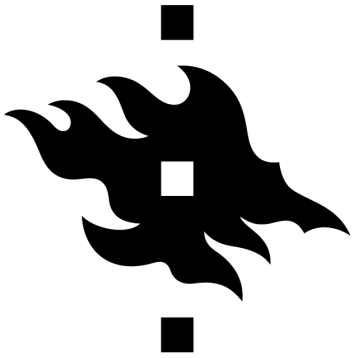

Master's Thesis

Master's Programme in Life Science Informatics

The Independent but Simultaneous Evolution of Host Resistance and Tolerance to Pathogens

Tanja Viitikko

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Tiivistelmä — Referat — Abstract

Pathogens are everywhere in nature, so organisms have developed various defense mechanisms in order to defend themselves against the pathogens. Two of the defense mechanisms are known as resistance and tolerance. Resistance describes the host's ability to avoid being infected by the pathogen, while tolerance describes the host's ability to reduce the fitness loss caused by the infection. We assume that investing into resistance reduces the transmission rate of the pathogens and investing into tolerance reduces the host's virulence. Developing the defense mechanisms is costly to the host. In this thesis, we assume that the resources invested into resistance and tolerance are taken away from the host's fecundity.

The independent but simultaneous evolution of resistance and tolerance is modeled with an SIS model. The model is studied with the methods of adaptive dynamics. We concentrate on finding continuously stable strategies, which serve as the evolutionary end points for the population. We study the varying ecological parameters to determine which strategies are optimal for the host in different environments.

We find that for low values of transmission rate, the hosts favor resistance over tolerance. When the transmission rate increases, resistance is traded for tolerance and the host benefits more from high tolerance. Low values of virulence result in tolerance being favored over resistance. Increasing virulence leads to a change in the defense mechanism as for high values of virulence investing into resistance is more beneficial to the host. The same holds for recovery rate, as tolerance is favored for low values of recovery rate and changed for resistance when the recovery rate increases.

Patterns and associations between resistance and tolerance are also studied. Positive correlation between resistance and tolerance is found with low values of transmission rate, low and high values of virulence and high values of recovery rate. Resistance and tolerance correlate negatively with high values of transmission rate, intermediate values of virulence and low values of recovery rate.

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Contents

Chapter 1

Introduction

Living organisms are likely to interact with pathogens or parasites during their lifetime [1]. Diseases and pathogens are everywhere in nature and they can influence the direction of evolution, as the host population dynamics are influenced by them [2]. In order to survive, hosts must develop defense mechanisms to avoid or limit infections. Infections in a population might for example lead to decrease in population density if additional deaths due to the disease are assumed. However, the host can evolve to defend itself against pathogens.

There are many types of defense mechanisms and the ways to model how hosts can defend themselves against parasites or pathogens can vary, as one aspect of the complex mechanisms is emphasised over some other. Regardless of the model type, it is often assumed that evolving a defense mechanism is costly to the host [3]. We are aiming to understand how the different defense mechanisms and their ecological feedback lead the evolution of variance.

In nature, the defense mechanisms of hosts can either get rid of an infection via an immune response or limit its spread within the host [4]. A defense mechanism can also be a physical barrier against a parasite, such as skin, gut wall or surface chemicals which exclude the pathogen. What these mechanisms have in common is that pathogens or parasites invasion fitness is essentially limited by them, and the fitness of the host is improved by them [4]. The two main defense mechanisms that the host can evolve are called resistance and tolerance and they can be presented in different forms [3], [4]. These are also the two defense mechanisms we study in this thesis.

Tolerance is defined as the host's ability to limit the damage an infection can cause [5]. It is used to describe a situation where a host's immune system evolves so that the host can live with the disease without it causing too much harm to the host. Tolerance is assumed to reduce virulence [3]. With high tolerance the hosts live longer and have time to spread the disease so the disease will become common in the population. Tolerance

will keep evolving until it costs unbearable amounts of resources from the host.

Resistance is defined as the host's ability to prevent an infection in the first place, and it means that a host evolves to reject the pathogens and avoids getting the disease. Resistance is assumed to reduce the transmission rate of the disease which will lead to decrease of the prevalence of the disease [6]. As it is usually assumed that evolving resistance draws resources away from reproduction, it is not useful to evolve resistance higher when the disease is rare in the population [4], [6].

In the literature on the defense mechanisms, resistance and tolerance have sometimes been used interchangeably [4]. The reason behind the mixing of the terms is that tolerance strategies, while they limit the spread of the pathogens when the host is already infected, are thought as resistance strategies because they also prevent the pathogen from reproducing. The simple way to separate resistance and tolerance is to think that resistance acts before the host gets infected and tolerance acts when the host is under an infection.

Several studies have explored how resistance and tolerance evolve on their own and the thesis will contain a literature review for these studies. Some studies have been conducted on the simultaneous evolution of resistance and tolerance, and we will also review these studies. Singh and Best [5] developed a model to study tolerance and resistance with a trade-off between them, assuming that a host cannot have high tolerance at the same time with high resistance and vice versa. Independent evolution of resistance and tolerance has also been studied by Restif and Koella [7] with the assumption that tolerance restores the fecundity of an infected host when infected hosts in general have lower fecundity than susceptible hosts.

We aim to formulate a new model for the host population dynamics assuming independent but simultaneous evolution of resistance and tolerance. We will assume that both tolerance and resistance draw resources away from reproduction. The method of analysis is adaptive dynamics [8]. The models of Singh and Best [5] and Restif and Koella [7] are used as a starting point for our model.

The full model is studied with numerical analysis, as there are several independent variables within the differential equations for the susceptible and infected hosts. The numerical analysis is performed with software Mathematica [9], which is also used for creating graphs of the results. Finally, we study how our results relate to the previous studies.

Chapter 2

Background

Early assumptions on resistance and tolerance were that due to limited resources, either tolerance or resistance could be developed but they could not mutually exist [1]. The simultaneous existence of multiple defense mechanisms in an individual could be argued to be unlikely as individual that has high tolerance would not benefit from resistance as the infection does not affect the host's fitness. Similarly, an individual that has high resistance would not need tolerance as the host is unlikely to get infected in the first place. This argument has been proven wrong as the simultaneous existence of resistance and tolerance has been found in different plant populations in nature [1], [10], [11]. Because of their mutual occurrence in nature, the development of both defense mechanisms should be studied.

Studying which defense strategies or strategy combinations are favored under which epidemiological conditions has been approached in two ways [7]. The first approach concentrates on finding the optimal resistance and tolerance for the best reproductive success of an individual that is threatened by a factor that limits the individual's fitness. This approach often predicts the success of either complete resistance or complete tolerance. Resistance and tolerance act in a similar way in these models when they both produce a peak in the fitness function and thus can be interchangeable. A trade-off between resistance and tolerance accounts for this kind of approach [4], [5], but also linear costs in the presence of independent strategies can lead to favoring one strategy in the absence of the other [12].

Another approach uses an already infected population as a starting point and studies whether a population with a different defense mechanisms can invade the infected population [7]. In these models, complete resistance is not predicted to become fixed when the resistance is costly [4], [6]. One aspect that limits the benefit of complete resistance is the host resistance itself, as highly resistant hosts are less likely to get infected and thus there is no benefit in evolving resistance for better when the costs are considered [4].

2.1 Previous studies

Resistance and tolerance have been studied in nature in a few different ways. Variation in resistance among the population has been found in freshwater crustacean, which has to defend itself against bacterial pathogens [13]. Studies on bird populations of kittiwakes [14] and barn swallows [15] have also shown that varying resistance genes have an effect on the offspring parasite load. Studies on a mosquito and its parasite [16] and a bumblebee population [17] have found evidence of varying tolerance as the reduction of the host's virulence. Tolerance has also been interpreted as the plant's ability to regrow in response to herbivory [18], [19].

Furthermore, empirical studies on plant populations and their ability to defend against herbivory or infections have made a clear distinction between resistance and tolerance within the studies [20], [21]. Simms and Triplett [20] found a distinction in fitness costs of resistance and tolerance in the tall morning glory, *Ipomoea purpurea*, when its defense mechanisms were studied against fungal isolates causing infections.

Fineblum and Rausher [21] also argued that understanding the evolution of defense against insects attacking *Ipomoea purpurea* requires the consideration of both resistance and tolerance. They showed that a trade-off between resistance and tolerance yields more diverse evolutionary outcomes than studying only resistance. While only studying resistance has previously resulted in either complete resistance or no resistance at all, introducing tolerance to the study showed that the host can favor a combination of no resistance and complete tolerance. In the latter case, resistance did not increase when the amount of insects increased even though with only resistance present the increase in herbivores resulted also in increased resistance.

In addition to empirical studies, the evolution of defense mechanisms has been studied theoretically with a focus on resistance [6], [22] or on tolerance [3], [23]. Both resistance and tolerance have been included in some studies like [4], [5], [7], [12]. Studies on both resistance and tolerance have often included a trade-off between resistance and tolerance, in which case resistance and tolerance are often regarded as mutually exclusive defense mechanisms that alternate within the same species.

The studies on both resistance and tolerance paint a better picture on the evolution of the host defense mechanisms, as the fitness consequences of a host can be affected by both of them. The fitness consequence of a disease is defined as the loss of fitness in case of infection multiplied by the subjection to an infection the host experiences during its lifetime [4]. The combination of resistance and tolerance plays a role in the hosts fitness, as resistance prevents host from getting infected and if the host gets infected, the fitness loss is reduced by tolerance.

The methods to model resistance and tolerance have varied widely on previous studies. We will introduce the models of Restif and Koella [7] and Singh and Best [5] in more detail

Table 2.1: List of symbols

Symbol	Description
S	Density of the susceptible hosts
I	Density of the infected hosts
α_0	Virulence
β_0	Transmission rate
b_0	Birth rate of uninfected hosts
q	Crowding coefficient
f	Fecundity of infected hosts
μ	Natural death rate
γ	Recovery rate of infected hosts
r	Resistance
τ	Tolerance

as they are the starting points for our own model. Both [7] and [5] study a SIS-model, where S denotes the density of susceptible hosts and I denotes the density of infected hosts. The contact process of the hosts is density-dependent and the population is assumed to be homogeneous and well-mixed.

In both models, all hosts are born uninfected at a rate b_0 and the crowding effect q reduces the host's fecundity. Infected hosts have a reduced fecundity with f denoting this reduction. The disease is transmitted at a rate β_0, infected hosts recover to susceptible at a rate γ and both susceptible and infected hosts die of natural causes at a rate μ. The disease causes additional deaths at a rate α_0. Resistance and tolerance are denoted with r and τ respectively. The descriptions of the symbols can be found in table 2.1.

In our notation, the model of Restif and Koella [7] reads as follows:

$$\begin{aligned} \frac{dS}{dt} &= b(r,\tau)(1-q(S+I))(S+fI) - \mu S + (\gamma - \beta_0 S)I, \\ \frac{dI}{dt} &= (\beta_0 S - \alpha_0 - \mu - \gamma)I. \end{aligned} \tag{2.1}$$

Restif and Koella [7] introduce resistance and tolerance to the model as an improved recovery rate and as an improved fecundity of the infected hosts when the infection is assumed to lower the fecundity. In our notation, $\gamma = \gamma_0 r$ and $f = f_0\tau$ where γ_0 and f_0 are the scaling parameters for the relative benefit of resistance and tolerance respectively.

They study four different functions for birth rate $b(r,\tau)$, each representing the costs of resistance and tolerance as independent reductions of the birth rate. The costs are associated either additively or multiplicatively and they are assumed to be proportional

to the investment in the defense or its square. The functions for birth rate are

$$b(r,\tau) = b_0(1 - c_r r - c_\tau \tau), \tag{2.2}$$
$$b(r,\tau) = b_0(1 - c_r r^2 - c_\tau \tau^2), \tag{2.3}$$
$$b(r,\tau) = b_0(1 - c_r r)(1 - c_\tau \tau), \tag{2.4}$$
$$b(r,\tau) = b_0(1 - c_r r^2)(1 - c_\tau \tau^2), \tag{2.5}$$

with c_r and c_τ representing the decreases in host birth rate per the unit of increase in resistance or tolerance or their squares. We will discuss the results of [7] in chapter 6 and compare them to our model.

Singh and Best [5] model resistance and tolerance as direct reductions on the transmission rate and virulence. Their model is of the following form in our notation:

$$\begin{aligned} \frac{dS}{dt} &= (b_0 - q(S+I))(S + fI) - \mu S - (\beta_0 - r_s)SI + \gamma I, \\ \frac{dI}{dt} &= (\beta_0 - r_s)SI - ((\alpha_0 - \tau_s)) + \mu + \gamma)I, \end{aligned} \tag{2.6}$$

with subscript s denoting the resistance and tolerance of Singh and Best. We will return to their definition of resistance and tolerance in chapter 4.

As we can see, there is no reduction in the birth rate of uninfected hosts. Singh and Best implement a trade-off between resistance and tolerance via reducing resistance every time tolerance increases. Thus they define $r_s = r_s(\tau_s)$ as the trade-off function which leads to the advantage of investing into tolerance happening in an expense of decreased resistance. We will also take a look at their results in chapter 6.

2.2 Costs of the defense mechanisms

Increasing the investment into resistance and tolerance is costly to the host and the cost is often assumed to affect the host's fecundity [4], [6], [23]. For example, the energy used to develop thicker skin is reduced from the energy available to reproduce and thus the birth rate is reduced. The existence of costs to other traits has been proven empirically and the costs have been established for example in studies of plant populations [20], [21], [24], [25], insect populations [16], [26] and bird populations [27], [28]. However, the costs might not be present in every natural population, as Mauricio *et al.* [12] showed when they did not find linear costs associated with tolerance in their study of the annual plant *Arabidopsis thaliana*.

The shape of the costs of the defense strategies plays a big role in the evolutionary outcome [7]. Resistance and tolerance can be interchangeable, mutually exclude each

other or complement each other in a mixed strategy depending on how the costs are defined. The actual shape of the costs in biological systems is difficult to define without accurate data. Determining the costs of resistance and tolerance via an epidemiological model could prove useful for future empirical studies especially on plant populations and their interactions with herbivores or pathogens [7].

Boots and Haraguchi [6] showed that the shape of the cost function for resistance has great involvement in defining evolutionary outcomes. They studied host resistance to pathogens by implementing a cost to the growth rate so that high transmission rate resulted also in high growth rate. Peaks at the maximal and minimal resistance were found when resistance was decreasingly costly, so the host's favored either complete resistance or no resistance at all. However, when the cost of resistance increased, a single evolutionarily stable strategy appeared and the host maintained a stable transmission rate in response to the pathogen.

Restif and Koella [7] concentrated on varying the form of costs of the two defense strategies in their study. They found that mixed strategies are favored if the costs of defenses are nonlinear. In the case of linear costs, the form of combining the two costs affects which strategies are favored. Mixed strategies seem to develop if the costs are associated in a multiplicative way and fall under the same size category, whereas pure strategies are favored if the costs are associated in an additive way. They also showed that concentrating only on one strategy can hide the actual costs of the defense strategies when the two independent but simultaneously evolving strategies are studied. In the case of quadratic additive costs, fecundity seems to correlate negatively with tolerance when the transmission rate increases. Resistance does not show similar correlation, which might lead to a false impression that resistance appears without costs.

A negative correlation between resistance and tolerance has been found in empirical studies [20], [21]. Roy and Kirchner [4] argued that hosts with either high tolerance or high resistance would be in a better position than the hosts with combined strategies if both defense mechanisms are costly, and thus resistance and tolerance would be negatively correlated. That is why some studies like Best *et al.* [3] and Singh and Best [5] assumed a trade-off between resistance and tolerance. According to Best *et al.* [3] a trade-off between resistance and tolerance, where increased tolerance results in lower resistance, can lead to evolutionary branching when the cost of the investment in the defense mechanisms is included in the trade-off that affects the host's fecundity. Without the cost the trade-off does not lead to evolutionary branching.

The correlations are not universal, and one example of this is by Mauricio *et al.* [12] who found that *Arabidopsis thaliana* benefitted most by maintaining both resistance and tolerance. Restif and Koella [7] also proved that without a negative association between the two defense mechanisms, variation in resistance and tolerance is not limited to only one direction. In some environment resistance might be high when tolerance is low, but

it is also possible that resistance and tolerance appear high simultaneously when the evolutionary patterns are studied in different environments.

When studying the evolutionary outcomes of the defense mechanisms, one should not automatically assume trade-offs between resistance and tolerance as it is possible that the defense mechanisms do not have a genetic negative correlation and so they can mutually exist [1], [12]. The possible patterns of association between resistance and tolerance could be detected based on environmental factors if resistance and tolerance were studied as independent strategies that complement each other in their effects on the individuals or on disease transmission [7].

2.3 Evolutionary feedback

In the scale of a host, resistance and tolerance traits can have the same short-term benefit of reducing the fitness consequences of the infection. However, the evolutionary outcomes of these traits can be fundamentally different as the population dynamics are influenced by resistance and tolerance in different ways [1], [4]. The prevalence of the disease is also influenced by the way the host population evolves [5].

Concentrating only on developing resistance would not benefit the population in a long run [4]. When the population becomes very resistant against a pathogen, the pathogen cannot survive, and its incidence decreases as there is no longer as many hosts that could spread the pathogen. Once there are only few pathogens present in the population, there is not any advantage in having a high resistance or developing it even further. Thus, the selection in a host population does not allow resistance develop to perfect and the pathogens can start to grow again. The selection for resistance does not become fixed so the diseases cannot be fully eliminated by resistance.

Tolerance has an opposite effect on the host population and pathogens [4]. As the tolerance gene spreads in the population, the disease can become more common, and the advantage of developing tolerance rises. A host with high tolerance is less likely to experience virulence, so the hosts will continue to spread the pathogens. The selection for tolerance genes will eventually fix the tolerance to a certain level.

In conclusion, the spread of resistance as the defense strategy is limited by the negative feedback environment, while the tolerance benefits from a positive feedback environment. The feedback on the disease prevalence also differs depending on the strategy in which the investment increases [5]. Additionally, the varying epidemiological parameters show different effects on the prevalence of the disease. Singh and Best [5] found for example that with increasing virulence, the hosts benefit more from increasing resistance and the feedback environment becomes negative, meaning that the disease prevalence decreases. In the case of increasing transmission rate, they found that tolerance was favored which

resulted in positive feedback environment and increasing disease prevalence.

According to Singh and Best [5], the prevalence of the disease is also dependent on the host's recovery rate. Higher recovery rate accounted for a lower disease prevalence when there was no trade-off between resistance and tolerance but rather the strategies were fixed, in other words the host did not evolve. With the trade-off present and the host evolving, the disease prevalence was contrarily higher with high recovery rate. The incidence of infection seemed to increase indirectly via the higher recovery rate, as opposed to the intuitive argument of higher recovery rate leading to a lower disease prevalence. The indirect increase is due to a longer lifespan of infected hosts resulting from a higher investment into tolerance, which makes up for the costs of having more infected hosts.

Chapter 3

Adaptive dynamics

The main method of this thesis is adaptive dynamics. Adaptive dynamics is a mathematical theory that is used to study how long-term evolutionary changes in a population occur from natural selection and small mutations on the individual level. We begin with a resident population, a population which shares a unique strategy and is monomorphic with regards to this strategy [29]. Then we introduce a mutant population, which is a population with a slightly different strategy compared to the resident population. The term *trait* is also commonly used to portray a strategy or strategy set in the literature. In this thesis, we use trait to refer to resistance or tolerance, and these two traits form a trait vector which we call a strategy.

The main question is how the population dynamics of the resident and mutant evolve over time. Which strategy provides the best abilities to survive or invade a population? What are the long-term consequences in terms of evolving new strategies based on previous invasion or extinction events? Adaptive dynamics has tools to answer these questions. Resident and mutant are used to refer to both the individual of the population and the whole population. This section is mainly based on Geritz *et al.* [8], which introduces the method in detail. In the beginning of this chapter, we introduce the basic concepts of adaptive dynamics with one trait value, and later in section 3.3 we extend these concepts to include the evolution of two different trait values.

The four core assumptions of adaptive dynamics are the following:

1. Clonal reproduction or strong associative mating

   By this assumption, offspring have initially the same strategy as their parents, unless a mutation occurs. Clonal reproduction helps us to focus on ecological processes instead of complex genetic variations.

2. Time-scale separation

Mutations happen on a relatively long timescale compared to a fast timescale of population dynamics. We assume that the changes on individual level are fast so that the population has reached an equilibrium or other population attractor before a mutation happens.

3. Initially rare mutant population

   Having few mutant individuals present when the resident population has reached an attractor allows for the possible invasion to be modeled by the growth rates of the strategies. This is also biologically reasonable, as a new mutation is not likely to appear in large amounts when it first occurs in nature.

4. Small changes when a mutation occurs

   Once a mutation happens, it does not drastically change the strategy of the host. However, we do not assume infinitesimally small changes. This allows for the strategy dynamics to be analysed with differential calculus.

These assumptions give us the framework to describe the evolutionary processes with systems of differential equations.

3.1 Invasion fitness and selection gradient

Whether a mutant can invade a resident population or not is determined by its invasion fitness. Invasion fitness describes the long term growth of a mutant population when it is introduced to an environment set by the resident population [30]. Consider a resident with a strategy x and a mutant with a strategy y. We write the invasion fitness of this mutant as $s_x(y)$. Note that an individual with a same strategy as the resident has invasion fitness $s_x(x) = 0$ as the resident population has reached a steady state for the strategy x.

If the invasion fitness is positive, $s_x(y) > 0$, the mutant can invade the resident population. However, there is a probability of invasion not happening as the small initial density of the mutant allows for random extinction before invasion can happen. If the invasion fitness is negative, $s_x(y) < 0$, the mutant will not invade the resident population and is headed to extinction.

As we assume small mutation steps, we can take a linear approximation of the invasion fitness:

$$s_x(y) = s_x(x) + \left[\frac{\partial s_x(y)}{\partial y}\right]_{y=x} (y - x). \tag{3.1}$$

We want to pay attention to the *selection gradient*, which is the derivative of the invasion with respect to the mutant strategy evaluated at the resident strategy,

$$\left[\frac{\partial s_x(y)}{\partial y}\right]_{y=x}. \tag{3.2}$$

From (3.1) we see that the sign of the selection gradient determines whether a mutant can invade or not. If the selection gradient is negative, only mutants with $y < x$ can invade, and if the selection gradient is positive, only mutants with $y > x$ can invade.

When we set the selection gradient to zero and solve for the strategy x, we find a singular strategy (or a singularity) which we denote by x^*. With invasion in mind, singular strategies are either the best or the worst strategy values an individual can have as these strategies are also maxima and minima of the invasion fitness.

3.2 Properties of the singular strategies

We introduce four important properties that are useful when one wants to analyze singular strategies. An *evolutionarily stable strategy* (ESS) is a singular strategy that cannot be invaded [8]. This means that every mutant strategy y in the neighbourhood of the singular strategy x^* is unable to invade, $s_x^*(y) < 0$ with all $y \neq x^*$. The invasion fitness reaches a (local) maximum at the ESS,

$$\left[\frac{\partial^2 s_x(y)}{\partial y^2}\right]_{y=x} < 0. \tag{3.3}$$

A *convergence stable strategy* (CS) is a singular strategy that is a (local) attractor [8], [29]. If there is a resident strategy x near the singular strategy x^*, the mutant strategy y that is able to invade the resident is even closer to x^*, in other words $s_x(y) > 0$ for $x < y < x^*$ and $x^* < y < x$. For a singularity that is CS the selection gradient is positive for $x < x*$ and negative for $x > x^*$, so the sign of the selection gradient changes at the singularity. Thus, at the CS the derivative of the selection gradient should be negative,

$$\left[\frac{\partial}{\partial x}\left[\frac{\partial s_x(y)}{\partial y}\right]_{y=x}\right]_{x=x^*} = \left[\frac{\partial^2 s_x(y)}{\partial x \partial y} + \frac{\partial^2 s_x(y)}{\partial y^2}\right]_{y=x=x^*} < 0. \tag{3.4}$$

If both x and y have a positive invasion fitness against each other, $s_x(y) > 0$ and $s_y(x) > 0$, the strategies can *mutually invade*. If mutual invasion is possible near a convergence stable singular strategy, an initially monomorphic population evolves eventually

to a dimorphic population [8]. The conditions for a dimorphic population to evolve to monomorphic again depend on the evolutionary stability of the strategies.

When a singular strategy is convergence stable but is not an ESS, we find a *branching point*. In this situation a dimorphic population will stay dimorphic, and the population will not return to the monomorphic state. If the singularity is not an ESS, $\left[\frac{\partial^2 s_x(y)}{\partial y^2}\right]_{y=x^*} > 0$ holds and the invasion fitness reaches its minimum value at the singularity ($s_x(x^*) = 0$) as a convex function. As x^* is not an ESS, all nearby mutants have positive invasion fitness and are able to invade. With x_1 and x_2 as the resident strategies in a situation of small perturbations, the mutant strategies further away from x^* than the resident strategies can invade. The successful invasion events push the two strategies further away from each other and the population will live on as dimorphic. The process of initially monomorphic population evolving into dimorphic population is called *evolutionary branching.* The branching points are repellors for dimorphic populations, but because of the convergence stability, they are attractors for monomorphic populations.

If a singular strategy is both ESS and CS, it is called a *continuously stable strategy* (CSS). The long-term evolutionarily consequences for a monomorphic population are characterized by continuously stable strategies. If a CSS starts off as rare strategy, it might be unable to take over other strategies and can only be approached from two directions. Mutual invasibility opens the way for a converging dimorphism when a singulars strategy is continuously stable.

Consider a resident singular strategy x^* and small perturbations from this strategy that are also resident strategies, x_1 and x_2. If x^* a CSS, x_1 and x_2 are on the opposite sides of $x*$. In this case, a mutant strategy y that is closer to the singular strategy x^* than x_1 and x_2, can invade the resident strategies x_1 or x_2. The distance between the two strategies narrows if the population stays dimorphic. However, the dimorphism is only temporary. As these invasion steps are repeated, the dimorphism converges towards x^* [29]. Once the mutant is sufficiently close to x^*, the population becomes monomorphic as the mutant replaces both resident strategies [8]. Strategies that are further away from x^* than x_1 and x_2 are not able to invade.

3.3 Properties of the singular strategies in two dimensions

In the case of a strategy which consists of two traits, we have to extend the definition of the selection gradient (3.2) to include both traits. Consider a resident with strategy (x, y), and a mutant with a strategy (x_m, y_m). The mutant's invasion fitness is described by $s_{x,y}(x_m, y_m)$. As in one dimension, when we take a linear approximation of the invasion

fitness we find the selection gradients for each trait separately,

$$\left[\frac{\partial s_{x,y}(x_m, y_m)}{\partial x_m}\right]_{x_m=x} \quad \text{and} \quad \left[\frac{\partial s_{x,y}(x_m, y_m)}{\partial y_m}\right]_{y_m=y}. \tag{3.5}$$

By setting the selection gradients to zero, we can find single trait singularities or a joint singularity (x^*, y^*). To study the evolutionary stability, we must consider whether mutants can differ only in one trait or if they could differ in both traits simultaneously. The biologically reasonable choice would be to let them differ in both, as the genes that control the traits might not be independent and both traits might be able to evolve concurrently.

To study the possible difference in both traits we need to consider the invasion fitness as a function of the two mutant traits and make sure that the surface of this function is a dome that goes down in every direction from the singularity, i.e. the singularity is a multivariant maximum. However, to start off we might want to check whether the invasion fitness reaches a maximum along the horizontal and vertical line, as if either one is does not happen, the singular strategy is not a multivariant maximum. This can be checked by determining whether the second derivatives of the selection gradients (which we note by X_m and Y_m) are negative,

$$X_m = \left[\frac{\partial^2 s_{x,y}(x_m, y_m)}{\partial x_m^2}\right]_{x_m=x=x^*} < 0, \quad Y_m = \left[\frac{\partial^2 s_{x,y}(x_m, y_m)}{\partial y_m^2}\right]_{y_m=y=y^*} < 0. \tag{3.6}$$

If we find that X_m and Y_m are negative, the next step is to study the Hessian matrix and the second partial derivative test for the invasion fitness function. This theorem helps to determine is a singular strategy a minimum, maximum or a saddle point of the invasion fitness [31].

The Hessian matrix H consists of the second order partial derivatives of the twice differentiable function $s : \mathbb{R}^2 \to \mathbb{R}$:

$$H = \begin{bmatrix} \frac{\partial^2 s_{x,y}(x_m,y_m)}{\partial x_m^2} & \frac{\partial^2 s_{x,y}(x_m,y_m)}{\partial x_m \partial y_m} \\ \frac{\partial^2 s_{x,y}(x_m,y_m)}{\partial x_m \partial y_m} & \frac{\partial^2 s_{x,y}(x_m,y_m)}{\partial y_m^2} \end{bmatrix}. \tag{3.7}$$

If the Hessian is positive definite (all of its eigenvalues are positive) at the singular strategy, f has a local minimum at the singular strategy [32]. If the Hessian is negative definite, f has a local maximum at the singular strategy. As we have a 2x2 matrix, we can use the determinant of the Hessian matrix $D(x_m, y_m)$ to determine the nature of the singular strategies, as the determinant is the product of the eigenvalues.

Theorem 3.8. ***Second derivatives test.*** *Let $s_{x,y}(x_m, y_m)$ be a continuous function in the neighbourhood of a singular strategy (x^*, y^*) and have all of its first and second partial derivatives also be continuous in the same neighbourhood. Let*

$$D(x_m, y_m) = \left[\frac{\partial^2 s_{x,y}(x_m, y_m)}{\partial x_m^2} \frac{\partial^2 s_{x,y}(x_m, y_m)}{\partial y_m^2} - \left[\frac{\partial^2 s_{x,y}(x_m, y_m)}{\partial x_m \partial y_m} \right]^2 \right]. \tag{3.9}$$

- *If $D(x^*, y^*) < 0$, then f has a saddle point at (x^*, y^*).*
- *If $D(x^*, y^*) > 0$ and $X_m > 0$, then $s_{x,y}(x_m, y_m)$ has a local minimum at (x^*, y^*).*
- *If $D(x^*, y^*) > 0$ and $X_m < 0$, then $s_{x,y}(x_m, y_m)$ has a local maximum at (x^*, y^*).*
- *If $D(x^*, y^*) = 0$, there is not enough information to tell the nature of the singular strategy.*

Thus, if the invasion fitness has a local maximum at (x^*, y^*), the singularity is an ESS. Similarly to the ESS conditions, we can extend the notions of convergence stability to include a strategy that consists of two traits. The singular strategy is convergence stable in one dimension if the following conditions hold with either x or y fixed.

$$\left[\frac{\partial^2 s_{x,y}(x_m, y_m)}{\partial y \partial y_m} + Y_m \right]_{y_m = y = y^*} < 0, \tag{3.10}$$

$$\left[\frac{\partial^2 s_{x,y}(x_m, y_m)}{\partial x \partial x_m} + X_m \right]_{x_m = x = x^*} < 0. \tag{3.11}$$

These conditions are not enough to provide us knowledge of convergence stability when we are studying convergence stability in more than one dimension. To determine the convergence stability in every direction, we use *phase plane analysis*. If the convergence stability cannot be determined by phase plane analysis, we will turn to the *canonical equation of adaptive dynamics* [33]. With these quantities we can determine the evolutionary paths of mutants and different strategies.

Chapter 4

The model

The system we study is a SIS system, similar to what Singh and Best [5] and Restif and Koella [7] have studied. We assume that the susceptible hosts S and the infected hosts I have a density-dependent contact process and that the host population is well-mixed and homogeneous. Similarly to Singh and Best [5], we consider resistance as a factor that reduces the transmission rate and tolerance as a factor that reduces the virulence.

The difference to Singh and Best's system comes from the fact that in their study, resistance and tolerance are dependable on each other via a trade-off, where increasing resistance leads to a decrease in tolerance. In our study, resistance and tolerance are independent, but they both have an effect on the birth rate. Restif and Koella [7] also studied how independent resistance and tolerance affect the host's fecundity, but they modeled resistance and tolerance as factors that are linked to the infected host's fecundity and recovery rate.

Singh and Best [5] model resistance and tolerance respectively as direct reductions on the transmission rate and virulence. We implement these reductions by thinking that the transmission rate and virulence are functions that depend on the amount of energy that is invested into the development of resistance and tolerance. The system that we study is given by the following differential equations:

$$\begin{aligned} \frac{dS}{dt} &= (b(r,\tau) - q(S+I))(S+fI) - \mu S - \beta(r)SI + \gamma I, \\ \frac{dI}{dt} &= \beta(r)SI - (\alpha(\tau) + \mu + \gamma)I. \end{aligned} \tag{4.1}$$

The birth rate b of the susceptible hosts is dependable on the amount of energy used to the development of resistance and tolerance. Every host is born uninfected. The fecundity is reduced by the crowding effect described by q. Additionally, the fecundity of

Table 4.1: List of symbols

Symbol	Description
S	Density of the susceptible hosts
I	Density of the infected hosts
$\alpha(\tau)$	Tolerance-dependent virulence
$\beta(r)$	Resistance-dependent transmission rate
$b(r,\tau)$	Birth rate of uninfected hosts
b_0	Birth rate without resistance or tolerance
α_0	Virulence without tolerance
β_0	Transmission rate without resistance
r	Energy invested into development of resistance
τ	Energy invested into development of tolerance
c_1	Return parameter of tolerance
c_2	Return parameter of resistance
c	Scaling parameter
q	Crowding coefficient
f	Fecundity of infected hosts
μ	Natural death rate
γ	Recovery rate of infected hosts

the infected hosts is reduced by the factor f. Both susceptible and infected hosts have a natural death rate μ. Infected hosts recover at rate γ, and recovering means that they become susceptible again. The transmission rate β is dependent on the amount of energy invested into developing resistance r, and the virulence is dependent on the amount of energy invested into tolerance τ. The symbols are gathered in table 4.1. We define birth rate, transmission rate and virulence as the following functions:

$$b(r, \tau) = b_0(1 - c(r^2 + \tau^2)) \tag{4.2}$$

$$\alpha(\tau) = \alpha_0 \left(1 - \frac{\tau}{\tau + c_1}\right), \tag{4.3}$$

$$\beta(r) = \beta_0 \left(1 - \frac{r}{r + c_2}\right). \tag{4.4}$$

The costs of resistance and tolerance are not necessarily easily combined, for example a lot might need to be invested into resistance in order to decrease the transmission rate via visible amount, which would mean that resistance is very costly and investment into tolerance would be almost negligible or the other way around. Thus, we do not think of $b(r, \tau)$ as a direct function of resistance and tolerance but rather as a function of how much energy is invested into developing either of them. So, r and τ denote the amount of energy a host invests to resistance and tolerance, respectively.

In nature, the form of these costs is hard to determine [7]. The association of the costs of different strategies could be linear or multiplicative depending on the life form that is studied. As we assume that resistance and tolerance have independent effects on the birth rate, we say that the amounts of energy invested to them are reduced additively from the birth rate and the investment to each strategy is squared. We assume that the cost of resistance and tolerance is proportional to the square of the investment of both trait values.

We might want to consider the case of a linear function for the birth rate, where

$$b_{lin}(r, \tau) = b_0(1 - c(r + \tau)). \tag{4.5}$$

However, the linear case is trivial as r and τ are truly the energy that is reduced from reproduction. We cannot find any biologically admissible singular strategies that would be CSS points with linear additive costs. The reason behind this is that the possible interior singularities are not evolutionary stable when the host investments simultaneously to

both traits, $r > 0$ and $\tau > 0$. The host will favor either pure resistance or pure tolerance. Hence, we will study a nonlinear function for the birth rate. The function for birth rate is similar to one of the functions studied in [7].

The functions for transmission rate and virulence both have a hyperbolic function inside the brackets, which is biologically reasonable as it should not be useful to invest high amounts of energy to improving resistance. After a certain amount the investment does not help and we get diminishing returns.

The return parameter of tolerance is expressed by the parameter c_1 which is the decrease in virulence per unit of increase in $\frac{\tau}{\tau+c_1}$. Similarly the return parameter of resistance is expressed by the parameter c_2 which is the decrease in transmission rate per unit of increase in $\frac{r}{r+c_2}$. The higher the return parameter, the less the epidemiological parameter will decrease when the host invests to the defense mechanisms.

The host's environment is represented by all the other parameters that are independent of r and τ. It is good to note that r and τ do not have a theoretical negative connection [7]. We can assume that the costs of resistance and tolerance should not change form during an infection, at least not when we disregard the possibility of phenotypic variation [7].

The resistance and tolerance we introduce differ from the resistance and tolerance of Singh and Best [5], which we denoted with r_s and τ_s in section 2.1. When we present our resistance-dependent transmission rate as $\beta(r) = \beta_0 - r_s$ and tolerance-dependent virulence as $\alpha(\tau) = \alpha_0 - \tau_s$ we find that resistance and tolerance that correspond to our model in Singh and Best's model are

$$r_s = \frac{\beta_0 r}{r + c_2} \quad \text{and} \quad \tau_s = \frac{\alpha_0 \tau}{\tau + c_1}. \tag{4.6}$$

4.1 Equilibria and stability

We begin the analysis by studying the equilibria of the system (4.1). The equilibrium solution is found by looking for a solution that does not change in time. Thus, we set our equations from (4.1) to zero and solve for the densities of the susceptible and infected hosts.

There are three biologically reasonable equilibria and one equilibrium where the infected hosts would have negative population density, so we concentrate on the first three. The first one is a trivial $(0, 0)$ equilibrium. The second one is a disease-free equilibrium

$(S, I) = (S_0, I_0)$, where

$$\begin{aligned} S_0 &= \frac{b(r,\tau) - \mu}{q}, \\ I_0 &= 0. \end{aligned} \tag{4.7}$$

The third and the most interesting one is the endemic equilibrium $(S, I) = (\hat{S}, \hat{I})$, where

$$\begin{aligned} \hat{S} &= \frac{\mu + \alpha(\tau) + \gamma}{\beta(r)}, \\ \hat{I} &= \frac{1}{2f}\left(-X + \sqrt{X^2 + 4f\left(\frac{\mu + \alpha(\tau) + \gamma}{\beta(r)}\right)\left(\frac{b(r,\tau) - \mu}{q} - \frac{\mu + \alpha(\tau) + \gamma}{\beta(r)}\right)}\right) \end{aligned} \tag{4.8}$$

with

$$X = (1 + f)\frac{\mu + \alpha(\tau) + \gamma}{\beta(r)} + \frac{fb(r,\tau) - \mu - \alpha(\tau)}{q},$$

when $f \neq 0$. If $f = 0$, we have

$$\hat{I}_{f=0} = \frac{(\mu + \alpha(\tau) + \gamma)(-q(\mu + \alpha(\tau) + \gamma) + \beta(r)(b(r,\tau) - \mu))}{\beta(r)(q(\gamma + \mu + \alpha(\tau)) + \beta(r)(\mu + \alpha(\tau)))}. \tag{4.9}$$

We need the endemic equilibrium $(\hat{S}, \hat{I})$ to be positive as otherwise there would be no infected individuals. When the fecundity is not zero, for $\hat{I} > 0$ we require that the square root in $\hat{I}$ is greater than X. In addition, the endemic equilibrium exists if the discriminant of the square root in $\hat{I}$ is positive. Thus, one required condition is

$$\frac{b(r,\tau) - \mu}{q} > \frac{\mu + \alpha(\tau) + \gamma}{\beta(r)}. \tag{4.10}$$

The condition (4.10) is also the condition for $(\hat{S}, \hat{I})$ to be positive when $f = 0$. We will check numerically that all the $(\hat{S}, \hat{I})$ equilibria presented in this thesis meet these conditions.

Next we want to determine the stability of equilibria. If the eigenvalues of the Jacobian matrix for the given system at the equilibrium have negative real parts, the equilibrium is linearly stable. We also utilize the fact that we have a two-dimensional system and use the trace and the determinant of the Jacobian to determine the stability of one equilibrium.

The theory of linear stability analysis can be studied in more detail for example from [34]. We omit the arguments of the functions for this part.

The Jacobian matrix of the system (4.1) is

(4.11)
$$J(S,I) = \begin{bmatrix} b - q(S+I) - q(S+fI) - \mu - \beta I & f(b - q(S+I)) - q(S+fI) - \beta S + \gamma \\ \beta I & \beta S - (\alpha + \mu + \gamma) \end{bmatrix}.$$

We evaluate this Jacobian at the equilibria. $J(S,I)$ at $(0,0)$ becomes

$$J(0,0) = \begin{bmatrix} b - \mu & fb + \gamma \\ 0 & -\alpha - \mu - \gamma \end{bmatrix}. \tag{4.12}$$

$J(0,0)$ is an upper triangular matrix, so the eigenvalues of $J(0,0)$ are its diagonal elements. The first eigenvalue $-\alpha - \mu - \gamma$ is clearly negative, and the second eigenvalue $b - \mu$ is positive when the endemic equilibrium exists and the system is biologically viable. As we have one negative and one positive eigenvalue, (0,0) is a saddle point.

The second equilibrium (S_0, I_0) has a Jacobian

$$J(S_0,I_0) = \begin{bmatrix} \mu - b & \gamma + f\mu + \mu - b - \frac{\beta(b-\mu)}{q} \\ 0 & \frac{\beta(b-\mu)}{q} - \alpha - \mu - \gamma \end{bmatrix}. \tag{4.13}$$

$J(S_0, I_0)$ is also an upper diagonal matrix with eigenvalues on the diagonal. The first eigenvalue $\mu - b$ is negative when (0,0) is a saddle point, so we have at least one negative eigenvalue. When the condition (4.10) holds and the endemic equilibrium (4.8) exists, the second eigenvalue $\frac{\beta(b-\mu)}{q} - \alpha - \mu - \gamma$ is positive. Thus the second equilibrium is also a saddle point. When the endemic equilibrium does not exist, this is the only stable equilibrium of the system (4.1).

The endemic equilibrium $(\hat{S}, \hat{I})$ has a much more complicated Jacobian when we substitute the equilibrium to $J(S,I)$, so we do not write it out. After some algebra we find that

$$\begin{aligned} \det(J(\hat{S},\hat{I})) = {} & (b - q(\hat{S}+\hat{I}) - q(\hat{S}+f\hat{I}) - \mu - \beta\hat{I})(\beta\hat{S} - (\alpha+\mu+\gamma)) \\ & - \beta\hat{I}(f(b - q(\hat{S}+\hat{I})) - q(\hat{S}+f\hat{I}) - \beta\hat{S} + \gamma), \end{aligned} \tag{4.14}$$

and

$$\mathrm{Tr}(J(\hat{S},\hat{I})) = b - q(\hat{S}+\hat{I}) - q(\hat{S}+f\hat{I}) + \beta(\hat{S}+\hat{I}) - \alpha - \gamma - 2\mu. \tag{4.15}$$

For stability, we require that $\det(J(\hat{S},\hat{I})) > 0$ and $\mathrm{Tr}(J(\hat{S},\hat{I})) < 0$. We will check numerically that all the presented $(\hat{S},\hat{I})$ equilibria fulfill these conditions.

4.2 Invasion fitness

Once resident population has reached an equilibrium, a mutant strategy can spread only if that equilibrium is unstable in a system with both resident and mutant strategies present [5]. We use invasion fitness to investigate the mutant's ability to invade the host population. To derive the invasion fitness, we consider the dynamics of a population with both resident and mutant host. We denote the quantities of a mutant host with a subscript m and the quantities of the resident host with a subscript r. The full system is given by

(4.16)
$$\begin{aligned}
\frac{dS_r}{dt} &= [b(r_r,\tau_r) - q(S_r + I_r + S_m + I_m)](S_r + fI_r) - \mu S_r - \beta(r_r)S_r(I_r + I_m) + \gamma I_r,\\
\frac{dI_r}{dt} &= \beta(r_r)S_r(I_r + I_m) - (\alpha(\tau_r) + \mu + \gamma)I_r,\\
\frac{dS_m}{dt} &= [b(r_m,\tau_m) - q(S_r + I_r + S_m + I_m)](S_m + fI_m) - \mu S_m - \beta(r_m)S_m(I_r + I_m) + \gamma I_m,\\
\frac{dI_m}{dt} &= \beta(r_m)S_m(I_r + I_m) - (\alpha(\tau_m) + \mu + \gamma)I_m.
\end{aligned}$$

When we assume the mutant to be rare in the beginning, we can assume that the resident population has reached a stable equilibrium $(\hat{S}, \hat{I})$, which is the equilibrium from (4.8) with $f \neq 0$. Thus, the mutant dynamics are described by

(4.17)
$$\begin{aligned}
\frac{dS_m}{dt} &= [b(r_m,\tau_m) - q(\hat{S} + \hat{I})](S_m + fI_m) - \mu S_m - \beta(r_m)S_m\hat{I} + \gamma I_m,\\
\frac{dI_m}{dt} &= \beta(r_m)S_m\hat{I} - (\alpha(\tau_m) + \mu + \gamma)I_m.
\end{aligned}$$

A 4x4 Jacobian matrix J_{full} with the resident at the equilibrium and mutant not present determines the transversal stability of the full system (4.16). This matrix is formed by four independent 2x2 matrices as following:

(4.18)
$$J_{full} = \begin{bmatrix} J_{res} & J_{oth} \\ \mathbf{0} & J_{mut} \end{bmatrix}, \text{ with}$$

(4.19)
$$J_{res} = \begin{bmatrix} b(r_r,\tau_r) - \mu - q(\hat{S} + \hat{I}) - q(\hat{S} + f\hat{I}) - \beta(r_r)\hat{I} & f(b(r_r,\tau_r) - q(\hat{S} + \hat{I})) - q(\hat{S} + f\hat{I}) - \gamma - \beta(r_r)\hat{S} \\ \beta(r_r)\hat{I} & \beta(r_r)\hat{S} - (\alpha(\tau_r) + \mu + \gamma) \end{bmatrix},$$

$$J_{oth} = \begin{bmatrix} -q(\hat{S}+f\hat{I}) & -q(\hat{S}+f\hat{I}) - \beta(r_r)\hat{S} \\ \beta(r_r)\hat{S} & 0 \end{bmatrix}, \tag{4.20}$$

$$\begin{aligned} J_{mut} &= \begin{bmatrix} b(r_m,\tau_m) - q(\hat{S}+\hat{I}) - \mu - \beta(r_m)\hat{I} & fb(r_m,\tau_m) - fq(\hat{S}+\hat{I}) + \gamma \\ \beta(r_m)\hat{I} & -(\alpha(\tau_m)+\mu+\gamma) \end{bmatrix} \\ &= \begin{bmatrix} A & B \\ C & D \end{bmatrix}. \end{aligned} \tag{4.21}$$

The lower left block is a zero matrix (denoted by a bolded 0). We see that J_{full} is an upper triangular block matrix and the stability is determined by the blocks on the diagonal. As the first block is the block of the resident dynamics which we know to be stable, the stability is determined by the lower right block J_{mut} which describes the mutant dynamics at 0.

The eigenvalues of the matrix are used to investigate the stability of the system. The maximum eigenvalue of J_{mut} determines the invasion fitness of the mutant strategy [8], [30]. The eigenvalues of J_{mut} are

$$\lambda^+, \lambda^- = \frac{1}{2}[A+D \pm \sqrt{(A+D)^2 - 4(AD-BC)}] = \frac{1}{2}[A+D \pm \sqrt{(A-D)^2 + 4BC}]. \tag{4.22}$$

As we can see, C is positive and D is negative. For B to be positive, we require $b(r_m,\tau_m) > q(\hat{S}+\hat{I})$, which holds by default as the fecundity of the hosts exceeds the amount the fecundity is reduced by the crowding effect. We do not know the sign of A.

Because B and C are positive, the discriminants of the eigenvalues are positive and there are always two real eigenvalues. When $A < 0$, we find that $\lambda^- < 0$ because D is also negative. When $A \geq 0$ and $D < 0$, we have that $|A+D| \leq |A-D|$ and therefore $\lambda^- < 0$. We see that λ^- is always negative and smaller of the two eigenvalues, so λ^+ is the maximum eigenvalue and also the invasion fitness.

When $\lambda^+ < 0$ there is no invasion and $\det(J_{mut}) = \lambda^-\lambda^+ > 0$. When $\lambda^+ > 0$ the mutant can invade and $\det(J_{mut}) = \lambda^-\lambda^+ < 0$. We come to the conclusion that the invasion fitness $\lambda^+ = s_{r,\tau}(r_m,\tau_m)$ is a sign equivalent to the negative determinant of the mutant Jacobian. Thereby the invasion fitness can be written as:

$$\begin{aligned} s_{r,\tau}(r_m,\tau_m) = (b(r_m,\tau_m) - q(\hat{S}+\hat{I}) - \mu - \beta(r_m)\hat{I})(\alpha(\tau_m)+\mu+\gamma) \\ + \beta(r_m)\hat{I}(fb(r_m,\tau_m) - fq(\hat{S}+\hat{I})) + \gamma)). \end{aligned} \tag{4.23}$$

As we discussed, the mutant can invade if the invasion fitness is positive, and if it is negative, the mutant will not be able to invade the resident population.

Chapter 5

Results

We study the possible singularities numerically with Mathematica [9]. To begin with we take a notice on the parameter values. Parameters q, μ and c can be fixed to 1 without a loss of generality, as the crowding factor q has the unit of population density, the death rate μ has the unit of time and the scaling cost parameter c has the unit of the two strategies and these units are arbitrary.

Other parameter values cannot be fixed without a loss of generality, and further research might be needed to evaluate all possible combinations. In this thesis we focus on the epidemiological parameters (virulence, transmission rate and recovery rate) and also take a brief look at the return parameters. We begin with fixing $f = 1, \gamma = 0, \alpha_0 = 2, b_0 = 5, c_1 = 1, c_2 = 1$ and $\beta_0 = 3$. All the values are collected in table 5.1.

To analyze the evolution of resistance and tolerance, we look for singular strategies, which are the points where the dynamics of the mutant stop evolving. As we are studying both resistance and tolerance, we determine the fitness gradient for each strategy separately and look for a joint singularity. As we want to understand the long-term evolution of investment into each strategy, we try to find a continuously stable strategy (CSS). For that, we need to find a singular strategy that is both evolutionarily stable (ESS) and convergence stable (CS).

Our goal is to find a joint singularity of resistance and tolerance, so we begin with fixing a value for tolerance and find the singularities for resistance. When we go through different values of fixed τ, we find a r-isocline for the resistance singularities. Once we have found the line of singularities for r, we repeat the process for τ. The isoclines

Table 5.1: Values for numerical analysis

Symbol	b_0	α_0	β_0	c_1	c_2	c	q	f	μ	γ
Default value	5	2	3	1	1	1	1	1	1	0

found with our choice of parameters are presented in figure 5.1, where the dashed line is the τ-isocline and the solid line is the r-isocline. We have checked numerically that the singularity shown in figure 5.1 meets all required conditions presented in this thesis and the population densities are positive at it.

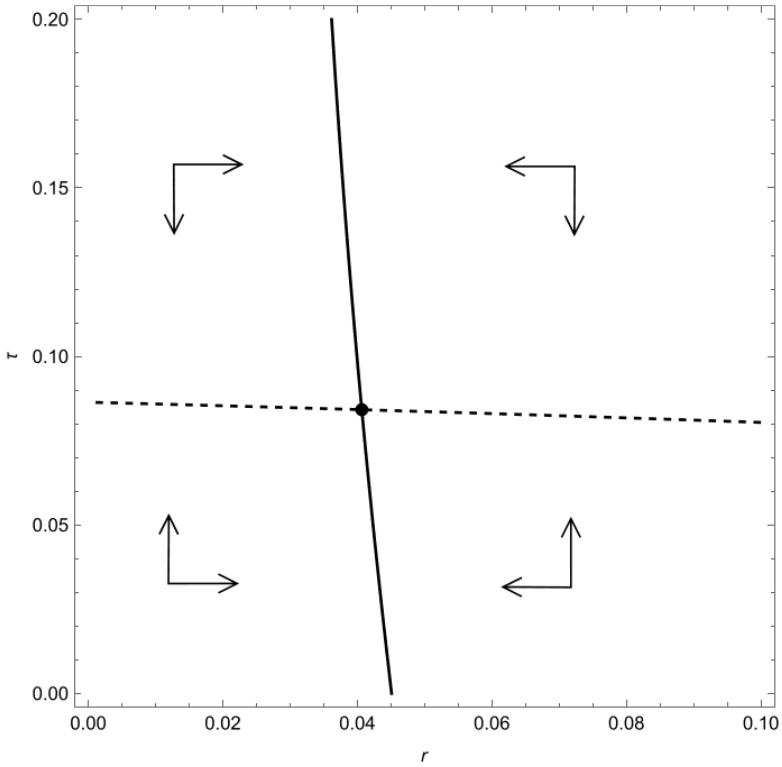


Figure 5.1: Plot of the isoclines against resistance and tolerance. Dashed line is the τ-isocline and solid line is the r-isocline. Black dot indicates the singular strategy (r^*, τ^*). Investment to tolerance on the vertical axis and investment to resistance on the horizontal axis.

First we confirm that the singularity is convergence stable in one dimension as the conditions (3.10) and (3.11) hold with our parameter values with either τ or r fixed at the singular strategy. However, we want to know is the singularity convergence stable in every direction and for that we study convergence stability with phase plane analysis from figure 5.1.

The idea is to choose any point from the neighbourhood of a singular strategy (r^*, τ^*) and see where the population with a strategy defined by that point evolves to from that point. The arrows in figure 5.1 indicate the direction of movement. For example, if we

start from the upper right corner, the population will move left and down and towards the singularity. From the phase plane analysis we can detect that regardless of where we begin, we will always end at the singularity. Therefore, the singularity (r^*, τ^*) is a CS.

We continue to study whether (r^*, τ^*) is an ESS. With our choice of parameters we find that

$$X_m = \left[\frac{\partial^2 s_{r,\tau}(r_m, \tau_m)}{\partial r_m^2}\right]_{r_m=r=r^*} < 0 \quad \text{and} \quad Y_m = \left[\frac{\partial^2 s_{r,\tau}(r_m, \tau_m)}{\partial \tau_m^2}\right]_{\tau_m=\tau=\tau^*} < 0, \tag{5.1}$$

which means that we have an ESS at least along the vertical and horizontal lines of possible values for resistance and tolerance. We use the second derivatives test to find out evolutionary stability in other directions. We have

$$D(r^*, \tau^*) = \left[\frac{\partial^2 s_{r,\tau}(r_m, \tau_m)}{\partial r_m^2}\frac{\partial^2 s_{r,\tau}(r_m, \tau_m)}{\partial \tau_m^2} - \left[\frac{\partial^2 s_{r,\tau}(r_m, \tau_m)}{\partial r_m \partial \tau_m}\right]^2\right]_{r=r_m=r^*, \tau=\tau_m=\tau^*} > 0 \tag{5.2}$$

with our parameter values. As the determinant of the Hessian matrix of our invasion fitness gives us a positive result and $X_m < 0$, we find that (r^*, τ^*) is a maximum. This means that (r^*, τ^*) is evolutionarily stable in every direction and no mutant can invade it.

We conclude that (r^*, τ^*) is a continuously stable strategy as it is both CS and ESS. Any nearby monomorphic or dimorphic population will eventually stabilize to this final monomorphic outcome [8].

5.1 Resistance or tolerance

Next we study what happens to the CSS investments when we vary the epidemiological parameters such as transmission rate and virulence. We want to determine whether the host benefits more from investing into resistance or tolerance or might mixed investments have a better outcome for the host.

First we have to confirm that the singularity remains a CSS along the curves presented in our figures. To do that, we have numerically checked that the second derivative test condition for evolutionary stability is complied with the variable we are studying when other parameters are fixed. For example, we find that when the transmission rate is greater than 0.19, $D(r^*, \tau^*) > 0$ for the invasion fitness and $X_m < 0$ for all r^* and τ^*. All the curves presented in the following figures are located in areas where the ESS conditions hold. We also check convergence stability with phase plane analysis, utilizing the Table

command in Mathematica [9] for the selection gradients with varying the parameters we study.

We begin with varying the transmission rate. From figure 5.2 we can see that for low values of transmission rate the investment into resistance is more beneficial than investment into tolerance. As the pathogen does not spread widely in the population, it is reasonable to use more resources to prevent an infection in the first place. When the hosts are unlikely to contradict the disease, they do not benefit from maintaining high tolerance.

When the transmission rate increases, the benefit of investing into tolerance overtakes the benefit of investing into resistance. As the pathogen appears more and more in the population, the hosts cannot avoid it regardless of their resistance and thus investing into tolerance is more helpful to the hosts. Investing into tolerance continues to increase as the transmission rate increases, whereas investing into resistance starts to decrease. The results are similar to [5] and [7].

In the case of varying virulence, figure 5.3 tells us that the hosts benefit more from investing into tolerance when the virulence is low. As the virulence increases, investing into resistance is favored over investing into tolerance. However, for higher values of virulence neither investment into resistance or tolerance do not further benefit the host. Investment into tolerance starts to decrease before investment to resistance, so for intermediate values of virulence the hosts benefit more from advancing resistance than tolerance.

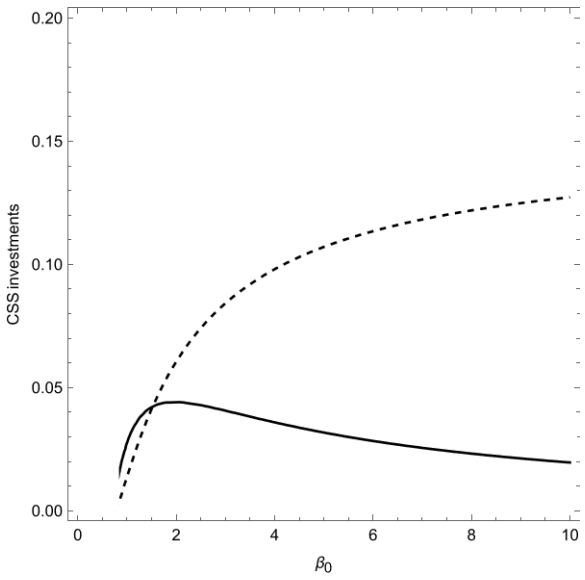


Figure 5.2: CSS investments plotted against transmission rate β_0. Solid line is the investment into resistance and dashed line the investment into tolerance. Parameter values are found in table 5.1.

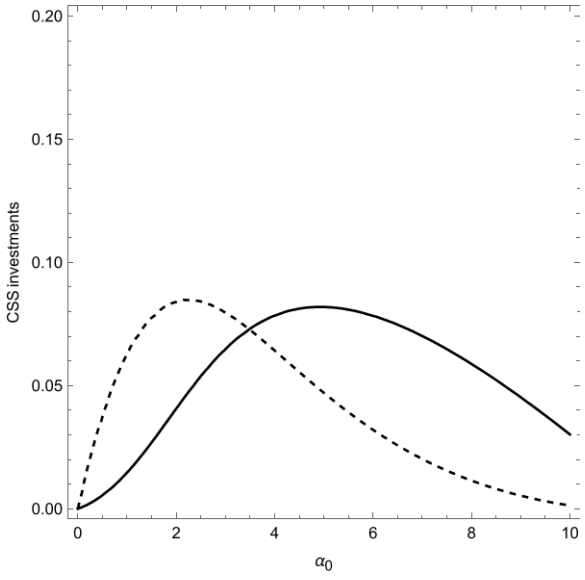


Figure 5.3: CSS investments plotted against virulence α_0. Solid line is the investment into resistance and dashed line the investment into tolerance. Parameter values are found in table 5.1.

Tolerance is more efficient to the lower values of virulence, and the cost of increasing it becomes too high when the virulence increases. Investing into resistance becomes more profitable when the disease is more likely to kill the host and the host is better off by not getting infected in the first place. Again, the results are consistent with the previous studies [5] and [7].

Studying the recovery rate with CSS investments shows that both investments decrease when recovery rate increases (figure 5.4). This is evident as if the host recovers fast, it does not need efficient defense mechanisms against the disease. When the recovery rate is low and host is unlikely to recover from the disease, it benefits most from high investment to tolerance. When the host has already caught the disease, the sensible thing to do would be to minimize the fitness loss of the infection as preventing it is impossible at that point. Figure 5.4 also shows that the investment into resistance goes slightly up for low values of recovery rate.

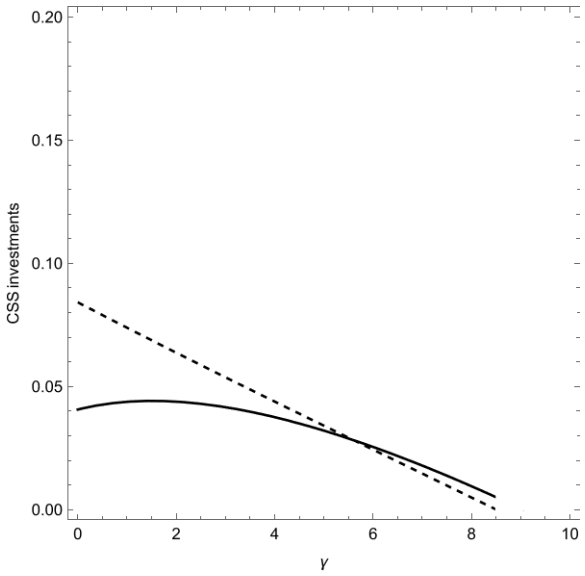


Figure 5.4: CSS investments plotted against recovery rate γ. Solid line is the investment into resistance and dashed line the investment into tolerance. Parameter values are found in table 5.1.

Plotting the CSS investments against the basic birth rate (the rate of births when there is no investments into either resistance or tolerance) shows that the birth rate has more effect on the investments into tolerance than resistance (figure 5.5). Investing into resistance stays relatively consistent when the birth rate varies, although there is a minor increase in investments for low values of the birth rate. The host should invest into

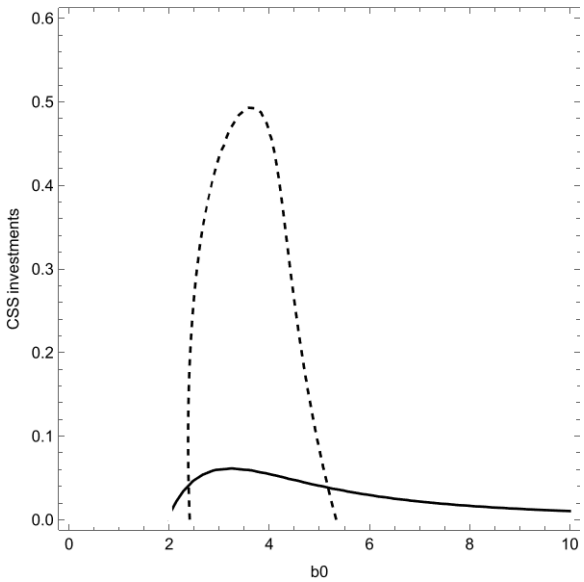


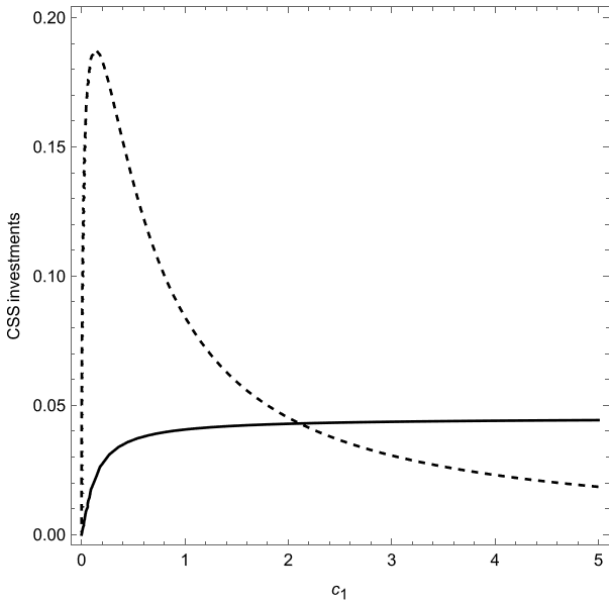
Figure 5.5: CSS investments plotted against basic birth rate b_0. Solid line is the investment into resistance and dashed line the investment into tolerance. Parameter values are found in table 5.1.

resistance regardless of the value of the birth rate.

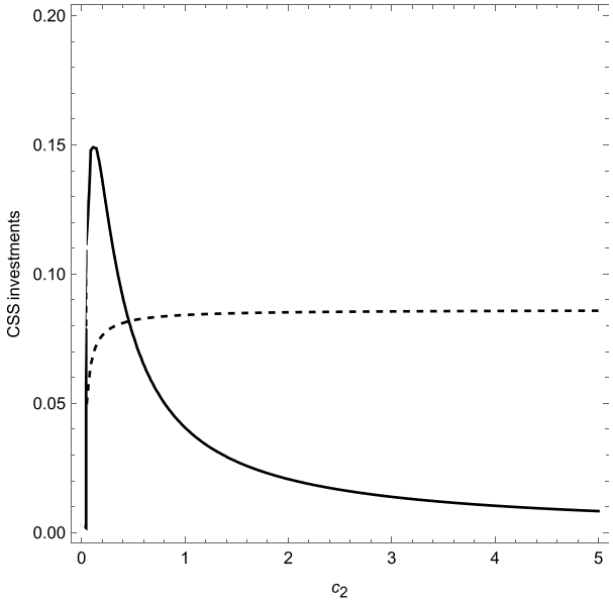
The case of investing into tolerance is more interesting. The hosts do not seem to invest into tolerance at all for high values of the basic birth rate. As the birth rate is low, investing into tolerance is much more beneficial to the host than investing into resistance. The CSS investment of tolerance increases significantly before decreasing rapidly as the birth rate increases.

The CSS investment into resistance and tolerance do not differ much in the shape when plotted against either of the parameters that determine the amount of return from investing into the defense mechanisms, as we can see from figures 5.6a and 5.6b. When either $c_1 = 0$ or $c_2 = 0$, there is no transmission or no virulence and consequently there is no reason to invest into either of the defense mechanisms. With low values of c_1 and c_2, the investments show a momentarily peak on the particular CSS investment whose parameter it is plotted against. As the returns for tolerance diminish, i.e. c_1 increases, investing into resistance seems to increase and then to establish at a certain level. Similarly, the investment into tolerance sets to a certain level when the returns for resistance diminish and c_2 goes up.

As the return parameter of tolerance grows, the investment to tolerance starts to decrease. This is reasonable, as the host does not benefit from investing into the strategy



(a) Return parameter of tolerance



(b) Return parameter of resistance

Figure 5.6: CSS investments plotted against (a) Return parameter of tolerance c_1 and (b) Return parameter of resistance c_2. Solid line is the investment into resistance and dashed line the investment into tolerance. Parameter values are found in table 5.1.

when the returns are no longer good. The same happens with resistance, but there is a minor difference to tolerance. The notable thing is that the point where the CSS investments cross is at a higher value for the return parameter when the CSS investments are plotted against the return parameter of tolerance. For the return parameter of resistance, CSS investment of resistance overtakes the CSS investment of tolerance at a low value of return parameter of resistance. It appears that investing into resistance becomes unprofitable to the host faster once the return parameter of resistance increases and the returns of investing into resistance flatten.

We want to know do patterns and associations emerge between resistance and tolerance in host populations in different environments. The environmental factors can help to observe the patterns when resistance and tolerance are studied independently [7]. The main question is are resistance and tolerance positively or negatively correlated.

With low values of the transmission rate they are positively correlated, the host invests into both strategies and the total cost is decreased. As the transmission rate increases, resistance is traded for tolerance and the strategies are negatively correlated. For virulence the correlations are not so simple. The areas for positive correlations exist for low and high values of virulence while resistance and tolerance are negatively correlated for the intermediate values of virulence. In the case of recovery rate, resistance and tolerance start off with negative correlation for low recovery rate but begin correlating positively as the recovery rate increases.

Chapter 6

Discussion

In this thesis, we studied simultaneously but independently evolving resistance and tolerance by modelling the evolution of host dynamics motivated by the works of Singh and Best [5] and Restif and Koella [7]. We showed that the evolution of resistance and tolerance reaches a continuously stable strategy which represents a possible evolutionary end point of these defense mechanisms. We determined how varying ecological scenarios define which CSS investments are optimal for the hosts.

Resistance evolves more probably when the transmission rate is low and virulence is high, while tolerance evolves in the opposite cases. Tolerance is favored when the recovery rate is low, but high values for recovery rate result in resistance becoming more profitable. The return parameters of each trait also had an effect on the CSS investments. When the returns of one trait have a steep curvature i.e. the return parameters are low, the hosts benefit more from investing to that particular trait. As the returns of investing into that particular trait even out, i.e. the return parameter is high, it becomes more favorable to invest into the other trait.

This thesis strengthens the existing notions of the evolution of host defense mechanisms as our results comply with previous studies. Restif and Koella [7] found a positive correlation for the investments with quadratic additive costs with high values of recovery rate and virulence in addition to low values of the transmission rate. Our findings go along with theirs as we also found positive correlations for similar values of the epidemiological parameters. Similarly, the negative correlations where investing to tolerance is traded for resistance were experienced with comparable parameter values.

Singh and Best [5] found that increasing virulence results in decreasing tolerance and increasing resistance when resistance and tolerance are linked with a trade-off. We find similar results for the intermediate values of the virulence. However, our results differ for low and high values of virulence, as we find that resistance and tolerance both increase for low values and decrease for high values. Despite the difference, we see that resistance

is favored with high values of virulence even though it is decreasing.

In the case of transmission rate, investment into tolerance increases as the transmission rate increases, similarly to [5]. Our model without a trade-off shows that for low values of transmission rate, resistance increases before it begins to decrease. This differs from Singh and Best's model and so does the behavior when recovery rate is investigated. In our model, infected hosts are able to reproduce and Singh and Best found that the fertility of infected hosts affects the investments when they are plotted against recovery rate. They found that with $f = 1$ resistance increases and tolerance decreases as the hosts are able to recover better. The behavior of tolerance is same in our model, but we see increase in resistance only for low values of recovery rate. For higher values of recovery rate resistance begins to decrease, but it will become more beneficial than tolerance regardless of the decrease. The differences to Singh and Best [5] can be found in some areas, as their model cannot predict positive correlations due to a negative trade-off, but the overall results seem to be the same.

Our findings are supported by the feedback environments presented by Roy and Kirchner [4]. The prevalence of the disease decreases with higher resistance, so when the virulence is high the population benefits from developing resistance. Logically, when the transmission rate is high, recovery rate is low and virulence is low the prevalence of the disease grows and the population should invest more into tolerance, which is the case with our model. The more tolerant hosts are able to outcompete others in an environment with high disease prevalence. Restif and Koella [7] also suggest that hosts would benefit from maintaining a pathogen-filled environment via tolerating the pathogen that is more harmful to the competitors.

The model that we studied is a simple one-host one-pathogen model, which does not appear without weaknesses. The diversity of the populations and interactions that are evident in the nature cannot be fully captured by our model. More complex models might reveal evolutionary branching or other evolutionary outcomes [3]. One attribute of the natural systems we left out is co-evolution of the host and pathogen, even though co-evolution is the most common form of natural systems. The evolution of the pathogen is likely to influence the selection of host strategies [7].

Also, the nature of the costs is not clear in real life and we should be cautious to draw conclusions of the true costs of the defense strategies. More empirical studies are needed to confirm how the costs of resistance and tolerance appear in nature, as the hosts' ability to reproduce might not be the only feature that is affected [3]. Simms and Triplett [20] proposed that with two varying traits of which only tolerance had an effect on the fecundity might give a false impression on the patterns of associations. This was also confirmed by Restif and Koella [7], as the environment in which the continuously stable strategies and their effect on fecundity are studied can affect the appearance of the costs and one of them might not seem costly at all.

Caution in interpretations is particularly worthwhile when studying natural systems as the underlying structure of the costs and how the host invests in the development of strategies is not evident. Simms and Triplett [20] showed that even when both resistance and tolerance varied, only tolerance had effects on the host fitness in a disease-free environment. Thereby they suggested that the costs of resistance and tolerance could interact and the patterns of associations might lead us astray.

It would also be important to know how tolerance appears in reality as Best *et al.* [3] found that sterility tolerance and mortality tolerance can have highly different predictions. When the infected hosts have weakened fecundity due to infection, the ability defend against decrease in fecundity is called sterility tolerance. Sterility tolerance does not necessarily have a positive feedback loop if the infection is not transmitted vertically. The difference in the ecological feedback may mean that there are different evolutionary outcomes. We concentrated on mortality tolerance, i.e. the host's the ability to fight against disease-induced death, so the effects of sterility tolerance remain in the dark in our model. Best *et al.* [3] mentioned that if sterility tolerance and mortality tolerance correlate positively, tolerance might not become fixed.

There remains a need for further study. We did not study the case of sterile infected hosts, and it might have different outcomes for some of the epidemiological variables such as recovery rate, as Singh and Best [5] suggest. They also showed that the crowding factor plays a role in the investments only when the infected hosts are able to reproduce, and we did not look into this in our model. The shape of the costs could also be considered more thoroughly, like Restif and Koella [7] did. In addition to additive functions for the birth rate, multiplicative functions could also be studied.

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