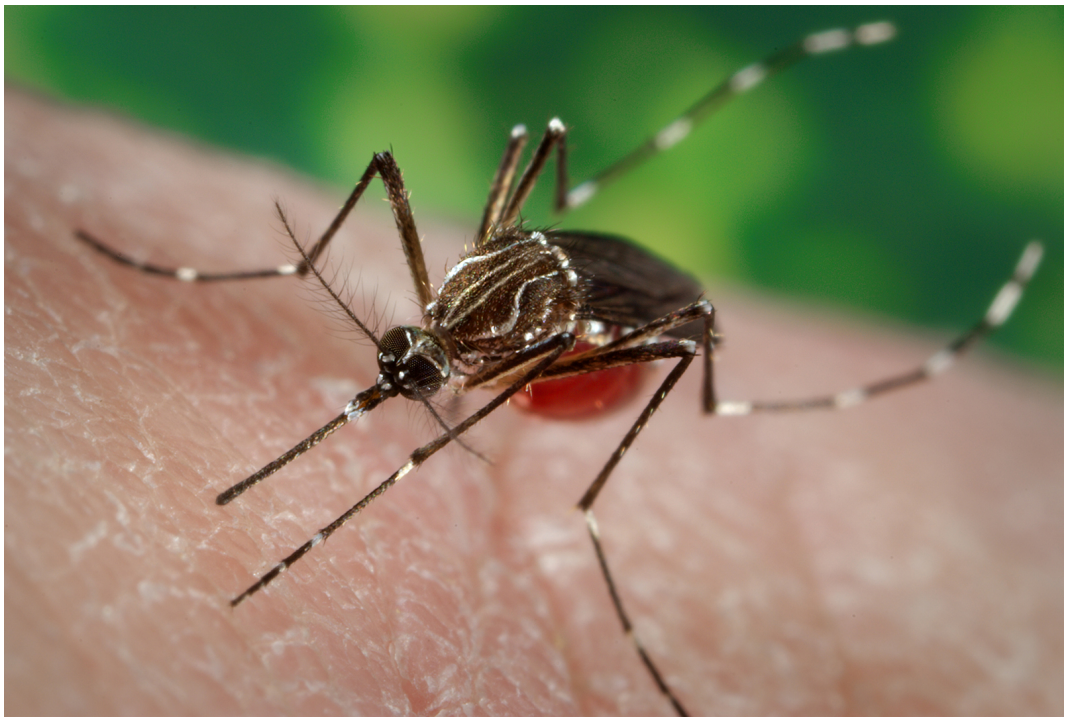
Eco-Evolutionary Dynamics of Vector-Borne Diseases and the R_0 Optimisation Paradigm



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Master Thesis

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Abstract

In epidemiology, there exists the R_0 optimisation paradigm. It states that evolution should lead to parasites maximising their R_0. Thus, when a trait like virulence is observed, the trait should evolve to a value that maximises the R_0. Adaptive dynamics is a mathematical framework allowing one to model various ecological systems in search of evolutionary endpoints, and can readily be applied to epidemiology. We used the adaptive dynamics approach to see the conditions under which the R_0 paradigm applies to a model of vector-borne disease, such as malaria.

KEYWORDS: Adaptive dynamics, Malaria, R_0 maximisation, Vector-borne disease

Contents

1 Introduction

Parasites will evolve towards intermediate levels of virulence due to a trade-off in transmission and recovery. The theory is that with increased virulence, both recovery/death and transmission will increase due to increased symptoms, viral load etc., but due to these factors the disease will be more acute and be resolved more quickly or kill the host more quickly, leading to a decreased duration for the infection. In an epidemiological context, virulence refers to the overexploitation of host resources by the parasite (Cressler et al., 2015). Eventually these two factors will balance each other out, leading to an evolutionary stable strategy (ESS). An ESS refers to a local fitness maximum for the resident parasite (Metz et al.). In this kind of approach, we assume that every host can only be infected by one strain of parasite at one time, but the parasite doing so can change over time, and that the various factors in our model only depend on the genotypes of the parasite and the environment set by the host.

In theory, a pathogen should always try to find a most optimal combination of transmission and recovery. This is expressed as the R_0 optimisation paradigm, which is a ecological/epidemiological theory that a parasite should always optimise their R_0. The R_0, in the context of a parasite, refers to the number of secondary infections caused by a infected individual. This means that with a R_0 of 2, one initially infected individual will cause two other people to get infected. Thus, oftentimes it is assumed that an optimal strategy for a parasite is one where it is able to increase its R_0 as much as possible, thus its traits should evolve in such a way as to cause an optimal R_0. This is called the R_0 optimisation paradigm (Lion and Metz, 2018).

Adaptive dynamics explores the scenario where a small mutation occurs in a resident population, and when the new mutant will be able to out-compete and replace the resident population. Adaptive dynamics relies on differential equations and is focused on studying the evolution of specific traits. Thus, rather than looking at micro- or macro- evolution, adaptive dynamics looks at the meso-evolution (Metz, 2012). The result of such an analysis can be shown as a pairwise invasibility plot, hereafter referred to as a PIP plot, which shows the evolution of one trait of a population of interest (Brännström et al., 2013).

1.1 The standard SIR model

One of the most basic and fundamental epidemiological models is the Kermack-McKendrick model, or the SIR model. This model was developed by Kermack and McKendrick in 1927. Their model follows the basic idea of having a susceptible population, from which some individuals become infected and thus move to the infected compartment, and these individuals finally recover or die (Kermack and McKendrick, 1927).

The standard SIR model is structured as follows:

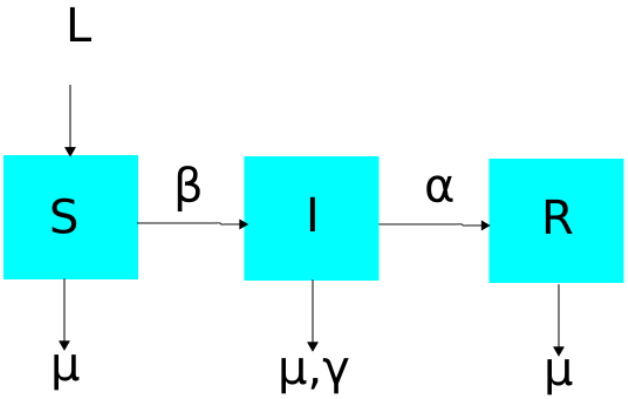
$$\frac{dS}{dt} = L - \beta \cdot S \cdot I - \mu \cdot S \tag{1}$$

$$\frac{dI}{dt} = \beta \cdot S \cdot I - \gamma \cdot I - \mu \cdot I - \alpha \cdot I \tag{2}$$

$$\frac{dR}{dt} = \alpha \cdot I - \mu \cdot R \tag{3}$$

(Xiaozhuo et al., 2018; Martcheva, 2015; Brauer et al., 2019)

Notably, there are three compartments in the classical SIR model. The equations describe the ecological dynamic between the susceptible (S), infected (I) and recovered (R) classes, with the assumption that one cannot go from the recovered to the susceptible class, i.e., the disease immunises (Martcheva, 2015; Brauer et al., 2019). Which can be visualised as shown below.



Where the L is the inflow into the susceptible class, β is the transmission rate, μ is the natural death rate and γ is the death caused by the parasite. Very often, it is thought that parasites will cause death at some specific rate in their host population due

to the symptoms they cause, and that the symptoms they cause are what allows parasites to spread between hosts, whether it is through an aerosol produced through coughing, or through waterborne transmission through vomiting and gastrointestinal problems. By increasing parasite load through more aggressive reproduction etc., a parasite can increase the severity of its symptoms and the rate of transmission. Similarly, through increased parasite load, blood-borne parasites like malaria can probably increase the probability of getting transmitted between their human and mosquito hosts. Virulence, in this sense, is a quite abstract concept, since it is generally, in mathematical terms, considered to be a "decrease in the fitness of the host", rather than the severity of the symptoms as in a clinical setting (Cressler et al., 2015).

In accordance to the transmission-virulence trade-off (Alizon, 2008), the beta and gamma-functions can be shown as functions of the virulence, which will be referred to as x in equations henceforth.

$$\beta(x) = \frac{\beta_{max} \cdot x}{\beta_{half} + x} \tag{4}$$

$$\gamma(x) = x \tag{5}$$

These functions are of this form for biological realism, as the transmission should saturate at some level. This causes the parasite to evolve towards some optimal level of virulence. The death being linear with the virulence might not be very realistic, since the there is no right way to quantify this trait, as infections can be lethal without affecting the patient in ways other than the lethal pathway, and otherwise debilitating infections may not be very lethal. However, in general, when the severity of the symptoms increases, one can expect the mortality to also increase. Thus, virulence is often defined as the decrease in the fitness of the host (Dieckmann et al., 2002). This kind of relationship between the α and β -functions is justified, since many parasites benefit from the symptoms they cause by being able to more easily spread.

1.2 Population Equilibria

When modelling the spread of parasites, one is usually most interested in the equilibria of infected and susceptible populations the parasites will cause. It is important to define the

disease free equilibrium (DFE, $\hat{S}$) and the endemic equilibrium (EE, S^*) (Lion and Metz, 2018; Martcheva, 2015). A population to which a parasite is introduced will either return to the DFE if the parasite has a reproduction number R_0 (as shown in equation 6) of less than one, meaning that one infection will, over the duration of the infection, lead to less than one secondary infection. Thus, the parasite can't sustain itself, and will die out in the population. If the reproduction number is over one, the population will converge towards its endemic equilibrium, which refers to the equilibrium which is reached when the parasite is fully established in the population and the dynamics between susceptible and infected populations are stable.

When modelling this kind of system using adaptive dynamics, one can distinguish between the ecological and the evolutionary timescale (Brännström et al., 2013). The ecological timescale describes how the environment changes in the short term. This includes things like the R_0, which refers to the number of secondary infections that an infected individual will cause in the population:

$$R_0(x) = \frac{\beta(x) \cdot \hat{S}}{\mu + \gamma + \alpha} = \frac{\hat{S}}{S^*(x)} \tag{6}$$

where the $\hat{S}$ is the maximal size of the population with no parasite present, which can be obtained by dividing the total inflow by the natural death (this is the DFE).

$$\hat{S} = \frac{L}{\mu} \tag{7}$$

While the $R_0(x)$ is larger than 1, the parasite can infect the population, which will lead the population to assume its endemic population sizes instead of its disease-free population sizes. The two equations above are equivalent because the $S^*(x)$ is of the form:

$$S^*(x) = \frac{\mu + \gamma(x) + \alpha}{\beta(x)}$$

This means that there is a analytical solution reliably showing these relationships in this system.

The equilibria can nonetheless also be found using ordinary differential equations, which is how we obtained population-sizes when no mathematical formula was available. Differential equations refer to equations that give information about the derivatives of functions. Ordinary differential equations specifically are such functions that involve

ordinary derivatives with respect to one independent variable. We used the package "deSolve" in R to work with these functions in the context of adaptive dynamics. This package is the successor of the package "odesolver", and offers various tools for solving initial value problems of ordinary differential problems, as well as differential algebraic equations and partial differential equations. Only the initial value problems will be of interest here, since these refer to ODE:s with associated initial values. For more information on the package, one can refer to the paper: Karline et al. (2010). This package is used throughout this project for working with the population sizes.

2 Adaptive dynamics of the SIR model

The fitness-function refers to an expression that encapsulates the per-capita growth rate of a mutant parasite in an environment set by the resident. The fitness function for the SIR model is:

$$\omega(x_m|x) = \beta(x_m) \cdot S^*(x) - (\gamma(x_m) + \mu)$$

(at least for the SIR model without recovery). This equation gives rise to the direction of the evolution. As long as ω is positive, the mutant strain will be able to out-compete the resident strain and become the new dominant strain. When the fitness function is positive, the new mutant will be able to replace the resident parasite in the population, and when it is negative, the mutant will not invade and cannot replace the resident (Brännström et al., 2013). The underlying assumptions of this method are, that mutations will be small and only cause small changes in the trait-values, and that new mutants will only be present in very small, initially negligible numbers. The values produced by the fitness function can be shown as the so-called pairwise-invasibility plot, where the values are plotted as contours. The first term $\beta(x_m) \cdot S^*(x)$ represents the rate of infection caused by the mutant with a new value of virulence: the rate of infection times the susceptible population caused by the current resident parasite, and from this product is subtracted the new mortality caused by the mutant. This represents the inflow and outflow from the infected population, and is very similar to the R_0. The way in which this gives rise to an ESS is that eventually a susceptible population will be reached that is so small, that no new mutant will be able to get a positive value for ω, meaning that no new mutant will ever be able to establish themselves in the population. Thus, that is the evolutionary endpoint. This is in accordance with the pessimisation principle (Lion and Metz, 2018).

The sign of the contour in relation to the zero-lines determines if the point is convergence stable (Brännström et al., 2013). When the values are positive left and right of the equilibrium, as they are in the case of figure 1, the point is convergence stable. Since the SIR model is quite simple, the stability of the evolutionary strategy can also be found analytically by solving for susceptible and infected population sizes, and the stability of the points can be found by taking the second partial derivatives of the ω. This allows for the linearisation of the system. When this equation is solved using the numerical values, if both solutions are positive, the obtained equilibrium will be stable. This notably won't work on more complex models, which will be relevant for the malaria model.

The PIP presented on the top of figure 1 shows the tendency of the parasite to evolve

towards some optimal level of virulence. The zero-lines are what separates the positive from the negative regions of the contour. Notably, equal values of the trait (virulence) should not be able to replace the resident, since the resident shouldn't be able to replace itself, so one zero-line should be a straight line (Brännström et al., 2013). The optimal virulence in this case is the virulence that maximises the R_0 (shown on the third plot in figure 1). Showing that this model acts according to the optimisation principle. This optimal value of virulence can be found at the intersection of the zero-lines of the contour. Figure 1 also shows that the model follows the pessimisation principle, meaning that the evolution of the parasite will lead to the worst possible environment, which in this case is the minimum number of susceptibles, and thus is able to prevent other mutants from invading. This is shown in the second plot of figure 1, where the number of susceptible individuals is plotted against the virulence. That means that the version of the parasite that is able to survive in this worst possible environment has blocked all other versions of the parasite from invading (Lion and Metz, 2018).

The R (reproduction number) of the form $R(x_m|x)$ (x_m being the virulence of a new mutant arising among the parasites) is:

$$R(x_m|x) = \frac{\beta(x_m) \cdot S^*(x)}{\mu + \gamma(x_m) + \alpha} = \frac{S(x)}{S^*(x_m)} = \frac{R_0(x_m)}{R_0(x)} \tag{8}$$

The equivalence of these functions are an interesting property of the SIR model, and we will test if these hold for the malaria-model as well later on. This function naturally leads to the evolutionary timescale, where one tries to model the way in which the system evolves over multiple mutations. This leads to the fitness function.

From the equation 8, one can see that the $\frac{\beta(x_m) \cdot S^*(x)}{\mu + \gamma(x_m) + \alpha}$ is equivalent to the R_0 for the mutant parasite entering the environment created by the resident. This directly leads to an explanation as to what the relationship of the R_0 and the ω is:

$$\omega = \beta(x_m) \cdot S^*(x) - (\gamma(x_m) + \mu + \alpha) = (\gamma(x_m) + \mu + \alpha) \cdot (\frac{\beta(x_m) \cdot S^*(x)}{\mu + \gamma(x_m) + \alpha} - 1)$$

Here, one can see that the $R(x_m|x)$ is included in the fitness function itself. The $\frac{\beta(x_m) \cdot S^*(x)}{\mu + \gamma(x_m) + \alpha} - 1$ is the same equation as the $R(x_m|x)$, which means that in order for the fitness function to be positive, the $R(x_m|x)$ needs to be greater than one.

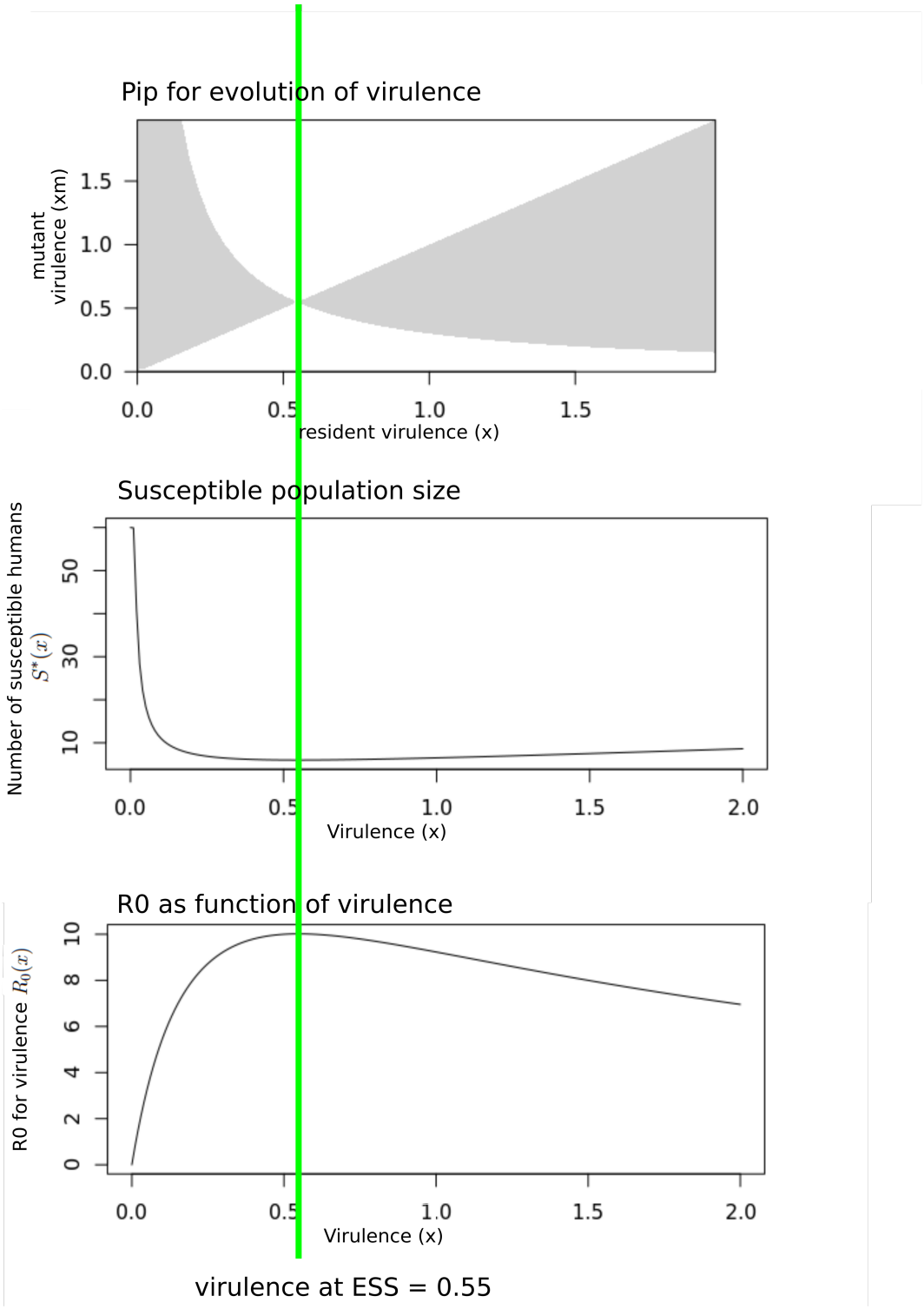


Figure 1: Optimisation as seen in the SIR-model: the PIP (uppermost figure) for classic SIR model was produced using filled.contour function in R, using the fitness function $\omega = \beta(x_m) \cdot S^*(x) - (\gamma(x_m) + \mu)$. The grey area is where the contour is positive, while the white area is where the contour is negative. The second plot shows the minimisation of the susceptible population at the optimal R_0. Finally, the third plot shows that at this virulence the R_0 peaks.

3 Application of adaptive dynamics to a model of malaria

Malaria is the most important vector-borne disease of modern times, causing 200 million cases of malaria as well as 600 000 deaths annually (Cowman et al., 2016). It is a protozoan capable of infecting red blood cells, and can cause a range of different symptoms. The sexual life-cycle of the parasite occurs in the mosquito's gut, while the maturation occurs inside the human. There are six subspecies of malaria which cause illness in humans, Plasmodium falciparum being the most dangerous. Knowing these factors, we can construct the following model for malaria spread:

$$\frac{dS_h}{dt} = L - \beta_h(x) \cdot S_h \cdot I_v - \mu \cdot S_h \tag{9}$$

$$\frac{dI_h}{dt} = \beta_h(x) \cdot S_h \cdot I_v - (\gamma_h(x) + \mu) \cdot I_h \tag{10}$$

$$\frac{dS_v}{dt} = L_v - \beta_v(x) \cdot S_v \cdot I_h - \mu \cdot S_v \tag{11}$$

$$\frac{dI_v}{dt} = \beta_v(x) \cdot S_v \cdot I_h - (\gamma_v(x) + \mu) \cdot Iv \tag{12}$$

This model was inspired by the model presented in (Brauer et al., 2019), but instead of taking the proportion of infected individuals in the total population, we used the absolute number of infected individuals. The model contains two separate populations, the human (h) and the vector (v). There are some things which should be noted about how this model was used: the β function, for most of the analysis was symmetric, meaning that the same β function was used for both the human and vector populations. The model was later also evaluated for different asymmetric beta-functions, and it was shown that this doesn't cause any qualitative differences in the mathematical relationships discussed later. Further, the base model doesn't include any term for recovery. A model with recovery included was tested separately, and yet again, the model was qualitatively the same. However, recovery was, most of the time not included, because it slows down the simulations greatly. The reason for this is that the populations converge to their equilibria much more slowly.

The γ function represents the additional mortality caused by the virulence, but can also be interpreted as the total removal from the susceptible group, meaning that these individuals are considered to be removed from the system, which implies immunity to

the parasite. The additional mortality for the vector-population has been set to zero, since the exact effect of the Plasmodium-parasite on the vector is not fully understood, we will assume that the mosquito will die before its fitness is affected by the parasite. This might not be entirely true, since there has been research on the mosquito-competence (the ability of the mosquito to transmit the parasite) as well as evidence that the parasite might cause reduced lifespans in its vector by increasing biting rate (Lefevre et al., 2017), but these factors are somewhat outside of the scope of this project. Furthermore, the literature on the mathematical implications of the malaria parasite on the vector are scarce, which further justifies the usage of a simplified model.

The γ function can be any increasing function, as long as it is biologically reasonable. For an ESS to be formed, the slope of the γ function needs to be such that it can eventually overtake the beta-function to create an equilibrium. Conversely, if the mortality in the system is too high, the turnover of individuals can become such that the parasite isn't able to establish itself in the population. This can be resolved by increasing the beta-function. It's relationship with the natural mortality needs to also be such that the total mortality isn't too low, since then the time needed for the system to reach any kind of equilibrium will explode and any simulation to find the ESS will take too long.

Another assumption that might raise eyebrows is the assumption that virulence leads to an increased transmission from the mosquito to the human as well as from the human to the mosquito. The justification for this is that a more virulent variant of the parasite would be more likely to establish an infection in the human host, and that with increased virulence the parasite density in blood would presumably also be increased. This last assumption especially might not be true in reality, but the density of parasites in blood is a marker that is used to classify cases in a clinical setting, and there is a correlation between parasite density and the severity of the disease (Hassan et al., 2008). The assumption that there will be more transmission from the human host to the vector as a result from this comes from the rationale that, due to the higher density in the blood of the human, the blood-meal of the mosquito will contain more parasites, and thus is more likely to cause the parasite to establish itself in the mosquito. There is literature supporting this assumption. (Mackinnon and Read) in their paper "Virulence in malaria: an evolutionary viewpoint" describe average lifetime transmission potential for mice infected with malaria to be the gametocyte density or the proportion of cells infected with gametocytes. This measure was used alongside very objective measurements, such as the measured proportion of mosquitoes that became infected with malaria after feeding on a mouse during peak gametocytaemia (highest concentration of gametes in the blood).

In their paper, (Mackinnon and Read) also show that malaria parasites with higher replicative potential cause more anaemia and weight loss, in addition to causing longer infections. This all supports the assumptions taken for the model used here: the parasite can more easily establish itself in a host through aggressive replication, which boosts mosquito to human transmission, and through higher replication and a longer infection, the human to mosquito transmission is also increased. Factors that are not accounted for in this model include: area of endemicity, age groups of the host, malaria strain and type of malaria disease, which are all extremely important for a medical practitioner, but which cannot be feasibly implemented in a model, in the scope of this project.

The disease-free equilibria for both vector and human populations are obtained by dividing the inflow (natural birth, L) by the natural death rate, mu μ:

$$\hat{S} = \frac{L}{\mu} \qquad \hat{S}_v = \frac{L_v}{\mu_v} \tag{13}$$

The R_0 for this model is:

$$R_0(x) = \frac{\beta_h(x) \cdot \beta_v(x) \cdot S_h^* \cdot S_v^*}{(\mu + \gamma(x)) \cdot \mu_v} \tag{14}$$

When this expression is over one, like in the SIR model, the populations will go away from their disease-free equilibria to endemic equilibria. The endemic equilibria are $S_v^*(x)$ and $S_h^*(x)$, for the vector and human populations respectively. The endemic equilibria don't have a usable mathematical expression, since they depend on a dynamic between the two populations, and thus we don't have a $S_h^*(x)$ or $S_v^*(x)$, and it is necessary to obtain these values by means of ODE:s or other such mathematical methods.

3.1 Simulating the populations

Because of the complexity of this model, a analytical solution is not possible. This is because of the additional dimensions caused by the compartments. The ESS for the malaria-model can nonetheless be found in two ways: constructing a fitness-function for the system, or by expanding the model by adding two dimensions for the new mutants and the populations infected by them. Such a six-dimensional model can then be iteratively simulated, and the turning-point where a new mutant cannot any longer invade the ecosystem can be identified. When doing so, the starting value for the new mutant will

always have to be set to one, while the resident population needs to be at its equilibrium. The system of equations needed are shown below.

$$\frac{dS_h}{dt} = L - \beta_h(x) \cdot S_h \cdot Iv - \mu \cdot S_h - \beta_h(x_m) \cdot S_h \cdot I_{vm} \tag{15}$$

$$\frac{dI_h}{dt} = \beta h(x) \cdot S_h \cdot Iv - (\gamma_h(x) + \mu) \cdot I_h \tag{16}$$

$$\frac{dS_v}{dt} = L_v - \beta_v(x) \cdot S_v \cdot I_h - \mu \cdot S_v - \beta_v(x_m) \cdot S_v \cdot I_{hm} \tag{17}$$

$$\frac{dI_v}{dt} = \beta_v(x) \cdot S_v \cdot I_h - (\gamma_v(x) + \mu) \cdot I_v \tag{18}$$

$$\frac{dI_{hm}}{dt} = \beta_h(x_m) \cdot S_h \cdot I_{vm} - (\gamma_h(x_m) + \mu) \cdot I_{hm} \tag{19}$$

$$\frac{dI_{vm}}{dt} = \beta_v(x_m) \cdot S_v \cdot I_{hm} - (\gamma_v(x_m) + \mu) \cdot I_{vm} \tag{20}$$

where vm=vector mutant and hm=human mutant, referring to the number of individuals infected by the mutant version of the vector.

This simulation can be run by always choosing the new values for the susceptible populations as what the current version of the parasite caused, and by choosing a parasite with the virulence increased by one increment. This way, once the population sizes and the virulences of the current version of the mutant are such that a convergence stable ESS has been reached, a new mutant will not be able to persist in the simulation. In such a case, the system with the new mutant will, after some time, return to the endemic equilibrium of the current variant. In this way, by choosing an appropriate step-size for incrementing the virulence, one can relatively simply determine what value of virulence is optimal. This value should be the same as the result for the adaptive-dynamics approach, although finding it this way is much slower than when using the adaptive-dynamics approach.

3.2 Adaptive dynamics approach

The fitness function is as follows:

$$\omega(x_m, x) = \beta_h(x_m) \cdot \beta_v(x_m) \cdot S_h^*(x) \cdot S_v^*(x) - (\gamma(x_m) + \mu) \cdot \mu$$

And the R for a new mutant given the current resident mutant is of the form:

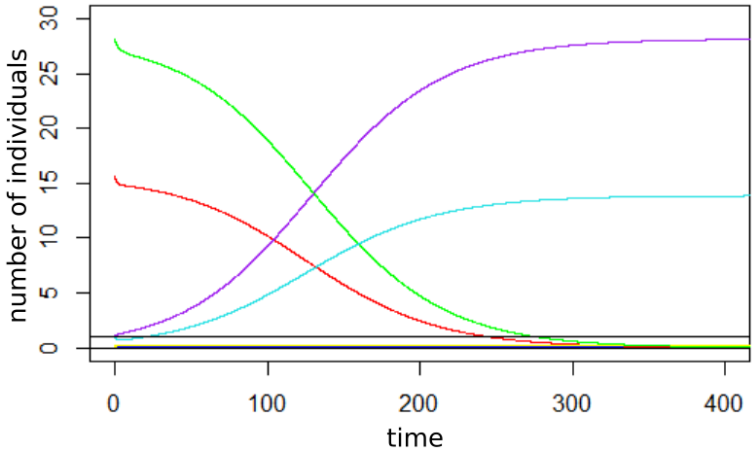


Figure 2: Outcompetition of the resident populations (green for the infected vector population and red for the infected human population) by a new mutant (purple being the vector population infected by the new mutant and cyan being the human population infected by the new mutant).

$$R(x_m, x) = \frac{\beta_h(x_m)\cdot\beta_v(x_m)\cdot S_h^*\cdot S_v^*}{(\mu+\gamma(x_m))\cdot\mu_v}$$

Where the S^*:s refer to the equilibrium susceptible populations of human and vector populations caused by the resident parasite, encapsulating the environment. It is important to note that, unlike in the SIR model, in this malaria-model we work with the product of the susceptible population-sizes. The resulting PIP is shown in figure 3. Both the adaptive dynamics approach and the six-dimensional simulation show that the ESS is convergence stable, and both of them arrive at the same value of virulence for the ESS, which is what was expected to happen. The virulence that is found in this way is the one that maximises the R_0, showing that the optimisation principle is also true for the malaria-model (figure 4). One question this leads to is whether or not the pessimisation-principle is also true.

The plot below (figure 3, second plot) shows that the pessimisation-principle is still true to some extent in this model, but it is the product of the two susceptible populations that is minimised. When one looks at how the populations respond to the increasing virulence, the susceptible vector population starts increasing at very high levels of virulence. This is probably because there are less frequent infections due to the very low human population density. In our model, the virulence does not cause increased death in the vector, so their population densities are not affected in the same way as for the human population. Thus, when the human population reaches very low densities, there will be no infection of the vector due to a lack of humans. Do the mathematical relationships

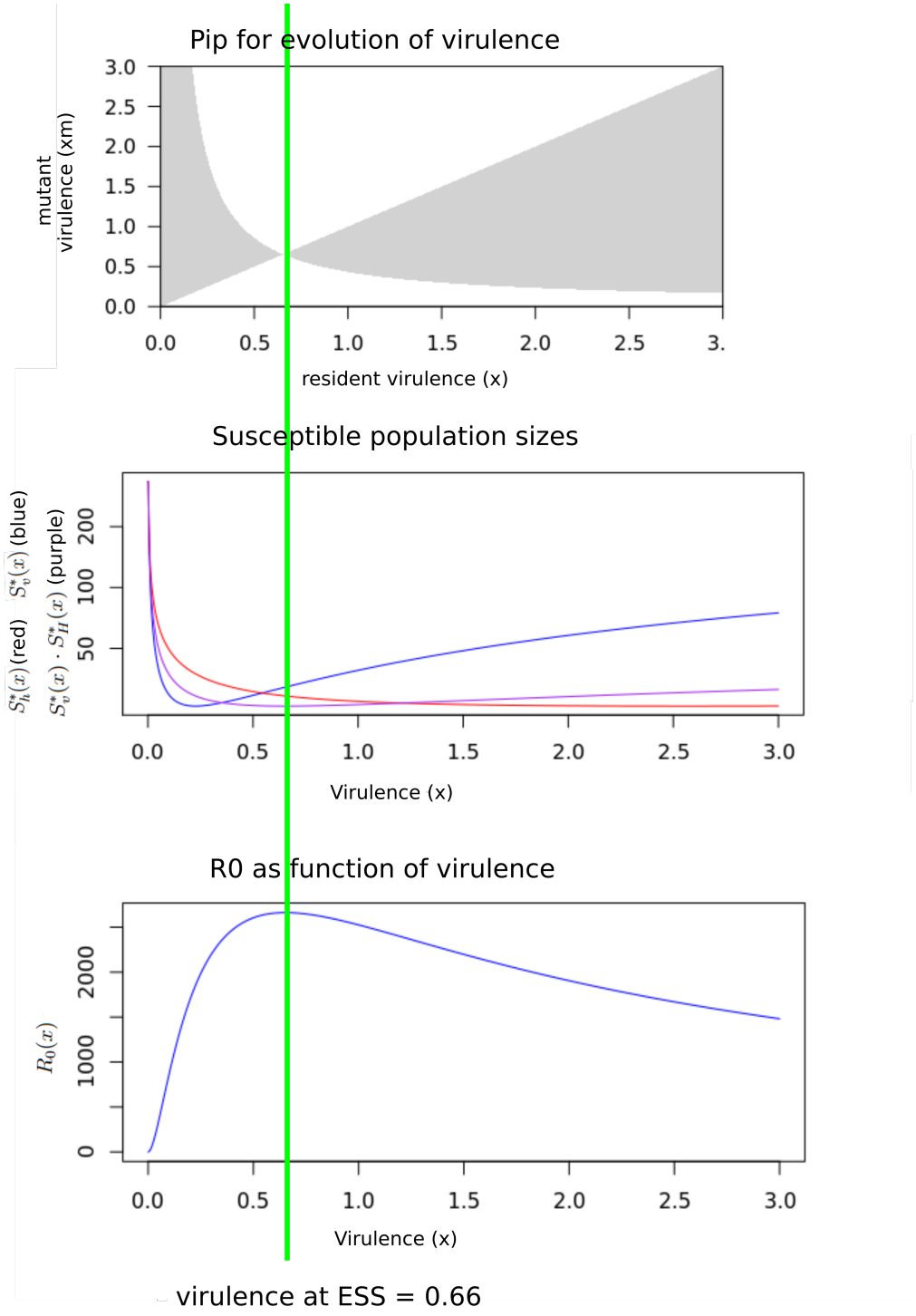


Figure 3: Optimisation as seen in the malaria-model.

described in the SIR model hold for the malaria-model as well? When the following functions:

$$\frac{S_v^*(x) \cdot S_H^*(x)}{S_v^*(x_m) \cdot S_H^*(x_m)} = \frac{R_0(x_m)}{R_0(x)} = R(x_m|x) \tag{21}$$

are plotted, where the previous value of virulence is used (as the resident x) and is plotted against the next (which is used as the value for the mutant x_m), the curves are completely identical, as can be seen in figure 4. This provides strong evidence that these relationships are true.

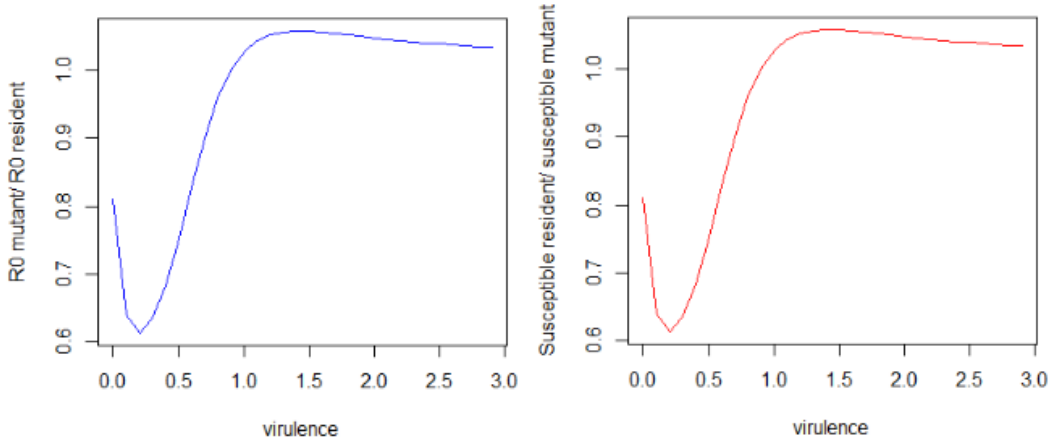


Figure 4: The division of the $\frac{S_v^*(x) \cdot S_H^*(x)}{S_v^*(x_m) \cdot S_H^*(x_m)}$ plotted in red (right side) and the $\frac{R_0(x_m)}{R_0(x)}$ plotted in red, taking small steps in increasing virulence. This shows that the obtained curves are completely identical, providing numerical proof that the equations are equivalent.

The next step would be to explore additional biological assumptions that would cause the breakdown of R_0. Generally speaking, only the most basic models should optimise R_0 and minimise the susceptible population. Additional environmental feedback can be added in the form of, for example, density-dependent mortality, and the disease can be more realistically modelled. (Lion and Metz, 2018)

4 Breakdown of R0

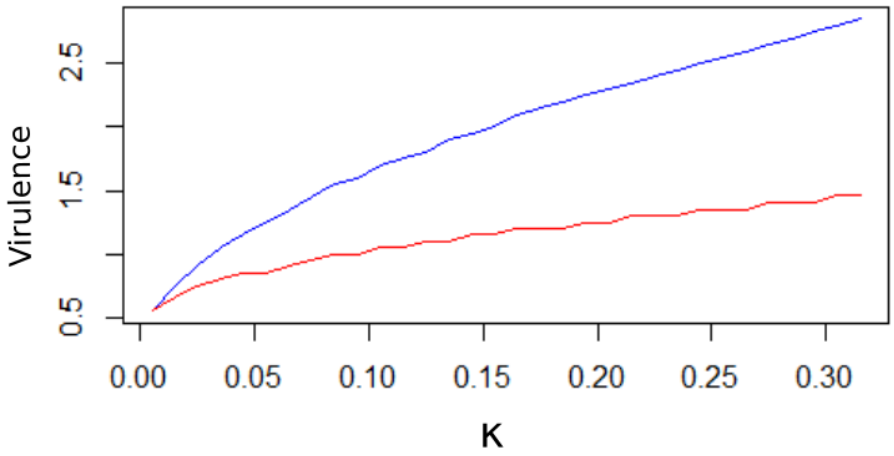
4.1 R_0 breakdown in the SIR model

It is said that only the most simple models of epidemiology cause the optimisation of R_0. This is because there are a number of problems with the R_0 optimisation paradigm: it excludes diversification and always causes minimisation of the susceptible population. This does not seem realistic from a biological point of view. (Lion and Metz, 2018) In order to adapt a model to allow us to break away from the R_0 maximisation paradigm, we can incorporate more environmental feedback into the model. Ways to do so are to make mortality density-dependent, allow vertical transmission (as one would see in the case of Plasmodium falciparum), and maybe allow multiple infections. (Cowman et al., 2016) (Milner Jr, 2017; Lefevre et al., 2017)

When making the R_0 density dependent, one needs to set a baseline mortality, μ_0, as well as a variable to express the dependence of density and the additional mortality this causes, $\kappa \cdot N$. Here, the added mortality is expressed with κ, kappa.

$$\mu^{tot} = \mu_0 + \kappa \cdot N_{tot} \tag{22}$$

Thus, the changing density will cause the variable for the natural mortality to change at every step. This will mean that the effective reproduction number will change from the R_0, favouring mutants that can maximise this effective R_0 rather than the initial R_0. Implementing this first for the SIR-model will show what is to be expected for this kind of system, and how the formation of the ESS is affected.



The figure 5 demonstrates what is to be expected when using the density-dependent mortality. The resulting ESS will be reached at lower values of virulence. By causing a decrease in total population size, the resident parasite will decrease the natural mortality rate, meaning that the pessimisation principle, or minimisation of the susceptible population, will be achieved at a lower virulence. This also means that the more the natural mortality depends on the density, the larger the discrepancy between the virulence maximising the R_0 and the true virulence at the ESS is going to be. This demonstrates that when more environmental feedback is incorporated in the model, there can't be one fitness proxy that is getting optimised during evolution. The effective reproduction number is still maximised at each value for the relationship-variable (kappa, κ), but this cannot be predicted ahead of time. However, using adaptive dynamics, the ESS can still be found. Below, the R_0 for the optimal strategy, as predicted by R_0 maximisation, as well as the R_0 at which the ESS is reached with density-dependent mortality, are plotted.

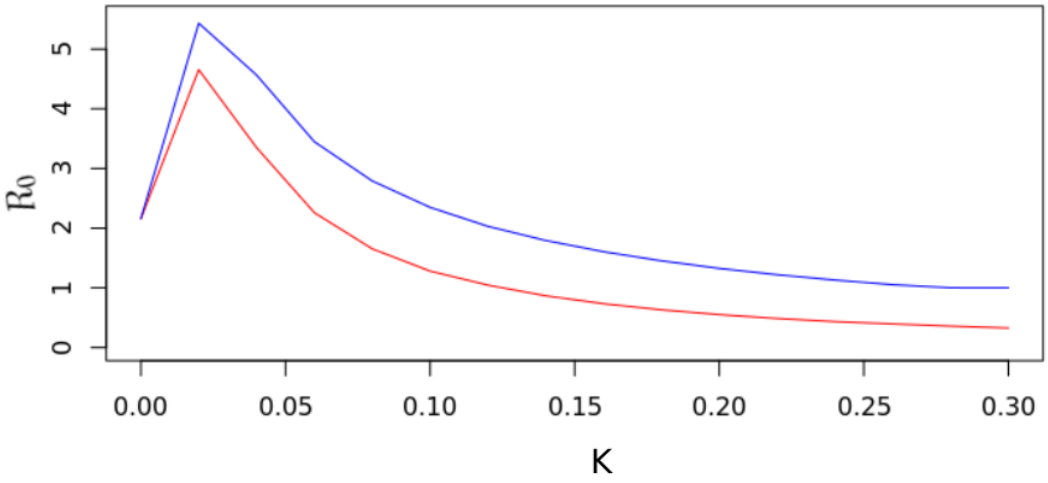


Figure 6: The R_0 that is optimal plotted in blue and the R_0 that actually lead to an ESS when density dependent mortality is included in the model (red)

As one can see, the optimal R_0 and the actual R_0 diverge more as the dependence of the mortality on the density increases. This is of course to be expected, since the virulences for the predictions and the true values also diverge with a increased κ.

4.2 R_0 breakdown in the malaria model

Something similar is observed when density-dependence is added to the human population in the malaria-model.

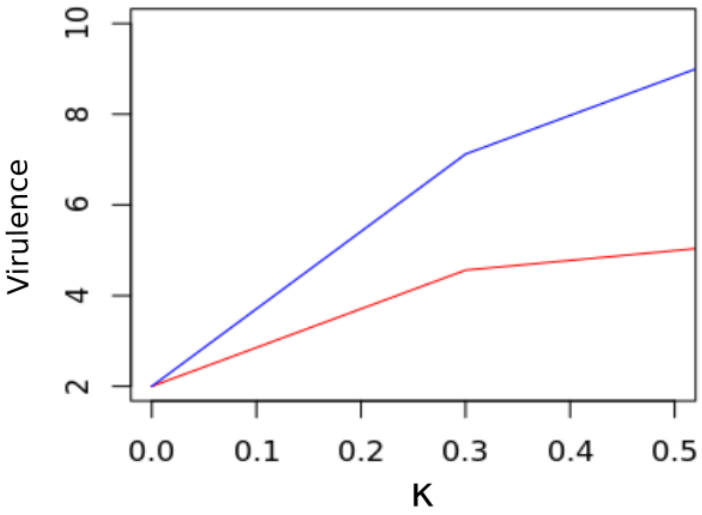


Figure 7: Virulence optimising the R_0 as predictor of the ESS in blue, and the virulence actually causing an ESS when density dependent mortality is considered. The virulence is the y axis and the κ used is the x axis

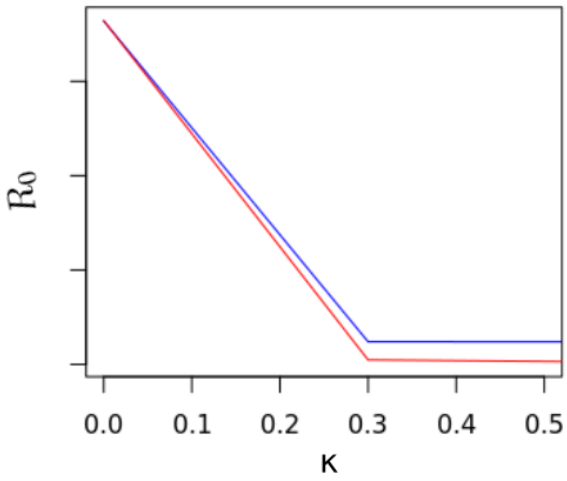


Figure 8: The difference in R_0 between the predicted ESS based on R_0 optimisation (blue) and the R_0 caused by the actual optimum (red).

One can see that the divergence of the $R_0 : s$ in the malaria model is quite slight when the model has asymmetric density dependence. One could assume that this tendency for the values to diverge would be more noticeable with a symmetric model, where both populations are density-dependent, but due to time-constraints, this was not addressed during this project; expanding the model further will cause it to become more and more cumbersome to work with. However, another probably more important reason for the slight difference is that the two virulences (the one that optimises R_0 and the one that

causes an ESS with density-dependence) are both values close to the peak of the R_0. The R_0 usually has very slight differences around the peak. Thus the difference in R_0 caused by differences in virulence is also going to be slight.

5 Discussion

5.1 Properties of the models

The adaptive-dynamics approach for the malaria model works quite nicely, even when a analytical solution isn't possible, and thus allows the exploration of traits, such as virulence, and hypothesising of their evolution.

As explained in previous sections, the susceptible population is minimised in the SIR model, and R_0 is maximised. This signifies that the most potent pathogen can out-compete other variants and create an environment where it cannot be replaced by any new mutants. Something very similar was observed in the malaria-model, but rather than just the human susceptible population getting minimised, the product of the susceptible humans and susceptible vectors is minimised.

When density-dependent mortality is incorporated, the estimation of a initial, optimal R_0-value no longer works. The more dependent the mortality rate is on the population density, the greater the difference between the optimal virulence predicted by the R_0 and the virulence that actually causes a fitness peak is. What makes adaptive dynamics useful is that it allows the user to find the ESS even when no analytic approach is available. As previously discussed, the dependence on the density causes an ESS at a different value of virulence, since a lower density will cause the mortality to also decrease somewhat. Thus, in a way, the pessimisation principle is satisfied at this new value (the population reaches its minimum density), but this cannot be analytically predicted due to the changed mortality. The more environmental feedback is added, the more the optimal virulence diverges from the virulence that leads to an ESS. This also leads to an increasing difference in the R_0 between the optimal virulence and the virulence that maximises the R_0. With more environmental feedback, this effect would increase further. Solving such a system and finding the ESS analytically would be impossible. Even so, by just working with the equations representing these different relationships, we were able to apply adaptive dynamics to this model and were able to find the correct ESS, even under conditions where the R_0 optimisation paradigm broke down.

Interestingly, a lot of the mathematical relationships found in the SIR model are also true for the malaria-model presented here, which made the malaria model easy to work

with. The following mathematical relationship being true:

$$\frac{S_v^*(x) \cdot S_H^*(x)}{S_v^*(x_m) \cdot S_H^*(x_m)} = \frac{R_0(x_m)}{R_0(x)} = R(x_m|x) \tag{23}$$

shows an interesting property of a vector-borne disease model. In this model, the product of the susceptible populations is what is important for the fitness. This was shown numerically both through iterative simulation (section 3.1), as well as with the adaptive dynamics approach (section 3.2), where in both cases the optimal virulence was the one where the susceptible population was minimised. Testing this using both an iterative simulation as well as the new fitness function with adaptive dynamics also serves a second purpose. It shows that the fitness-function was indeed correctly deduced, since the iterative simulation in no way relied on any expression of fitness, only on the ode:s representing the six-dimensional system that included the populations infected by the new mutant parasite. When constructing a new fitness function, verifying it is an important step to see if it is valid. Here, we did so in two ways: once by comparing the result to what was obtained with the iterative simulation, and also by checking if equal virulences cause a straight line in the PIP, meaning that equal virulences between the parasite and resident cause an ω of zero.

5.2 Virulence management

It has been of theoretical interest in microbiology and epidemiology to create selective pressures against more virulent variants of pathogens (Ebert1and and Bull; Ewald, 1993). Paul W. Ewald was one of the first ones to explore this concept in his writings (Ewald, 1993). He writes that, in a clinical setting, it is necessary to take measures to ensure that pathogens don't continually get an evolutionary advantage by increasing their virulence as a result of the practices employed by clinicians. Further, he writes that rather than trying to eliminate persistent, versatile pathogens (such as malaria), it might be of interest to create a scenario where such hard-to-deal-with pathogens will evolve to be benign by artificially making this the most desirable outcome for a pathogen.

In a epidemiological setting, after one has managed to identify all the most important factors affecting a parasites transmission (meaning the trade-offs involved), it is possible to build a model to be used with adaptive dynamics and evaluate the impact of different decisions in disease management. Using adaptive dynamics one can then predict the evolution of the different trait values involved. This would not be unlike what we have

tried to demonstrate using the malaria model; there are no previous examples of adaptive dynamics being applied to this model of malaria in the literature. Thus, this is a novel application of the adaptive dynamics approach to modelling the meso-evoltion of malaria virulence. This hopefully shows that adaptive dynamics does have potential for virulence management in the context of predicting the interplay of different ecological factors during an epidemic.

The R_0 breakdown was also a demonstration of this, albeit a grim one: since humans started dying due to the virulence of the parasite, the density of the population decreased, which led to more death, leading to an ESS at a lower virulence and thus causing a less virulent evolutionary endpoint, which is the aim of virulence management. (Ebert1and and Bull; Ewald, 1993) Of course, from a virulence management standpoint, density dependent mortality might not necessarily be very useful, since it is of more interest to find relationships that can be implemented to control the evolution of virulence, but as said previously, this has been a proof of concept, and we have sufficiently shown that adaptive dynamics can indeed be implemented in such a way that it can predict deviations from the classical R_0 maximisation. However, density dependence is a very realistic form of environmental feedback, and is a very common environmental factor in other ecological models. From the perspective of virulence management, it is still interesting that an ancient natural mechanism might be contributing to the reduction of virulences without human interference.

5.3 Limitations of the project

Concerning the results obtained here, they are still quite limited. The model was not based on any empirical data, and could thus not be compared to any such data to test the validity of the model. Further, due to the parameter sizes in real epidemics, (at least concerning what can be found in the data available online), this model might not be optimal for modelling a real epidemic in the first place, since real mortality rates and infection rates are so low that a simulation would take a very long time, unless a correct parameterisation is found. Further, as previously discussed, the model leaves out many factors that might be of interest when modelling a malaria epidemic. Should the work on this model continue, it might be of interest to try to apply it to empirical data, as well as trying to include common preventative factors like a quarantined and exposed class, as well as the presence of multiple strains of malaria, and see how these would affect the evolution of virulence.

6 Conclusions

On a general note, adaptive dynamics can readily be applied to many kinds of ecological models. Very complex models cannot be analytically solved, and adaptive dynamics provide a way to nonetheless find the ESS strategies for such models. Here, we explored the application of adaptive dynamics on the SIR model as well as a model of malaria transmission, and showed how adaptive dynamics can be used to find an evolutionarily stable strategy for a trait of interest in an epidemiological setting.

We found that adaptive dynamics can be easily applied to models to which it hasn't been applied yet, as long as the fitness function can be deduced. Using this method, one can find evolutionary endpoints for values even when they cannot be predicted ahead of time. This was demonstrated by using the malaria-model, where due to the vector-borne mode of transmission, it becomes hard to find analytical solutions to population sizes at equilibrium. We further demonstrated this fact by adding additional environmental feedback in the form of density-dependent mortality, showing that using adaptive dynamics, one can predict the optimal value for virulence even when considering a case where R_0 cannot be used to predict the optimal value for virulence.

When it comes to the difference in R_0 demonstrated with density-dependence, the breakdown of the R_0 optimisation paradigm could be shown for both the malaria-model as well as the SIR model. One issue that was present when demonstrating the difference in the R_0 for the malaria model, was that the difference itself was quite slight, even when the difference in virulence was significant. This was because the virulences were around the peak of R_0 even with density-dependence.

The significance of these findings may include potential use for virulence management in the form of evaluating the interplay of different preventative and other measures taken by authorities during epidemics, and how this impacts the evolution of a pathogen.

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