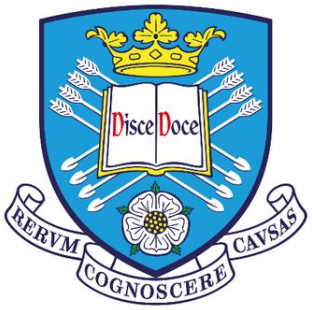

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The evolution of host tolerance to disease and the impact of predators

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Abstract

In this Thesis, we focus on the effects of the evolution of tolerance to disease in a susceptible–infected–susceptible model and on the impact of including a predator species.

Host defence against parasite infection can rely on two broad strategies: resistance and tolerance. While resistance strategies aim to lower parasite fitness, tolerant hosts can bear the effects of the disease without reducing its prevalence. Here, we first examine the potential for the host to drive parasites to extinction in the host-parasite system through the evolution of one or other defence mechanism. When defence comes with costs, it is impossible for the host to eliminate the infection through resistance, because costly resistance is selected against when parasites are at low prevalence. We uncover that the only path to disease clearance in the presence of costs is through tolerance. Paradoxically, however, it is by lowering tolerance -and hence increasing disease-induced mortality- that extinction can occur.

We then consider how the introduction of a predator species changes both host-parasite ecological and evolutionary dynamics. At the ecological level, a key role is played by predator selectivity for either healthy or infected prey. When predators feed mainly on susceptible prey we find region of bi-stability between coexistence and parasite extinction. Conversely, when predator selection is strongly towards infected prey, total prey population density can be maximal when the three species coexist, consistent with the 'healthy herd' hypothesis. At the evolutionary level, the presence of predators allows for the evolutionary branching of tolerance, which is impossible in the host-parasite case. Predation also decreases selection for tolerance when it reaches an optimal value and increases the possibilities for parasite extinction. We found a general pattern of higher tolerance at higher infection risk and low predation density.

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Chapter 1

Introduction

This work analyses the evolution of host defence in a host-parasite system and the interplay with the ecological environment represented by a predator species, which feeds on the host without getting infected. Our focus has been to unravel both the ecological and the evolutionary effects that are involved in this three species interaction. Host-parasite evolutionary dynamics are often studied in two-species models, nevertheless, it is necessary to incorporate other environmental variables in order to develop more realistic models (Betts et al., 2016). We show here that the introduction of a new species in the system not only enriches the ecological outcomes, but it also allows evolutionary results that would be impossible in the two species scenario.

Host-parasite compartmental models have been widely used in the past decades to grasp general trends in the spreading and the evolution of infectious diseases (Kermack and McKendrick, 1927; Murray, 1989; Keeling and Rohani, 2007; Diekmann et al., 2012). Host defence against the disease is usually modelled in terms of resistance (Antonovics and Thrall, 1994; Bowers et al., 1994; Donnelly et al., 2015), i.e. the ability of fighting the parasite by lowering its fitness, however, interest is growing for a different class of strategies. Specifically, tolerance refers to the faculty of a host to bear the consequences of infection without affecting its development (Roy and Kirchner, 2000). First evolutionary models to consider tolerance have been published in the late nineties (Boots and Bowers, 1999; Roy and Kirchner, 2000), while the first experimental study to prove genetic variation for tolerance in vertebrates is dated 2007 (Råberg et al., 2007). Therefore, despite the recent increase, the body of theoretical results and experimental work on the role of tolerance is still limited.

Evolutionary models show that tolerance strategies have a different evolutionary behaviour compared to resistance ones (Boots and Bowers, 1999; Roy and Kirchner, 2000). When a tolerant trait spreads in a population it can increase infection prevalence and, thus, selection for higher tolerance. Therefore, tolerance is predicted by basic models to evolve towards fixation, while experimental studies are finding more and more evidence for genetic variation of tolerance (Read et al., 2008; Råberg, 2014; Adelman and Hawley, 2017; Soares et al., 2017). Moreover, tolerance is thought to not impose a strong selective pressure on parasite fitness , and, therefore, to avoid deleterious parasite counter-adaptations (Soares

et al., 2017). Nevertheless, some concerns have been risen about the lack of a complete understanding of tolerance evolutionary effects (Miller et al., 2005; Vale et al., 2014; Hozé et al., 2018).

Theoretical models have only recently started to merge ecological, epidemiological and evolutionary dynamics all together (Morozov and Adamson, 2011; Hoyle et al., 2012; Kisdi et al., 2013; Best, 2018). Introducing a predator species into a host-parasite evolutionary model can have different effect. Predators can increase both the host and the parasite potential for polymorphism (Morozov and Best, 2012; Hoyle et al., 2012), namely the coexistence of different traits in the same population. Under predation, parasite can evolve to be more virulent (Morozov and Adamson, 2011), while host resistance can show non monotonic pattern when predator capture rate increases (Toor and Best, 2015). Nevertheless, at the best of our knowledge, there is not a study on tolerance evolution in the presence of a predator species

In this work we will first consider the evolution of tolerance and resistance strategies in the host-parasite model, to determine which circumstances favour parasite extinction. We will then introduce a predator species in the system and perform a complete analysis of the ecological scenarios at which the three species model can converge. We conclude by letting the host evolve tolerance in the full model and comparing the new evolutionary outcomes with the ones of the host-parasite case. Throughout our work, we have been surprised by the amount of different and sometime unexpected behaviours this model can capture. We also found that analysing tolerance evolution can bring to new results even in the simplest host-parasite model.

1.1 The mathematical modelling of host-parasite dynamics

In this project we will apply ordinary differential equations in order to describe, understand and predict the spreading of a disease in a population. The first of this kind of models appeared as special case in Kermack and McKendrick (1927) and it is called the SIR model. Under the hypotheses of a well-mixed fixed population in a homogeneous environment a host can be in one of three different states: susceptible, infected, and recovered (SIR). For each stage an ODE is formulated to describe how the number of hosts in the stage changes according to the interaction with the parasite. Particularly, in the SIR model transition rates are constant in time, meaning that the average time spent by an individual in a class follows an exponential distribution. Assuming that the disease does not impact on host

demography, the dynamics of the infection is modelled as

$$\begin{aligned}\frac{dS}{dt} &= -kSI \\ \frac{dI}{dt} &= kSI - lI \\ \frac{dR}{dt} &= lI.\end{aligned}$$

Thus, the transmission process is assumed to be proportional to the infected density by the coefficient k, while l represents the recovery rate. The advantage of this so-called compartmental model is in the flexibility of shaping it according to the host and infection features desired, like multiple infectious stages, density-dependent effects, more complex contact laws.

Later, Anderson and May (1981) expanded this model by adding the demographic dynamics of the host population, bringing together ecological population modelling and invertebrate pathology. In the simplest case where the total population H is assumed constant, the number of infected individuals as function of time $Y(t)$ can be found by solving

$$\frac{dY}{dt} = \left[(\beta H - \alpha - b - \gamma) - \beta Y\right] Y$$

where b is the host natural mortality, α the parasite-induced mortality, named virulence, γ the recovery rate and β the transmission rate. Starting from this example, Anderson and May (1981) showed how to include in the model a broad variety of host and parasite characteristics like parasite-induced infertility, vertical transmission, latency period, and others. Across these variations, the authors derived the thresholds for the host density required for the parasite to spread and the conditions under which pathogens could control the host population. They found that more lethal parasites can control host population, even if the fraction of infected individuals remains low, better than widely spread and non-lethal ones. The authors used this result to gain insights on the usage of parasites for agricultural pest control but warned about the potential evolutionary consequences of such a remedy.

Already in the work of Anderson and May (1981), it is possible to observe that sometimes more important that solving the equations for the temporal development of an epidemic is the derivation of threshold quantities and qualitative observations on how equilibrium values change with model parameters. Surely, the most known of these threshold quantities is R_0, the basic reproductive number of a disease, which tells whether a disease can spread in a population composed by only susceptible individuals (Anderson and May, 1981; Diekmann et al., 1990). From this first approximation, indications can be derived on the minimum amount of population that is necessary to vaccinate to prevent a disease to spread. Here, we will use bifurcation theory to derive threshold quantities where the behaviour of the model changes abruptly as a parameter changes.

After these seminal papers, the field of mathematical modelling of infectious diseases has rapidly flourished and models have been enriched with different features (Keeling and

Rohani, 2007; Murray, 2011; Diekmann et al., 2012). The hypothesis of a well-mixed homogenous population can be removed in favour of a structured population, for example to consider the effects of age or within host dynamics (Diekmann et al., 2012). Contacts can be modelled considering a spatial structure like a lattice (Satō et al., 1994) or more complex network (Danon et al., 2011). Seasonal effects can be introduced in the environment or in the transmission term (Aron and Schwartz, 1984). According to the system of interest, different features can be chosen, nevertheless, there is a trade-off between the mathematical and computational tractability of a model and its complexity (Keeling and Rohani, 2007).

Here, we model the host-parasite dynamics using an SIS model, an SIR model without the recovered class, i.e. hosts return in the susceptible class after recovery. We choose to keep the transmission dynamics quite simple because we are interested in focusing on the evolutionary dynamics that occurs on larger time-scale and on the impact of a predator species on it. The mathematical tractability of the model allows us to fully explore the effects of predation for a wide range of parameter choices.

1.2 Modelling Evolution

Almost concurrently with the appearance of the first epidemiological models, the formulation of the evolutionary theory took a leap forward thanks to the modern synthesis, happened during 1930s and 1940s (Provine, 2001). In those years, scientists were finally able to reconcile the Darwinian theory of natural selection with Mendel's theory of genetics heritability, practically, recognising both selection and mutation as essential parts of the evolutionary process. This theoretical progress was possible also thanks to the first appearance of mathematical models for describing variations of heritable traits in a population (Futuyma, 2009). Since then, different frameworks have been developed to model evolution, each contributing to an increasingly vast and differentiated literature of mathematical models. We sketch here the approaches behind some of the most used methods, starting from the classical theory of population genetics, which focuses on tracking changes in the genetics composition of a population. Other frameworks like quantitative genetics and evolutionary game theory consider, instead, the evolution of phenotypical traits under selection. We then analyse in more details the assumptions behind the adaptive dynamics framework, which stemmed from evolutionary game theory, as we will use it to model evolution in Chapter 2 and 4.

Theoretical population genetics is the field of evolutionary biology dedicated to the mathematical modelling of how the genetic composition of a population changes under the effects of mutation and selection. First models were developed by Haldane, Wright and Fisher during the modern synthesis and described variations between generations in the frequency of alleles at one locus in a randomly mating population (Provine, 2001). Later works, expanded the theory to include other fundamental processes like non-random mating, genetic drifts and migration (Crow, 1970; Felsenstein, 1976; Gillespie, 2004). While this method is largely adopted in genetics studies, it is less suited to model interactions between evolution-

ary and ecological dynamics. In fact, the majority of studies consider a constant selection in the derivation of an allele fitness, overviewing frequency-dependent effects derived from ecological considerations. Nevertheless, it is worth mentioning that several attempts have been made to include more realistic assumptions on the impact of ecological effects on fitness (Bürger and Wagner, 2002).

The quantitative genetics framework developed from theoretical population genetics to the aim of describing the evolution of quantitative phenotypical traits in sexually-structured populations. A quantitative trait is assumed to result from the additive contribution of small genetics effects given by a large number of different loci (Barton and Turelli, 1989). This assumption largely simplifies the dynamics at the genetics level and allow to focus on the phenotypical one. Each phenotypical trait is modelled as a unimodal distribution across the population characterised by its moments like mean and variance. The first equation to model changes in the mean value of a trait was formulated by Lande (1976). Lande (1976) describes how the mean value evolves towards a fitness maximum in a phenotypical landscape under the effects of natural selection and genetics drift. This is achieved by introducing a fitness gradient, which accounts also for the ecological dynamics that embeds the evolving population.

Contemporary to the development of quantitative genetics, another approach has been undertaken to model phenotypical evolution, namely evolutionary game theory. Main idea of the method is to apply the mathematical theory of games developed by von Neumann and Nash for economical applications to evolutionary dynamics (Von Neumann, 1944; Nash, 1950; McGill and Brown, 2007). Evolution is modelled as a game played by the individuals of a population where strategies consist in phenotypical traits (McGill and Brown, 2007). To adapt the theory to the new game field, it has been necessary to extend it to continuous strategies, which can capture the dynamics of quantitative traits. In a game, a new mutant individual plays against the whole population with a pay-off established by its reproductive fitness. The 'winners' of the game have been named by Smith and Price (1973) as 'evolutionary stable strategies' (ESS) and consist in those strategies which cannot be invaded by any other. Evolutionary-stable-strategy approaches focus on computing the set of ESS of a game, neglecting the transitory dynamics (Abrams, 2001).

Lastly, the adaptive dynamics framework expanded evolutionary game theory to incorporate the convergence dynamics of a phenotypical trait and its feedback with the ecological environment(Dieckmann and Law, 1996; Geritz et al., 1998). Adaptive dynamics shares similar assumptions on small additive genetics effects and on the selection gradient with quantitative genetics but models mutation as a stochastic process of small steps of invasions and substitutions (Abrams, 2001; Boots et al., 2009). Similarly, it also overlooks the genetics processes underlying evolution in order to incorporate ecological aspects and frequency-dependent selection. Differently from quantitative genetics, adaptive dynamics relies on the assumption of clonal reproduction and starts from a monomorphic population, where all individuals carry the same trait, similarly to evolutionary game theory. Another

main difference with quantitative genetics is a time-scale separation between the evolutionary dynamics and the ecological one. The ecological dynamics is assumed to be fast enough to reach an equilibrium state, which can be also cyclical, before a new mutation arises in the population.

While these modelling assumptions allow for a good mathematical tractability and a graphical representation of the evolutionary process, they restrict the applicability of the adaptive dynamics method. The assumption of clonal reproduction tightens the kind of species that can be modelled with the adaptive dynamics frameworks, making it more suitable for microorganisms like bacteria. Nevertheless, by incorporating population genetics aspects, Dieckmann and Doebeli (1999) and Kisdi and Geritz (1999) extended the framework to diploid sexual populations. Due to the time-scale separation between the evolutionary and ecological dynamics, adaptive dynamics models might fail in describing systems where the two overlaps. In recent years, a growing amount of studies is challenging the so-far widely accepted idea that evolution is slower than population turnover (Hairston et al., 2005; Govaert et al., 2019). However, sometime population dynamics can be included in the evolutionary one as in (Boldin and Kisdi, 2016). Lastly, adaptive dynamics results might overlook cases where a mutation might not be small or might have a large effect (Barton and Polechová, 2005).

We conclude with a comment on how the adaptive dynamics framework can capture feedbacks between individual fitness and population evolution. It has been hypothesised that natural selection can occur at different levels; the genetic level, the individual level and even at the population one (Futuyma, 2009). This hypothesis was formulate in the attempt to explain the spreading of altruistic traits, meaning a trait that is disadvantageous for the individual but benefits the population as a whole. As evolution does not forecast the future and does not occur 'for the good of the species', it might be possible to observe such traits, because selection has acted on others at the population level. The reasoning is that populations carrying a selfish trait, which is advantageous for the individual but deleterious for the population, might in the long term goes extinct, e.g. due to resources over-exploitation. This contrast between individual benefit and population benefit can be observed in adaptive dynamics models where 'evolutionary suicide' (Parvinen, 2005) occurs. Namely, when the selection gradient pushes a population through the boundary of extinction. Examples of models with this behaviour can involve prey timidity (Matsuda and Abrams, 1994), intra-species competition (Gyllenberg et al., 2002), and parasite virulence (Boldin and Kisdi, 2016).

1.3 The adaptive dynamics framework

Adaptive dynamics is a mathematical framework created to model the evolution of phenotypical traits taking into account their interplay with the surrounding environment (Dieckmann and Law, 1996; Geritz et al., 1998; Marrow et al., 1996). In fact, by overlooking the details

of the underlying genetics, adaptive dynamics focuses on the dynamical feedbacks between evolution, population densities and ecological variables. The crucial assumption that allows this analysis is a timescale separation between the fast time at which population dynamics occurs, the ecological timescale, and the slow evolutionary one. At the ecological timescale all traits are assumed fixed and populations, called resident, converge to a stable state, which can be an equilibrium or a cycle. At the equilibrium, whether a new mutant can grow and fixate, depends on the environment set by the resident populations. If a mutant can replace the residents it becomes the new resident, setting a new environment and the dynamics is iterated. Therefore, at the slow evolutionary time scale, an evolutionary path is composed by a sequence of trait invasion and substitution, where populations at each step have reached an ecological attractor.

We give a sketch now on how this sequence of trait invasion and substitution has been modelled as a stochastic process by Dieckmann and Law (1996). Considering N populations evolving together, the ith population is characterised by the trait x_i, with $i = 1 \dots N$, and the state of the system at each time step is represented by $x = (x_1, \dots, x_N)$. At each stage, which mutations can occur and whether they can spread depends only on the configuration of the resident populations at the time, therefore, the evolutionary process is assumed to be Markovian. The transition probabilities are built assuming that new mutants are rare and do not impact on the demographic values, that mutational steps are finite but small and that a new mutation occurs in only one population per time. The probability per unit of time that the i population mutates from trait x_i to y_i is given by

$$w_i(y_i, x) = \mathscr{M}_i(y_i, x) \cdot \mathscr{S}_i(y_i, x)$$

where $\mathscr{M}_i$ takes into account the randomness of the mutation process and $\mathscr{S}_i$ the selective effect of demographic stochasticity for the new mutant to survive at an initially low density. The Markovian process is then approximated by averaging over an infinite number of realizations to get the mean path approximation for the evolution of trait x_i, namely

$$\frac{dx_i}{dT} = \frac{1}{2}\mu_i(x_i)\sigma_i^2(x_i)\bar{n}_i(x)D(x_i). \tag{1.1}$$

where T is the evolutionary timescale. Parameter μ_i represents the fraction of births that give rise of mutation of the species i, $\bar{n}_i$ is its ecological equilibrium value, and σ^2 the variation of the mutation process. These three terms compose the evolutionary rate coefficient of the species i. $D(x_i)$ is called the selection derivative and accounts for the impact on the population per capita growth rate, i.e. its fitness, of a change in the trait x_i. Equation (1.1) is called the canonical equation of adaptive dynamics and states that the mean evolutionary path of a species follows the local direction of growth of its fitness.

From now on we will focus on the mean path approximation and look at the evolution of a single trait. When a rare mutant Y with trait y spreads in a resident population of trait

x the demographic dynamics can be written in the form

$$\frac{dY}{dt} = r(y, E_x)Y$$

where E_x is a combination of the resident values at the stable state and represent the environment set by the resident. We define $s_x(y)$ as the invasion fitness of the mutant trait y in the environment set by the resident x as its long-term exponential growth rate (Metz et al., 1992; Geritz et al., 1998), namely

$$s_x(y) = \int_0^\infty \frac{d\ln(Y)}{dt}dt = \int_0^\infty r(y, E_x)dt. \tag{1.2}$$

When the resident stable state is an equilibrium and not a cycle, equation (1.2) becomes simply $s_x(y) = r(y, E_x)$. If the invasion fitness of a mutant strain is positive it means that the mutant is able to grow exponentially in the environment set by the resident, otherwise it dies out. Notice that $s_x(x) = r(x, E_x) = 0$ as the resident population is assumed to be at a stable state. The selection gradient in equation (1.1) can be obtain as the derivative of the invasion fitness calculated when $y = x$, which is the direction of local growth of the mutant fitness

$$D(x) = \left.\frac{\partial s_x(y)}{\partial y}\right|_{y=x}.$$

When $D(x)$ is positive traits with $y > x$ can invade, while the opposite holds when $D(x)$ is negative.

If the selection gradient evaluated at a trait x^* is equal to zero, it means that the evolutionary path cannot move away from it and x^* is called a singular strategy (Geritz et al., 1998). Singular strategies can have two different evolutionary properties; evolutionary stability and convergence stability. An evolutionary stable strategy (ESS) cannot be invaded by any other close mutants, while a convergence stable strategy attracts nearby evolutionary paths. These two properties can hold independently. An ESS that is also convergence stable is called a continuous stable strategy (CSS) and it is an end point of the evolutionary process. A convergence stable strategy that is not evolutionary stable is called a branching point. When an evolutionary path reaches a branching point, evolution shifts from a monomorphic case, where the resident population is composed by a single strain, to a dimorphic case, where two strains co-exist in the same population. If a singular strategy is evolutionary stable but not convergence stable is called 'Garden of Eden' since no evolutionary path can reach it, while a singular strategy that does not satisfy either properties is called a repellor. The evolutionary properties of a singular strategy can be determined by checking conditions on the derivatives of the selection gradient. For a singular strategy to be an ESS, it has to be a local maximum of the invasion fitness (Geritz et al., 1998), that is

$$\left.\frac{\partial^2 s_x(y)}{\partial y^2}\right|_{y=x=x^*} < 0.$$

For convergence stability, the selection gradient has to be positive for values of x at the left of x^* and negative for values at the right, therefore, $D(x^*)$ has to be locally a decreasing function, i.e.

$$\left.\frac{dD(x)}{dx}\right|_{y=x=x^*} = \left.\frac{\partial^2 s_x(y)}{\partial y^2}\right|_{y=x=x^*} + \left.\frac{\partial^2 s_x(y)}{\partial x \partial y}\right|_{y=x=x^*} < 0.$$

There is a simple graphical tool that give a quick overview on the singular strategies of a model and their properties, the pairwise invasibility plot (PIP) Geritz et al. (1998). Pairwise invasibility plots are realized by plotting the sign of the invasion fitness $s_x(y)$ on a plane with the resident strategy x on the horizontal axis and the mutant strategy y on the vertical one (figure 1.1). Singular strategies (black dots in figure 1.1) can be found at the intercepts between the diagonal line and another zero-contour line of the invasion fitness. Starting from a random initial trait (white dot in figure 1.1a), neighbour mutants that are in the region where the invasion fitness is positive (grey regions) can invade (vertical arrows) and become new residents (horizontal arrows). Figure 1.1a shows a case where a singular strategy is convergence stable, as it attracts nearby evolutionary paths, and evolutionary stable, since any of the other possible mutant traits can invade (the dashed line of possible mutant traits lies in the region where the invasion fitness is negative). The singular strategy in Figure 1.1b is a branching point, as, when reached, every local mutant can invade, while 1.1c represents a repellor. There are in total eight possible local configurations of PIPs in the neighbourhood of a singular strategy, classified by Geritz et al. (1998).

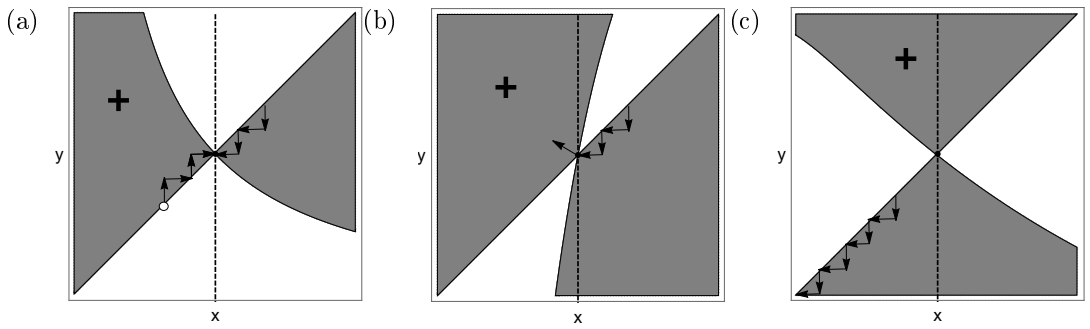

Figure 1.1: Examples of pairwise invasibility plots. On the horizontal axis there are the resident strategies, while the mutants traits are represented on the vertical axis. The grey regions mark where the invasion fitness of mutants is positive. Black dots are singular strategies, and the arrows indicate the direction of local evolutionary paths, while the white dot is a random starting point. The dashed lines help to observe which mutants might invade the different singular strategies.

1.4 Tolerance to infection as a defence strategy

Throughout this work we are going to refer to tolerance to disease as the host ability to endure the effects of parasite infection without reducing its fitness or its prevalence. Conversely, resistance strategies are those that directly reduce parasite fitness, either by avoiding transmission (avoidance), or by parasite clearance to increase recovery rate. We will adopt

a host-centred point of view, leaving the control of mortality under infection to its tolerance level, nevertheless, we will refer to virulence when the same ability is controlled by the parasite. Confusion between these three categories is quite common in literature due to different reasons. Firstly, different disciplines that address host-parasite interactions attribute different meanings to the word 'tolerance' (Read et al., 2008). Secondly, the development of an operative methodology to homogenize tolerance measurements across different experimental studies is recent and still debated (Kutzer and Armitage, 2016). Third, researchers are still in the process to unravelling the complexity of both the interplay between the two kinds of host defence and the interaction with parasite counter-strategies.

Tolerance to disease has been well documented in plant studies for long time; already at the beginning of the 20th century different studies noticed a variation in yield loss in crops affected by parasites (Schafer, 1971). As an example, Salmon (1932) documented that Fulhard wheat had a considerable better yield when compared with other crops subject to the same levels of leaf rust due to *Puccinia triticina*, and that, similarly, Kansas 2627 wheat performed better than others under *Septoria tritid* infection. In spite of this and other empirical observations, it emerged the need to formalise the concept of tolerance in a way that would have made it possible to discern its effect from the ones of resistance strategies like slowed rusting (Caldwell et al., 1958; Schafer, 1971). To this end, it has been crucial to define tolerance as a reduction in yield or fitness loss of a crop *in comparison with* other suffering by the same parasite load. More recent works found evidence for genetic variation in plant species of tolerance to diseases (Simms and Triplett, 1994), herbivores (Tiffin and Rausher, 1999) or other parasitic plants (Koskela et al., 2002).

The distinction between tolerance and resistance developed for plants has been introduced in theoretical evolutionary models firstly by the works of Boots and Bowers (1999) and Roy and Kirchner (2000). Boots and Bowers (1999) analysed the evolution of host defence through either two resistance strategies, avoidance of transmission and increased recovery, and a tolerance one, reduced mortality under infection. This work marked an important difference between the evolutionary behaviour of these two kinds of defence. Specifically, they noticed that tolerance is less likely to evolve to polymorphism, where two of more strains of the same trait can coexist in a population. This result is better understood in light of Roy and Kirchner (2000), as they unravelled the crucial role played by the feedback loop between host defence and parasite prevalence. Namely, when resistance increases it reduces the selective pressure for more resistant strains by lowering parasite prevalence and, conversely, selection for tolerance increases as more tolerant strains spread in a population. Therefore, tolerance strategies are expected to evolve to fixation, where only a highly tolerant trait can survive to a widely spread disease. Moreover, since tolerance evolution does not reduce parasite prevalence it might prevent its counter-adaptation by lowering the selective pressure for more aggressive strains.

The large body of knowledge on plant immunology together with these promising theoretical results motived the first experimental study aimed at showing genetic variation for toler-

ance in vertebrates. In 2007, Råberg et al. (2007) applied for the first time the methodology developed to measure tolerance in plant studies to mice defence against malaria. Specifically, they plotted values of anaemia and weight loss, indicators of host fitness, of five mouse strains infected by three different strains of malaria (*Plasmodium chabaudi*) against parasite load. As a result, the regression lines for the five mouse strains showed different slopes, namely different reaction norms, providing evidence for genetic variation in tolerance between them. Strains with a slower slope were more tolerant than ones where health conditions decayed faster with increasing parasite burden. Measuring tolerance as a reaction norm against parasite load can be technically demanding as it requires the comparison between different strains, but it is necessary to rule out other sources of diversity in fitness under infection. In fact, a variation in health between two infected individuals could be due to a lower parasite burden, which is a sign of a resistance strategy or to different general vigour, measurable as the intercept of the regression line with the y-axis (Råberg et al., 2009).

Following the work of Råberg et al. (2007), more and more evidence has emerged in the past years on the role played by tolerance strategies in invertebrate and vertebrate immune response. For examples, genetic variation for tolerance has been found in human and primate response to HIV and SIV (Chahroudi et al., 2012; Regoes et al., 2014), in wild bird immune system (Sorci, 2013; Staley and Bonneaud, 2015), and in mice defence against viral flu (Iwasaki and Pillai, 2014). An important contribution to tolerance is played by tissue damage control, namely the activity of those cells and molecules that repair epithelial barriers to preserve cell homoeostasis without preventing parasite transmission (Medzhitov et al., 2012; Soares et al., 2014). These mechanisms can be activated both by external stressor like pathogen toxins and virulence factors, or by the damages caused by the immune response itself. Notice that, the role of tolerance during immunopathology like sepsis complicates the interplay between the two kinds of defence, making it more difficult to classify the underlying mechanisms. Tolerance strategies are also involved in the mitigation of sickness behaviours like lethargy, anorexia, and social withdrawal (Adelman and Hawley, 2017). Moreover, tolerance might play a role in the spreading of infectious diseases, due to highly tolerant super spreaders (Gopinath et al., 2014) or vectors (Oliveira et al., 2020), e.g. mosquitoes can bear high density of arboviruses without suffering a high fitness loss. Thus, a better understanding of tolerance mechanisms might also improve disease control strategies.

Clearly, there is a discrepancy between the theoretical prediction that tolerance traits stabilize at an extreme value in a population and the genetic variation found by experimental studies, which testifies for an on-going evolutionary selection for tolerance. Best et al. (2008) contributed in filling this gap, by showing in a theoretical study two possible routes to tolerance diversification. First, when the host can limit disease induced reduction in reproductive rate, namely sterility tolerance, it does not increase parasite prevalence and it avoid the positive feedback that would prevent less tolerant strategies to coexist. Second, if a trade-off is present between resistance and tolerance at the costs of reduced reproductive ability, tolerance polymorphism is possible. Such trade-offs have been detected in some

studies (Råberg et al., 2007; Klemme and Karvonen, 2017). Moreover, Best et al. (2008) showed that the coevolution with a parasite is not enough to promote variation in tolerance. Seasonality is another possible factor behind tolerance diversification, as shown by the model analysed in Ferris and Best (2019). Nevertheless, the quest for theoretical explanations of observed variation in tolerance is still open.

Interest for studying tolerance to disease is often motivated by the possibility of developing treatments where classical routes fail, for example when parasites develop anti-microbial resistance or when it is not possible to create a vaccine (Read et al., 2008). Nevertheless, due to the novelty of the concept, the possible consequences of increasing tolerance to disease in a population are not yet fully understood. The theoretical model of Miller et al. (2006) firstly consider the effects of co-evolution between host tolerance and parasite virulence. Tolerance can decrease the costs for the parasite to increase transmission by reducing mortality under infection. Therefore, evolution towards a form of commensalism between a highly tolerant host and a highly virulent parasite can come with a high death toll for the host. Moreover, Hozé et al. (2018) assessed the possible risks of deploying tolerance-based treatments for public health systems using a compartmental model. While in theoretical predictions tolerance reaches fixation in a population, and every individual can bear high levels of infection, it is not necessarily possible to reach the same coverage with public interventions. Particularly, reducing disease induced mortality in the case of a chronic disease can be dangerous at the population level, because individuals keep being infective and recovery can take a long time. Thus, following the increase of experimental evidences of the important role played by tolerance strategies, it is important to keep deepening the theoretical understanding on their ecological and evolutionary consequences.

1.5 Predators' impact on host-parasite evolution

A first effect of the introduction of the predator in a host-parasite system can be the shifting of pathogen evolution to more virulent strains as in Morozov and Adamson (2011). Morozov and Adamson (2011) used an SIS model to analyse parasite evolution under the assumption that predators feed only on infected individuals. As a result, they found that the possible evolutionary outcomes strongly depend on the choice of the trade-off function between transmission and virulence. Trade-offs are in important ingredient in evolutionary models, as they represent the energetic costs and genetic constraints of an evolving trait. In this case, increased transmission comes at the cost of an increased possibility to kill the host. When pathogen evolution stabilises at an optimal strategy, the value of virulence increases when predation rate increases due to the predator removal of infected individuals.

Moreover, Morozov and Adamson (2011) found that pathogen evolution can cause predator extinction when virulence increases up to a value such that predators cannot feed enough to survive. The extinction of one or more species in the model due to evolution of a trait is a common evolutionary outcome. Hoyle et al. (2012) focused on the possibility of the host

to drive either the parasite or the predator species to extinction when resistance evolves. Again, they assumed that defence is costly in terms of reproduction. Predator extinction occurs through two different mechanisms. Firstly, predators go extinct in a deterministic way when resistance increases, lowering infected density and reducing the amount of available prey. Secondly, it can happen when mutation stochasticity is introduced around an optimal strategy that is very close to the extinction boundary. In this case, the pathogen can also go extinct due to increased resistance and when the host is alone, resistance is minimised to the benefit of reproduction. This scenario can be avoided when predators can counter fast enough resistance evolution with increased predation, causing pathogen disappearance.

Another effect of predation observed in theoretical model is to increase the possibility for both parasite and host polymorphism. Morozov and Best (2012) showed that evolutionary branching of virulence can occur under the hypothesis that more virulent strains are subject to higher predation. Moreover, the branching region does not depend monotonously from model parameters and branching is possible for both highly and lowly selective predators. In Hoyle et al. (2012), the presence of the predator species allows for the evolutionary branching of host resistance to happen for parameter choices that would not permit it in the host-parasite case. Also Toor and Best (2015) observed, in a similar model, that the possibility for resistance branching increases when the predator capture coefficient increases. Therefore, predators could be an important contribution to host and parasite diversity.

The effect of predation on resistance evolutionary optimal strategy can also be non-monotonous as found by Toor and Best (2015). Toor and Best (2015) extended the work of Hoyle et al. (2012) by looking at other effects of predation on resistance evolution. Toor and Best (2015)'s analysis focused on the impact of predator capture rate on resistance optimal strategy while varying other parameters. Generally, the optimal strategy showed a 'U-shape', with the maximal level of defence at intermediate predation rate. Two different factors contribute to this shape; the risk of getting infected and the cost of dying while infected. At low predation rate, predator density is low but disease prevalence is high, therefore, there is a high risk of being infected but a low cost of dying during infection. Thus, there is not a selective advantage in investing in reduced transmission, which means higher resistance, when predation rate is low. The same happens for high predation rate, where the cost of infection is high due to predator abundance, but the risk of infection is low because of the removal of infected prey by predators. Building defence becomes advantageous only an intermediate value of the capture rate where both the risk and the cost of infection are limited. A similar pattern appears also when parasite virulence increases. Toor and Best (2015) found that Boots and Haraguchi (1999) result that highly virulent parasites select for lower defence holds for high predation rate and not for low as one might expect

The study of this model has been carried on by assuming that the host has a limited amount of resource to be invested either in defence against the parasite (reduced transmission) or in anti-predator behaviour (Toor and Best, 2016). Their main result is that the host increases its defence against the most threatening opponent. Despite this result seems

intuitive, it can be used to explain complex effects caused by variation of life-history traits on evolutionary selection. Interestingly, they also found that co-existence is possible between two traits specialised in defence against one or the other enemy.

Eventually, the introduction a predator species in a theoretical model can also lead to eco-evolutionary cycles (Kisdi et al., 2013). In all the works mentioned the end points of evolution are either singular strategies or boundary values, while Kisdi et al. (2013) focused on the conditions under which evolution stabilises on a cycle. To this end, Kisdi et al. (2013) performed a time-scale separation between the host dynamics considered fast and the slow eco-evolutionary dynamics of predator population and virulence evolution. The evolutionary cycle is the effect of a complex biological mechanism, due to the trade-off between virulence and transmission rate and the positive correlation between virulence and predator capture rate of infected individuals. When the predator density is high, the parasite evolves to lower virulence and reduce the predator capture rate of infected. In response, the predator density decreases and favours an increase of virulence that induce the predator capture rate and the predator density to rise again. This periodic behaviour is present when the speed of pathogen evolution is comparable to the one of predator dynamics while, at slow pathogen evolution Kisdi et al. (2013) recovered the result of Morozov and Best (2012) of virulence branching.

All these studies have analysed the effects of predation on the evolution of a host-parasite system using compartmental models and adaptive dynamics. There many ways in which a predator species can alter the evolution of host resistance and parasite virulence. At the best of our knowledge there is not a similar study on tolerance evolution in presence of a predator species.

1.6 Thesis Outline

Chapter 2 serves as an introduction to host-parasite dynamics and the adaptive dynamics framework. We model the host-parasite dynamics using a simple SIS model, commonly used when the host lacks acquired immunity, for example, in the case of bacterial populations. Nevertheless, despite the simplicity of the model, we detected a novel result while considering the evolution of host tolerance in presence of a trade-off between host defence and reproduction. Specifically, when a host has an advantage, in terms of increased reproductive rate, for lowering tolerance against disease symptoms it can lead the parasite toward extinction. This is interesting because parasite extinction cannot occur when the host directly fights the parasite through resistant types of defence. Ultimately, this chapter build the ground for the comparison with the case where the predator species is present and the host-parasite alone dynamics.

Chapter 3 analyses in details the population dynamics of the full model that includes a host, a parasite a predator species that feeds upon both healthy and infected prey. Particularly, we focus here on unravelling the implications of predator preference towards either

infected or healthy preys on the system asymptotic behaviours. To this end, we used results of stability analysis and bifurcation theory, specifically center-manifold theory. The case where predators focus on healthy preys was particularly overlooked in the literature and, by considering it, we discovered an interesting case of backward bifurcation. Moreover, when predators favour healthy prey we found two different regions of bistability between different ecological equilibria. When selection is towards infected prey, we extend to the specialist case the already known result that the decrease in parasite prevalence can have a positive impact on host population to the extent that total prey density can increase. We conclude the chapter by looking at how different model parameters impact on population densities at the equilibrium.

Chapter 4 builds on chapter 3 by introducing the possibility for the host to evolve tolerance as in the first chapter. As first result, the presence of the predator species allows for the evolutionary branching of tolerance to occur, which is impossible in the host-parasite system. We noticed that the branching region increases when the capture coefficient increases. When tolerance evolves toward a stable strategy, predation lowers the optimal level of tolerance by lowering infection prevalence and selection for host defence. Generally, we found higher tolerance when the infection risk is high and predator density is low. The predator species makes the extinction of the parasite driven by tolerance evolution more likely, as in the host-parasite case this can occur when tolerance is lowered. When selection favours lower levels of tolerance also the predator species can go extinct. Finally, we analysed what happens after the branching point and considered the evolution of a dimorphic population where two traits of tolerance co-exist. In this case, evolution stabilises at population composition where a highly tolerant and frequent strategy co-exist with a rare strain with an intermediate level of tolerance.

Chapters 2 and 3 have been published as Vitale and Best (2019a) and Vitale and Best (2019b).

Chapter 2

The paradox of tolerance: parasite extinction due to the evolution of host defence

2.1 Introduction

While facing a parasite infection, hosts can defend themselves by reducing parasite fitness through mechanisms that lower transmission or clear the parasite, namely *resistance* strategies (Bowers et al., 1994; Malo and Skamene, 1994; Boots and Haraguchi, 1999; Boots et al., 2009; Hoyle et al., 2012). However, a second category of strategies has recently gained the attention of both experimental and theoretical studies. Hosts can develop *tolerance* to the detrimental effects of infection without any negative impact on parasite fitness (Boots and Bowers, 1999; Roy and Kirchner, 2000; Miller et al., 2007; Best et al., 2008; Boots, 2008; Best et al., 2009, 2014). Particularly, we [1] consider tolerance strategies that reduce parasite-induced mortality under infection. This kind of defence was observed firstly in plant studies (Caldwell et al., 1958; Clarke, 1986; Simms and Triplett, 1994), where tolerance has been defined as the reaction norm between plant fitness and an environmental gradient (Simms, 2000). Råberg et al. (2007) adapted this definition to show genetic variation of tolerance in mice, opening the way for several empirical studies focused on animal systems (Råberg et al., 2009; Little et al., 2010; Medzhitov et al., 2012; Råberg, 2014; Kutzer and Armitage, 2016; Adelman and Hawley, 2017). Among them, recent empirical works have addressed the question on how tolerance might play a role in ameliorating the effects of immunopathology (Sears et al., 2011; Soares et al., 2017) or other severe diseases like HIV (Chahroudi et al., 2012; Regoes et al., 2014).

While defining tolerance as a reaction norm has contributed to mounting experimental evidence of genetic variation in tolerant traits, in theoretical studies like ours, tolerance is often modelled using a single parameter. As we assume that evolution occurs at a much

[1] It is an author's choice to use the pronoun 'we' instead of the classical 'I' to undeline that, despite the author's major contribution, none of this would have been possible without a collective effort.

slower timescale than population turnover we neglect within-host dynamics. To this aim, we consider that in a tolerant individual, as pathogen load increases, its effect on some measure of health decreases compared to less tolerant individuals. Thus, across that gradient tolerant hosts can cope better with any particular load (particularly higher loads) and we might conclude this means lower mortality.

The importance of a distinction between tolerance and resistance traits is most clearly understood in the context of their evolution and its impact on the ecological feedback in host-parasite systems (Boots and Bowers, 1999; Roy and Kirchner, 2000; Miller et al., 2005, 2007; Best et al., 2008; Boots et al., 2009; Best et al., 2009, 2014). Both mechanisms positively affect host fitness but resistance lowers parasite fitness while tolerance is either neutral or increases it. Therefore, there exists a negative feedback between selection for resistance and parasite prevalence, which allows evolutionary branching to coexistence (Antonovics and Thrall, 1994). On the contrary, tolerance evolves towards fixation (Boots and Bowers, 1999; Miller et al., 2007) under general hypotheses (Best et al., 2008) because the spread of a tolerant trait in a population increases disease prevalence and thereby generates an environment not suitable for less tolerant strains. Generally, these studies focused on how quantitative investment in costly defence varies across ecological and epidemiological gradients, and on the potential for evolutionary branching. While reviewing these studies we noticed an overlooked effect of tolerance evolution, which might inspire further experimental work. Namely, we posed the question: can the host drive parasites to extinction through evolving defence?

Host-driven parasite extinction is not just a theoretical possibility, but has been observed in experimental studies of host-parasite co-evolution. Co-evolution of host resistance and parasite virulence can result in antagonistic dynamics (Woolhouse et al., 2002). Moreover, environmental factors like temperature gradient (Zhang and Buckling, 2011), host population bottleneck (Hesse and Buckling, 2016), alterations of resources availability (Zhang and Buckling, 2016; Wright et al., 2016; Gómez et al., 2015) or population mixing (Wright et al., 2016) have been shown to slow down parasite counter-adaptation to the extreme point where they can not keep pace with host defence evolution and extinction results. In these cases, the extinction therefore occurs due to external perturbations of the system. However, we do not have a general understanding of whether parasite extinction is possible due to host evolution in the absence of such environmental factors.

A key assumption in almost all theoretical evolution studies is that defence is costly in terms of fitness in the absence of infection, given both theoretical arguments (Stearns, 1992; Hoyle et al., 2008) and experimental support (Boots and Begon, 1993; Kraaijeveld and Godfray, 1997; Mealor and Boots, 2006). The underlying idea is that mounting a defence response is demanding and it limits the development of other life history traits. An important example is the well-documented trade-off between resistance and growth rate in *Plodia interpunctella* (Boots and Begon, 1993; Bartlett et al., 2018). If there were no costs to evolving defence, we would expect resistant or tolerant strains to have always higher fitness than other strategies and defence to reach maximization. In this case, we might expect

parasite extinction to be a common outcome. The presence of costs, however, is likely to offset the benefit of evolving to high levels of defence. In this scenario, resistant and tolerant strains have lower fitness than non-defensive ones in the absence of the parasite. Under infection, selection promotes higher defence when the benefits against infection overcome the costs of defence. Costs are also necessary to the generation of diversity when either avoidance (Antonovics and Thrall, 1994; Boots and Haraguchi, 1999) or increased recovery (Boots and Bowers, 1999) evolves. In fact, resistance traits are predicted to evolve toward polymorphism rather than fixation (Roy and Kirchner, 2000), when decelerating costs are considered (Boots and Haraguchi, 1999). In the latter case, a weakly resistant strain can coexist with a strongly resistant one, due to the low parasite prevalence. The question remains, therefore, as to whether the presence of costs can prevent host defence evolving to the point where extinction would occur.

In conclusion, our focus in this chapter is on deriving the conditions on host defence and its cost function that allow for parasite eradication. With this aim, we model the host-parasite dynamics using a Susceptible-Infected-Susceptible framework. This choice makes our study comparable with classic literature and, due to its mathematical tractability, allows us to concentrate on the evolutionary dynamics and, in the next chapters, on the ecological one. To model the long-term evolutionary dynamics, we adopted an evolutionary invasion analysis (adaptive dynamics) framework (Dieckmann and Law, 1996; Marrow et al., 1996; Geritz et al., 1998). The assumptions of clonal reproduction, underlying the adaptive dynamics framework, and the absence of permanent recovery from infection make our model more suitable for microbial systems. Given these modelling choices, we found that, when costs are considered, parasite extinction can occur only when selection promotes lower levels of tolerance. Initially, we assume also that the parasite sterilises infected individuals to facilitate mathematical tractability, but we show in 2.3.3 that the occurrence of parasite extinction does not depended upon the sterility of infected individuals. As we focus on host defence evolution, we assume that the impact on host mortality while infected caused by the parasite (virulence) does not change during the evolutionary process. Thus, we do not address theoretically the case of host-parasite co-evolution. Nevertheless, we relax this assumption in the numerical simulations, where we recovered that parasite extinction due to tolerance evolution can occur despite parasite co-evolution of virulence.

2.2 Model

We use a classic host-parasite model (Anderson and May, 1981) to study the evolutionary outcomes of host defence, given by

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

Parameter	Definition	Default value
a	Host birth rate	2
b	Host mortality rate	0.1
q	Impact of crowding on host birth rate	0.2
β	Infection transmission coefficient	0.3
γ	Recovery rate	0.3
α	Disease-induced mortality rate	1

Table 2.1: Summary of model parameters

Model parameters are listed in Table 2.1. Variables X and Y represent respectively the densities of susceptible and infected individuals. The parameter a is the host birth rate and b is the host natural death rate, while q models the effect of crowding on births. The disease spreads with a transmission coefficient β. As an effect of infection, the infected hosts suffer from an increased death rate by α, namely the parasite virulence. In addition, infected individuals are infertile and do not contribute to reproduction, however, we will relax this assumption in section 2.3.3. Moreover, hosts can recover at rate γ and be susceptible to infection again.

Following previous studies (Boots and Bowers, 1999; Roy and Kirchner, 2000), we consider two different types of resistance strategies. The first one includes those mechanisms that prevent infection by limiting the possibilities of contagion, for example through barriers or by reducing interactions with other hosts. This category is called avoidance and we model it as a decrease of the transmission coefficient β. The second category involves mechanisms that help the clearance of the parasite inside the host and reduce the time under infection and increase the possibility of recovery. Thus, we model it as an increase in the recovery rate γ. Tolerance is modelled as a reduction in the disease-induced mortality rate α. This choice is in accordance with the definition that tolerance has a non negative impact on parasite fitness, as infected individuals experience lower additional mortality without effects on other parasite traits as reproductive rate or transmission.

In the absence of disease, the susceptible population reaches the equilibrium $\overline{X}_0 = (a - b)/q$. The disease can spread under the condition

$$R_0 = \frac{\beta \overline{X}_0}{\Gamma} = \frac{\beta(a-b)}{q(\alpha + b + \gamma)} > 1, \tag{2.2}$$

with $\Gamma = \alpha + b + \gamma$. System (2.1) shows a unique endemic equilibrium where the disease persists

$$\begin{aligned} \overline{X} &= \frac{\Gamma}{\beta} \\ \overline{Y} &= \frac{a - b - q\overline{X}}{q + \beta\left(1 - \frac{\gamma}{\Gamma}\right)}, \end{aligned} \tag{2.3}$$

that is positive and stable, provided (2.2) is satisfied.

We analyse the evolution of both defence strategies under the assumptions of either cost-free or costly defence. To include the costs, we introduce trade-off functions between defence and birth rate. As an example, when analysing avoidance evolution with cost, the birth rate is represented by function $a(\beta)$ that it is lower at low values of β, i.e. when resistance is higher.

According to adaptive dynamics theory, when a resident population has reached its equilibrium, in this case (2.3), a new mutant strain can invade if its invasion fitness in the environment set by the resident strategy is positive. Specifically, mutant invasion fitness is defined as "the long-term exponential growth rate of a rare mutant in an environment set by the resident" and in structured population it is calculated as the leading eigenvalue of the mutant invasion matrix (Metz et al., 1992). When the direct computation of the invasion fitness is difficult, it is possible to adopt a fitness proxy instead. As defined in Parvinen and Dieckmann (2018), a fitness proxy is a function that is, up to a constant, sign equivalent to the invasion fitness. Adapting Hoyle et al. (2012) proof, we use the negative of the determinants of the mutant invasion matrices as proxies for the sign of the invasion fitness. We outline now the proof for the fitness proxy $s_\beta(\beta, \beta_m)$, analogous arguments hold for $s_\gamma(\gamma, \gamma_m)$ and $s_\alpha(\alpha, \alpha_m)$.

Given a resident population of trait β at the demographic equilibrium $\left(\overline{X}, \overline{Y}\right)$, the dynamics for a new mutant strain β_m is

$$\begin{aligned} \frac{dX_m}{dt} &= \left[a(\beta_m) - b - q\left(\overline{X} + \overline{Y}\right) - \beta_m \overline{Y}\right] X_m + \gamma Y_m \\ \frac{dY_m}{dt} &= \beta_m X_m - (\alpha + b + \gamma) Y_m. \end{aligned} \tag{2.4}$$

The underlying assumption is that at the beginning mutant prevalence is low and does not influence the environment set by the resident. The mutant strain can spread if the equilibrium (2.3) is unstable in the full system, i.e. if the Jacobian matrix with respect to the mutant variables

$$\begin{pmatrix} a(\beta_m) - b - q(\overline{X} + \overline{Y}) - \beta_m \overline{Y} & \gamma \\ \beta_m \overline{Y} & -\Gamma \end{pmatrix} \tag{2.5}$$

has at least one eigenvalue with positive real part. Therefore, the mutant fitness is defined as the leading eigenvalue of (2.5). Hoyle et al. (2012) proved that the negative of the determinant of (2.5) has equivalent sign of the leading eigenvalue and thus it can be used as fitness proxy. We name the fitness proxy for resistance as s_β, this is a function of both the resident trait β and the mutant trait β_m. Using a similar notation for recovery and tolerance, we get

$$s_\beta(\beta, \beta_m) = (b + \alpha + \gamma)\left[a(\beta_m) - b - q\left(\overline{X} + \overline{Y}\right) - \beta_m \overline{Y}\right] + \gamma \beta_m \overline{Y}, \tag{2.6}$$

$$s_\gamma(\gamma, \gamma_m) = (b + \alpha + \gamma_m)\left[a(\gamma_m) - b - q\left(\overline{X} + \overline{Y}\right) - \beta \overline{Y}\right] + \gamma_m \beta \overline{Y}, \tag{2.7}$$

$$s_\alpha(\alpha, \alpha_m) = (b + \alpha_m + \gamma)\left[a(\alpha_m) - b - q\left(\overline{X} + \overline{Y}\right) - \beta \overline{Y}\right] + \gamma \beta \overline{Y}. \tag{2.8}$$

In (2.6)-(2.8) the dependence from the resident strategies lies in $\overline{X}$ and $\overline{Y}$, as can be seen in (2.3).

The evolutionary dynamics of one trait stops when it reaches either a singular strategy or the extinction boundary of one species. Singular strategies are characterised by the condition that the derivative of the invasion fitness with respect to the mutant strain, namely the selection gradient, is equal to zero. In this model the selection gradients are

$$\left.\frac{\partial s_\beta}{\partial \beta_m}\right|_{\beta_m=\beta} = \Gamma a'(\beta) - (b+\alpha)\overline{Y}, \tag{2.9}$$

$$\left.\frac{\partial s_\gamma}{\partial \gamma_m}\right|_{\gamma_m=\gamma} = \Gamma a'(\gamma) + \beta\left(1-\frac{\gamma}{\Gamma}\right)\overline{Y}, \tag{2.10}$$

$$\left.\frac{\partial s_\alpha}{\partial \alpha_m}\right|_{\alpha_m=\alpha} = \Gamma a'(\alpha) - \frac{\beta}{\Gamma}\gamma\overline{Y}. \tag{2.11}$$

Moreover, the selection gradient indicates in which direction the evolutionary path is moving. In fact, at the slow time-scale of evolution T we can approximate the change in the resident strategy, e.g. avoidance, as

$$\frac{d\beta}{dT} \approx \mu \left.\frac{\partial s_\beta}{\partial \beta_m}\right|_{\beta_m=\beta} \tag{2.12}$$

where $\mu > 0$ is a coefficient that takes into account rate and variance of the mutation process. Therefore, a positive selection gradient implies that evolution is moving towards higher values of β and a negative selection gradient that selection favours lower values of β. When the evolutionary path leads towards a singular strategy β^*, the singular strategy is called convergence stable (Geritz et al., 1998). This happens when the following condition is satisfied

$$\left.\frac{\partial^2 s_{\beta_m}}{\partial \beta_m^2}\right|_{\beta_m=\beta=\beta^*} > \left.\frac{\partial^2 s_{\beta_m}}{\partial \beta^2}\right|_{\beta_m=\beta=\beta^*} \tag{2.13}$$

The same holds for tolerance and recovery.

Throughout this study, we will support our results with numerical simulations to relax the hypothesis of a timescale separation between ecological and evolutionary dynamics. Specifically, in the simulations a new mutation can occur before the resident population has reached a stable equilibrium. We will also allow for parasite counteradaptation of transmission at the cost of higher virulence. Host-parasite co-evolution can be addressed analytically but the analysis would go further the scope of this study, however, we use simulations to check whether parasite extinction it is still possible when the parasite counter-adapts tolerance evolution. To perform numerical simulations, we followed a method similar to Hoyle et al. (2012). For tolerance evolution, we set a system for n_H possible host strain values of α^H and initialised as non zero the initial condition for a random strain. At every step the system is solved for a fixed time that is not long enough for the population dynamics to reach the dynamical equilibrium. Strains with frequency less than 0.1% are then removed from the system and a new mutant close to the most frequent strain is introduced randomly. Moreover, the parasite is removed from the system when its prevalence drops under 0.01%.

Notice that changing these thresholds does not impact on tolerance evolutionary end points, but it effects the range of strains that coexist at each time step and the time needed for parasite extinction to occur.

Similarly, to simulate co-evolution between host tolerance (α^H) and parasite virulence (α^P) at every step we solve the system

$$\begin{aligned}\frac{dX_i}{dt} =& a\left(\alpha_i^H\right) X_i - q\left(\sum_i^{n_H}\sum_j^{n_P} Y_{ij} + \sum_i^{n_P} X_i\right) X_i - X_i \sum_{i=1}^{n_H}\sum_{j=1}^{n_P} \beta\alpha_j^P Y_{ij} \\ &+ \gamma \sum_{j=1}^{n_P} Y_{ij}, \quad i = 1, \ldots, n_H \\ \frac{dY_{ij}}{dt} =& \beta\left(\alpha_j^P\right) Y_{ij} X_i - \left(\alpha_i^H \alpha_j^P + b + \gamma\right) Y_{ij}, \quad i = 1, \ldots, n_H \quad j = 1, \ldots, n_P,\end{aligned} \tag{2.14}$$

where X_i is the density of the host population with tolerance strain α_i^H and Y_{ij} is the density of infected with tolerance strain α_i^H from the parasite strain α_j^P. The number of host strains is n_H and the number of parasite strains is n_P, $a\left(\alpha_i^H\right)$ is defined as in (2.28), $\beta(\alpha_j^P)$ is a monotonously increasing function (e.g. Fig.2.7) and the others parameters have same interpretation as in (2.1). After a fixed time, populations with frequency under 0.1% are set to zero and a new mutant strain is introduced randomly with the same probability of being a new host or a new parasite.

2.3 Results

2.3.1 Evolution of resistance

We start by reviewing the well-known results for resistance evolution and the possibility for parasite extinction, to allow for the comparison with the effects of tolerance evolution. We firstly consider the case of evolving avoidance without costs, i.e. when the birth rate $a(\beta)$ is equal to a positive constant $\bar{a}$ for every resistance strategy β. Under this assumption, the selection gradient

$$\left.\frac{\partial s_\beta}{\partial \beta_m}\right|_{\beta_m=\beta} = -(\alpha + b)\overline{Y} < 0 \tag{2.15}$$

and it is equal to 0 when $\overline{Y} = 0$. Therefore, evolution leads towards lower value of β to the point where $R_0 = 1$ and the disease can not spread enough to survive. A similar conclusion can be drawn when increased recovery evolves without cost. We choose $a(\gamma) = a_m(\gamma) = \bar{a}$ positive constant such that (2.2) is satisfied for some γ. Consequently, the selection gradient

$$\left.\frac{\partial s_\gamma}{\partial \gamma_m}\right|_{\gamma_m=\gamma} = \beta\left(1 - \frac{\gamma}{\Gamma}\right)\overline{Y} > 0 \tag{2.16}$$

for every γ such that $\overline{Y} > 0$ and equal to zero at $\overline{Y} = 0$, since $\gamma < \Gamma$. Thus, the evolutionary dynamics reaches the extinction boundary, where the recovery rate is too high for the infec-

tion to persist. The reason for this is that an increase in γ means a decrease in the length of the infectious period and, consequently, in R_0.

We use the graphical tool of pairwise invasibility plot (PIP) (van Tienderen and de Jong, 1986; Geritz et al., 1998) to show the evolutionary dynamics. In the PIPs, the sign of the invasion fitness is plotted in the plane spanned by the resident and the mutant strategies. When the positive region (positive regions are shaded and negative regions are white) is above the diagonal the evolutionary dynamics moves to the right, while it moves to the left when the positive region is below the diagonal. In both cases of Fig.2.1 the absence of costs allows defence to be favoured even at low values of disease prevalence, where selection for resistance is weaker.

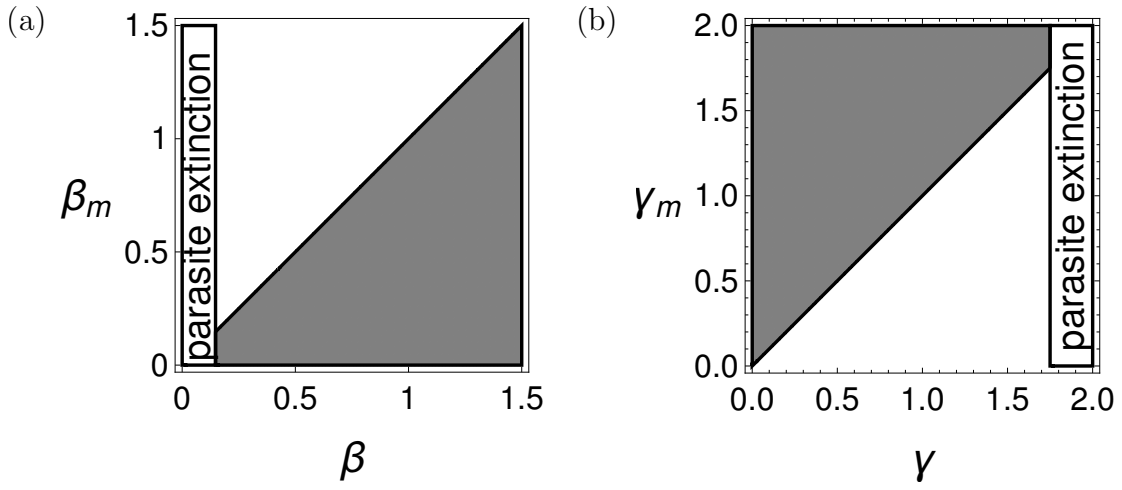

Figure 2.1: Pairwise invasibility plot for resistance evolution without costs. In (a) the sign of $s_\beta(\beta, \beta_m)$ is plotted in the β-β_m plane under the hypothesis that $a'(\beta) = 0$. Analogously, (b) shows the sign of $s_\gamma(\gamma, \gamma_m)$ as function of γ and γ_m. In both panels the gray region marks where the sign is positive.Parameter values are summarised in Tab 2.1, $\alpha = 1$.

This result does not hold when resistance comes with costs. In line with previous theoretical models and experimental studies (Hart, 1990; Stearns, 1992; Hoyle et al., 2008) we assume a monotonically increasing trade-off $a = a(\beta)$ between avoidance and birth rate. To understand if parasite extinction is possible for some value of β, we analyse the selection gradient when $\overline{Y} \approx 0$ such that we are nearby the point of extinction. Since $a'(\beta) > 0$, at the limit for low values of infected population the selection gradient

$$\lim_{\overline{Y}\to 0^+} \frac{\partial s_\beta}{\partial \beta_m}\bigg|_{\beta_m=\beta} = \Gamma a'(\beta) > 0 \tag{2.17}$$

Resistance reduces the infection prevalence and, as consequence, lowers the risk of infection under the level where the costs of resistance exceed the benefits. Therefore, when $\overline{Y}$ is close to zero, selection promotes lower resistance and the parasite avoids extinction.

Similarly, we consider a trade-off $a = a(\gamma)$ that is monotonically decreasing with respect to γ and satisfies (2.2) for some γ. Close to the extinction boundary the limit of the selection

gradient is

$$\lim_{\overline{Y}\to 0^+} \frac{\partial s_\gamma}{\partial \gamma_m}\bigg|_{\gamma_m=\gamma} = \Gamma a'(\gamma) < 0 \tag{2.18}$$

and mutants with lower values of resistance will invade.

It can be shown that R_0 and disease prevalence $\overline{Y}/\left(\overline{X}+\overline{Y}\right)$, with $\overline{X}$ and $\overline{Y}$ defined in (2.3), are monotonically increasing for decreasing resistance, therefore, the host cannot clear the disease by lowering defence. Notice also that we proved that extinction cannot occur in the deterministic model under the assumption of small mutations. When $\overline{Y}$ is close to 0, extinction could be possible if stochastic effects are taken into account.

In order to represent graphically the previous results, we define the trade-off function explicitly

$$a(\beta) = a^* - \frac{a'(\beta^*)^2}{a''(\beta^*)}\left[1 - e^{\frac{a''(\beta^*)}{a'(\beta^*)}(r-\beta^*)}\right] \tag{2.19}$$

$$a(\gamma) = a^* - \frac{a'(\gamma^*)^2}{a''(\gamma^*)}\left[1 - e^{\frac{a''(\gamma^*)}{a'(\gamma^*)}(\gamma-\gamma^*)}\right]. \tag{2.20}$$

This choice easily allows to determine the local shape close to a chosen point (β^*, a^*) or (γ^*, a^*) and consequently, by absolute monotonicity, a wide range of global behaviours, e.g. different steepness or concavity. Specifically, $a'(\beta^*)$ and $a'(\gamma^*)$ are chosen such that β^* and γ^* are a singular strategy, i.e. the selection gradients in (2.6)-(2.8) are equal to zero. Notice that this choice respects the assumption of monotonically increasing costs. We derive the intervals for $a''(\beta^*)$ and $a''(\gamma^*)$ such that the singular strategies are convergence stable from (2.13). If β^* and γ^* are convergence stable, parasite extinction is trivially avoided (Fig.2.2a and Fig.2.2c). More interesting, when β^* and γ^* are convergence unstable a second singular strategy close to the boundary necessarily emerges and prevents the disease dying out (Fig.2.2b and Fig.2.2d).

2.3.2 Evolution of tolerance

In the absence of costs, the selection gradient (2.8) for tolerance is

$$\frac{\partial s_\alpha}{\partial \alpha_m}\bigg|_{\alpha_m=\alpha} = -\frac{\beta\gamma}{\Gamma}\overline{Y} < 0 \tag{2.21}$$

when the infection is present and equal to zero at the extinction boundary. Therefore, the evolutionary dynamics moves towards tolerance maximisation and balance the effect of parasite virulence. Contrary to the case of resistance, disease prevalence increases when tolerance is selected and parasite extinction does not occur. This can be observed in the simulation in Fig.2.3.

We consider now the case of costly tolerance. As in the resistance case, we assume that investing in tolerant strategies limits the allocation of resources for reproduction. When we consider the costs of tolerance, the trade-off $a(\alpha)$ is assumed to be monotonically increas-

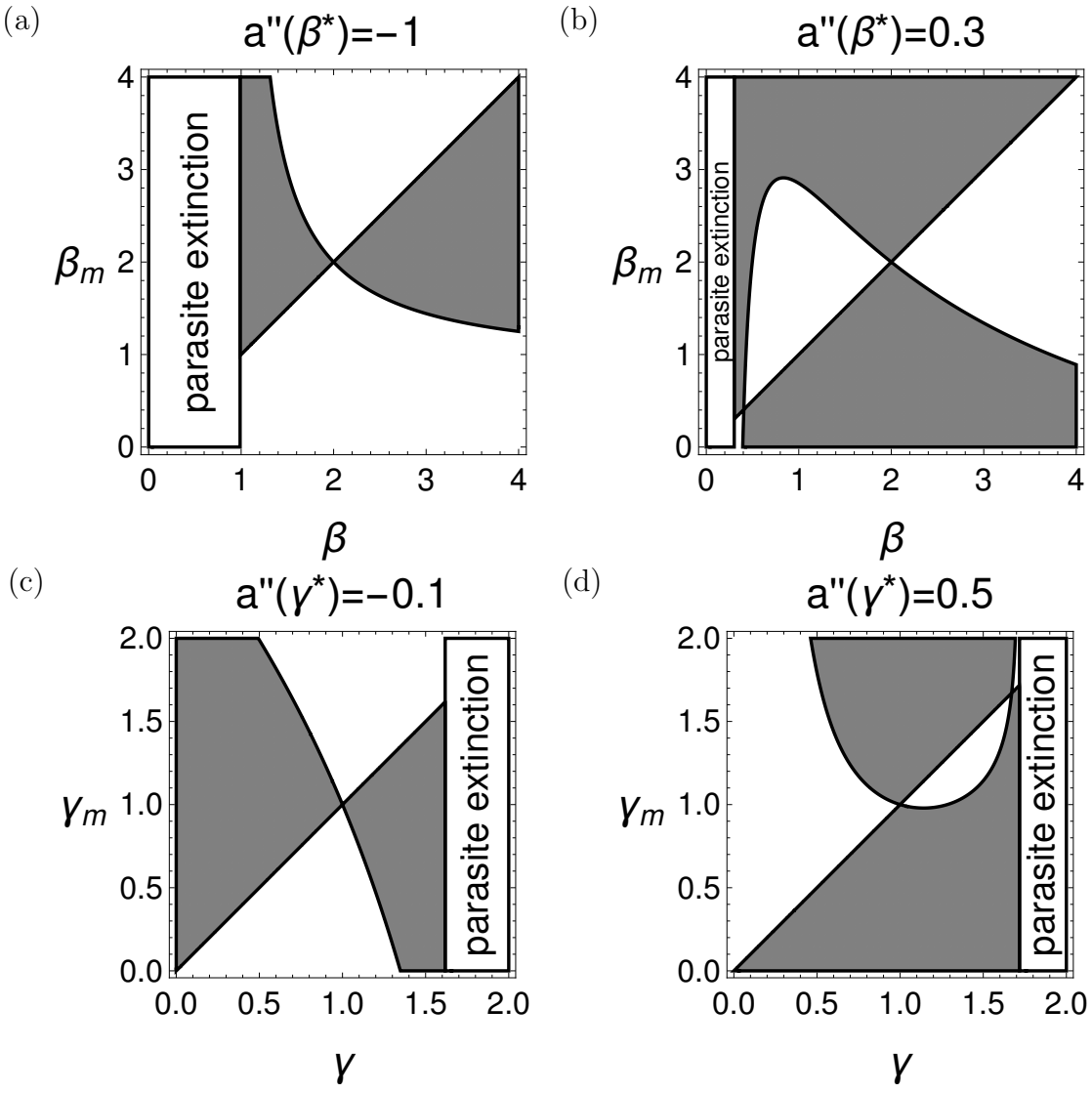

Figure 2.2: Pairwise invasibility plots for resistance evolution with costs. In all the panels, resident traits lie on the x-axis and mutant traits are on the y-axis. The gray regions mark the resident and mutant couples for which the mutant invasion fitness is positive and the mutant trait can invade the resident environment. In (a) and (b) the region where the sign of the invasion fitness $s_\beta(\beta, \beta_m)$ is positive is plotted for two different values of the second derivative of the trade-off function $a(\beta)$. Similarly, in (c) and (d) the sign of $s_\gamma(\gamma, \gamma_m)$ is plotted for two different values of $a''(\gamma^*)$. $\alpha = 1$, in (a) and (b) $\beta^* = 2; a(\beta^*) = 2; a'(\beta^*) = 0.78$. In (c) and (d) $\gamma^* = 1; a(\gamma^*) = 2; a'(\gamma^*) = -0.1$.

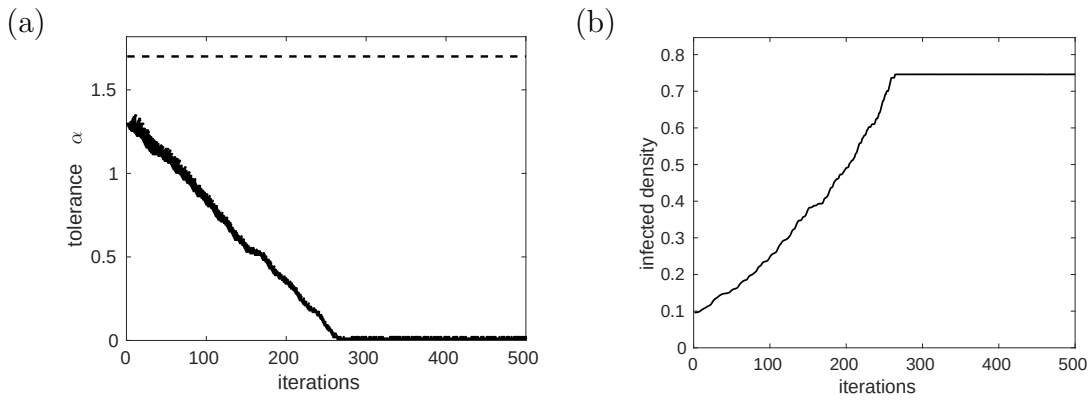

Figure 2.3: Simulation of the evolution of tolerance in absence of costs, conducted as explained in section 2.2. In the left panel, the black region represents the values of α of the strains present at each iteration and the dashed line the parasite extinction boundary. In the right panel, the continuous curve represents the disease prevalence. $n_H = 200$

ing with respect to α. Under this assumption, near the extinction boundary the selection gradient (2.8) is

$$\lim_{\overline{Y}\to 0^+} \frac{\partial s_\alpha}{\partial \alpha_m}\bigg|_{t^*=t} = \Gamma a'(\alpha) > 0, \tag{2.22}$$

meaning that selection for *lower* tolerance can lead to parasite extinction. Such situations are illustrated in Fig.2.4a and Fig.2.4b, in which the sign of $s_\alpha(\alpha, \alpha_m)$ is plotted for different values of both mutant and resident strategies. Compared to the case without costs, the zero of the selection gradient that was on the extinction boundary has now entered the region of parasite viability, changing the direction of selection for low $\overline{Y}$.

We investigate now under which conditions on the trade-off function host evolution drives the parasite to extinction by lowering tolerance. As a first condition, we need the parasite to be present in the system, meaning $R_0 > 1$. By rearranging condition (2.2), we found that it holds when

$$a(\alpha) > b + \frac{q(\gamma + b)}{\beta} + \frac{q}{\beta}\alpha \tag{2.23}$$

for some values of α. Secondly, we need parasite extinction to be possible in the system, i.e.

$$a(\alpha) = b + \frac{q(\gamma + b)}{\beta} + \frac{q}{\beta}\alpha \tag{2.24}$$

must be satisfied for at least one real and positive α, otherwise the parasite is viable for every value of α as in Figure 2.4c. To derive the last condition, we notice that, under the assumption of a decreasing trade-off $a(\alpha)$, R_0 can be non monotonous with respect to α and the parasite can be not viable for both low and high values of tolerance (e.g. in Fig.2.4a). The selection gradient close to extinction boundary is given in (2.22) and is positive, therefore, parasite extinction can occur only for lower values of tolerance. Notice that extinction can happen only when parasite prevalence is locally monotonically decreasing with respect of α,

so it decreases as α decreases. Infection prevalence I is defined as

$$I = \frac{\overline{Y}}{\overline{X} + \overline{Y}} = \frac{q\left(\overline{X}_0 - \overline{X}\right)}{a + \alpha}. \tag{2.25}$$

Consequently, the derivative of I with respect of α is

$$\frac{dI}{d\alpha} = \frac{\left(a'(\alpha) - q\frac{d\overline{X}}{d\alpha}\right)(a(\alpha) + \alpha) - q(a'(\alpha) + 1)\left(\overline{X}_0 - \overline{X}\right)}{(a + \alpha)^2}, \tag{2.26}$$

which it is positive when

$$a'(\alpha) > \frac{\beta(a(\alpha) - b) + q\left(a(\alpha) - b - \gamma\right)}{\beta(\alpha + b) + q\Gamma}. \tag{2.27}$$

When we evaluate the right-hand side of (2.27) at (2.24), we get that the slope of the trade-off evaluated at the boundary has to be less than q/β, which is the ratio between host internal competition and the parasite transmission coefficient. To summarise, considering a trade-off that satisfies (2.23) for some α, parasite extinction is possible when (2.24) has at least one real and positive root where the slope of the trade-off function is less than q/β.

Notice that another consequence of the non-monotony of disease prevalence is that (2.24) may not have any real and positive roots and the disease does not die out for any values of α. Due to the trade-off between birth rate and tolerance, if the increase in reproduction is considerable the large susceptible inflow compensates the shortening of the infectious period and the disease persists despite tolerance decreasing.

We can give a graphical representation to the conditions for parasite extinction by plotting the right-hand side of (2.24), i.e. the thick line in Fig.2.5. Condition (2.23) is satisfied if a trade-off function is above the line for some value of α and condition (2.24) holds when the trade-off intersects it. Moreover, the slope of the line is q/β and if a trade-off function intersects it with a smaller gradient parasite extinction is possible. Choosing the trade-off function

$$a(\alpha) = a^* - \frac{a'(\alpha^*)^2}{a''(\alpha^*)}\left[1 - e^{\frac{a''(\alpha^*)}{a'(\alpha^*)}(\alpha - \alpha^*)}\right], \tag{2.28}$$

in Fig.2.5 we check if the conditions for extinction hold for different values of $a''(\alpha^*)$, namely the value of the second derivative of the trade off function evaluated at α^*.

Accordingly, the evolutionary outcomes of tolerance evolution can be observed in Fig.2.4. In the first two panels parasite extinction occurs through reduced tolerance, while in the third panel condition (2.27) is satisfied before evolution reaches the extinction boundary and the disease persists.

It can be noticed that in the first panel of Fig.2.4, extinction occurs for a narrower range of initial strategies than in the second panel. To quantify the range of initial strategies from which natural selection leads to parasite clearance, we define the basin of attraction of the extinction boundary as the difference between the extinction value of α that satisfies

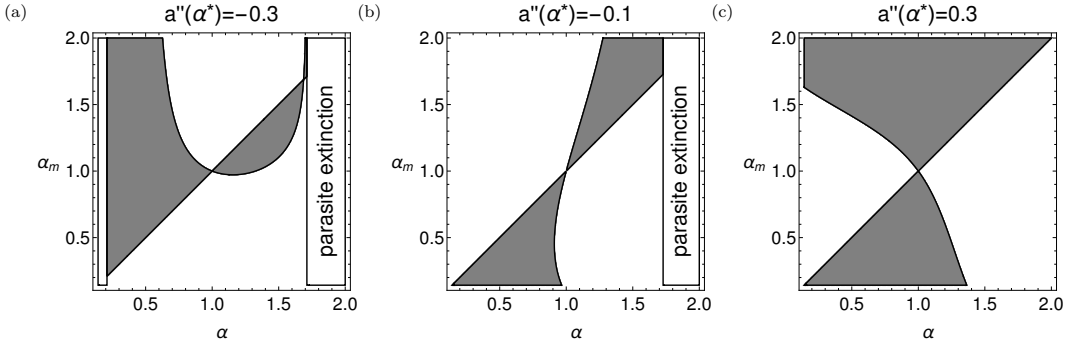

Figure 2.4: Pairwise invasibility plot for tolerance evolution with costs. In the α-α_m plane, $s_\alpha(\alpha, \alpha_m)$ is positive in correspondence with gray regions. The three panels are related to different values of the parameter $a''(\alpha^*)$ of the trade-off function $a(\alpha)$. $\alpha^* = 1; a(\alpha^*) = 1.5; a'(\alpha^*) = 0.049$.

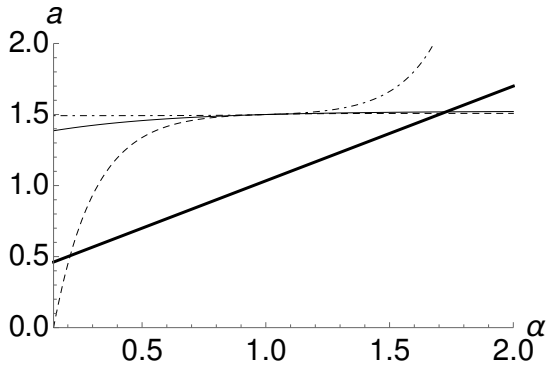

Figure 2.5: Conditions for parasite extinction. The thick line represents the RHS of (2.24) and the thin curves are plots of (2.23) for different values of $a''(\alpha^*)$. The parasite population is viable, when $a(\alpha)$ is above the thick line, and the extinction boundaries are at the cross between $a(\alpha)$ and the thick line. For $a''(\alpha^*) = -0.3$ (dashed curve) parasite are not viable for both high and low values of tolerance, for $a''(\alpha^*) = -0.1$ (continuous curve) parasite are not viable for low values of tolerance and for $a''(\alpha^*) = 0.5$ (dot-and-dashed curve) parasite are always viable. Parasite extinction can occur only for the higher value of α, since at the higher one the gradient of the trade-off is less than q/β. $\alpha^* = 1; a(\alpha^*) = 1.5; a'(\alpha^*) = 0.049$.

conditions (2.23), (2.24) and (2.27) and either the closest singular strategy, which is always a repeller, or 0 when there are not positive singular strategies. As it can be seen in Fig.2.6, extinction can occur for a wide range of choices of trade-off parameters $a'(\alpha^*)$ and $a''(\alpha^*)$ and different combinations of q and β. Particularly, extinction happens mostly for negative $a''(\alpha^*)$, i.e. for accelerating costs. For low values of $a'(\alpha^*)$, the basin of attraction is narrow due to a repeller strategy close to the boundary. When $a'(\alpha^*)$ increases the repeller strategy either disappears through a fold bifurcation (black curve in Fig.2.6) or its value decreases and the basin of attraction increases. Moreover, when q/β increases extinction occurs for a wider range of values with smaller basin of attraction due to a decrease in R_0 and an increase in the steepness of the bold line in Fig.2.5.

Numerical simulations (for details see section 2.2),where we relaxed the hypothesis of a timescale separation between evolutionary and ecological time, showed the occurrence of parasite extinction due to tolerance evolution. Furthermore, we questioned whether such

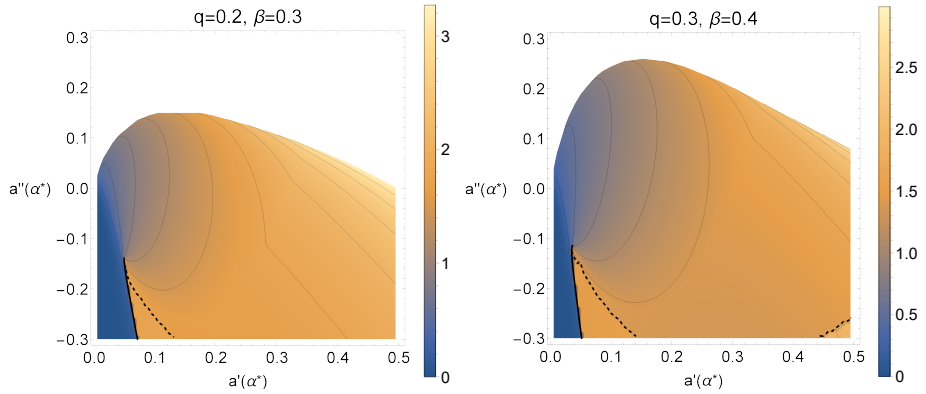

Figure 2.6: Density plots of the attraction basin of the extinction boundary as function of $a'(\alpha^*)$ and $a''(\alpha^*)$ for different values of q and β. The basin is measured as the difference between the value of α that satisfies conditions (2.23)-(2.24) and the closest singular strategy, which is an evolutionary repeller. In the white regions, equation (2.24) does not have a real and positive solution and extinction cannot occur. The continuous black line marks a discontinuity in the basin of attraction due to a fold bifurcation between two singular strategies. Below the dashed curves, there are not positive singular strategies and extinction occurs for every initial value of α. $\alpha^* = 1; a(\alpha^*) = 1.5.$

extinctions could still occur when the parasite is able to co-evolve its virulence strategy and gain faster transmission by increasing virulence. In this case, mortality under infection is the product of both the host and the parasite contribution, i.e. $\alpha = \alpha^H \alpha^P$. Running numerical simulations of the co-evolution of host tolerance and parasite virulence we found it easy to obtain examples where extinction did still occur (Fig.2.7a). Depending upon initial values, co-evolution can also lead to parasites avoiding extinction by lowering virulence as in Fig.2.7b.

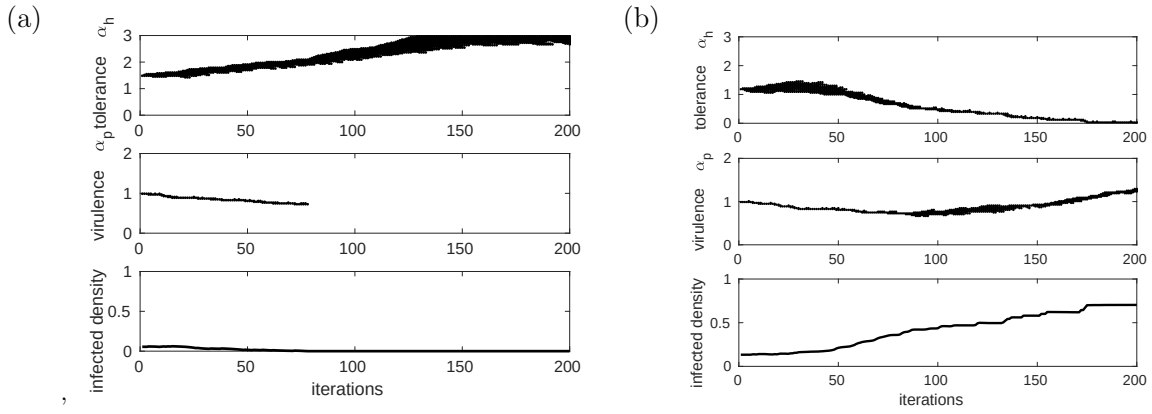

Figure 2.7: Numerical simulations of host-parasite co-evolution (for details see section 2.2) for two different initial values. Parasite virulence α^P is linked with disease transmission by the function $\beta(\alpha^P) = 0.3 - 0.05\left[1 - e^{-2(\alpha^P - 1)}\right]$.
$\alpha^* = 1; a(\alpha^*) = 1.5; a'(\alpha^*) = 0.049; a''(\alpha^*) = -0.1; n_P = 100; n_H = 100.$

2.3.3 Impact of fertility under infection

We show here that even when hosts reproduce while infected, parasite extinction through tolerance evolution can still occur. We assume that the reproduction rate of infected individuals is reduced by a coefficient f. Considering this hypothesis, the model is

$$\begin{aligned}\frac{dX}{dt} &= a(\alpha)\,(X + fY) - bX - q(X+Y)(X+fY) + \beta XY + \gamma Y \\ \frac{dY}{dt} &= \beta XY - (\alpha + b + \gamma)Y.\end{aligned} \tag{2.29}$$

The dynamics of (2.29) differs from the one of (2.1) as it can show more than one internal equilibrium. Here, we assume that the dynamics reaches a stable internal equilibrium $\left(\overline{X}, \overline{Y}\right)$, leaving the details to a more deepened study. The invasion fitness for a mutant strategy with tolerance α_m, calculated as in section 2.2, is:

$$\begin{aligned}s_\alpha(\alpha, \alpha_m) =& (\alpha_m + b + \gamma)\left[a(\alpha_m) - b - q\left(\overline{X} + \overline{Y}\right) - \beta\overline{Y}\right] \\ &+ \beta\overline{Y}\left[\gamma + a(\alpha_m)f - qf\left(\overline{X} + \overline{Y}\right)\right].\end{aligned} \tag{2.30}$$

Consequently, the selection gradient is

$$\left.\frac{\partial s_\alpha(\alpha, \alpha_m)}{\partial \alpha_m}\right|_{\alpha_m = \alpha} = -\left[a(\alpha) - b - q\left(\overline{X} + \overline{Y}\right) - \beta\overline{Y}\right] + a'(\alpha)(\alpha + b + \gamma)(1 + f), \tag{2.31}$$

which, taking the limit at the extinction boundary, becomes

$$\lim_{\substack{\overline{Y}\to 0 \\ \overline{X}\to \overline{X}_0}} \left.\frac{\partial s_\alpha(\alpha, \alpha_m)}{\partial \alpha_m}\right|_{\alpha_m = \alpha} = a'(\alpha)(\alpha + b + \gamma)(1 + f) > 0 \tag{2.32}$$

as the reproduction rate is increasing with respect of α. Equation (2.32) shows that the selection gradient at the extinction boundary for low level of tolerance points towards the region of parasite extinction. Therefore, parasite extinction due to tolerance minimisation occurs also when infected individuals can reproduce. In fact, PIP in Fig.2.8 show a qualitatively similar behaviour as in Fig.2.4, despite f close to 1. Moreover, this behaviour is not affect also by lower values of the recovery rate.

2.4 Discussion

We analysed the possibility for parasite extinction due to the evolution of costly host defence and found that only tolerance can lead to deterministic host-driven parasite extinction. Interestingly, it is by lowering tolerance, and therefore suffering more damaging effects from infection, that eradication of the parasite occurs. To our knowledge, this is the first study to demonstrate this possibility through a dynamic evolutionary process. We have also recovered previously known results that hosts can eradicate the disease by evolving resistance

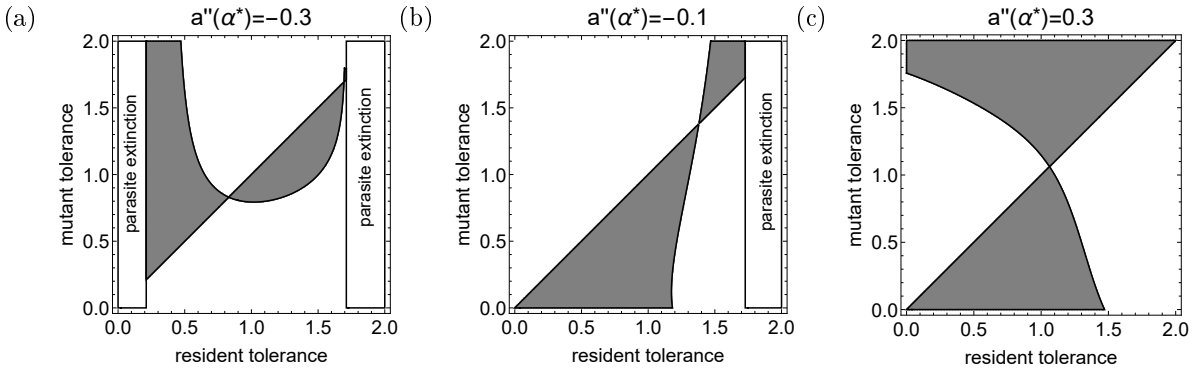

Figure 2.8: Pairwise invasibility plot for tolerance evolution with costs when infected hosts can reproduce. In the α-α_m plane, $s_\alpha(\alpha, \alpha_m)$ is positive in correspondence with gray regions. The three panels are related to different values of the parameter $a''(\alpha^*)$ of the trade-off function $a(\alpha)$. $\alpha^* = 1; a(\alpha^*) = 1.5; a'(\alpha^*) = 0.049; f = 0.8$.

mechanism if costs are not present (Antonovics and Thrall, 1994), but that eradication of infection is impossible through costly resistance since selection for resistance always vanishes before parasite extinction (Roy and Kirchner, 2000). Our work not only identifies a potential route for host-driven parasite extinction but also further highlights the crucial distinction between resistance and tolerance mechanisms.

An important question that arises is whether such host-driven extinctions are possible in natural systems. Experimental studies of coevolutionary bacteria-phage interactions have found that phage can be driven to extinction through the evolution of host resistance when the pathogen is subjected to some external pressure, for example population bottlenecks (Hesse and Buckling, 2016) or reduced resource availability (Zhang and Buckling, 2016). Interestingly, a similar result has been predicted theoretically by Hoyle et al. (2012), where it was found that the presence of a predator species adds environmental pressure on the parasite that can lead to parasite extinction. Moreover, we have shown that the presence of costs is a necessary conditions for parasite extinction to occur when tolerance evolves. Since our general understanding on the mechanisms behind tolerance is still limited, there is still few evidence for such a trade-off (Jackson et al., 2014; Kutzer and Armitage, 2016). Further experimental work is required to determine whether the evolution of tolerance mechanisms can lead to extinction in the absence of external pressures as we have predicted here.

Questioning if parasite extinction would be possible requires understanding whether selection could promote the lowering of tolerance in an already tolerant population. A few potential routes can be hypothesized. Firstly, tolerance that has evolved due to exposure to different pathogens in the past could be lost due to different selection pressures from a novel pathogen. Evidence of such a change has been found by Ayres and Schneider (2008), where a single gene was found lowering tolerance in Drosophila according to different microbial challenge. Secondly, the concept of "behavioural tolerance" has been described by Sears et al. (2013) and Adelman and Hawley (2017). In this case organisms may evolve behavioural adaptations to face infection, like anorexia or lethargy, that increase the severity of disease symptoms. Similarly there is the potential for hosts to evolve immunopathological

responses (Read et al., 2008; Medzhitov et al., 2012), whereby the host immune response inflicts damage to infected hosts, and can in some sense be seen as the opposite side of the coin to tolerance. There continues to be much interest in exploring tolerance mechanisms across a range of host-pathogen interactions (Råberg, 2014; Kutzer and Armitage, 2016; Soares et al., 2017).

Previous evolutionary studies on tolerance focused either on the changing of the optimal evolutionary strategy according to environmental gradients or on the possibility of speciation through evolutionary branching (Restif and Koella, 2003; Miller et al., 2005, 2007; Best et al., 2008, 2014). These have generally reinforced the distinction that resistance mechanisms produce a negative feedback to prevalence to evolution while tolerance mechanisms produce a positive feedback. Here we have shown that, under certain trade-off shapes, prevalence can in fact increase as tolerance is lowered, while it always decreases in absence of costs. The key to this result is in including costs in to our understanding of ecological feedbacks. This trend occurs when the increase in reproduction rate for lower values of tolerance is large enough to compensate for the decrease in the infectious period. Therefore, if costs play an important role, there will be cases where high parasite density does not relate to high tolerance, as we would expect given the traditional theory on tolerance (Boots and Bowers, 1999; Roy and Kirchner, 2000). Another example of non-monotonous relation between tolerance and disease prevalence can be observed in Miller et al. (2006). This may be in contradiction with the assumption that tolerance should increase parasite prevalence (Read et al., 2008; Kutzer and Armitage, 2016). We suggest that long-term evolutionary studies that include data on population densities are vital for fully understanding the potential evolutionary outcomes, including the potential for pathogen extinction.

It is interesting to note that the mechanism for parasite extinction occurs such that selection starts to promote traits that at the individual level worsen the possibility of mortality under infection. In this sense we see a paradox when the gain at the population level (reduced prevalence and ultimately disease eradication) is achieved by a loss at the individual level (increased mortality) in favour of reproduction. Conceptually, this phenomena is reminiscent of evolutionary suicide, which is the catastrophic extinction of a population caused by natural selection (Parvinen, 2005; Ferrière et al., 2009). One of the possible routes to evolutionary suicide occurs when natural selection favours a trait - like prey timidity (Matsuda and Abrams, 1994) or "the tragedy of the commons" (Hardin, 1968), virulence for parasite (Boldin and Kisdi, 2016)- that is beneficial for the individual but in the long term reduces the population reproductive rate under the threshold of viability. Naively, it appears that here we see the opposite case. However, it is important to note that across both the increased mortality and increased reproduction, lowered tolerance is still beneficial for the individual's fitness.

A future development of this study would be to investigate the robustness of extinction against parasite counter-adaptation of virulence. Preliminary simulations showed that both parasite extinction and parasite survival are possible outcomes when higher virulence

is linked with faster transmission. It is worth noting that as the parasite population declines due to host evolution, its relative mutation rate will slow, limiting its co-evolutionary response. However, it has been shown theoretically that selection for tolerance might promote an increase in virulence by lowering its cost when virulence is linked with an advantage in pathogen replication or transmission (Miller et al., 2006; Best et al., 2014). This result explains why tolerance could impose selection upon parasites without lowering their prevalence and igniting the co-evolutionary arms race typical of resistance (van Baalen, 1998). When tolerance decreases we might therefore expect a reduction in transmission rate (Restif and Koella, 2003), which would increase the chances of extinction, or a reduction in virulence (Miller et al., 2006), which would decrease the extinction risk. Moreover, co-evolution might end in forms of commensalism. This poses an additional challenge in discerning the effects of host tolerance and parasite virulence in experimental work in a way that (Little et al., 2010) detected as the problem of intimacy. Another possible expansion of this model would be to add a recovery class. It is likely that parasite extinction would still occurs due to the reduction of the susceptible class.

The gap between the theoretical dichotomy of resistance and tolerance and the complexity of experimental results is still wide. In the theoretical framework, tolerance and resistance are clearly defined as distinct and predicted to lead to different evolutionary consequences. In experimental studies, even when it is possible to distinguish among the two traits it is still challenging to unravel all the implication of their interplay. While some studies found a trade off between tolerance and resistance (Råberg, 2014), others suggest a more complementary dynamics, as tolerance contributes to reducing the effects on tissues caused by resistance mechanisms (Medzhitov et al., 2012; Soares et al., 2017). Filling this gap would be beneficial for both theoretical and experimental development. A better understanding of the mechanisms behind tolerance would improve the reliability of evolutionary models that in return could facilitate the design of experimental studies. In this sense, the aim of this work is to further highlighted the crucial role that host tolerance may play in host-parasite systems, and as such it is vital that modellers and empiricists identify avenues for further research with closer integration.

Chapter 3

The impact of selective predation on host-parasite SIS dynamics

3.1 Introduction

Parasites can be an important factor in shaping host ecology and evolution (Schmid-Hempel, 2011). Consequently, a rich class of mathematical models has been developed in the past decades in the attempt to unravel the implications of host-parasite interactions (Kermack and McKendrick, 1927; Anderson and May, 1981; Keeling and Rohani, 2007; Diekmann et al., 2012). Nevertheless, host-parasite interactions occur in an environment that can alter them and be altered by them (Betts et al., 2016). Thus, it is essential that we incorporate host ecology in epidemiological models (Morand and Gonzalez, 1997; Collinge and Ray, 2006; Betts et al., 2016). Hosts will experience an array of different community interactions within a particular ecosystem that we could account for. This work focuses on the ecological implication of a predator species that feeds upon both healthy and infected hosts.

Considering a predator species in a host-parasite system can lead to interesting and sometime counter-intuitive results due to the interplay of both direct effect on host demography and indirect effects on the host-parasite dynamics. As an example, Packer et al. (2003) formulated the 'healthy herd' hypothesis, namely that predators might be beneficial for their prey in the presence of an endemic disease, as a possible explanation for the observed trend (Sih et al., 1985; Hudson et al., 1992) of decreasing prey density after predator removal. Specifically, Packer suggested that by removing infected individuals, predation shortens the lifespan under infection and reduces infection prevalence. Furthermore, if predators select specifically for infected individuals, as they might be easier to catch, this can even lead to an increased total prey density compared to the host-parasite case. Later studies (Duffy et al., 2005) provided some empirical support for Packer's hypothesis, but see Duffy (2007), Duffy et al. (2011) and Malek and Byers (2016). Moreover, further theoretical work derived some potential constraints like host heterogeneity (Williams, 2008; Su and Hui, 2011) or acquired immunity (Holt and Roy, 2007; Roy and Holt, 2008) on the indirect benefits of a predator species.

Predator selectivity, meaning predator preference towards either infected or susceptible prey, plays an important role on the effects of predation. Infected individuals can be preferable because infection makes them easier to catch; as an example, bacterial infections of *Daphnia* turn this zoo-plankton from transparent to pale (Duffy et al., 2005). Also, prey behaviour under infection might change in favour of predation, e.g. several species of fish have been found closer to the sea surface when infected (Chattopadhyay and Bairagi, 2001). Altogether, a combination of infection symptoms and prey altered behaviour can determine an increased selection for infected prey (Hudson et al., 1992). Conversely, there are cases where predators select for healthy prey (Haque and Greenhalgh, 2010) or there is no preference at all (Malek and Byers, 2016). Thus, while selectivity towards infected prey can be a common pattern, other cases should be also considered.

We adopted a SIS system with density-dependent host birth rate to model host-parasite interactions and introduced a specialist predator with a linear functional response. These choices allow a complete analysis of the system behaviour and a full exploration of the parameter space related to the possible long-term outcomes. Morevoer, this model is easily comparable with previous theoretical studies as Packer et al. (2003) and Hethcote et al. (2004). Nevertheless, there are few differences with Packer et al. (2003) as here host growth rate is density-dependent, infected individuals do not reproduce and predator density is a dynamical variable, which depends upon the state of the system. We let predator selectivity vary from infected prey to susceptible ones. This choice allowed us to notice interesting patterns of bistability when predators feed mostly on healthy prey and to generalise some results of Packer et al. (2003) to the case of a specialist predator species. Moreover, we performed a bifurcation analysis to study the transitions between different asymptotic behaviours.

3.2 Model

We will begin by briefly discussing the host-parasite and host-predator models in subsections 3.2.1 and 3.2.2 then we introduce the full model in subsection 3.2.3. All parameter definitions are summarised in Table 3.1 and all equilibria coordinates are given in Table 3.2.

3.2.1 Host-parasite dynamics

To model host-parasite dynamics, we consider a Susceptible-Infected-Susceptible (SIS) model (Boots and Haraguchi, 1999) where the infected hosts can recover and return in the susceptible class. The system for susceptible X and infected Y densities is

$$\begin{aligned}\frac{dX}{dt} &= (a-b)X - q(X+Y)X + \gamma Y - \beta XY \\ \frac{dY}{dt} &= \beta XY - \Gamma Y.\end{aligned}$$

	Definition	Dimension	Default value
a	Susceptible per capita birth rate	$1/t$	2
b	Intrinsic prey per capita mortality rate	$1/t$	0.1
q	Impact of competition on prey birth rate	$1/(t{\cdot}pop.density)$	0.7
β	Infection transmission coefficient	$1/(t{\cdot}pop.density)$	0.8
γ	Per capita recovery rate	$1/t$	0.2
α	Disease-induced per capita mortality rate, virulence	$1/t$	0.1
c	Predator capture coefficient	$1/(t{\cdot}pop.density)$	0.2
ϕ	Predator selectivity		0.4
θ	Predator conversion coefficient		0.6
d	Predator per capita death rate	$1/t$	0.4

Table 3.1: Definition of model parameters

with $\Gamma = b + \alpha + \gamma$. The prey dynamics obey logistic growth in the absence of the disease with crowding and internal competition impacting on reproduction. The force of infection is density-dependent, infected individuals do not reproduce and suffer from additional disease-induced mortality (virulence). The analysis of a more general version of this model can be found in Zhou and Hethcote (1994).

There are three possible equilibria, the extinction $E_0 = (0, 0)$, the prey-only $E_1 = (X_1, 0)$ and the host-parasite co-existence $E_2 = (X_2, Y_2)$ (see Table 3.2 for full coordinates). The prey-only equilibrium is positive if the prey birth rate is larger than the death rate and host-parasite co-existence is possible if

$$R_{0I} = \frac{\beta X_1}{\Gamma} = \frac{X_1}{X_2} > 1.$$

R_{0I} is called the basic reproduction number of the infection and it represents the number of secondary cases caused by an infected individual in a disease-free population during its whole lifetime (Diekmann et al., 1990). The X-axis is an invariant set and trajectories starting from it converge to E_0 when the prey population is not viable and to E_1 when it is. Trajectories starting on the Y-axis enter the quadrant $\mathbb{R}^+_2$, therefore, $\mathbb{R}^+_2$ is an invariant set. Trajectories that start from the interior of $\mathbb{R}^+_2$ converge to E_1 when $R_0 \leq 1$ and to E_2 when $R_0 > 1$. Specifically, E_2 is globally asymptotically stable when $R_0 > 1$.

It is possible to prove the global stability of E_2 by adapting the Lyapunov function commonly used for Lotka-Volterra systems (Takeuchi, 1996). Explicitly, we choose the coefficients for the function

$$V(X, Y) = X - X_2 - X_2 \ln \frac{X}{X_2} + \left(1 - \frac{\gamma}{\Gamma} + \frac{q}{\beta}\right)\left(Y - Y_2 - Y_2 \ln \frac{Y}{Y_2}\right), \tag{3.1}$$

such that (3.1) is well-defined when $R_0 > 1$ and the mixed terms in X and Y disappear when deriving it along the trajectories. The derivative of (3.1) along the trajectories in the

Equilibrium	Coordinates	Details	Description
E_0	$(0,0,0)$		extinction
E_1	$(X_1,0,0)$	$X_1=\dfrac{a-b}{q}$	prey-only
E_2	$(X_2,Y_2,0)$	$X_2=\dfrac{\Gamma}{\beta}\quad Y_2=\dfrac{q(X_1-X_2)}{q+\beta\left(1-\frac{\gamma}{\Gamma}\right)}$	host-parasite co-existence
E_3	$(X_3,0,P_3)$	$X_3=\dfrac{d}{\phi\theta c}\quad P_3=\dfrac{q}{\phi c}(X_1-X_3)$	predator-prey co-existence
E_4	(X_4,Y_4,P_4)	$X_4=\dfrac{B+\sqrt{\Delta}}{2q(\Phi-1)}$ $Y_4=\dfrac{1}{\Phi}(X_3-X_4)$ $P_4=\dfrac{\beta(X_4-X_2)}{(1-\phi)c}$	host-parasite and predator co-existence
E_5	(X_5,Y_5,P_5)	$X_5=\dfrac{B-\sqrt{\Delta}}{2q(\Phi-1)}$ $Y_5=\dfrac{1}{\Phi}(X_3-X_5)$ $P_5=\dfrac{\beta(X_5-X_2)}{(1-\phi)c}$	host-parasite and predator co-existence

$\Gamma=\alpha+b+\gamma$, $\Phi=(1-\phi)/\phi$, $B=\Phi qX_1+\alpha+b-X_3(q+\beta)$, and $\Delta=B^2+4\gamma qX_3(\Phi-1)$

Table 3.2: Summary of all the possible equilibria of system (3.2)

interior of $\mathbb{R}^+_2$ (Teschl, 2010) is

$$\begin{aligned}\frac{dV}{dt}(X(t),Y(t)) =&(X-X_2)\left[a-b-q(X+Y)-\beta Y+\gamma\tfrac{Y}{X}\right]+\left(1-\tfrac{\gamma}{\Gamma}+\tfrac{q}{\beta}\right)(Y-Y_2)(\beta X-\Gamma)\\ =&-q(X-X_2)^2+\frac{\gamma}{XX_2}(YX_2-Y_2X+XY-XY)(X-X_2)\\ &-\frac{\gamma}{X_2}(Y-Y_2)(X-X_2)=-\left(q+\frac{\gamma Y}{XX_2}\right)(X-X_2)^2\leq 0.\end{aligned}$$

The only invariant set on the line $X=X_2$ is E_2, therefore, by LaSalle's invariant principle, all the trajectories in the interior of $\mathbb{R}^+_2$ converge to E_2.

3.2.2 Prey-Predator dynamics

Regarding the infection-free dynamics, we model a specialist predator P that feeds on a prey population X following mass-action

$$\begin{aligned}\frac{dX}{dt}&=(a-b-qX-cP)X\\ \frac{dP}{dt}&=(\theta c\phi X-d)P.\end{aligned}$$

This is a generalised Lotka-Volterra system with a well-studied asymptotical behaviour (Takeuchi, 1996). In addition on the same boundary equilibria as the host-parasite system, $(0,0)$ and $(X_1,0)$, the system shows a prey-predator co-existence equilibrium (X_3,P_3) that is globally asymptotically stable when positive.

3.2.3 Host-Parasite-Predator Model

To merge the two systems, we introduce the coefficient ϕ that quantifies predator selectivity towards susceptible or infected prey. Specifically, when $\phi > 1/2$ predators capture relatively more susceptible prey, at $\phi = 1/2$ predators do not select prey type and when $\phi < 1/2$ infected prey are preferred. Notice that this modelling choice might not represent an optimal strategy for the predator feeding behaviour, as it favours one kind of prey at time regardless its quality (for alternative choices of the predator functional response see van Baalen et al. (2001)). Nevertheless, it allows for the comparison with previous models as Hethcote et al. (2004) and Haque and Greenhalgh (2010), where selection is fixed on one kind of prey, and to track changes in solution behaviour as predators preference varies continuously from infected to susceptible prey. Under this hypothesis, the full model is

$$\begin{aligned}
\frac{dX}{dt} &= (a-b)\,X - q(X+Y)X - \beta XY + \gamma Y - \phi c X P \\
\frac{dY}{dt} &= \beta XY - \Gamma Y - (1-\phi) c Y P \\
\frac{dP}{dt} &= \theta c\left[\phi X + (1-\phi)Y\right] P - dP.
\end{aligned} \tag{3.2}$$

Boundary equilibria

The full system presents four boundary equilibria: the all-population extinction E_0, prey-only survival E_1, host-parasite co-existence E_2, predator-prey co-existence E_3. Assuming that the prey-only population is viable, E_0 is always unstable in the X direction. E_1 is unstable in the Y direction if $R_{0I} > 1$ and in the P direction if

$$R_{0P} = \frac{\phi\theta c X_1}{d} = \frac{X_1}{X_3} > 1.$$

The dynamics on the X-Y plane are analogous to the SIS one, with the addition that E_2 becomes unstable in the P direction if

$$R_P = \frac{X_2 + \Phi Y_2}{X_3} > 1,$$

with $\Phi = (1-\phi)/\phi$. Similarly, the behaviour in the X-P plane follows the prey-predator model. E_3 is positive and stable in the X and P directions if $R_{0P} > 1$ and unstable in the Y direction if

$$R_I = \frac{\beta X_3}{\Gamma + \Phi q\,(X_1 - X_3)} > 1.$$

Trajectories that start in the Y-P plane leave it to enter the octant $\mathbb{R}^+_3$. Notice that, following Hilker and Schmitz (2008), R_{0P}, R_I and R_P can be interpreted similarly to R_0 as the average numbers of offspring (or secondary infection) due to a single individual in a virgin environment.

Internal equilibria

In addition to the boundary equilibria, the full system can show up to two equilibria (E_4 and E_5) in the interior of $\mathbb{R}^+_3$, with X-coordinates solutions of

$$q(1-\Phi)X^2 + BX + \gamma X_3 = 0 \tag{3.3}$$

with $B = \Phi q X_1 + \alpha + b - X_3(q+\beta)$. When $\Phi > 1$, which implies $\phi < 1/2$, predators feed mainly on infected prey and only X_4 is positive. At $\Phi = 1$, there is only one real root that is either positive or negative depending on the sign of B. For $\Phi < 1$ ($\phi > 1/2$), both X_4 and X_5 are positive when $\Delta = B^2 + 4\gamma q X_3(\Phi - 1) > 0$ and $B < 0$. When $\Delta = 0$, X_4 and X_5 undergo a fold bifurcation at the value

$$X_{fold} = \sqrt{\frac{\gamma X_3}{q(1-\Phi)}}. \tag{3.4}$$

Additionally,regardless of the value of ϕ also $Y_{4,5}$ and $P_{4,5}$ have to be positive for E_4 and E_5 to be biologically acceptable, i.e.

$$X_2 < X_{4,5} < X_3. \tag{3.5}$$

This last condition implies that, despite predator selection, the susceptible density at E_4 is larger than in the host-parasite case. For parameter sets such that the susceptible density at the internal equilibrium is lower than at the host-parasite one, the total prey density is not large enough to sustain both the predator and the parasite. When the susceptible density at the internal equilibrium is higher than at the prey-predator one, the infection cannot persist in the system due to the high predation pressure. Notice that for (3.5) to be satisfied, it is necessary that

$$R_{0I} > R_{0P}. \tag{3.6}$$

Thus, the three populations can coexist only if the parasite is more efficient than the predator in colonising a host-only population. Indeed, similarly to Hethcote et al. (2004), if the predator is viable then $R_I < R_{0I}$, and it is more difficult for a parasite to invade the predator-prey equilibrium than the prey-only one. To see that $R_I < R_{0I}$ it is enough to

notice that since $R_{0P} > 1$ then $R_I > 0$ and

$$\begin{aligned} R_{0I} - R_I &= \beta \left[\frac{X_1}{\Gamma} - \frac{X_3}{\Gamma + \Phi q \left(X_1 - X_3 \right)} \right] \\ &= \beta \frac{\left(X_1 - X_3 \right) \left(\Gamma + \Phi q X_1 \right)}{\Gamma + \Phi q \left(X_1 - X_3 \right)} > 0. \end{aligned}$$

Local stability of the internal equilibria

The Jacobian matrix evaluated at $E_{4,5}$ is

$$J\left(X_{4,5}, Y_{4,5}, P_{4,5}\right) = \begin{pmatrix} -\gamma \dfrac{Y_{4,5}}{X_{4,5}} - q X_{4,5} & -(q+\beta) X_{4,5} + \gamma & -c\phi X_{4,5} \\ \beta Y_{4,5} & 0 & -c(1-\phi) Y_{4,5} \\ \theta \phi c P_{4,5} & \theta c (1-\phi) P_{4,5} & 0 \end{pmatrix}$$

with characteristic equation

$$\begin{aligned} p_J(\lambda) &= \lambda^3 + \left(\gamma \frac{Y_{4,5}}{X_{4,5}} + q X_{4,5} \right) \lambda^2 + \left\{ \beta Y_{4,5} \left[(q+\beta) X_{4,5} - \gamma \right] + c^2 \theta \phi^2 P_{4,5} \left(X_{4,5} + \Phi^2 Y_{4,5} \right) \right\} \lambda \\ &+ c^2 \theta (1-\phi) \phi Y_{4,5} P_{4,5} \left[\Phi \gamma \frac{Y_{4,5}}{X_{4,5}} + \left(\Phi - 1 \right) q X_{4,5} + \gamma \right] \\ &= \lambda^3 + \zeta_2 \lambda^2 + \zeta_1 \lambda + \zeta_0 = 0. \end{aligned} \tag{3.7}$$

To check the local stability of E_4 and E_5, we use the Routh-Hurwitz criterion, which states that $p_J(\lambda)$ has all roots with negative real part if and only if $\zeta_0 > 0$, $\zeta_2 > 0$ and $\zeta_2 \zeta_1 > \zeta_0$. Notice that ζ_2 and ζ_1 are positive since

$$X_{4,5} > X_2 > \frac{\gamma}{q+\beta}.$$

ζ_0 is clearly positive when $\Phi > 1$. The term of ζ_0 in square brackets can be rewritten as

$$\begin{aligned} \Phi \gamma \frac{Y_{4,5}}{X_{4,5}} + \left(\Phi - 1 \right) q X_{4,5} + \gamma &= \frac{1}{X_{4,5}} \left[\gamma \left(X_3 - X_{4,5} \right) + (\Phi - 1) q \left(X_{4,5} \right)^2 \right] \\ &= \frac{(1-\Phi) q}{X_{4,5}} \left[X_{fold}^2 - {X_{4,5}}^2 \right], \end{aligned}$$

with X_{fold} defined in (3.4). When $\Phi < 1$, the last term is positive for X_4, since $X_4 < X_{fold}$. Conversely, X_5 is larger than X_{fold} and ζ_0 is negative, which implies that E_5 is unstable. Moreover,

$$\zeta_2 \zeta_1 - \zeta_0 = \left(\gamma \tfrac{Y_{4,5}}{X_{4,5}} + q X_{4,5} \right) \beta Y_{4,5} \left[(q+\beta) X_{4,5} - \gamma \right] + c^2 \theta P_{4,5} \phi^2 \left[\gamma (1-\Phi) Y_{4,5} + q X_{4,5} X_3 \right] \tag{3.8}$$

is positive for $\Phi < 1$, implying that, when predators prefer susceptible prey, E_4 is locally stable. For $\Phi > 1$, we checked condition (3.8) numerically.

Region	Threshold criteria			Dynamical Attractor
1	$R_{0P} < 1$	$R_P < 1$		E_2 is globally stable
2	$R_{0P} < 1$	$R_P > 1$		E_4 is locally stable
3	$R_{0P} > 1$	$R_I < 1$	$R_P > 1$	E_3 is locally stable
3a	$\phi > 1/2$	$\Delta > 0$	$B < 0$	E_3 and E_4 are locally stable
4	$R_{0P} > 1$	$R_I > 1$	$R_P < 1$	E_2 is globally stable
5	$R_{0P} > 1$	$R_I > 1$	$R_P > 1$	E_4 is locally stable
6	$R_{0P} > 1$	$R_I < 1$	$R_P < 1$	E_2 and E_3 are locally stable

Table 3.3: Stability regions in the model parameter set

3.3 Results

We start by partitioning the parameter space according to the possible long-term ecological outcomes. In this process, we found interesting patterns of bi-stability, so far overlooked, when predators prefer susceptible prey. Then, we perform a bifurcation analysis to better understand transitions between different ecological scenarios, where we show that the 'healthy heard' hypothesis holds when considering a specialist predator species. Moreover, we found the occurrence of a hysteresis effect when varying predator death rate in order to control disease spreading.

3.3.1 Stability regions

In this section we explore the different regions in which the possible asymptotic behaviours of (3.2) divide the parameter space. Assuming that the prey species alone is viable ($a > b$), if the parasite cannot invade the prey-alone equilibrium ($R_{0I} < 1$) there are only two possible scenarios; either also the predator is not viable and all trajectories converge to the prey-only equilibrium or the predator is viable ($R_{0P} > 1$) and all trajectories converge to the prey-predator equilibrium E_3. Notice that in the latter case E_3 remains always locally stable when positive, because, as shown before, $R_{0P} > 1$ implies that $R_I < R_{0I}$, which is less than one. Moreover, any internal equilibria can have all positive coordinates since condition (3.6) is not satisfied.

We now focus our attention on the case where the parasite can invade the prey-only equilibrium, thus, we assume that E_2 is positive. Under this assumption, in our analysis we tracked seven possible asymptotic behaviours that are summarised in Table 3.3. In regions 1 and 4, the predator cannot survive and all trajectories converge to the prey-parasite equilibrium E_2. Global stability of E_2 can be proven by adapting Proof 4.2 of Hethcote et al. (2004).

In regions 2 and 5 all the boundary equilibria are unstable and E_4 is present in the interior of the octant $\mathbb{R}^+_3$. Similarly to Hethcote et al. (2004), in region 2 a predator species that can not survive with a population of only healthy prey is kept alive by the presence of the parasite. Notice that this case occurs only when predators feed mainly on infected prey.

In regions 3 (and 3a), E_3 is locally stable. If also $\phi < 1/2$ and $\Delta > 0$, the two internal

equilibria are present. In region 3a, a parasite that would not be able to invade the prey-predator equilibrium starting from a low density can still be present in the system at high density at the stable internal equilibrium, where predator density is lower than in the prey-predator case. In region 6, both E_2 and E_3 are locally stable and E_5 is positive and unstable. Here, both the parasite and the predator species are able to invade the prey-only equilibrium but prey densities at the two stable boundary equilibria are too low for the other species to invade. Thus, the asymptotic dynamics depend upon which of the two equilibria a trajectory approaches first. Therefore, there are two possible cases of bistability: between E_3 and E_4 (Case 3a) and between E_2 and E_3 (Case 6).

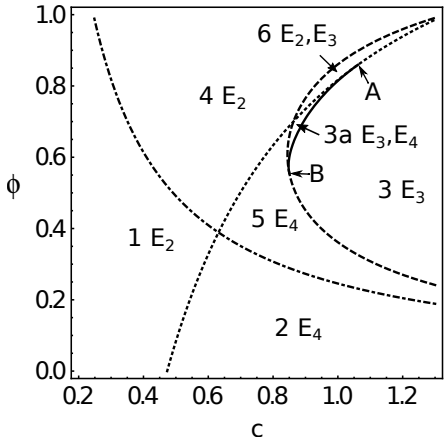

Figure 3.1: Bifurcation lines in the c-ϕ plane. The dot-and-dashed line represents the transcritical bifurcation between E_1 and E_3. The dotted line marks a transcritical bifurcation between E_2 and an internal equilibrium when $R_P = 1$. On the dashed curve, a transcritical bifurcation occurs between E_3 and an internal equilibrium as $R_I = 1$. On the continuous curve the two internal equilibria undergo through a fold bifurcation. Point A and B mark where the fold bifurcation line intersects the transcritical ones. For each region, the number label follows the classification in Table 3.3 and the stable equilibria are listed. Parameter values are listed in Table 3.1

Clearly, there is an evident connection between the regions created by the combinations of R_{0I}, R_{0P}, R_I and R_P and the number of solutions of (3.3). It is a bit less immediate to see where the relation lies analytically. To undercover it, we firstly name the left-hand side of (3.3) as $\pi(x)$. $\pi(x)$ is an downward-opening parabola when $\phi < 1/2$ and an upward-opening one otherwise. Then, we notice that condition (3.5) corresponds to the requirement that the roots of $\pi(x)$ belong to the interval between X_2 and X_3. When $\pi(x)$ is evaluated at X_2, it can be re-written as

$$\pi(X_2) = X_3 \left(X_2 + \alpha + b\right)\left(R_P - 1\right),$$

thus, it is positive if $R_P > 1$, while

$$\begin{aligned}\pi(X_3) &= X_3 \left[\Phi q \left(X_1 - X_3\right) + \beta \left(X_2 - X_3\right)\right] \\ &= X_3 \left[\Phi q \left(X_1 - X_3\right) + \beta X_2\right]\left(1 - R_I\right).\end{aligned}$$

Now, it is easier to see that in regions 2 and 5, E_4 is positive. More specifically, in region 2 the parabola is downward-opening since $\Phi > 1$. In fact,

$$R_P = \frac{X_2 + \Phi Y_I}{X_3} > 1 \Rightarrow \Phi > \frac{X_3 - X_2}{Y_2}$$

and

$$\begin{aligned}\frac{X_3 - X_2}{Y_2} &= \frac{X_3 - X_2}{X_1 - X_2}\frac{q + \beta\left(1 - \frac{\gamma}{\Gamma}\right)}{q} \\ &\geq \frac{X_3 - X_2}{X_1 - X_2} = \frac{X_3 - X_1 + X_1 - X_2}{X_1 - X_2} \\ &= \frac{X_3(1 - R_{0P})}{X_2(R_{0I} - 1)} + 1 \geq 1\end{aligned}$$

because $R_{0P} < 1$ and $R_{0I} > 1$. In this region $\pi(X_2)$ is positive and $\pi(X_3)$ is negative, thus, X_4 is in the interval of condition (3.5) (see Fig.3.2a) and E_4 has all positive coordinates. Similarly, this happens in region 5 since $\pi(x)$ still assumes values of opposite sign at the border and X_4 remains in the interval. With the same reasoning, it can be proven the existence of E_5 in region 6 as shown in Fig.3.2b. Notice that in region 3, $\pi(x)$ is upward-opening with positive values at the extremes, therefore, additional conditions are required to discern when (3.3) has two (Fig.3.2c), one or zero solutions (Fig.3.2d).

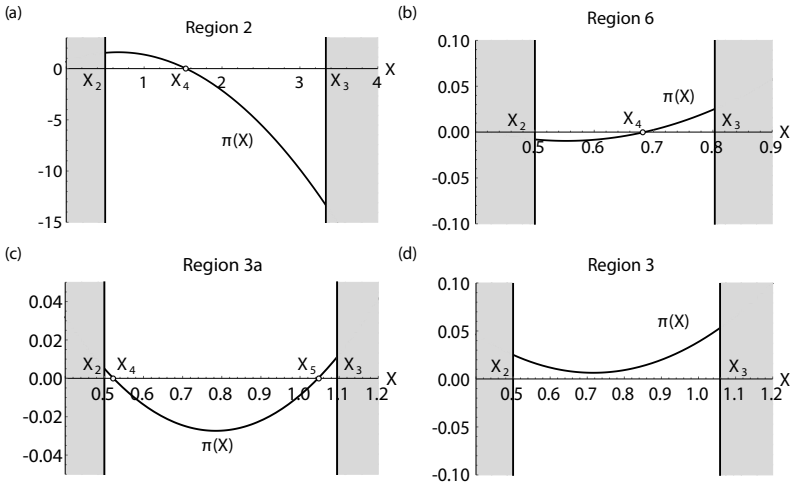

Figure 3.2: Plots of $\pi(x)$ in the different stability regions. The grey regions mark the interval outside condition (3.5). In (a) $c = 1$ and $\phi = 0.2$, in (b) $c = 1$ and $\phi = 0.83$, in (c) $c = 0.87$ and $\phi = 0.7$, and in (d) $c = 0.9$ and $\phi = 0.7$

3.3.2 A numerical example of fold bifurcation

We can observe the transitions among the seven different asymptotic behaviours listed in the previous subsection by looking at numerical examples in Fig.3.1 and Fig.3.3. In Fig.3.1, the seven stability regions are shown as functions of ϕ and c, while, in Fig.3.3, ϕ assumes fixed values near the fold bifurcation region and the panels show how susceptible density

changes as a function of c. Again, we assume $a > b$ and $R_{0I} > 1$, i.e., E_0 is always unstable and E_1 and E_2 are positive for every value of c and ϕ. In Fig.3.1, the dot-and-dashed line marks the transcritical bifurcation in the X-P plane between E_1 and E_3. The dotted line marks where $R_P = 1$ and a transcritical bifurcation occurs between E_2 and an internal equilibrium. Analogously, on the dashed curve, a transcritical bifurcation occurs between E_3 and an internal equilibrium when $R_I = 1$. The thick curve marks where $\Delta = 0$ and a fold bifurcation occurs between the two internal equilibria.

We used theorem 4.1 of Castillo-Chávez and Song (2004) to determine the local direction of the transcritical bifurcations along the curves $R_P = 1$ and $R_I = 1$. Particularity, the aim is to discern whether a transcritical bifurcation is backward, meaning that the branch of internal equilibria is on the same side of the stable branch of the boundary equilibria with respect of the bifurcation point (as occurs in both bifurcations showed in Fig.2.3c). We will explain later why such a case has interesting implications in terms of disease control. We analyse first the transcritical bifurcation occurring between E_2 and an internal equilibrium when $R_P = 1$ taking c as bifurcation parameter. The value of c is assumed fixed such that $R_P = 1$. In order to distinguish between a forward or a backward bifurcation, we need to compute the quantities

$$\tilde{a} = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(X_2, Y_2, 0)$$
$$\tilde{b} = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial c}(X_2, Y_2, 0)$$

where v and w are respectively the left and right eigenvectors corresponding to the zero eigenvalue of $J(X_2, Y_2, 0)$, f represents the right-hand-side of (3.2) and x are the system coordinates. We added a tilde to the original paper notation to not confuse $\tilde{a}$ and $\tilde{b}$ with the prey birth and death parameters. In our system,

$$v = \begin{bmatrix} 0 \\ 0 \\ \frac{1}{w_3} \end{bmatrix}, \quad w = \begin{bmatrix} \frac{c(1-\phi)}{\beta} w_3 \\ \frac{c}{\gamma-(q+\beta)X_2}\left[\phi X_2 + \left(\gamma\frac{X_2}{Y_2} + qX_2\right)\frac{(1-\phi)}{\beta}\right] w_3 \\ w_3 \end{bmatrix}$$

and w_3 can be chosen arbitrarily, e.g. $w_3 = 1$. It follows that

$$\begin{aligned} \tilde{b} &= v_3 w_3 \theta c Y_2 = \theta[\phi X_I + (1-\phi)Y_2] > 0 \\ \tilde{a} &= 2v_3\theta c[w_1 w_3 + \phi w_2 w_3] = 2\theta c(w_1 + \phi w_2) \\ &= \frac{c(1-\phi)}{\beta X_2} \frac{(1-\phi)(\gamma Y_2 + qX_2^2) + \phi X_2(\gamma - qX_2)}{\gamma - (q+\beta)X_2}. \end{aligned}$$

Thus, according with Castillo-Chávez and Song (2004) the transcritical bifurcation is forward

on the curve $R_P = 1$, when $\tilde{a} < 0$, i.e.

$$\phi < \frac{qX_2^2 + \gamma Y_2}{2qX_2^2 + \gamma(Y_2 - X_2)} = \bar{\phi},$$

and backward (Fig.3.3d) for $\phi > \bar{\phi}$.

Similarly, on the curve $R_I = 1$, $\tilde{b} < 0$ and the transcritical bifurcation is backward for decreasing c up to

$$\bar{\Phi} = \frac{-(\Gamma + \gamma - qX_1) + \sqrt{(\Gamma + \gamma - qX_1)^2 - 4X_1(\gamma\beta - q\Gamma)}}{2qX_1},$$

and forward for decreasing c for higher values of Φ (lower values of ϕ).

It is possible to observe these transitions in Fig.3.1, where the transcritical bifurcation is forward (E_2 loses stability and E_4 becomes positive) on the curve $R_P = 1$ up to point A and backward (E_2 loses stability and E_5 becomes negative) for higher values of ϕ. On the curve $R_I = 1$, E_3 gains stability at the transcritical bifurcation. For values of ϕ lower than point B, E_4 becomes negative at the bifurcation, while for higher ϕ E_5 becomes positive. Therefore, the two internal equilibria are both present in the region between the two transcritical curves and the fold bifurcation (region 3a in Fig.3.1).

Starting from region 4 at intermediate values of ϕ (Fig.3.3a), E_2 is stable and E_3 is unstable. Moving to region 5 as c increases, E_2 looses its stability and E_4 enters the octant $\mathbb{R}^+_3$. From region 5 to region 3, E_4 undergoes a transcritical bifurcation with E_3 that becomes locally stable. For higher ϕ (Fig.3.3b), from region 5 the dynamics enters region 3a, where E_3 acquires stability through the transcritical bifurcation with E_5 leading to bi-stability between E_4 and E_3. For higher c, E_4 and E_5 rapidly disappear due to the fold bifurcation, leaving E_3 as the only stable equilibrium (region 3).

For higher ϕ (Fig.3.3c and Fig.3.3d), from region 4 to region 6, E_3 gains local stability and E_5 enters the octant $\mathbb{R}^+_3$. E_5 disappears either through the fold bifurcation with E_4, which becomes positive in region 3a due to the forward transcritical bifurcation with E_2, as in Fig.3.3c or because of the backward transcritical bifurcation with E_2 (region 6 to 3) as in Fig.3.3d.

Bi-stability regions are possible when the unstable equilibria E_5 has positive coordinates, that is when $\phi < 1/2$ and predators favour susceptible preys. Moreover,E_5 is in the positive octant for intermediate values of c since, for lower values predators do not feed enough to survive and for higher values, infected prey do not live long enough to spread the disease. As expected, bi-stability is impossible for $\phi > 1/2$ because susceptible density X_5 of E_5 is negative. Interestingly, susceptible density at the unstable internal equilibrium is negative even though predators favour infected prey.

Notice that, when c increases X_4 increases from X_2 to X_3 and, conversely, disease prevalence decreases to 0 (result not shown). Thus, the combination of these two effects give rise to non-monotonic shape of the total prey density as function of c, as can be seen in

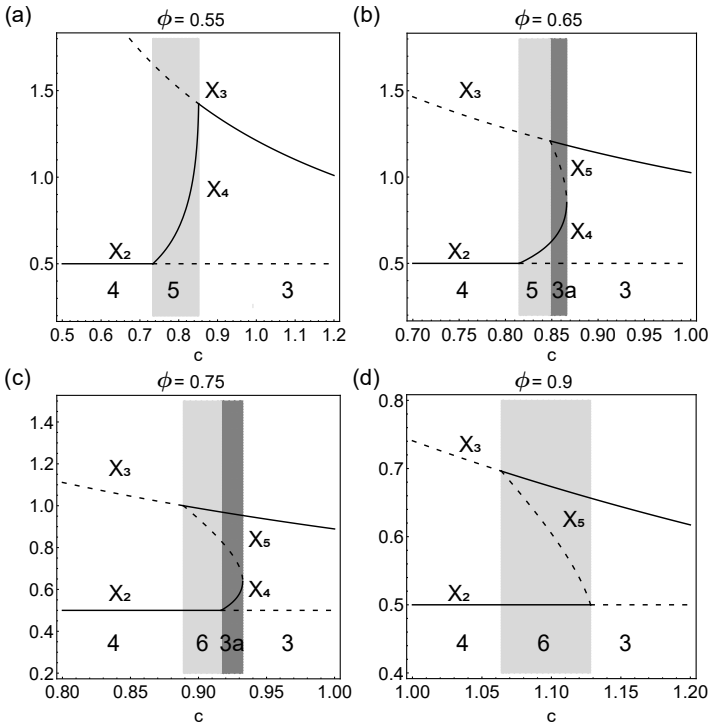

Figure 3.3: In the four panels the values of the variable X of all the positive equilibria are plotted as function of c for different values of ϕ. The continuous line is used for locally stable equilibria while the dashed one is used for unstable equilibria. The different shading and the related numbers at the bottom mark the different cases listed in subsection 3.3. Fixed parameter values are listed in Table 3.1

Fig.3.4. In particular, we see that when selective predation to infected prey is relatively strong (Fig.3.4a), the total prey density can be greater when the predator is present in the host-parasite system than when it is absent, fitting with the 'healthy herd' hypothesis. The more selection is towards infected, the more the non-monotonicity is emphasised. When predators feed mainly on susceptible prey (ϕ> 1/2), the total population density decreases with increased attack rate (Fig.3.4c and Fig.3.4d). The presence of backward bifurcations plays an important role when calculating threshold values for infection control. Here, we consider the possibility of reducing the infected density by regulating the death rate of the predator species. In Fig.3.5, the density of infected prey is plotted against predator death rate. It is possible to observe that, even if the predator death rate is lower than the threshold for the host-parasite equilibrium to become unstable, the disease can still be present in the system at the internal equilibrium. This is due to the backward bifurcation between E_3 and E_4

For fixed c and ϕ, in the case predators feed mostly upon susceptible prey, we can observe how stability regions change for different values of prey and parasite parameters and when bi-stability is more likely to occur. In Fig.3.6a, it is possible to notice that region 3a is wider for intermediate values of q. The presence of both E_4 and E_5 is possible only when the vertex X_{fold}, defined in (3.4), is between X_2 and X_3. When q is too low, E_5 has negative

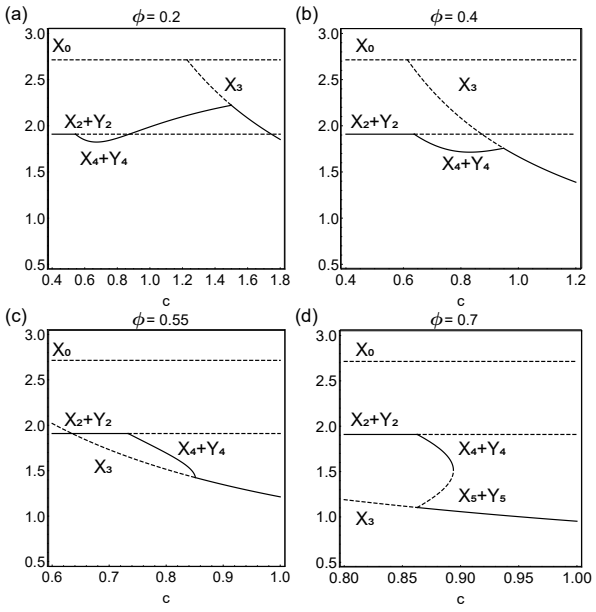

Figure 3.4: Total population densities at all the equilibria as function of c for different values of ϕ. Continuous line marks stability while the dashed one is for unstable equilibria

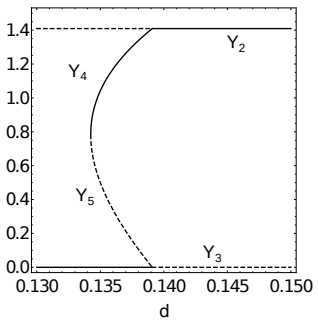

Figure 3.5: Infected prey densities at all the equilibria as function of d. Continuous line marks stability while the dashed one is for unstable equilibria

Y coordinate and, when q is too high, E_4 has negative P coordinate. For a similar reason, low values of α favour bi-stability between E_4 and E_3 as they imply a lower value of X_2, reducing the threshold for the predator coordinate to be positive. Region 6 increases and move upwards as q increases. Higher host competition implies lower values of Y_2 and P_3, making it more difficult for the predator to invade the host-parasite equilibrium and easier for the parasite to invade the host-predator one. The first effect determines the increase of region 6, while the second causes the upward shift.

Higher values of β (Fig.3.6d) decrease X_2 and increase Y_2, which implies an increase in R_I and a variable effect on R_P depending on predator selectivity. Region 3a increases as β increases for the lowering of the predator threshold. In Fig.3.6d, region 6 increases and moves upwards for the increase of R_I and a reduction in R_P.

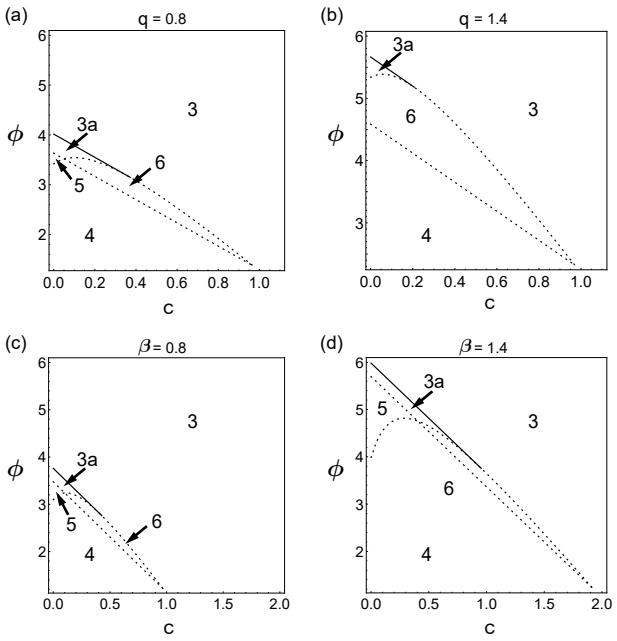

Figure 3.6: Bifurcation lines in the c-ϕ plane for different values of q in (a) and β in (b). As in Fig.3.1, the dashed line marks where $R_I = 1$, the dotted one where $R_P = 1$ and continue one where the fold bifurcation occurs. The different stability region follows the numeration of subsection 3.3. The plots show only the region where $R_{0I} > 1$ and $R_{0P} > 1$. Fixed parameter values are listed in Table 3.1

3.4 Discussion

In this work, we studied the implication of predation on the ecology of a prey population that suffers from an endemic disease. We first proved the global stability of the endemic equilibrium in the the host-parasite system. We then analysed the full model, which includes also a predator species that can choose to feed mainly on either healthy or infected prey. We performed a threshold analysis to classify the different asymptotic behaviours of the system. For wide regions of parameter space a stable internal equilibrium guarantees the co-existence of the three species. Moreover, when predators favour healthy prey, interesting patterns of bi-stability arise. Lastly, we used bifurcation theory to better understand how variations in different parameters impact the long-term outcomes.

A key result from our model is that we recovered the "healthy herd" effect (Packer et al., 2003; Duffy et al., 2005; Hall et al., 2005), as the total prey density can be higher at the internal equilibrium than at the predator-free one, but only when selective predation is strongly biased towards infected hosts as in Packer et al. (2003). Generally, when predators feed mainly on infected prey, the total prey density can show non monotonic patterns with respect of predation rate, which are not present in Packer et al. (2003). Similarly to Packer et al. (2003), when selectivity is toward susceptible prey, predators can still increase the density of healthy prey by reducing the time under infection while lowering total population density. However, predators can increase susceptible density only at intermediate predation values, higher predation pressure drives the disease to extinction and lowers prey density

at the predator-prey equilibrium. This result resembles that of Haque and Greenhalgh (2010) where they modelled a predator species that feed only on susceptible prey and has an alternative resource of food to remain always viable. Under this assumption, high predation can cause prey extinction, which is impossible with a specialist predator. Conversely, in our model total population density can change abruptly at the fold bifurcation, a result that does not occur in the range of biologically relevant solutions for Haque and Greenhalgh (2010).

As stated, selective predation towards susceptible prey can lead to two different kinds of bi-stability: either between the predator-free and the infection-free equilibria or between the infection-free and the co-existence ones. This means that under the same parameter set the system can converge to different states depending on the initial population size. As a consequence, in the case of bi-stability between the infection free and the co-existence equilibrium, a disease that cannot invade the disease-free equilibrium at low initial density, can still reach fixation in the system for large initial population densities. From a different angle, it also follows that the control effort needed to eradicate an established disease is larger than the one estimated from an invasion-threshold analysis (Roberts, 2007). Additionally, backward bifurcations cause an hysteresis effect with the disease re-emerging when control lowers. This kind of bi-stability is favoured for intermediate crowding effect. Higher levels of intraspecific competition imply a lower carrying capacity of the prey that can not sustain both predator and parasite simultaneously. This effect favours bi-stability between the two boundary equilibria. Differential intraspecific competitiveness between susceptible and infected host can also cause patterns of bi-stability, as found by Sieber et al. (2014).

A similar model to ours has previously been analysed by Hethcote et al. (2004). Despite some important differences in the assumptions made in the population dynamics (density-dependent prey death rate, frequency-dependent transmission, fertility under infection), the possible asymptotic behaviours when predators select for infected prey are qualitatively similar. Nonetheless, there are two main differences in the two models. Firstly, Hethcote et al. (2004) do not consider the case where selection is mainly on susceptible prey due to mathematical intractability. Our work shows that this region shows rather different ecological dynamics, and may be more realistic for many natural systems. Secondly, in their system the disease does not impact on prey demography, while ours is built from the classical epidemiological literature (Anderson and May, 1981). This makes their model more suitable for non-fatal diseases and ours for the more general case where the parasite impacts host dynamics. Comparing the results of the two models provides interesting insights in to the similarities and differences that arise from differing assumptions about the underlying population dynamics, in particular whether the host 'carrying capacity' is principally set by the parasite or the predator (Best, 2018).

The complex feedbacks between different populations in ecological systems constitute an interesting avenue for mathematical modelling. Clearly, the mathematical tractability of the model decreases according to the biological features that are included in the system. If prey develop immunity after the first infection as in Holt and Roy (2007) and Roy and

Holt (2008), disease prevalence as a function of predator abundance can become "hump-shaped". Alternatively, an important role is played by the predator functional response. For example, a saturating functional response combined with strong selection for infected prey can generate complex dynamics as in Hall et al. (2005). In their model, for intermediate predation pressure, a fold bifurcation can drive the whole prey population to extinction or, at higher levels of predation, solutions starts to cycle. Additionally, the predator itself could get infected like in Hadeler and Freedman (1989); Bairagi et al. (2007); Chaudhuri et al. (2012). Lastly, when infected prey are able to reproduce, we still expect the occurrence of bi-stability regions as in the case of sterility under infection. However, as the expressions of ecological attractors might differ, patterns of bi-stability may involve different equilibria from the one analysed here. These and several other different hypotheses could be considered for further work to more fully account for the impacts of community dynamics on host-parasite systems.

Chapter 4

The evolution of tolerance under selective predation

4.1 Introduction

Interspecies interactions in natural ecosystems are complex due to the interplay between direct and indirect effects that regulate the different population densities. Nevertheless, classical mathematical models focused on two-species interactions like predator-prey (Volterra, 1928; Rosenzweig, 1971) and host-parasite ones (Kermack and McKendrick, 1927; Anderson and May, 1981). This discrepancy is particularly relevant when considering host-parasite evolutionary models (Betts et al., 2016). As evolution occurs in an ecosystem, it shapes it and it is shaped by it, therefore, modelling frameworks need to take this eco-evolutionary feedback into account (Dieckmann and Law, 1996; Geritz et al., 1998; Dieckmann and Metz, 2006).

The impact of parasitism on hosts is not limited to the reduction in host population but effect also their evolution as hosts develop defence strategies against infections (Rausher, 2001; Woolhouse et al., 2002; Schmid-Hempel, 2011; Bourgeois et al., 2017). Host defence has been generally studied in terms of resistance, meaning those strategies that aim to fight the parasite by reducing parasite load or avoiding infection. More recently, attention has also been given to the ability of hosts to bear the effects of being infected without reducing parasite fitness, namely tolerance (Clarke, 1986; Råberg et al., 2007; Boots, 2008). The repercussion on host-parasite dynamics of these two kinds of defence can be very different, as an example, parasite prevalence can be reduced by resistance strategies and not be effected or even increased by tolerance ones (Roy and Kirchner, 2000). The interplay between these two kinds of strategies is yet to be fully understood, as tolerance might play a role in ameliorating the side effects of resistance strategies (Medzhitov et al., 2012; Soares et al., 2014). As the body of experimental studies considering tolerance has increased in the past decade (Read et al., 2008; Råberg et al., 2009; Medzhitov et al., 2012; Kutzer and Armitage, 2016; Martins et al., 2019), more theoretical understanding is needed to not overlook the ecological and evolutionary consequences of tolerance strategies (Vale et al., 2014; Hozé et al., 2018).

In an ecosystem, predators are an important factor that alter prey density either directly through consumption or indirectly due to trait-mediated effects like anti-predator strategies (Preisser et al., 2005). Predators can also have an impact on prey parasites, for example, by reducing their prevalence when selecting on infected individuals (healthy herd hypothesis, Packer et al., 2003; Duffy et al., 2005). From an evolutionary prospective, theoretical models have predicted predation to make more likely the polymorphism of both parasite virulence (Morozov and Best, 2012) and host resistance (Hoyle et al., 2012). Predation can also modify host-parasite co-evolution by dampening it, shifting it to milder dynamics as shown by the experimental study of (Friman and Buckling, 2013). In fact, predators can lower the evolutionary pressure on hosts also due to the existence of trade-off between anti-predator behaviour and defence to disease (Friman and Buckling, 2013; Toor and Best, 2016). While previous work focused on the impact of predation on the evolution of resistance, there are few experimental studies that examined tolerance strategies under predation (Stephenson et al., 2015), and, at the best of our knowledge, none theoretical.

Another important aspect to be considered is that mounting a defence to parasites might be costly for the host. The existence of trade-offs between evolving traits is studied in the life-history theory and it is the result of a combination of genetic, physiological and phenotypical constrains (Stearns, 1989). Such constraints can also narrow the range of possible evolutionary trajectory, limiting them into a spectrum between fast-living (fast reproduction, short lifespan) species or slow-living ones (pace-of-life theory, Ricklefs and Wikelski, 2002). Particularly, long-lived species might benefit more from investing parasite defence compared to short-living ones (Lee, 2006; Miller et al., 2007). Nevertheless, there are still few experimental studies that consider the cost of tolerance strategies. Among them, Johnson et al. (2012) found that reptiles with fast pre-metamorphosis life were more subject to the effects of the disease and hypothesised that tolerance strategies were involved together with resistance ones. Ganeshan et al. (2019) found that an external reduction in temperature triggered mice to give up homoeothermic and metabolic functions to increase tissue repair. In this study, we will assume that tolerance can be developed at the expense of a slower reproductive rate.

We use here a similar model to the one in Hoyle et al. (2012), where they analysed resistance evolution under predation focusing on the possibility for the host to drive predators or parasites to extinction. With this choice, we allow for the comparison between tolerance and resistance evolutionary outcomes in the presence of a predator species. The host-parasite evolutionary dynamics has been explored in chapter 2, while chapter 3 dealt with the stability analysis of the ecological dynamics. In this chapter we merge the two systems and look at the interactions between predation and tolerance evolution. We start by observing the changes that introducing a predator species causes on the outcomes of tolerance evolution and then we look in details to each different result. The main difference we found between the two systems is that predators allow for evolutionary branching of tolerance to happen. Moreover, predation lowers the value of tolerance when it evolves to a stable strategy, conversely, we

found high level of tolerance for high infected and low predator density. Finally, parasite extinction becomes a more common outcomes in the three species system and tolerance evolution can lead to both predator and parasite extinction when lower values are selected. In all of these cases, the shape of the trade-off function played an important role in determining the different outcomes.

4.2 Model

4.2.1 Ecological dynamics

In our model we consider a predator species feeding upon a prey one that suffers from the effects of being infected by a parasite. The dynamics of the prey species alone is logistic; b is the per capita death rate and q models the impact of inter-specific competition on reproduction. The prey per-capita reproductive rate $a(\alpha)$ is a function of extra-mortality under infection α, more details on this assumption will be given at the end of the section. Disease transmission is density-dependent with coefficient β, infected individuals are sterile, they can recover at rate γ, and they suffer from extra-mortality α due to the detrimental effects of the disease. Predators die at rate d, capture prey at a rate proportional to their density with coefficient c, and reproduce proportionally to their feeding effort with conversion coefficient θ. Predators can have a preference for either healthy prey, if sick prey show clear symptoms of the disease, or for infected prey if they are easier to catch. Predator selectivity is modelled by the parameter ϕ; $\phi < 1/2$ indicates a preference for infected prey and $\phi > 1/2$ a preference for susceptible ones. Taking into account these assumptions, we obtain the following model for the three population densities

$$\begin{aligned}
\frac{dX}{dt} &= [a(\alpha) - b]\, X - q(X+Y)X - \beta XY + \gamma Y - \phi c X P \\
\frac{dY}{dt} &= \beta XY - (\alpha + b + \gamma)Y - (1-\phi)cYP \\
\frac{dP}{dt} &= \theta c\,[\phi X + (1-\phi)Y]\, P - dP,
\end{aligned} \tag{4.1}$$

where X is the healthy prey density, Y the infected prey density and P is the predator density. This system shows at most one stable equilibrium $\left(\overline{X}, \overline{Y}, \overline{P}\right)$ ((X_4, Y_4, P_4) in chapter 3) where the three species coexist. Stability analysis and the study of the asymptotic behaviour of (4.1) have been conducted in chapter 3.

As in chapter 2, we assume that there is a cost in mounting a tolerance strategy in terms of a reduced reproductive rate and we use the trade-off function

$$a(\alpha) = a^* - \frac{a'(\alpha^*)^2}{a''(\alpha^*)}\left[1 - e^{\frac{a''(\alpha^*)}{a'(\alpha^*)}(\alpha - \alpha^*)}\right]. \tag{4.2}$$

Parameters α^* and a^* are chosen such that the parasite is viable at this specific point. The value for $a'(\alpha^*)$ is chosen to set a singular strategy at α^*, namely such that the selection

gradient of the host-parasite system is zero. These parameters (α^*,a^*, and $a'(\alpha^*)$) will be kept fixed throughout this chapter. Instead, we are interested in varying values for $a''(\alpha^*)$ as it has a strong impact on tolerance evolutionary outcomes. Parameter $a''(\alpha^*)$ allows us to choose the value for the second derivative of the trade-off function at the point (α^*, a^*) and determine the evolutionary properties of α^*. Moreover, choosing $a''(\alpha^*)$ determines the sign of the second derivative of (4.2) for every value of α. When $a''(\alpha^*)$ is positive, (4.2) is a convex function and it models the case where costs for adopting a tolerant strategy are decelerating. Decelerating costs means that the same increment in tolerance cost less the more tolerant an individual is. Conversely, when $a''(\alpha^*)$ is negative, (4.2) is a concave function and developing tolerance becomes more costly the more an individual is tolerant (accelerating cost). Some examples of (4.2) as $a''(\alpha^*)$ varies are shown in figure 4.1, these trade-off functions will be used in future plots.

Parameter values used throughout the whole chapter are listed in table 4.1.

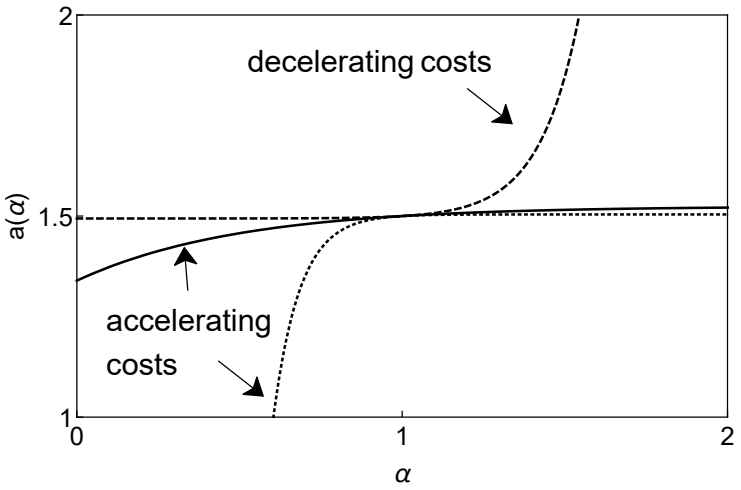

Figure 4.1: Examples of the trade-off function (4.2) as $a''(\alpha^*)$ varies. At the dotted curve $a''(\alpha) = -0.6$, at the continuous curve $a''(\alpha) = -0.1$, and at the dot-dashed curve $a''(\alpha) = 0.4$

4.2.2 Evolutionary dynamics

We use the adaptive dynamics framework to model the evolutionary dynamics of host tolerance. The basic assumption of this method is that mutations arise rarely and new mutant traits differ slightly from the resident population. These assumptions allow a time-scale separation between the fast ecological time-scale t and the slow evolutionary time-scale T. When a new mutation occurs, the resident population is at the demographic equilibrium and the new mutant trait can spread if its long-term exponential growth rate, i.e. its invasion fitness (Metz et al., 1992), is greater than zero. As in chapter 2, we use a fitness proxy for the invasion fitness, a function that is sign equivalent to the invasion fitness minus a constant (Best et al., 2011).

We are interested in modelling the evolution of prey tolerance to the disease, identified

by α. As in chapter 2, we use the negative of the determinant of the mutant invasion matrix as proxy for the sign of the invasion fitness of a new tolerant strain α_m in an environment set by a resident population with strain α, that is

$$s_\alpha(\alpha_m) = \left[b + \alpha_m + \gamma + c(1-\phi)\overline{P}\right]\left[a(\alpha_m) - b - q\left(\overline{X}+\overline{Y}\right) - \beta\overline{Y} - c\phi\overline{P}\right] + \gamma\beta\overline{Y}. \quad (4.3)$$

An evolutionary path is modelled as a succession of small steps of mutation and substitution in the direction pointed by the selection gradient, which is the derivative of (4.3) with respect to α_m evaluated at $\alpha_m = \alpha$. An evolutionary path can reach an accumulation point when it approaches a so called "singular strategy" α_{SS} that is convergence stable. Singular strategies can be found by equating the selection gradient to zero, in this case the selection gradient is

$$\begin{aligned}\left.\frac{\partial s_\alpha}{\partial \alpha_m}\right|_{\alpha_m=\alpha} &= a(\alpha) - b - \beta\overline{Y} - q\left(\overline{X}+\overline{Y}\right) - \phi c\overline{P} + a'(\alpha)\left[\alpha + b + \gamma + (1-\phi)c\overline{P}\right] \quad (4.4)\\ &= -\frac{\gamma\overline{Y}}{\overline{X}} + a'(\alpha)\beta\overline{X},\end{aligned}$$

where in the second line we plugged in the equations for the internal equilibrium. Equating (4.4) to zero, we obtain that singular strategies α_{SS} are characterised by

$$a'(\alpha_{SS}) = \frac{\gamma\overline{Y}}{\beta\overline{X}^2}. \quad (4.5)$$

We are mainly interested in two properties of singular strategies, evolutionary stability and convergence stability. If a singular strategy is a maximum of the invasion fitness, meaning that no other mutant strain can invade its environment, it is called evolutionary stable strategy (ESS). If evolutionary paths can converge to a singular strategy, the singular strategy is called convergence-stable (CS). An ESS that is also CS is a continuously stable strategy (CSS). A CS strategy that is not an ESS is an evolutionary branching point (BP), after which different strains of the same trait can coexist in the same environment. In order to study these properties we need to compute the second derivatives of (4.4)

$$\frac{\partial^2 s_\alpha(\alpha_m)}{\partial \alpha_m^2} = \left[\alpha + b + \gamma + (1-\phi)c\overline{P}\right]a''(\alpha_m) + 2a'(\alpha_m) \quad (4.6)$$

$$\frac{\partial^2 s_\alpha(\alpha_m)}{\partial \alpha \partial \alpha_m} = -(q+\beta)\frac{\partial \overline{Y}}{\partial \alpha} - q\frac{\partial \overline{X}}{\partial \alpha} + c\left[\phi + a'(\alpha_m)(1-\phi)\right]\frac{\partial \overline{P}}{\partial \alpha} \quad (4.7)$$

where

$$\frac{\partial \overline{X}}{\partial \alpha} = \frac{\overline{X}^2\left[(1-\phi)a'(\alpha)+\phi\right]}{(1-2\phi)q\overline{X}^2 + \frac{\gamma d}{\theta c}} \quad (4.8)$$

$$\frac{\partial \overline{Y}}{\partial \alpha} = -\frac{\phi}{1-\phi}\frac{\partial \overline{X}}{\partial \alpha} \quad (4.9)$$

$$\frac{\partial \overline{P}}{\partial \alpha} = \frac{1}{c(1-\phi)}\left(\beta\frac{\partial \overline{X}}{\partial \alpha} - 1\right). \quad (4.10)$$

	Definition	Default value
b	Intrinsic prey per capita mortality rate	0.1
q	Impact of competition on prey birth rate	0.2
β	Infection transmission coefficient	0.8
γ	Per capita recovery rate	0.3
α	Extra-mortality under infection, host tolerance	varies
c	Predator capture coefficient	varies
ϕ	Predator selectivity	0.1
θ	Predator conversion coefficient	1
d	Predator per capita death rate	0.6
α^*, a^*	Host tolerance-reproduction trade-off parameters	$1, 1.5$
$a'(\alpha^*), a''(\alpha^*)$		0.04918, varies
Γ	$\alpha + b + \gamma$	

Table 4.1: Definitions and values for model parameters.

For a singular strategy α_{SS} to be an ESS, it is enough that (4.6) evaluated when $\alpha = \alpha_m = \alpha_{SS}$ is negative, while for convergence stability we need that the sum of (4.6) and (4.7) evaluated at α_{SS} is negative (Geritz et al., 1998).

4.3 Results

This section collects the major results we unravelled in the evolutionary analysis of system (4.1). In the first section we answer the question: What happens to the evolutionary outcomes of the host-parasite system when a predator species is slowly introduced in the system? Starting from this general picture, we focus in the following sections on the different outcomes emerged. In section 4.3.2, we consider when tolerance evolves toward an evolutionary stable strategy and outline the main trends for the optimal level of tolerance when model parameters are varied. Section 4.3.3 extends the result on parasite extinction due to tolerance evolution of chapter 2 by including also predator extinction. Moreover, we study there the effects of tolerance evolution on the possibility of co-existence of the three species. Section 4.3.4 takes into account the evolutionary outcome of branching, result that is generally uncommon for tolerance evolution (Boots and Bowers, 1999; Roy and Kirchner, 2000) and not possible in the host-parasite case. Finally, in the last section we explore what can happen after the branching point and how tolerance evolve in a population where two strains of tolerance can co-exist.

4.3.1 Predators' impact on tolerance evolutionary outcomes

To study how the introduction of a predator species impacts on tolerance evolution, we start by looking at the evolutionary dynamics of the host-parasite system analysed in chapter 2 (that is equivalent to (4.1) with $c = 0$) and then we observe how increasing the capture coefficient c from 0, where the predator cannot persist, alters it. This choice allows us to

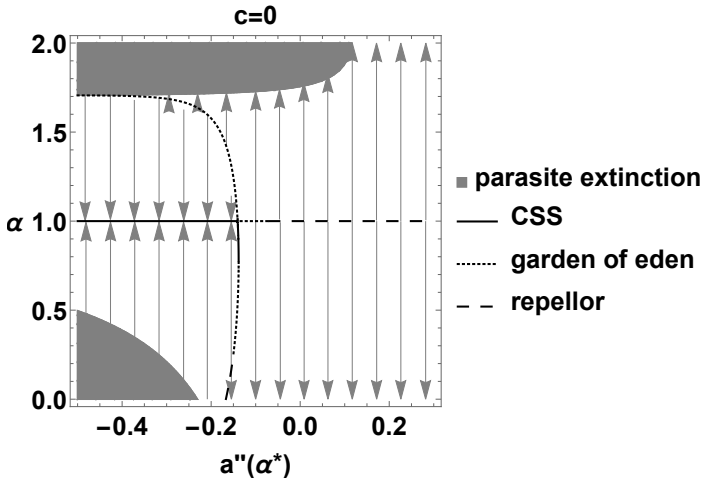

Figure 4.2: Singular strategies of the host-parasite system for different values of $a''(\alpha^*)$. The grey region marks where the parasite is not viable and arrows point in the direction of the selection gradient. Parameter values can be found in Table 4.1

have a smooth transition between the ecological dynamical attractors of the two systems.

The evolutionary dynamics of the host-parasite system when ($c = 0$) can converge to four possible evolutionary outcomes, depending on the shape of the trade-off function: convergence towards an evolutionary stable strategy, tolerance maximisation ($\alpha = 0$), tolerance minimisation, and parasite extinction. These outcomes are shown in Fig.4.2, where the parameter $a'(\alpha^*)$ of the trade-off function (4.2) has been chosen in order to set a singular strategy at $\alpha^* = 1$. By varying $a''(\alpha^*)$, we can modify the properties of the singular strategy α^*, namely evolutionary and convergence stability. α^* is evolutionary and convergence stable (CSS) for largely negative values of $a''(\alpha^*)$ (accelerating costs). In this case, most of the evolutionary paths converge to α^*, while few paths converge towards parasite extinction due to a second singular strategy (which is a 'Garden of Eden', evolutionary stable but impossible to reach) close to the extinction boundary. α^* loses convergence stability at $a''(\alpha^*) \approx -0.14$, after which a second CSS is present for a narrow range of $a''(\alpha^*)$ and then evolution can lead either to parasite extinction or to tolerance maximization. At $a''(\alpha^*) \approx 0.12$ the boundary for parasite extinction folds in such a way that parasite extinction is not possible any more and, instead, tolerance is either minimized or maximized. Here, the host reproductive rate is large enough to sustain parasites even at high rate of mortality under infection.

Now we introduce predation by setting $c > 0$. Choosing a trade-off function such that α^* is a CSS, we can see in figure 4.3a the effects of increasing c. Predictably, predators cannot invade the host-parasite system when c is close to zero. Tolerance evolution in the three species system converges to a CSS, as in the host-parasite case, up to the point where the CSS disappears due to a fold bifurcation with a repellor. After the bifurcation, parasite extinction becomes the only possible outcome. Notice that as the capture rate increases, the level of tolerance at the stable strategy decreases (higher mortality under infection α means lower tolerance). By increasing the risk of dying under infection, predators reduce the benefits of enduring infection. We will analyse this trend in more details in section 4.3.2.

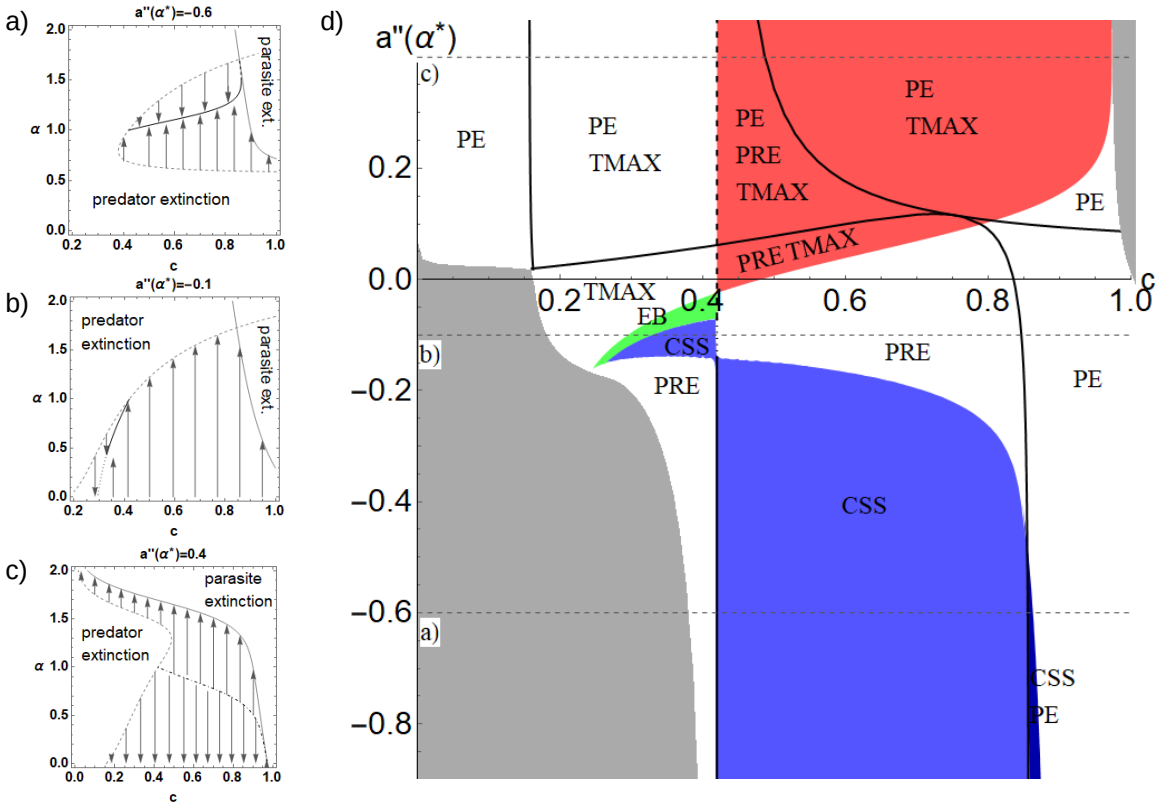

Figure 4.3: Figures 4.3a, b and c, show the singular strategies and the extinction boundaries of the host-parasite-predator system as c increases for different values of $a''(\alpha^*)$. Black continuous trait marks convergence stable strategies, dot-dashed trait marks convergence repellor strategies and the dotted one evolutionary branching points. Parasite extinction boundary is represented by a continuous grey curve, predator one by a grey dashed curve, and in the grey regions there is not an internal equilibrium for any values of α. Arrows indicates the direction of the selection gradient (4.4). In figure 4.3d the outcomes of tolerance evolution in the host-parasitee-predator system are shown as c and $a''(\alpha^*)$ vary. The outcomes are: predator extinction (PRE), parasite extinction (PE), tolerance maximization (TMAX), evolutionary branching (EB), and convergence to an evolutionary stable strategy (CSS). In the boundary grey regions, the host-parasite-predator system does not show a positive internal equilibrium. In the blue region there is a continuous stable strategy (CSS), in the dark blue region a repellor is present together with a CSS, in the green region, there is an evolutionary branching point, while in the red region there is a repellor strategy. The vertical line at $c = 0.4194$ corresponds to where the host-parasite singular strategy α^* crosses the predator extinction boundary. The style on this line shows the evolutionary properties of α^* in the host-parasite system as in figure 4.2. The dashed grey lines mark the values of $a''(\alpha^*)$ of figures 4.3a, b and c.

The more different outcome between the two systems is obtained when α^* is evolutionary stable but not convergence stable (garden of Eden) in the absence of predation, i.e. values of $a''(\alpha^*)$ between -0.14 and -0.07. This strategy enters in the host-parasite-predator system at $c \approx 0.42$ (figure 4.3b) and, due to a discontinuity in the mixed derivative, it gains convergence stability and becomes a CSS. Interesting, in this case, the singular strategy runs backwards from the entry point and it is present for lower c. As c decreases, also (4.6) changes sign and the CSS becomes a branching point, a singular strategy that is convergence stable but where where a second trait can invade and co-exist. This is an important difference with the host-parasite system where branching cannot occur (for a more detailed discussion see section 4.3.4).

The last case we consider is when $a''(\alpha^*)$ is positive and α^* is neither convergence or evolutionary stable in the host-parasite system. In figure 4.3c, it is possible to see that these evolutionary properties are maintained in the three species system. The value of α at the evolutionary repellor (dot-dashed line in 4.3c) decreases with respect of c, which implies an increase in the basin of attraction for parasite extinction. Interestingly, due to a fold in the boundary for predator extinction, predators can be present in the system even for values of c close to 0. This is possible because, with this choice of trade-off function, for low levels of tolerance (high α) the host reproductive rate is high enough to support the predator species. Notice also that this implies that there are two disjoint intervals of α where system (4.1) converges to an internal equilibrium and tolerance can evolve towards maximization or either parasite or predator extinction depending on the starting point.

The previous cases are summarised in figure 4.3d, which shows all the possible outcomes of tolerance evolution as c and $a''(\alpha^*)$ vary. There are five possible outcomes that can occur in overlapping regions of the parameter space, depending on the initial value of tolerance. Notice that, as a difference with the host-parasite case, in this example tolerance minimization cannot occur when both parasite and predator species are present. In fact, when hosts evolve towards higher α, parasites go extinct due to predator preference for infected. For the same reason, parasite extinction becomes possible for every trade-off function when c approaches 1. Generally, the evolutionary properties of the singular strategies are preserved between the two systems. The only exception is when $-0.14 < a''(\alpha^*) < -0.2$, i.e. when evolutionary branching occurs. Here, a discontinuity in the mixed derivatives changes α^* from a Garden of Eden to a CSS or from a repellor to a branching point.

4.3.2 Predators' impact on tolerance evolutionary optimal strategy

This section focuses on the interplay between the ecological population densities and the evolutionary optimal tolerance strategy. The Adaptive Dynamics framework underpins an evolutionary loop between the fitness of an evolving trait and the environment in which the trait is embedded. The time-scale separation allows to take into account both that a trait changes the environment (e.g. predator and parasite densities) when it reaches fixation and that the environment determines which mutant can invade. Said so, it is not easy to describe

how different components of the feedback loop interact with each other, particularly because, in this model, the host population is structured into two classes, susceptible and infected.

Analytically, it is possible to understand how a change in tolerance affects population densities at the ecological equilibrium by looking at the derivatives of the equilibrium coordinates. From (4.8) we observe that susceptible density decreases with respect of tolerance, while infected density increases when tolerance increases, see (4.9). The more an individual is tolerant to the effects of disease, the more they remain in the infected state and transmit the disease, lowering the density of susceptible host. Moreover, the combined effect of an increase in tolerance on the total prey population density depends upon predator selectivity. Specifically, if predators prefer infected prey, total prey density decreases when tolerance increases, and vice-versa, when selection is towards susceptible prey, total prey density increases with tolerance. Differently, it is less straightforward to draw a general and simple rule on how predator density varies with respect of tolerance from (4.10) as it depends on the value of $\frac{\partial X}{\partial \alpha}$.

On the opposite, it is complex to determine analytically how population densities impact on the level of tolerance at an evolutionary attractor. Instead, we approached it numerically, specifically, by looking at density plots of α value at the CSS as two parameters vary. The trend that emerged is that higher levels of tolerance correspond with higher parasite density and lower predator one. Therefore, tolerance increases when the risk of getting infected is high but the cost of being infected, and dying because of predation, is low. In the remaining part of this section we focus on two examples of the density plots just mentioned. Notice that in both of them, predators preference is for infected as, with our choice of parameters and trade-off function there is not a CSS when predators prefer susceptible prey.

Figure 4.4 shows how optimal tolerance and the relative population densities vary with respect of the predator parameters c and ϕ. We compared these plots with the density plots of population variables when α is kept fixed at 1(not shown). Beside the narrow region close to the top boundary where α is higher (and tolerance lower), these two sets of plots do not vary much. Therefore, it is reasonable to use figure 4.4 to understand how ecological quantities affect tolerance evolutionary attractor.

At low c predators are not very effective in catching prey and remain rare, thus, infected density is as high as in the host-parasite model and total prey density is the lowest due to the impact of the disease. At intermediate c, predator density reaches the highest values, correspondingly, infected population starts to decline as predators are more efficient in catching prey and the total prey population increases. At high c infected density is close to 0 and, since predators feed mostly on infected, also predators density declines, as a result total prey density is maximal. Instead, the more predators select for infected ($\phi \to 0$), the less available prey they have and the less they can reproduce, allowing infected density to increase and, thus, total prey density to decline. The result is that tolerance is higher for low c and low ϕ that is where infected density is higher and predator one is lowest.

We recover here the "healthy herd" effect analysed in chapter 3. Namely,when predators

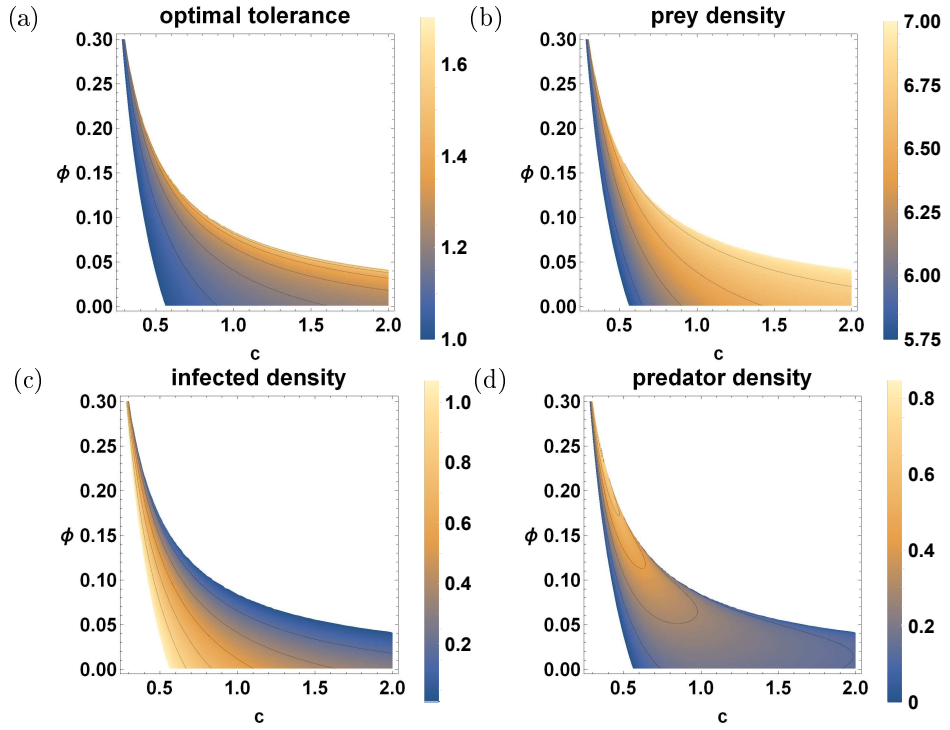

Figure 4.4: Density plots of α at the continuosly stable strategy and population densities as capture coefficent c and predator selectivity ϕ vary. $a''(\alpha^*) = -0.4$.

prefer infected prey, total prey population is higher in the three species system then in the host-parasite one, as predators reduce disease impact. This effect can be enhanced by tolerance evolution, when selection favours lower tolerance. In fact, we compared population densities in Fig 4.4 with the ones obtained keeping α fixed (not shown), and found the main differences in the region where α is higher. Particularly, corresponding to the orange region of Fig 4.4a infected density is lower when tolerance evolves compared to when it is kept fixed, due to the increase in mortality under infection. The reduction in infected prey determines also a reduction in predator population and, therefore, an increase in total prey population, which amplifies the "healthy herd" effect.

Also when parasite parameters vary (figure 4.5), population densities calculated at the evolutionary optimal strategy do not change from the ones evaluated at α^*. Predictably, infected density increases as transmission increases and recovery decreases, while total prey density behaves in the opposite way. Conversely, predator density shows a more interesting pattern as it is non monotonous with respect both γ and β. Again, predator density is maximal when there is a balance between total prey density and the proportion of infected prey. Tolerance evolution is influenced by both trends as it increases with respect of β but it is non monotonic with respect of γ. At low β an increase in γ promotes tolerance, conversely, at high β tolerance is more advantageous at lower recovery rates due to the lower predator density. This example shows how the interplay between a high risk of infection and a low risk of predation while infected are both needed to an evolutionary increase in tolerance.

We found that the pattern of high tolerance for high parasite density and low predator density is common also when changing other pairs of parameters. Therefore, we conclude

that when selection is towards infected it advantageous to reduce mortality under infection when risk of getting infected is high but cost of dying while infected due to predation is low.

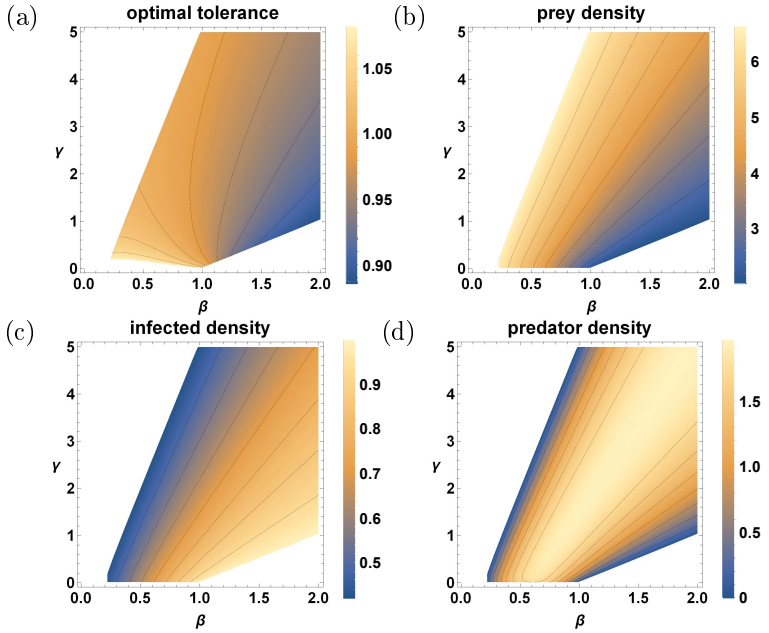

Figure 4.5: Density plots for tolerance CSS and population densities as infection coefficent β and recovery rate γ vary. $a''(\alpha^*) = -0.4$, $c = 0.6$.

4.3.3 Tolerance evolution and co-existence regions

Parasite or predator extinction are common outcomes of tolerance evolution, as it is possible to observe in figure 4.3. Similarly to the host-parasite case analysed in chapter 2, it is by lowering tolerance than the extinction of one or both species can occur.

The trade-off parameter $a''(\alpha^*)$ plays an important role to the determine which species goes extinct first. For negative $a''(\alpha^*)$, i.e. for accelerating costs, predators are more likely to disappear, especially for low capture coefficient c. Figure 4.6a shows an example where tolerance evolves towards predator extinction in the three-species system and then to a CSS in the host-parasite one. For higher values of $a''(\alpha^*)$ and c (see figure 4.6b), after predator extinction, evolution in the host-parasite system can converge also to parasite extinction. Conversely, for decelerating costs (positive $a''(\alpha^*)$) parasite extinction is a common outcome of tolerance evolution. In fact, in the presence of predators, parasite extinction can occur for any positive $a''(\alpha^*)$, while, in the host-parasite case (Fig.4.2b), parasite extinction is possible only for values of $a''(\alpha^*)$ up to ≈ 0.12 (for higher $a''(\alpha^*)$, the reproductive rate is always high enough to maintain the parasite in the system despite changes in α). Figure 4.6c shows an example where parasite extinction, which would have not been possible in the host-parasite system, occurs in the host-parasite-predator one. Nevertheless, there is a possibility for the parasite to survive extinction. Namely, for lower c (Figure 4.6d) predator extinction can occur before parasite one, preventing the latter to disappear as long as predators are

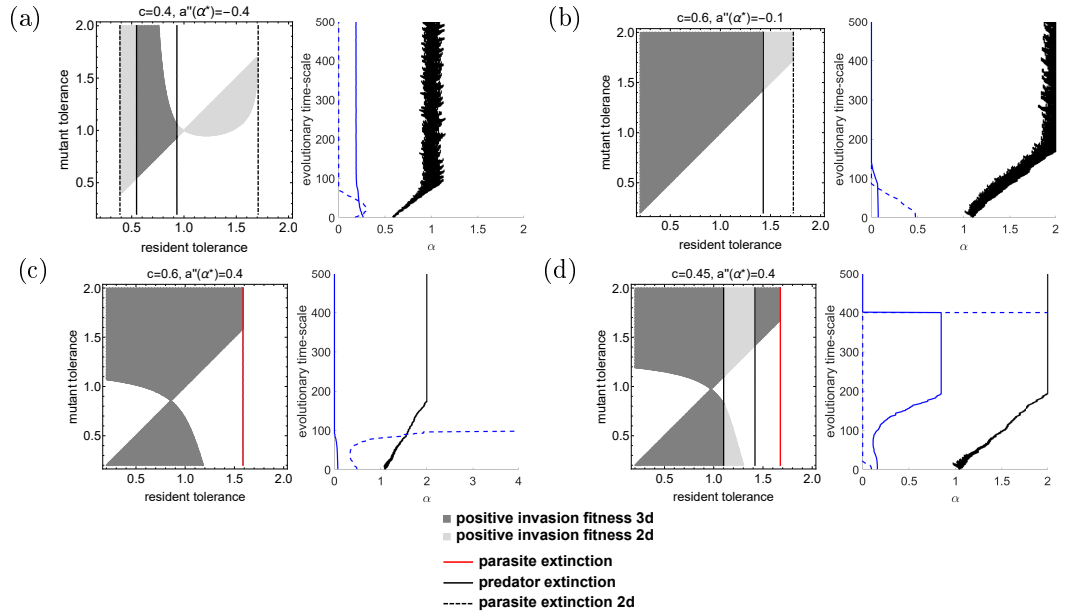

Figure 4.6: Pairwise invasibility plots for different values of c and $a''(\alpha^*)$. For each panel we show a simulation of the tolerance evolutionary dynamics conducted as in section 2.2. The continuous blue line represents infected density, while the dashed one predator density. In (d) predators are re-introduced in the system at a low density at $T = 400$.

not re-introduced. Starting from an initial condition between the internal repellor and the boundary for predator extinction, evolution converges towards predator extinction and then to tolerance minimization. For α large enough, parasites can remain in the system only if the predator species is not reintroduced, otherwise, they rapidly go extinct (as at $T = 400$ in the simulation).

4.3.4 Evolutionary branching of tolerance

In this section we analyse the possibility of evolutionary branching in the host-parasite-predator system. Specifically, we provide a proof that evolutionary branching is impossible in the host-parasite system we considered in chapter 3, while it is possible when the predator species is introduced.

Firstly, we show that evolutionary branching of tolerance is impossible without predators. As shown in section 3.2.1, the host-parasite system shows an unique endemic equilibrium $(\overline{X}_{HP}, \overline{Y}_{HP})$ which is globally stable if positive. Assuming the resident population at this equilibrium, a new mutant invasion fitness can be approximated by the fitness proxy

$$s_\alpha(\alpha_m) = (b + \alpha_m + \gamma)\left[a(\alpha_m) - b - q\left(\overline{X}_{HP} + \overline{Y}_{HP}\right) + \beta\overline{Y}_{HP}\right] + \gamma\beta\overline{Y}_{HP}. \tag{4.11}$$

Taking the partial derivative of (4.11) with respect to α_m and plugging in the equations for the population densities at the ecological equilibrium we get the proxy for the selection gradient

$$\left.\frac{\partial s_\alpha}{\partial \alpha_m}\right|_{\alpha_m=\alpha} = \Gamma a'(\alpha) - \frac{\beta\gamma}{\Gamma}\overline{Y}_{HP} \tag{4.12}$$

with $\Gamma = \alpha + b + \gamma$. Equation (4.12) implies that at a singular strategy α_{SS}

$$a'(\alpha_{SS}) = \frac{\beta\gamma}{\Gamma^2}\overline{Y}_{HP}. \tag{4.13}$$

For a singular strategy α_{SS} to be an evolutionary branching point, it has to be convergence stable but not evolutionary stable. To check these conditions we need to compute the second derivatives of (4.11)

$$\frac{\partial^2 s_\alpha(\alpha_m)}{\partial \alpha_m^2} = \Gamma a''(\alpha_m) + 2a'(\alpha_m)$$
$$\frac{\partial^2 s_\alpha(\alpha_m)}{\partial \alpha \partial \alpha_m} = -(q+\beta)\frac{\partial \overline{Y}_{HP}}{\partial \alpha} - q\frac{\partial \overline{X}_{HP}}{\partial \alpha}$$

where

$$\frac{\partial \overline{X}_{HP}}{\partial \alpha} = \frac{1}{\beta} \tag{4.14}$$
$$\frac{\partial \overline{Y}_{HP}}{\partial \alpha} = \frac{\beta\Gamma^2 a'(\alpha) - (\beta^2\gamma\overline{Y}_{HP} + q\Gamma^2)}{\Gamma^2\beta\left[q + \beta\left(1 - \frac{\gamma}{\Gamma}\right)\right]}. \tag{4.15}$$

Notice that the derivative of $\overline{Y}_{HP}$ with respect of α can be either positive or negative depending on whether $a'(\alpha)$ is high enough to compensate for the negative term at the numerator. Conversely, susceptible density is monotonically increasing with respect of α. A singular strategy α_{SS} is not evolutionary stable when

$$\left.\frac{\partial^2 s_\alpha(\alpha_m)}{\partial \alpha_m^2}\right|_{\alpha_m=\alpha=\alpha_{SS}} = \Gamma a''(\alpha^*) + \frac{2\beta\gamma}{\Gamma^2}\overline{Y}_{HP} > 0 \tag{4.16}$$

that is when

$$a''(\alpha_{SS}) > -\frac{2\beta\gamma}{\Gamma^3}\overline{Y}_{HP}. \tag{4.17}$$

For convergence stability, we need

$$\left.\frac{d}{d\alpha}\frac{\partial s_\alpha(\alpha_m)}{\partial \alpha_m}\right|_{\alpha_m=\alpha=\alpha_{SS}} = \left.\left(\frac{\partial^2 s_\alpha(\alpha_m)}{\partial \alpha_m^2} + \frac{\partial^2 s_\alpha}{\partial \alpha \partial \alpha_m}\right)\right|_{\alpha_m=\alpha=\alpha_{SS}} < 0 \tag{4.18}$$

Notice that the first term is positive because of (4.16) while the second term is positive

because

$$\begin{aligned}\left.\frac{\partial^2 s_\alpha(\alpha_m)}{\partial\alpha\partial\alpha_m}\right|_{\alpha_m=\alpha=\alpha_{SS}} &= -(q+\beta)\left.\frac{d\overline{Y}_{HP}}{d\alpha}\right|_{\alpha=\alpha_{SS}} - \frac{q}{\beta} \\ &= \frac{q}{\beta}\left[\frac{q+\beta}{q+\beta\left(1-\frac{\gamma}{\Gamma}\right)} - 1\right] \\ &= \frac{q\gamma}{\Gamma\left[q+\beta\left(1-\frac{\gamma}{\Gamma}\right)\right]} > 0\end{aligned}$$

Therefore condition (4.18) cannot be satisfied and a singular strategy that is not evolutionary stable cannot be convergence stable.

When we consider the host-parasite-predator system, a singular strategy α_{SS} is not evolutionary stable when

$$\left.\frac{\partial^2 s_\alpha(\alpha_m)}{\partial\alpha_m^2}\right|_{\alpha_m=\alpha=\alpha_{SS}} = \frac{2\gamma\phi}{(1-\phi)\beta\overline{X}^2}\left(\frac{d}{\phi\theta c} - \overline{X}\right) + a''(\alpha_{SS})\beta\overline{X} > 0 \tag{4.19}$$

that is

$$a''(\alpha_{SS}) > -\frac{2\gamma\phi}{(1-\phi)\beta^2\overline{X}^3}\left(\frac{d}{\phi\theta c} - \overline{X}\right). \tag{4.20}$$

While, for convergence stability we need

$$\begin{aligned}\left.\frac{\partial^2 s_\alpha(\alpha_m)}{\partial^2\alpha_m}\right|_{\alpha_m=\alpha=\alpha_{SS}} + \left.\frac{\partial^2 s_\alpha(\alpha_m)}{\partial\alpha\partial\alpha_m}\right|_{\alpha_m=\alpha=\alpha_{SS}} = \\ a''(\alpha_{SS})\beta\overline{X} + \frac{\phi^2\gamma(\frac{d}{\phi\theta c} - \overline{X})(\frac{2d}{\phi\theta c} - \overline{X})}{(1-\phi)\beta\overline{X}^2\left[(1-2\phi)q\overline{X}^2 + \frac{\gamma d}{\theta c}\right]} < 0\end{aligned}$$

that is when

$$a''(\alpha_{SS}) < -\frac{\phi^2\gamma(\gamma - \overline{X})(\frac{2d}{\phi\theta c} - \overline{X})}{(1-\phi)\beta^2\overline{X}^3\left[(1-2\phi)q\overline{X}^2 + \frac{\gamma d}{\theta c}\right]}. \tag{4.21}$$

Differently form the host-parasite case, conditions (4.20) and (4.21) can both hold for the same parameter set. In fact, when the predator is present the mixed derivative of the invasion fitness can be negative at a singular strategy that is not an ESS. Particularly, when $\phi = 0$ the right-hand side of (4.21) is always lower than the one of (4.20), meaning that for every parameter set for which the co-existence equilibrium is positive there is a range a values for $a''(\alpha^*)$ such that evolutionary branching is possible. Accordingly, in a numerical example we observed that the region of $a''(\alpha^*)$ and c such that evolutionary branching occurs shrinks with respect of ϕ, figure 4.7. On the other extreme, when $\phi = 1$ there are not internal equilibria and, trivially, evolutionary branching cannot occur.

4.3.5 Dimorphic population

After the evolutionary branching point discussed in the previous session, evolutionary dynamics can continue while two populations of prey with different values of tolerance coexist

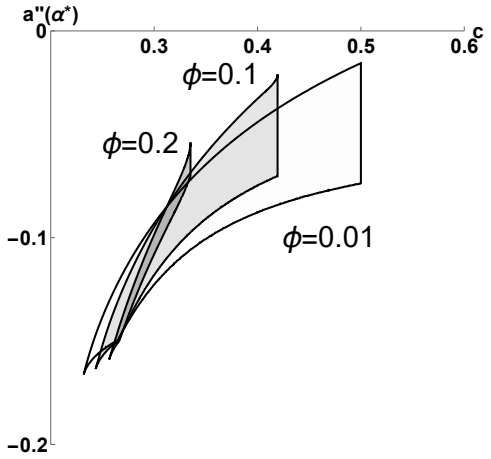

Figure 4.7: Branching regions in the c - $a''(\alpha^*)$ plane for different values of ϕ.

in the same environment. Equations for the population density become

$$\begin{aligned}
\frac{dX_i}{dt} &= (a(\alpha_i) - b)\, X_i - qX_i \sum_{i=1,2} (X_i + Y_i) - \beta X_i \sum_{i=1,2} Y_i + \gamma Y_i - \phi c X_i P \\
\frac{dY_i}{dt} &= \beta X_i \sum_{i=1,2} Y_i - (\alpha_i + b + \gamma) Y_i - (1-\phi) c Y_i P \qquad i = 1,2 \\
\frac{dP}{dt} &= \theta c \left[\phi\,(X_1 + Y_1) + (1-\phi)\,(X_2 + Y_2)\right] P - dP.
\end{aligned} \tag{4.22}$$

We do not analyse (4.22) analytically but we use it for numerical simulations. Assuming that (4.22) has reached a stable equilibrium $\left(\overline{X}_1, \overline{Y}_1, \overline{X}_2, \overline{Y}_2, \overline{P}\right)$, it is possible to define the invasion fitness for a new mutant strain of one of the two strains as

$$\begin{aligned}
s_{(\alpha_1,\alpha_2)}(\alpha_m) = \left[b + \alpha_m + \gamma + (1-\phi)c\overline{P}\right] &\left[a(\alpha_m) - b - q \sum_{i=1,2} \left(\overline{X}_i + \overline{Y}_i\right) + \beta \sum_{i=1,2} \overline{Y}_i - \phi c \overline{P}\right] \\
&+ \gamma\beta \sum_{i=1,2} \overline{Y}_i.
\end{aligned} \tag{4.23}$$

We simulated the evolutionary dynamics of (4.22) in two different ways. In Fig4.8a we used the same method as in section 2.3.2, which relaxes the assumption of time-scale separation between the evolutionary and ecological dynamics. After the branching point we can see two different strain coexisting at the evolutionary time-scale. The most frequent strains rapidly maximize tolerance, while the other branch stabilises at an intermediate value around $\alpha \approx 0.56$ instead of reaching full minimization. It is interesting to notice that tolerance of the less frequent strain do not reach the minimum possible value but it stops at an intermediate one. With this choice of $a''(\alpha^*)$, the trade-off function is quite flat, particularly for higher α (see figure 4.1), thus, the benefit in reproductive rate for less tolerant strains is not enough to bear the high predator pressure.

This result has been confirmed also by plotting a mutual invasibility plot (MIP) and simulating a realization of the adapting dynamics canonical equation (Fig.4.8). The grey

regions of the MIP mark where one of the two resident strategy is not present at the stable equilibrium of (4.22), while the arrows point in the direction of the selection gradient derived by 4.23. The red points is a realization of an evolutionary path obtained using the canonical equation of adaptive dynamics (Dieckmann and Law, 1996). Also this simulation converges towards the boundary point where $\alpha_1 \approx 0$ and $\alpha_2 \approx 0.56$, in accordance with the direction field of the selection gradient. By symmetry, the same behaviour can occur with the two strains switched. Notice that if α_2 was the only strain present in the system, predator species would not have survived, thus, predators are kept in the system by the most frequent strain.

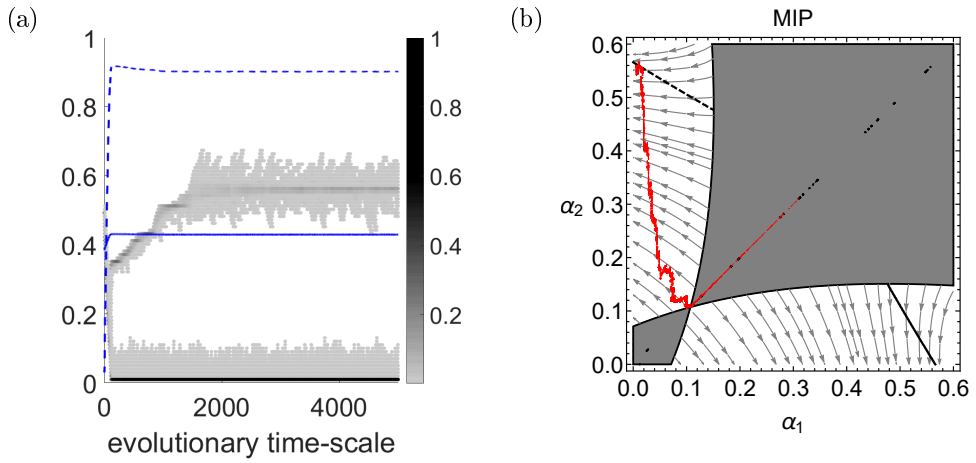

Figure 4.8: a) Simulation of dimorphic evolution with reduced time-scale separation between ecological and evolutionary dynamics (for details see section 2.2). b) Mutual invasibility plot between two co-existing strains of tolerance and a simulation of the adaptive dynamic canonical equation. The black line mark where the section gradient for α_1 is equal to zero, and the dashed line where the section gradient for α_2 is equal to zero. The continuous blue line represents infected density, while the dashed one predator density. $a''(\alpha^*) = -0.1$, $c = 0.3$.

4.4 Discussion

We studied the evolution of host defence in a host-parasite-predator system, focusing on the changes that the presence of the predator species introduces on the evolution of tolerance to disease. When comparing with evolution in the host-parasite case we found several differences in the possible outcomes. First, the presence of the predator can allow for evolutionary branching of tolerance, as, for a small region of the parameter space, it changes the convergence properties of the evolutionary attracting strategies. Second, an increase in predation rate reduces the level of tolerance at the optimal strategy. More generally, we observed a trend of high tolerance for high risk of getting infected and low cost of being infected due to lower predation pressure. Third, we found that parasite extinction due to tolerance minimization becomes more possible when there is also a predator involved. Moreover, the predator species can also go extinct by the same mechanism. Finally, we looked at a case

of tolerance evolution in a dimorphic population, where the dynamics converge towards the coexistence of a common and highly tolerant strategy and a rare one with intermediate level of tolerance.

Our result that at an high predation risk the level of tolerance at an optimal strategy is lower is corroboreted by the field study of Stephenson et al. (2015). To support the hypothesis that, in accordance with the pace-of-life theory, extra-mortality due to predation promotes evolution towards less defence and faster reproduction, they compared host defence in guppy population under low and high predation regimes. Accordingly, guppies under stronger predation pressure showed a lower disease tolerance, in contrast with previous studies that have not found support for this hypothesis when measuring resistance levels. In fact, while analysing the evolution of resistance under selective predation in a model very similar to ours Toor and Best (2015) found maximum optimal resistance at intermediate levels of predation, where both risk and cost of infection are high. Our work combined with Toor and Best (2015) provides further theoretical support for the hypothesis that higher predation might favour more tolerant, rather than more resistant, strategies. It would be interesting to see an experimental test of this hypothesis.

We have shown that predation allows for evolutionary branching of tolerance, that is impossible in the host-parasite model. To better understand this result it is necessary to look at the important role played by ecological feedbacks between host defence and population densities (Roy and Kirchner, 2000). When a tolerant strategy spreads in a population, it increases parasite prevalence and, consequently, selection for higher tolerance. This positive feedback between tolerance fitness and parasite prevalence creates an unsustainable environment for less tolerant strategies. Therefore, in classical models (Boots and Haraguchi, 1999; Roy and Kirchner, 2000; Restif et al., 2004; Miller et al., 2005; Boots et al., 2009), tolerance is commonly predicted to evolve towards fixation, in opposition to resistant strategies that reduce disease prevalence, making co-existence of different strains more likely. Best et al. (2008) explored possible routes to explain the discrepancy between this classical result and genetic variation of tolerance observed in experimental studies. Specifically, they found two mechanisms that avoid or mitigate the positive feedback with parasite prevalence: when tolerance reduces the disease effects on infected fertility (sterility tolerance) and when there is a trade-off between resistance and tolerance at the cost of reduced host reproduction. Noticeably, they showed that co-evolution with parasite virulence is not enough to promote polymorphism in host tolerance, a result further strengthened in Best et al. (2014) by using different approaches to model co-evolution. Ferris and Best (2019) found that also a seasonal birth rate can create a negative feedback between an increase in tolerance and the maximum parasite density reach in a cycle, which allow for branching. Here, we found that for weakly accelerating costs, the positive effect on parasite prevalence of a higher survival during infection is overcome by a higher risk of dying due to selective predation. As a result, the overall feedback between tolerance and host fitness can become negative for weakly accelerating costs. However, we found a narrow range of parameter values for which branching can

occur, thus, further work is required to assess the sensitivity of this result to changes in the model assumptions. Nevertheless, we suggest predation as a possible factor that contributes to explain genetic variation in disease tolerance in natural systems as it can introduce a negative feedback between tolerance and infected density.

When tolerance stabilizes at an optimal strategy, we also found higher levels of tolerance in correspondence with higher risk of infection, i.e. for higher values of the transmission coefficient. We expect this might be a common pattern in tolerance evolution as it appears in other theoretical studies (Boots and Haraguchi, 1999; Restif and Koella, 2003; Restif et al., 2004; Best et al., 2008; Carval and Ferriere, 2010). When the risk of getting infected is high, it is advantageous to increase the chances of surviving infection and return to the susceptible class in order to be able of reproducing. Furthermore, Boots and Haraguchi (1999) hypothesize that tolerance might be favourable when routes to other kinds of defence are made more costly by the strength of the parasite (low recovery rate or high transmission coefficient). Further understanding of this pattern has been given in Restif et al. (2004) and in Carval and Ferriere (2010), as they modelled resistance and tolerance evolving together at the cost of reduced reproduction. In both papers, evolution towards a tolerant pure strategy is favoured by high evolutionary costs of resistance, high transmission coefficient and low virulence. Here, we gave further support that tolerance is promoted by those factors that leads to high infection prevalence.

Another main difference between tolerance and resistance evolution is in the way that host evolution can cause parasite or predator extinction. In our host-parasite model, parasite extinction cannot occur by resistance evolution but it can when tolerance evolves towards minimization(Vitale and Best, 2019a). Due to the negative feedback between resistance fitness and parasite prevalence, close to the parasite extinction boundary (where resistance is higher and prevalence lower) selection promotes lower resistance and evolution stabilises at an optimal value. Oppositely, when tolerance decreases in a population, parasite prevalence can decrease accordingly and promote a further reduction in tolerance that leads to parasite extinction. When host defence evolves under predation, parasite or predator extinction can occur via both tolerance (as shown here) and resistance evolution, as shown in Hoyle et al. (2012). Hoyle et al. (2012) analysed whether parasite extinction due to resistance evolution was possible in an ecological dynamic like the one considered here, with the only difference that infected individuals can reproduce. They found that both predator and parasite species can go extinct when resistance increases in a population, conversely, it is by minimization that tolerance can drive the other species to extinction, as in the host-parasite case. Moreover, Hoyle et al. (2012) showed that, as for tolerance evolution, predation can introduce a discontinuity in the condition for convergence stability allowing for a repellor to become a branching point or a CSS. Furthermore, the range of trade-off functions that allow for branching increases as the predation coefficient increases, similarly to what found in Toor and Best (2015) for resistance evolution and here for tolerance one.

The role of trade-off functions in determining the evolutionary outcomes in adaptive

models of host defence is well-recognised (Bowers et al., 1994; Boots and Haraguchi, 1999; Restif and Koella, 2003; Restif et al., 2004; Best et al., 2008; Hoyle et al., 2008), despite measuring their shape in experimental settings still represents a challenging task Stearns (1989). We found that for decelerating costs, tolerance evolves towards the boundaries of possible values, leading to tolerance maximization or minimization, and consequent predator or parasite extinction. For trade-off functions that have a negative second derivative but still close to zero (weakly accelerating cost), evolutionary branching is possible, while, for more negative curvatures, tolerance can reach an optimal value. This pattern is well analysed in Hoyle et al. (2008), where they proved that strongly non-linear trade-offs lead to either CSS when accelerating or a repellor when decelerating, while weakly non-linear functions can lead to different outcomes. In fact, Hoyle et al. (2012) found a similar pattern for resistance evolution under predation, with branching possible for both weakly accelerating and decelerating costs, and Best et al. (2010) for sterility tolerance evolution, with branching happening for weakly decelerating trade-off. Here, we showed another model that confirms Hoyle et al. (2008)'s study. However, notice that there is still a gap between the sensitivity of theoretical models to the shape of trade-off functions and the experimental evidence of the costs of immunity (Lochmiller and Deerenberg, 2000).

An important improvement of this study would be to incorporate parasite counter-adaptation by virulence evolution. While resistant strategies are often predicted to give rise to an arms race with the parasite, tolerance gained some attention as a possible route to either reach a stable end point of co-evolution Roy and Kirchner (2000) or even to evolve towards mutualism Miller et al. (2006). Nevertheless, there are crucial implications of co-evolution that cannot be ignored. For example, Restif and Koella (2003) found that when host and parasite share the control of extra-mortality under infection, evolution of higher tolerance supports increased virulence as it reduces its costs. Similarly, Miller et al. (2006) suggested that this kind of commensalism could hide high evolutionary costs for the host, as it may increase parasite reproductive rate, creating also a dangerous environment for less tolerant hosts. Similarly, Best et al. (2014) found that co-evolution between tolerance and virulence can reverse the trend that for long-lived hosts parasites can invest less in transmission at the benefit of less virulence. When long lived hosts invest in tolerance, parasite can increase transmission due to a reduced cost of extra-mortality under infection. Since there is not a co-evolutionary study that considers the presence of a predator, we can only hypothesize here which effects predation could have on tolerance and virulence co-evolution, given also what it is known about resistance (Best, 2018). Predation might limit the fitness of a tolerant strategy by lowering infection prevalence, therefore, reducing the level of extra-mortality at the co-evolutionary equilibrium. Nevertheless, virulence might still be higher than in the host-parasite case, as predation reduces infected lifespan pushing the parasite to increase transmission and virulence.

This model could be developed further by incorporating more assumptions. First, it would be interesting to include the possibility for the parasite to infect also the predator

species. Under this hypothesis, the model could encompass ecological scenarios where parasites can alter host behaviour to reach the predator as final host. Some evidence of this kind of strategy has been observed in fish (Lafferty and Morris, 1996) and shrimp populations (Kunz and Pung, 2004). More generally, this could also contribute to a better understanding of the role of tolerance in the formation of zoonotic reservoirs for disease (Mandl et al., 2015). Second, it would be possible to include also resistance strategies in the allocation of energy between reproduction and defence as in Restif et al. (2004), Miller et al. (2005), Best et al. (2008) and Carval and Ferriere (2010). This would provide a further understanding on the interplay between these two kinds of strategies under predation. Specifically, it would be interesting to check whether the result that tolerance is favoured at low predation rate and high disease prevalence still holds in the case where an alternative resistance strategy is also available.

Studying the impact and the consequences of tolerance strategies and their evolution is still an open question in both theoretical and experimental studies. We contributed here with the mathematical analysis on how adding more ecological complexity in a classical model enriches the host-parasite evolutionary dynamics with new and different outcomes. We hope that further contributions will be made for a better understanding of the complexity of the innate immune system and its interaction with the ecological environment. Particularly, we emphasise the importance of mathematical modelling to study eco-evolutionary host-parasite dynamics as both an exciting theoretical challenge and an important tool to unravel unexpected biological insight.

Chapter 5

Discussion

5.1 Thesis summary

The focus of this thesis has been on analysing the effects of the evolution of tolerance and the presence of a predator species on a classical host-parasite SIS model. In Chapter 2 we performed an evolutionary study of host defence in the host-parasite case focusing on the possibilities for parasite eradication. Hosts were able to evolve either resistance, through avoidance or parasite clearance, or tolerance modelled as a reduction in mortality under infection. For both kind of strategies, considering or not the assumption of a trade-off between defence and reproduction lead to very different sets of evolutionary outcomes. In the absence of costs, both tolerance and resistance evolve towards maximisation. For the latter, maximization in this case implies also parasite extinction as the disease does not spread enough to survive.

When costs are considered, the more resistant the population is the more selection for resistance decreases, since getting infected becomes a rare event. Here, parasite extinction is impossible and evolutionary paths converge to a singular strategy close to the extinction boundary. Oppositely, parasite extinction, impossible for tolerance evolution without costs, becomes possible if costs are involved when selection promotes lower levels of tolerance. Interestingly, while at the individual level lower tolerance means worse conditions under infection, but higher reproductive rate, the whole population benefits from disease clearance. Although, we derived this result for a sterilizing infection we showed that the same dynamics can occur when infected can reproduce.

To check whether parasite extinction due to tolerance evolution can be a common outcome when changing the cost functions, we derived simple mathematical conditions on the slope of the function for it to occur. We found that for some trade-offs parasite prevalence can decrease for increasing tolerance, contrary to what is normally expected (Roy and Kirchner, 2000). This happens when the cost function has a rapidly increasing slope close to the parasite extinction boundary. Parasite extinction was more likely for accelerating cost functions, where the cost of an increase in tolerance is higher the more tolerant is the individual. We concluded the study with numerical simulations, where we relaxed

the hypothesis of a timescale separation between ecological and evolutionary dynamics. In some simulations, parasite extinction due to lowered tolerance occurred even when parasites could counter-adapt tolerance evolution by decreasing their virulence at the price of lowered transmission.

Chapter 3 focused on the stability analysis of the ecological scenarios in the case where a predator species is added to the host-parasite model considered in Chapter 2. We assumed that predators feed on both susceptible and infected prey but could prefer one or the other. We performed a classical stability analysis of the equilibria of the system, proving global stability of the internal equilibria in the host-parasite case. The full system could show up to two internal equilibria, one stable and one unstable, where the three species could coexist. We derived the threshold quantities for the predator and the parasite species to be able to survive in the system, namely where the number of new offspring by a single individual is larger than one. These conditions partitioned the parameter space into different possible asymptotic scenarios, among which, some had interesting interpretations. For example, in one region a predator species that would not survive in a population composed by only healthy individuals, could survive in the presence of the parasite by feeding mainly on infected hosts. Moreover, when predators fed mainly on healthy prey, we found regions of bistability, where, depending on the initial conditions, the dynamics can converge to one of two possible stable equilibria. As some of these regions are quite sensitive to changes in parameter values, we expect also these results to be strongly effected by a different predator functional response.

After determining the conditions on parameters for the system to converge to one of the possible asymptotic regions, we used bifurcation theory to understand how changing a parameter shaped the transitions between these regions. When predators preferred susceptible preys, we found a fold bifurcation between the two internal equilibria and a backward bifurcation between the stable internal equilibrium and the prey-predator one. In the latter case the condition for pathogen persistence in the system does not correspond with the one derived from threshold analysis, which can be problematic when predators are used for disease control. When predators select more for infected prey, we found that the healthy herd hypothesis (Packer et al., 2003) was valid in our system. Specifically, the presence of the predators can be beneficial to the prey species when they reduce the prevalence of an endemic disease, even to the extent that total prey density can increase with increasing predation pressure.

In Chapter 4 we merged the evolutionary analysis of Chapter 2 with the ecological dynamics of Chapter 3, namely, we allow for tolerance evolution in the three species system. Predators could still prefer either susceptible or infected prey, but we focused on the second case due to easer tractability. We started by looking at how the evolutionary outcomes analysed in Chapter 2 changed while increasing the capture coefficient. Depending on the shape of the trade-off function predators could be present in the system for low values of the predation coefficient, especially for decelerating cost functions. With the introduction of the predator species, the convergence stability of singular strategies changed, allowing

for the evolutionary branching of tolerance, which was impossible in the host-parasite case. After reaching a branching point the population became dimorphic, namely two different strains of tolerance could coexist in the same population. We simulated an example of evolution of the dimorphic population and found out that the path stabilized in a scenario where a widespread strain with maximal level of tolerance coexisted with a rare one with an intermediate level of tolerance.

Additionally, we found that when tolerance stabilised at an optimal value, increasing predation pressure lowered the optimal level of tolerance. Generally, while changing different parameter values, higher levels of tolerance corresponded with high parasite density and a low predator one. Thus, high tolerance seems favoured when the risk of catching the disease is high but the cost of dying due to predation while infected is low. In fact, we found high tolerance for low capture coefficient and mild predator selection for infected prey, or at high transmission coefficient but low recovery rate. Tolerance evolution towards lower values can lead, as in the host-parasite case, to the extinction of the predator and parasite species. Moreover, the presence of predators made evolutionary infection clearance more likely, particularly for decelerating costs of tolerance.

Previous theoretical studies have highlighted the important distinction between resistance and tolerance evolutionary outcomes and their feedback on host-parasite ecology. In this work, we have further showed how this distinction is crucial when looking at the possibility for parasite eradication. In the host-parasite case, not only do parasite extinctions occur under opposite assumptions on costs but also it occurred when selection moved in opposite directions, i.e. higher resistance and lower tolerance. Even in the presence of a predator species, tolerance evolution can lead to parasite eradication while it has been showed in Hoyle et al. (2012) that this is impossible in case of resistance, when considering finitely small evolutionary steps. Moreover, this work contributes to the theoretical knowledge on tolerance evolution by suggesting that predation might be a factor behind the observed genetic variation in tolerance traits.

In Chapter 3 and 4, we observed how introducing a predator species in the model enriched the variety of possible outcomes of both the ecological and the evolutionary dynamics. At the ecological timescale, population dynamics became more complex due to the occurrence of a fold bifurcation, and the possibility for bistability regions. At the evolutionary timescale, the evolutionary properties of singular strategies could change, allowing for tolerance branching. Clearly, these results came at the cost of more difficult analytical and numerical tractability of the mode. Nevertheless, we are convinced that this is a cost worth to be paid for the development of eco-evolutionary models that could better capture the complex feedback loops between evolution and population dynamics.

5.2 Can host tolerance be exploited to develop new disease-control approaches?

In the past years much attention has risen for the increase in pathogen strains resistant to classical treatments like antimicrobial drugs (Soares et al., 2017). Methodologies so far regarded as the most reliable showed a limit in their efficiency due to their evolutionary consequences on parasite fitness. In fact, it is the selection imposed by antimicrobials drugs that has prompted pathogen counteradaptation. Therefore, an interest has grown for new therapeutic approaches that are evolution-proof like, among others, the possibility to enhance host tolerance to disease (Vale et al., 2016). Since tolerance does not reduce parasite fitness, it should not contribute to the selective pressure for more resistant strains. Nevertheless, tolerance mechanisms are far from fully understood and their consequences at the population level are still unclear. While the experimental body of research increases, mathematical models can contribute by highlighting the possible effects of tolerance strategies on ecological systems and even forecast potential evolutionary outcomes.

Some drugs that are widely adopted for the common self-treatment of minor infections like ibuprofen or aspirin can be classified already as tolerance-based treatments because they provide an anti-inflammatory response without targeting pathogens (Vale et al., 2016). Recently, thanks to the development of an experimental framework for the measurement of tolerance and an early understanding of some mechanisms behind it, some studies have suggested possible routes for tolerance-based treatments. For example, the pharmacological reduction of the concentration of free haem, a component of *haemoglobin*, in the bloodstream can promote tissue-damage repair and ameliorate the effects of sepsis and malaria in mice (Soares et al., 2017). Other therapeutic approaches involve the direct reduction of the inflammatory response or of resistance mechanisms behind immunopathology (Medzhitov et al., 2012; Soares et al., 2017).

Among the possible strategies for improving host health during infection without directly reducing parasite fitness, Vale et al. (2014) warned on the distinction between host-centred ones and ones aimed to lower parasite virulence. While the former can be ascribed under the theoretical definition of tolerance adopted so far, the latter may indirectly constrain parasite growth, e.g. when it exists a trade-off between virulence and transmission. Keeping a distinction, when possible, between tolerance and resistance mechanisms is important for the development of a theoretical understanding of their impact on host-parasite dynamics (Miller et al., 2005).

The main concern raised from mathematical models on the applicability of tolerance-based treatments is due to the positive feedback between selection for tolerance and parasite prevalence. While from an individual prospective a relief from infection symptoms is therapeutically more than desirable, at the population level there is a conflict between the benefits of the reduced mortality of tolerant hosts and the costs of not limiting disease spreading (Hozé et al., 2018). More specifically, tolerant individuals might contribute more to transmission

than non-tolerant ones by being infective for a longer time, an effect that may be deleterious for chronic diseases (Hozé et al., 2018). Furthermore, treatment coverage required for overcoming the costs at the population level might not be achievable (Hozé et al., 2018) and milder symptoms might lead to difficulties in the trackability of the infection (Vale et al., 2014). Even from an evolutionary prospective the hypothesis that tolerance might impose lower selection for more resistant pathogens does not have enough empirical support yet and theoretical models have predicted possible complications (see section 5.3).

Our result that parasite extinction is possible due to the evolution of host defence when selection promotes lower levels of tolerance is another consequence of the increase in parasite prevalence when more tolerant strains spreads in a population. While this result might not be directly applicable for designing new treatment for humans there is a case where promoting selection for lower tolerance might be useful; when a disease spreads through a vector. Particularly, little is known on how insects can bear high levels of arboviruses like Dengue, Zika, and Yellow Fever in their body without a significant loss in fitness. Recently, mosquito tolerance to viruses has gained attention due to an increase in host resistance to insecticides and in virus counteradaptation to resistance-based approaches (Lambrechts and Saleh, 2019; Oliveira et al., 2020). Thus, more studies on the mechanisms behind tolerance are hoped to find new type of interventions aimed at the impairment of insect tolerance. Notably, Goic et al. (2016)'s experimental study showed a possible path to reduce tolerance to dengue and chikungunya in two species of *Aedes* by inhibiting the host transcription of viral DNA, which is hypothesised to trigger the tolerance response. Since arboviruses are rare in mosquito populations, this kind of approach should not impact on host evolution, nevertheless it might affect virus evolution as it reduces transmission (Lambrechts and Saleh, 2019). If bearing a tolerance strategy is costly in term of reproduction, we showed that there is an evolutionary route for parasite eradication. Understanding whether these costs exist and if such a route could be promoted might contribute at a tolerance-based approach for arboviruses control.

Another scenario where our results might be useful to gain insight on the role of tolerance on ecological interactions is when a pathogen is endemic in zoonotic reservoirs. The jump of a pathogen from a wild species to humans is thought to be behind the epidemics of HIV, flu and even coronaviruses. So far, little is known about why these intra-specific jumps can occur and how the same virus can affect different species in different ways. Surely, the reasons behind such a diversity lie in the complex interplay between both host and parasite variations (Mandl et al., 2015). In spite of controlling zoonotic disease reservoirs an interest has been given to the effects of natural predators (Ostfeld and Holt, 2004). When predators feed on infected hosts we showed that their presence might be beneficial demographically for lowering disease prevalence and, in this case, also evolutionary for lowering host tolerance. Nevertheless, it is not clear yet how strong is predation contribution in limiting disease spillover from zoonotic reservoir (Ostfeld and Holt, 2004) and more studies like Stephenson et al. (2017) are needed for addressing the impact of predation on tolerance evolution.

To understand whether tolerance strategies can be exploited in designing new ways for disease control there needs to be both more experimental and theoretical work. From the experimental point of view, a better understanding of the mechanisms is needed behind tolerance and how they vary across different host groups and species (Vale et al., 2016). Attention should be given to the interplay between tolerance and resistance strategies, as new approaches might benefit from adopting a combination of the two (Hozé et al., 2018). From a modelling prospective, further studies would be beneficial to evaluate the possible long-term consequences of varying tolerance. Particularly, more work is required to address the effects of host-parasite coevolution (Little et al., 2010).

5.3 Further developments

We consider here some of the possible features that could be introduced to adapt the model analysed here to more realistic scenarios. As the attention on tolerance is strongly motived by its consequences on parasite counter-adaptation, it is important to develop mathematical models that consider coevolutionary dynamics (Little et al., 2010). In this sense, our study constitutes a good starting point to a better understanding of the role of predation on host-parasite coevolution. Not only the parasite could adapt to the host defence, but it would be interesting to see a more dynamical allocation of host resource between resistance and tolerance strategies (Restif et al., 2004; Best et al., 2008; Carval and Ferriere, 2010). Also, this model would benefit from the inclusion of antipredator behaviours and predator evolution, as in Toor and Best (2016).

The optimism on the development of tolerance-based treatments is rooted in the idea that tolerance does not impose strong selection on parasite fitness, since it does not reduce its prevalence. Nevertheless, some theoretical studies have objected that tolerance does impose a selection by changing the environment in which parasites grow. For example, if virulence and transmission are positively correlated, tolerance is expected to decrease the cost, in term of host mortality under infection, of faster transmission, allowing for the spreading of more virulent parasites (Restif and Koella, 2003). This effect is predicted to be more evident for longer lived hosts. We used a similar assumption in numerical simulations to address whether parasites could avoid extinction due to selection for lower tolerance, finding both outcomes possible. It would be useful to understand better under which circumstances parasite extinction is more likely. In fact, not every model predicts an increase in virulence for higher tolerance as host-parasite coevolution can lead to form of commensalism (Miller et al., 2006; Best et al., 2014). In this kind of scenario, parasite extinction should be difficult as selection promotes strains able to coexist with a widely spread parasite, making the environment unsuitable for less tolerant ones. Also Best et al. (2014) found evidence for cases of bistability between co-evolutionary outcomes making the dynamics sensitive to external perturbations. Therefore, to ensure our results are robust co-evolution should be considered. Particularly, it would be useful to understand under which conditions parasites are able to

avoid extinction at low tolerance by increasing virulence and transmission.

In this thesis and most other studies, the evolution of host defence is analysed by considering one type of defence a time, in order to fully understand its possible outcomes. A more realistic assumption would be to allow for more than one strategy to evolve simultaneously. One way is by introducing a trade-off between resistance and tolerance to resemble the genetic trade-off found by some experimental studies (Råberg et al., 2007). With such a trade-off, it becomes possible for a tolerance strategy to reach evolutionary branching, when mounting a defence is costly in terms on reproduction (Best et al., 2008). Therefore, adding a trade-off between resistance and tolerance strategies might increase the possibility for tolerance branching also under predation, showing how genetic variation for tolerance can be an effect of both host traits and external forces. Nevertheless, it is also possible to not define a trade-off explicitly and let the host to allocate resources from reproduction between tolerance and resistance strategies independently. This choice allows us to gain insights on the conditions that favour one or another defence and on what kind of correlation patterns can arise between the two. For example, tolerance is expected to evolve as pure strategy for high transmission rates (Restif et al., 2004; Carval and Ferriere, 2010), low virulence (Restif et al., 2004), and high costs of resistance (Restif et al., 2004; Carval and Ferriere, 2010). Moreover, tolerance and resistance can show both positive and negative correlations (Carval and Ferriere, 2010; Restif et al., 2004), also depending from the cost function assumed (Restif et al., 2004). Carval and Ferriere (2010) also let the parasite evolve virulence in both two-way and three-way coevolution, finding that virulence is lower when evolving with tolerance than with resistance, reaching the highest values for the three coevolving together. This result casts further doubts for evolution-proof treatments and calls for a better understanding of the complexity of coevolutionary patterns when more than one strategy evolves.

When host-parasite dynamics are embedded in a broader ecological framework that includes the interaction with a predator species, the impact of predation might not be limited only to demographic effects. Specifically, adaptation to predators might also impact host evolutionary response to infection. For example, predators can induce changes in host phenotypic traits, namely trait-mediated indirect effects (Preisser et al., 2005), that might benefit the spreading of the parasite (Duffy et al., 2011). Duffy et al. (2011) found that *Daphnia dentifera* individuals grew a larger body size to avoid predation by phantom midge larvae but also released a larger yield of yeast spores when infected. Furthermore, some studies have found a direct trade-off between anti-predator behaviour and defence to infection (Friman et al., 2009). This kind of trade-off can cause a reduction in the selective pressure of the host-parasite coevolutionary arms race and lead to the differentiation between hosts specialized in only one kind of defence(Friman and Buckling, 2013). This experimental finding has been backed up by the theoretical study of Toor and Best (2016), where in a model similar to the one analysed here, they introduced a trade-off between resistance and anti-predator defence. They found that selective pressure was determined by the most prevalent threat with evolutionary branching between the two defences possible when the two enemies den-

sity were similar. Therefore, we expect our result of higher investment in tolerance for low predator density and high disease prevalence to be further enhanced when hosts can invest in anti-predator behaviour.

Finally, it would be possible to allow also for the predator species to take part in the evolutionary process. While some theoretical studies have addressed the impact of predation on host-parasite evolution (Choo et al., 2003; Morozov and Adamson, 2011; Morozov and Best, 2012; Toor and Best, 2015) and coevolution (Best, 2018), fewer studies have taken into account predator counteradaptation to infected prey. Hoyle et al. (2012) analyse the possibility for parasite and predator extinction due to the evolution of host resistance and found in numerical simulations that the predator species could avoid extinction by rapidily increasing its capture coefficient. Similar simulations could be easily added in our model leading to predator extinction to become less likely for lower values of the capture coefficent. The lack of studies that consider predator evolution are because predator dynamics is usually assumed to be slower than host-parasite ones. To capture this, Kisdi et al. (2013) assumed a timescale separation between the fast demographic host-parasite dynamics and the slow timescale where evolution of virulence occurs together with the changes in predator density. This hypothesis leads to eco-evolutionary cycles where selective predation increases selection for higher virulence and reduced parasite prevalence, but parasites could escape extinction by lowering virulence. This result might be offset by tolerance evolution, as the key assumption is that predation is proportional to the level of mortality under infection. While the parasite benefits from decreasing virulence to avoid extinction due to predation, selection would not promote an increase in tolerance at a high predation density and low parasite one.

It is clear that further study of tolerance and its interaction in complex networks is needed to understand more about real-world disease systems and. We have contributed here by analysing the differences between tolerance and resistance strategies in driving parasite extinction and how predation can impact on host-parasite dynamics when tolerance evolves. We hope to see further theoretical work on the co-evolution between tolerance and parasite virulence under predation, as it could offer relevant insights for developing possible intervention strategies.

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