The University of Sheffield

PhD Thesis

Trade-offs between Host Defense Mechanisms: Impacts on Evolutionary and Coevolutionary Dynamics of Host-Parasite Interactions

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Dedicated to

My parents, Mrs. Rakesh Rani

&

Mr. Virendra Pal Singh,

for making my education a priority and the endless love.

Thesis abstract

Evolution plays a key role in shaping the trajectory of infectious diseases and it is important to comprehend the mechanisms that allow parasites to mutate and adapt to new environments. Studying host-parasite interactions provides essential insights that are crucial for disease control and prevention. In this thesis, I utilise mathematical models and evolutionary invasion theory to explore how hosts allocate investments in defence mechanisms against parasites. I specifically examine how investments are influenced by the presence of negative correlations between these mechanisms.

Hosts' defence mechanisms against parasites are usually divided into two classes: resistance and tolerance. Resistance strategies act to reduce the fitness of parasites, while tolerance strategies mitigate the negative impact on host fitness without directly harming the parasites. First, I investigate the simultaneous evolution of resistance and tolerance in a host population where they are negatively correlated by a trade-off. Here I focus on examining the optimal investment patterns in resistance and tolerance and predicting the favoured strategy under diverse ecological and epidemiological conditions. Next, I study a case where the host can evolve both sterility tolerance and mortality tolerance as defences against parasitic infection, with a direct trade-off between the two strategies. The primary objective here is to predict the evolutionary outcomes based on the trade-off shape: polymorphism, stable investments, or maximization/minimization. I then extend this model into a coevolutionary framework, investigating the coevolution of hosts and parasites while considering explicit trade-offs between host sterility-mortality tolerance and parasite recovery-transmission.

My results reveal the underlying feedbacks created by the impact of trade-offs, disease prevalence, fluctuating ecological dynamics, and various epidemiological traits on the selection of defence strategies. This work contributes to better understanding of host-parasite evolution and serves as a potential theoretical base for future experiments in this field.

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Contents

List of Tables

List of Figures

Chapter 1

Introduction

"As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be naturally selected" - Darwin, On the Origin of Species, 1859.

1.1 Why do we study evolution of host-parasite interactions

The COVID-19 pandemic has had a devastating impact on the world, claiming approximately 6.9 million lives to date and continuing to cause widespread illness and death. The pandemic has highlighted the urgent need for increased investment in infectious disease surveillance, prevention, and control programs, as well as research on emerging infectious diseases that threaten global health security (WHO, 2023). Parasites and other pathogens have the potential to evolve and adapt quickly to their environment, making it difficult to develop effective interventions and vaccines (O'Neill, 2016). Evolution plays a notable role in determining the fate of infectious diseases, and it is imperative to understand the evolutionary mechanisms that enable pathogens to evade immune responses, adapt to new environments, and develop drug resistance. Despite significant advances in infectious disease research, there are

still many crucial aspects that require further exploration and understanding. For instance, researchers need to improve their understanding of the host's defence mechanisms against pathogens, including how these mechanisms are interrelated within a species and how they shape the evolution of host-parasite dynamics.

The COVID-19 pandemic has heightened the interest in the use of mathematical modelling to combat infectious diseases (Kucharski et al., 2020). Mathematical models provide a powerful tool for simulating the spread and evolution of parasite-transmitted diseases, enabling the development of effective control strategies. Over the past few decades, a wide range of host-parasite compartmental models have been developed to capture the general trends in the spreading and evolution of infectious diseases (Kermack & McKendrick, 1932; Anderson & May, 1979; Murray, 1993; Venturino, 2001; Lipsitch et al., 2003; Ferguson et al., 2006; Diekmann et al., 2013; Porter et al., 2013; Sofonea et al., 2015). Many questions regarding the evolutionary dynamics of host-parasite interactions have been investigated, such as the nature and significance of infection genetics (Frank, 1993; Sasaki, 2000; A. Agrawal & Lively, 2002; Tellier & Brown, 2007; Mostowy et al., 2012; Boots et al., 2014), trade-offs between defence and host life-history traits (Boots & Bowers, 1999; Boots & Haraguchi, 1999; Restif & Koella, 2003; Best et al., 2010a; Boots et al., 2013; Best et al., 2017b), the difference between host resistance and tolerance (Boots & Bowers, 1999; Roy & Kirchner, 2000; Restif & Koella, 2004; Miller et al., 2006; Vitale & Best, 2019), the effect of adding a third species, such as a predator (Morozov & Adamson, 2011; Morozov & Best, 2012; Kisdi et al., 2013; Toor & Best, 2015; Best, 2018), and more. Although more empirical data can improve our understanding of how biological nuances can affect the patterns and contribute to the exceptions, our theoretical understanding of the evolution of infectious diseases in even the simplest systems still has significant gaps. Once such gap in current understanding of host-parasite interactions is how the host and parasite evolve, independently or jointly, when investing in one defence mechanism comes at the expense of another. In other words, when there is a direct trade-off between the efficacy of two different host defence mechanisms, what mechanisms do hosts and

parasites employ to maintain their survival and reproductive success?

In this thesis, we use the concept of adaptive dynamics to model the evolutionary dynamics of hosts and parasites, with a specific focus on the evolution of host defence mechanisms. By incorporating both ecological and evolutionary dynamics through this approach, we aim to provide insights into the selection pressures driving epidemiological traits in host populations that harbor parasitic infections. Throughout the course of the thesis, our central focus remains on how the assumption of a trade-off between two distinct host defence mechanisms influences host evolution. We conduct an extensive analysis of the various ecological environments that hosts evolve in and how they impact optimal defence investment, ultimately determining which defence mechanism is favored under different ecological conditions. This research underscores the significance of trade-off functions in determining evolutionary outcomes. For a major part of the thesis, we work on purely host evolutionary frameworks, assuming negative correlations between various host defence mechanisms, i.e., a resistance-tolerance and a tolerance-tolerance trade-off. Later on, we expand the tolerance-tolerance trade-off analysis to a coevolutionary framework that allows the parasite to evolve through a transmission-recovery trade-off.

1.2 Resistance and tolerance as two arms of host defence

When attacked by a parasite, the host can evolve a variety of defence mechanisms which are often classified into resistance and tolerance (Miller et al., 2006; Råberg et al., 2007; Råberg et al., 2009; Medzhitov et al., 2012; Sorci, 2013; DeSimone et al., 2018; Grab et al., 2019). Resistance in theoretical evolutionary models is usually defined as the host's ability to act against the pathogens and reduce their fitness (Antonovics & Thrall, 1994; Bowers et al., 1994; Restif & Koella, 2004; Miller, 2006; Best et al., 2008), while tolerance is generally defined as the host's ability to limit the damage caused by parasitic infection without negatively affecting their fitness (Boots & Bowers, 1999; Roy

& Kirchner, 2000; Miller et al., 2005; Vitale & Best, 2019). In plants, resistance traits have been detected in the form of the production of leaf trichomes in the perennial herb *Arabidopsis lyrata* (Sletvold et al., 2010), higher glucosinolate concentration in *Arabidopsis thaliana* (Mauricio, 1998), or a range of secondary defence chemicals such as diterpenes and phenolics (Gershenzon, 1994; Strauss & Agrawal, 1999; Hull-Sanders et al., 2007). In insects, resistance can manifest through physiological barriers such as the gut wall to prevent parasites from infecting them or through a highly efficient immune system which provides resistance to parasites (Dunn et al., 1994; Medzhitov & Janeway, 1997; Boots & Haraguchi, 1999; Zuk & Stoehr, 2002; Schmid-Hempel & Ebert, 2003; Schmid-Hempel, 2005). On the other hand, examples of tolerance traits in plants include the ability to adjust photosynthesis and nutrient uptake rates, and to exhibit plasticity in allocation patterns and developmental rates (Núñez-Farfán et al., 2007). Other examples include root storage for regrowth after damage (Strauss & Agrawal, 1999), increased progeny production after infection (Carr et al., 2003), and longer post-infection survival rates (Roy et al., 2000; Vijayan et al., 2017). Additionally, plants have been observed to exhibit other tolerance traits such as leaf addition rate, relative growth rate, specific leaf area, and delayed leaf senescence (Meyer, 1998; Hakes & Cronin, 2011). Insects, like the bumblebee *Bombus terrestris*, can also evolve tolerance when attacked by intestinal parasites (Imhoof & Schmid-Hempel, 1998).

The concept of a two-component defence response - involving resistance and tolerance, is well described by plant ecologists to assess plant health in plant-pathogen interactions (Schafer, 1971; D. Clarke, 1986; Stowe et al., 2000; Kover & Schaal, 2002; Schwachtje et al., 2006; Schneider & Ayres, 2008). While both resistance and tolerance are traits that the hosts can evolve to combat the negative effects of infection, it is important to differentiate between both strategies as they can have distinct ecological and evolutionary implications (Restif & Koella, 2004; Pagán & García-Arenal, 2018). For instance, resistance acts to reduce the risk of infection and parasite replication within the host, while tolerance does not (Råberg, 2014). The spread of a resistance gene in the host population leads to a decline in the parasite prevalence, reducing the

fitness advantage associated with carrying the resistance gene, thus establishing a negative feedback loop (Roy & Kirchner, 2000; Råberg et al., 2009; Hayward et al., 2014). This negative frequency dependence prevents the fixation of a resistant trait within the host population, potentially resulting in polymorphisms (Boots & Bowers, 1999; Boots & Bowers, 2004). In contrast, tolerance alleviates disease severity and allows tolerant hosts to live longer, thereby increasing disease prevalence. Unlike resistance, a tolerance trait will become fixed in a host population as it is positively selected for (Schneider & Ayres, 2008; Råberg et al., 2009). The distinction between both defence strategies has also been documented experimentally. For example, resistance mechanisms, such as immune responses, can kill parasites and reduce costs associated with parasite exposure, such as blood loss (Owen et al., 2010). On the other hand, tolerance mechanisms, such as resource compensation or tissue repair, do not eliminate the parasite but instead allow the host to cope with increased parasite exposure (Christe et al., 1996; Morrison & Johnson, 2002; Medzhitov et al., 2012; Knutie et al., 2016). Thus, both resistance and tolerance can have a significant, but different impact on the evolution of host-parasite interactions. In recent decades, researchers have made significant efforts to comprehend the evolutionary consequences of both defence strategies. Nevertheless, while there is a substantial body of literature on resistance to plant pathogens, tolerance has received comparatively less attention.

Theoretical studies have modelled resistance and tolerance mechanisms using various simplified assumptions. As such, resistance can evolve as "avoidance", which reduces the host's susceptibility of getting infected and resistant hosts therefore have a lower infection transmission rate (Boots & Bowers, 1999; McLeod & Day, 2015; Best et al., 2017b; Donnelly et al., 2017), or as "clearance" which involves increased rate of recovery through more efficient immune system (Baalen, 1998; Restif & Koella, 2004; Miller et al., 2007; Best et al., 2008; Best et al., 2017b), or as "acquired immunity" where the host cannot be reinfected once recovered from the infection (Miller, 2006; Best & Hoyle, 2013; Boots et al., 2013; Donnelly et al., 2015), and more. Likewise, tolerance can evolve in two forms: tolerance to parasite impact on host mortality known

as mortality tolerance (Miller et al., 2005; Miller et al., 2007; Råberg, 2014; Kutzer & Armitage, 2016; Pagán & García-Arenal, 2018), or tolerance to the effects of parasite on host fertility, termed as sterility tolerance (Best et al., 2008; Sloan et al., 2008; Best et al., 2010b; Vale & Little, 2012; Abbate et al., 2015; Budischak & Cressler, 2018). There is a critical difference in how mechanisms of tolerance act towards pathogens. As such, mortality tolerance can extend the lifespan of infected hosts, raising parasite prevalence and thus promoting the positive frequency dependence and fixation of the tolerance trait (Roy & Kirchner, 2000; Kada & Lion, 2015). This is in contrast to the mechanisms of resistance which generally tend to lower parasite prevalence, leading to negative frequency dependence and possible polymorphism in a resistance trait (Miller et al., 2007; Budischak & Cressler, 2018). So, polymorphism is not possible in models of mortality tolerance given their positive frequency dependence on parasite fitness (Best et al., 2009, 2014) (unless external conditions are imposed, see Ferris and Best (2019) for example). Sterility tolerance, however, remains either neutral towards parasite fitness, or can negatively impact it, depending upon the costs incurred (Best et al., 2008; Best et al., 2010b; B. J. Parker et al., 2014). Therefore, investment in sterility tolerance can lead to negative frequency dependence and polymorphism if the cost involves reduction of host fitness attributes. These distinctions in tolerance mechanisms have crucial implications for ecological and evolutionary dynamics, and require thorough investigation.

There is extensive theoretical literature on the evolution of resistance mechanisms along with empirical backup (Simms & Triplett, 1994; Mauricio, 1998; Stevens et al., 2007; Kraaijeveld & Godfray, 2008; Sletvold et al., 2010; Klemme & Karvonen, 2017). However, despite the ample empirical evidence for the presence of both tolerance mechanisms in host-parasite systems (Stowe, 1998; Juenger et al., 2000; Blanchet et al., 2010; Vale & Little, 2012; Klemme & Karvonen, 2017; Pagán & García-Arenal, 2018; Montes et al., 2020), models of mortality tolerance (Roy & Kirchner, 2000; Restif & Koella, 2003; Miller et al., 2005; Miller et al., 2006, 2007; Best et al., 2009, 2014; Råberg, 2014; Kutzer & Armitage, 2016; Best et al., 2017a; Ferris & Best, 2019; Vitale

& Best, 2019) significantly outnumber the models of sterility tolerance (Best et al., 2008; Sloan et al., 2008; Best et al., 2010b; Abbate et al., 2015; Budischak & Cressler, 2018). In this thesis, we extensively explore the evolution of two forms of tolerance - sterility tolerance and mortality tolerance - in both a host evolution framework and then in a coevolutionary framework.

1.3 Trade-offs between different host defence mechanisms

Host defence mechanisms can be costly and therefore the hosts have to balance between these investments with other important processes such as reproduction, migration, and foraging to maximize their fitness (Sheldon & Verhulst, 1996; Lochmiller & Deerenberg, 2000; Graham et al., 2010; Graham et al., 2011; van der Most et al., 2011). The idea of trade-offs has been a prominent feature in evolutionary thought for various reasons, particularly in relation to the factors that constrain an organism's adaptability. For instance, why do only a few plant species remain untouched by herbivores, and why are polar and equatorial climates too extreme for most animals? Biologists have largely accepted that trade-offs play a crucial role in setting limits to adaptation (Futuyma & Moreno, 1988). A trade-off can simply be defined as a scenario where an organism's fitness cannot be maximized due to conflicting demands, resulting in opposing selection pressures on a particular trait (known as one-trait trade-off) or selection to increase multiple traits that share a limiting resource (termed as multiple-trade trade-off) (A. A. Agrawal et al., 2010). One-trait and multiple-trait trade-offs can be fundamentally different, as in a one-trait trade-off there is opposing selection, while in a multiple-trait trade-off selection acts to increase investment in all traits. Both types of trade-offs are also sometimes referred to as costs (Futuyma, 1998). Plants may face a trade-off in allocating resources towards anti-herbivore defences, balancing the benefits of lowered herbivory with the costs of diverting resources from other functions. Additionally, prioritizing resources towards one type of defence may come at

the expense of other defence mechanisms. This widely accepted concept of "trade-offs" between various host defences has been successfully detected in many host-parasite systems (Berenbaum et al., 1986; Björkman & Anderson, 1990; Fineblum & Rausher, 1995; Stowe, 1998; Ruuhola et al., 2001; Rudgers et al., 2004; Råberg et al., 2007; Baucom & Mauricio, 2008; Erb et al., 2011; Mikaberidze & McDonald, 2020).

In theoretical evolutionary models, trade-offs are essential assumptions used to explain the mechanisms by which ecological feedbacks generate frequency-dependent selection. The majority of the host-parasite evolutionary models are based on the assumption that evolving host defence is costly and considered trade-offs between defence strategies and other host fitness traits (Boots & Haraguchi, 1999; Gandon et al., 2002; Boots et al., 2009; Best et al., 2010a; Best et al., 2010b; Boots et al., 2012; Best et al., 2015; Donnelly et al., 2015; Best et al., 2017b; Donnelly et al., 2017). Another popular shorthand approach in evolutionary ecology has been to examine correlations (whether phenotypic, genetic, or between species) between two traits that are presumed to have a positive association with fitness (A. A. Agrawal et al., 2010). Because a multiple-trait trade-off is expected to be reflected in a negative correlation between traits, increasing attention was directed towards such correlations (Rausher, 1984; Futuyma & Moreno, 1988; James et al., 1988). As an example of a negative correlation, van der Meijden et al. (1988) argued that resistance to and tolerance of herbivory could be alternative strategies. As such, plant species that can resist herbivory (i.e., are not attacked) are unlikely to experience strong selective pressure to tolerate herbivory (i.e., have little fitness damage). Conversely, species that exhibit tolerance are not expected to face strong selection for resistance. This pattern has been observed in genotypes within plant species (Fineblum & Rausher, 1995; Stowe, 1998; Pilson, 2000; Fornoni et al., 2003; Mikaberidze & McDonald, 2020; Montes et al., 2021), as well as in animal genotypes (Råberg et al., 2007), though it is not universally applicable (Núñez-Farfán et al., 2007; Pagán et al., 2007; Montes et al., 2019). The first demonstration of an ontogenetic trade-off between resistance and tolerance was given by Boege et al. (2007) in a study done on *Raphanus sativus*. In the context of other stressors, such as frost and

herbicide application, there is evidence of selection favouring a negative correlation between resistance and tolerance due to alternative fitness peaks that promote either high resistance and low tolerance or low resistance and high tolerance (A. A. Agrawal et al., 2004; Baucom & Mauricio, 2008). The observed effect is likely due to the fact that these traits are both redundant and costly, leading to a selection for a negative correlation between them.

Furthermore, numerous experimental studies demonstrated that negative correlations exist within the traits of resistance itself. For instance, Berenbaum et al. (1986) found that greater selection for one resistance mechanism (i.e., bergapten proportion in the seed) reduce the selection for another resistance mechanism (i.e., sphondin proportion in the seed). Likewise, Björkman and Anderson (1990) studied two distinct morphs of *R. bogotensis* and found that trade-offs exist between anti herbivore defences (resistance traits) within each phenotype. Then Rudgers et al. (2004) detected a strong negative correlation between the direct resistance traits, trichomes and leaf gland in the cotton clade (Gossypieae). There is more empirical evidence for trade-offs between resistance traits, both within and across species (Zangerl & Berenbaum, 1990; Mauricio et al., 1997; Ruuhola et al., 2001; Ward & Young, 2002; Erb et al., 2011). Conversely, although empirical investigations on the correlations between two tolerance traits within a host population are rare, some studies suggest the existence of such trade-offs and emphasize the need for further research in this domain (Pagán et al., 2008; Pagán & García-Arenal, 2018; Pike et al., 2019; Montes et al., 2020).

While a large number of experiments have confirmed the presence of trade-offs between different host defence mechanisms, theoretical models rarely worked upon this assumption (Restif & Koella, 2004; Best et al., 2008; Best et al., 2017b; Boots & Best, 2018). Out of these, Best et al. (2008) explored the possibility of polymorphism through trade-offs between mortality tolerance and resistance (via clearance), and between sterility tolerance and natural death rate. They found that branching is not possible for the resistance-tolerance trade-off but can occur for the sterility tolerance-death rate trade-off. They emphasized the importance of understanding where tolerance acts:

mortality or sterility. Similarly, Restif and Koella (2004) examined the evolution of clearance and sterility tolerance as distinct, independent traits, with a focus on the effects of using different cost-function shapes. They found that the concurrent evolution of these two defence mechanisms could obscure their actual costs, even when genetically independent. In another study, Best et al. (2017b) briefly examined trade-offs between different defence mechanisms but primarily investigated the impact of parasite-induced sterility on various defence investments. Finally, Boots and Best (2018) predicted that a trade-off between constitutive and induced defence mechanisms is unlikely to result in branching. Thus, most of these studies focused on whether such trade-offs lead to branching or not, and none of them fully investigated the impact of ecological feedbacks over stable investments in defence strategies. Chapter 2 of this thesis proposes a model that fills this gap by incorporating a trade-off between resistance (through avoidance) and mortality tolerance. Here we focus on how variation in different host and parasite traits affects the stable investments in resistance or tolerance as host defence strategies.

However, while very few theoretical models have looked at a trade-off between two defence mechanisms, many have examined trade-offs between two fitness-enhancing traits, particular between fecundity and longevity. This trade-off is considered among the most significant in host life-history theory (Stearns, 1989; Roff & Fairbairn, 2007). This can be linked to a hypothesis from plant defence evolution that shared precursors may limit the production of diverse, beneficial defence strategies, leading to an allocation trade-off (Berenbaum et al., 1986; A. Agrawal & Lively, 2002). Several theoreticians have explored the possibility of hosts adjusting their resource allocation between reproduction and survival in response to infection, resulting in a fecundity-longevity trade-off (Hochberg et al., 1992; Hurd, 2001; Gandon et al., 2002; Bonds, 2006; Leventhal et al., 2014). Although there is an appreciation for the potential role of this trade-off in systems with sterilizing pathogens (Baudoin, 1975; Ebert et al., 2004; Sloan et al., 2008), epidemiological host-parasite models rarely consider it (Berec & Maxin, 2012; Janoušková & Berec, 2018, 2020). Some parasites affect both reproduction and survival in their hosts (Roy & Kirchner, 2000; Jensen et al., 2006; Vale

& Little, 2012), and empirical evidence suggests that host reproductive abilities can be costly for its survival under infection (Hurd, 2001; Pike et al., 2019). Since two mechanisms of tolerance, sterility tolerance and mortality tolerance, act against the parasite's impact on host reproduction and survival, a negative correlation between investments in the two mechanisms can arise through resource allocation (Montes et al., 2020). While such a correlation has been suggested in a few experiments (Budischak & Cressler, 2018; Pike et al., 2019; Montes et al., 2020), none of the existing evolutionary models have considered a direct trade-off between two tolerance forms. Chapter 3 of this thesis presents a model that proposes a trade-off in the allocation of host defence between the impact of pathogens on both fecundity and mortality, i.e., a sterility-mortality tolerance trade-off. The model takes into account the evolution of the host's response to both types of parasitic consequences.

1.4 Using adaptive dynamics to model host-parasite system

The basic principle of evolution "survival of the fittest", was first introduced by Charles Darwin in his book *On the origin of species, 1859*. Since then, a lot of work in evolutionary theory has been developed to unravel the biological basis of adaptation and natural selection. Population genetics (Crow, Kimura, et al., 1970), quantitative genetics (Lande, 1976; Falconer, 1996), and evolutionary game theory (Maynard Smith, 1982; Hofbauer, Sigmund, et al., 1998) are some well-known methods to model evolution, each emphasizing different aspects of the evolutionary process. Population genetics, for instance, focuses on how the genetic composition of a population changes due to mutation and selection. Initial population genetics models described variations in allele frequency between generations at a single locus in a randomly mating population (Provine, 2001), and later extended to include other processes such as non-random mating, migration, genetic drifts etc (Crow, Kimura, et al., 1970; Felsenstein, 1976; Gillespie, 2004). Quantitative genetics, on the other hand, describes the

evolution of quantitative phenotypical traits, assuming they result from the additive contribution of small genetic effects at numerous loci (Barton & Turelli, 1989). This simplifies the genetic dynamics, allowing for a focus on the phenotypical level. In contrast to genetics-focused approaches, evolutionary game theory doesn't consider genetic details but instead includes frequency-dependence, which is the ecologically relevant concept that the success of a strategy depends on its frequency in the population. The method applies mathematical game theory to study evolutionary dynamics by modelling evolution as a game played by individuals in a population with strategies based on phenotypical traits (Neumann & Morgenstern, 1947; McGill & Brown, 2007).

The adaptive dynamics framework expands evolutionary game theory by considering the long-term consequences of small mutations in phenotypical traits and their feedback with the ecological environment (Dieckmann & Law, 1996; Geritz et al., 1998). While sharing similar assumptions on small additive genetics effects, adaptive dynamics models mutations as a stochastic process of small steps of invasions and substitutions (Abrams, 2001). A key feature of adaptive dynamics lies in that it links population dynamics and evolutionary dynamics, thus incorporating the fundamental concept of frequency-dependent selection from game theory. Such linkage can cause a monomorphic population to diversify into multiple sub-populations with different traits (Brännström et al., 2013). In addition, interesting evolutionary outcomes such as evolutionary suicide (Nonaka et al., 2013; Boldin & Kisdi, 2016) and Red-Queen dynamics (Marrow et al., 1996; Dercole et al., 2006) can also emerge.

The two basic assumptions of adaptive dynamics are: first, that the resident population can be considered to be in a dynamic equilibrium when a new mutant type appears; and second, that the ultimate outcome of mutant invasions can be predicted based on the initial growth rate of the rare mutant population in the resident population. These two assumptions allow for a separation of the slower evolutionary time scale from the faster ecological time scale by assuming that ecological dynamics are fast enough to reach equilibrium even before a new mutation arises in the resident population (Marrow et al., 1996; Geritz et al., 1998; Brännström et al., 2013). At the ecological timescale,

all traits are considered to be fixed and resident populations converge to a stable point, which can be either equilibrium or cyclic (Metz et al., 1992). The possibility of a new mutant's emergence and invasion at this equilibrium depends on the environment set by the resident population. If a mutant invades successfully, it replaces the resident population, setting a new environment, and the process is iterated. The evolutionary path thus comprises a sequence of trait invasions and substitutions, with each population reaching the ecological attractor at every step. Therefore, evolution progresses through small, discrete steps.

However, certain assumptions may not hold under specific scenarios. For example, adaptive dynamics may falter when evolutionary changes, such as bacteria developing antibiotic resistance, occur rapidly in relation to ecological changes. Significant phenotypic changes, like those seen in certain fly species where single mutations drastically alter wing attributes, can also challenge these assumptions (Weber et al., 2001). Furthermore, rapidly changing environments, such as those brought on by abrupt climate shifts or habitat destruction, can disrupt the assumption of the population reaching equilibrium before new mutations emerge (Chevin et al., 2010). Therefore, while adaptive dynamics is a powerful analytical tool, its assumptions must be carefully considered in the context of the specific biological system under study.

1.4.1 Methodology

In this subsection, we use the theory developed by Metz et al. (1992), Metz et al. (1995), Dieckmann and Law (1996), and Geritz et al. (1998) to outline how adaptive dynamics can be employed to investigate the evolutionary path of a trait in a mathematical model. The first step in this analysis is to identify which traits are undergoing evolutionary change. A model of demographic dynamics that accounts for the factors influencing individual life history can then be formulated. Once the model is established, it is possible to determine the *invasion fitness*: the initial growth rate of a rare mutant attempting to invade the resident population. The mutant's ability to invade depends on the sign of its invasion fitness, with a positive sign indicating successful

invasion and replacement of the resident, and a negative sign indicating otherwise. So the method involves repeatedly introducing new mutants with a trait value close to that of the resident trait.

For our host-parasite model with evolving defence strategies (resistance/tolerance), this means that we add a rare mutant host with defence strategy (y) close to that of the resident host with strategy (x). The next step is to investigate the sign of the mutant host's fitness, which represents its long-term exponential growth rate in the resident environment and is denoted by $s_x(y)$. If $s_x(y) > 0$, the mutant host grows and replaces the current resident population. If $s_x(y) < 0$, the mutant dies out and the resident population remains unchanged. The process is repeated with the addition of another mutant to the population, and changes in the defence strategy over time can be tracked to establish the evolutionary trajectory.

To provide an example of invasion fitness, we will use the model presented in Chapter 2. In this model, the host evolves resistance $r(\tau)$ by reducing infection transmission, which incurs a cost in terms of lowered mortality tolerance τ. The dynamics of the resident susceptible population X and infected population Y are described by the following equations:

$$\begin{aligned} \frac{dX}{dt} &= (a-b)X - qX(X+Y) - (\beta - r)XY + \gamma Y, \\ \frac{dY}{dt} &= (\beta - r)XY - (\alpha - \tau + b + \gamma)Y. \end{aligned} \tag{1.1}$$

A mutant host added to the resident population will have tolerance τ_m and resistance $r(\tau_m)$. The equations describing the dynamics of mutant susceptible and infected populations X_m and Y_m, respectively, can be written as:

$$\begin{aligned} \frac{dX_m}{dt} &= (a-b)X_m - qX_m(N^* + N_m) - (\beta - r(\tau_m))X_m(Y^* + Y_m) + \gamma Y_m, \\ \frac{dY_m}{dt} &= (\beta - r(\tau_m))X_m(Y^* + Y_m) - (\alpha - \tau_m + b + \gamma)Y_m, \end{aligned} \tag{1.2}$$

where X^*, Y^* represent the stable equilibrium densities of the resident population prior to the introduction of the mutant, and $N^* = X^* + Y^*$ is the total resident population.

Similarly, $N_m = X_m + Y_m$ represents the total mutant population. It is assumed that the mutant population is initially significantly smaller than the resident population, i.e., $N_m << N^*$, leading to the following reduced dynamics for the mutant population:

$$\begin{aligned} \frac{dX_m}{dt} &= (a-b)X_m - qX_mN^* - (\beta - r(\tau_m))X_mY^* + \gamma Y_m + \mathcal{O}(N_m^2), \\ \frac{dY_m}{dt} &= (\beta - r(\tau_m))X_mY^* - (\alpha - \tau_m + b + \gamma)Y_m + \mathcal{O}(N_m^2), \end{aligned} \tag{1.3}$$

where $\mathcal{O}(N_m^2)$ denotes the second order approximation error in the linearized differential equations, i.e., $N_m^2 << N^2$ and can be ignored in the equations. We can write these approximately linear equations in the form:

$$\frac{dx}{dt} = Jx, \tag{1.4}$$

where $x = (X_m(t), Y_m(t))$ and J is a 2 x 2 Jacobian matrix formed from the mutant dynamics system 1.3. It can be shown that the mutant fitness is equivalent to the maximum eigenvalue of J, which can be derived by finding a solution expression for system 1.4. However, an easier approach is to use the negative of the determinant of matrix J as a proxy for the mutant fitness expression (Hoyle et al., 2012; Toor & Best, 2015). To prove this, we first find the Jacobian matrix J as follows:

$$J = \begin{pmatrix} a - b - q(X^* + Y^*) - (\beta - r(\tau_m))Y^* & \gamma \\ (\beta - r(\tau_m))Y^* & -(\alpha - \tau_m + b + \gamma) \end{pmatrix} = \begin{pmatrix} A & B \\ C & D \end{pmatrix}.$$

Here, $B > 0$ (positivity of parameters), $C > 0$ (as $r(\tau_m) < \beta$), $D < 0$ and the sign of A is unknown. The eigenvalues of matrix J are then given by:

$$\begin{aligned} \lambda_+, \lambda_- &= \frac{(A+D) \pm \sqrt{(A+D)^2 - 4(AD - BC)}}{2}, \\ &= \frac{(A+D) \pm \sqrt{(A-D)^2 + 4BC}}{2}, \end{aligned} \tag{1.5}$$

where the subscript on λ denotes the sign taken in solution. Since the discriminant is

positive, we will always obtain two real eigenvalues. We can then show that the smaller eigenvalue, λ_-, will always be negative. Therefore, the sign of the determinant (and hence the fitness) will always depend on the larger eigenvalue, λ_+.

As $D < 0$, it follows that if $A < 0$, then $\lambda_- < 0$; if $A \geq 0$, then $|A - D| \geq |A + D|$, i.e., $\sqrt{(A-D)^2 + 4BC} > A + D$, again giving $\lambda_- < 0$. Hence λ_- will always be negative. In addition, since $\lambda_+ > \lambda_-$, λ_+ is the greatest eigenvalue and thus is the mutant fitness s. Using the property $det(J) = \lambda_+\lambda_-$ and that $\lambda_- < 0$, we get two possibilities:

(i) If $s = \lambda_+ > 0$ (mutant can invade), then $det(J) = \lambda_+\lambda_- < 0$;

(ii) If $s = \lambda_+ < 0$ (mutant cannot invade), then $det(J) = \lambda_+\lambda_- > 0$

Therefore mutant fitness is sign equivalent to the negative determinant of the Jacobian matrix and it can be used as a fitness proxy expression, as given below:

$$\begin{aligned} s_\tau(\tau_m) &= -det(J) \\ &= (\alpha + b + \gamma - \tau_m)(a - b - q(X^* + Y^*) - (\beta - r(\tau_m))Y^*) + \gamma Y^*(\beta - r(\tau_m)). \end{aligned} \tag{1.6}$$

If the resident and mutant host traits are equal, i.e., $\tau = \tau_m$, the introduced mutant will be identical to the resident, resulting in no change in the mutant dynamics. Thus, the population remains at equilibrium, and the fitness $s_\tau(\tau_m)$ will always be zero. In this manner, the population will evolve in the direction of the selection gradient $\frac{\partial s_\tau(\tau_m)}{\partial \tau_m}$ until an evolutionary singularity is reached (Metz et al., 1992; Geritz et al., 1998). The singular strategy is thus an evolutionary steady state that satisfies

$$\left.\frac{\partial s_\tau(\tau_m)}{\partial \tau_m}\right|_{\tau_m = \tau = \tau^*} = 0. \tag{1.7}$$

1.4.2 Properties of singular strategies

Singular strategies can have two different evolutionary properties: evolutionary stability and convergence stability. A singular strategy τ^* is evolutionary stable (ES),

if no nearby mutant can invade the resident population, i.e., it has to be a local fitness maximum with respect to the mutant trait (Geritz et al., 1998). Mathematically, this can be defined as:

$$\left.\frac{\partial^2 s_\tau(\tau_m)}{\partial \tau_m^2}\right|_{\tau_m=\tau=\tau^*} < 0. \tag{1.8}$$

A singular strategy that is ES is an evolutionary trap in the sense that once it has become established in a population, no further evolutionary change are possible by small mutations.

On the other hand, convergence stability (CS) concerns whether the singular strategy is attracting or not (Christiansen, 1991; Geritz et al., 1998). Mathematically, at a convergence stable strategy τ^*,

$$\left.\left(\frac{\partial^2 s_\tau(\tau_m)}{\partial \tau_m^2} + \frac{\partial^2 s_\tau(\tau_m)}{\partial \tau \partial \tau_m}\right)\right|_{\tau_m=\tau=\tau^*} < 0. \tag{1.9}$$

If this condition is met, then all strategies in the singularity's vicinity will evolve towards it. In a mathematical sense, it means that the singularity is stable towards any perturbations in the resident strategy.

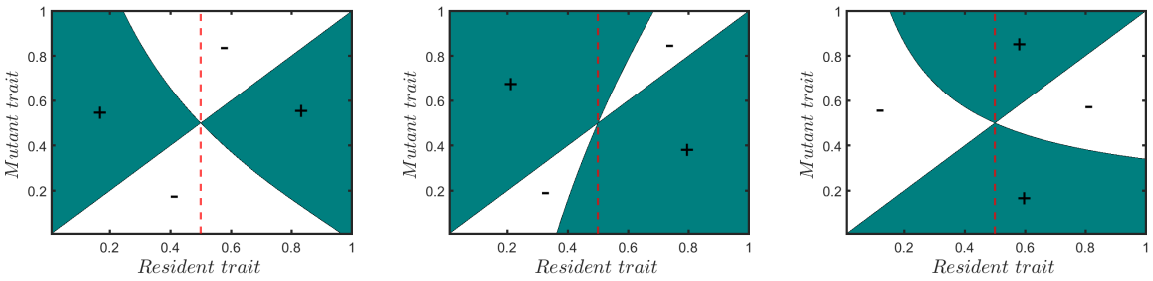
The evolutionary outcomes can vary based on the combinations of stability properties exhibited by the singular strategy. A strategy that possesses both evolutionary stability and convergence stability is known as a *continuously stable strategy* (CSS) or an *attractor* (Eshel, 1983). If a population reaches the CSS point, it will continue to remain there and do not change with further mutations. In contrast, a singular strategy that is neither evolutionary stable nor convergent stable is a *repeller*, and it will drive the population away from itself. Another type of singularity is known as the *Garden of Eden*. This is an evolutionary stable but not a convergent stable strategy, meaning that although the point is a local fitness maximum, selection will drive the population away from it. Lastly, a type of singular strategy which is often considered interesting is the one which is convergent stable but not evolutionary stable, i.e., a *branching point*. In this case, the population will evolve towards the singularity, but when it reaches close to it, disruptive selection occurs, causing the population to branch into coexisting

sub-populations (Christiansen, 1991; Metz et al., 1992).

Pairwise invasibility plots (PIP) provide a simple way to understand the evolutionary behavior of a system and visually represent the singular strategies (Geritz et al., 1998). These plots are commonly employed to understand the effects of a sequence of invasion events. In a PIP, the mutant fitness is graphed as a function of the resident strategy for all possible combinations of resident and mutant traits. Fig. 1.1 shows three examples of PIPs that correspond to the sterility-mortality tolerance trade-off model presented in Chapter 3. The shaded regions indicate where the mutant has positive fitness and can invade the resident (marked with "+"), while unshaded regions indicate where the mutant fitness is negative and invasion is impossible (marked with "-"). The main diagonal of the PIP represents where the mutant and the resident have identical traits, resulting in a fitness of zero. Singular points occur where a curve intersects the main diagonal. The population will evolve in small mutation steps along the main diagonal, either upward or downward. Fig. 1.1a shows a convergent stable strategy (CSS): the strategy which can be attained gradually and cannot be invaded after that. On the other hand, in Fig. 1.1b, the singularity represents a branching point: a strategy that attracts neighbouring strategies but can be invaded by mutants both above and below the resident strategy at the same time. Lastly, Fig. 1.1c displays a repeller that can be invaded by nearby mutants and population evolves away from it, leading to either maximisation or minimisation of the trait (Geritz et al., 1998).

1.4.3 Adaptive dynamics in a coevolutionary framework

The concept of adaptive dynamics can also be extended to multi-dimensional systems where two or more species coevolve (Marrow et al., 1996; Matessi & Di Pasquale, 1996; Kisdi, 2006). One such example is a system where both the host and parasite coevolve their respective traits. In such systems, a coevolutionary singularity corresponds to evolutionary steady states of the host and parasite populations. Such a singularity, known as a co-singularity in a coevolutionary process, requires that the selection gradients of both host and parasite populations are simultaneously zero. Evolutionary



(a) (b) (c)

FIGURE 1.1: *Examples of pairwise invasibility plots showing (a) CSS, (b) branching point, and a (c) repeller. The shaded regions marked with a "+" sign represents where the mutant has the positive invasion fitness, while unshaded regions with a "-" sign represents negative invasion fitness. Singular point occurs where primary diagonal intersects the curve.*

stability generalizes directly from single-species evolution to coevolving species (Geritz et al., 1998; Rueffler et al., 2004), i.e., each evolving species must satisfy their respective evolutionary stability condition as in equation (1.8). However, convergence stability cannot be easily extended to higher dimensions as the evolution of one species can influence the selection on the other species (Dieckmann & Law, 1996; Marrow et al., 1996; Matessi & Di Pasquale, 1996; Kisdi, 2006).

For example, consider a host-parasite coevolution model where the host evolves tolerance trait f and the parasite evolves through recovery rate γ. Here, we denote the host fitness by s, and f_m represents the host mutant tolerance trait. Similarly, we indicate the parasite fitness by r, and its mutant recovery trait by γ_m. Then we can obtain the conditions to determine the convergence stability using a two-dimensional Jacobian matrix formed from the second-order derivatives of the fitness equations (Marrow et al., 1996; Best et al., 2009), given below:

$$J = \begin{pmatrix} \phi_h X^*\left(\frac{\partial^2 s}{\partial f_m^2} + \frac{\partial^2 s}{\partial f \partial f_m}\right) & \phi_h X^*\left(\frac{\partial^2 s}{\partial f_m \partial \gamma}\right) \\ \phi_p Y^*\left(\frac{\partial^2 r}{\partial \gamma_m \partial f}\right) & \phi_p Y^*\left(\frac{\partial^2 r}{\partial \gamma_m^2} + \frac{\partial^2 r}{\partial \gamma_m \partial \gamma}\right) \end{pmatrix}.$$

Here ϕ_h and ϕ_p represent the speeds of mutation of the host and parasite, respectively, and incorporates the rate and variance of mutation (Dieckmann & Law, 1996). If all

the eigenvalues of the Jacobian matrix have a negative real part, the co-singularity is convergent stable, and both the host and parasite populations will converge to the co-singularity. Conversely, if either or both eigenvalues have a positive real part, the co-singularity is not convergent stable. In summary, the convergence stability of a coevolutionary system is determined by the linear stability analysis of the Jacobian matrix, which is associated with the two-dimensional canonical equation of adaptive dynamics (Dieckmann & Law, 1996).

1.5 Why do we study coevolution?

Is is clear that hosts can develop various defence mechanisms to combat parasitic infections, which parasites can counter-adapt to through mechanisms such as molecular mimicry or chemical suppression. As Darwin noted, finely tuned adaptations between species likely result from each species evolving in response to changes in the other. The process in which two species, such as host and parasite, influence each other's evolutionary changes is known as "coevolution" (Penn, 2001). Although studying single-species is valuable, many real-life systems show that hosts and parasites coevolve due to their interaction with each other. Both species continually adapt to changes in the other, as demonstrated in various studies (Ebert, 2008; Salvaudon et al., 2008; Hall et al., 2011; Lopez Pascua et al., 2014; Obbard & Dudas, 2014; Edger et al., 2015; Montes et al., 2019). Despite substantial empirical evidence, most of the evolutionary host-parasite models assume that the evolution of host defence or parasite infectivity is determined by the balance of their evolutionary costs and benefits solely from the perspective of either the host or the parasite. These models, as evidenced by studies (Beck, 1984; Lambrechts et al., 2006), often consider the other species to be constant. Historically, coevolutionary theory has been extensively studied using genetic-based methods (Sasaki, 2000; A. A. Agrawal et al., 2004; Fenton & Brockhurst, 2007; Peters & Lively, 2007; Tellier & Brown, 2007; Ashby & Gupta, 2014), and ecology-driven methods (Baalen, 1998; Gilchrist & Sasaki, 2002; Best et al., 2009; Gandon & Day, 2009; Best

et al., 2010b; Carval & Ferriere, 2010; Best et al., 2014; Boots et al., 2014; Ashby & Boots, 2015; Kada & Lion, 2015; Best et al., 2017a). Recent research has shown a trend towards using more complex models of host-parasite coevolution to gain a better understanding of various factors such as eco-evolutionary feedbacks (Gokhale et al., 2013; MacPherson & Otto, 2018; Ashby et al., 2019), advanced models of host defence (Nuismer & Dybdahl, 2016; Akçay, 2017), and the impact of additional species interactions (King & Bonsall, 2017; Best, 2018; Seppälä et al., 2020). It has been predicted that results obtained from coevolutionary frameworks may not be directly predictable from single-species evolution (Restif & Koella, 2003). For instance, Best et al. (2009) found that coevolution can lead to more virulent parasites compared to those resulting from parasite evolution alone. Therefore, incorporating coevolution into mathematical models is often necessary to enhance evolutionary and epidemiological predictions.

Theory suggests that the coevolution of hosts and parasites can result in various outcomes, including a coevolutionary stable strategy for both host and parasite (Baalen, 1998; Best et al., 2009), polymorphism in one or both species (Tellier & Brown, 2007; Best et al., 2009; Best et al., 2010a; Boots et al., 2014), arms race dynamics (ARD) (Gandon et al., 2008; Hall et al., 2011), and fluctuating selection dynamics (FSD) (Jayakar, 1970; Sasaki, 2000; A. Agrawal & Lively, 2002; Ashby & Boots, 2017). Fluctuating selection, also known as coevolutionary cycling or Red Queen dynamics, is a particularly important coevolutionary outcome as it can persist indefinitely in a stable environment (Best et al., 2017a). It occurs when the direction of selection changes, leading to non-monotonic variation in host and parasite traits over time, or when there is no stable distribution of genotypes resulting in oscillations in allele frequencies (Ashby & Boots, 2017; Buckingham & Ashby, 2022). FSD has implications for diverse biological phenomena, including maintenance of diversity, selection for sex and recombination, and local adaptation (B. C. Clarke, 1979; Morgan et al., 2005; Lively, 2009, 2010a). Due to its importance, an increasing number of theoretical (Jayakar, 1970; Sasaki, 2000; A. Agrawal & Lively, 2002; Ashby & Boots, 2017; Best et al., 2017a; MacPherson & Otto, 2018), and empirical (Gómez & Buckling, 2011; Hall et

al., 2011; Harrison et al., 2013; Lopez Pascua et al., 2014; Gómez et al., 2015) studies of host-parasite coevolution have investigated the potential for FSD in their systems. Therefore, the occurrence of fluctuating selection in host-parasite coevolution has been a major focus of theoretical research (Lively, 2010b; Ashby & Boots, 2015).

Although there is an abundance of theoretical literature on host resistance in coevolution models, the mechanisms of host tolerance are seldom explored within a coevolutionary framework (Best et al., 2009, 2014). In Chapter 4 of this thesis, we aim to fill this gap by investigating the coevolutionary dynamics of two host tolerance mechanisms, sterility tolerance and mortality tolerance, in the presence of a coevolving parasite. Specifically, we develop a mathematical model that allows the parasite to simultaneously coevolve its transmission and recovery rates in response to the host's tolerance mechanisms. In this work, we uncover various interesting coevolutionary outcomes, including fluctuations in both ecological and evolutionary dynamics.

1.6 Thesis Outline

In this thesis, we focus on how trade-offs between different host defence mechanisms shapes the evolutionary dynamics of host and parasite. We thoroughly investigate, in particular, the evolution of two tolerance mechanisms of the host: sterility tolerance and mortality tolerance when they are in direct trade-off with each other. In the first two chapters, we focus only on host evolution with a resistance - tolerance and a tolerance - tolerance trade-off, respectively. We then extend this tolerance - tolerance trade-off to a coevolutionary framework where we allow the parasite to coevolve with a transmission-recovery trade-off. Our work highlights the need for more experimental testing for such trade-offs, specifically for trade-offs between two tolerance forms. This work also provides a potential base for future theoretical models examining trade-offs between different host defence mechanisms and how such trade-offs shape the host-parasite coevolution.

In Chapter 2, we develop a model to examine the simultaneous evolution of resistance and tolerance in a host population where they are negatively correlated by a trade-off. The model assumes that tolerance decreases the mortality rate induced by infection, while resistance reduces the susceptibility to infection. Despite the well-established existence of a resistance-tolerance trade-off in numerous host-parasite systems, such a trade-off is rarely considered in theory before. Employing such a trade-off function within the evolutionary invasion theory, we examine the optimal investment patterns in resistance and tolerance. Throughout, our primary objective is to predict the favoured strategy under different ecological and epidemiological conditions. The key findings from this model highlight the impact of host recovery and sterility on defence investments, and emphasize the importance of fecundity in driving host evolutionary dynamics. The chapter ends with a discussion section that illustrates the relevance of our findings and model to the existing literature.

In Chapter 3, we illustrate the critical differences between two tolerance forms; mortality tolerance and sterility tolerance. While previous theoretical studies have explored the negative correlation between tolerance and resistance mechanisms, none have yet examined this correlation within different modes of tolerance. Here we model two tolerance strategies in a host population exposed to a pathogen and use adaptive dynamics to study their evolutionary behaviour. We find that such a trade-off can cause the host population to split into dimorphic strains, leading to the coexistence of sterile hosts with low mortality and fully fertile hosts with high mortality rates. Besides, a broader range of trade-off shapes can lead to branching at intermediate or high infected population size. This study presents novel predictions regarding the evolutionary behaviour of two tolerance strategies with this trade-off.

In the previous chapters, we focused solely on the host evolution, i.e., how host evolves various defence mechanisms under different contexts or trade-off assumptions. In Chapter 4, we extend the model from Chapter 3 into a coevolutionary framework. As such, we study the coevolution of host and parasite, assuming explicit trade-offs

between host sterility-mortality tolerance on the one hand and parasite recovery-transmission on the other hand. It means that the host evolves sterility tolerance at the cost of increased mortality and the parasite can increase its transmission rate at the cost of increased recovery rate (reduced infection duration). Here we explore the coevolution of host and parasite traits which have been traditionally analysed independently. One key finding is that branching in the host can drive the parasite to branch and fluctuating population dynamics can prevent coexisting strains from reaching their extremes. We aim to understand the differences in the outcomes of coevolutionary dynamics to the previous model that considered only host evolution.

Finally, in Chapter 5, we summarise the previous chapters and outline potential directions for future research in this area. We specifically emphasize how the shapes of trade-off functions influence the evolutionary and coevolutionary outcomes within diverse ecological scenarios. Our findings underscore the need for more empirical research on trade-offs between different host and parasite strategies. Future work could build on by incorporating more complex scenarios such as considering the impact of seasonality or additional populations, such as predators, into the models we studied.

Chapters 2 and 3 of this thesis have been published in international journals, and Chapter 4 is a manuscript under preparation, as detailed below:

- Chapter 2: Singh, P. and Best, A., 2021. Simultaneous evolution of host resistance and tolerance to parasitism. Journal of Evolutionary Biology, 34(12), pp.1932-1943, (doi: 10.1111/jeb.13947).

- Chapter 3: Singh, P. and Best, A., 2023. A sterility–mortality tolerance trade-off leads to within-population variation in host tolerance. Bulletin of Mathematical Biology, 85(3), p.16, (doi: 10.1007/s11538-023-01119-6).

- Chapter 4: Singh, P. and Best, A. The impact of sterility-mortality tolerance and recovery-transmission trade-offs on host-parasite coevolution. *In prep.*

Chapter 2

Simultaneous evolution of host resistance and tolerance to parasitism

2.1 Introduction

An important aspect of infectious disease models is to explore how ecological factors affect the evolution of different host defence strategies. Broadly, hosts can either live with the infection by limiting the damage pathogens cause (termed "tolerance") or can evolve to fight the pathogens and reduce their fitness (termed "resistance") (Roy & Kirchner, 2000; Restif & Koella, 2004; Miller et al., 2005; Best et al., 2008; Boots, 2008). In other words, resistance is the ability to reduce infection burden on the host, and tolerance controls the damage that infection causes (Fornoni et al., 2004b; Råberg et al., 2007). Together, tolerance and resistance form two basic components of antipathogen defence which influences disease severity (Råberg et al., 2007). Several theoretical studies have analyzed the evolution of each of these defence mechanisms and the factors governing their selection in the environment (Boots & Bowers, 1999; Boots & Haraguchi, 1999; Roy & Kirchner, 2000; Boots & Bowers, 2004; Restif & Koella, 2004; Miller et al., 2005; Miller et al., 2007; Best et al., 2008). The simultaneous evolution of resistance and tolerance as independent traits has been studied by Restif

and Koella (2004). Then Best et al. (2008) considered a resistance-tolerance trade-off but with an additional overall cost to the host birth rate, and examined the possibilities of evolutionary branching to dimorphism as a possible outcome. Carval and Ferriere (2010) investigated a model that looked at the coevolution of virulence in parasites and tolerance/resistance in the host, under multiple physiological and environmental scenarios. However, none of these theoretical studies has focused on the simultaneous evolution of resistance and tolerance where they are traded off against each other.

Tolerance and resistance may lead to distinct evolutionary outcomes even when their short-term benefits are equivalent for the host (Roy & Kirchner, 2000). Resistance mechanisms directly inhibit infection spread and reduce parasite fitness (Roy & Kirchner, 2000). So, as a resistance trait spreads in the population, parasite prevalence falls. Following this, there is less chance of being infected and hence less selection for resistance in the population, implying that resistance creates a negative feedback on its own selection (or fitness) as a defence strategy (Boots & Bowers, 1999; Boots & Haraguchi, 1999; Restif & Koella, 2004). On the contrary, mechanisms of tolerance may increase parasite prevalence by allowing infected hosts to live longer and consequently have a positive feedback on their own selection in the environment (Boots & Haraguchi, 1999; Roy & Kirchner, 2000; Miller et al., 2005; Råberg et al., 2007; Boots, 2008). Restif and Koella (2004) studied the simultaneous evolution of resistance as increased recovery and tolerance as distinct, independent traits focusing on the effects of using different cost-function shapes and found that the concurrent evolution of these two traits of defence might conceal their actual costs, even when they are genetically independent. Then Best et al. (2008) considered a trade-off between tolerance to disease-induced mortality and resistance through increased recovery and found that such a trade-off does not allow evolutionary branching[1] (Geritz et al., 1998), but branching is possible for a standard trade-off between sterility tolerance (tolerance to disease-induced reduction in reproduction) and natural death rate. They emphasized the importance of understanding differences in where tolerance acts i.e., in mortality

[1] when an initially monomorphic population experiences disruptive selection at a fitness minimum and branches into two distinct strains

or sterility. Furthermore, Boots and Best (2018) demonstrated that it is unlikely that a trade-off between constitutive defence (such as resistance evolving as reduced infection transmission) and induced defence (such as tolerance) will lead to branching. In brief, much of the previous work that considered trade-offs between different defence mechanisms have focused on how different ecological feedbacks lead to branching or not. However, we have instead focused on the stable investments at CSS points[2].

The distinction between tolerance and resistance has been well reviewed in many host-pathogen systems in both plant and animal studies (Simms & Triplett, 1994; Fineblum & Rausher, 1995; Tiffin & Rausher, 1999; Råberg et al., 2007; Råberg et al., 2009). The affiliation between the two mechanisms in plant-pathogen systems gathered much attention since a negative correlation was found between them in *Ipomoea purpurea* (Fineblum & Rausher, 1995). Further experiments by Mauricio et al. (1997), Stowe (1998) and Tiffin and Rausher (1999) suggested interactions between resistance and tolerance as a trade-off and described patterns of selection acting on them. There is however, a need for more theoretical models to investigate such patterns/interactions.

A crucial assumption of most evolutionary studies is that investment in defence is costly and impedes other attributes of the host, such as their reproduction rate or ability to recover (Simms & Triplett, 1994; Fineblum & Rausher, 1995; Boots & Haraguchi, 1999; Roy & Kirchner, 2000; Miller et al., 2007). There is evidence of costs in host-parasite interactions of both plant and animal systems (Simms & Triplett, 1994; Tiffin & Rausher, 1999; Råberg et al., 2009). In plant populations, the evolution and maintenance of resistance and tolerance are expected to be influenced by their corresponding fitness costs and/or benefits (Núñez-Farfán et al., 2007). Their evolutionary behaviour can also be altered by the genetic interactions between these two defence mechanisms (Kover & Schaal, 2002). Several empirical studies have found a trade-off linking resistance and tolerance with such interactions (Fineblum & Rausher, 1995; Stowe, 1998; Strauss et al., 2003; Råberg et al., 2007), and then there are some who found no evidence of such a trade-off (Tiffin & Rausher, 1999; Stevens et al., 2007). Råberg et al.

[2]stable and evolutionary attracting singular strategies

(2007) studied a rodent malaria model considering a negative genetic correlation across mouse strains and demonstrated that tolerance can be costly in terms of resistance. Similarly, a negative correlational selection between frost tolerance and resistance was detected in a plant family of annual wild radish *Raphanus raphanistrum* (A. A. Agrawal et al., 2004). In an another genetic selection study on the population of wild mustard *Brassica rapa* infected by two of its insect herbivores: flea beetles (*Phyllotreta cruciferae*: Chrysomelidae) and weevils (*Ceutorhynchus assimilis: Curculionidae*), it was found that the evolution of defensive response towards flea beetles was constrained by a negatively correlated trade-off between resistance to the weevils and tolerance of weevil damage (Pilson, 2000). A recent study on tolerance to a fungal pathogen *Zymoseptoria tritici* in European wheat cultivars found compelling evidence of a trade-off between tolerance and resistance in the context of plant-pathogen interactions (Mikaberidze & McDonald, 2020). So, there is clear evidence of a resistance-tolerance trade-off in many systems, yet very few models have looked at what happens when the two are traded-off against one another.

Here, we use the theory of adaptive dynamics, which assumes a series of small mutations and invasions lead to long-term evolutionary changes in a trait (Geritz et al., 1998), to study evolutionary dynamics of a host that evolves tolerance to disease-induced mortality at the cost of reduced resistance to infection (or increased transmission). We test how investment in resistance and tolerance varies with both host and parasite life-history traits. We focus on exploring the conditions that favour resistance, tolerance, or a combination of the two and the relative investment in each of the defence strategies.

2.2 The model

We construct a host-parasite epidemiological model ultimately based on the SIS (Susceptible-Infected-Susceptible) framework given by (Anderson & May, 1981). We keep general assumptions such as a homogeneous and well-mixed host population, and

Notation	Host-dependant traits	Default value
a	Host birth rate	5
b	Host natural death rate	0.05
q	Crowding effect (competition)	0.2
	Parasite-dependant traits	
α	Disease induced mortality rate (virulence)	4
β	Infection transmission coefficient	6
γ	Recovery rate of infected hosts	0.5
f	Factor by which infection diminishes host birth rate	varies
	Evolving defence strategies of host	
r	Host resistance (reduction in infection transmission)	varies
τ	Host tolerance (reduction in virulence)	varies

TABLE 2.1: Description of parameters for resistance-tolerance trade-off model

the contact process between susceptible hosts X and infected hosts Y is assumed to be density-dependent. As parasites use hosts to survive, they need not be modeled separately, and their dynamics are expressed by the infected host population. We study the cases of sterile and non-sterile infected hosts separately. The overall host population dynamics when infected hosts are sterile is given by following coupled differential equations:

$$\begin{aligned} \frac{dX}{dt} &= (a-b)X - qX(X+Y) - (\beta - r)XY + \gamma Y, \\ \frac{dY}{dt} &= (\beta - r)XY - ((\alpha - \tau) + b + \gamma)Y. \end{aligned} \tag{2.1}$$

Susceptible hosts reproduce by rate a and all the hosts (susceptible and infected) die naturally at rate b, whereas q is the crowding effect on host birth rate. The disease spreads with a transmission coefficient β and infected hosts die with an increased rate α, termed as the parasite virulence. All hosts are born uninfected and infected hosts can recover from the infection at a rate γ and become susceptible to infection again. The default values of parameters and their definitions are given in Table (2.1) for reference.

On the other hand, the population dynamics when infected hosts can reproduce (non-sterile) is given by the following system:

$$\begin{aligned}\frac{dX}{dt} &= (a - q(X+Y))(X + fY) - bX - (\beta - r)XY + \gamma Y,\\ \frac{dY}{dt} &= (\beta - r)XY - ((\alpha - \tau) + b + \gamma)Y.\end{aligned} \tag{2.2}$$

System (2.2) has a unique endemic equilibrium given by $(\bar{X}, \bar{Y})$, where $\bar{X} = \frac{\alpha+b+\gamma-\tau}{\beta-r}$, and $\bar{Y}$ is a positive solution to $qf\bar{Y}^2 - (af - q(1+f)\bar{X} - (\beta - r)\bar{X} + \gamma)\bar{Y} + (q\bar{X}^2 - a\bar{X} + b\bar{X}) = 0$. Here we assume that infection diminishes the reproduction rate of infected hosts by a factor denoted by f, where high f illustrates that infected hosts reproduce more and low f means they reproduce less ($0 \leq f \leq 1$), such that $f = 0$ indicates infected hosts can not reproduce at all and $f = 1$ means they reproduce as much as the healthy hosts.

On similar lines to previous studies (Vitale & Best, 2019), we consider avoidance to be modelled as a reduction r in the transmission coefficient β. This defence mechanism reduces the possibility of getting infected by inhibiting contact with other hosts through certain barriers such as skin, surface chemicals, mucus etc. or possibly through behavioural adaptations (Boots & Bowers, 1999; Boots & Haraguchi, 1999; Roy & Kirchner, 2000). On the other hand, tolerance is modelled as a reduction τ in parasite-induced mortality rate α. This mechanism reduces the detrimental effects of the disease in the host by reducing deaths caused by the parasite (Boots & Haraguchi, 1999; Roy & Kirchner, 2000).

First, we consider the case of sterile hosts. We start with finding the equilibrium points of system (2.1). We obtain three equilibrium points: the trivial i.e., $(0, 0)$, infection free equilibrium (X_0, Y_0), and endemic equilibrium point (X^*, Y^*), where $X_0 = \frac{a-b}{q}$, $Y_0 = 0$, and

$$\begin{aligned}X^* &= \frac{\alpha + b + \gamma - \tau}{\beta - r},\\ Y^* &= \frac{(\alpha + b + \gamma - \tau)(bq + ar - br + q\alpha - a\beta + b\beta + q\gamma - q\tau)}{(r - \beta)(bq - br + q\alpha - r\alpha + b\beta + \alpha\beta + q\gamma - q\tau + r\tau - \beta\tau)}.\end{aligned}$$

For infection to persist, the basic reproduction number R_0 must be greater than 1. This number represents the expected number of individuals that a single infected host will infect in a fully susceptible host population during its entire infectious period (Diekmann et al., 1990). For our model, the basic reproduction number can be calculated using the next generation matrix method (Van den Driessche & Watmough, 2002), and is given by $R_0 = \frac{(\beta-r)X_0}{(\alpha+b+\gamma-\tau)} = \frac{(\beta-r)(a-b)}{q(\alpha+b+\gamma-\tau)}$, where $X_0 = (a-b)/q$ is the disease-free equilibrium attained by the susceptible host population.

We work towards modelling the evolution of host defence in response to infection caused by a parasite, using the adaptive dynamics framework (Metz et al., 1992; Metz et al., 1995; Geritz et al., 1998). The evolutionary behavior can be determined by assessing the fitness of a rare mutant host trying to invade the environment set by the resident host, at its equilibrium (X^*, Y^*). A small mutation step occurs when a mutant with strategy $y = (\tau_m, r_m)$ appears. At the beginning, its density is not high enough to alter the environment set by the resident host with strategy $x = (\tau, r)$. The mutant strain could spread if the equilibrium (X^*, Y^*) is unstable in the full system i.e., if the Jacobian matrix with respect to mutant variables has at least one eigenvalue with positive real part. The fitness is then given by the maximum eigenvalue of this matrix (Metz et al., 1992; Geritz et al., 1998). It has been proved by Hoyle et al. (2012) that the negative of the determinant of this Jacobian matrix (mutant part) has the same sign as that of the leading eigenvalue and therefore, can be used as the mutant fitness proxy. The formula for the fitness proxy of this model '$s_\tau(\tau_m)$' is obtained using the method illustrated in the appendix of Best et al. (2017b) and is given by

$$s_\tau(\tau_m) = (\alpha + b + \gamma - \tau_m)(a - q(X^* + Y^*) - b - (\beta - r_m)Y^*) + \gamma Y^*(\beta - r_m). \quad (2.3)$$

This fitness equation then determines whether a new mutant can invade the resident population or not, such that if $s_\tau(\tau_m) > 0$, the mutant can invade, else, it dies out. The evolutionary path is then shaped by the successive invasion steps.

At a singular strategy, the derivative of the fitness expression with respect to the

mutant strategy is zero and this derivative is called the fitness gradient (Geritz et al., 1998). We look for singular strategies as these are the points where the evolutionary dynamics of a trait stops ($\frac{\partial s}{\partial \tau_m}|_{\tau_m=\tau=\tau^*} = 0$). The evolutionary outcome mainly depends upon two stability conditions that are governed by the second order derivatives of the fitness gradient i.e., $\frac{\partial^2 s}{\partial \tau_m^2}|_{\tau=\tau_m=\tau^*} < 0$ for evolutionary stability which determines if the singular point is evolutionary invadable, and $\frac{\partial^2 s}{\partial \tau_m^2} + \frac{\partial^2 s}{\partial \tau \partial \tau_m}|_{\tau=\tau_m=\tau^*} < 0$ for convergence stability to determine if the point is evolutionary attracting. A singularity that is both evolutionary stable (ES) and convergence stable (CS) is a CSS (continuously stable strategy) and attracts all the nearby strategies (Geritz et al., 1998). Here, we will focus on CSS points so as to understand the stable investments in the two arms of host defence. The CSS investments in defence mechanisms of a host depend on the prevalence of infection in the system, commonly termed as "disease prevalence" and is given by the following formula

$$P = \frac{Y^*}{X^* + Y^*}. \tag{2.4}$$

Here X^* and Y^* are the values of susceptible and infected hosts densities at optimal tolerance strategies (CSS). The supplementary file A shows how a change in the disease prevalence changes the forces of selection acting on resistance and tolerance.

2.2.1 Trade-off between resistance and tolerance

We consider a trade-off linking the two defence strategies r (resistance) and τ (tolerance) in a manner such that for every increment in τ, there is a reduction in r. This indicates that the benefit from an increase in tolerance is bought at the cost of a reduction in resistance. Let us define the trade-off function explicitly in a similar form as used by Hoyle et al. (2012) and Toor and Best (2015),

$$r(\tau) \;=\; r(\tau^*) - \frac{r'(\tau^*)^2}{r''(\tau^*)}\left(1 - e^{\frac{r''(\tau^*)(\tau-1)}{r'(\tau^*)}}\right). \tag{2.5}$$

Here primes stand for the derivatives such as $r'(\tau^*) = \frac{\partial r}{\partial \tau}|_{\tau=\tau^*}$, $r''(\tau^*) = \frac{\partial^2 r}{\partial \tau^2}|_{\tau=\tau^*}$, and $(\tau^*, r(\tau^*))$ is the singular strategy. Assuming that $(\tau^*, r(\tau^*))$ is fixed at $(1, 1)$, we find the slope $r'(\tau^*)$, and curvature $r''(\tau^*)$ of the trade-off curve at this point. $r'(\tau^*)$ is calculated such that τ^* is a singular strategy and is obtained from the equation $\frac{\partial s}{\partial \tau_m}|_{\tau_m=\tau=\tau^*} = 0$. On the other hand, $r''(\tau^*)$ is chosen such that τ^* is an evolutionary and convergence stable strategy, i.e., $\frac{\partial^2 s}{\partial \tau_m^2} < 0$ and $\frac{\partial^2 s}{\partial \tau_m^2} + \frac{\partial^2 s}{\partial \tau \partial \tau_m} < 0$ at τ^*. This choice reflects the observation that the slope determines that chosen point is an evolutionary singularity, whereas curvature predicts the behaviour at that point.

We use this trade-off function to locate the continuously stable strategies (CSS) as they are the probable end points of evolution. Figure (2.1) shows examples for the trade-off curves with different curvatures.

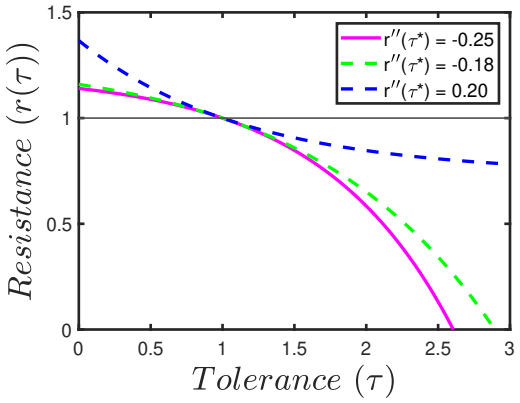


FIGURE 2.1: *Trade-off curve examples for various values of trade-off curvature and gradient* $r'(\tau^*) = -0.23$. *Straight black line through* 1 *represents the value of resistance when there is no evolving tolerance i.e., constant tolerance. Further throughout, we consider* $r'(\tau^*) = -0.23$ *and* $r''(\tau^*) = -0.25$ *for singular strategy* $(\tau^*, r(\tau^*)) = (1, 1)$.

2.3 Results

We consider tolerance as our focal evolutionary variable and look at the effects of varying ecological parameters on the investment in tolerance and resistance at attracting and evolutionary stable strategies (CSS). We will discuss the variation in CSS points

with lifespan $(1/b)$ when certain parasitic characteristics (virulence, transmission rate, recovery rate) are varied.

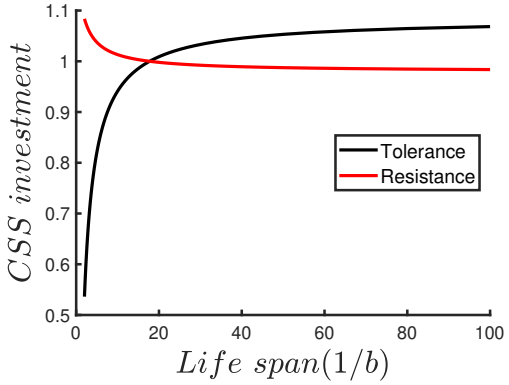


FIGURE 2.2: *Variation in tolerance and resistance as continuously stable strategies (CSS) along with the lifespan. Trade-off gradient and curvature are* $r'(\tau^*) = -0.23$ *and* $r''(\tau^*) = -0.25$*, respectively, and remaining parameters are same as mentioned in Table* (2.1).

First we show variation in the investment in tolerance and resistance as continuously stable strategies with respect to lifespan (Fig. 2.2). We see that when lifespan increases, the optimal (CSS) investment in tolerance increases and investment in resistance decreases. When lifespan is high, there are greater chances of an individual host getting infected (or infecting others) in its lifetime. This leads to a higher infected density, and selection is to increase tolerance to survive and recover. As the tolerant trait spreads in the population, it increases the average infectious period of infected hosts, making infection even more likely and enhancing the benefits of investment in tolerance as a defence strategy. On the other hand, a very high level of resistance would be needed to fight (avoid) the infection effectively at this stage, making it a costly strategy and reducing its benefits. So, longer lived host populations are more likely to evolve tolerance than resistance in response to parasitism.

We now focus on the CSS investment in tolerance and resistance as both lifespan and other epidemiological parameters are varied (Fig. 2.3). From Fig. (2.3a-2.3c), we observe that the investment in tolerance decreases and that in resistance increases, as

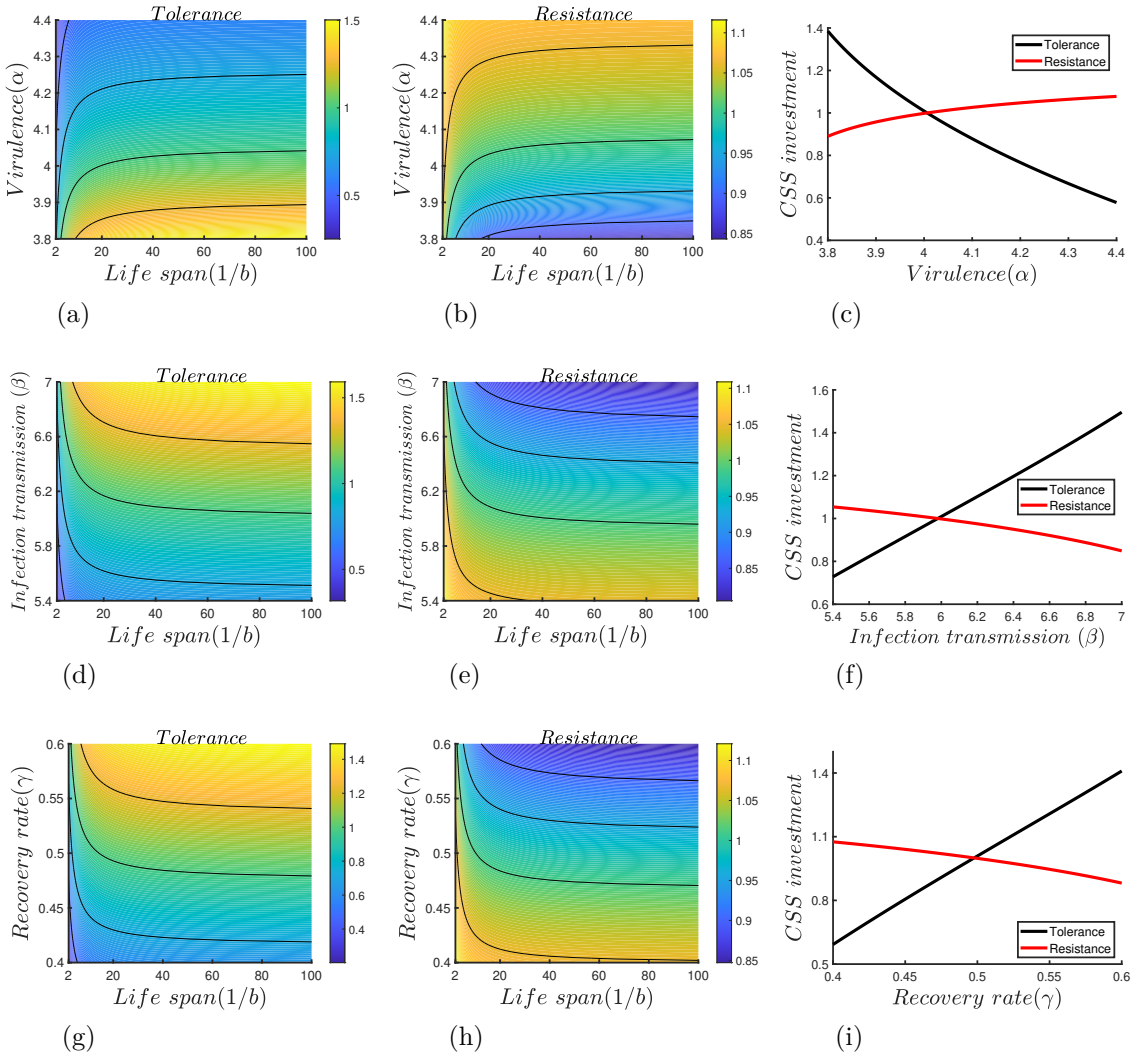


FIGURE 2.3: *Contour plots showing the combined effects of varying lifespan (x-axis, first and second columns) with virulence α (top row), infection transmission β (middle row), and recovery γ (bottom row). Plots represent the CSS investment variation in tolerance ((a), (d) and (g)), and resistance ((b), (e) and (h)). Here yellow hues indicate high tolerance/resistance investment and blue hues indicate lower investments. Figures (c), (f), and (i) show how the CSS investment in tolerance and resistance varies together along with α, β, and γ respectively. Remaining parameters are the same as mentioned in Table (2.1).*

virulence (α) increases. To counter a highly virulent parasite (high α), a small investment in tolerance is not enough. To reduce deaths significantly, the host would need very high levels of tolerance, making it a costly defence strategy. However, high virulence leads to a lower infected density, reducing the likelihood of getting infected and

making resistance accessible as an effective defence mechanism. Further, an investment in avoidance will be less "costly", as the additional mortality (due to the trade-off) is a relatively small marginal increase. As being infected could be fatal, the better strategy is not to get infected at all, i.e., more resistance. This could seem counterintuitive as one might expect that an increased virulence could be balanced by increasing tolerance, and a highly virulent parasite should therefore select for a more tolerant host, but we have shown how feedbacks with disease prevalence and the effective costs of each defence mechanism drive our results.

Next, we evaluate the optimal investment pattern for different values of infection transmission coefficient β (Fig. 2.3d-2.3f). We note that with increasing β, investment in tolerance increases and that in avoidance decreases. A low transmission coefficient leads to lower prevalence of infection, making it easier for a healthy host to avoid encounters with an infected host (i.e., less chances of getting infected) and investment in avoidance is preferred. But when transmission increases, it becomes very unlikely to avoid the infection, so it is best to reduce the damage due to infection by increasing the investment in tolerance instead. Again, this is not very intuitive in a general sense as high transmission could also be expected to evolve more resistant hosts. However, the presence of recovery means that infected hosts can indirectly contribute to the population fitness provided they survive long enough by tolerance to recover.

Similarly, looking at the CSS investment pattern for varying recovery rate, we found that increasing recovery selects for an increasing investment in tolerance and decreasing resistance (Fig. 2.3g-2.3i). When infected hosts are sterile, they can contribute substantially to the fitness only when they recover and become susceptible (fertile) again. So if the recovery rate is very low i.e., the chances of recovering are less, infected hosts make almost no positive contribution to the overall fitness. Increasing tolerance is not beneficial as it will be futile to increase the lifespan of infected hosts when they can not recover and reproduce, and hence selection is for a strategy that tends to keep the population in its fertile (susceptible) state i.e., resistance. In contrast, a high recovery rate means infected hosts can contribute to the fitness and tolerance will further

increase the chances of surviving and reproducing again. Besides, high recovery will lead to a higher susceptible host density that will make investment in avoidance more costly (due to high contact rate).

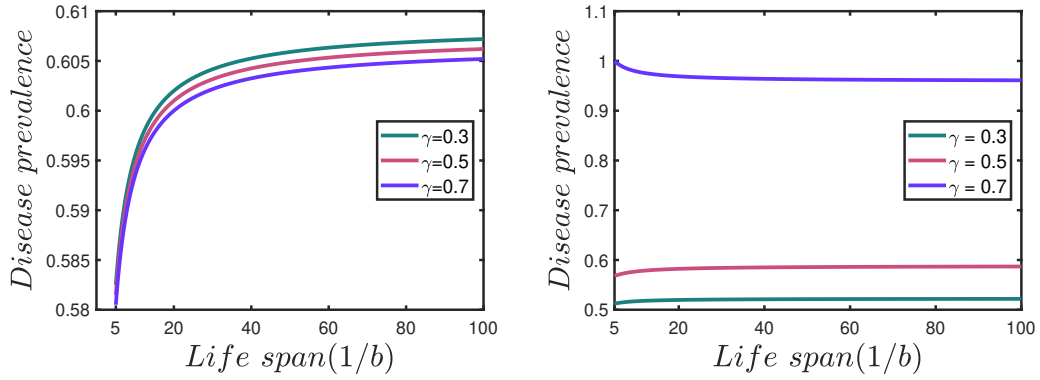


FIGURE 2.4: *Disease prevalence plots for varying recovery rates, (a) when there is no trade-off i.e., no evolving strategy, and (b) when resistance and tolerance are traded-off against each other.*

For comparison, we study the disease prevalence patterns with and without the trade-off function, for different values of the recovery rate γ (Fig. 2.4). When neither of the defence strategies evolves (no cost-function) and are assigned some constant values ($r = 1, \tau = 1$), we see that the prevalence is lower when recovery rate is high and increases with lifespan (Fig. 2.4a). However, when defence strategies are evolving (corresponding to the CSS investment in tolerance), we observe a rather contrary behaviour i.e., infection prevalence increases with increasing recovery rate (Fig. 2.4b). In addition, we get a much greater response in prevalence now for a small change in recovery. As we earlier observed that high recovery selects for increased tolerance (Fig. 2.3g), so a greater number of infected hosts survive the infection which consequently leads to a higher infection prevalence. This is interesting for the reason that high recovery also indicates a higher number of infected hosts recovering quickly and that might be expected to lead to a lower infection prevalence. However, the increased investment in tolerance due to high recovery increases the lifespan of infected hosts, which brings us to the conclusion that this contribution to fitness through increased

tolerance outweighs the cost of having more individuals infected. On the other hand, when none of the defence strategies evolve, high recovery is just equivalent to fewer infected hosts, and hence the lower prevalence.

2.3.1 Effects of infected hosts fecundity

Now we study the case where infected hosts can reproduce and discuss how the infected host's reproduction factor f, or simply termed as "fecundity" here, affects the optimal investment in resistance and tolerance.

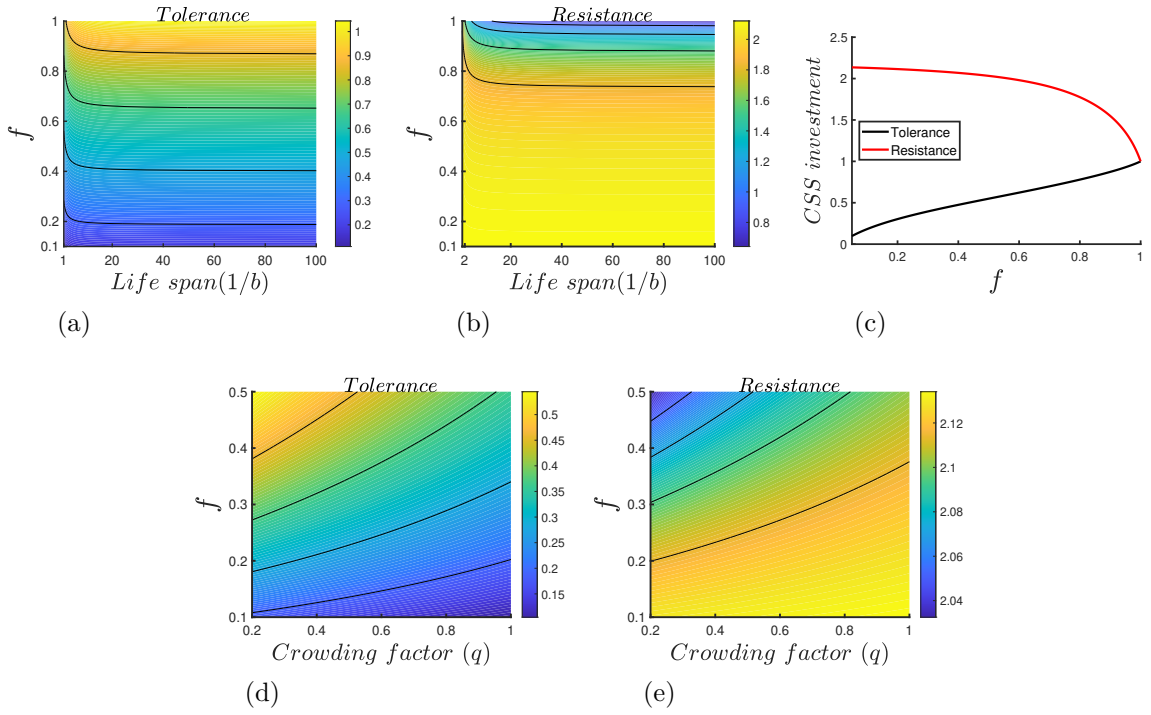


FIGURE 2.5: *(a) and (b) are contour plots indicating the variation in the CSS investment in tolerance and resistance, respectively, when infected hosts fecundity is varied along with lifespan, for system (2.2). (c) is the overall CSS investment change in tolerance and resistance along with fecundity factor f. Figures (d) and (e) show the combined effect of varying fecundity f and crowding factor q on the CSS investment. Parameters used are: $a = 5$, $b = 0.1$, $\alpha = \beta = 5$, $\gamma = 0.3$, $q = 0.2$, $r'(\tau^*) = -5.865$ and $r''(\tau^*) = -30$ for $\tau^* = r(\tau^*) = (1, 1)$.*

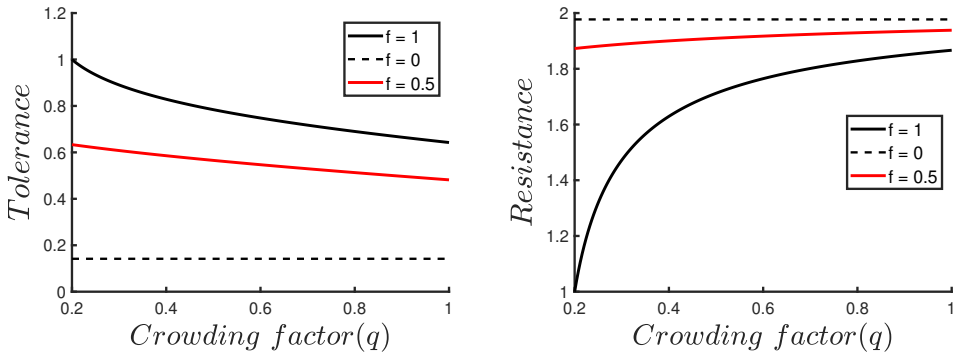
Fig. (2.5) shows the effects of varying the infected hosts' fecundity factor on the

optimal investment in tolerance and resistance. We also look at how much the investments differ from the case where we assumed that infected hosts can not reproduce. With increasing level of fecundity, investment in tolerance increases while resistance decreases (Fig. 2.5a-2.5c). It is well established that when infected hosts' fecundity is nonzero, there is an extra overall fitness benefit contributed by the reproduction of infected hosts (Best et al., 2017b). So if fecundity is positive, investment in tolerance would mean a higher chance of surviving the infection and contributing to the fitness. In fact, when f is nearly 1 (i.e., maximum) and virulence is very low, then both susceptible and infected hosts contribute almost equally to the overall fitness and being infected is not too harmful. At that point, the need for investment in either of the strategies (resistance or tolerance) will be minimized as their effects will almost be neutral. On the other hand, when f is low, infected hosts reproduce less and hence do not contribute substantially to the population fitness. Then selection acts to keep more hosts in the fecund susceptible state by increasing the investment in avoidance. Furthermore, we found a sudden drop in resistance when f is very close to 1 (Fig. 2.5c). This indicates that when fecundity becomes too high, the benefit from resistance rapidly decreases.

Next, we examine the combined effects of varying fecundity f and crowding factor q on the CSS investments (Fig. 2.5d, 2.5e). For a combination of low q and high f, investment in tolerance is maximised, and investment in resistance is minimised. For a high carrying capacity (less crowding effect), the competition for resources will be less and a greater number of hosts will survive the infection. So, if the infected hosts are contributing significantly to the fitness (high f), being infected is not too harmful and a better strategy would be to survive the infection. For resistance, the pattern reverses with a higher investment for high q and low f.

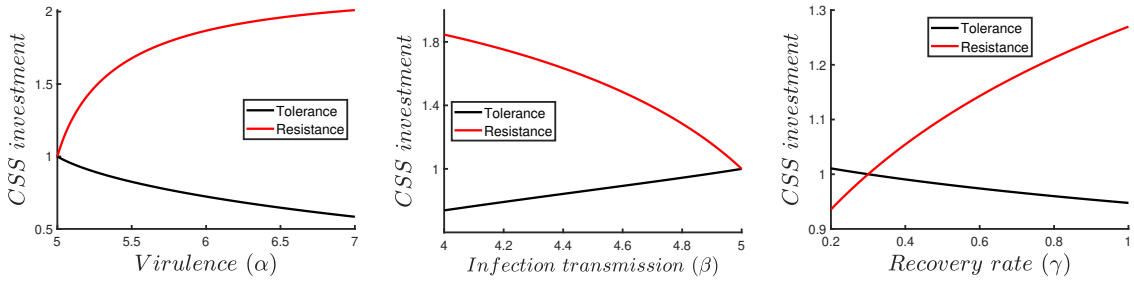
To further improve our understanding regarding the impact of crowding on investment patterns, we analyze the variation in CSS strategies along with crowding, for different values of fecundity (Fig. 2.6). When $f = 0$, there is no change in the investment as q varies (straight dashed lines) i.e., crowding has no effect on optimal

strategies. When $f > 0$, we get a response in the CSS investment such that tolerance decreases and resistance increases for increasing crowding (Fig. 2.6a, 2.6b). An increased crowding is equivalent to more competition for resources and thus leads to a decline in the density of infected hosts. So, fewer infected individuals will survive even if they evolve some tolerance to the infection when the crowding effect is high. Therefore, the selection is for the mechanism that avoids infection, i.e., resistance.



(a) (b)

FIGURE 2.6: *Variation in tolerance and resistance as CSS points for different values of infected hosts fecundity factor f, along with crowding factor q. Parameters used are: $a = 5$, $b = 0.1$, $\alpha = \beta = 5$, $\gamma = 0.3$, $r'(\tau^*) = -5.865$ and $r''(\tau^*) = -35$.*



(a) (b) (c)

FIGURE 2.7: *CSS investment variation in tolerance and resistance for varying α, β and γ for model system (2.2). Parameters used are: $a = 5$, $b = 0.1$, $f = 1$, $\alpha = \beta = 5$, $\gamma = 0.3$, $q = 0.2$, $r'(\tau^*) = -5.865$ and $r''(\tau^*) = -30$ for strategy $\tau^* = r(\tau^*) = (1, 1)$.*

Finally, we briefly discuss the variation in optimal strategies with other parasitic

characteristics when infected hosts can reproduce (Fig. 2.7). As before, the CSS investment in resistance increases (tolerance decreases) for increasing virulence (Fig. 2.7a). Similarly, increasing infection transmission (β) selects for high tolerance and lower resistance (Fig. 2.7b). For recovery rate, however, we obtain a rather contrary behaviour such that increasing recovery now selects for increasing avoidance and decreasing tolerance (Fig. 2.7c). When infected hosts reproduce and contribute to the overall fitness (here $f = 1$ so they reproduce as much as the susceptible hosts), the density of infected hosts increases, leading to a higher infection prevalence. However, increased recovery in this case brings a reduction in the prevalence (see appendix A), thus reducing the benefits of tolerance and making it more costly, and consequently reducing the investment in it.

Table 2.2 summarizes the effects of varying different ecological parameters on the prevalence of disease and indicates which of the strategy (resistance or tolerance) is selected when the respective parameter's value is increased.

Varying parameter (low to high values)	**Feedback on disease prevalence**	**Selected strategy (strategy in which investment increases)**
For f=0		
α	negative	resistance
β	positive	tolerance
γ	positive	tolerance
q	no effect	-
For f>0		
α	negative	resistance
β	positive	tolerance
γ	negative	resistance
q	negative	resistance
f	positive	tolerance

TABLE 2.2: *Table summarising the feedback of varying different parameters on the disease prevalence and selection of defence strategy for both cases: sterile and non-sterile infected hosts. Positive (negative) feedback indicates that the prevalence increases (decreases), and selected strategy indicates the strategy in which the investment increases as the corresponding parameter value increases.*

2.4 Discussion

We studied a theoretical model including a trade-off that linked resistance and tolerance and evaluated their evolutionary responses to determine the ecological and epidemiological conditions that favored one or other of the defence strategies. We found that tolerance is more likely to evolve as a response to low virulence and high transmission, similarly to when each defence trait evolves on its own but with costs to reproduction (Boots & Bowers, 1999; Restif & Koella, 2003). When infected density is high, the greater number of infected individuals in the population make it harder to avoid infection and therefore investment in tolerance is selected to reduce the damage. But due to the trade-off, this will reduce the investment in resistance, increasing the disease prevalence even further. Counter-intuitively, then, when the chance of getting infected is higher, tolerance should be selected and when the chances of dying are greater, avoidance would be better. Further key results surround the impact of recovery and sterility of infected hosts. We discovered that for the highest recovery rate, disease prevalence was maximised when we assume a resistance-tolerance trade-off, but minimised when there was no evolution or trade-off. This points to a counter-intuitive argument that high recovery indirectly leads to more infection when the host evolves subject to a tolerance-resistance trade-off. We also found including reproduction from infected hosts could dramatically impact the results. Highly sterilising diseases drive selection for avoidance whereas less sterilising ones for tolerance. Further, when infected hosts are non-sterile ($f > 0$), we found that the CSS investment pattern with varying recovery reversed, such that high recovery drives increasing avoidance and decreasing tolerance.

The level of resistance or tolerance that a host evolves depends strongly on its ecological and epidemiological background, which further depends upon its life-history traits. One such important aspect of life-history in this context is the host's lifespan (Van Boven & Weissing, 2004; Miller et al., 2007; Donnelly et al., 2015), and it has been found that increasing lifespan leads to an increased overall host density (Boots

et al., 2013). Here we found that increasing lifespan selects for an increased investment in tolerance and decreasing avoidance. The optimal avoidance is lesser in longer-lived hosts as they are very likely to get infected at some point. Provided the host can recover, there is little benefit of costly investment in avoidance of an inevitable infection (Miller, 2006). On the other hand, as a longer-lived host has high chances of getting infected, it is advantageous to invest in tolerance in order to increase its chances of survival and recovery. This increases the average infectious period, consequently increasing the infection prevalence, providing further evidence of a positive feedback on selection of tolerance as a defence strategy (Roy & Kirchner, 2000).

A common hypothesis is that the costs of evolving resistance/tolerance and benefits to fitness vary with changing ecological conditions resulting in different combinations of investment levels in these two strategies (Mauricio, 2000; Roy & Kirchner, 2000). Here we found that a combination of high infection rate and low virulence selects for tolerance, and the opposite combination favours resistance. Such combinations in the plant-pathogen literature have been discussed before (Roy & Kirchner, 2000). For example, a system of rust fungi; *Puccinia punctiformis* and its host *Circium arvense*, where host selects for low resistance/high tolerance towards leaf lesions (a less virulent but highly infectious form of attack) and high resistance/low tolerance to systemic infections (a highly virulent but less infectious form of attack) (Roy & Kirchner, 2000). In about half of the studies (Alexander, 1991; Wennström et al., 1995) summarized by Roy and Kirchner (2000), the fitness implications of infection such as increased mortality were quite low even when disease incidence (transmission) was very high, indicating selection of low resistance and high tolerance. Others (M. A. Parker, 1987; Wennström & Ericson, 1991; Roy, 1993; Roy & Bierzychudek, 1993) found severe impacts on the host's fitness even for a low incidence (transmission), suggesting that resistance was commonly selected but there was little or no tolerance towards infection. These studies discussed at least one case with resistance evolving as reduced infection transmission and tolerance as reduced infection-induced deaths, similar to our assumptions in this study. When virulence is low, the average infectious period is high and the potential

for transmission increases (Miller et al., 2007). Then, due to high infected density, a very high investment in resistance is needed to avoid the infection, making it less likely to be successful in improving the host's fitness. On the contrary, a high transmission indicates that the host will most probably get infected in its lifetime so selection is for investment in tolerance.

Disease prevalence plays an important function in directing the evolution of defence mechanisms, such as tolerance to disease-induced mortality or sterility, resistance as either increased recovery or as reduced transmission, etc. Miller et al. (2007) and Donnelly et al. (2015) have discussed patterns of disease prevalence with respect to lifespan, looking at the evolution of various defence forms, but with a focus on the absence/presence of acquired immunity. Here we found that disease prevalence is higher for a high recovery rate for evolving defence strategies, but the pattern is reversed when there is no trade-off and no evolution. For increasing lifespan, the prevalence usually increases, provided the recovery rate and mortality rates are not too high. In general, prevalence should decrease when recovery increases, as individuals recovering quickly implies fewer infected hosts at a time. But interestingly, high recovery also selects for higher investment in tolerance (Fig. 2.3g), increasing the average infectious period which ultimately leads to an increased infection prevalence. This illustrates the direct relationship between evolution of defence and prevalence of infection. We further obtained some interesting evolutionary patterns after introducing infected hosts' fecundity in the model. We know that the additional reproduction by infected hosts leads to a higher infected density. So when infected hosts reproduce, they can contribute to the total fitness either directly (by reproducing) or indirectly (if they go on to recover). Thus evolution selects for lengthening the lifetime of infected hosts to give them more chance to reproduce by increasing tolerance. This matches the findings of Best et al. (2017b) that increasing fecundity selects for lower investment in resistance, as the need to keep hosts in the fertile susceptible state is less when they can reproduce in the infected state as well. We noted a sudden drop in resistance when fecundity becomes very high indicating that avoidance is only beneficial as long as there is a significant

loss to the reproduction. This is relatable to the predictions by Donnelly et al. (2015) that when parasites do not affect sterility (i.e., $f = 1$), CSS investments are only driven by the benefits of resistance. The evidence of such diseases have been found before, for example several insect larval diseases do not allow infected hosts to either reproduce or even recover once infected (Boots, 2004).

It is well established that population density can affect the evolution of defence strategies (Gokhale et al., 2013; Ashby et al., 2014; Song et al., 2015). Here we found that if infected hosts do not reproduce ($f = 0$), then varying crowding (which is linked to the system's carrying capacity) has no impact on the optimal investments in either resistance or tolerance. Boots and Best (2018) also showed that induced defence (increased recovery rate) remained unaffected but constitutive defence (avoidance) reduced with increased susceptibility to crowding, when the parasite is a castrator ($f = 0$). For nonzero fecundity, however, we observed that varying crowding can significantly change the evolutionary dynamics. When the crowding effect is high, i.e., competition for resources is more, fewer hosts successfully reproduce, thus reducing the infected density, and that further reduces the benefit from tolerance. Studying the combined effect of crowding and infected hosts' fecundity, we discovered that a combination of high fecundity and low crowding selects for higher investment in tolerance (and lower avoidance), and a reverse combination selects for lower tolerance. These results fit the findings by Best et al. (2017b) who considered that increased defence (avoidance, tolerance, and recovery) is costly in terms of reduced reproduction, and demonstrated that a combination of high fecundity and lower crowding selected for high tolerance, and overall investment in all defence mechanisms was highest for low crowding factor and low sterility (or high population density). From this, we conclude that large-sized populations that are slightly sterile are more likely to evolve tolerance.

When parasites do not completely sterilize the hosts ($f > 0$), we found that our results with infection transmission and virulence were similar to the case with no fecundity, but the investment pattern for recovery was reversed. When parasites are sterilizing ($f = 0$), the contribution of infected hosts towards overall fitness is low, and

selection for resistance mechanisms that keep hosts in the susceptible stage increases (Best et al., 2017b). Investment in tolerance will increase as it reduces infection induced mortality and improves the host's chances to recover and reproduce again. Therefore, a combination of high recovery and increased tolerance is most likely to move an infected host into the fertile susceptible stage. On the other hand, when infected hosts contribute to the fitness as much as their susceptible counterparts ($f = 1$) and recovery is high, i.e., there is less life-history cost involved with being infected and hosts do not stay infected for long, the benefit from tolerance will be less and avoidance is selected instead to further avoid any deaths due to infection. However, when recovery is low and fecundity is high, tolerance might still be beneficial as it will prolong the time to give birth to offspring (Best et al., 2017b). This highlights the role of fecundity in driving the evolutionary dynamics of defence mechanisms. Again, disease prevalence plays a major role here in driving the CSS investment patterns. We found that increasing recovery leads to higher disease prevalence for sterilizing parasites, but to lower prevalence when infected hosts reproduce. This creates a direct feedback on CSS investments such that high tolerance is selected when prevalence is high.

There has been some debate about whether resistance and tolerance evolve as mutually exclusive adaptions in response to parasites i.e. if natural selection favors one of the strategies, not both (Belsky et al., 1993; Mauricio et al., 1997). This comes from the idea that having both defensive traits might incur more overall fitness costs than just having one (Mauricio, 2000). In fact, the generality of the presence of trade-offs between resistance and tolerance is not very straightforward (Strauss & Agrawal, 1999). A few experiments suggested that the costs of resistance and tolerance can vary within populations (Pilson, 2000; Fornoni et al., 2004b), but not much is known about the ecological conditions that predict the extent of redundancy between the two strategies. According to Mauricio (2000), there are reasons to hypothesize that complete tolerance and resistance (at the same time) can be redundant: a plant that is fully resistant might not benefit by investing in tolerance as it is least likely to be attacked and a plant that has complete tolerance against herbivore damage need not gain any benefit

from resistance. Furthermore, it is even more important to understand the correlation between tolerance and resistance in the context of genetic manipulations or immune interventions, where enhancing investment in one of the defence strategies could be fatal to the host health (Råberg et al., 2009). For instance, increased tolerance in the absence of parasites may lead to a reduced fitness in some plants (Tiffin & Rausher, 1999; Koskela et al., 2002), and animal species (Wambua et al., 2006). Likewise, in agricultural sectors, attempts to obtain bigger yields could end up worsening things if resistance and tolerance are traded-off against each other (Råberg et al., 2009). Besides, in real host-parasite systems, the parasite's infectiousness and virulence are very likely to evolve along with the host's defence (Restif & Koella, 2004), and Restif and Koella (2003) showed that hosts with high tolerance favor the evolution of even more virulent parasites. A coevolutionary study incorporating these components is therefore needed to get better insights into host-defence evolution. In natural systems, where it is not possible to estimate the actual physiological costs or it is not feasible to predict whether the investment in tolerance will be more than in resistance, phenotypic correlations need to be considered cautiously (Restif & Koella, 2004). Resistance protects the host at the expense of parasite fitness and tolerance protects the host without causing any harm to the parasite. Thus, resistance leads to a decline in disease prevalence, but tolerance has either neutral or no negative effect over the same (Roy & Kirchner, 2000; Miller, 2006). These fundamental differences are likely to affect the epidemiology of infectious diseases and it is, therefore, important to identify the evolutionary consequences of these two defence strategies.

It is clear that resistance and tolerance are different enough that we could expect them to evolve along distinct trajectories (Roy & Kirchner, 2000). Breaking down the components of host fitness into host tolerance, host resistance, and host and parasite life-history traits, as well as the interactions between these components can be useful to better understand the evolutionary patterns of defence. Here we studied the simultaneous evolution of only two defence forms but there are more that can be looked at with a similar negative correlation, such as resistance through the ability to reduce

parasite load (Kutzer & Armitage, 2016), and tolerance to parasite induced loss of reproduction. Another possible extension could be a study on the coevolution of host and parasite in such a scenario. This work, therefore, emphasizes a need for more theory on resistance-tolerance trade-off to examine the impact of pathogens on various host-life histories. Our work also requires experimental support to make better predictions in real host-parasite systems. There is significant empirical literature on plant and animal systems that have found evidence of such a trade-off, but how various population feedbacks affect the relative investment in defence, needs to be tested.

Chapter 3

A sterility–mortality tolerance trade-off leads to within-population variation in host tolerance

3.1 Introduction

It is understood that host defence mechanisms against parasites can broadly be divided into two types: resistance and tolerance (Roy & Kirchner, 2000; Råberg et al., 2009). Both type of defense strategies act to increase the host's fitness but can have distinct evolutionary implications (Roy & Kirchner, 2000). In particular, polymorphisms have been widely identified in models of resistance mechanisms (Boots & Haraguchi, 1999; Best et al., 2010a; Boots et al., 2012; Hoyle et al., 2012; Best et al., 2017b), but very few have detected polymorphism in tolerance (Best et al., 2008; Best et al., 2010b; Ferris & Best, 2019). A number of host-parasite evolutionary models have discussed and compared the evolution of different resistance mechanisms (Antonovics & Thrall, 1994; Boots & Haraguchi, 1999; Miller et al., 2007; Carval & Ferriere, 2010), but the distinction between the two forms of tolerance - reducing mortality or sterility effects - is comparatively less studied (Best et al., 2008; Best et al., 2010b). In Chapter 2, we studied resistance through avoidance and tolerance to parasite-caused mortality and found that a trade-off between these two traits is unlikely to result in polymorphism.

In this chapter, we examine the simultaneous evolution of two tolerance strategies and outline the potential evolutionary outcomes.

The form of tolerance that reduces parasite impact on host mortality is referred to as "mortality tolerance" and has been well studied both theoretically (Miller et al., 2005; Miller et al., 2007; Best et al., 2014), and experimentally (Mauricio et al., 1997; Tiffin & Rausher, 1999; Roy & Kirchner, 2000). Another form of tolerance that reduces parasite implications on host's reproduction is termed as "sterility tolerance" and is less explored (Abbate et al., 2015), with studies largely limited to exploring the impact of sterilising pathogens on host evolution either theoretically (Best et al., 2008; Best et al., 2010b; Kada & Lion, 2015; Best et al., 2017b; Janoušková & Berec, 2018; Bartlett & Boots, 2021), or experimentally (Sloan et al., 2008; Lafferty & Kuris, 2009; Vale & Little, 2012; Kutzer et al., 2018; Montes et al., 2020). There are critical differences between these two arms of tolerance - mortality and sterility - as a host defence strategy. In general, only mortality tolerance creates a positive feedback on the fitness of horizontally-transmitted pathogens (but see Vitale and Best (2019)), whereas sterility tolerance is either neutral or costly to such pathogens' fitness, depending on the trade-off considered (Best et al., 2008; Boots et al., 2009). A negative feedback can cause a decline in the parasite prevalence, leading to negative frequency-dependence and the potential for the coexistence of polymorphic host strains (Roy & Kirchner, 2000). This means that strains with different levels of tolerance to pathogen-induced sterility can coexist within host populations (Best et al., 2008). As such, there are possibilities of polymorphism in sterility tolerance, but not in mortality tolerance (unless external conditions like seasonality are imposed, see Ferris and Best (2019) for instance). An experiment on pea aphid genotypes against fungal pathogens supports this theory, as they found no variation among mortality tolerance traits but did so within traits of fecundity tolerance (B. J. Parker et al., 2014). Willink and Svensson (2017) also found that two female morph types in *I. elegans* evolve different tolerance levels to fecundity reduction caused by parasitic mites. This gives rise to an unresolved question of whether correlations between investment in sterility and mortality tolerance could lead

to within-population variation in mortality tolerance.

The theoretical literature is largely based on the assumption that evolving defence is costly, suggesting trade-offs between defence strategies and other host fitness attributes (Boots & Haraguchi, 1999; Restif & Koella, 2003, 2004; Donnelly et al., 2015). Nonetheless, there is evidence of trade-offs between mechanisms of resistance and tolerance as well (Fineblum & Rausher, 1995; Pilson, 2000; A. A. Agrawal et al., 2004; Råberg et al., 2007; Baucom & Mauricio, 2008; Mikaberidze & McDonald, 2020), but there has been a less theoretical investigation of such a scenario (Restif & Koella, 2004; Best et al., 2008; Best et al., 2017b; Singh & Best, 2021). Investment in sterility tolerance has previously been assumed to be bought at the cost of host characteristics such as increased natural death rate (Best et al., 2008; Best et al., 2010b) or reduced intrinsic birth rate (Restif & Koella, 2004). A model by Best et al. (2017b) explored the consequences of varying infected hosts fecundity on mortality tolerance and found that high fecundity levels select for greater investment in mortality tolerance. Further, a negative correlation between host fecundity and longevity has been studied in theory from a pest control perspective (Berec & Maxin, 2012; Janoušková & Berec, 2018), or with a focus on host resource allocation (Janoušková & Berec, 2020). In parallel to these studies, other theoretical works have indicated that hosts could adjust their resource allocation between reproduction and survival following infection (Hochberg et al., 1992; Hurd, 2001; Gandon et al., 2002; Bonds, 2006; Leventhal et al., 2014). Budischak and Cressler (2018) considered models of sterility vs mortality tolerance in a resource-dependent context, and some experiments have investigated the association between these two components of tolerance (Pagán et al., 2008; Pagán & García-Arenal, 2018; Montes et al., 2020). Another study by Pike et al. (2019) found population-level mortality to be negatively correlated with an investment in fecundity following staph exposure, thus suggesting a fecundity-mortality trade-off in the wild type $N2$ strains of *C. elegans* that were exposed to *S. aureus*. While these correlations between fecundity and mortality of infected hosts have been found in various contexts, the balance of host strategies of tolerance to parasite implications on either of these traits (i.e, correlations

between mortality tolerance and sterility tolerance) are lacking. As such, experimental evidence of a direct trade-off between both tolerance forms as two arms of defence is rare. Here we model a host-parasite evolutionary scenario where the host obeys such a trade-off and aim to provide useful insights for future empirical investigations.

Theoretical models have examined the evolution of tolerance to parasite-induced mortality and sterility as independent adaptive traits, but with an assumption that evolving these strategies is costly to other host fitness traits (Restif & Koella, 2003, 2004; Miller et al., 2005; Best et al., 2008; Best et al., 2010b, 2017b; Vitale & Best, 2019). Therefore, we have no clear predictions of what will happen when these two arms of tolerance are directly traded-off with one another. Forming such a sterility-mortality tolerance trade-off as the basis of this study, we explore the interrelation between epidemiological feedbacks and evolutionary outcomes under this trade-off. Importantly, we demonstrate that the negative feedback created by sterility tolerance on parasite prevalence can lead to polymorphism in mortality tolerance through evolutionary branching for a wide range of trade-offs and parameter values. We also compare disease prevalence patterns with and without evolving host defence strategies.

3.2 The model

We extend a classic host-parasite SIS model from Anderson and May (1981) by considering a trade-off between tolerance to disease-induced mortality and tolerance to disease-induced reduction in the host's reproduction. We also keep general assumptions such as the density-dependent contact process between susceptible and infected hosts and a well-mixed, homogeneous population of hosts. The population dynamics governing the densities of susceptible hosts X and infected hosts Y is given below:

$$\begin{aligned} \frac{dX}{dt} &= (a - q(X+Y))(X + fY) - \beta XY - bX + \gamma Y, \\ \frac{dY}{dt} &= \beta XY - ((\alpha - \tau) + b + \gamma)Y. \end{aligned} \tag{3.1}$$

Parameters are described in Table (3.1). All hosts reproduce by rate a and parasite reduce the reproduction of infected hosts by a factor denoted by f, such as high f indicates that infected hosts reproduce more and low f indicates that they reproduce less, with $0 < f < 1$. All hosts die with natural death rate b, and q denotes the impact of crowding on the host birth rate. The disease transmits with a coefficient β, and α is the additional death rate of infected hosts caused by parasitic infection, also known as virulence. Further, γ is the rate at which infected hosts can recover from the infection and move into susceptible state again.

Parameters	Definition	Default value
a	Host birth rate	2.5
b	Host natural death rate	0.05
q	Crowding effect	0.5
α	Disease induced mortality rate (virulence)	2
β	Infection transmission coefficient	1
γ	Recovery rate of infected hosts	0.3
f	Sterility tolerance	varies
τ	Mortality tolerance	varies
$\tau'(f^*)$	trade-off gradient	-1.6122

TABLE 3.1: List of parameters for tolerance-tolerance trade-off model

In addition to the basic assumptions, we assume that the host evolves tolerance to both: impact of disease on fertility and on additional mortality of infected hosts. Tolerance to disease-induced sterility will be evolved by increasing f, and tolerance to mortality is given by a reduction τ in the infection-induced mortality rate α. More simply put, high f means the host is more tolerant to parasite impact on its reproduction (and that infected hosts reproduce more but cannot evolve compensatory reproduction i.e. $f < 1$), and high τ implies that the host is more tolerant to the deaths caused by the parasite (i.e., reduced mortality). τ and f are further related by a trade-off function which is defined in a later subsection. We choose our parameters such that the parasite persists in the system ($R_0 = \frac{\beta(a-b)}{q(\alpha+b+\gamma-\tau)} > 1$) at an endemic equilibrium

(X^*, Y^*), where

$$X^* = \frac{\alpha + b + \gamma - \tau}{\beta},$$
$$Y^* = \frac{-(1+f)q\beta(b+\alpha+\gamma-\tau) + \beta^2(-b+af-\alpha+\tau) + \sqrt{A}}{2fq\beta^2},$$

and $A = \beta^2(-4fq(-a\beta + b(q+\beta) + q(\alpha+\gamma-\tau))(b+\alpha+\gamma-\tau) + (b(q+fq+\beta) + (1+f)q(\alpha+\gamma-\tau) - \beta(af-\alpha+\tau))^2)$.

3.2.1 Adaptive dynamics

We use the adaptive dynamics framework (Metz et al., 1995; Geritz et al., 1997; Geritz et al., 1998) to model the evolution of two forms of tolerance as defence strategies against parasitism. This method involves assuming small, rare mutations occurring in order to invade the resident host at its set environment (equilibrium). A mutant strain with strategy $(f_m, \tau(f_m)) = (f_m, \tau_m)$ tries to invade the resident equilibrium strategy $(f, \tau(f))$, and can achieve so if its fitness (long-term exponential growth rate of the mutant) is positive in the given environment. Here we use the expression for a fitness proxy that has been proved to be sign-equivalent to that of the mutant's growth rate or fitness by Hoyle et al. (2012). The formula for fitness proxy is calculated using the method described in the appendix of Best et al. (2017b) and is given by

$$s(f, f_m) = (\alpha + b + \gamma - \tau_m)(a - q(X^* + Y^*) - b - \beta Y^*) + \beta Y^*(af_m - qf_m(X^* + Y^*) + \gamma), \quad (3.2)$$

where X^* and Y^* are the susceptible and infected equilibrium densities, respectively, and are the functions of f (see appendix B for more mathematical details). To achieve stable investment in tolerance strategies, we look for singular strategies; the points where the derivative of the fitness expression with respect to the mutant strategy also known as the fitness gradient $(\frac{\partial s}{\partial f_m}|_{f_m=f=f^*})$ is zero. These are the potential points where evolution of a trait stops, potentially temporarily (Metz et al., 1995; Geritz et al.,

1998). Then two stability conditions obtained from the second order derivatives of the fitness gradient determine the evolutionary outcome of evolving strategies. First is the evolutionary stability (ES) that requires $\frac{\partial^2 s}{\partial f_m^2}|_{f=f_m=f^*} < 0$, and second is convergence stability (CS) that must have $\frac{\partial^2 s}{\partial f_m^2} + \frac{\partial^2 s}{\partial f \partial f_m}|_{f=f_m=f^*} < 0$. We found that depending on the combinations of these stability conditions, three different types of evolutionary outcomes can occur at the singular strategy: a continuously stable strategy (CSS) representing stable investments, evolutionary branching, or a repeller. In this chapter, our main focus will be on the strategies corresponding to either CSS investments or branching points.

3.2.2 Sterility tolerance-mortality tolerance trade-off

Trade-offs have been widely used to predict the evolutionary behaviour of ecological systems (Bowers et al., 2005). So whether a singular strategy is a CSS, branching point, or a repeller can be determined by the trade-off shape. Fixing the singularity at a point, we can choose the trade-off curvature to get the relevant evolutionary behaviour.

Here we assume a trade-off function that links two forms of tolerance as different defence strategies such that the benefit from an increased investment in either of the tolerance strategy comes at the cost of a reduced investment in another one. So, if the host increases its reproduction by increasing tolerance to parasite-induced sterility (f), tolerance to mortality viz. $\tau(f)$ will decrease (or mortality will increase), and the converse holds as well. The trade-off function is of the same form as used in previous literature (Hoyle et al., 2012; Vitale & Best, 2019), and is given by

$$\tau(f) \;=\; \tau^* - \frac{\tau'(f^*)^2}{\tau''(f^*)}\left(1 - e^{\frac{\tau''(f^*)(f-f^*)}{\tau'(f^*)}}\right). \tag{3.3}$$

Here, $\tau^* = \tau(f^*)$, $\tau'(f^*) = \frac{\partial \tau}{\partial f}|_{f=f^*}$, $\tau''(f^*) = \frac{\partial^2 \tau}{\partial f^2}|_{f=f^*}$, and (f^*, τ^*) is the singular strategy. Assuming that (f^*, τ^*) is fixed at $(0.5, 1)$, we can chose the slope $\tau'(f^*)$, and curvature $\tau''(f^*)$ of the trade-off curve such that the chosen strategy is a continuously stable strategy (CSS), using the conditions of ES and CS. So $\tau'(f^*)$ is calculated such

that f^* is a singular strategy i.e., fitness gradient is zero at f^* and value of $\tau''(f^*)$ is chosen such that f^* is a CSS. We use this trade-off function to observe the variation in singular points and to show different evolutionary outcomes, depending on its curvature.

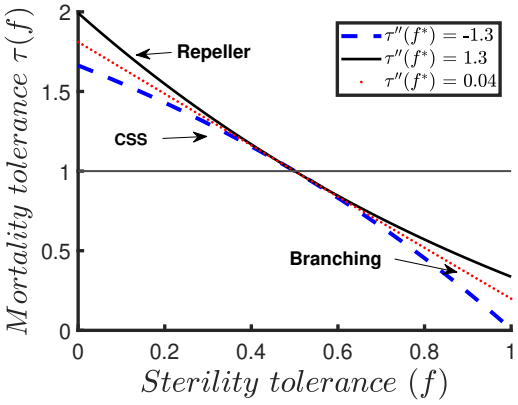


FIGURE 3.1: *Examples of trade-off curves that lead to different evolutionary outcomes corresponding to different curvature values, and gradient* $\tau'(f^*) = -1.6122$. *As such,* $\tau''(f^*) = -1.3$ *gives a CSS,* $\tau''(f^*) = 1.3$ *gives a repeller and* $\tau''(f^*) = 0.04$ *leads to evolutionary branching. The thin black line passing through* 1 *is the value of constant mortality tolerance at* $f^* = 0.5$.

In Fig. 3.1, we indicate three different trade-off shapes, that lead to distinct evolutionary outcomes for when the singular point is fixed at $(f^*, \tau^*) = (0.5, 1)$. If the trade-off is a concave-shaped function such as the dashed line in Fig. 3.1 (i.e., when investment in sterility tolerance becomes increasingly costly), the singularity will be a CSS: host population evolves towards this point and does not change with further mutations. On the other hand, evolutionary branching occurs for a range of slightly convex or weakly decelerating trade-off shapes (close to the dotted line). We also found the occurrence of branching for nearly linear trade-off shapes. Furthermore, for a strongly decelerating trade-off such as the dark line in Fig. 3.1, the singularity will be a repeller: population evolves to either maximum or minimum investments in both arms of defence.

3.3 Results

3.3.1 Branching

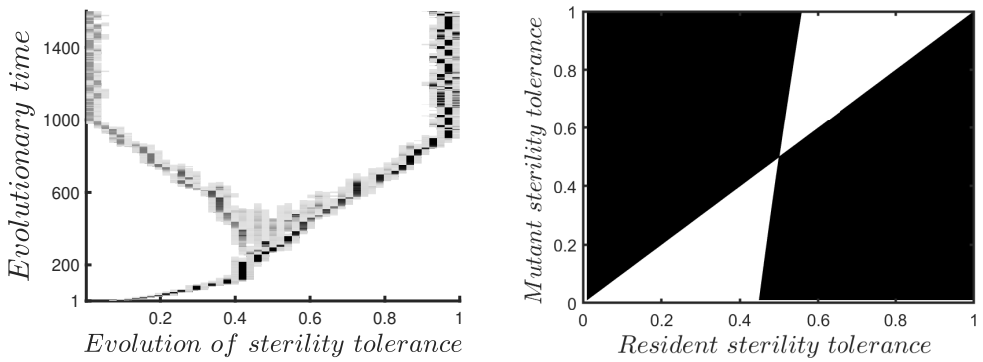


FIGURE 3.2: *(a) Simulation output for the evolution of sterility tolerance when directly traded-off with mortality tolerance. The relative darkness of shading represents the relative susceptible population densities of the host. (b) Corresponding PIP plot with resident strategy on the x-axis and mutant's strategy on y-axis. Shaded part indicates the probable invasion regions of the invading species (mutant host).* $\tau''(f^*) = 0.04$*, for strategy* $(f^*, \tau^*) = (0.5, 1)$*, and remaining parameters are same as in Table 3.1.*

We used the numerical simulation technique from Hoyle et al. (2012) to demonstrate the occurrence of stable dimorphic strains (branching) in our model system (Fig. 3.2a). We found that for weekly decelerating trade-offs, evolutionary branching in the two tolerance mechanisms can occur for a wide range of parameters (Fig. 3.3). This means that the host strains with maximum and minimum sterility tolerance can coexist in the population. An initially monomorphic host population evolves towards the branching point but when close to it, branches into two sub-populations or strains with distinct tolerance levels. One of the strains has minimal sterility tolerance and high mortality tolerance, whereas the other has maximum sterility tolerance but low mortality tolerance (extreme dimorphic strains).

Given alongside is the pairwise invadibility plot (PIP) (see Metz et al. (1995) and Geritz et al. (1997) for details on the construction of PIP) in which the black region

indicates where the mutant can invade the resident host and white region is where the invasion is impossible (Fig. 3.2b). The point of intersection is the branching point and strains from either side of this point can invade the resident, but disruptive selection leads to evolutionary branching. Furthermore, the dark grey shades in Fig. 3.2a indicate higher susceptible population densities, and light grey indicates lower population densities. We observe that the strain with maximum sterility tolerance is darker, i.e., has higher susceptible densities. This suggests that the sub-population in which infected hosts reproduce fully but have higher chances of dying is larger than the one in which infected hosts are sterile.

Now we explore the parameter range space that allows evolutionary branching. We follow the method detailed by Kisdi (2006) that involves checking the sign of a quantity M to predict the mutual invadibility of distinct traits (also see Best et al. (2008), Best et al. (2010b)). The conditions of evolutionary stability (ES), and convergent stability (CS) are analytically expressed as

$$\begin{aligned} ES &= \frac{\partial^2 s}{\partial f_m^2}\Big|_{f^*} < 0, \\ CS = ES + M &= \frac{\partial^2 s}{\partial f_m^2} + \frac{\partial^2 s}{\partial f \partial f_m}\Big|_{f^*} < 0. \end{aligned}$$

So, to get branching at a singular strategy, we need $CS < 0$ but $ES > 0$. At a fixed singular strategy (f^*, τ^*), we can write ES and M as functions of the trade-off. In that case, ES will be a function of the trade-off curvature, but M is not. For a set of parameters at which $M < 0$, we can always choose an appropriate trade-off curvature that satisfies the required conditions and leads to branching. The more negative M is, the greater the range of trade-offs that can allow branching to occur.

To examine the potential of branching under different ecological conditions, we check the sign of M corresponding to different model parameters (Fig. 3.3). Here we calculate the trade-off gradient at each value of the varying parameter such the chosen point $(f^*, \tau^*) = (0.5, 1)$ is singular. We found that M is negative for a wide range of parameters and attains greater negative values at intermediate values of the displayed

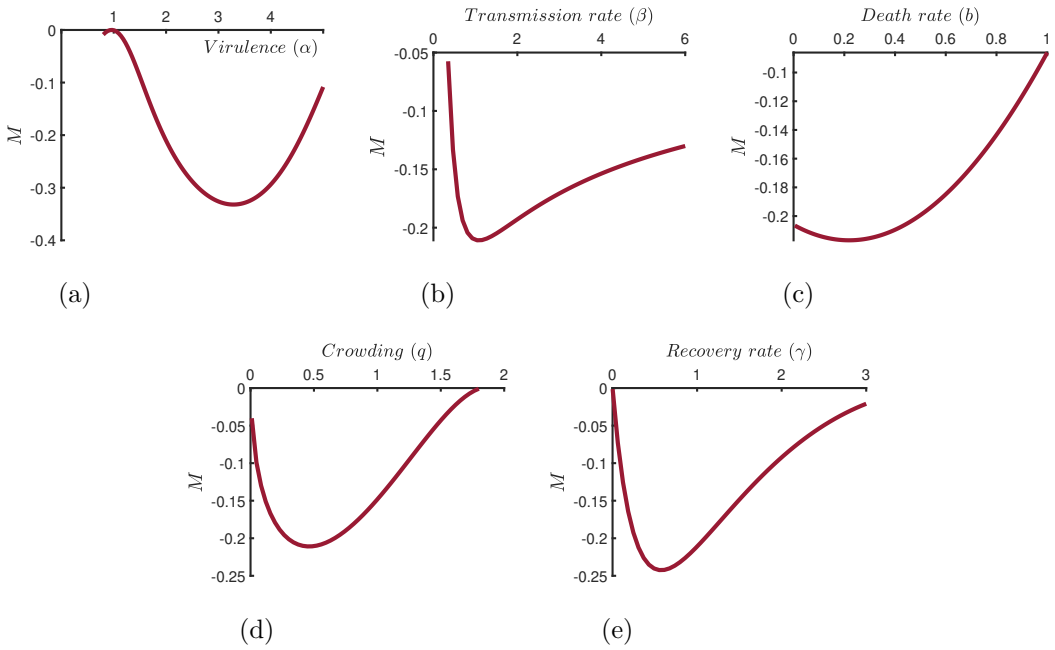


FIGURE 3.3: *Plots showing the sign of mutual invadibility expression (M) corresponding to different parameters. Singular strategy is fixed at $(f^*, \tau^*) = (0.5, 1)$, and remaining parameters are same as in Table 3.1.*

parameters (Fig. 3.3a-3.3e). The parameter ranges where a number of trade-off curvatures exist for which the singular point is CS but not ES (a branching point) coincides with an intermediate or high average infected population size (low b, low/intermediate q and γ, intermediate α and intermediate/high β). This suggests that the infected population size (or infection prevalence) could be a driver of the host variation in sterility and mortality tolerance when linked with such a trade-off.

3.3.2 Evolution drives CSS and disease prevalence patterns

Next, we focus on CSS points to study stable investments in defence mechanisms, i.e., consider the accelerating trade-off. We then examine the role of evolution in driving the selection of two tolerance mechanisms by creating feedback on disease prevalence under varying ecological conditions. Initially, we demonstrate how virulence in the form of additional mortality drives the evolutionary dynamics. For an accelerating trade-off, we found that the host evolves highest sterility tolerance and lowest mortality

tolerance at intermediate levels of disease-induced mortality rate (Fig. 3.4a). Initially, as virulence starts to increase, hosts compensate for the loss due to additional deaths by increasing reproduction. As long as the virulence is not too high and infected hosts live long enough to reproduce, the host shall benefit more by increasing fecundity, such that the maximum sterility tolerance is evolved at intermediate virulence. However, with further increments in virulence, host lifespan decreases rapidly and chances to reproduce become very low, making sterility tolerance an inadequate strategy. As such, increasing fecundity is not enough to maintain fitness at high virulence, and the host has to increase its tolerance to the additional mortality instead.

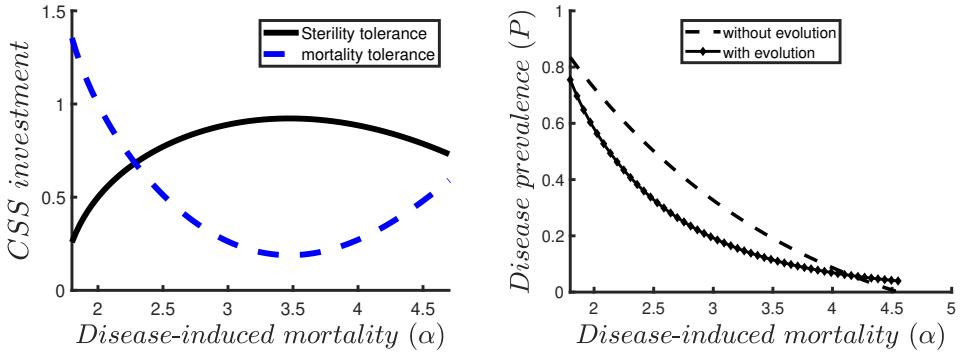


FIGURE 3.4: *(a) CSS investment variation in sterility and mortality tolerance along with varying virulence α. (b) Disease prevalence plot with evolution (prevalence at corresponding CSS investment) and without evolution (prevalence at equilibrium values of X^* and Y^* for f ranging from 0.01 to 1, and τ taking values as per the trade-off), as α varies. Parameters are same as in Table 3.1, for $\tau'(f^*) = -1.6122$, $\tau''(f^*) = -1.3$, and strategy $(f^*, \tau(f^*)) = (0.5, 1)$.*

The host investment in either of the tolerance strategies (CSS) depends significantly upon the disease prevalence $P = Y^*/(X^* + Y^*)$, where X^* and Y^* denote the susceptible and infected hosts' densities at CSS points. The adjacent plot shows the disease prevalence corresponding to varying α when there is no evolution (dashed line) and prevalence at corresponding CSS points (solid line) (Fig. 3.4b). We found the prevalence to continuously decrease with increasing virulence in both cases, although the decline is sharper with no evolution. As virulence α starts to increase, the lifespan

of infected hosts $1/(b+\alpha+\gamma-\tau)$ reduces and prevalence drops. Even when mortality turns too high and mortality tolerance starts to increase again (Fig. 3.4a), the prevalence continues to fall.

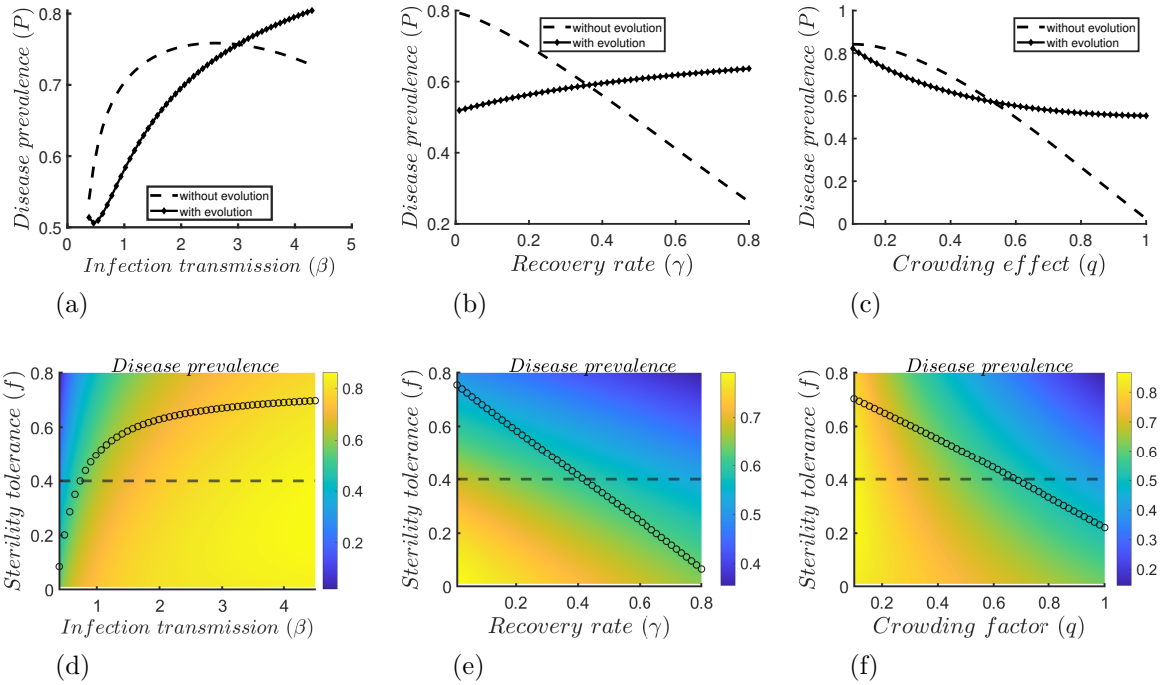


FIGURE 3.5: *Patterns displaying how evolution drives the disease prevalence for varying β, γ, and q. The top row shows the difference in prevalence with and without evolution (plots a, b, c). For no evolution case, prevalence P is calculated at the values of f ranging from 0.01 to 1, and for evolution case, P is calculated at the corresponding CSS points. The coloured surfaces show prevalence overlayed with evolving strategies i.e. CSS points (plots d, e, f). Remaining parameters are the same as in Table 3.1, for singular strategy $(f^*, \tau(f^*)) = (0.5, 1)$ and $\tau''(f^*) = -1.3$.*

Next, we discuss how evolution affects the patterns of disease prevalence with respect to infection transmission rate, crowding effect and recovery rate due to the feedback on tolerance investments (Fig. 3.5). In the top row, dashed lines represent prevalence when there is no evolution of either form of tolerance and diamond-shaped dots represent prevalence when host evolves sterility and mortality tolerance against parasitic consequences (Fig. 3.5a-3.5c). In the second row, we have the coloured surface plots that represent disease prevalence levels through a colour gradient, for when there is no evolution. Plots are overlayed with points (black rings) indicating the

CSS investment in sterility tolerance along with respective parameters on the x-axis (Fig. 3.5d-3.5f). The dashed horizontal line indicates constant level of investment when there is no evolution. The path followed by dashed line and the black rings can be compared to see how evolution drives the prevalence.

For non-evolving strategies, we found that the disease prevalence initially increases with increasing transmission rate β, but starts to decline when β goes too high, forming a concave down shape (Fig. 3.5a). When the host evolves, following a tiny downward bump in the beginning, prevalence continues to increase along with β (Fig. 3.5a). As transmission increases, more hosts move from susceptible to infected state, thereby increasing the average infected density and hence prevalence. When transmission is too high and no tolerance mechanism evolves, an increased average infected density leads to higher mortality, creating a negative feedback on prevalence. With evolution, however, as transmission increases, the host increases its reproduction which comes at the cost of greater infected mortality. While this additional mortality would push prevalence even lower, the increased reproduction will indirectly lead to a larger infected population, reversing the negative feedback. The corresponding surface plot demonstrates this behaviour of increased reproduction at high transmission, where sterility tolerance is an increasing saturating function of β (Fig. 3.5d).

We further found that evolution completely reverses the disease prevalence pattern corresponding to the recovery rate γ. As such, prevalence is a rapid decreasing function of γ without evolution but an increasing function of γ when the host evolves (Fig. 3.5b). From Fig. 3.5e, we clearly see that the black dashed line goes from higher to lower prevalence, but evolving strategies denoted by black rings go from lower to higher prevalence. When there is no evolution, increasing recovery rate simply indicates fewer hosts in the infected state, thus lowering the prevalence. When the host evolves, however, we see that increasing recovery leads to a rapid drop in sterility tolerance and hence a rise in mortality tolerance (Fig. 3.5e). This is driven by high recovery rate leading to less selection for sterility tolerance since hosts can contribute to fitness when they return to susceptible state. The increase in mortality tolerance outweighs

the increase in recovery to lead to higher prevalence.

Finally, we found that prevalence rapidly decreases with increasing crowding when there is no evolution, but it is a slowly decreasing saturating function of crowding when strategies evolve (Fig. 3.5c). From the corresponding surface plot, we observe that sterility tolerance is a rapidly decreasing function of q (Fig. 3.5f). It is understood that increasing crowding acts on net births and reduces overall infected density (varying q only affects the equilibrium density of infected hosts Y^* as X^* is free of q), thus lowering the prevalence. Reduced overall reproduction due to smaller infected population size leads to lower sterility tolerance when competition is high. To maintain the fitness, mortality tolerance increases, thus slowing down the reduction in prevalence (evolution case, Fig. 3.5c).

3.4 Discussion

The fitness costs of parasites on their hosts can generally be classified into reduced fecundity or mortality of hosts. Here we studied a host attacked by a parasite that adversely affects both fecundity and mortality, and we assume that the host can respond by evolving tolerance to both forms of parasitic impact but is subject to a sterility-mortality tolerance trade-off. Using this modelling framework, we identify the following key results: (i) stable dimorphism can arise for a weakly decelerating trade-off at which the most fecund and sterile host strains can coexist in the population; (ii) a wider range of trade-off shapes can lead to branching for parameters corresponding to intermediate/high infected population sizes; (iii) the host evolves maximum sterility tolerance and minimum mortality tolerance at intermediate virulence; and (iv) evolution changes patterns of disease prevalence creating a feedback on the CSS investments, where the prevalence pattern corresponding to recovery rate completely reverses.

Existing theory predicts that due to positive frequency dependence and positive impact on parasite fitness, the mechanisms of tolerance do not lead to polymorphisms or evolutionary branching in standard models (Roy & Kirchner, 2000; Miller et al., 2005)

(but see Ferris and Best (2019) when there is seasonality). However, only tolerance to mortality has a positive impact on parasite prevalence, whereas tolerance to sterility is either neutral or costly to the parasite and thus could lead to polymorphic strains (Best et al., 2008; Best et al., 2010b). In this study, we have shown the existence of dimorphism through evolutionary branching for a direct trade-off between two arms of tolerance, with no additional cost to any other host life-history trait. Note that the branching in mortality tolerance follows from the branching in traits conferring sterility tolerance due to the trade-off. So, in one of the existing strains, infected hosts cannot reproduce ($f = 0$), but they are most protected against infection-induced mortality and are least likely to die. In contrast, the infected hosts in another strain reproduce fully ($f = 1$) but are more prone to death due to infection. This supports the theoretical predictions of Antonovics and Thrall (1994) and Bowers et al. (1994) that dimorphism can only occur in two dissimilar strains. Evidence of polymorphisms in both forms of tolerance is widely available in the plant-pathogen literature. Populations of *Arabidopsis thaliana* infected by *Cucumber mosaic virus* (CMV) displayed large genetic variation in sterility tolerance (tolerance to the effects on host progeny production) between and within-host populations (Pagán et al., 2007, 2008; Montes et al., 2019), whereas Montes et al. (2020) detected polymorphism in both mortality and fecundity tolerance. Koskela et al. (2002) also found genetic variation in sterility tolerance of *Urtica dioica* to *Cuscuta europea* measured in terms of reproductive biomass. Further, Vijayan et al. (2017) investigated the evolution of mortality tolerance (as expected time until death after infection) in *A. thaliana* and *Brassica juncea* to *Turnip mosaic virus* (TMV) and found genetic variation in this tolerance trait among host species. A recent study also suggested the possibility of variation in different tolerance strategies between unprotected (hosts exposed to food bacterium) or protected (hosts exposed to food bacterium plus *E. faecalis*) treatments of hosts (Rafaluk-Mohr et al., 2022). While numerous experimental studies have demonstrated within-population variation in host tolerance, few theoretical studies have ever demonstrated the evolution of polymorphism in tolerance.

We further found that branching can occur for a substantial region of parameter space, but a wider range of trade-off shapes leading to branching exists at parameters corresponding to intermediate or high infected population size. In previous work, Best et al. (2010b) discovered that a broader range of trade-off shapes could lead to branching in sterility tolerance at low intrinsic death rates (indicating high infected population density). Furthermore, Ferris and Best (2019) had similar findings for the host mortality tolerance in a seasonal environment with infected fecundity added to their model, suggesting that parasites that temporarily sterilise their hosts are more likely to promote diversity. They concluded that branching in host tolerance is more likely in a fluctuating environment with a high average infected population size. Since evidence of tolerance mechanisms leading to branching are rare (Best et al., 2010b; Ferris & Best, 2019), possibilities of branching have been mostly discussed in models of host resistance evolution (Boots & Haraguchi, 1999; Hoyle et al., 2012; Toor & Best, 2015; Best et al., 2017b). For example, for both avoidance and clearance models, Best et al. (2017b) predicted that when parasite-induced sterility is not too low, a number of trade-off curvatures allowed branching and that the potential for branching decreased with increasing fecundity of infected hosts. The relationship between branching and infected population density has been demonstrated experimentally by Blanchet et al. (2010), where they found higher variation in host tolerance in a wild dace population with a high parasite burden. Our findings are consistent with the trend of higher chances of diversity at high infected population sizes, suggesting that branching in any host tolerance strategy requires high infection prevalence.

The allocation to different tolerance mechanisms of the host depends upon the cost and how virulent/deadly the parasite is. For instance, when resistance (via reduced transmission) is traded-off with mortality tolerance, hosts infected with low virulent parasites experience selection for greater mortality tolerance than those infected by highly virulent parasites (Singh & Best, 2021). Similarly, mortality tolerance evolves in an experimental system with a 'protected' treatment in which virulence is low, whereas fecundity tolerance evolves in an unprotected treatment in which virulence is

high (Rafaluk-Mohr et al., 2022). We observed that the host initially shows similar behaviour in our model, but then the pattern reverses, thus evolving maximum sterility tolerance and minimum mortality tolerance at intermediate virulence. Best et al. (2010b) had a similar finding where they considered increased fecundity comes at the cost of an increased natural death rate and obtained maximum sterility tolerance at intermediate levels of virulence. On the other hand, we found prevalence to continuously decrease with increasing α, suggesting lower infected equilibrium densities at high virulence, in alignment with the theoretical findings of Miller (2006) and Miller et al. (2007). However, a study by Thrall et al. (1998) on the evolution of sexual and non-sexual transmission modes identified that for a fixed level of sterility, population densities are minimized at intermediate levels of virulence. This suggests that further work is needed to understand the different impacts of tolerance on disease prevalence under different biological conditions.

In combination with genetic constraints, epidemiological feedbacks can produce a wide range of potential evolutionary outcomes. Here we identify that increased intra-host crowding leads to monotonically decreasing pattern for both disease prevalence and sterility tolerance. So, a host with high carrying capacity will be more tolerant to the parasitic effects on fertility. This is analogous to the results of Donnelly et al. (2015) that infected density and prevalence decrease monotonically with increasing crowding. Krist (2001) found that if parasite castration diminishes the density of snails in highly prevalent populations, reduced competition for resources could increase the energy available for reproduction, indicating the selection of high sterility tolerance at low crowding. Other empirical works made a similar inference (Goulson & Cory, 1995; Reilly & Hajek, 2008; Lindsey et al., 2009). Likewise, theory has typically explored how tolerance varies along gradients of different epidemiological parameters. Transmission rate is one of the most commonly explored gradients, and the investment in sterility or mortality tolerance is predicted to increase with infectivity (Boots & Bowers, 1999; Miller et al., 2005; Miller et al., 2007; Best et al., 2010b). On the other hand, hosts evolved highest mortality tolerance at a high recovery rate when

infected with a sterilising parasite, but at low or intermediate recovery rates when parasite impacts on sterility were low (Best et al., 2017b). Here we found that sterility tolerance is selected in response to high transmission rate and low recovery rate. So when infected with a highly infectious parasite, the host will benefit more by increasing its reproductive efforts. However, quick recovery from the infection will lead to lower selection for sterility tolerance as the infected hosts can reproduce after becoming susceptible again. Additionally, we discovered that the evolutionary trend with varying recovery rate completely reversed compared to when no defence evolved. Therefore, the importance of recovery rate in influencing tolerance selection highlights the need for empirical data sets that explicitly measure recovery rate.

A number of parasites have been found to affect both reproduction and survival in their hosts. For example, the bacterium *Pasteuria ramosa* can castrate its host *Daphnia magna*, and also leads to its premature death (Jensen et al., 2006; Vale & Little, 2012). Other examples include parasitic nematode *Trichostrongylus tenuis* in red grouse, fungal infections caused by *Puccinia* spp. in European weeds (Roy & Kirchner, 2000), and bank voles and wood mice infected by the cowpox virus (Feore et al., 1997). On the other hand, there is enough empirical evidence to support the idea that the reproductive abilities of the host can be costly for its survival under infection. For instance, females of mealworm beetle *Tenebrio molitor* infected by the rat tapeworm *Hymenolepis diminuta* had reduced reproduction, but their lifespan significantly increased (Hurd, 2001). Despite the empirical evidence (Pike et al., 2019; Montes et al., 2020), few of the theoretical models to date specifically addressed a reproduction-survival (or equivalently, a sterility-mortality) trade-off and those who did (Best et al., 2008; Best et al., 2010b), considered survival as a host fitness trait and did not recognise the effects of parasite-induced mortality. Our model assumes that the host's response to pathogen's impact on its mortality evolves along with their impact on the fecundity, and trade-off amounts for the distributed allocation of host defence between these two parasitic repercussions. As such, our sterility-mortality tolerance trade-off considers both forms of parasite impacts and is the first trade-off of its kind

in theory.

Given the limited empirical studies on the evolution of tolerance to both components of infection-induced fitness loss, sterility and mortality, theory can provide excellent insights for future empirical research and a better understanding of their implications. Here we stressed how epidemiological feedbacks drive the evolution of two linked tolerance mechanisms and discovered that polymorphism could occur in the traits of mortality and sterility tolerance for a wide range of trade-offs and parameter values. We would encourage the development of experimental testing concerning such trade-offs in real systems, particularly where high within-population variation has been found. We also highlighted the need for studies on the impact of recovery rate on tolerance investments, which could play a crucial role in host evolution but are seldom examined in the literature. In real-life systems, the long-term behaviour of host-parasite interactions is directly linked to the interplay between host and parasite evolutionary characteristics, i.e., the coevolutionary dynamics. Therefore, the future work may incorporate the coevolution of host and parasite for a similar trade-off function or when sterility and mortality tolerance evolves together but with costs to other host-life history traits.

Chapter 4

The impact of sterility-mortality tolerance and recovery-transmission trade-offs on host-parasite coevolution

4.1 Introduction

Coevolution is a key driver in shaping the structure of host-parasite interactions. A major portion of the literature assumes that the hosts and parasites evolve in isolation. However, in natural systems, both species interact, and the long-term behaviour of such interactions can be directly linked to the interplay between host and parasite evolutionary characteristics, i.e., the coevolutionary dynamics (Penn, 2001; Buckingham & Ashby, 2022). Existing coevolutionary models have primarily focused on the coevolution of host resistance and parasite infectivity, either in an evolutionary invasion framework (Baalen, 1998; Gandon et al., 2002; Restif & Koella, 2003; Best et al., 2009; Best et al., 2010a; Boots et al., 2014; Best et al., 2017a; Best, 2018), or in a gene-for-gene (GFG) framework (Flor, 1956; Frank, 1992; Sasaki, 2000; Tellier & Brown, 2007; Ashby et al., 2014; Ashby & Boots, 2017) as well as in a matching allele (MA) framework (Frank, 1993, 1994). Despite an increasing number of experimental

and theoretical studies exploring host-parasite coevolution (Brockhurst et al., 2004; Boots et al., 2009; Brockhurst & Koskella, 2013; Brockhurst et al., 2014; Koskella & Brockhurst, 2014; Betts et al., 2016; Papkou et al., 2016), further research is required to comprehend how various attributes of host-parasite interactions may impact coevolutionary dynamics. In particular, since most evolutionary theory examining tolerance is host centric, there is a definite need to acknowledge tolerance in a coevolutionary framework (Little et al., 2010; Best et al., 2014).

The number of coevolutionary invasion models which investigated either component of host tolerance (sterility/mortality) (Restif & Koella, 2003; Best et al., 2009, 2010b, 2014), is lower compared to those that considered host resistance (Baalen, 1998; Best et al., 2014; Boots et al., 2014; Best et al., 2017a; Best, 2018; Ferris et al., 2020). Furthermore, these studies have only examined the evolution of one type of tolerance, either sterility or mortality, in conjunction with parasite evolution, but not both. Recently, a purely evolutionary model has explored the trade-off between sterility tolerance and mortality tolerance of the host (Singh & Best, 2023), and had empirical support (Pike et al., 2019; Montes et al., 2020). They examined how the host evolves CSS investments in both tolerance strategies under different ecological conditions, and identified which trade-off shapes and parameters are more likely to result in evolutionary branching. They found that a trade-off between two tolerance strategies can cause the host population to split into dimorphic strains, with branching more likely at intermediate or high infected population sizes (refer to Chapter 3).

Meanwhile, parasite evolution within a coevolutionary framework is predominantly looked at under the assumption of a transmission-virulence trade-off (Baalen, 1998; Gandon et al., 2002; Best et al., 2009, 2014; Best et al., 2017a; Best, 2018). Alizon (2008) claimed that such a parasite trade-off fails to recognise the evolution of sub-lethal parasite effects, and taking recovery as the primary selection pressure for the parasite (instead of virulence) can address this problem. They showed how a trade-off between parasite transmission and recovery can emerge from within-host dynamics if immune activation is allowed to depend on the parasite's growth rate and answered

how the immunological state of the host drives the optimal growth rate of the parasite. Both transmission-virulence and transmission-recovery trade-offs follow from an underlying idea that by increasing its host exploitation strategy, the parasite evolves higher transmission rate but also reduces the infection duration (Anderson & May, 1982; Frank, 1996; Alizon, 2008). Following this, Greischar et al. (2019) developed a data-driven model focusing on malaria parasites to study the evolutionary impact of ecology on transmission investment, considering host recovery as a main driver of parasite evolution. Their research indicated that a positive correlation between transmission and recovery creates a strong selection pressure for parasite proliferation (trait influencing disease severity and spread) at the expense of transmission. A few more studies focusing on spatial structure acknowledged or observed the emergence of trade-offs between transmission and recovery in their models, but did not analyze the trade-off itself (Van Baalen, 2002; Van Ballegooijen & Boerlijst, 2004; Read & Keeling, 2006). Empirical evidence of this trade-off has also been observed in the context of the dengue virus and host immune response (Ben-Shachar & Koelle, 2018), as well as in a study of Zika virus transmission via mosquito bites to mice, where a higher number of infectious bites led to a shorter infection duration (Hanley et al., 2019). Despite empirical evidence supporting the trade-offs between sterility-mortality tolerance in hosts and transmission-recovery in parasites, none of the current models have explored the potential outcomes when both trade-offs are considered within a coevolutionary framework. As many real-life systems exhibit coevolutionary dynamics, it is essential to determine whether the results from purely evolutionary systems hold true in coevolutionary systems. To fill this gap, we develop a model constructed around the assumptions of a sterility-mortality tolerance trade-off in the host and a transmission-recovery trade-off in the parasite and ask how the interplay between both species shapes their coevolution.

Furthermore, existing coevolutionary models are based on one of two key assumptions: (i) each evolving trait is controlled solely by either the host or the parasite, with no interaction between the two (Baalen, 1998; Restif et al., 2001), or (ii) both

host and the parasite share control over an evolving epidemiological trait (Frank, 1993; Restif & Koella, 2003; Best et al., 2009, 2010b, 2014; Boots et al., 2014; Best et al., 2017a; Best, 2018). In the later case, the evolving trait therefore depends upon the combined investment levels of both host and the parasite rather than their specific strategies. Most of these models considered transmission and virulence to be the traits controlled by both host and parasite (Frank, 1993; Restif & Koella, 2003; Best et al., 2009, 2010b, 2014; Boots et al., 2014; Best et al., 2017a). In this study, we do not consider control share, unlike most previous coevolutionary approaches. This means that we assume both the host and parasite can evolve their traits without sharing control over a common epidemiological trait.

The key objective of this study is to explore the coevolution of host and parasite traits, which have been traditionally analysed independently. Our analysis starts by examining the stable investment levels of the host and the parasite to enhance our knowledge of how ecological factors stimulate coevolution. We then investigate the potential for diversity through the coevolutionary process, either due to cycles or through the coexistence of multiple host and parasite strains. Additionally, we examine how various host and parasite trade-off shapes influence coevolutionary outcomes, aiming to identify differences between coevolution and independent host-parasite evolution.

4.2 Model and methods

We investigate the coevolutionary dynamics of hosts and parasites using a generic susceptible-infected-susceptible (SIS) model framework (Anderson & May, 1979). Extending the host evolutionary model studied in Chapter 3, we assume that the host evolves both sterility and mortality tolerance and the two tolerance components are related by a trade-off function. Additionally, we assume that the parasite coevolves with the host and follows a transmission-recovery trade-off. As such the parasite can increase its transmissibility but at the cost of a reduced infectious period due to increased

recovery. We further consider a density-dependent birth rate and a homogeneous, well-mixed host population. The following equations describe the population dynamics of the ceoevolutionary model where X and Y denote the densities of susceptible and infected hosts, respectively:

$$\begin{aligned} \frac{dX}{dt} &= (a - qN)(X + fY) - \beta XY - bX + \gamma Y, \\ \frac{dY}{dt} &= \beta XY - ((\alpha - \tau) + b + \gamma)Y. \end{aligned} \tag{4.1}$$

Here $N = S + I$, and the parameters are detailed in Table (4.1). The birth rate of all hosts is a, but infection diminishes the reproduction of infected hosts by a factor of f, where the value of f indicates the relative birth rate of infected hosts ($0 < f < 1$). The natural death rate of all hosts is b, and q represents the impact of crowding on overall host birth rate. Susceptible hosts can get infected by a mass-action transmission process with coefficient β. α is the additional death rate due to parasite-caused infection, and γ is the rate at which infected hosts recover from the infection and become susceptible to infection again.

Additionally, we assume that the host evolves two traits: sterility and mortality tolerance (f and τ), while the parasite evolves its transmission and recovery rate (β and γ). High/low values of f and τ indicate higher/lower investment in respective tolerance traits. Similarly high/low values of β and γ indicate higher/lower values of parasite transmission and recovery rate, respectively. We chose our parameters in a way that the parasite persists in the system (i.e., $R_0 > 1$) at an endemic equilibrium (refer to Chapter 3 for equilibrium points).

4.2.1 Modelling within the adaptive dynamics framework

We model the coevolution of the host and parasite using the classic adaptive dynamics framework (Marrow et al., 1996; Geritz et al., 1997; Geritz et al., 1998; Kisdi, 2006). We assume that the resident host strain with strategy (f, τ) and the resident parasite strain with strategy (γ, β) have reached a stable, positive equilibrium. We

Parameters	Definition	Default value
a	Host birth rate	2.5
b	Host natural death rate	0.05
q	Crowding effect	0.5
α	Disease induced mortality rate (virulence)	2
β	Infection transmission coefficient	varies
γ	Recovery rate of infected hosts	varies
f	Sterility tolerance	varies
τ	Mortality tolerance	varies
$\tau'(f^*)$	Host trade-off gradient	-1.3996
$\beta'(\gamma^*)$	Parasite trade-off gradient	0.97561

TABLE 4.1: Description of parameters for coevolution model.

then determine the invasion fitness of a mutant host strain with strategy (f_m, τ_m) and a mutant parasite strain with strategy (γ_m, β_m) that are attempting to invade the resident equilibrium. The expression for the mutant host fitness is given by

$$s(f, f_m, \gamma) = \frac{Tr + \sqrt{Tr^2 - 4Det}}{2}, \tag{4.2}$$

where

$$\begin{aligned} Tr &= \{a - q(X^* + Y^*) - b - \beta(\gamma)Y^*\} - (\alpha + b + \gamma - \tau(f_m)), \\ Det &= \{a - q(X^* + Y^*) - b - \beta(\gamma)Y^*\}\{\tau(f_m) - \alpha - b - \gamma\} \\ &\quad -\beta(\gamma)Y^*\{af_m - qf_m(X^* + Y^*) + \gamma\}, \end{aligned}$$

and the parasite invasion fitness is given by

$$r(\gamma_m, \gamma, f) = \beta(\gamma_m)X^* - (\alpha + b + \gamma_m - \tau(f)), \tag{4.3}$$

where X^* and Y^* are the susceptible and infected population densities evaluated at the resident equilibrium. Here Tr and Det are the trace and determinant of the host mutant dynamics system (see Chapter 1 and appendix C for more details, also see appendix of Best (2018)).

Assuming that mutations are small and rare, the coevolutionary dynamics of the host and parasite traits f and γ over evolutionary time T can be approximated by the following pair of equations:

$$\frac{df}{dT} = \phi_h X^* \frac{\partial s}{\partial f_m}\bigg|_{f_m=f}, \tag{4.4}$$

$$\frac{d\gamma}{dT} = \phi_p Y^* \frac{\partial r}{\partial \gamma_m}\bigg|_{\gamma_m=\gamma}, \tag{4.5}$$

where ϕ_h and ϕ_p control the mutation speed of the host and parasite, respectively. Then the host and parasite coevolve along their respective fitness gradients, $\frac{\partial s}{\partial f_m}|_{f_m=f}$ and $\frac{\partial r}{\partial \gamma_m}|_{\gamma_m=\gamma}$, until a co-evolutionary singular point is attained where the two gradients become simultaneously zero (Marrow et al., 1996; Durinx, Meszéna, et al., 2008). Depending upon the signs of the second-order derivatives of the fitness expressions and speed of evolution of both species, we observe the following coevolutionary outcomes: (i) a continuously stable strategy (co-CSS) where both host and parasite invest in optimal levels of investment, (ii) evolutionary branching in either or both species, (iii) coevolutionary cycles, and (iv) maximization/minimization of the evolving host and/or parasite traits to their physiological bounds. Additional details of these methods are given in appendix C.

Host and parasite trade-offs

To conduct our coevolutionary analysis, we adopt the assumption that the host evolves two tolerance strategies that are inversely linked by a trade-off function. Consequently, investing more resources in one tolerance strategy would come at the expense of reduced investment in the other. Meanwhile, the parasite can evolve increased infection transmission, but this leads to an increment in the host recovery rate, which indirectly incurs a cost in terms of a reduced infectious period for the parasite. We consider generic trade-off forms for both host and parasite (see Hoyle et al. (2012) and

Toor and Best (2015) for more details on the trade-off form) given as follows:

$$\tau(f) = \tau(f^*) - \frac{\tau'(f^*)^2}{\tau''(f^*)}\left(1 - e^{\frac{\tau''(f^*)(f-f^*)}{\tau'(f^*)}}\right), \tag{4.6}$$

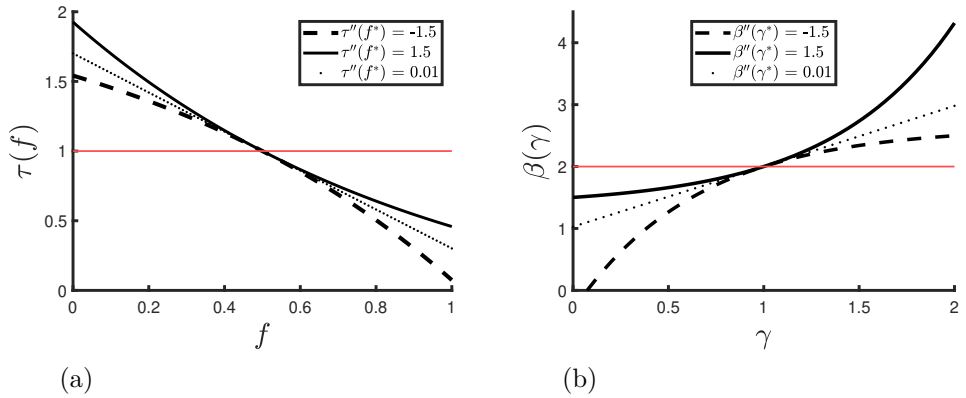
$$\beta(\gamma) = \beta(\gamma^*) - \frac{\beta'(\gamma^*)^2}{\beta''(\gamma^*)}\left(1 - e^{\frac{\beta''(\gamma^*)(\gamma-\gamma^*)}{\beta'(\gamma^*)}}\right). \tag{4.7}$$

Here primes denote the derivatives and $(f^*, \tau(f)^*)$ and $(\gamma^*, \beta(\gamma^*))$ are the singular strategies for the host and parasite, respectively. The choice of such a trade-off form allows us to fix the singular strategy at a chosen point and then find the slope and curvature of the trade-off function at that chosen strategy. Here we fix the host singular strategy at $(0.5, 1)$ and parasite strategy at $(1, 2)$. Then slopes $\tau'(f^*)$ and $\beta'(\gamma^*)$ are calculated such that the singularities occur at these chosen points (i.e, host and parasite fitness gradients become zero at f^* and γ^* respectively). The curvatures $\tau''(f^*)$ and $\beta''(\gamma^*)$, on the other hand, can be chosen as per the requirement for an accelerating or decelerating cost function. The graphical representation of both trade-offs with different curvature values are given in Fig. 4.1. The concave-shape indicates that the investments in strategies become increasing costly $(\tau''(f^*) < 0, \beta''(\gamma^*) < 0)$. A convex-shape, on the other hand, indicates decelerating costs $(\tau''(f^*) > 0, \beta''(\gamma^*) > 0)$. We later discover how the selection of different trade-off shapes lead to entirely different coevolutionary outcomes.

4.3 Results

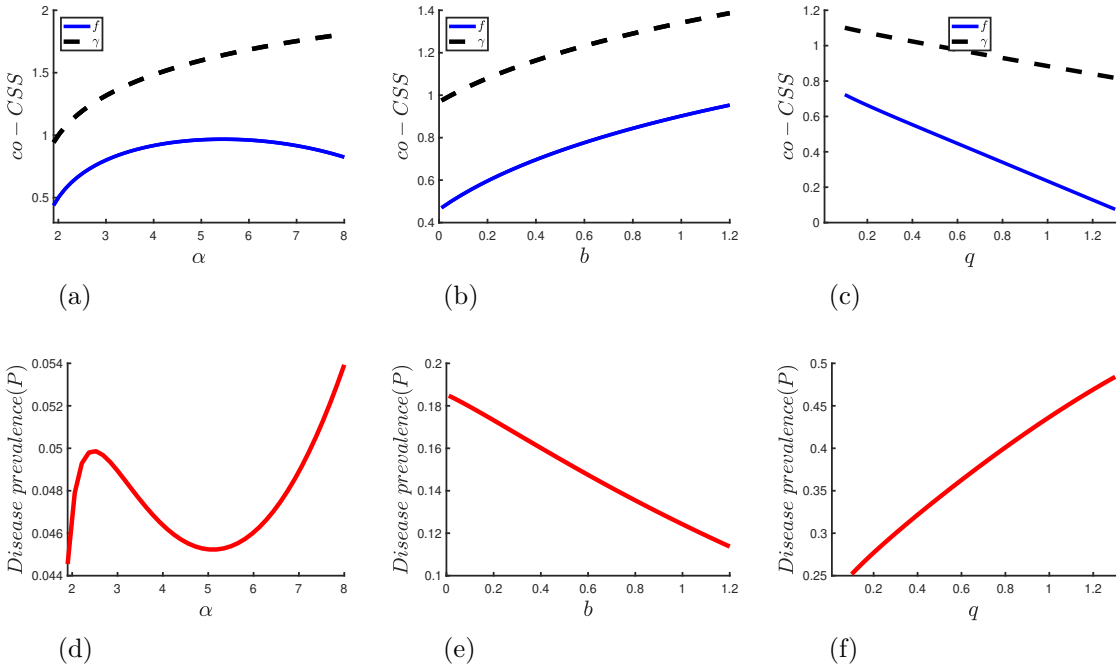
4.3.1 Impact of ecological parameters over co-CSS

Initially, we assume accelerating trade-offs for both the host and parasite, which typically results in stable investments at a coevolutionary stable strategy (co-CSS), as noted by Hoyle et al. (2012). This assumption suggests that investing more in tolerance to parasite-induced sterility for the host and higher transmission for the parasite will become progressively more costly.



(a) (b)

FIGURE 4.1: *(a) Host trade-off curves for different curvature values when parasite traits are fixed at* $\gamma = 1$ *and* $\beta = 2$ *with gradient* $\tau'(f^*) = -1.3996$. *(b) Parasite trade-off curves when host traits are fixed at* $f = 0.5$ *and* $\tau = 1$ *with gradient* $\beta'(\gamma^*) = 0.9756$. *The straight thin lines crossing the intersection points in both figures indicate the fixed host and parasite trade-offs at* $(f^* = 0.5, \tau = 1)$ *and* $(\gamma = 1, \beta = 2)$, *respectively. Remaining parameters are same as in Table 4.1.*



(a) (b) (c)

(d) (e) (f)

FIGURE 4.2: *Variation in co-CSS strategies along with varying (a) disease-induced mortality rate* α, *(b) natural death rate* b, *and (c) crowding factor* q. *In the second row, we present the corresponding disease prevalence plots for respective parameters. Here we use trade-offs with accelerating costs:* $\tau''(f^*) = -1.5$ *and* $\beta''(\gamma^*) = -1.5$, *and remaining parameters are same as in Table 4.1.*

To reveal how ecological and epidemiological factors drive coevolution, we present the variation in co-CSS points for the disease-induced mortality rate α, intrinsic death rate b, and crowding factor q (Fig. 4.2). We found that host investment in sterility tolerance is maximized at intermediate virulence, but that the recovery rate increases monotonically as virulence increases (Fig. 4.2a). This means that the host can benefit from increasing infected reproduction as long as the virulence is not too high and infected hosts live long enough to reproduce. However, extreme levels of virulence means infected hosts are dying quickly and will reduce the benefit of sterility tolerance as a host strategy. The parasite, on the other hand, increases investment in transmission rate, which leads to a higher recovery rate due to the trade-off (Fig. 4.2a). This makes sense because the parasite cannot survive for long at high virulence, so it benefits more by quickly transmitting instead. Furthermore, these coevolutionary trends align with our purely evolutionary results (see appendix C and Chapter 3), suggesting that coevolution at high virulence is comparable to a short infectious period or an acute infection.

In addition, we present the corresponding disease prevalence plots since the feedback to host and parasite selection is directly linked to the prevalence of the parasite in the system (Fig. 4.2d-4.2f). The parasite prevalence is given by the formula $P = Y^*/(X^* + Y^*)$, where X^* and Y^* are the susceptible and infected hosts' densities at the corresponding co-CSS points. The prevalence initially increases with α, then experiences a sharp decline for intermediate virulence, and finally increases again as virulence becomes excessively high (Fig. 4.2d). This is intriguing because high levels of virulence should lead to lower prevalence due to the increased mortality of infected hosts (see Fig. 3.4b in Chapter 3), but as the parasite coevolves, the combined impact of high infection transmission and high birth rates at that point overshadows the effect of high virulence. Our prevalence patterns closely align with the trends of mortality tolerance throughout the study, similar to what is generally predicted by purely evolutionary models (Roy & Kirchner, 2000; Miller et al., 2005).

As natural death rate b increases, both host fecundity tolerance f and recovery

rate γ increase rapidly (Fig. 4.2b). It is understood that a high death rate leads to reduced parasite prevalence by lowering the lifespan, as confirmed by Fig. 4.2e. Therefore, when the death rate is high, an investment in mortality tolerance, which acts to lengthen the infectious period, will be a less beneficial strategy. This will reduce selection for mortality tolerance as a host strategy and consequently lead to higher fecundity tolerance due to the trade-off. Moreover, the host can balance out the greater number of deaths by increasing reproduction through increased selection for fecundity tolerance. On the other hand, since the parasite's infectious period is short due to its high intrinsic death rate, it benefits more by increasing its transmission, which leads to higher recovery via trade-off (as shown in Fig. 4.2b). Again, these patterns match the purely evolutionary trends (see appendix C).

Next, we have the co-CSS pattern corresponding to the increasing crowding effect q (Fig. 4.2c). Contrary to the patterns observed for varying b, now we get strictly decreasing host and parasite investments in their respective strategies, where the decline is sharper for the host strategy f. As crowding increases, the overall birth rate diminishes and lowers the benefit of sterility tolerance as a host fitness strategy, hence decreasing it. On the contrary, we found the disease prevalence to continuously increase as crowding increased (see Fig. 4.2f). This is in contrast to our pattern from the host-only evolution model (see Fig. 3.5c in Chapter 3), where we observed that prevalence was a decreasing function of crowding, with or without evolution. This suggests that the coevolution of the parasite creates a reverse feedback on prevalence, resulting in an increment in prevalence. So, the increased prevalence driven by the host strategy (high mortality tolerance) results in a reduced need for investment in transmission as a parasite strategy. Instead, the parasite can benefit more from a longer infectious period through lowered recovery rate as crowding increases, as shown in Fig. 4.2c. While the pattern for sterility tolerance remains the same as in the host-only evolution scenario, varying crowding creates no impact on recovery rate when the parasite evolves in isolation (refer to appendix C). Thus, it is evident that coevolution can significantly alter the co-CSS trends.

4.3.2 Parasite evolution (host fixed at CSS)

To further explore the interaction between our host and parasite strategies, we demonstrate the impact of a small perturbation in the host's singular strategy over the parasite's. In doing so, we highlight the sensitivity of parasite fitness towards variation in the host singular strategy (Fig. 4.3).

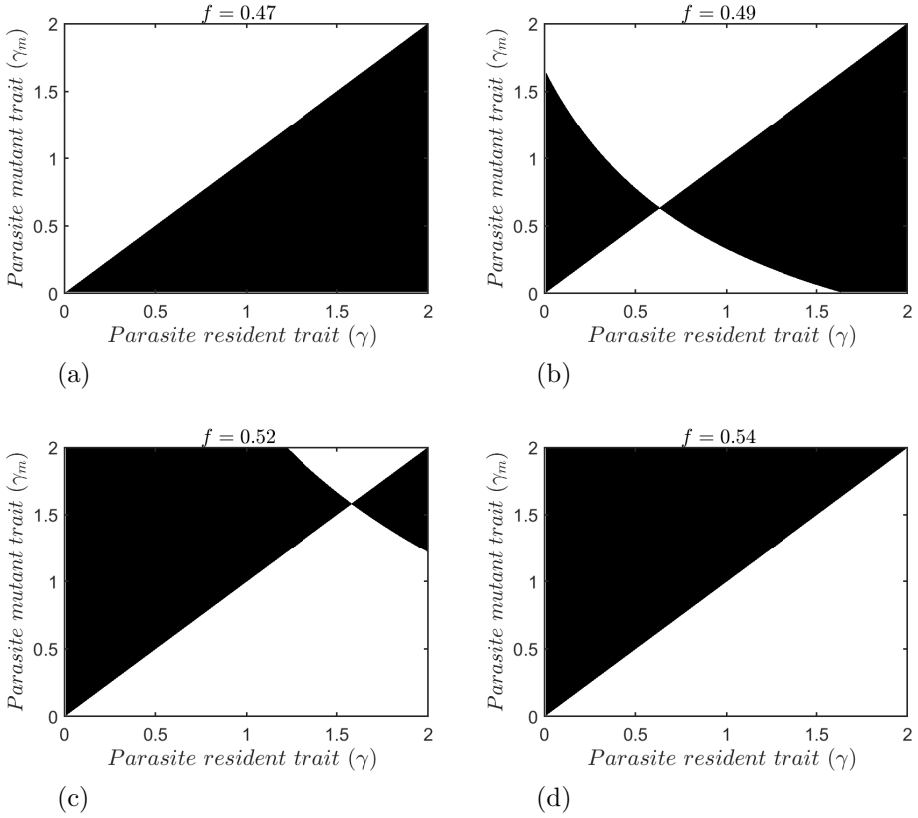


FIGURE 4.3: *Pairwise invadibility plots showing the impact of varying host mutating strategy over parasite fitness. The host and parasite singular strategies should occur at* $f = 0.5$ *and* $\gamma = 1$*, respectively. As the resident host shifts from slightly below its strategy to slightly above it, the parasite's strategy moves from minimization, through increasing recovery levels, and eventually maximizing the recovery (and hence transmission). Here we have chosen host trade-off with curvature* $\tau''(f^*) = -0.5$ *and parasite trade-off with curvature* $\beta''(\gamma^*) = -0.02$*. Remaining trade-off values and parameters are same as in Table 4.1.*

It is apparent that even a minor alteration in the host strategy can completely shift the parasite strategy. When the host resident is set slightly below its default singular strategy ($f = 0.47$), the parasite's strategy is minimized (Fig. 4.3a). As the

resident host reaches close to its singular strategy, the parasite's CSS level is at a lower recovery rate (Fig. 4.3b). After the host moves slightly beyond its singular strategy, the CSS level of the parasite's strategy goes up (Fig. 4.3c), and a further increment in host strategy leads to the maximization of the parasite strategy (Fig. 4.3d). So the parasite's singular strategy is highly sensitive to the location of the host singular strategy. Overall, Fig. 4.3 tells us that as the host's sterility tolerance increases, the parasite responds by increasing its transmission which results in increasing recovery levels. It can be deduced that an increase in sterility tolerance, which corresponds to low mortality tolerance or a high mortality rate, will enhance the selection pressure for a higher transmission rate in the parasite. This allows the parasite to transmit quickly in the face of high mortality, resulting in a shorter infectious period or higher recovery rate due to the associated costs.

4.3.3 Coevolutionary outcomes

To better understand how the host and parasite populations interact and lead to various coevolutionary outcomes, we performed numerical simulations following the algorithm outlined in the appendix of Best et al. (2017a). We consider 30 strains of each host and parasite species and set all densities except one of each strain (one host, one parasite) to 0. Then we numerically solve the population dynamics for a time sufficient for the populations to reach their equilibria. We allow the host and parasite to mutate with equal probabilities; mutant strains are generated by small deviations nearby the current traits. The population dynamics are then solved again for a further time and strains with densities below a set threshold (0.001) are considered to be extinct and removed. We also introduce an approximate demographic stochasticity function which ensures that the relative speeds of the evolution of both coevolving species match the analytical approach (Dieckmann & Law, 1996). This process is then repeated to follow the directional evolution of both species (see Best et al. (2009) and Boots et al. (2014) for more details on the simulation process). The framework with

m types of each host and parasite species is given by the following equations:

$$\begin{aligned}\frac{dX_h}{dt} &= \left(a - q\Big(\sum_{h=1}^{m} X_h + \sum_{p=1}^{m}\sum_{h=1}^{m} Y_{hp}\Big)\right)\Big(X_h + f_h \sum_{p=1}^{m} Y_{hp}\Big) - X_h \sum_{p=1}^{m} \beta_p \sum_{h=1}^{m} Y_{hp} \\ &\quad - bX_h + \sum_{p=1}^{m} \gamma_p Y_{hp}, \qquad (4.8)\\ \frac{dY_{hp}}{dt} &= X_h \beta_p \sum_{h=1}^{m} Y_{hp} - (\alpha - \tau_h + b + \gamma_p) Y_{hp},\end{aligned}$$

where X_h represents the density of susceptible hosts of type h and Y_{hp} represents the infected hosts of type h infected by parasite type p. Here f_h, τ_h, γ_p and β_p are the respective host and parasite traits, obeying their respective trade-offs. The parameters and evolving traits are the same as for the one host-one parasite system (4.1).

We found that the coevolutionary singularity is convergent stable (co-CSS) if the benefit of higher sterility tolerance to the host and higher transmission to the parasite have accelerating costs (concave trade-off curvatures, i.e. $\tau''(f^*) < 0$ and $\beta''(\gamma^*) < 0$). For such cost functions, the host and parasite would coevolve to their co-CSS strategies and invest in stable levels of investment. Furthermore, a range of qualitative outcomes can occur depending upon the trade-off shapes and speed of mutation in both species. As such, the host can branch into two coexisting host strains if the investment in its strategy becomes decreasing costly (while the parasite stays at its CSS). However, we later discuss how branching in the host can force the parasite to branch. Besides co-CSS and branching in both species, we also observed coevolutionary cycles (FSD) for a limited choice of trade-off shapes and mutation speed.

Evolutionary branching

Similar to the findings of our host evolution model (Chapter 3), we found that the host population can branch in our coevolutionary set up for a limited selection of weakly decelerating host trade-off curves while the parasite remains at its CSS (Fig. 4.4). It is well understood that for the occurrence of a branching point, the singular strategy

must be convergent stable but not evolutionary stable (see appendix C for more details on these stability conditions). In addition, the concerned species must satisfy the condition of mutual invadibility i.e., ($MH = \frac{\partial^2 s}{\partial f \partial f_m} < 0$ or $MP = \frac{\partial^2 r}{\partial \gamma \partial \gamma_m} < 0$), where MH and MP denote the expressions for mutual invadibility of the host and parasite respectively (Geritz et al., 1998; Kisdi, 2006). Based on our analytical calculations, we observed that the host population meets the criteria for branching across a broad range of parameters, whereas the parasite population does not. Consequently, under suitable trade-off choices, both host and parasite population will evolve towards the cosingular point but when close to the singularity, the host will branch to become dimorphic (Fig. 4.4a), whereas the parasite will remain monomorphic (Fig. 4.4b).

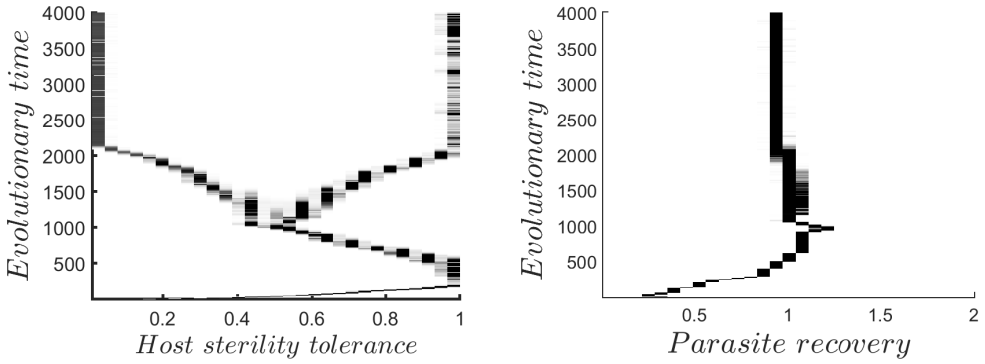


FIGURE 4.4: *Simulation output showing branching in the (a) host strategy f, while (b) parasite strategy γ evolves to its CSS over evolutionary time. Here we consider a weakly decelerating host trade-off with curvature $\tau''(f^*) = 0.05$ and weakly accelerating parasite trade-off with $\beta''(\gamma^*) = -0.15$. Remaining trade-off values and parameters are same as in Table 4.1.*

Branching in the host can force parasite to branch

After the host undergoes branching, the resident population now consists of two host-one parasite strains at equilibrium. So there are two susceptible host classes X_1 and X_2, with strategies $(f_1, \tau(f_1))$ and $(f_2, \tau(f_2))$ and one infected class, $Y = Y_1 + Y_2$, with parasite strategy $(\gamma, \beta(\gamma))$. The population dynamics of such system is given by

the following equations:

$$\begin{aligned}
\frac{dX_1}{dt} &= (a - qN)(X_1 + f_1 Y_1) - \beta X_1(Y_1 + Y_2) - bX_1 + \gamma Y_1, \\
\frac{dX_2}{dt} &= (a - qN)(X_2 + f_2 Y_2) - \beta X_2(Y_1 + Y_2) - bX_2 + \gamma Y_2, \\
\frac{dY_1}{dt} &= \beta X_1(Y_1 + Y_2) - (\alpha - \tau_1 + b + \gamma)Y_1, \\
\frac{dY_2}{dt} &= \beta X_2(Y_1 + Y_2) - (\alpha - \tau_2 + b + \gamma)Y_2.
\end{aligned} \tag{4.9}$$

Please note that even though we introduce two infected types Y_1 and Y_2 here, there remains just one parasite with strategy $(\gamma, \beta(\gamma))$. Here $\tau_1 = \tau(f_1)$, $\tau_2 = \tau(f_2)$ and $\beta = \beta(\gamma)$. The growth of the mutant parasite is now dependent upon the equilibrium densities of both host strains. To determine the mutant parasite's growth rate (i.e., fitness) in an environment with two host strains, we consider the mutant dynamics consisting of equations corresponding to two infected types,

$$\begin{aligned}
\frac{dY_{1m}}{dt} &= \beta(\gamma_m) X_1^*(Y_{1m} + Y_{2m}) - (\alpha - \tau(f_1) + b + \gamma_m)Y_{1m}, \\
\frac{dY_{2m}}{dt} &= \beta(\gamma_m) X_2^*(Y_{1m} + Y_{2m}) - (\alpha - \tau(f_2) + b + \gamma_m)Y_{2m}.
\end{aligned} \tag{4.10}$$

Then fitness expression for the mutant parasite can be obtained by taking the negative determinant of the Jacobian matrix of system 4.10, and is given by:

$$\begin{aligned}
r(\gamma_m, \gamma, f_1, f_2) \;=\; & \beta(\gamma_m) {X_1}^*(\alpha - \tau_2 + b + \gamma_m) + \beta(\gamma_m) {X_2}^*(\alpha - \tau_1 + b + \gamma_m) \\
& -(\alpha - \tau_1 + b + \gamma_m)(\alpha - \tau_2 + b + \gamma_m),
\end{aligned} \tag{4.11}$$

where X_1^* and X_2^* are the equilibrium densities of two host strains and are functions of (f_1, γ) and (f_2, γ), respectively. We further assume that for a chosen pair of host strategies (f_1, f_2), the parasite will be at a singular strategy $(\gamma^*, \beta(\gamma^*))$. To demonstrate the possibility of branching in the parasite within system 4.9, we numerically evaluate the values of the mutual invadibility expression $MP = \frac{\partial^2 r}{\partial \gamma \partial \gamma_m}$ (and similarly for ES and CS), at its singular point. From our calculations, we find that the parasite fulfils

the required conditions for branching under appropriate choices of trade-offs and host strategies. Our simulations confirm this finding, as branching occurs in the strict order of first host, then parasite (Fig. 4.5a, 4.5b). Here we chose our trade-offs as per the analytic analysis to allow host and parasite branching. So for a dimorphic resident host, the parasite can branch into two coexisting strains. In one of these strains, infected hosts can rapidly recover from the infection, while in the other they will persist for a longer duration.

However, an unconventional pattern that we noticed for a variety of trade-off shapes is that the dimorphic strains are not extreme. This means that the coexisting strains in both host and the parasite settle at values different from the bounds of evolution, i.e $f \in (0, 1], \gamma \in [0.01, 2]$. This result is distinctive compared to the findings of majority of the theory (Antonovics & Thrall, 1994; Bowers et al., 1994; Best et al., 2008; Best et al., 2009, 2014; Best, 2018; Best & Ashby, 2023; Singh & Best, 2023). A possible explanation could be due to the impact of fluctuating ecological dynamics over coevolution. It is understood that population dynamics play a considerable role in the host-parasite evolution and feedbacks caused by the ecological and evolutionary interactions can lead to qualitative shifts in the evolutionary outcomes (Gokhale et al., 2013; Best et al., 2017a; Ashby et al., 2019; Best & Ashby, 2023). By examining our model system consisting of two hosts and two parasites (system 4.8 for $m = 2$), we were able to identify limit cycles in the population dynamics (as shown in Fig. 4.5e). This fluctuating behaviour in our ecological model can cause shifts in the evolutionary outcomes, affecting the coexistence of such dimorphic strains (see Best and Ashby (2023) for more details).

In Fig. 4.5c-4.5f, we demonstrate how limit cycles emerge in our two host - two parasite population dynamics system as four different sets of host and parasite strategies are chosen from values after host branching, i.e. after evolutionary time step 1200. As such, when the sterility tolerance of the two host strains and the parasite's current strategy are taken at time 2000, we find the population densities to converge to the equilibrium (Fig. 4.5c). For strategies chosen after further evolutionary time with

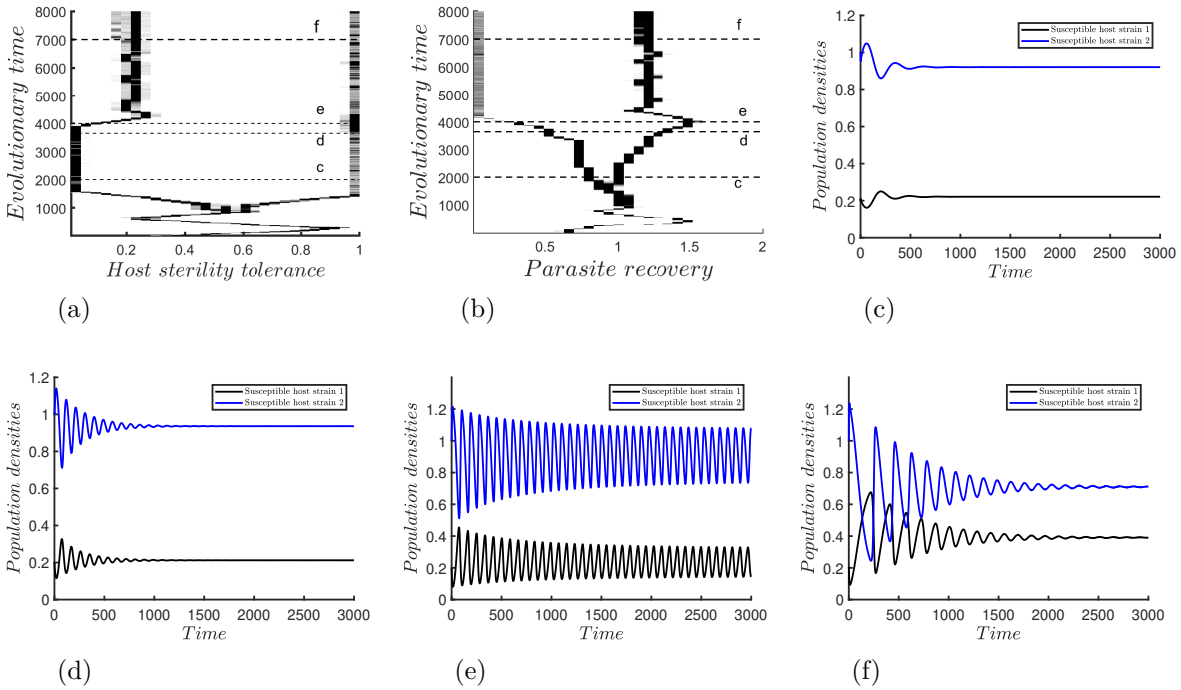


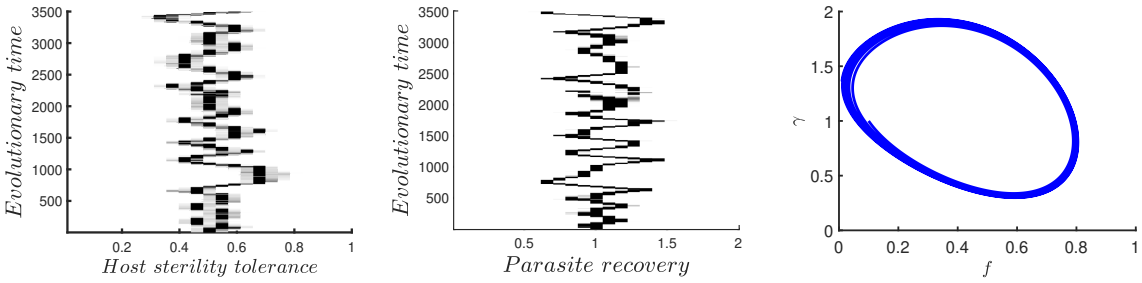
FIGURE 4.5: *(a, b) Simulations showing that branching in the parasite occurs after the host branches. Horizontal dashed lines indicate the strategies taken at that time in the corresponding population dynamics plots. (c, d, e, f) Limit cycles in the population dynamics of the two host-two parasite strain model emerge after the host branching. In (c),* $f_1 = 0.01$, $f_2 = 1$, $\gamma_1 = 0.76$, *and* $\gamma_2 = 1.05$*; (d)* $f_1 = 0.01$, $f_2 = 1$, $\gamma_1 = 0.5$, *and* $\gamma_2 = 1.382$. *(e) Non-damped oscillations emerge when* $f_1 = 0.01$, $f_2 = 1$, $\gamma_1 = 0.2$, *and* $\gamma_2 = 1.45$. *(d) Population dynamics again tends to stabilise when* $f_1 = 0.2$, $f_2 = 1$, $\gamma_1 = 0.01$, *and* $\gamma_2 = 1.17$. *Here we used a weakly decelerating trade-off for host with curvature* $\tau''(f^*) = 0.1$ *and an accelerating trade-off for parasite with* $\beta''(\gamma^*) = -0.1$. *Remaining trade-off values and parameters are same as in Table 4.1.*

greater differences between the host strains' values, we detect increasing fluctuations (Fig. 4.5d). At $T = 4000$ when parasite strains are even further apart, we obtain stable limit cycles (Fig. 4.5e). However, for strategies chosen after this stage, we find that the population dynamics again start to converge to the equilibrium (Fig. 4.5f), matching the behaviour observed in the corresponding branching plots. These plots indicate that the coevolutionary dynamics tend to settle along the boundary of equilibria and cycles. In general, cycles in our ecological system depend predominantly upon the initial chosen values of f and γ and are more likely when the difference between strategies is

higher.

Occurrence of ecological and coevolutionary cycles/FSD

Besides co-CSS and branching in the host and parasite populations, we discovered evolutionary cycles (also called fluctuating selection dynamics or FSD) in our coevolutionary model (Fig. 4.6a, 4.6b). Coevolutionary cycles result from negative frequency dependence due to epidemiological feedback on disease prevalence resulting from the evolution of host and parasite traits. Furthermore, such cycles can arise corresponding to a wide range of trade-off shapes and parameters but are more likely when costs to increase parasite transmission are weakly decelerating. Besides trade-off curvatures, the speed of host/parasite mutation also plays a significant role in determining whether cycles are generated and the amplitudes of fluctuations.



(a) (b) (c)

FIGURE 4.6: *Simulation output showing the coevolutionary cycles in both host and the parasite, along with the corresponding phase portrait. Here we have* $\tau''(f^*) = -0.05$ *and* $\beta''(\gamma^*) = 0.1$. *Phase portrait correspond to the system formed of the host and parasite fitness gradient equations, with host strategy on the x-axis and parasite strategy on the y-axis (c). Remaining trade-off values and parameters are same as in Table 4.1.*

To confirm the presence of coevolutionary cycles, we performed theoretical analysis as outlined by Lehtinen and Geritz (2019) (also see Best et al. (2017a) and Kisdi et al. (2013) for more details on the analysis of finding coevolutionary cycles). For this, it is sufficient to show that parameters and trade-offs exist which produce a Hopf bifurcation (a critical point where a system's stability switches from an equilibrium to a limit cycle). We have shown the existence of limit cycles through phase portraits formed

by the system of equations corresponding to the host and parasite fitness gradients (Fig. 4.6c). It has been proved that a sufficient condition to confirm the Hopf bifurcation is that the Jacobian matrix J formed of the fitness gradient equations has purely imaginary eigenvalues. This occurs when system cross the path where trace $T(J) = 0$ and determinant, $D(J) > 0$. The explicit form of the Jacobian matrix is given below:

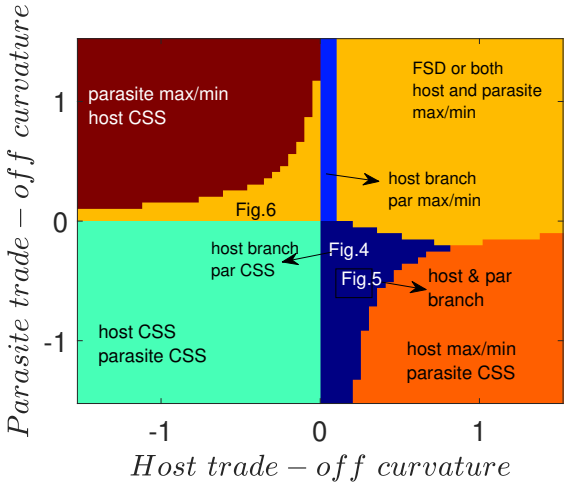
$$J = \begin{pmatrix} \phi_h X^*(\frac{\partial^2 s}{\partial f_m^2} + \frac{\partial^2 s}{\partial f \partial f_m}) & \phi_h X^*(\frac{\partial^2 s}{\partial f_m \partial \gamma}) \\ \phi_p Y^*(\frac{\partial^2 r}{\partial \gamma_m \partial f}) & \phi_p Y^*(\frac{\partial^2 r}{\partial \gamma_m^2} + \frac{\partial^2 r}{\partial \gamma_m \partial \gamma}) \end{pmatrix}.$$

We found that the mutation speed parameters ϕ_h, ϕ_p and trade-offs can be adjusted to satisfy the conditions necessary for the generation of cycles. For example, in Fig. 4.6, the parasite's mutation speed is assumed to be twice the mutation speed of the host. The cycles are expected to occur for a range of trade-off shapes and mutation speed parameters which satisfy $T(J) > 0$ and $D(J) > 0$. However, they are more likely to occur when the host trade-off is weakly accelerating and the parasite's trade-off is weakly decelerating. Finally, we noticed from our simulations that the cycles can either occur indefinitely or be lost, resulting in different outcomes. These outcomes include stable polymorphism, or branching following the cyclic pattern but one of the two coexisting strains dies out, or both the host and the parasite evolve towards minimization or maximization (see appendix C). These irregular transitions are caused by stochastic variations between simulations, such as when cycles with small amplitude are close enough to a branching point or a repeller, or when low population densities are approximated to zero. In the next section, we answer how the potential for coevolutionary cycles depend upon the host and parasite trade-off shapes.

4.3.4 Impact of trade-off shapes on coevolutionary behaviour

To finally summarise how different combinations of host and parasite trade-off shapes influence the coevolutionary outcomes in this model, we categorise our simulation output for the default parameter set (Fig. 4.7). We express the fitness equations and stability conditions as functions of the trade-off shapes at the singular strategies

and classify the coevolutionary behaviour in terms of these shapes. In particular, we display the potential coevolutionary outcomes at the cosingularity ($f^* = 0.5, \gamma^* = 1$) for different host and parasite trade-off curvatures, $\tau''(f^*)$ and $\beta''(\gamma)$, respectively. It should be noted that for mathematical simplicity, we have not varied the speed of host/parasite mutations and have considered $\phi_h = \phi_p = 1$. Therefore, the outcomes may differ if these factors are included.



(a)

FIGURE 4.7: *Classification of coevolutionary outcomes depending upon the analytical conditions as the host and parasite trade-off shapes vary. For each combination of host and parasite trade-off curvature, the system consisting of two fitness gradients is solved for a co-singular point. The behaviour at each co-singularity is then classified according to the theoretical conditions it satisfies. CSS - convergent singular strategy, max/min - maximization or minimization of the evolving trait, FSD - fluctuating selection dynamics or coevolutionary cycles. Trade-off gradients and parameters are same as in Table 4.1.*

We recall that the trade-offs are accelerating (i.e. investment becomes increasingly costly) when the curvatures are negative and decelerating when they are positive. In the context of weakly decelerating trade-offs, we are referring to a small positive value of the respective curvature. When the trade-offs of both host and parasite populations are accelerating, we get a co-CSS or stable investment levels. For a combination of weakly decelerating host trade-off and weakly accelerating parasite trade-off, we observe that the host can branch, while the parasite mostly evolves either to its CSS or maximising/minimising investment. For a similar set of trade-offs, we find that the

branching in the host can lead to branching in the parasite population. In Fig. 4.7, we have classified the output in terms of the behaviour at the first singular strategy that the system attains. As branching in the parasite occurs after the host branches, we get the same signs of stability conditions for when the host branches or remains at its CSS, and thus both behaviours are represented by the same colour shades (dark blue). If either the host or parasite trade-off decelerates, we observe the respective species evolving towards maximum or minimum levels of investment, while the other species approaches its CSS. However, in such cases, as one species evolves towards maximization or minimization, the location of the CSS of the other species can change. We have demonstrated this behaviour in Fig. 4.3, where altering the host singular strategy resulted in shifts in the parasite CSS. On the other hand, if both trade-offs decelerate, we get either fluctuating selection dynamics (cycles) or both the host and parasite evolve away from the cosingularity to reach the bounds of evolution.

4.4 Discussion

To adequately reflect the dynamics of natural systems, it is necessary for mathematical models to incorporate a variety of interconnected aspects of ecology and coevolution, including different trade-offs. Our study specifically examined the coevolution of traits corresponding to sterility tolerance and transmission, when traded-off with mortality tolerance and recovery rate, respectively. We subjected our coevolutionary model to test how various factors such as ecological dynamics, life-history traits, and trade-off shapes influence the eco-evolutionary framework. We also highlighted a crucial feature of our model that is often overlooked but has a significant impact on coevolutionary outcomes: fluctuating ecological environments. Our analysis yielded several important results, including: (1) co-CSS patterns corresponding to increasing virulence and natural death rate closely match the purely evolutionary CSS trends, but coevolution drives the parasite strategy to decrease as crowding increases, in contrast to when the parasite evolves alone; (2) branching in the host can drive the parasite

to branch and fluctuating population dynamics can prevent coexisting dimorphic host and parasite strains from reaching their extremes; (3) changes to the host's singular strategy can significantly impact the parasite fitness; (4) our two host-two parasite population dynamics model exhibits limit cycles; and coevolutionary cycles can occur across a range of trade-off shapes and parameters.

Host-parasite coevolution models can produce a variety of outcomes depending on ecological and evolutionary factors, such as stable investments in both host and parasite strategies (co-CSS), evolutionary branching in either or both species, coevolutionary cycles, or maximization/minimization of evolving traits to their physiological bounds (Frank, 1993; Baalen, 1998; Sasaki, 2000; Gandon et al., 2002; Restif & Koella, 2003; Best et al., 2009; Boots et al., 2014; Best et al., 2017a; Best, 2018). It is commonly believed that tolerance mechanisms do not result in evolutionary branching due to non-negative frequency dependence (Roy & Kirchner, 2000; Miller et al., 2005; Best et al., 2008), although some exceptions exist (Ferris & Best, 2019). However, Singh and Best (2023) recently found that branching can occur in the traits of host sterility and mortality tolerance if both are directly correlated by a trade-off. As per our research, branching in host tolerance is not yet documented in any of the coevolutionary theoretical studies. Out of the few coevolutionary models looking at host tolerance, Best et al. (2008) and Carval and Ferriere (2010) demonstrated that coevolution alone cannot lead to genetic variation in host tolerance. Later, Best et al. (2014) investigated the potential for diversity in mortality tolerance using fully coevolutionary theoretical frameworks and concluded that neither evolutionary branching nor coevolutionary cycles could occur in either the host or parasite population, thereby failing to generate diversity in tolerance. So both kinds of trade-off that we considered here: host sterility-mortality tolerance and parasite transmission-recovery, are not yet tested for branching in a coevolutionary framework. This study reveals that when the parasite coevolves, the host can still branch with a sterility-mortality tolerance trade-off, i.e., coevolution does not prevent the host from branching. In fact, it can cause the parasite to branch as branching occurs in the strict pattern of first host, then parasite, similar to what

Boots et al. (2014) found. It should be noted that branching does not occur in the parasite population when it evolves in isolation (we tested the analytical conditions for a wide range of parameters). Additionally, we discovered that the coexisting dimorphic strains are not extreme, which is a departure from conventional evolutionary/coevolutionary theoretical studies (Best et al., 2009, 2014). We also detected diversity through coevolutionary cycles for a wide range of trade-off shapes, a key result which is not yet observed in coevolutionary invasion models of tolerance.

It is well established that population dynamics can create qualitative and quantitative effects on host-parasite coevolutionary models due to eco-evolutionary feedbacks (Frank, 1991), with precise effects depending on the model (Buckingham & Ashby, 2022). In particular, fluctuating population dynamics can impact the selection of evolving traits by affecting contact rates between hosts and parasites (Ashby et al., 2019). While most models of host-parasite coevolution focus on fluctuations in trait values or allele frequencies (Gokhale et al., 2013; Best et al., 2017a; MacPherson & Otto, 2018; Ashby et al., 2019; Best & Ashby, 2023), some theoretical models have examined the impact of fluctuating ecological dynamics on parasite and host evolution (Koelle et al., 2005; Sorrell et al., 2009; Best et al., 2013; Donnelly et al., 2013; Ferris & Best, 2018; Hite & Cressler, 2018; Ferris & Best, 2019). However, only one study has investigated this for a host-parasite coevolutionary model (Ferris et al., 2020). A recent study by Best and Ashby (2023) serves relevant insights in this context, showing when cycles occur in the ecological system, host evolution can shift the system between cycles and ecological equilibria. Testing how ecology and coevolution interact to drive host-parasite interactions remains a key area of theoretical research. In our ecological system with two hosts and two parasites, increasing differences between evolving trait values resulted in limit cycles, causing quantitative changes in coevolutionary outcomes. Our analysis puts an emphasis on exploring how fluctuating behaviour in population dynamics can prevent dimorphic strains in the coevolutionary model from reaching their extremes.

Our work again highlights the significance of trade-off shapes in coevolution. Small

changes in trade-off choice can drastically alter coevolutionary outcomes, as previously noted (Kisdi, 2006). Changing fitness costs can result in the dynamics shifting between stable investment and fluctuating selection, as shown by previous studies (Sasaki, 2000; Fenton & Brockhurst, 2007; Best et al., 2010a). However, predicting definite outcomes based on trade-off shapes is challenging in coevolutionary models (Best et al., 2010a). In particular, it becomes difficult to predict which trade-off choice leads to stable polymorphism in either the host or parasite or when coevolutionary cycles occur. While coevolutionary cycles can arise for various trade-off shapes, our model shows that stable branching in both species only occurs for a few trade-off curvatures.

Although host evolution in theoretical models has been studied through an extensive range of trade-offs, parasite evolution is primarily investigated through trade-offs between parasite-induced mortality (virulence) and transmission. This transmission-virulence trade-off hypothesis postulates that a more aggressive host exploitation strategy increases parasite transmission, but it also leads to higher virulence (Ewald, 1983; Massad, 1987). Studying the evolution of parasite sublethal effects, however, becomes difficult using this framework where negative effects of parasite are only characterized as host mortality (Alizon, 2008). It is important to consider the evolution of parasite sublethal effects as many parasites are nonlethal but can cause moderately virulent infections (Walther & Ewald, 2004). Recently, Greischar et al. (2019) emphasized the significance of investigating interactions between transmission investment and recovery rates. They found that higher transmission through a reduced rate of parasite proliferation can lead to quicker recovery from infection. This positive correlation between transmission and recovery (as immune clearance) has also been observed in data-based studies on *Plasmodium chabaudi* in laboratory mice (Metcalf et al., 2011) as well as in both rodent malaria and human malaria parasite, *P. falciparum* (Mackinnon & Read, 2004). In our literature search, we identified only two theoretical studies which explicitly explored the interactions between traits of transmission and host recovery (Alizon, 2008; Greischar et al., 2019). Infection transmission (Eichner et al., 2001) and recovery rates (Sama et al., 2006; Childs & Buckee, 2015) have been estimated separately

from historical time series, but since there is potential for interactions between these traits, it is crucial to develop approaches that can estimate both traits simultaneously. However, the relationship between recovery and transmission rates in the context of a trade-off between the two remains unexplored with regards to when recovery is solely controlled by the parasite. Besides, additional empirical data is needed to determine the appropriate form for more complex models studying the impact of this on host tolerance evolution. In our coevolutionary model, we considered transmission and recovery as parasite-driven traits, with host tolerance traits coevolving and influencing each other's evolution. The association between the transmission-recovery approach, which originates from the host's immunological response, and tolerance as a host defence strategy may hold significant implications. This model has the potential to establish a theoretical framework for investigating this connection through experimental research. Additionally, a transmission-recovery trade-off can fill the gap between experiments and theory, shedding light on the evolution of parasite host-exploitation strategies.

It is important to note that some of the key results from purely evolutionary models do hold in our fully coevolutionary framework, such as co-CSS patterns concerning virulence and natural death rate, and branching in the host. In this study, we examined the coevolution of a host with a trade-off between two defence mechanisms and a parasite with a transmission-recovery trade-off, without assuming shared control over any particular epidemiological trait. Our model provides initial predictions on coevolutionary patterns, especially regarding coevolutionary branching and cycles in host tolerance. These results underline the importance of experimental testing to confirm these patterns. We identify various aspects for future research that should advance the explanatory power of coevolutionary models. To comprehend the diversity generation in host-parasite systems fully, a combination of theory and empirical work is essential. Our model also lays the groundwork for future studies to explore the impact of third species, such as predators, in a similar coevolutionary framework. Additionally, our parasite trade-off hypothesis may have implications for anti-parasite treatments,

as it allows the host to recover more quickly from infections. Implementing these epidemiological findings can improve predictions for how parasites evolve in response to treatments.

Chapter 5

Discussion

5.1 Thesis summary

Infectious diseases not only threaten public health but also have significant economic impacts on agriculture and the wider economy. The constantly evolving nature of parasites and pathogens makes it crucial to continue studying these diseases. The recent COVID-19 pandemic underscores the need for ongoing research to explore the evolutionary processes involved in infectious diseases in order to prevent their spread and mitigate their effects. Host-parasite interactions are complex, and there are various factors to consider when studying how hosts evolve in response to parasitic infections (Penn, 2001). In this thesis, we primarily focused on how hosts allocate investments in different defence mechanisms to cope with parasitic infections. Prior to this work, there was limited theoretical research exploring how the interactions between host defence mechanisms can shape the evolution and coevolution of host defence systems (Restif & Koella, 2004; Best et al., 2008; Best et al., 2017b). We have demonstrated a variety of analytical findings that offer valuable insights into the concept of trade-offs between various host defence traits. These results not only contribute to the theoretical understanding of coevolutionary dynamics but also have practical implications for designing future experimental studies. Here we summarize the key findings and implications from this thesis, and suggest potential areas for future research.

In Chapter 2, we developed a SIS model to investigate the evolution of two host

defence strategies, resistance and tolerance, against parasitism. While both mechanisms enhance host fitness, they have distinct implications for parasite fitness, and may lead to entirely distinct evolutionary implications. Importantly, even though a negative correlation between these two traits of host has often been found experimentally (Fineblum & Rausher, 1995; Stowe, 1998; Pilson, 2000; Fornoni et al., 2003; Mikaberidze & McDonald, 2020), very few theoretical studies have considered such a correlation, i.e., a resistance-tolerance trade-off. In this study, we modelled tolerance as reduction in the mortality rate due to infection and resistance as reduction in the susceptibility of getting infected. Using the assumption of such a trade-off, we studied how the host simultaneously evolves resistance and tolerance to counter the parasite. Applying our modelling framework within the adaptive dynamics theory, we analyzed how ecological factors affect the optimal investment patterns in each defence strategy.

This model yielded several significant findings concerning the impact of recovery and fecundity of infected hosts. For instance, with a resistance-tolerance trade-off, disease prevalence was maximised at the highest recovery rate, but minimised when there was no evolution or trade-off. This led to an unexpected argument that high recovery can indirectly lead to more infection when the host evolves with respect to a tolerance-resistance trade-off. On the other hand, the level of reproduction from infected hosts can significantly drive the evolutionary patterns, such that highly sterilising diseases drive selection for resistance whereas less sterilising ones for tolerance. The results on the combined effect of crowding and infected hosts' fecundity suggested that large-sized populations that are slightly sterile are more likely to evolve tolerance. In addition, we found that tolerance is more likely to evolve under conditions of low virulence and high transmission rates, matching the predictions of Boots and Bowers (1999) and Restif and Koella (2003) where they examined the evolution of resistance and tolerance separately but with associated costs to host birth rate. Our analysis on infected hosts' fecundity revealed that selection for resistance diminishes as fecundity levels increase. This observation supports the predictions made by Donnelly et al. (2015) that investments in resistance are primarily influenced by the benefits it provides

when parasites do not affect sterility.

In this chapter, we focused on the simultaneous evolution of only two defence forms: resistance as reduced susceptibility and tolerance as reduced infection-induced mortality. However, it is worth noting that there are additional defence mechanisms that can be examined with a similar negative correlation. For example, resistance can be studied as acquired immunity (Miller et al., 2007), or as the ability to reduce parasite load (Kutzer & Armitage, 2016). Similarly, tolerance can be taken to be as reduction in the parasite-induced loss to host reproduction. Additionally, it's possible to consider such a negative correlation within two mechanisms of resistance (or within two tolerance mechanisms) itself. The most obvious extension of this study would involve the coevolution of the host and parasite in such a trade-off scenario. As there is huge gap in the experimental and theoretical literature concerning a resistance-tolerance trade-off, this study specifically highlights the need for more research looking at such trade-offs to investigate the impact of pathogens on host life histories.

By continuing the investigation on trade-offs between host defence mechanisms, in Chapter 3, we considered a trade-off between two tolerance mechanisms of the host and analysed the possible evolutionary outcomes. Although some theoretical studies have examined trade-offs between host tolerance and resistance mechanisms, none has considered a correlation within different tolerance mechanisms. The majority of the theoretical models did not distinguish between tolerance to the effects of infection-induced deaths (mortality tolerance) and tolerance to the parasite-induced reduction in the reproduction of infected hosts (sterility tolerance), and those that did (Best et al., 2008; Best et al., 2010b; Berec & Maxin, 2012; Budischak & Cressler, 2018; Janoušková & Berec, 2018, 2020), did not study the evolution of both mechanisms together where they are linked. We developed a model where the host can evolve both sterility tolerance and mortality tolerance against parasitic infection, and two tolerance strategies are directly traded-off against each other. In this chapter, we particularly focused on predicting the possible evolutionary outcomes based on the shape of the trade-off: polymorphism, stable investments, or maximization/minimization. Additionally, we

examined the interplay between epidemiological feedbacks and evolutionary outcomes and compared disease prevalence patterns with and without evolving strategies.

There exist critical differences between mortality and sterility tolerance as host defence strategies (Abbate et al., 2015). Mortality tolerance tends to create a positive feedback on pathogen fitness, whereas sterility tolerance is either neutral or costly to pathogen fitness (Best et al., 2008; Boots et al., 2009). As a result, a negative feedback can lead to negative frequency-dependence, which can enable the coexistence of polymorphic host strains (Roy & Kirchner, 2000). Therefore, there is the possibility of polymorphism in sterility tolerance but not in mortality tolerance. Hence, despite the existence of within-population variation in both sterility and mortality tolerance traits of the host as reported in several experimental studies (Koskela et al., 2002; Pagán et al., 2007, 2008; Vijayan et al., 2017; Montes et al., 2019), theoretical studies rarely predict the emergence of polymorphism in mortality tolerance traits. We have found that a trade-off between mortality and sterility tolerance can lead to the evolution of dimorphic host strains, with one strain having low mortality rate and low sterility tolerance, and the other strain having high mortality rate with high sterility tolerance. This shows that the possibility of polymorphism in the traits of mortality tolerance depends upon where the costs are incurred, and thus need further theoretical and empirical exploration. In addition, we observed that a wider range of trade-off shapes allows branching at intermediate or high infected population size, in alignment with the conclusions of Best et al. (2010b) and Ferris and Best (2019) that branching in any host tolerance strategy requires high infection prevalence. Furthermore, the evolutionary trend with varying recovery rate completely reversed compared to when no strategy evolved. This highlights the importance of recovery rate in influencing tolerance selection and the need for empirical data sets that explicitly measure recovery rate.

Tolerance is a host defence mechanism that enhances host survival or fecundity while not restricting the parasite growth or transmission rates, leading to an increase

in both host and parasite fitness. As a result, tolerance is expected to play a crucial role in modulating host-parasite coevolution and population dynamics of both species, as suggested by previous studies (Little et al., 2010; Pagán & García-Arenal, 2018). For instance, a study on *S. vulgaris* infected by two rust fungi *C. tussilaginis* and *P. lagenophorae* has provided evidence of the role of tolerance in plant-pathogen coevolution (Inglese & Paul, 2006). In Chapter 4, we expand upon the tolerance-tolerance trade-off model developed in Chapter 3 by incorporating coevolution of the parasite. Specifically, we investigate the coevolution of hosts and parasites while considering explicit trade-offs between host sterility-mortality tolerance and parasite recovery-transmission rates. Despite empirical evidence supporting the trade-offs between sterility-mortality tolerance in hosts and transmission-recovery in parasites, none of the current models have explored the potential outcomes when both trade-offs are considered within a coevolutionary framework.

This model highlighted a crucial feature that is often overlooked but has a significant impact on coevolutionary outcomes: fluctuating ecological environments. We found that fluctuations occurred in the form of cycles in both the population dynamics system, as well as in the coevolutionary system through simulations. A key finding from this chapter included that branching in the host can force parasite population to branch and fluctuating selection dynamics can prevent the coexisting host and parasite strains from reaching their extremes. Additionally, changes to the host's singular strategy can significantly impact the parasite fitness.

A major aim of this study was to understand the differences in our purely host evolutionary model and coevolutionary model. In the host evolution version (Chapter 3), branching was detected in the host population for weakly decelerating costs. We found that coevolution of the parasite does not prevent the host population from branching. Besides, a range of other outcomes such as fluctuating selection dynamics (cycles) in both the populations or directional selection can occur. While results on the stable investments from host-only evolution model matched the coevolutionary trends, there were differences in the pattern for varying crowding factor when only parasite

evolved (appendix C). As such, varying crowding created no impact on the parasite recovery when parasite evolved in isolation but coevolution drove the recovery rate to decrease as crowding increased. Furthermore, we observed notable distinctions in the disease prevalence patterns between the host-only evolution model and the coevolution model. In the host evolution model, prevalence exhibited a decreasing trend in response to both virulence and the crowding factor (Fig. 3.4b, 3.5f). In contrast, the coevolution model exhibited an initial increase in prevalence, followed by a decline, and subsequently a renewed increase in correspondence with increasing virulence (Fig. 4.2d). In terms of the crowding factor, the prevalence displayed an increasing pattern (Fig. 4.2f). These differences highlight how coevolution can generate varied feedback effects on parasite prevalence within the host population. This model made preliminary predictions about coevolutionary patterns, specifically with regard to coevolutionary branching and cycles in host tolerance. The parasite trade-off explored in this study has potential implications for anti-parasite treatments and may lead to better predictions on how parasites will evolve in response to such treatments.

The coevolutionary dynamics are typically influenced by the differential rates of evolution between the coevolving species, such as the host and parasite populations. The rate at which evolution occurs in each species is influenced by factors such as population sizes, mutation rates, and selection gradients (Dieckmann & Law, 1996; Marrow et al., 1996). Our research has revealed that the relative per capita mutation rates of the host and parasite play a significant role in shaping the outcomes of coevolution and determining whether diversity arises through coevolutionary cycles within the system. Through our simulations, we found that coevolutionary cycles occur when the parasite evolves at a faster pace than the host, primarily due to its twofold higher mutation rate (see Fig. 4.6). To gain a comprehensive understanding of these phenomena, it is crucial to delve into the underlying mechanisms and conduct further studies to validate our findings.

Throughout this thesis, we have given special attention to answering how the shapes of trade-off functions influence the evolutionary and coevolutionary outcomes within

diverse ecological scenarios. In particular, we focused on when stable investments, polymorphisms and maximization/minimization of the trait occurs and how this depends on whether the investments in strategies become increasing costly (accelerating costs) or become decreasingly costly (decelerating costs). In all the cases that we studied, evolution or coevolution, we found that strongly accelerating costs lead to evolutionary attractors i.e., stable investments. On the other hand, strongly decelerating costs lead to repellers i.e., maximization or minimization of the evolving trait. While we did not find branching in the resistance-tolerance model (Chapter 2), it was found to occur for a range of weakly decelerating costs in the tolerance-tolerance trade-off models (Chapter 3 and 4). Branching in Chapter 3 was directly dependent on the chosen trade-offs and was more likely for parameters corresponding to intermediate/high infected population sizes, matching the predictions made by Best et al. (2010b) and Ferris and Best (2019). In the coevolution model, however, the outcomes were not directly predictable based solely on the trade-off shapes and could vary depending on other factors, such as the mutation speeds of the host and parasite or the fluctuating ecological dynamics. For example, a combination of decelerating costs could lead to either coevolutionary cycles or both the host and parasite evolving away from the cosingularity in order to minimize or maximize. The dependence of coevolutionary outcomes on such factors have been noticed in previous studies (Hoyle et al., 2008; Best et al., 2010a; Best & Ashby, 2023). While the host population here primarily exhibited branching patterns with weakly decelerating trade-offs, both the host and parasite populations showed branching when the host trade-offs were weakly decelerating and the parasite trade-offs were weakly accelerating. Again, the outcome of polymorphisms here were quite sensitive to the mutation rates and trade-offs. As such, any random choice of trade-offs from this combination did not guarantee branching in the parasite. These findings establish a fundamental theoretical framework that can guide the prediction of evolutionary outcomes in similar, yet unexplored, ecological contexts.

5.2 Future work

Real-world trade-offs between host and parasite traits are complex and are not always well characterized. For instance, even though trade-offs between transmission, parasite virulence, and recovery rate are frequently modelled, the exact nature of their relationships is still not fully understood (Acevedo et al., 2019). Additionally, the extent to which a negative genetic correlation between two defence traits would impose evolutionary constraints remains uncertain. A trade-off between different defence traits can be responsible for causing genetic variation in the relevant traits, leading to unexpected evolutionary outcomes. For instance, a study on a natural host-parasite system found that a trade-off between resistance and tolerance was partly responsible for species-specific and population-specific variation in these defence traits (Klemme & Karvonen, 2017). Theoretical models have the advantage of being able to manipulate trade-offs and epidemiological parameters to investigate their impact on evolutionary patterns. However, to identify the most relevant and prevalent trade-offs in real-life scenarios, a deeper understanding of actual trade-offs is necessary. This calls for the development of mathematical models that incorporate more advanced and complex forms of trade-offs, drawing upon existing data. Furthermore, in order to comprehend the long-term evolutionary outcomes influenced by the presence of such trade-offs, additional experimental testing is essential. Therefore, future research should prioritize the integration of theoretical and experimental data, particularly in relation to trade-offs between different coevolving traits.

The shape of trade-offs can be difficult to detect empirically, with most studies only able to determine whether a trade-off exists rather than its precise shape (Bartlett et al., 2018). Differences in the cost function shape among species may be related to the type of defensive compounds, while within species, variation in the shape of the cost function may be related to the extent of resource limitation among populations (Fornoni et al., 2004a). Furthermore, the likelihood of branching in natural systems remains controversial, and understanding the relevance of cost structures in shaping

natural communities can only be achieved by measuring these structures (Hoyle et al., 2008). It is clear that measurement of trade-off shapes in nature is challenging. However, our research has highlighted that evolutionary outcomes are heavily reliant on the shape of trade-offs. Therefore, it is crucial to develop more accurate methods to measure trade-offs in order to better understand how they shape natural communities.

While models are useful in understanding real systems, they all rely on simplifying assumptions as it is impossible to capture the full complexity of these systems. As a result, when constructing a model, one must decide which features to include and which to exclude, while also considering the methods required to analyze the model. While the most realistic approach would be to allow all possible traits and species to evolve, studying such models can be extremely complicated. For example, organisms allocate various key limiting resources, such as carbon, water, and amino acids etc. among multiple traits simultaneously. Therefore, two traits that have minor resource requirements might not trade-off with each other but could trade-off with a more significant resource sink when combined (A. A. Agrawal et al., 2010). A possible future question can explore the possibility that trade-offs do not necessarily occur pairwise but can involve multiple traits simultaneously. One relevant example would be a resistance-tolerance trade-off where increase in either defence form will cause a reduction in the host birth rate. In such a case, we shall expect evolutionary branching to occur, given that there will be a negative frequency dependence selection in the resistance trait. As ecological scenarios become more intricate and multifaceted, the fitness landscapes also become more complex, thereby increasing the potential for branching to take place.

The mechanisms and genetic basis of tolerance in plant disease control are poorly understood compared to resistance, as evidenced by the limited use of tolerance (Pagán & García-Arenal, 2020). In particular, plant-pathogen coevolution and the role of tolerance mechanisms in it remain largely unexplored (Little et al., 2010; Pagán & García-Arenal, 2020). However, since host-parasite interactions are ubiquitous and associated with strong selection pressures, understanding the exact mechanisms involved is a primary goal of evolutionary biology. Testing host-pathogen coevolution in agricultural

settings is not feasible due to human-controlled host populations, which only allow the pathogen to evolve (Pagán & García-Arenal, 2020). However, keeping tolerance fixed in the host population and testing the prediction of pathogen evolution towards high virulence has been done (Desbiez et al., 2002; Desbiez et al., 2003). Despite the importance of tolerance in plant-pathogen coevolution, experimental tests of theoretical predictions of the effects of tolerance on host and pathogen evolution are scarce. Our results from tolerance-tolerance trade-offs, both in evolutionary and coevolutionary framework, revealed that there is a selection for maximum sterility tolerance and minimum mortality tolerance at intermediate virulence levels. As allocation to different tolerance mechanisms is contingent upon the costs involved and the virulence of the parasite (Miller et al., 2007; Vitale & Best, 2019), investigating these dynamics within natural systems would yield valuable insights for utilizing tolerance strategies in the development of novel disease control approaches.

Shifting gears, there are still several unanswered questions regarding the study of tolerance for the control of plant diseases. Firstly, while many models assume that evolving tolerance has a cost, such costs are not well quantified experimentally. Understanding these costs would aid in understanding the coexistence of resistance and tolerance in plants (Pagán & García-Arenal, 2018). Secondly, it is unclear which type of tolerance measurement (mortality or fecundity) captures the effects on host and pathogen fitness. Quantifying both should be done if the pathogen is both horizontally and vertically transmitted, while only mortality tolerance is needed if it is only horizontally transmitted (Pagán & García-Arenal, 2018). Addressing these questions would improve our understanding of the evolutionary dynamics of tolerance and help in the durable use of tolerance for disease control in plants.

The models that we studied describe a simplified one host-one parasite interaction, yet in natural ecosystems, hosts are often involved in complex interactions that encompass species competing for resources and multiple parasites. It is now evident that hosts are frequently attacked by more than one pathogen, leading to single and mixed infections (Syller, 2012; Seppälä et al., 2020), thereby necessitating the evolution of

host defences in a multi-pathogen setting. Montes et al. (2020) showed that in such situations, the evolution of both fecundity tolerance and mortality tolerance to a given virus is at the expense of increased susceptibility to other pathogens, which may result in the potential polymorphism in tolerance. Their results proved that for a more realistic analysis of the evolution of host defence strategies, it is necessary to consider the impact of multiple pathogens. Therefore, this research could further be continued to investigate the impact of incorporating resistance-tolerance and tolerance-tolerance trade-offs in the context of multiple pathogens.

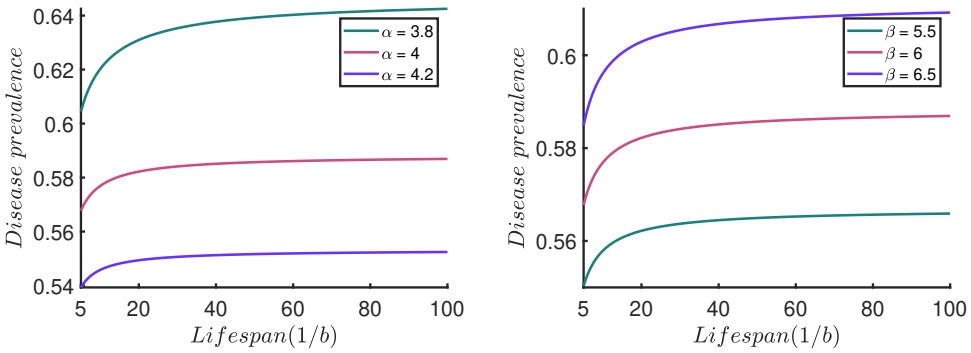
To expand on the research done in this thesis, future work can cover various aspects of real life scenarios. For example, it would be possible to allow for the additional species be part of the evolutionary process. Although previous theoretical studies have considered the impact of additional species, such as predators or defensive microbes, on host-parasite evolution (Morozov & Adamson, 2011; Hoyle et al., 2012; Morozov & Best, 2012; Toor & Best, 2015), and coevolution (King & Bonsall, 2017; Best, 2018), none of them have accounted for a trade-off between defence traits. Previous studies have shown that the presence of predator populations can influence the emergence of host diversity through evolutionary branching (Toor & Best, 2015). To assess the robustness of our findings, it would be valuable to incorporate additional populations and investigate whether the observed results hold or if they are modified in the presence of other population interactions. Similarly, we can explore the evolutionary dynamics of our resistance-tolerance and tolerance-tolerance trade-offs in a seasonal environment context, as the outcomes of host-parasite interactions are typically affected by the fluctuating environmental conditions (Donnelly et al., 2013; Ferris & Best, 2018). It is well established that theoretical studies often do not predict polymorphisms in tolerance traits (Roy & Kirchner, 2000; Miller et al., 2005; Best et al., 2014). However, recent research by Ferris and Best (2018) revealed that seasonal environments can induce branching in host tolerance. Our own findings, which indicate that branching is more likely in the parameter regions associated with larger infected population sizes (Chapter 3), align with their results. This suggests that infected population size may serve

as a catalyst for tolerance branching in both constant and temporal environments. However, more evidence is required to substantiate this hypothesis. Another interesting future approach would involve exploring our trade-offs within the framework of temporal heterogeneities in a coevolutionary context. Hence, there are many possible directions to extend this work, which could improve our understanding of host-parasite evolutionary dynamics.

The discipline of host-parasite evolution theory is constantly expanding, and a better understanding of the factors that shape their interactions is crucial for improving disease management. The mathematical models developed and investigated in this thesis contribute to our knowledge of epidemiological theory and raise important questions for future research. Specifically, this work emphasizes the need for more theoretical and empirical exploration into the trade-offs of host defence mechanisms. This will lead to a more cohesive understanding of biological systems and ultimately contribute to more effective disease management strategies.

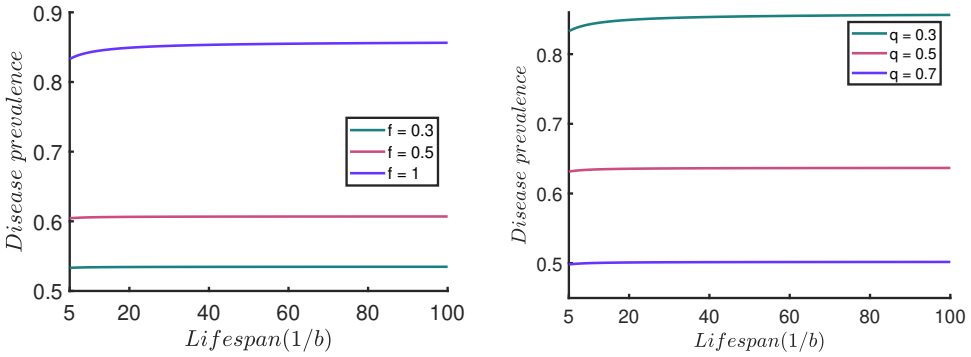
Appendix A

Disease prevalence plots for corresponding CSS investment patterns



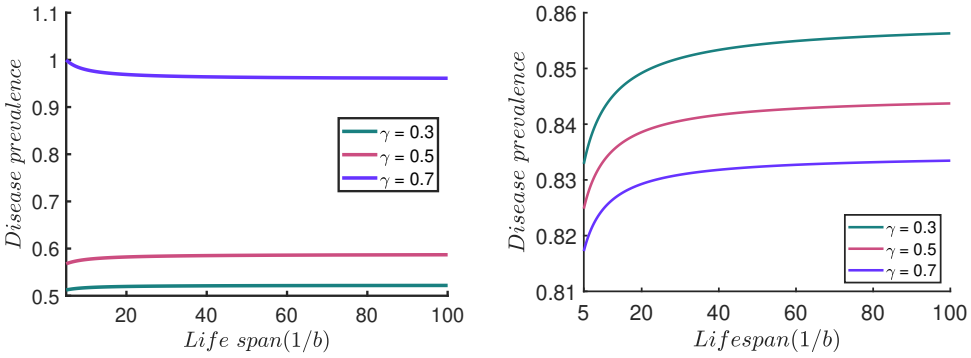
(a) (b)

FIGURE A.1: Disease prevalence plots with respect to lifespan for different values of virulence α and infection transmission coefficient β, respectively, when infected hosts do not reproduce. We can see that the prevalence is maximum for lowest value of virulence and highest value of transmission coefficient. So, chances of getting infected are higher when virulence is low and transmission is high, and investment in tolerance will be higher (see the results of Fig. 2.3).



(a) (b)

FIGURE A.2: Disease prevalence plots with respect to lifespan for different values of infected hosts' fecundity factor f and crowding factor q, respectively. We see that the prevalence increases with increasing fecundity level f and with decreasing crowding factor q. Therefore, tolerance should be selected for these conditions i.e., for high fecundity and low crowding.



(a) (b)

FIGURE A.3: Comparing the disease prevalence plots with respect to varying recovery rates. (a) is the prevalence plot for when infected hosts' fecundity is zero, and (b) is when fecundity is positive. It is clear that in (a), the prevalence is maximum for highest recovery rate and the pattern is reversed in (b). This changes the forces of selection acting on tolerance and resistance and therefore we get the pattern for CSS investments in tolerance/resistance in the Fig. 2.3g-2.3i and Fig. 2.7c.

Appendix B

Mathematical details for Chapter 3

Here we show the analysis that has been used to determine the host fitness proxy expression $s_f(f_m)$. As stated in the main text, we use the classic SIS model to study the host-parasite population dynamics, given by

$$\begin{aligned} \frac{dX}{dt} &= (a - q(X+Y))(X + fY) - \beta XY - bX + \gamma Y, \\ \frac{dY}{dt} &= \beta XY - ((\alpha - \tau) + b + \gamma)Y. \end{aligned} \tag{B.1}$$

To find the invasion fitness of the mutant host (f_m, τ_m) that tries to invade the resident host (f, τ) set at its equilibrium (X^*, Y^*), we write the dynamics of the mutant given by following equations:

$$\begin{aligned} \frac{dX_m}{dt} &= (a - q(X^* + Y^*))(X_m + f_m Y_m) - bX_m - \beta X_m Y^* + \gamma Y_m, \\ \frac{dY_m}{dt} &= \beta X_m Y^* - (\alpha + b + \gamma - \tau_m)Y_m, \end{aligned} \tag{B.2}$$

where a subscript m denote the mutant density or trait. Note that $\tau_m = \tau(f_m)$ from the trade-off function. The host fitness proxy $s_f(f_m)$ is obtained from the Jacobian matrix J of the mutant dynamics system (B.2) (w.r.t mutant variables) and is equivalent to its negative determinant, i.e., $s_f(f_m) = -det(J)$, where

$$J = \begin{pmatrix} a - q(X^* + Y^*) - b - \beta Y^* & af_m - qf_m(X^* + Y^*) + \gamma \\ \beta Y^* & -(\alpha + b + \gamma - \tau_m) \end{pmatrix}.$$

This means that we are guaranteed negative eigenvalues of J (i.e. the equilibrium is stable and the mutant cannot invade), if $det(J) > 0$ or if $s_f(f_m) < 0$.

The fitness gradient calculated by taking a derivative of the fitness proxy with respect to the mutant strategy is given by

$$\frac{\partial s}{\partial f_m}\Big|_{f_m=f=f^*} = -\tau'(f^*)(a - q(X^* + Y^*) - b - \beta Y^*) + \beta Y^*(a - q(X^* + Y^*)).$$

Next, we write explicit expressions for the conditions of evolutionary stability, and mutual invadibility as follows:

$$\begin{aligned} ES &= \frac{\partial^2 s}{\partial f_m^2}\Big|_{f^*} = -\tau''(f^*)(a - q(X^* + Y^*) - b - \beta Y^*), \\ M &= \frac{\partial^2 s}{\partial f \partial f_m}\Big|_{f^*} = \tau'(f^*)(q(X' + Y') + \beta Y') + \beta Y'(a - q(X^* + Y^*)) - q\beta Y(X' + Y'). \end{aligned}$$

Here, X' and Y' denote the derivatives of X and Y with respect to f. Convergence stability (CS) is then given by,

$$CS = ES + M < 0$$

So to get a CSS point, we require both $ES < 0$ and $CS < 0$.

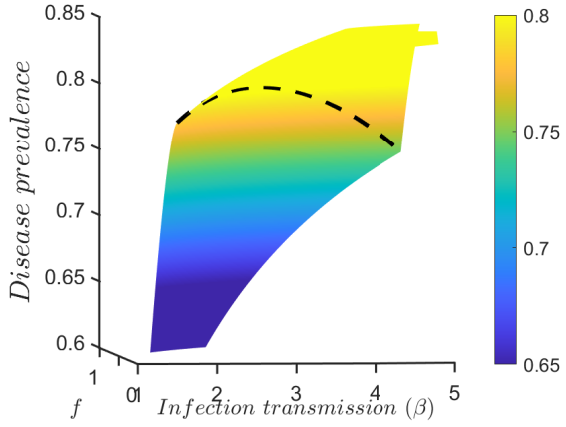


FIGURE B.1: *3-D image to show the downward bump through colour gradient in disease prevalence pattern with respect to varying β when there is no evolution (corresponding to Fig. 3.5d in the main text). The dashed line plots values of P for non-evolving strategies and goes from higher to lower range or prevalence (yellow to green).*

Appendix C

Supplementary information for Chapter 4

C.1 Stability conditions

We use the methods of adaptive dynamics to study our coevolutionary model (Dieckmann & Law, 1996; Marrow et al., 1996; Geritz et al., 1998). The host with sterility tolerance f and parasite with recovery rate γ will coevolve in the direction of their respective local fitness gradients until a singular point is reached where the two gradients become simultaneously zero, i.e.,

$$\left.\frac{\partial s}{\partial f_m}\right|_{f_m=f} = 0, \tag{C.1}$$

$$\left.\frac{\partial r}{\partial \gamma_m}\right|_{\gamma_m=\gamma} = 0. \tag{C.2}$$

Here, s and r indicate the invasion fitness of the host and parasite, respectively. Coevolution will continue until either a coevolutionary singular point is attained, or until the trait attains its maxima or minima, or it may continually cycle. The coevolutionary behaviour at a singular point depends upon the sign of second order derivatives of fitness gradients. Same as in single-species evolution case, for respective species to be evolutionary stable in coevolutionary framework, we need

$$EH = \frac{\partial^2 s}{\partial f_m^2} < 0, \tag{C.3}$$

$$EP = \frac{\partial^2 r}{\partial \gamma_m^2} < 0. \tag{C.4}$$

The cosingularity will be evolutionary stable when $EH < 0$ and $EP < 0$. Convergence stability, on the other hand, is more complex and will be determined by the 2x2 Jacobian matrix formed of the derivatives of the host and parasite fitness gradients,

$$J = \begin{pmatrix} \phi_h X^*(\frac{\partial^2 s}{\partial f_m^2} + \frac{\partial^2 s}{\partial f \partial f_m}) & \phi_h X^*(\frac{\partial^2 s}{\partial f_m \partial \gamma}) \\ \phi_p Y^*(\frac{\partial^2 r}{\partial \gamma_m \partial f}) & \phi_p Y^*(\frac{\partial^2 r}{\partial \gamma_m^2} + \frac{\partial^2 r}{\partial \gamma_m \partial \gamma}) \end{pmatrix},$$

evaluated at the co-singularity (Marrow et al., 1996). For mathematical ease, we assume equal host and parasite mutation speeds, i.e $\phi_h = \phi_p = 1$ for most of the analysis. So using the Routh-Hurwitz criteria, the cosingularity is convergence stable if and only if det $J > 0$ and Trace $J < 0$. These two conditions on trace and determinant can be further satisfied using the following set of conditions:

$$EH + MH < 0, \tag{C.5}$$

$$EP + MP < 0, \tag{C.6}$$

$$(EH + MH)(EP + MP) > |A_H A_P|, \tag{C.7}$$

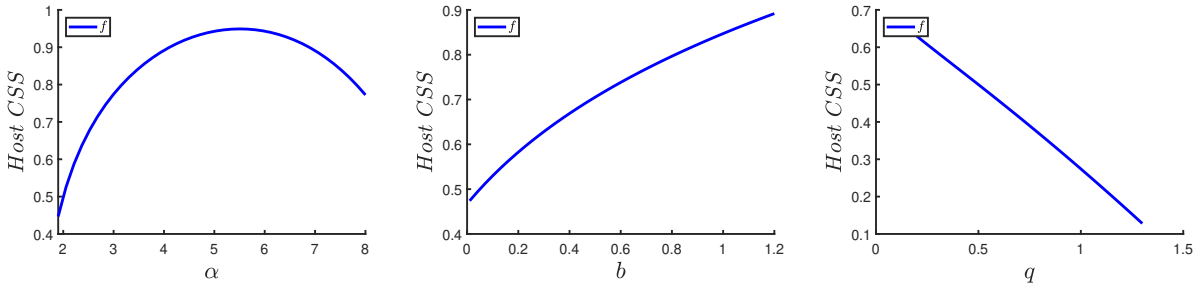
where $A_H = \frac{\partial^2 s}{\partial f_m \partial \gamma}$, and $A_P = \frac{\partial^2 r}{\partial \gamma_m \partial f}$. Conditions C.5 and C.6 refers to the isoclinic stability of the host and the parasite, respectively, and are equivalent to convergence stability in single-species evolution. Note that condition C.7 is a sufficient but not necessary to guarantee a co-CSS. So the cosingularity can be convergent stable even if condition C.7 does not hold but the isoclinic conditions hold.

For evolutionary branching, we need the cosingular strategy to be convergent stable but not evolutionary stable. In addition, we also require a separate condition of mutual invasibility (Kisdi, 2006). The mutual invadibility condition is given by the sign of the mixed derivative. For example, in the host,

$$MH = \frac{\partial^2 s}{\partial f \partial f_m} < 0, \tag{C.8}$$

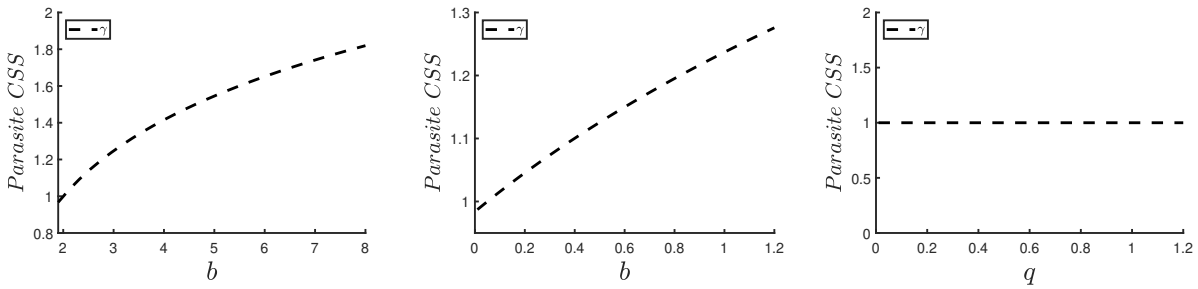
is a condition required for two host strains to coexist. Similarly for the parasite to be able to branch, it must satisfy $MP = \frac{\partial^2 r}{\partial \gamma_m \partial \gamma} < 0$.

C.2 CSS patterns when host and parasite evolves separately



(a) (b) (c)

FIGURE C.1: *Variation in CSS investment patterns along with varying (a) disease-induced mortality rate α, (b) natural death rate b, and (c) crowding factor q, when only host evolves and parasite strategy is kept fixed at $\gamma = 1$. Here $\tau''(f^*) = -1.5$, and remaining parameters are same as in Table. 4.1.*



(a) (b) (c)

FIGURE C.2: *Variation in CSS investment patterns along with varying (a) disease-induced mortality rate α, (b) natural death rate b, and (c) crowding factor q, when only parasite evolves and host strategy is kept fixed at $f = 0.5$. Here $\beta''(\gamma^*) = -1.5$, and remaining parameters are same as in Table. 4.1.*

C.3 Cycles ending in different outcomes

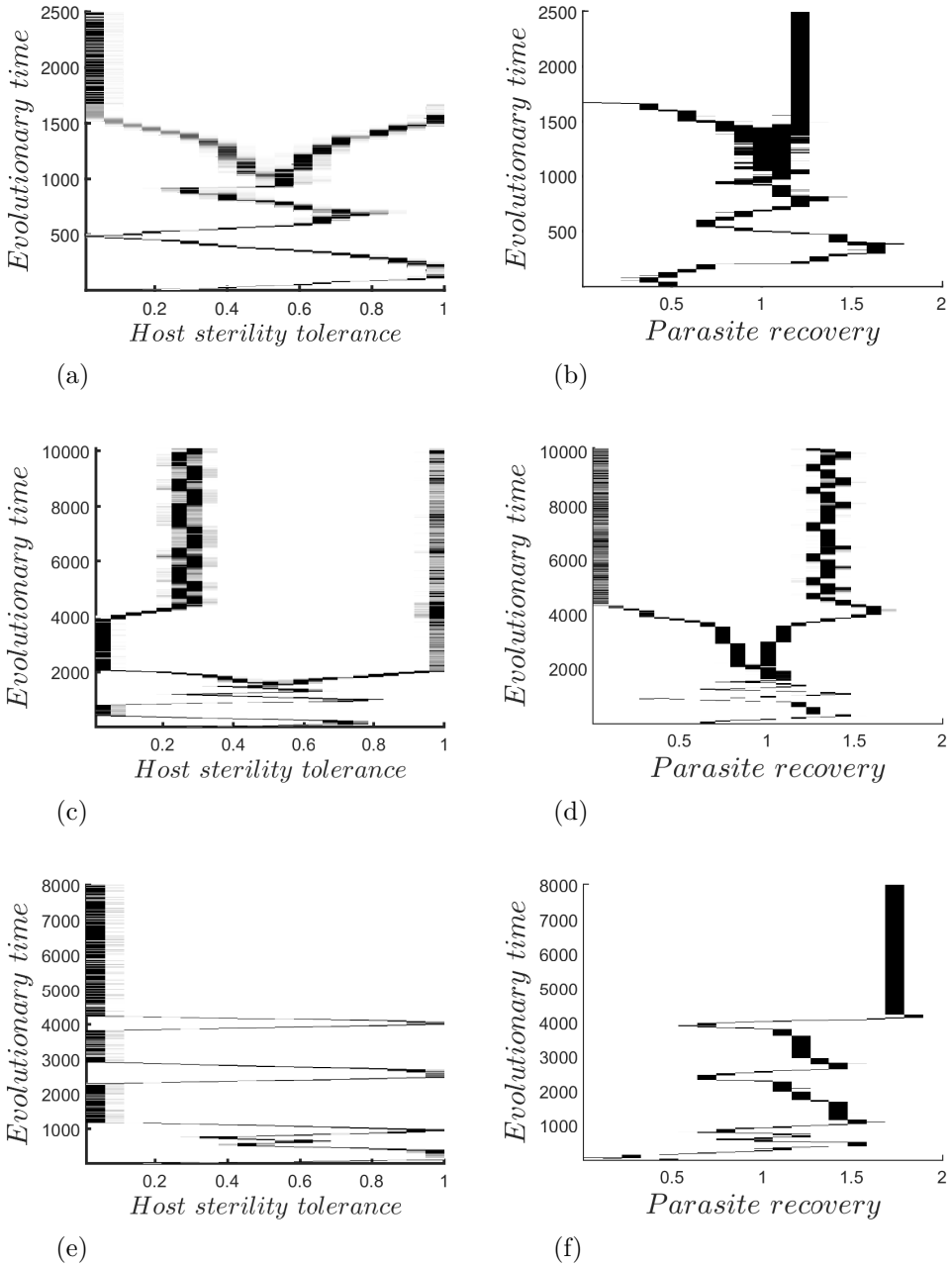


FIGURE C.3: *Coevolutionary cycles ending in different outcomes. (a, b)* $\tau''(f^*) = 0.05$ *and* $\beta''(\gamma^*) = 0.01$*, (c, d)* $\tau''(f^*) = 0.12$ *and* $\beta''(\gamma^*) = -0.07$*, (e, f)* $\tau''(f^*) = 0.05$ *and* $\beta''(\gamma^*) = 0.01$*. Remaining trade-off values and parameters are same as in Table. 4.1.*

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