.3. Virulence (α) as a function of the level of tolerance. The solid line gives the virulence when the pathogen is wild ($\varepsilon = \varepsilon_W^*$); the dashed line gives the virulence when the pathogen is selected ($\varepsilon = \varepsilon_T^*$). Left-hand panels, (A)-(C): $\eta = 2/3$; right-hand panels, (D)-(F): $\eta = 5$. Tolerance is costly in terms of a reduced intrinsic growth rate such that: $r = 2 - 0.05\rho$ (type I), $r = 2 - 0.05(v_W - v_T)/v_W$ (type II), $r = 2 - 0.05(a - 1)$ (type III). Other parameters are: $q = 0.05$, $\gamma = 1$, $b = 0.5$, $K = 5$, $v_W = 1$ and $m = 5$ (type III).

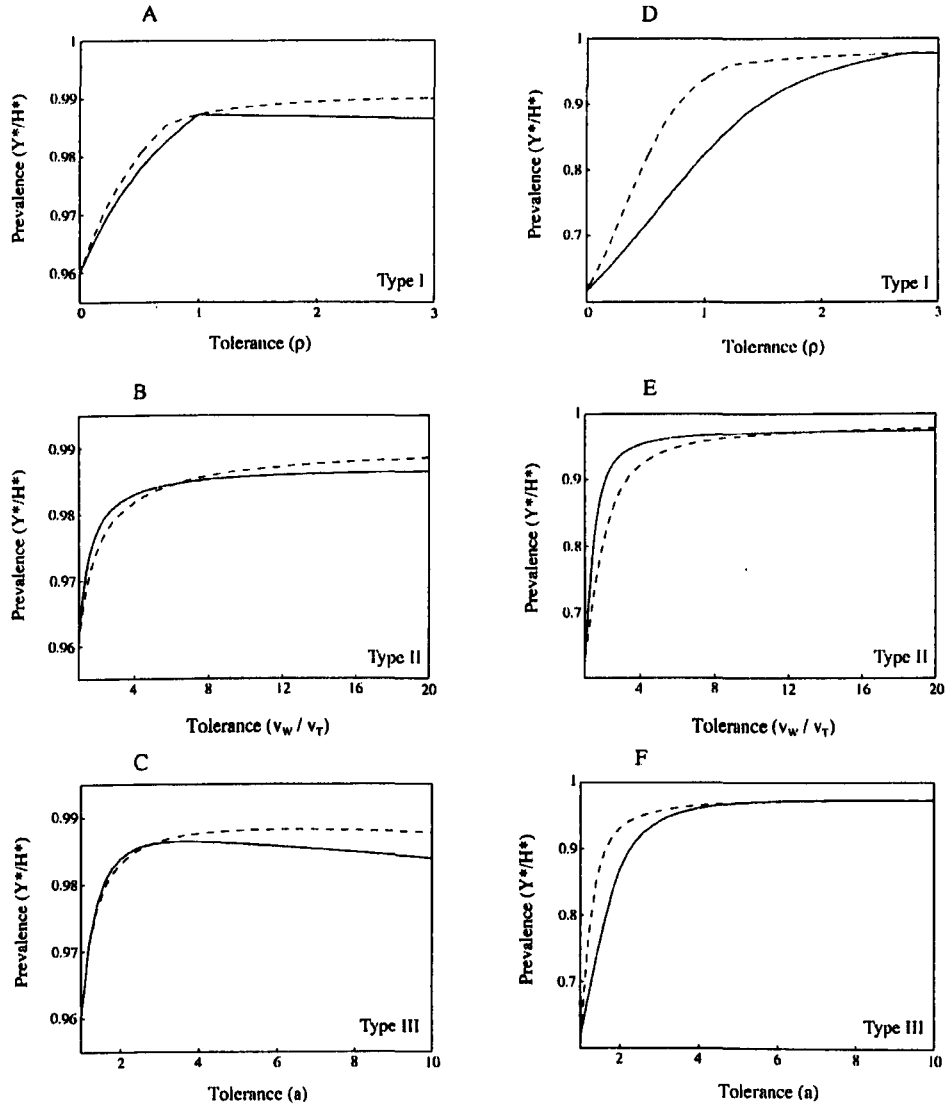

Figure 4.4. Disease prevalence (Y^*/H^*) as a function of the level of tolerance. The solid line gives the prevalence when the pathogen is wild ($\varepsilon = \varepsilon_W^*$); the dashed line gives the prevalence when the pathogen is selected ($\varepsilon = \varepsilon_T^*$). Left-hand panels, (A)-(C): $\eta = 2/3$; right-hand panels, (D)-(F): $\eta = 5$. All other parameters are as in Figure 4.3.

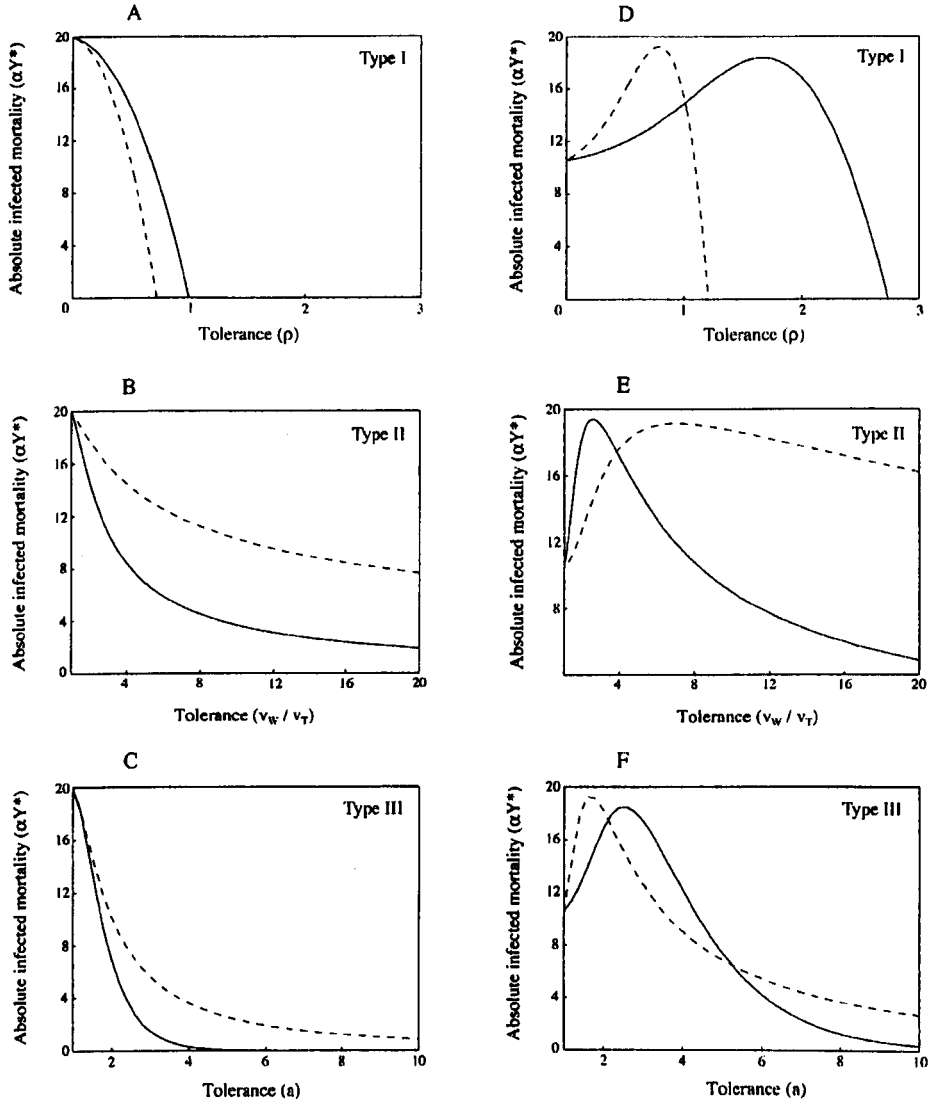

Figure 4.5. Absolute infected mortality (αY^*) as a function of the level of tolerance. The solid line gives mortality when the pathogen is wild ($\varepsilon = \varepsilon_W^*$); the dashed line gives mortality when the pathogen is selected ($\varepsilon = \varepsilon_T^*$). Left-hand panels, (A)-(C): $\eta = 2/3$; right-hand panels, (D)-(F): $\eta = 5$.All other parameters are as in Figure 4.3.

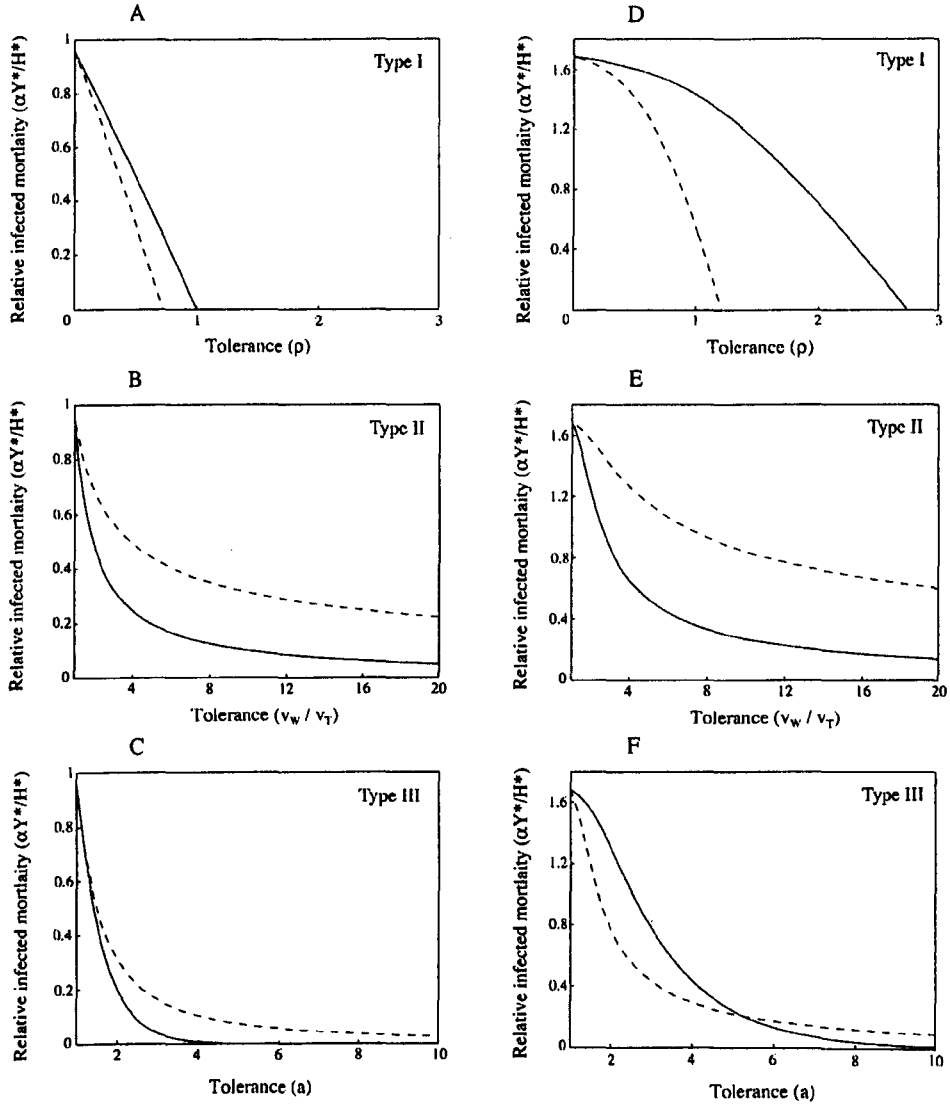

Figure 4.6. Relative infected mortality ($\alpha Y^*/H^*$) as a function of the level of tolerance. The solid line gives mortality when the pathogen is wild ($\varepsilon = \varepsilon_W^*$); the dashed line gives mortality when the pathogen is selected ($\varepsilon = \varepsilon_T^*$). Left-hand panels, (A)-(C): $\eta = 2/3$; right-hand panels, (D)-(F): $\eta = 5$ All other parameters are as in Figure 4.3.

4-3-2. Type II (constant) tolerance

Where tolerance manifests as a constant (type II) reduction in virulence, the optimal parasite replication rate is obtained by replacing ν_W with ν_T in (4.9)-(4.10):

$$\varepsilon_T^* = \sqrt{\eta(\gamma + b)/\nu_T} \tag{4.18}$$

The corresponding ES virulence is:

$$\alpha_T^* = \nu_T \varepsilon_T^* = \sqrt{\nu_T \eta(\gamma + b)} \tag{4.19}$$

Fixation of the tolerant genotype increases the ES replication rate (since $\nu_T < \nu_W$). Faced with a more robust host, the cost of a given level of replication in terms of virulence is reduced and this selects for higher parasite replication and transmission rates (Figs. 4.1B, 4.1F, 4.2B). The increase in replication rate (compared to ε_W^*) corresponds to an evolutionary increase in virulence and this reduces some of the benefit conferred by the tolerance mechanism. However, the level of virulence experienced by the tolerant host is always less than that of the wild type (compare equations (4.11) and (4.19); Figs. 4.3B, 4.3E).

Prevalence is likely to be higher in response to type II tolerance (Figs. 4.4B, 4.4E). If the parasite is selected, prevalence may increase less rapidly (Figs. 4.4B, 4.4E). This is not necessarily the case at high tolerance, where pathogen evolution may increase prevalence still further (Fig. 4.4B). Fixation of a tolerant genotype will often reduce total mortality (αY^*), particularly at low initial virulence (Fig. 4.5B). Alternatively, mortality may increase if the initial virulence is high. Indeed, if the pathogen evolves then mortality may be considerably higher, even at high tolerance (Fig. 4.5E). This result notwithstanding, tolerance is likely to reduce relative mortality ($\alpha Y^*/H^*$). The decrease is always less when the pathogen is selected, due to the higher replication rate and virulence (Figs. 4.6B, 4.6E). Extensive computer simulations suggest that relative mortality is generally reduced by type II tolerance,

although it may increase if the parameter η is sufficiently large. For extremely large η, even a highly tolerant population may experience greater relative mortality when the pathogen is selected.

4-3-3. Type III (saturating) tolerance

In this case numerical simulations were used to determine the optimal parasite strategy. This is given by the value $\varepsilon = \varepsilon_T^*$ satisfying:

$$\varepsilon(\varepsilon+\eta)av_W(\varepsilon/m)^{a-1} - \eta v_W m(\varepsilon/m)^a = \eta(\gamma+b) \qquad (4.20)$$

The evolution of saturating tolerance may select for either higher or lower parasite replication rates, compared to a wild type host. The parameter η strongly influences the evolutionary outcome. When η is small, transmission saturates relatively quickly and tolerance generally selects for increased replication and transmission rates (Fig. 4.1C, 4.1G, 4.2C). This eliminates some of the benefit of tolerance in terms of reduced virulence but never increases virulence above the level experienced by the wild host (Fig. 4.3C). At larger values of η, tolerance may select for either increased or decreased replication rates. Slower replicating pathogens are more likely to be selected if the tolerance mechanism is weak (Figs. 4.1D, 4.2C); this will lower the transmission rate (Fig. 4.1H), and further reduce virulence (Fig. 4.3F). High levels of tolerance are always likely to select for more exploitative pathogens (Fig. 4.2C). Computer simulations also suggest that when v_W is large, tolerance is more likely to select for faster replicating pathogens.

As with the previous two forms, saturating tolerance generally increases prevalence (Figs. 4.4C, 4.4F). If the pathogen evolves a lower replication rate, the increase in prevalence will be greater (Fig. 4.4F). When initial virulence is low, the evolution of tolerance generally reduces absolute infected mortality αY^* (Fig. 4.5C). At higher initial virulence, low levels of tolerance may result in greater absolute mortality (Fig. 4.5F). More efficient tolerance mechanisms are likely to reduce

absolute mortality (Fig. 4.5F), where the reduction in virulence outweighs the increase in prevalence. These same results are obtained when the pathogen is selected, although the extent of the increase/decrease in mortality depends on whether the evolved replication rate (ε_T^*) is higher or lower than the wild type (ε_W^*), and on the balance between prevalence and virulence in terms of their effect on mortality (Fig. 4.5F). Saturating tolerance is likely to reduce the relative infected mortality ($\alpha Y^*/H^*$), whether or not absolute mortality (αY^*) increases or decreases (Figs. 4.6C, 4.6F). If the pathogen is selected to increase (decrease) its replication rate then the reduction in mortality is less (more) pronounced (Fig. 4.6C).

To summarise the epidemiological effects, the evolution of host tolerance generally increases disease prevalence (Fig. 4.4). Consequently, the number of pathogen-induced deaths (αY^*) may actually increase, if the tolerance mechanism is weak and the initial virulence (α_W^*) is high (Figs. 4.5D-4.5F). When the wild host experiences less severe virulence, tolerance is more likely to reduce absolute mortality (Figs. 4.5A-4.5C). A high degree of tolerance always results in less absolute mortality, unless the mechanism is constant (type II) and the wild virulence (α_W^*) is high (Fig. 4.5E). The relative mortality due to infection ($\alpha Y^*/H^*$) is generally lower in tolerant populations (Fig. 4.6). An exception to this may occur with constant (type II) tolerance: if transmission saturates particularly slowly then pathogen evolution may result in greater relative mortality, even at high tolerance.

4-4. Discussion

The evolution of tolerance in hosts may act as an important selective pressure on parasites. The evolutionary outcome has been shown to be dependent on the nature of the tolerance mechanism. When tolerance reduces death rate by a constant factor (type II), this always selects for higher parasite replication rates. This is a somewhat intuitive result: the parasite responds to tolerance due to its ability to gain more transmission without paying as large a cost in terms of host mortality. However, the post-selection parasite-induced death rate never reaches the level prior to the evolution of the tolerance mechanism, implying that some of the benefit of tolerance is lost, but not all of it. Since tolerance increases prevalence there is also the possibility that it leads to greater total mortality in the population. Whether absolute mortality increases or decreases will depend not only on the degree of tolerance that evolves, but also the initial virulence of the pathogen in wild hosts. However, even if the number of deaths due to infection increases, the relative chance of any individual in the population dying of infection will probably be less.

When a tolerance mechanism evolves that is able to completely compensate for the damage the parasite causes at particular growth rates, there is the possibility of evolution from parasitism to commensalism. This is always the outcome if the natural, 'wild' parasite growth rate can be completely tolerated. Furthermore, if parasite strains with a higher growth rate than that of the ES wild type can be completely tolerated, the parasite will evolve to this higher growth rate, leading not only to commensalism, but also a higher level of transmission. Less intuitively, commensalism can also evolve if the level of complete tolerance is less than but relatively close to the natural ES growth rate. The parasite evolves to reduce its growth rate to the level that can be completely tolerated. In this case, transmission rate is reduced, although prevalence still increases. Complete (type I) tolerance therefore potentially selects for a parasite strain that causes no virulence, although this is not always the outcome. If the parasite growth rate that can be completely tolerated is significantly below that of the wild parasite, commensalism will not evolve. It should be noted that when commensalism does evolve, the resulting

commensal's growth rate within the host is still constrained by the transmission/virulence trade-off. The distinction between commensal and parasitic, in many groups of microorganisms in particular, is often far from clear-cut. Species considered 'commensal' may therefore be on the edge of parasitism with some strains causing damage to their hosts. Furthermore, when commensalism evolves through tolerance mechanisms in the host, there is likely to be a cost for the host. Once established, this 'apparent commensalism' shows no evidence of this evolutionary cost. It is interesting to speculate how many seemingly commensal interactions in nature have been bought at an evolutionary cost to the host. In such interactions, the removal of the 'commensal' may lead to benefits for the host if evolution selects against the redundant tolerance mechanism.

Saturating (type III) tolerance is similar to complete tolerance in that the mechanism is particularly efficient at tolerating relatively low replication rates. Indeed, the evolutionary dynamics are often similar. Low levels of tolerance may select for reduced parasite replication, although evolution to complete commensalism does not occur. That being said, interactions with parasite strains that cause very little virulence to their hosts may often evolve. Given the difficulty in measuring costs to parasites in the wild, such low levels of virulence may often not be detected. Saturating tolerance mechanisms may also therefore lead to the evolution of interactions that are thought to be commensal. Again these interactions will be characterised by high disease prevalence and as such they are likely to be relatively stable.

Consequently, the evolution of host tolerance may be partly responsible for the ubiquity of parasites in nature. Roy and Kirchner (2000) have pointed out that since tolerance leads to higher prevalence of the parasite, it more easily allows their persistence. My results lend support to this idea because, although the parasite increases its growth rate and transmission in the face of tolerance, it never attains the level of virulence prior to the evolution of tolerance. Individual selection for the evolution of tolerance, its tendency to become fixed in populations, and the subsequent individual selection on the parasite may have had important effects on

shaping natural communities. Parasites are ubiquitous in nature and tolerance in their hosts may therefore have contributed to this.

Tolerance is most often implicated in plant host-natural enemy interactions. The implications of tolerance to herbivores have received considerable theoretical and empirical attention (Fineblum and Rausher 1995; Mauricio et al. 1997; Strauss and Agrawal 1999; Tiffin and Rausher 1999; Tiffin 2000). Tolerance in plants to infectious organisms is also being increasingly considered in both crop (Zuckerman et al. 1997; Schurch and Roy 2004) and model systems (Simms and Triplett 1994; Kover and Schaal 2002). Although there is some issue with definitions, there is an increasing awareness that tolerance rather than other resistance mechanisms is most important in a number of host-parasite interactions. Schurch and Roy (2004) have suggested that tolerance may be non-linear and more likely to operate at low virulence. They note that in such cases, there may be no clear relationship between pathogen growth and host damage, since the deleterious effects of less virulent pathogens are ameliorated while virulent strains inflict significant fitness losses to the host. This resembles saturating (type III) tolerance according to my definitions. Given that pathogens may evolve lower replication rates in the face of such tolerance, this may be responsible for maintaining low virulence in such interactions.

The selective pressures caused by tolerance are different from those of resistance mechanisms that reduce the reproductive rate of the parasite. Understanding whether any response to infectious organisms is tolerance or another form of resistance is therefore vital if the final outcome of evolution is to be predicted. Tolerance mechanisms have received relatively little attention in animal-parasite interactions. Various forms of resistance are generally implicated in both the innate and acquired immune systems (Rolff and Siva-Jothy 2003). Whether tolerance mechanisms in animals really are rare remains to be determined and due to the importance of selection on parasites, it is a priority area.

There is growing interest in the use of parasite-tolerant crop plants as alternatives to chemical control. This study emphasizes it is important to consider

selection on the target parasites. Their evolution may lead to higher disease prevalence with lower, but still significant damage to the host. High levels of tolerance are more likely to be successful at reducing absolute mortality. Perfect or very high levels of tolerance should therefore ideally be achieved before the widespread use of tolerant crops, in order to reduce the problems of selection on the parasites. There may still be concerns, however, if the tolerance mechanism is constant (type II). If pathogen damage is measured as the individual risk of dying from infection (relative infected mortality), problems appear less likely. However, if the tolerance mechanism is constant in response to a wide range of parasite growth rates, then pathogen evolution may result in greater prevalence and mortality even in highly tolerant populations.

This model assumes only single infections. However, infected hosts may often harbour more than one parasite strain simultaneously. Models generally predict that multiple infection will select for higher virulence and the coexistence of multiple parasite strains (Bremermann and Pickering 1983; Frank 1992a, 1994, 1996; May and Nowak 1994, 1995; Nowak and May 1994; van Baalen and Sabelis 1995; Mosquera and Adler 1998). There has been relatively little work on host-parasite coevolution with the assumption of multiple infections. However, Gandon et al. (2002a) have shown that reducing the force of transmission may select for lower virulence by reducing the level of competition between parasite strains. Indeed, any mechanism (of the host or otherwise) affecting the probability of multiple infections will indirectly influence the evolution of virulence (Gandon et al. 2002a). Since tolerance is likely to increase disease prevalence (Roy and Kirchner 2000) it may also increase the level of competition between parasite strains. Assuming within-host exploitation rates are positively correlated with competitiveness, this would select for increased virulence. This is perhaps particularly important in the case of type II (constant) tolerance, where virulence might be restored to (or exceed) its pre-tolerance level. If instead, within-host competition (and virulence) is negatively correlated with host exploitation (Chao et al. 2000), by increasing the level of infection in the population, tolerance may conceivably select for reduced virulence. In super-infecting parasites, where the more virulent strains are more likely to be transmitted (Nowak and May

1994; Mosquera and Adler 1998), the evolution of reduced exploitation rates (type I and III tolerance) may well be constrained, as less exploitative parasites are selected against. These conclusions are however somewhat speculative and future work on the evolution of parasites in response to tolerance should consider the role of multiple infections in detail.

This chapter has shown how tolerance can select parasites to increase their replication rate within the host. Tolerance may only evolve in particular local populations of hosts. The implications for non-tolerant hosts coming into contact with a parasite that has evolved in response to tolerance in another population may be severe. Type II (constant) tolerance always selects for more exploitative parasites. The levels of virulence experienced by intolerant hosts exposed to an evolved pathogen may therefore be significantly higher than those optimal for the pathogen, and intolerant populations may suffer catastrophic levels of mortality. There are also problems when tolerance results in apparent commensalism. As demonstrated, commensal strains may have evolved higher replication and transmission rates. Intolerant hosts coming into contact with an evolved parasite would again experience high levels of virulence and transmissibility. The emergence of disease from seemingly commensal organisms may therefore occur without changes in the parasite, but due to a lack of tolerance mechanisms in new host populations.

I have emphasised how tolerance mechanisms may have important implications to the life histories of parasites and pathogens. Tolerance has not been greatly researched in animal-parasite interactions, but may have been important in shaping their community structure. The form of the tolerance mechanism has been shown to determine the selective pressure acting on parasites. A mechanistic understanding of tolerance is vital in order to understand its role in natural host-parasite and seemingly commensal interactions.

5. Disease dynamics under combined frequency-dependent and density-dependent transmission

5-1. Introduction

Theoretical models generally model disease transmission using one of two forms. In the first case, transmission is assumed to be 'density-dependent' and to be directly proportional to the density of infecteds in the population. This type of transmission is represented by the term βSI (McCallum et al. 2001; Begon et al. 2002). Here S is the density of susceptible hosts, I is the density of infecteds, and β denotes the probability of an infectious contact (i.e. the probability of a contact between an infected and a susceptible host, multiplied by the probability that an infection occurs). This form of transmission function is generally used to describe 'ordinary infectious diseases' (OIDs), since in these cases transmission is likely to be proportional to the density of infecteds. In contrast, transmission is often assumed to be 'frequency-dependent' and to depend on the proportion of contacts that are with infected hosts. This type of transmission is represented by the term $\beta SI/N$, where $S + I = N$ gives the total density (McCallum et al. 2001; Begon et al. 2002). As such, frequency-dependent transmission is more suitable for modelling the transmission dynamics of sexually transmitted diseases (STDs), since sexual contact rate is assumed to remain roughly constant as density changes (Getz and Pickering 1983; Antonovics et al. 1995). Vector-transmitted diseases may also follow frequency-dependent transmission, because relatively large vector populations and vector biting behaviour may compensate for changes in host density (Antonovics et al. 1995).

The assumptions of frequency- and density-dependent transmission lead to different theoretical predictions. Firstly, density-dependent transmission requires that the host density exceed a certain threshold before the pathogen is able to persist (Anderson and May 1981). In contrast, disease persistence under frequency-dependent transmission requires only a sufficiently large transmission rate (Getz and Pickering 1983; Thrall et al. 1995). This leads to the prediction that frequency-dependent diseases may be able to persist at lower population densities than density-dependent ones. Secondly, frequency-dependent transmission has the potential to cause extinction of the host population (Getz and Pickering 1983; Alexander and Antonovics 1988). Deterministic host extinction does not occur under density-

dependent transmission (Anderson and May 1981; Antonovics et al. 1995; Lockhart et al. 1996). The conditions promoting stable coexistence are generally thought to be more stringent under frequency-dependent transmission. In particular, host-parasite coexistence requires that the host population be regulated by some factor apart from the disease, such as a density-dependent birth rate (Getz and Pickering 1983; Thrall et al. 1993).

In natural populations, disease transmission often does not strictly conform to either pure frequency- or density-dependence. The transmission of OIDs may be partly frequency-dependent, if organisms live in defined social and family groups (Begon et al. 1999), or in rare, solitary species, where sexual contact provides the main opportunity for transmission (Lockhart et al. 1996). Similarly, density-dependent transmission may also influence STD dynamics (Antonovics et al. 1995; Thrall et al. 1995; Lockhart et al. 1996; Thrall et al. 1998; McCallum et al. 2001; Begon et al. 2002). Ryder et al. (2005) recently demonstrated experimentally that host population density may have a strong influence on STD transmission in *Adalia bipunctata* ladybirds. Among vertebrate groups such as birds, a number of studies have reported increases in the rate of extra-pair copulation with population density; density-dependent variation in sexual contact rate also seems to be commonplace among invertebrates (Ryder et al. 2005).

Therefore, whilst it may be convenient to characterize diseases as having either purely frequency- or purely density-dependent transmission dynamics, this simple view is challenged by the biology of many natural systems. Given that STD transmission probably often diverges from pure frequency-dependence, and that the transmission of OIDs may often be partly frequency-dependent, it is important to consider the implications for disease dynamics. In this chapter, the dynamical implications of incorporating varying amounts of frequency- and density-dependence into a single model are considered. In particular, I investigate the implications in terms of disease persistence, parasite-driven extinction and host-parasite coexistence. I present two variations of a novel form of transmission function, which allows the

level of frequency- and density-dependence to be varied either independently (model I) or together (model II).

5-2. Frequency- and density-dependence vary independently

5-2-1. Model and analysis

First consider a situation where the dynamics are described by the following equations:

$$\frac{dX}{dt} = (b - hN)N - \frac{v(c + mN)XY}{N} - uX \tag{5.1}$$

$$\frac{dY}{dt} = \frac{v(c + mN)XY}{N} - (u + \alpha)Y \tag{5.2}$$

It is assumed that infected (Y) and susceptible (X) hosts consume resources at the same rate and that infected individuals can reproduce. The total density of hosts is $N = X + Y$, the birth and natural death rates are b and u respectively, α is the rate of disease-induced mortality (i.e. virulence), v is the probability that an encounter between a susceptible and an infected host results in infection, and h is a coefficient of density-dependent host regulation. The carrying capacity is given by $K = r/h$, where $r = b - u$ is the intrinsic growth rate of the host population. There is no recovery from infection, and all parameters are assumed to be positive.

In equations (5.1)–(5.2) the term representing the rate of transfer from the susceptible to the infected class is:

$$\frac{v(c + mN)XY}{N} \tag{5.3}$$

The parameters c and m determine the amount of frequency- and density-dependent transmission, respectively. Disease transmission therefore has a frequency-dependent

component, $vcXY/N$ (where the term vc equates to the commonly used transmission coefficient in a frequency-dependent framework), and a density-dependent component, $vmXY$ (with vm equating to the transmission coefficient in a density dependent-dependent framework). This formulation is appropriate because it is the probability of infection, v, that remains common for both frequency- and density-dependent transmission, and not the transmission coefficient (Begon et al. 2002). Assuming $c > 0$, transmission approaches complete frequency-dependence as $m \to 0$, and assuming $m > 0$, transmission approaches complete density-dependence as $c \to 0$.

To simplify the analysis, I make the substitutions $N = X + Y$ and $p = Y/N$. The equations can then be rewritten in terms of the total host density (N) and the prevalence of infection (p):

$$\frac{dN}{dt} = (b - hN)N - uN - \alpha pN \tag{5.4}$$

$$\frac{dp}{dt} = p[v(c + mN)(1 - p) - (b - hN) - \alpha(1 - p)] \tag{5.5}$$

As will be shown, this substitution allows a more intuitive explanation of the equilibrium states.

There are four equilibrium solutions of equations (5.4)–(5.5). Taking the variables in the order (N, p), the equilibria are $(0,0)$, $(N_K, 0)$, $(0, \rho_E)$ and (N^*, p^*). The relevance and stability of the equilibrium values are determined.

(i) The trivial equilibrium, (0,0) has Jacobian matrix:

$$\begin{pmatrix} b - u & 0 \\ 0 & -b - \alpha + cv \end{pmatrix} \tag{5.6}$$

Assuming the birth rate (b) exceeds the natural death rate (u), the eigenvalue $\lambda_1 = b - u$ will be positive and the equilibrium is unstable. Throughout the analysis, it is assumed that this is always the case.

(ii) At the disease-free equilibrium $(N_K, 0)$, the population reaches its carrying capacity, $N_K = (b-u)/h$. The associated Jacobian matrix is:

$$\begin{pmatrix} -b+u & \dfrac{(-b+u)\alpha}{h} \\ 0 & -u-\alpha+\left(c+\dfrac{m(b-u)}{h}\right)v \end{pmatrix} \tag{5.7}$$

The first eigenvalue, $\lambda_1 = -b+u$, is always negative for positive parameters. Stability therefore depends upon the other eigenvalue, $\lambda_2 = -u-\alpha+\left(c+m(b-u)/h\right)v$, having negative sign. This condition can be expressed as:

$$v < \frac{u+\alpha}{c+(m(b-u)/h)} = v_t \tag{5.8}$$

Thus, if $v > v_t$ then the parasite is able to invade the uninfected host population, while a disease-free equilibrium requires that $v < v_t$. From (5.8), the persistence threshold increases with virulence (α). More virulent diseases require a higher probability of infection to be able to persist in the population.

(iii) At the third equilibrium state $(0, \rho_E)$, the parasite drives the host to extinction. The equilibrium is defined by $N = 0$ and $p_E = 1 - b/(vc-\alpha)$, and is feasible provided:

$$vc > b+\alpha \tag{5.9}$$

The associated Jacobian matrix is:

$$\begin{pmatrix} \cdot & -u-\alpha+\dfrac{bcv}{-\alpha+cv} & 0 \\ \left(1+\dfrac{b}{\alpha-cv}\right)\left(h+\dfrac{bmv}{-\alpha+cv}\right) & & b+\alpha-cv \end{pmatrix} \tag{5.10}$$

The second eigenvalue is given by $\lambda_2 = (b+\alpha)-cv$, which is negative provided the relevance criterion (5.9) is satisfied. The other eigenvalue is $\lambda_1 = -u-\alpha+bcv/(-\alpha+cv)$. The condition for a stable equilibrium can therefore be expressed as:

$$v > \frac{\alpha(u+\alpha)}{c(\alpha-b+u)} = v_c \tag{5.11}$$

Note that (5.11) requires that $\alpha > b-u = r$. Below this level of virulence, there is no possibility of extinction, since births outweigh deaths. Above this level, there is a non-monotonic relationship between virulence (α) and the infection probability (v) required to cause extinction. Thus, at low virulence, reproduction from infecteds provides a mechanism that reduces the cost of parasitism, and extinction can only occur if the infection probability is high. Extremely virulent parasites are also unlikely to cause extinction, because here infected hosts die very rapidly, which reduces the opportunities for transmission. It can be shown analytically that if infecteds are unable to reproduce, the threshold for persistence (5.8) is unchanged, but that the condition for stability of the extinction equilibrium reduces to the relevance criterion (5.9). This result is analogous to that obtained for a purely frequency-dependent model: allowing reproduction from infected individuals reduces the probability of extinction (Boots and Sasaki 2003).

(iv) The endemic (coexistence) equilibrium (N^*, p^*) is defined by:

$$N^* = \frac{-\Phi_c + \sqrt{\Phi_c^{\,2} + 4vmh\theta_c}}{2vmh}, \quad p^* = \frac{\Phi_I - \sqrt{\Phi_I^{\,2} - 4vm\alpha\theta_I}}{2vm\alpha} \tag{5.12}$$

Here $\Phi_c = v(ch + m\alpha - m(b-u))$, $\Phi_t = v(ch + m\alpha + m(b-u))$,
$\theta_c = vcb - vcu + \alpha(\alpha + u) - vc\alpha$ and $\theta_t = vch - h\alpha + vmb - vmu - uh$.
Assuming $r = b - u > 0$ it is known that $\Phi_t > 0$. Therefore $p^* > 0$ requires $\theta_t > 0$, which is the same as $v > v_t$ (see (5.8)). To obtain $N^* > 0$ there are two possibilities. If $\alpha > r$ then $\Phi_c > 0$ and $\theta_c > 0$ is required, which is the same as $v < v_c$ (see (5.11)). If $\alpha < r$ then $\theta_c > 0$ is always true and so $N^* > 0$. The coexistence equilibrium is therefore feasible if:

$$v_t < v < v_c \tag{5.13}$$

The associated Jacobian matrix is:

$$\begin{pmatrix} -hN^* & -\alpha N^* \\ p^*(vm(1-p^*) + h & -p^* v(c + mN^*) + \alpha p^* \end{pmatrix} \tag{5.14}$$

It can be shown that this matrix has negative trace and positive determinant, provided $0 < N^* < N_k$ and $0 < p^* < 1$. Thus, whenever the equilibrium (N^*, p^*) is feasible it is also stable. This requires that $v_t < v < v_c$.

These results are illustrated in Figure 5.1, in which the (v, α) parameter space is partitioned into regions where the three outcomes occur. The equilibrium regions are delineated by two thresholds in infection probability, v_t and v_c(see (5.8) and (5.11)). The lower threshold (v_t) delineates the boundary between the disease-free and endemic regions. The upper threshold (v_c) delineates the boundary between the endemic and extinction regions.

I consider the effect of independently varying the amount of frequency- and density-dependence, by allowing the values of c and m to vary. Figures 5.1A-5.1C show the effect of varying m whilst c is held constant. Conversely, Figures 5.1C-5.1E show the effect of varying c whilst m is held constant.

5-2-2. Probability of Disease Persistence

Increasing m from 0 to 10, with c fixed at 10 (i.e. moving from complete frequency-dependence to both frequency- and density-dependence), has the effect of increasing the size of the endemic region at the expense of the disease-free parameter space (Figs. 5.1A-5.1C). Thus, as the relative importance of density-dependent transmission is increased, disease persistence becomes possible at lower infection probabilities for a given level of virulence. Moving from complete density-dependence (Fig. 5.1E) to both frequency- and density-dependence (Fig. 5.1C) (increasing c from 0 to 10, with m fixed at 10) reduces the size of the disease-free region and therefore disease persistence occurs at lower infection probabilities.

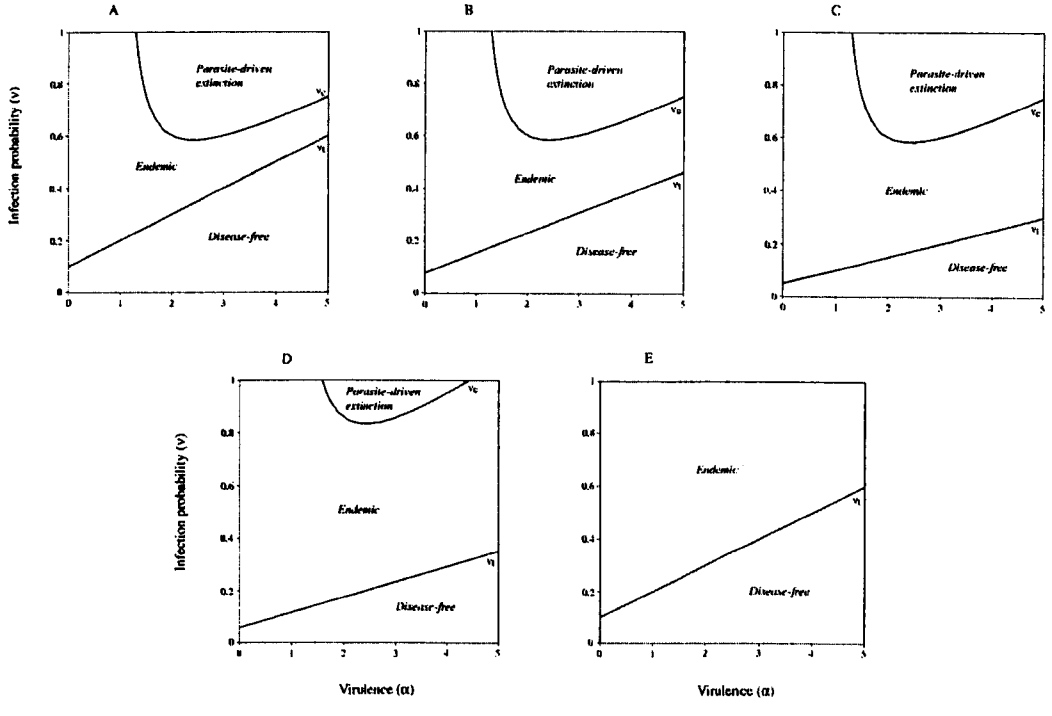

Figure 5.1. (Model I) Outcomes in (v, α) parameter space for different levels of frequency- and density-dependence: (A) $m = 0$, $c = 10$; (B) $m = 3$, $c = 10$; (C) $m = c = 10$; (D) $m = 10$, $c = 7$; (E) $m = 10$, $c = 0$. The other parameters are: $b = 2$, $u = 1$ and $h = 1$. The carrying capacity is $N_K = 1$.

5-2-3. Probability of Parasite-driven Extinction

The boundary of the parasite-driven host extinction region is unaffected by variation in m: increasing the amount of density-dependence does not affect this equilibrium (Figs. 5.1A-5.1C). In contrast, both the existence and size of the parasite-driven extinction region depends on c. When $c = 0$ (pure density-dependence, with $m = 10$), parasite-driven extinction cannot occur and the endemic region is unbounded for increasing values of ν (Fig. 5.1E). When a component of frequency-dependence is introduced, parasite-driven extinction becomes possible at high infection probability (Fig. 5.1D). Further increases in c lower the upper boundary of the endemic region, making extinction possible for a lower infection probability (Fig. 5.1C).

5-2-4. Probability of Endemic Persistence

Higher levels of density-dependent transmission always increase the probability of endemic persistence by lowering the boundary between the endemic and disease-free regions in (ν,α) parameter space. In contrast, higher levels of frequency-dependent transmission generally reduce the probability of endemic persistence, by lowering the boundary between the endemic and parasite-driven extinction regions. Figure 5.2 summarizes these results by plotting the disease-free, endemic and parasite-driven host extinction regions in (m,c) parameter space. As the value of m increases, the endemic region expands at the expense of the disease-free space, making disease persistence attainable for a smaller component of frequency-dependence (ν_t occurs at decreasing values of c as m increases). However, increasing the amount of density-dependence (m) has no effect on the parasite-driven extinction region (ν_c occurs at the same value with respect to c for varying m). Conversely, for any given value of m, the amount of frequency-dependence (c) determines whether the population is in disease-free, endemic or parasite-driven extinction parameter space.

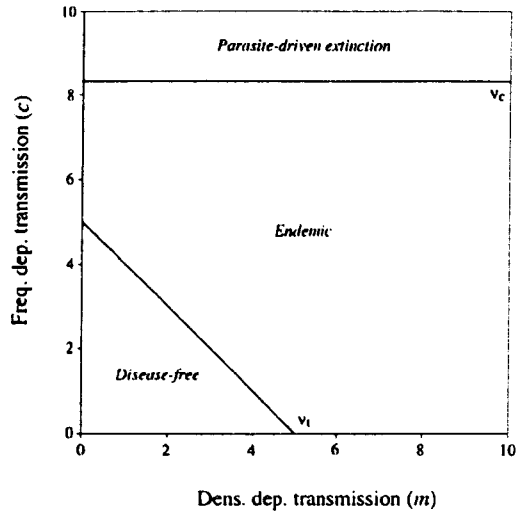

Figure 5.2. (Model I) Outcomes in (c, m) parameter space: $b = 2$, $u = 1$, $h = 1$, $\nu = 0.7$ and $\alpha = 2.5$. The carrying capacity is $N_K = 1$.

5-3. Frequency- and density-dependence are linked

5-3-1. Model and analysis

Now consider the situation where the frequency- and density-dependent components are linked. Here I introduce a parameter $f \in (0,1)$ and rewrite equations (5.1)-(5.2) as:

$$\frac{dX}{dt} = (b - hN)N - uX - \frac{\nu(fc + (1-f)mN)XY}{N} \tag{5.15}$$

$$\frac{dY}{dt} = \frac{\nu(fc + (1-f)mN)XY}{N} - (\alpha + u)Y \tag{5.16}$$

The term representing infection is now:

$$\frac{\nu(fc + (1-f)mN)XY}{N} \tag{5.17}$$

Disease transmission again has both a frequency-dependent component, $vfcXY/N$, and a density-dependent component, $v(1-f)mXY$. The parameter f measures the relative amount of frequency- to density-dependent transmission: $f = 0$ corresponds to purely density-dependent transmission, while $f = 1$ corresponds to pure frequency-dependence.

The analysis is again simplified by making the substitutions $N = X + Y$ and $p = Y/N$. Equations (5.15)-(5.16) are then rewritten in terms of the total host density (N) and the prevalence of infection (p):

$$\frac{dN}{dt} = (b - hN)N - uN - \alpha pN \tag{5.18}$$

$$\frac{dp}{dt} = p[v(fc + (1-f)mN)(1-p) - (b - hN) - \alpha(1-p)] \tag{5.19}$$

Analysis of equations (5.18)-(5.19) is identical to that of equations (5.4)-(5.5), with the exception that $m \rightarrow m(1-f)$ and $c \rightarrow cf$ in the equations.

The trivial equilibrium is again unstable, provided $r = b - u > 0$. The condition for stability of the disease-free equilibrium is:

$$v < \frac{u + \alpha}{cf + (m(1-f)(b-u)/h)} = v_t \tag{5.20}$$

If $v > v_t$ then the parasite will invade the uninfected host population. The condition for stability of the parasite-driven extinction equilibrium is:

$$v > \frac{\alpha(u + \alpha)}{cf(\alpha - b + u)} = v_c \tag{5.21}$$

If $v_t < v < v_c$, with v_t and v_c defined by (5.20) and (5.21), then the endemic equilibrium is both relevant and stable.

Figure 5.3 partitions the (v, α) parameter space into regions of the three non-trivial outcomes, delineated by the two threshold probabilities, v_t and v_c. I investigate the effect of increasing the relative amount of frequency- to density-dependent transmission, as measured by the parameter f.

5-3-2. Probability of Disease Persistence

Differentiation of equation (5.20) gives:

$$\frac{dv_t}{df} = \frac{h(\mu+\alpha)(m(b-u)-hc)}{(hcf+m(1-f)(b-u))^2} \tag{5.22}$$

Hence $dv_t/df < 0$ if and only if:

$$m(b-u)/h < c \tag{5.23}$$

A greater degree of relative frequency-dependence (f) will reduce the threshold for disease persistence (v_t) provided (5.23) is satisfied. Thus, if the relative importance of frequency-dependent transmission (as measured by c) is large compared to the importance of density-dependent transmission (as measured by the parameter m and by the carrying capacity, $N_K = (b-u)/h$), then increasing f lowers the threshold for persistence (Figs. 5.3A, 5.3B). On the other hand, if density-dependence is relatively more important in terms of transmission such that (5.23) is not satisfied, increasing the value of f instead raises the threshold for persistence (Figs. 5.3C, 5.3D). In this case the attendant decrease in v_t due to a greater frequency-dependent component, cf, is relatively small compared to the increase due to a lesser density-dependent component, $m(1-f)(b-u)/h$. Clearly, this is more likely if the population has a large carrying capacity, $N_K = (b-u)/h$. However, even at small carrying capacities, if m is large enough then density-dependence may still be relatively more important

in terms of transmission. In the particular case where $m(b-u)/h = c$, the threshold for persistence is independent of the value of f (here $v_t = u + \alpha$).

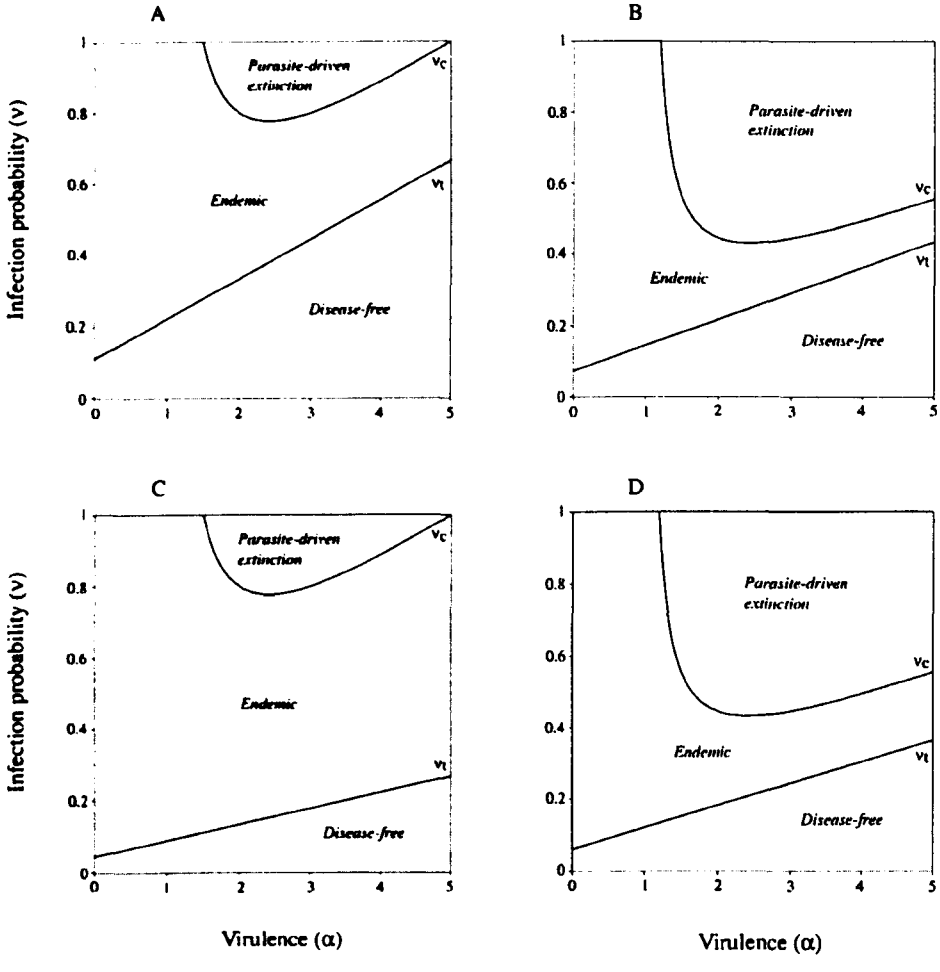

Figure 5.3. (Model II) Outcomes in (v, α) parameter space for different degrees of relative frequency-dependence (f). In (A), (C) $f = 0.5$; in (B), (D) $f = 0.9$. In (A), (B) the density-dependent component is $m = 3$; in (C), (D) $m = 30$. Other parameters are: $b = 2$, $u = 1$ and $h = 1$. The carrying capacity is $N_K = 1$.

5-3-3. Probability of Parasite-driven Extinction

From (5.21), increasing the relative amount of frequency-dependence (f) always reduces the threshold for parasite-driven extinction (v_c). Extinction is more likely if

transmission is highly frequency-dependent. As illustrated in Figure 5.3, extinctions occur over a wider range of infection probabilities (v) and virulences (α) as f increases.

5-3-4. Probability of Endemic Persistence

Assuming (5.23) is satisfied, such that higher relative frequency-dependence reduces the threshold for disease persistence (v_t), this does not necessarily increase the range of parameter space where we observe endemic persistence. This is because increasing the relative amount of frequency-dependence (f) also reduces the threshold for parasite-driven extinction (v_c), at the expense of the endemic region (Figs. 5.3A, 5.3B). The parasite more easily persists in the host population, but is also more likely to drive it to extinction.

On the other hand, assuming condition (5.23) is not satisfied, increasing the relative degree of frequency-dependence (f) will increase the persistence threshold (v_t), but reduce the threshold for extinction (v_c). As a result, endemic persistence of the parasite is always less likely (Figs. 5.3C, 5.3D). This suggests that the conditions favouring a stable endemic equilibrium are high carrying capacities ($(b-u)/h$) and strongly density-dependent transmission (low f, high m). Although strongly frequency-dependent infections (high f, high c) may more easily persist in smaller populations, they are also more likely to cause extinctions.

5-4. Discussion

My results show that where transmission follows conventional frequency-dependence, host-parasite coexistence is possible for intermediate transmission probabilities. Parasite-driven host extinction can also occur if the infection probability rises above the extinction threshold, v_c. In model I, where the relative contributions of frequency and density-dependence can be varied independently, incorporating density-dependent transmission (i.e. $m > 0$) has no effect on the position of v_c, which depends only on the frequency-dependent parameter, c.

However, increasing the amount of density-dependence lowers the boundary between the endemic and disease-free regions (v_r). Thus, if c is fixed, the probability of endemic persistence increases with the relative contribution of density-dependent transmission. Conversely, when frequency-dependence is incorporated into a conventional density-dependent model, there is again a reduction in the size of the disease-free region, and parasite-driven extinction also becomes possible for a sufficiently high infection probability. As c is increased further, the extinction equilibrium becomes stable for lower values of v, constraining the region within which coexistence is possible. In model II, density-dependence can only be introduced if the relative degree of frequency-dependence is simultaneously reduced. Provided density-dependence is relatively more important than frequency-dependence, this increases the probability of endemic persistence.

Parasites have been implicated in host extinctions a number of times, including in the Thylacine, a carnivorous marsupial (McCallum and Dobson 1995), African wild dogs (Burrows et al. 1995) and some amphibian species (Daszak and Cunningham 1999). OIDs are generally only implicated in extinctions if they lower the host population size, or cause destabilization leading to dramatic cycles in abundance, such that there is a higher risk of stochastic events causing extinction. Alternatively, if OIDs are shared by two hosts, one of which acts as a reservoir for the parasite when the other is at low density, there is also a possibility of extinction (McCallum and Dobson 1995). The results presented here suggest that a degree of frequency-dependence in such diseases will make extinction more likely. Parasite-driven extinction may indeed be a theoretical possibility in a wide variety of OIDs. The majority of OIDs are likely to have some component of frequency-dependence and even a small degree may be sufficient to place a population above v_c. For example, OIDs may be commonly transmitted during sexual activity, leading to a degree of frequency-dependent transmission. The transmission of OIDs may also be partly frequency-dependent when animals live in social or family groups. Contacts of all types within the group will often remain constant even if the density of the overall population varies (this will always be the case when there are fixed group sizes). As the overall density of the host population rises, the impact of density-dependent

transmission will be greater, but within-group transmission will still occur. When considering human diseases, social factors such as fixed class sizes in childhood may lead to a substantial frequency-dependent component of transmission dynamics (Bjornstad et al. 2002). The consequences of incorporating frequency-dependent transmission may be particularly important at low densities, where the likelihood of extinction may be greatest.

Animal-STD systems may often be stabilized to some degree by density-dependent transmission. Ryder et al. (2005) recently demonstrated that STD transmission has a large component of density-dependence in *A. bipunctata*. This may partly explain why coexistence is possible in this system, despite the regular occurrence of epidemic levels of infection (Webberley et al. 2006). A variety of studies have also reported relationships between mating rate and population density in both insects and birds (reviewed in Ryder et al. 2005). This introduces a component of frequency-dependence to the transmission of any STDs present. In birds, a number of studies have demonstrated that the rate of extra-pair copulation increases with population density, in species ranging from swallows to guillemots (Hatchwell 1988; Brown and Brown 1996). A number of insect studies have also found that mating rate is density-dependent (Harshman et al. 1988; Gage 1995). Density-dependent changes in mating rate are also likely in higher vertebrate groups, where a similar effect on the STD dynamics would be expected. In the red deer, increases in population density are associated with changes in the sex ratio, which in turn affects the number of males achieving a small number of matings (Clutton-Brock et al. 1997).

The model of Antonovics et al. (1995) placed these two forms of transmission at opposite ends of a continuum and incorporated greater behavioural complexity into the transmission process. As 'handling time' (i.e. time spent competing for access to sexual partners, pair formation, etc) increased relative to the total available search time, the relationship between the number of encounters per infected individual and host density changed from linear to asymptotic. When handling time was low, therefore, host density was the main determinant of encounter rate, making

transmission nearer to being density-dependent. Higher handling times constrained the encounter rate, pushing transmission towards frequency-dependence. In retaining the simplicity of the traditional linear functions, the combined transmission function presented here does not allow for the same level of behavioural complexity as this previous model. However, it has the advantage of being analytically tractable and the phenomenological emphasis should increase its general relevance. For example, contact rates may remain fairly constant at low densities, according to social structure, but increase at high densities as promiscuity begins to modify the usual sexual behaviour. The approach is well suited to the empirical modelling of such data. It is easy to convert the model to incorporate respective frequency- and density-dependent transmission coefficients: defining $vc = \beta_1$ and $vm = \beta_2$ (model I), the term representing the rate of transfer to the infected class becomes

$$\frac{v(c + mN)XY}{N} = \frac{\beta_1 XY}{N} + \beta_2 XY \qquad (5.24)$$

A recent study of *A. bipunctata* measured β_1 and β_2 experimentally (Ryder et al. 2005), but failed to demonstrate that the frequency-dependent term (β_1) had any significant explanatory power over and above the standard density-dependent term (β_2). However, a wide variety of animal-STD systems are likely to demonstrate both significant frequency- and density-dependent transmission and the combined transmission function provides a potential basis for determining where on the 'transmission continuum' such systems lie. As such, the approach may help to encourage the integration of theoretical and empirical approaches to STD ecology.

6. Male-biased parasitism and population dynamics

6-1. Introduction

There is considerable evidence in nature for sex-biased parasitism. Male-biased parasitism is thought to be much more common (Poulin 1996; Schalk and Forbes 1997; Perkins et al. 2003; Ferrari et al. 2004), although a study by McCurdy et al. (1998) observed higher levels of infection of blood parasites in female birds. Males may be more susceptible to infection, or alternatively, they may transmit it more easily. It has been pointed out, however, that in populations where males have higher levels of infection, they are also likely to cause most of the transmission to females (Skorping and Jensen 2004). There are several reasons why males may have more parasites. Sexual size dimorphism in mammals is often strongly correlated with higher male mortality; a comparative study by Moore and Wilson (2002) identified positive correlations between male-biased parasitism and the degree of sexual selection, and between male-biased parasitism and male-biased mortality. Two explanations have been suggested to explain this. Firstly, the larger body size of males may make them easier targets for parasites (Moore and Wilson 2002). Second, sexually selected traits that increase growth or reproductive effort require androgenic hormones (e.g. testosterone in vertebrates) and these may have a negative effect on the immune system (Folstad and Karter 1992; Moore and Wilson 2002). There is convincing evidence that males gain fitness largely through reproductive ability and females through longevity, suggesting males might often invest less in costly immune mechanisms (Rolff 2002; Rolff and Siva-Jothy 2003). Although they lack testosterone, insects are thought to increase their reproductive ability through the presence of the juvenile hormone at the cost of reducing their immunity.

Given that male-biased parasitism is considerably widespread, it is likely to have strong implications for population dynamics. Ecological models have the potential for extremely complicated dynamics (May 1974, 1976; May and Oster 1976), however natural populations tend to be relatively stable (Hassell et al. 1976; Berryman and Millstein 1989). In this chapter I investigate the effects of male-biased parasitism on the population dynamics. A common approach in theoretical studies is to assume that the dynamics of sexual populations can be understood by examining

only one of the genders in isolation. This approach can be justified if males and females have identical life cycles, or if one sex is completely dominant such that the dynamics are independent of the abundance of the other (Caswell and Weeks 1986). However, there are often significant demographic differences between the sexes (Allen 1980; Sherman and Morton 1984; Clutton-Brock 1991; Massot et al. 1992; Ohgushi and Sawada 1995). For example, mammalian species with polygynous mating often show strong sexual selection for larger males, which tend to have higher mortality (Clutton-Brock et al. 1982, 1985; Moore and Wilson 2002). The assumption of complete dominance also fails in many cases, where an uneven sex ratio may constrain reproduction due to limited availability of the scarcer sex. A consideration of sexual reproduction and the differences between sexual classes may have a profound effect on the dynamics, and appropriate 'two-sex' models should therefore consider each gender separately (Caswell and Weeks 1986; Caswell 2000).

Modelling separate classes for each sex has important implications for the dynamics, as here births will depend on both sexes. Caswell and Weeks (1986) analysed an explicit two-sex model where births were determined by a 'harmonic mean' function, where reproduction depended on the ratio of males to females, and declined to zero in the absence of either sex. As the authors showed, this birth function can be modified to accommodate polygynous or polyandrous mating systems. Crucially, since here births depend on the relative proportion of either sex, models using the harmonic function are strictly frequency-dependent (Caswell and Weeks 1986). The equilibrium sex ratio was derived and shown to be locally asymptotically stable under the assumption of pure frequency-dependence. The addition of an extra age class did not, in itself, alter the dynamic stability of the model. However, if individuals of different ages also competed for mates, this introduced a degree of density-dependence, possibly destabilizing the equilibrium sex distribution. In particular, if males and females had different survival, this could generate a stable five-point cycle, the amplitude of the oscillations increasing with the degree of competition. Where the sexes also differed in development time, a range of complex behaviour was observed, from periodic or quasi-periodic cycles, to apparently chaotic dynamics. Furthermore, with a sigmoidal birth function, a

sufficiently large perturbation from the equilibrium sex ratio could drive the species to extinction. The size of the perturbation needed to cause extinction increased with the clutch size (Caswell and Weeks 1986).

Following on from this, Lindstrom and Kokko (1998) compared the relative stability of sexual and asexual populations, in a model that included both polygyny and demographic sex differences. As the intrinsic growth rate increased, the asexual population exhibited a period-doubling route to chaos. With no demographic differences between the genders, a monogynous population exhibited greater stability than the asexual one, and polygynous populations were stable to a similar degree as asexual ones. Where males also experienced higher crowding, this had a destabilizing effect: chaos was observed at higher growth rates, and the dynamics no longer showed period-doubling bifurcations. Polygynous populations with higher male crowding were highly unstable, exhibiting chaos or cycles at all but very low growth rates.

In this chapter I use a theoretical approach to examine how male-biased parasitism affects dynamical stability, under different characteristic mating structures. In line with previous two-sex models, I include the effect of demographic gender differences. The basic model is derived from Lindstrom and Kokko's (1998) model for a disease-free sexual population, and the host-parasite framework of May and Anderson (1983). The epidemiological model therefore incorporates the specific demography of the individual male and female populations.

6-2. The Model

The model of May and Anderson (1983) describes a host-microparasite interaction with discrete, non-overlapping generations. Disease epidemics occur within a cohort such that only surviving hosts are able to reproduce. Here, I generalize the model to include both males and female hosts. For each gender, the densities of uninfected, infected and recovered hosts are X_i, Y_i and Z_i, and the total density is $N_i = X_i + Y_i + Z_i$. The epidemiological dynamics are described by the equations:

$$\frac{dX_i}{dt} = -\beta_i X_i(Y_i + Y_j) + \gamma_1 Y_i \tag{6.1}$$

$$\frac{dY_i}{dt} = \beta_i X_i(Y_i + Y_j) - (\alpha + \gamma_1 + \gamma_2)Y_i \tag{6.2}$$

$$\frac{dZ_i}{dt} = \gamma_2 Y_i \tag{6.3}$$

The subscript $i = m, f$ denotes males or females, respectively. The transmission rate of infection is β_i (this allows for different susceptibilities to infection for males and females, but both types of host are equally infectious). There is an increased death rate due to the disease (virulence) given by α. Infected hosts recover to the susceptible state (at rate γ_1) or to the immune class (at rate γ_2).

The condition for the host population to support the pathogen is that its basic reproductive ratio (R_0) exceeds unity (Anderson and May 1981, 1982). Since I am considering a heterogeneous population, the reproductive ratio will depend on the parasite fitness in both males and females and on their individual densities (Regoes et al. 2000):

$$R_0 = \frac{\beta_f N_f}{(\alpha + \gamma_1 + \gamma_2)} + \frac{\beta_m N_m}{(\alpha + \gamma_1 + \gamma_2)} \tag{6.4}$$

Throughout the analysis, it is assumed that $R_0 > 1$. The disease will therefore persist and cause an epidemic. At the end of a given cohort, the epidemic is assumed to have completely run its course such that there are no infected individuals left in the population. Defining $(1 - I)$ as the proportion of hosts who remain susceptible after the epidemic (May and Anderson 1983) the densities at the end of the cohort are:

$$X_{i,m} = N_i(1 - I_i) \tag{6.5}$$

$$Y_{i,\infty} = 0 \tag{6.6}$$

$$Z_{i,\infty} = N_i I_i (1 - \alpha/(\alpha + \gamma_2)) \tag{6.7}$$

The total number of surviving hosts is therefore:

$$N_{i,\infty} = X_{i,\infty} + Z_{i,\infty} = N_i[1 - I_i \alpha/(\alpha + \gamma_2)] \tag{6.8}$$

Reproduction occurs according to the harmonic mean function (Caswell and Weeks 1986; Caswell 2000). The number of births, B, therefore depends on the relative densities of males and females at the end of the previous cohort:

$$B(N_{f,\infty}, N_{m,\infty}) = \frac{2kN_{f,\infty}N_{m,\infty}}{N_{m,\infty} + N_{f,\infty}h^{-1}} \tag{6.9}$$

The parameter h gives the average harem size. This harmonic function assumes the total offspring per fertilized female is $2k$, and that births will fall to zero in the absence of either sex. With monogamous mating, $h = 1$, and males and females are equally important in terms of births. Values of h greater than one correspond to polygynous mating, where the birth rate is more dependent on females (Caswell and Weeks 1986; Lindstrom and Kokko 1998). The population is also assumed to experience density-dependence of the Moran-Ricker type (Moran 1950; Ricker 1954), as employed by Lindstrom and Kokko (1998). Population growth is therefore limited at high densities by intra-specific crowding, in terms of increased infant mortality. Assuming births are equally likely to be of either sex, the population densities in the next cohort are given as:

$$N_f = \frac{B(N_{f,\infty}, N_{m,\infty})}{2}\exp(-\mu_f(N_{f,\infty} + N_{m,\infty})) \tag{6.10}$$

$$N_m = \frac{B(N_{f,\infty}, N_{m,\infty})}{2}\exp(-\mu_m(N_{f,\infty} + N_{m,\infty})) \tag{6.11}$$

Note that males and females may experience different levels of crowding, as measured by the parameters μ_f and μ_m respectively.

The seasonal model of May (1985) implicitly assumed that infection was able to persist from one cohort to the next via some external mechanism, such as repeated inoculation. Koella and Doebeli (1999) later adapted the model, allowing infection to persist through vertical transmission. Recovered individuals were assumed to carry a stage of the parasite that they transmit to their offspring. I follow this approach and assume that the proportion of infected offspring, v, depends on the proportion of surviving females who recovered from infection, and also on a parameter σ measuring the efficacy of vertical transmission:

$$v = \frac{\sigma Z_{f,\infty}}{X_{f,\infty} + Z_{f,\infty}} \tag{6.12}$$

The equilibrium densities (6.5)-(6.7) were determined using computer simulations of the differential equations (6.1)-(6.3) until the system reached a stable state. Reproduction then occurred according to equations (6.10)-(6.11), with a proportion, $1-v$, offspring classified as susceptible and a proportion, v, classified as infected (according to equation (6.12)). This process was repeated 120 times to eliminate the initial transient effects and the population densities were plotted for the last 20 iterations. From the coincidence of the consecutive values it can be seen whether the system converges to a stable point, limit cycle, or displays other complex behaviour.

6-3. Results

I begin by reproducing the results of Lindstrom and Kokko (1998), showing how the inclusion of sexual reproduction affects dynamical stability. Unbiased parasitism is then added to the basic model, characterized by equal transmission rates of infection to each gender. Finally, the effect of male-biased parasitism is investigated, represented as a higher transmission rate of infection to males and a correspondingly

lower transmission to females. I investigate the impact of parasitism at different levels of virulence, in terms of the case mortality due to infection, $\chi = \alpha/(\alpha + \gamma_1 + \gamma_2)$.

6-3-1. Disease-free host population

To investigate the effects of parasitism (male-biased or otherwise) the dynamical behaviour in the absence of disease needs first to be established. This has been discussed in depth by Lindstrom and Kokko (1998). For a monogynous population with no density-dependent differences between the sexes, the dynamics are generally stable with two-point limit cycles occurring at high fecundity (Fig. 6.1A). In polygynous populations, the density of males is less important in terms of births, and the dynamics follow a period-doubling route to chaos (Fig. 6.1B).

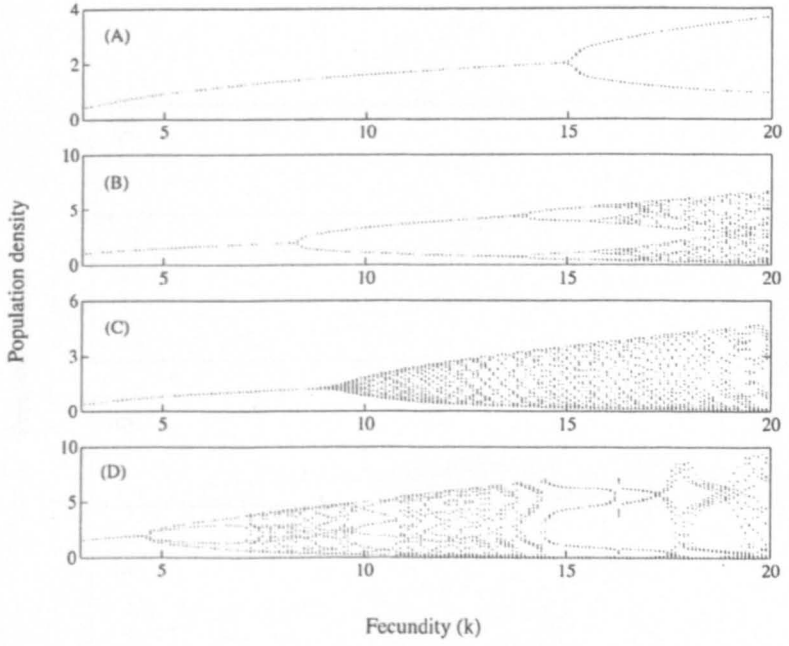

Figure 6.1. Population dynamics in the absence of parasitism. (A) Monogyny (h = 1), males and females are equally vulnerable to crowding ($\mu_f = \mu_m = 1$); (B) polygyny (h = 10), males and females are equally vulnerable to crowding ($\mu_f = \mu_m = 1$); (C) monogyny (h = 1), males have a greater vulnerability to crowding ($\mu_f = 0.4$, $\mu_m = 1.6$); (D) polygyny (h = 10), males have a greater vulnerability to crowding ($\mu_f = 0.4$, $\mu_m = 1.6$). The rate of vertical transmission is $\delta = 0.2$.

Returning to the monogynous mating system but assuming that males are more vulnerable to crowding, the dynamics become highly unstable at high fecundities and no longer follow a period-doubling route to chaos (Fig. 6.1C). For a polygynous population that also experiences greater male crowding, the dynamics are generally complex, with alternating regions of chaos and limit cycles (Fig. 6.1D).

6-3-2. Unbiased parasitism

I examine the effect of adding parasitism to each of the model systems. Initially, I assume a low case mortality such that $\chi = 0.08$ (infected individuals have a 92% chance of recovering). The dynamical behaviour is essentially unaffected (Fig. 6.2). There is, however, a slight shift to the right of the initial bifurcation point. Unbiased parasitism therefore corresponds to a mild increase in dynamical stability if case mortality is low.

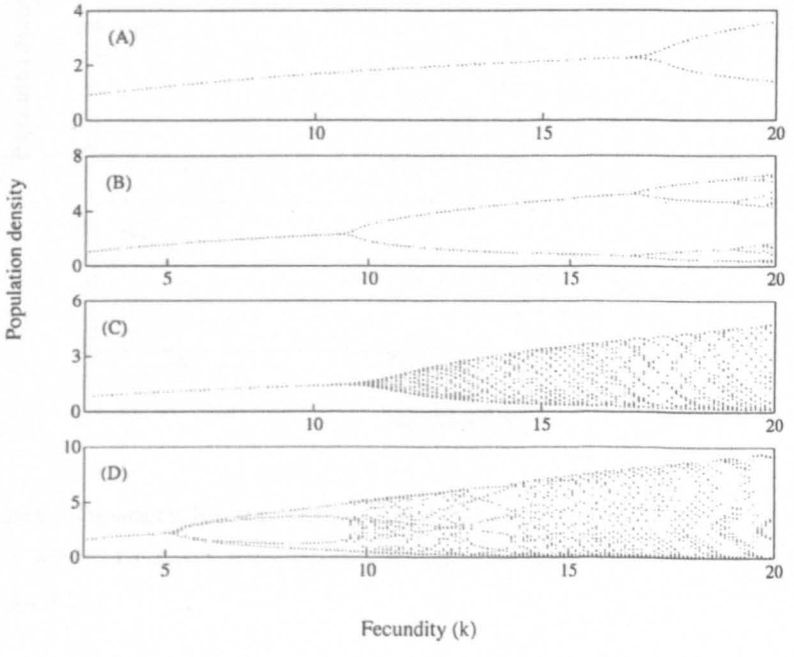

Figure 6.2. Population dynamics with unbiased parasitism. (A) $h = 1$, $\mu_f = \mu_m = 1$; (B) $h = 10$, $\mu_f = \mu_m = 1$; (C) $h = 1$, $\mu_f = 0.4$, $\mu_m = 1.6$; (D) $h = 10$, $\mu_f = 0.4$, $\mu_m = 1.6$. Other parameters are: $\beta_f = \beta_m = 1.2$, $\alpha = 0.08$, $\gamma_1 = \gamma_2 = 0.46$ and $\delta = 0.2$.

Increasing case mortality (χ) generally increases the stability of the system: the initial bifurcation shifts further towards the right (Fig. 6.3). For high enough mortality rates, the populations are completely stabilized (over the given range of fecundities). This applies to all four mating systems. The pattern of increased stability with higher case mortality holds true generally, but there are some exceptions. Very high case mortalities (typically in excess of 95%) tend to promote cyclic dynamics, which are generally of period two. For an extremely high case mortality (99.9%) the system may exhibit high-period cycles or even chaos. This appears to be more likely at high transmission rates (Fig. 6.4B). Lower transmission rates tend to generate two-point cycles or a stable equilibrium (Fig. 6.4A).

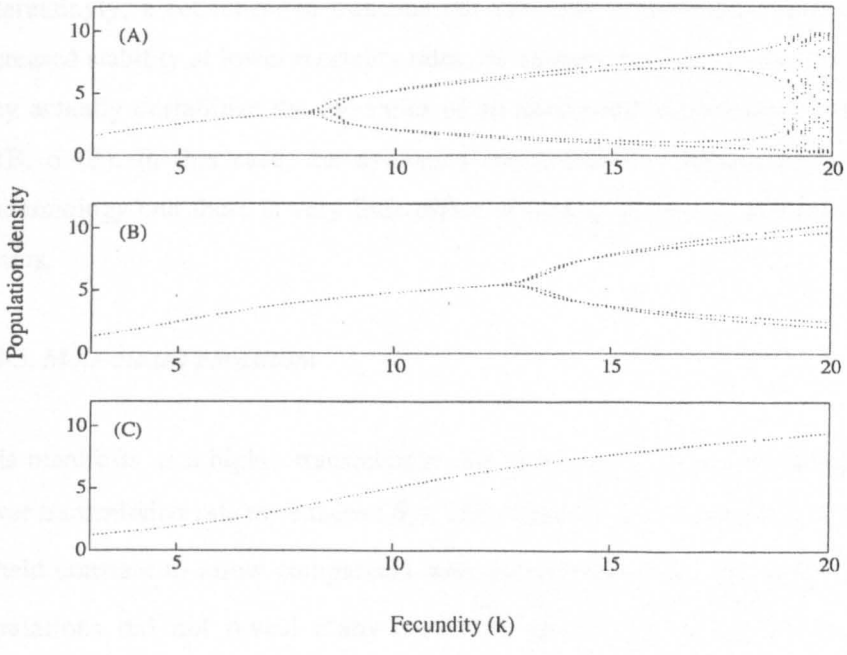

Figure 6.3. Population dynamics with unbiased parasitism. (A) $\alpha = 0.3$, $\gamma_1 = \gamma_2 = 0.35$; (B) $\alpha = 0.5$, $\gamma_1 = \gamma_2 = 0.25$; (C) $\alpha = 0.7$, $\gamma_1 = \gamma_2 = 0.15$. Other parameters are: $\beta_f = \beta_m = 1.2$, $h = 10$, $\mu_f = 0.4$, $\mu_m = 1.6$ and $\delta = 0.2$.

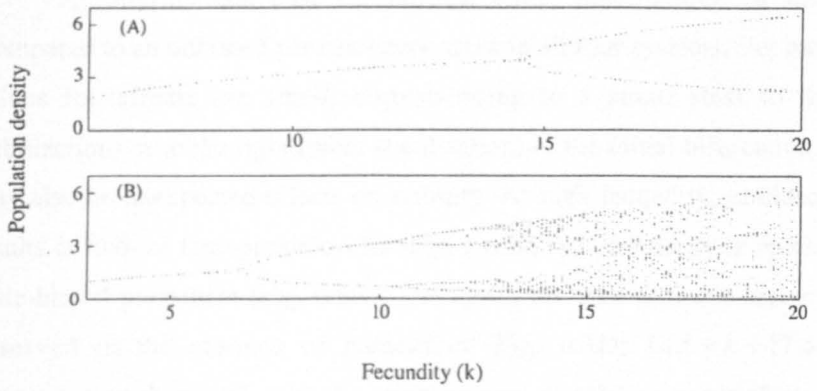

Figure 6.4. Population dynamics with unbiased parasitism. (A) $\beta_f = \beta_m = 0.6$; (B) $\beta_f = \beta_m = 1.2$. Other parameters are: $h = 10$, $\mu_f = \mu_m = 1$, $\alpha = 0.999$, $\gamma_1 = \gamma_2 = 0.0005$ and $\delta = 0.2$.

Interestingly, a reduction in transmission rate was occasionally associated with increased stability at lower mortality rates. At extreme mortality, however, infection may actually destabilize the dynamics of an uninfected population (compare Figs 6.1B, 6.4B). In this case, the dynamics are determined almost entirely by the epidemiology and there is very little effect of mating system or density-dependent factors.

6-3-3. Male-biased parasitism

This manifests as a higher transmission rate to males (β_m), and a correspondingly lower transmission rate to females (β_f). The overall force of transmission ($\beta_m + \beta_f$) is held constant to allow comparison with the unbiased case ($\beta_m = \beta_f$). Extensive simulations did not reveal many consistent results; the effect of male-biased parasitism appears to be heavily parameter-dependent, although some general patterns did emerge. Firstly, at low mortality rates there appears to be very little effect of male-biased parasitism (Fig. 6.5). There is mild stabilization of an uninfected population, in terms of a later initial bifurcation (Fig. 6.1), but little difference compared to an unbiased parasite (Fig. 6.2).

At intermediate case mortalities, either stabilization or destabilization (compared to an unbiased parasite) may occur in all four systems. For most parameter values the effects are small, corresponding to a small shift to the left (less stabilization) or to the right (more stabilization) of the initial bifurcation point. There may also be unexpected effects on stability. At high fecundity, unbiased parasitism results in two- or four-period cycles (Fig. 6.6A); the periodicity is much higher with male-biased parasitism (Fig. 6.6B). The cycles are also of much higher period than observed in the absence of parasitism (Fig. 6.1D; $14.5 < k < 17.5$). In some circumstances then, male-biased parasitism may destabilize an uninfected population at intermediate mortalities.

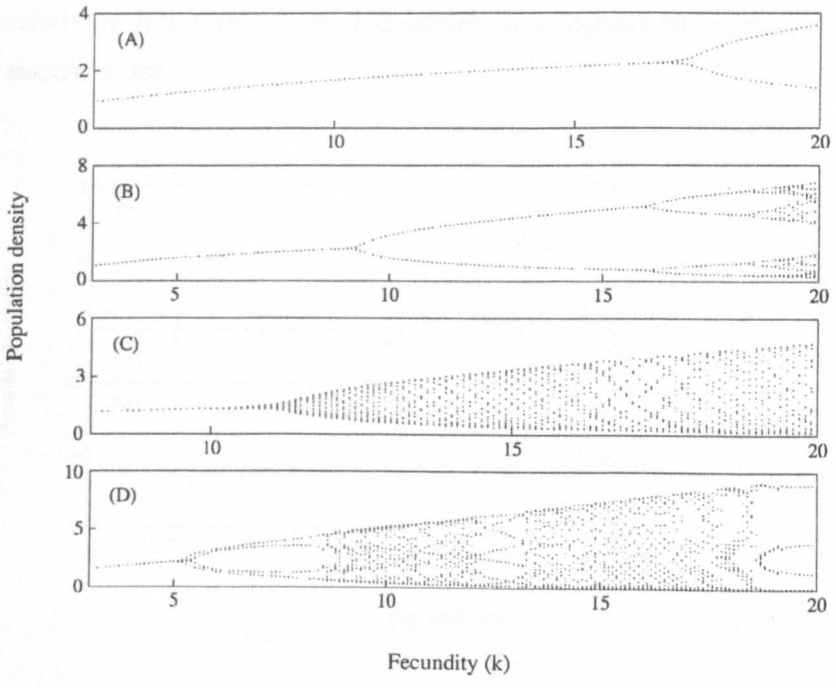

Figure 6.5. Population dynamics with male-biased parasitism. (A) $h = 1$, $\mu_f = \mu_m = 1$; (B) $h = 10$, $\mu_f = \mu_m = 1$; (C) $h = 1$, $\mu_f = 0.4$, $\mu_m = 1.6$; (D) $h = 10$, $\mu_f = 0.4$, $\mu_m = 1.6$. Other parameters are: $\beta_f = 0.6$, $\beta_m = 1.8$, $\alpha = 0.08$, $\gamma_1 = \gamma_2 = 0.46$ and $\delta = 0.2$.

At mortality rates greater than 90% (greater than 80%, if there is monogyny and higher male crowding), there may be significant effects of male-biased parasitism; these are observed only for specific parameter combinations.

Monogynous populations may be relatively less stable compared to an unbiased parasite. Where the unbiased system reaches a stable point, the male-biased system exhibits two-point cycles (Fig. 6.7). There may also be destabilization of an uninfected population (compare Figs. 6.1A, 6.7B). Under polygyny, the effects of male-biased parasitism are less straightforward; if males and females experience equal crowding then the dynamics are generally more stable. In particular, where the unbiased parasite generates cycles at high fecundity (Fig. 6.8A), the male-biased system attains a stable point (Fig. 6.8B). If males experience higher crowding and there is polygynous mating, the effect of male-biased parasitism is strongly parameter-dependent. It may result in greater stability at high fecundity, but be less stable at low fecundity (Figs. 6.8C, 6.8D). Alternatively, the male-biased system may be relatively less stable at all fecundities; this appears to be the case for most parameter values.

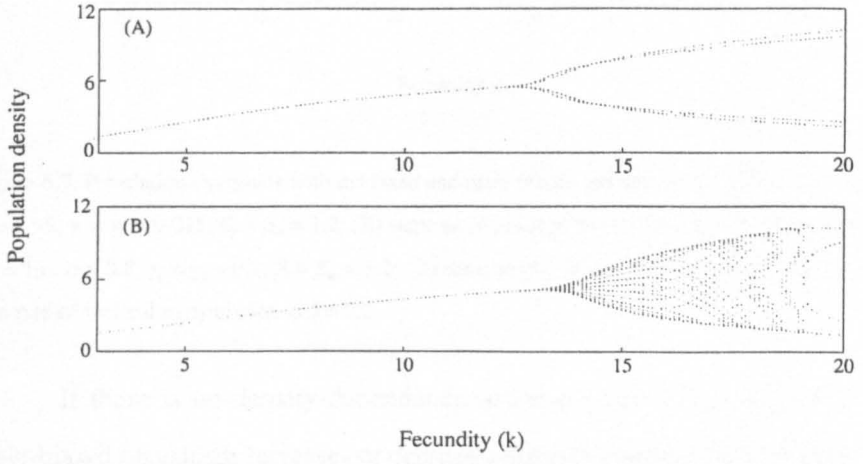

Figure 6.6. Population dynamics with male-biased parasitism. (A) $\beta_f = \beta_m = 1.2$; (B) $\beta_f = 0.6$, $\beta_m = 1.8$. Other parameters are: $h = 10$, $\mu_f = 0.4$, $\mu_m = 1.6$, $\alpha = 0.5$, $\gamma_1 = \gamma_2 = 0.25$ and $\delta = 0.2$.

The results given in the preceding paragraph are generalized from a large number of simulations, but exceptions do exist. For example, at extremely high mortality rates (99.9%), male-biased parasitism may be relatively less stabilizing to a

polygynous population when the genders experience equal crowding. This results in limit cycles with higher periodicity compared to the unbiased parasite.

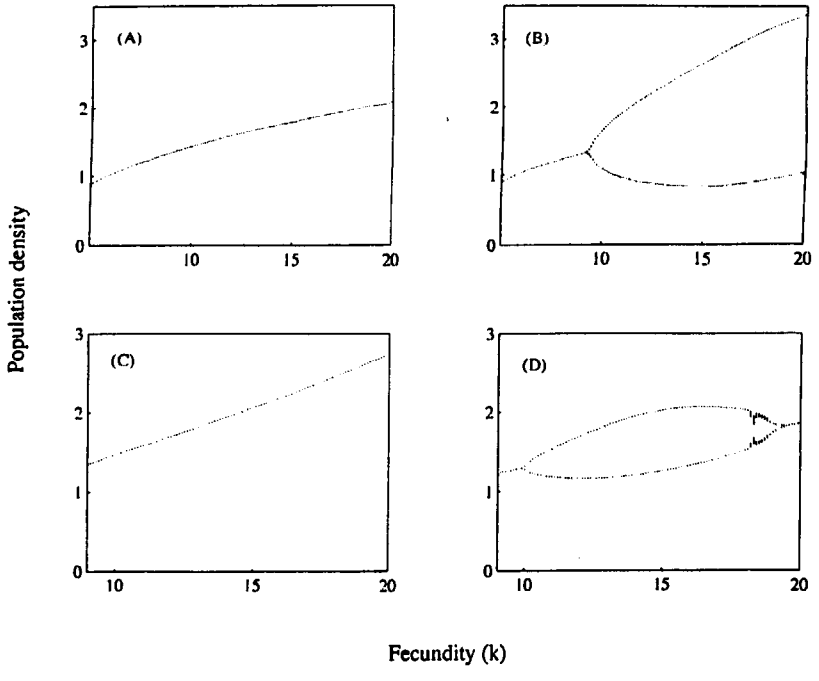

Figure 6.7. Population dynamics with unbiased and male-biased parasitism. (A) $h = 1$, $\mu_f = \mu_m = 1$, $\alpha = 0.95$, $\gamma_1 = \gamma_2 = 0.025$, $\beta_f = \beta_m = 1.2$; (B) same as (A) except $\beta_f = 0.4$ and $\beta_m = 2$; (C) $h = 1$, $\mu_f = 0.4$, $\mu_m = 1.6$, $\alpha = 0.8$, $\gamma_1 = \gamma_2 = 0.1$, $\beta_f = \beta_m = 1.2$; (D) same as (C) except $\beta_f = 0.6$ and $\beta_m = 1.8$. The rate of vertical transmission is $\delta = 0.2$.

If there is no density-dependence in the population ($\mu_f = \mu_m = 0$), whether male-biased parasitism increases or decreases stability may be due to an interaction of the mating system with the fecundity. Figure 6.9 partitions the (k, h) parameter space into regions where the dynamics reach a stable point, a two-cycle, or more complex dynamics (higher point cycles or chaos). There is extreme mortality of infected hosts ($\chi = 0.99$). With unbiased parasitism, point equilibria occur only in monogynous populations and only at very low fecundity (Fig. 6.9A). At intermediate fecundities the dynamics are always two-point cycles. High fecundities may result in either two-point cycles or more complex dynamics; populations with very high fecundity always exhibit two-point cycles provided there is a significantly high degree of polygyny.

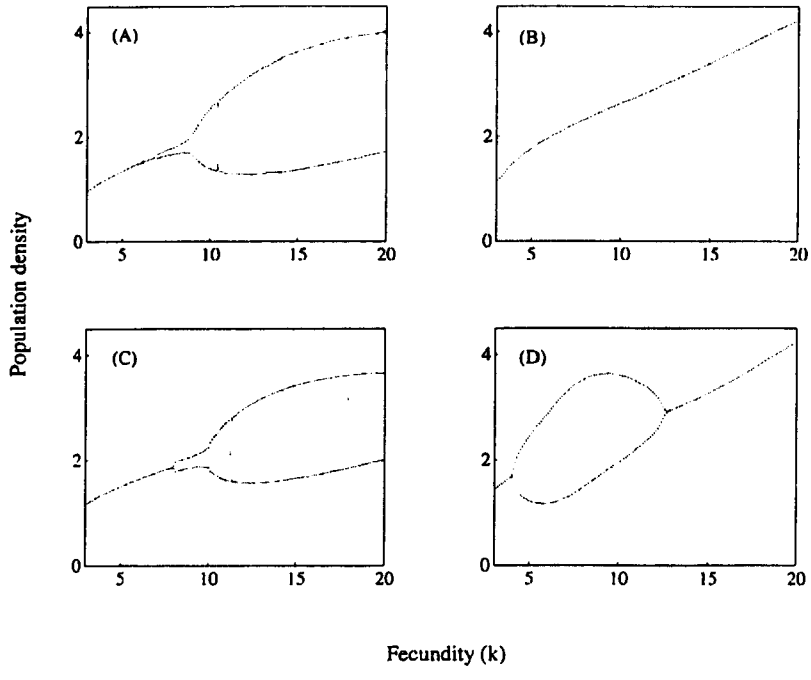

Figure 6.8. Population dynamics with unbiased and male-biased parasitism. (A) $h = 10$, $\mu_f = \mu_m = 1$, $\alpha = 0.97$, $\gamma_1 = \gamma_2 = 0.015$, $\beta_f = \beta_m = 1.2$; (B) same as (A) except $\beta_f = 0.6$ and $\beta_m = 1.8$; (C) $h = 10$, $\mu_f = 0.4$, $\mu_m = 1.6$, $\alpha = 0.97$, $\gamma_1 = \gamma_2 = 0.015$, $\beta_f = \beta_m = 1.2$; (D) same as (C) except $\beta_f = 0.6$ and $\beta_m = 1.8$. The rate of vertical transmission is $\delta = 0.2$.

Under male-biased parasitism, at very low fecundity the population always reaches a stable point (Fig. 6.9B). For a sufficiently high degree of polygyny, the population exhibits either a two-point cycle or (for high fecundity) reaches a stable point. Higher point cycles occur only at lower harem sizes and are always likely at high fecundity. In contrast to the unbiased case, high point cycles may also occur at quite low fecundities. In the absence of density-dependence, male-biased parasitism is generally more stabilizing at high fecundity and harem size. Lower harem sizes tend to be less stable under male-biased parasitism.

Returning to the density-dependent case, where parasitism is highly biased towards males ($\beta_m >> \beta_f$), the dynamics may be highly complex. At extreme mortality, there is a range of bifurcations leading to high point cycles and possibly

chaos. This is more likely with monogyny (Fig. 6.10A), but may also occur in polygynous systems, in particular if males are also more vulnerable to crowding (Fig. 6.10B).

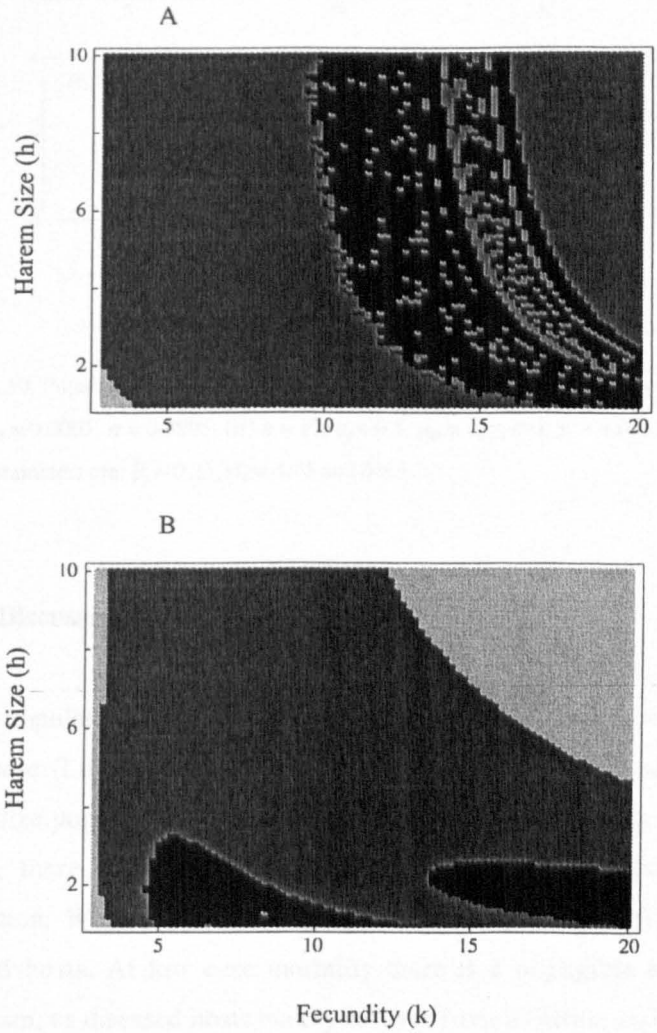

Figure 6.9. Stability plots. Regions shaded light grey correspond to a stable equilibrium, dark grey regions correspond to 2-point limit cycles, and regions shaded black correspond to high-period cycles or chaotic dynamics; (A) $\beta_f = \beta_m = 2.5$; (B) $\beta_f = 1.25$ and $\beta_m = 3.75$. Other parameters are: $\alpha = 0.495$, $\gamma_1 = 0$, $\gamma_2 = 0.005$ and $\delta = 1$.

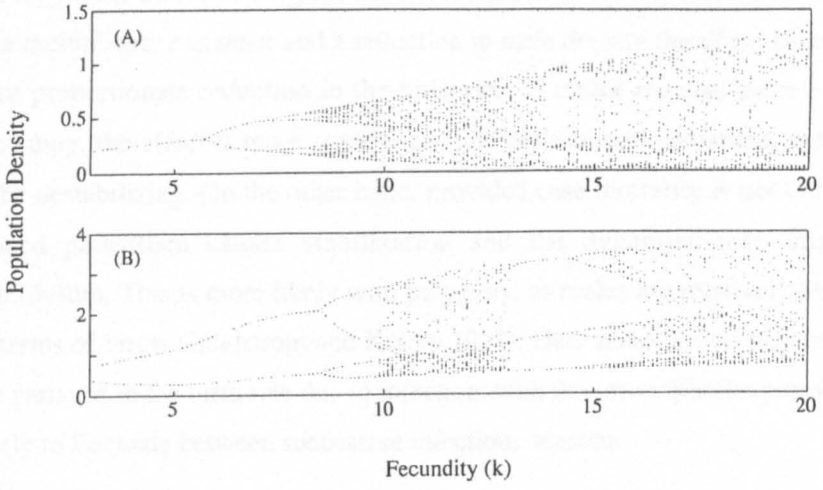

Figure 6.10. Population dynamics with male-biased parasitism. (A) $h = 1$, $\mu_f = \mu_m = 2$, $\gamma_1 = 0$, $\gamma_2 = 0.0005$, $\alpha = 0.4995$; (B) $h = 10$, $\mu_f = 0.5$, $\mu_m = 2$, $\gamma_1 = 0$, $\gamma_2 = 0.005$, $\alpha = 0.495$. Other parameters are: $\beta_f = 0.25$, $\beta_m = 4.75$ and $\delta = 1$.

6-3-4. Discussion

Sexual populations may exhibit complex dynamics quite independently of the effects of disease (Lindstrom and Kokko 1998). It is generally thought that disease will destabilize population dynamics. However, I have shown that if parasitism is male-biased, there may be either stabilization or destabilization of an uninfected population. What happens is highly dependent on the level of case mortality of infected hosts. At low case mortality there is a negligible effect of male-biased parasitism, as diseased hosts mainly recover from infection and there is only a slight difference in male and female densities. This corresponds to a small increase in stability in terms of a marginal shift to the right of the onset of bifurcations, although the bifurcation pattern is unaffected. At intermediate case mortalities, the degree of stabilization is generally greater; however, over a range of high fecundities, male-biased parasitism may induce cycles with higher periodicity than occur in the unparasitized model. This destabilization is due to scarcity of male mating partners. This is also evident at high mortality rates, in particular if the population is

monogynous. Under monogyny, the birth function is equally dependent on both sexes in a multiplicative manner and a reduction in male density therefore generates a more than proportionate reduction in the birth rate. If males are also more vulnerable to crowding, the effect is more pronounced and male-biased parasitism is highly likely to be destabilizing. On the other hand, provided case mortality is not too high, male-biased parasitism causes stabilization and the dynamics may attain a point equilibrium. This is more likely with polygyny, as males are relatively less important in terms of births (Lindstrom and Kokko 1998). Here male-biased parasitism reduces the variance in the birth rate due to infection, with the result that the population is less likely to fluctuate between successive infectious seasons.

There is a similar effect of unbiased parasitism. In many cases, this also stabilizes the dynamics, provided the case mortality is not too high. A proportion of the population dies from infection, reducing both the male and female densities and therefore the birth function. As such, infectious disease may be seen to stabilize the population by reducing its overall growth rate. However, at high case mortalities both male-biased and unbiased parasitism often generate two-point cycles. At extremely high case mortality, the degree of instability is greater and the dynamics are prone to exhibit high-point cycles or even chaos. This is because the prevalence of infection is much lower and the mating system and density-dependence effects (which define the population's growth) interact with the infectious disease in determining the dynamics.

Population cycles are a feature of continuous models that include disease transmission via a free-living infective stage (Anderson and May 1981; White et al. 1996). In particular, cycles are predicted when the increased mortality rate due to infection (α) is high. There exists a parallel with my results, where cycles occur at high case mortality. Population cycles are also predicted at high case mortality in the discrete asexual model (May 1985; Koella and Doebeli 1999). Following a large epidemic, a high case mortality will strongly depress the male and female densities. The next epidemic is therefore much smaller and the number of hosts surviving to reproduce is higher. This allows the population to recover to high levels, which

triggers another large epidemic, and in the long run the population oscillates between high and low density.

The Allee effect (Allee 1931, 1938) is implicit in the form of the birth function. This is essentially a cost of rarity for sexual populations, due to scarcity of breeding partners. At low density, sexual populations may be expected to have reduced reproduction. Population growth rates may also be reduced at low density due to associated factors, such as social dysfunction and inbreeding depression (Scheuring 1999). There is indeed considerable empirical evidence for such effects of low density (McCarthy 1997). In the absence of infection, an uneven sex ratio is likely to destabilize the dynamics: period-doubling bifurcations is a common feature of the disease-free model (Lindstrom and Kokko 1998). In the host-microparasite model presented here, an Allee effect is theoretically possible whenever male-biased parasitism results in an uneven sex ratio, but does not always occur. Monogynous populations appear to be particularly vulnerable to Allee effects. In contrast, reproduction is only constrained in polygynous species if males are also more vulnerable to crowding. Interestingly, where females experienced relatively greater crowding, male-biased parasitism was found to increase dynamic stability in many cases. This further implies that unequal sex ratios are destabilizing, whether due to disease or other demographic factors.

There is considerable evidence for male-biased parasitism in vertebrates (Poulin 1996; Schalk and Forbes 1997; Moore and Wilson 2002). However the mechanisms behind this are not wholly understood. Males are predicted to have greater exposure to parasites, due to their larger home ranges and increased activity levels (Perkins et al. 2003). Increased male susceptibility is often attributed to the immunocompetence handicap hypothesis (Hamilton and Zuk 1982; Folstad and Karter 1992; Schalk and Forbes 1997). In mammals, sex-biased parasitism is associated with sexual size dimorphism, with males the larger and more heavily parasitized sex (Moore and Wilson 2002; Wilson et al. 2002). Furthermore, there is now convincing evidence that not only do males have greater susceptibility and support higher parasite intensities, they may also be responsible for the majority of

disease transmission. Perkins et al. (2003) investigated the role of key hosts in the yellow-necked mouse, *Apodemus flavicollis*. These are parasitized by the sheep tick, *Ixodes ricinus*, the vector of the zoonotic tick-borne encephalitis (TBE) (Labuda et al. 1997). Sexually mature males of high body mass were identified as a functional group responsible for driving most of the transmission. Removal of this group (which constituted 26% of the total population) was shown to reduce transmission potential by 79%. In another study on *A. flavicollis*, Ferrari et al. (2004) experimentally reduced the helminth community to either sex, of the dominant macroparasite nematode, *Heligmosomoides polygyrus*. Reducing the parasite intensity of males significantly reduced the intensity in females, estimated through faecal egg counts, although reducing the intensity in females had no significant effect on the intensity in males. Furthermore, 20% of the most infected individuals (62% of males) were found to be responsible for 73% of the total eggs expelled. These two studies both roughly conform to the '20/80 Rule', by which 20% of the individuals account for 80% of the transmission potential (Woolhouse et al. 1997). Male-biased parasitism may often be responsible for the persistence of diseases, by maintaining the basic reproductive ratio (R_0) of the pathogen above unity (Perkins et al. 2003). Males may often have an increased susceptibility to infection; they may also cause the majority of female infections. Indeed, the most heavily parasitized individuals are likely to be the ones most responsible for disease transmission (Skorping and Jensen 2004). Males may also be intrinsically more infectious, due for example to their increased activity and/or host range. Investigating the effects of higher male susceptibility and infectiousness may form the basis of future work.

The aim of this chapter was to examine the effect on dynamical stability of male-biased parasitism. As with unbiased parasitism, there is generally an increase in dynamic stability, provided the case mortality is not too high. For sufficiently high case mortality both unbiased and male-biased parasitism are likely to induce cycles or even chaos. In this case, a population experiencing male-biased parasitism is relatively less stable if there is monogyny; in contrast, a polygynous species may be relatively more stable.

7. Discussion chapter

7-1. Conclusions and general perspectives

In chapter 2, the evolution of tolerance and control were shown to have fundamentally different dynamics. Tolerance confers a reduction in virulence and invasion by a tolerant strain therefore increases the prevalence of infection. Consequently, tolerance may only ever result in monomorphism. In contrast, invasion by a control strain may reduce the prevalence of infection. Under a decelerating trade-off this may lead to polymorphism. Given that avoidance is also associated with a reduction in disease prevalence (Roy and Kirchner 2000), this suggests that forms of resistance that reduce pathogen fitness (avoidance, control, recovery, acquired immunity) have at least some potential to evolve polymorphism. Indeed, polymorphism in avoidance strategies has been predicted in several models (Boots and Haraguchi 1999; Bowers et al. 2003). In the model presented in chapter 2, only marginally decelerating trade-offs were associated with polymorphism. This relates to the recent theory of trade-off and invasion plots (TIPs; Bowers et al. 2005). According to this theory, polymorphism will only evolve under trade-offs of intermediate curvature (though these need not necessarily be decelerating). Interestingly, a decelerating trade-off between virulence on different hosts has been associated with polymorphism in parasite strategies (Regoes et al. 2000).

Chapter 3 examined how the evolution of different forms of resistance is dependent on the host's lifespan. The basic assumption that longer-lived species should always invest in relatively greater resistance was shown to be invalid in a number of cases. In particular, if hosts have acquired immunity, there is often a non-monotonic relationship between lifespan and the level of innate resistance that evolves. Longer-lived populations tend to have higher levels of density-dependence, which reduces the density of susceptibles and in turn the infection prevalence. This extends previous work on lifespan and resistance (van Boven and Weissing 2004), highlighting that the prevalence of immunity must be sufficiently large for density-dependence to reduce the selection for resistance. This is likely if there is a high probability of acquiring immunity and a low rate of loss of immunity. The evolution of acquired immunity itself was also investigated. Depending on how immunity

evolves, the host's investment either increased monotonically with lifespan (although here there was bistability at low lifespan), or initially increased with lifespan and then decreased towards zero.

The phenomenon of evolutionary bistability can occur in many situations. There is often evolutionary bistability in tolerance outcomes (chapters 2, 3; Boots and Bowers 1999). In contrast, there is no bistability in recovery (chapter 3), unless the parasite also coevolves with the host (van Baalen 1998). Longer-lived populations may show evolutionary bistability in avoidance, in particular if they benefit from acquired immunity (chapter 3). This is somewhat surprising, given that avoidance and recovery both reduce the prevalence of infection and have similar evolutionary dynamics (Boots and Bowers 1999). The difference is likely to be due to the fact that recovery is beneficial only after a host becomes infected, while avoidance confers a benefit to susceptible hosts. The evolution of parasite virulence may also exhibit bistability (Andre and Gandon 2006).

Chapter 4 examined the evolution of the pathogen in response to a fixed level of host tolerance. The outcome was shown to depend on the form of the tolerance. In agreement with previous theory (Restif and Koella 2003), if tolerance reduces virulence by a constant factor, this always selected for higher replication rates and virulence, assuming these traits are positively correlated (Frank 1996). Where tolerance reduces virulence in an additive manner this often selected for lower replication rates, possibly leading to an apparent commensalism. The fact that tolerance is costly for the host (modelled as a lower intrinsic birth rate) may be interpreted as a morbidity cost of parasitism, although the mortality cost (virulence) is zero. Of particular interest is the fact that a high level of additive tolerance may result in commensalism at a higher replication rate than prior to the evolution of tolerance.

Chapter 5 considered the implications of varying degrees of density- and frequency-dependent transmission. The conditions for disease persistence, host-pathogen coexistence, and parasite-driven extinction were derived. In particular, increasing the amount of frequency-dependence was shown to allow extinction for a

lower probability of infection. When the two forms of transmission were traded-off, host-parasite coexistence was most likely when the population had a high carrying capacity, transmission was highly density-dependent, and there was an intermediate probability of infection per contact. Provided there is some element of frequency-dependence in the transmission mode, a high infection probability may cause the host to go extinct. Pure frequency-dependent transmission is generally predicted to result in parasite-driven extinction at high transmission rates, unless the host has a sufficiently high birth rate (Getz and Pickering 1983; Thrall et al. 1993; Alexander and Antonovics 1988; Boots and Sasaki 2003). In these previous models, a high birth rate prevents extinction by keeping the average per capita growth rate above zero. I have shown that endemic persistence may also be maintained if disease transmission is partly density-dependent. This raises the question of whether pathogens should evolve to be more density- or more frequency-dependent. High population densities favour density-dependent transmission, while low densities select for frequency-dependence (Thrall and Antonovics 1997; Thrall et al. 1998). If frequency-dependent transmission is associated with sterilizing effects, and density-dependence with virulence, then mixed strategies or polymorphism in transmission mode may evolve (Thrall and Antonovics 1997; Thrall et al. 1998). Given that STDs tend to be associated with sterility costs and OIDs with mortality costs (Lockhart et al. 1996), pathogens may often evolve such complementary transmission strategies.

Chapter 6 investigated the population dynamics due to male-biased parasitism, in comparison to unbiased parasitism, or an uninfected host population. This was modelled as a higher male susceptibility to infection (lower avoidance). Males and females were therefore modelled explicitly as separate population classes, where the birth function depended on the relative densities (Caswell and Weeks 1986; Lindstrom and Kokko 1998). The case mortality of parasitism was shown to have a strong influence on the dynamics. At low case mortality, male-biased parasitism was similar to unbiased parasitism and had a stabilizing effect on the dynamics. This was generally the case at intermediate mortalities, although in some cases male-biased parasitism increased the periodicity of cyclic dynamics. At high mortalities, there was shown to be a strong effect of the mating system: monogynous populations exhibiting

male-biased parasitism were generally less stable, while polygynous ones could be either more or less stable.

7-2. Implications for further work

The evolution of parasite virulence is likely to be constrained by relationships between other aspects of parasite fitness. This requires that both within-host and between-host (epidemiological) factors be considered (Gandon 2004). Virulence is likely to be positively correlated with transmissibility (Anderson and May 1982; Frank 1996; Ebert and Weisser 1997; Lipsitch and Moxon 1997) and negatively correlated with recovery (Fenner and Ratcliffe 1965; Anderson and May 1982). As such, most epidemiological models make simplifying assumptions about the nature of the parasite dynamics within infected hosts. Although such simplifications have their utility, models have recently begun to consider within-host parasite dynamics explicitly (Antia et al. 1994; Ganusov et al. 2002; Gilchrist and Sasaki 2002; Andre et al. 2003; Alizon and van Baalen 2005; Andre and Gandon 2006). In such models, transmissibility, virulence and recovery are therefore determined as a result of the interaction between the host's immune system and the parasite's replication. Antia et al. (1994) investigated the evolution of parasite virulence, assuming a threshold parasite density above which the parasite automatically kills the host. Parasite fitness was shown to be maximal for an intermediate virulence, equivalent to maximizing the parasite's basic reproductive rate (R_0). The model also defined a range of intermediate virulences over which the parasite is able to persist. This is particularly relevant in the context of multiple infections, which generally select for higher virulence (May and Nowak 1994, 1995; Nowak and May 1994). Virulence evolution will therefore be constrained to within an upper bound, as extremely virulent parasites will go extinct. Andre and Gandon (2006) considered how vaccination conferring a higher rate of replication of lymphocytes (equivalent to host resistance in this context) would select the parasite. The optimal parasite replication rate was shown to increase with the proportion of vaccinated hosts. This is consistent with earlier models that do not explicitly consider the within-host dynamics (Gandon et al. 2001, 2003). Another interesting parallel is that the case mortality due to infection

was lower in vaccinated hosts, even when the parasite evolved. Virulence (the instantaneous rate of parasite-induced mortality) may often increase in response to tolerance, but never totally erodes the benefit of the initial tolerance (chapter 4; type II). Although case mortality and virulence provide different measures of parasite damage, these are likely to be correlated in many cases. Models combining within-host and epidemiological dynamics may also be useful in investigating host-parasite coevolution. Here, the replication rate of lymphocytes could be taken as a dynamic variable (equivalent to the level of host resistance) and coevolve with parasite replication rate.

Coevolutionary processes are particularly characterised by the antagonistic interactions between host and parasites (van Baalen 1998). Parasite virulence is generally predicted to increase in response to a higher recovery rate of the host (chapter 4; van Baalen and Sabelis 1995; Day 2001; Restif and Koella 2003). In turn, higher virulence may cause the host to evolve a higher recovery. The actual case mortality may therefore either increase or decrease, although the duration of an infection will be much shorter (Day 2002a; Day and Burns 2003). It is clearly important, therefore, to consider whether the particular measure under investigation (i.e. virulence, case mortality, duration of infection) provides an accurate characterisation of the evolutionary processes.

Recent publications have demonstrated that complex relationships between parameters may confound many of the predictions regarding virulence evolution (Day 2001, 2002a, 2003; Williams and Day 2001; Day and Proulx 2004). Ebert and Mangin (1997) provide an interesting case in point. In their study, a horizontally transmitted microsporidian gut parasite, *Glugoides intestinalis*, was artificially selected in response to increasing background mortality of the host. Virulence was positively correlated with within-host replication rate. However, selected lines evolved lower virulence. In contrast, the basic transmission-virulence trade-off predicts that optimal virulence should increase with background mortality (chapter 4; van Baalen and Sabelis 1995; Day 2001; Restif and Koella 2003). This disparity was thought to be due to multiple infections. Higher background mortality reduces the

frequency of multiple infections and therefore the intensity of within-host competition, and this selects for reduced virulence (Ebert and Mangin 1997). Day and Proulx (2004) suggest that it is the relative importance of susceptible and infected hosts as sources of potential transmission that actually determines the direction of virulence evolution. Higher background mortality increases the density of susceptible hosts, and decreases the density of infecteds. If the latter are more important in terms of transmission (i.e. if multiple infections are common), increasing background mortality should therefore select for reduced virulence. In modelling host-parasite interactions, therefore, there are clearly no panaceas.

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