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Lethal pathogens, non-lethal synergists and the evolutionary ecology of resistance

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ABSTRACT

Mixed pathogenic infections are known to have profound effects on the ecological and evolutionary diversity of both hosts and parasites. Although a variety of mechanisms have been proposed by which hosts can withstand parasitic infections, the role of multiple infections and the trade-off in multiple defence strategies remain relatively unexplored. We develop a stage-structured host–pathogen model to explore the ecological and evolutionary dynamics of host resistance to different modes of infection. In particular, we investigate how the evolution of resistance is influenced through infection by a lethal pathogen and a non-lethal synergist (that only acts to enhance the infectivity of the pathogen). We extend our theoretical framework to explore how trade-offs in the ability to withstand infection by the lethal pathogen and the ability to tolerate the synergist affect the likelihood of coexistence and the evolution of polymorphic host strategies. We show how the underlying structure of the trade-off surface is crucial in the maintenance of resistance polymorphisms. Further, depending on the shape of the trade-off surface, we predict that different levels of host resistance will show individual responses to the presence of non-lethal synergists. Our results are discussed in the wider context of recent developments in understanding the evolution of resistance to pathogen infections and resistance management.

1. Introduction

Parasitism is a diverse life-history strategy spanning all major taxa. Understanding the impact of disease on the distribution and abundance of species is a central and unifying theme in population biology (Kennedy, 1975; Anderson and May, 1986; Hudson et al., 2002). In many species, individuals may be infected with single disease strains, more than one strain of the same conspecific pathogen or may even harbor multiple infections of closely related heterospecific pathogens. These single and mixed infections and their potential impact are widely predicted to affect the ecological and evolutionary dynamics of both hosts and parasites (Moore, 2002; Bonsall, 2004; Thomas et al., 2005).

Pathogens are known to affect the population dynamics of their hosts through direct infections (Anderson and May, 1978; May and Anderson, 1978), indirect (covert) routes of infection (Holt and Pickering, 1985; Boots et al., 2003; Bonsall et al., 2005a) and sublethal mechanisms (Sait et al., 1994). Original work on the dynamics of microparasites and their hosts demonstrated that pathogens have the propensity to cause cyclic variation in host abundance (Anderson and May, 1980, 1981). The characteristic combination of high levels of parasite-induced mortality, large pathogen yields, long-lived resting stages and low population growth rates were predicted to lead to population cycles. More recently, the debate over whether pathogens are capable of inducing population instabilities has focused on the role of additional biological realism including the effects of competition within (e.g. White et al., 1996; Bonsall et al., 1999; Liu et al., 2007) and between species (e.g. Holt and Pickering, 1985; Hochberg and Holt, 1990), the role of refuges (e.g. Hochberg, 1989) and the effects of age-structure (e.g.Briggs and Godfray, 1995, 1996).

While it is clear that these natural enemies can have important effects on the demography of host populations through lethal infections, recent theoretical and empirical work highlights how pathogens are able to affect host dynamics through covert or sublethal infections (Hughes et al., 1993, 1997). These infection strategies arise where a class of hosts is partially or wholly resistant to infection and theoretical studies have illustrated the importance of this immunity in understanding host–pathogen interactions (Boots et al., 2003; Bonsall et al., 2005a). For instance, covert infection strategies which do not confer immunity and allow infections through both sublethal and overt routes are predicted to lead a range of dynamical outcomes including a persistent stable state between the covertly infected hosts and the pathogen only. Strategies that confer immunity (resistance to further infection) are also predicted to show a range of population

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dynamic outcomes from stable interactions to unstable population cycles depending on the propensity of covert infections to develop, and the strength of disease reactivation (Bonsall et al., 2005a).

Emphasis on the evolution and maintenance of resistance has mainly focused on genetic descriptions (see for example, Frank, 1991; Segarra, 2005). However, as pointed out by Antonovics and Thrall (1994), it is entirely plausible that population dynamics and population densities are critically important in generating and maintaining polymorphisms. Gillespie (1975) illustrates that resistance to infection is influenced by both frequency- and density-dependent selection such that the advantage conferred on a resistant genotype increases with density, and the frequency of susceptibles determines the benefits (or costs) to different genotypes. Along similar lines, Antonovics and Thrall (1994) also argue that the maintenance of protected polymorphisms is a response determined by numerical as well as gene-frequency dynamics. In particular, persistence of alternative resistant and susceptible host phenotypes is driven by the epidemiological interaction between the pathogen and the host. Resistant host strains are expected to reduce disease incidence (and, therefore, pathogen abundance), favor the spread of susceptible host strains (and a change in host abundance) and consequently affect the persistence of the resistant strain (Antonovics and Thrall, 1994).

In addition to developing resistance to infection, hosts may tolerate infections. These two traits, resistance and tolerance, have direct impacts on host fitness. Resistance reduces the exposure to infection while tolerance reduces fitness losses once an infection has established (Roy and Kirchner, 2000). Although both these strategies for dealing with disease have short-term fitness benefits, their evolutionary dynamics are quite distinct. The fitness costs of resistance can prevent the fixation of resistance alleles through pleiotropic and density-dependent feedbacks whereas the prevalence of tolerance genes and the fitness advantages that these genes confer can accelerate time to fixation of this strategy (Roy and Kirchner, 2000). Understanding how tolerance and resistance interact has important applied (see below) and evolutionary implications. From an evolutionary perspective, selection for both resistance and tolerance could favor polymorphisms when resistance is high and favor fixation when tolerance is stronger (Roy and Kirchner, 2000). Traits that favor high tolerance and low resistance are more likely to promote monomorphic strategies. Our goal in this study is to develop this theme and explore how the evolution of resistance to pathogens in stage-structured populations is modulated by the presence of a non-lethal synergistic microbe (that hosts must tolerate). We begin by outlining the biological motivation for the study, before presenting the theoretical model. We show that the effects of a synergistic, non-lethal microbe can affect the maintenance of alternative polymorphisms, that this effect is influenced by the underlying population dynamics and that different phenotypes can respond differentially to the action of the synergist. The results are discussed with reference to recent developments in the evolution of resistance to pathogens.

2. Biological motivation

As mentioned, resistance can be manifested as mechanisms to avoid, recover from or tolerate infections (Boots and Bowers, 1999; Miller et al., 2005). In contrast to conventional approaches to exploring the evolutionary ecology of resistance based on how it affects host fecundity (Anderson and May, 1982; May and Anderson, 1983), models are developed here to explore trade-offs based, more realistically, on the ability of hosts to survive and reach maturation (to an invulnerable stage). This is a much more appropriate framework in which to explore the ideas of the evolutionary ecology of resistance for a range of host–parasite interactions including a wide range of insect host–pathogen interactions.

Our main motivation for this study and the development of the theoretical framework is to explore how the action of a non-lethal synergist is tolerated by a host and how this affects the evolution of resistance to lethal pathogens. One example where non-lethal synergists might affect the infectivity of lethal pathogens is the interaction between toxin-producing strains of Bt (*Bacillus thuringiensis*) and non-pathogenic, opportunistic strains of *Bacillus cereus* in insects. Bt is widely used as an alternative to conventional, synthetic pesticides for the control of numerous entomological pests such as Lepidoptera (Bt subsp *kurstaki*), Diptera (Bt subsp. *israelensis*), and Coleoptera (Bt subsp. *tenebrionis*). Using applications of Bt as a microbial spray or in transgenic plants captures the unique property of Bt: its ability to produce toxic, insecticidal crystal proteins (Cry proteins). Following ingestion, proteins are released from these soluble crystals which bind to the midgut membrane, induce pore formation and cell lysis that eventually kills the insect. This pattern of infection and consequently, transmission in Bt (and other microbes) is well-known to be dose-dependent (e.g. Raymond et al., 2005).

Although Bt toxin production is specific, numerous insect pests have developed resistance to this microbe (Ferré and Van Rie, 2002). The degree of resistance is under genetic control and there is a clear fitness cost to resistance (Ferré and Van Rie, 2002; Bourguet et al., 2004) that can be dependent on the local environment (Raymond et al., 2005). The distribution of resistance amongst insects is principally confined to the laboratory strains although some insects (such as the diamondback moth, Tabashnik et al., 1990, and the cabbage looper, *Trichoplusia ni*, Janmaat and Myers, 2003) show differential levels of resistance to Bt in the field or glasshouse. However, to date, these studies neither predict how resistance will develop in the field nor how fitness costs associated with resistance might be modulated, mitigated or enhanced by the presence of additional non-lethal microbial synergists.

Resistance to infection is known to be affected by a variety of different genetic and ecological factors (e.g. Gardner et al., 1998; McKenzie and Batterham, 1998; Raymond et al., 2005, 2007). Recent work on Bt has illustrated how resistance to infection might be modulated by genetic and ecological characteristics. Contrary to expectation, the fitness of susceptible and resistant host strains does not necessarily differ in the absence of the pathogen. Susceptible and resistant strains of diamondback moth may have equivalent development times, growth and survival—yet pleiotropic fitness costs associated with resistance may emerge on particular host plants or under competition for resources and thereby provide the selective basic for maintaining resistance/susceptible polymorphisms (Raymond et al., 2005, 2007). Similar effects have been documented for *T. ni*. Bt resistant and susceptible moth strains may show no overall differences in larval survival or size on high quality host plants (Janmaat and Myers, 2005). However, between host plants there are clear differences leading to the maintenance of polymorphisms. Resistance to infection, in general, can induce pleiotropic costs in terms of development and/or survival (Groeters et al., 1993; Tang et al., 1997; Erb et al., 2001; Raymond et al., 2005). Similarly the fitness benefits of resistance toinfection are usually improved survival and/or development time in the presence of pathogens (Gould and Anderson, 1991). To explore this theme, we incorporate the effects of resistance (together with the effects of tolerance) through trade-off functions (see below) affecting maturation rate. In particular, we explore the idea that, in the