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

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Abstract

Host defence against parasite infection can rely on two broad strategies: resistance and tolerance. The spread of resistance traits usually lowers parasite prevalence and decreases selection for higher defence. Conversely, tolerance mechanisms increase parasite prevalence and foster selection for more tolerance. Here we examine the potential for the host to drive parasites to extinction through the evolution of one or other defence mechanism. We analysed theoretical models of resistance and tolerance evolution in both the absence and the presence of a trade-off between defence and reproduction. In the absence of costs, resistance evolves towards maximisation and, consequently, parasite extinction. Tolerance also evolves towards maximisation but the positive feedback between tolerance and disease prevents the disappearance of the parasite. On the contrary, when defence comes with costs it is impossible for the host to eliminate the infection through resistance, because costly resistance is selected against when parasites are at low prevalence. We uncover that the only path to disease clearance in the presence of costs is through tolerance. Paradoxically, however, it is by lowering tolerance -and hence increasing disease-induced mortality- that extinction can occur. We also show that such extinction can occur even in the case of parasite counter-adaptation. Our results emphasise the importance of tolerance as a defence strategy, and identify key questions for future research.

Keywords: adaptive dynamics, tolerance evolution.

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1. Introduction

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

The importance of a distinction between tolerance and resistance traits is most clearly understood in the context of their evolution and its impact on the ecological feedback in host-parasite systems (Boots and Bowers, 1999; Roy and Kirchner, 2000; Miller et al., 2005, 2007; Best et al., 2008; Boots et al., 2009; Best et al., 2009, 2014). Both mechanisms positively affect host fitness but resistance lowers parasite fitness while tolerance is either neutral or increases it. Therefore, there exists a negative feedback between selection for resistance and parasite prevalence, which allows evolutionary branching to coexistence (Antonovics and Thrall, 1994). On the contrary, tolerance evolves towards fixation (Boots and Bowers, 1999; Miller et al., 2007) under general hypotheses (Best et al., 2008) because the spread of a tolerant trait in a population increases disease prevalence and thereby generates an environment not suitable for less tolerant strains. Generally, these studies focused on how quantitative

investment in costly defence varies across ecological and epidemiological gradients, and on the potential for evolutionary branching. Here, we consider a different question: can the host drive parasites to extinction through evolving defence?

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

A key assumption in almost all theoretical evolution studies is that defence is costly in terms of fitness in the absence of infection, given both theoretical arguments (Stearns, 1992; Hoyle et al., 2008) and experimental support (Boots and Begon, 1993; Kraaijeveld and Godfray, 1997; Mealor and Boots, 2006). The underlying idea is that mounting a defence response is demanding and it limits the development of other life history traits. An important example is the well-documented trade-off between resistance and growth rate in in a moth-virus system (Boots and Begon, 1993; Bartlett et al., 2018). If there were no costs to evolving defence, we would expect resistant or tolerant strains to have always higher fitness than other strategies and defence to reach maximization. In this case, we might expect parasite extinction to be a common outcome. The presence of costs, however, is likely to offset the benefit of evolving to high levels of defence. In this scenario, resistant and tolerant strains have lower fitness than non-defensive ones in the absence of the parasite. Under infection, selection promotes higher defence when the benefits against infection overcome the costs of reduced reproduction. Costs are also necessary to the generation of diversity when either avoidance (Antonovics and Thrall, 1994; Boots and Haraguchi, 1999) or increased recovery (Boots and Bowers, 1999) evolves. In fact, resistance traits are predicted to evolve toward

Parameter	Definition	Default value
a	Host birth rate	2
b	Host mortality rate	0.1
q	Impact of crowding on host birth rate	0.2
β	Infection transmission coefficient	0.3
r	Host avoidance	0
γ	Recovery rate	0.3
α	Disease-induced mortality rate, virulence	varies
τ	Host tolerance	0

Table 1: Summary of model parameters

polymorphism rather than fixation (Roy and Kirchner, 2000) as at low parasite prevalence the costs outweigh the benefits. The question remains, therefore, as to whether the presence of costs can prevent host defence evolving to the point where extinction would occur.

Using a classic Susceptible-Infected-Susceptible model framework, we analyse the evolution of both resistance and tolerance with and without costs. To model the long-term evolutionary dynamics, we adopted an evolutionary invasion analysis (adaptive dynamics) framework (Dieckmann and Law, 1996; Marrow et al., 1996; Geritz et al., 1998). In this context, evolution is modelled as a sequence of steps of trait invasion and substitution under the assumptions of finitely small and rare mutational events and clonal reproduction. These assumptions and the absence of permanent recovery from infection make our model more suitable for microbial systems, e.g. bacteria-phage systems. Our main focus is host defence evolution, therefore, we assume that the impact on host mortality while infected caused by the parasite (virulence) does not change during the evolutionary process. Thus, we do not address theoretically the case of host-parasite co-evolution. Nevertheless, we relax this assumption in the numerical simulations, to address whether parasite extinction can occur despite parasite co-evolution of virulence. We assume also that the parasite sterilises infected individuals to facilitate mathematical tractability. However, we show in Appendix B that the occurrence of parasite extinction due to tolerance evolution does not depend upon the assumption of sterility under infection.

2. Model

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

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

Model parameters are listed in Table 1. Variables X and Y represent respectively the densities of susceptible and infected individuals. The parameter a is the host birth rate and b is the host natural death rate, while q models the effect of crowding on births. The disease spreads with a transmission coefficient β. As an effect of infection, the infected hosts suffer from an increased death rate by α, namely the parasite virulence. In addition, infected individuals are infertile and do not contribute to reproduction. Moreover, hosts can recover at rate γ and be susceptible to infection again.

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

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

$$R_0 = \frac{(\beta - r)\overline{X}_0}{\Gamma} = \frac{(\beta - r)(a-b)}{(\alpha - \tau + b + \gamma)q} > 1, \tag{2}$$

with $\Gamma = \alpha - \tau + b + \gamma$. System (1) shows a unique endemic equilibrium where the disease

persists

$$\begin{aligned} \overline{X} &= \frac{\Gamma}{\beta - r} \\ \overline{Y} &= \frac{a - b - q\overline{X}}{q + (\beta - r)\left(1 - \frac{\gamma}{\Gamma}\right)}, \end{aligned} \tag{3}$$

that is positive and stable, provided (2) is satisfied.

We analyse the evolution of both defence strategies under the assumptions of either cost-free or costly defence. To include the costs, trade-off functions have been introduced between defence and birth rate a.

According to adaptive dynamics theory, when a resident population has reached its equilibrium, in this case (3), a new mutant strain can invade if its invasion fitness in the environment set by the resident strategy is positive. Specifically, mutant invasion fitness is defined as "the long-term exponential growth rate of a rare mutant in an environment set by the resident" and in a structured population it is calculated as the leading eigenvalue of the mutant invasion matrix (Metz et al., 1992). When the direct computation of the invasion fitness is difficult, it is possible to adopt a fitness proxy instead. As defined in Parvinen and Dieckmann (2018), a fitness proxy is a function that is, up to a constant, sign equivalent to the invasion fitness. Adapting Hoyle et al. (2012) proof, we use the negative of the determinants of the mutant invasion matrices as proxies for the sign of the invasion fitness (Appendix A). We name the fitness proxy for resistance as s_r, this is a function of both the resident trait r and the mutant trait r_m. Using a similar notation for recovery and tolerance, we get

$$s_r(r, r_m) = (b + \alpha - \tau + \gamma)\left(a(r_m) - b - q\left(\overline{X} + \overline{Y}\right) - (\beta - r_m)\overline{Y}\right) + \gamma(\beta - r_m)\overline{Y}, \tag{4}$$

$$s_\gamma(\gamma, \gamma_m) = (b + \alpha - \tau + \gamma_m)\left(a(\gamma_m) - b - q\left(\overline{X} + \overline{Y}\right) - (\beta - r)\overline{Y}\right) + \gamma_m(\beta - r)\overline{Y}, \tag{5}$$

$$s_\tau(\tau, \tau_m) = (b + \alpha - \tau_m + \gamma)\left(a(\tau_m) - b - q\left(\overline{X} + \overline{Y}\right) - (\beta - r)\overline{Y}\right) + \gamma(\beta - r)\overline{Y}. \tag{6}$$

In (4)-(6) the dependence from the resident strategies lies in $\overline{X}$ and $\overline{Y}$, as can be seen in (3).

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

selection gradient, is equal to zero. In this model the selection gradients are

$$\left.\frac{\partial s_r}{\partial r_m}\right|_{r_m=r} = \Gamma a'(r) + (\alpha - \tau + b)\overline{Y}, \tag{7}$$

$$\left.\frac{\partial s_\gamma}{\partial \gamma_m}\right|_{\gamma_m=\gamma} = \Gamma a'(\gamma) + (\beta - r)\left(1 - \frac{\gamma}{\Gamma}\right)\overline{Y}, \tag{8}$$

$$\left.\frac{\partial s_\tau}{\partial \tau_m}\right|_{\tau_m=\tau} = \Gamma a'(\tau) + \frac{\beta - r}{\Gamma}\gamma\overline{Y}. \tag{9}$$

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

$$\frac{dr}{dT} \approx \mu \left.\frac{\partial s_r}{\partial r_m}\right|_{r_m=r} \tag{10}$$

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

$$\left.\frac{\partial^2 s_{r_m}}{\partial r_m^2}\right|_{r_m=r=r^*} > \left.\frac{\partial^2 s_{r_m}}{\partial r^2}\right|_{r_m=r=r^*} \tag{11}$$

The same holds for tolerance and recovery.

3. Results

3.1. Evolution of resistance

We firstly consider the case of evolving avoidance without costs, i.e. when the birth rate $a(r)$ is equal to a positive constant $\bar{a}$ for every resistance strategy r. Under this assumption, the selection gradient

$$\left.\frac{\partial s_r}{\partial r_m}\right|_{r_m=r} = (\alpha - \tau + b)\overline{Y} > 0 \tag{12}$$

and it is equal to 0 when $\overline{Y} = 0$. Therefore, evolution leads towards higher value of r to the point where $R_0 = 1$ and the disease can not spread enough to survive. A similar conclusion

can be drawn when increased recovery evolves without cost. We choose $a(\gamma) = a_m(\gamma) = \bar{a}$ positive constant such that (2) is satisfied for some γ. Consequently, the selection gradient

$$\left.\frac{\partial s_\gamma}{\partial \gamma_m}\right|_{\gamma_m=\gamma} = (\beta - r)\left(1 - \frac{\gamma}{\Gamma}\right)\overline{Y} > 0 \tag{13}$$

for every γ such that $\overline{Y} > 0$ and equal to zero at $\overline{Y} = 0$, since $\gamma < \Gamma$. Thus, the evolutionary dynamics reaches the extinction boundary, where the recovery rate is too high for the infection to persist. The reason for this is that an increase in γ means a decrease in the length of the infectious period and, consequently, in R_0.

We use the graphical tool of pairwise invasibility plot (PIP) (van Tienderen and de Jong, 1986; Geritz et al., 1998) to show the evolutionary dynamics. In the PIPs, the sign of the invasion fitness is plotted in the plane spanned by the resident and the mutant strategies. When the positive region (positive regions are shaded and negative regions are white) is above the diagonal the evolutionary dynamics moves to the right, while it moves to the left when the positive region is below the diagonal. In both cases of Fig.1 the absence of costs allows defence to be favoured even at low values of disease prevalence, where selection for resistance is weaker.

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

$$\lim_{\overline{Y}\to 0^+} \left.\frac{\partial s_r}{\partial r_m}\right|_{r_m=r} = \Gamma a'(r) < 0 \tag{14}$$

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

Similarly, we consider a trade-off $a = a(\gamma)$ that is monotonically decreasing with respect to γ and satisfies (2) for some γ. Close to the extinction boundary the limit of the selection

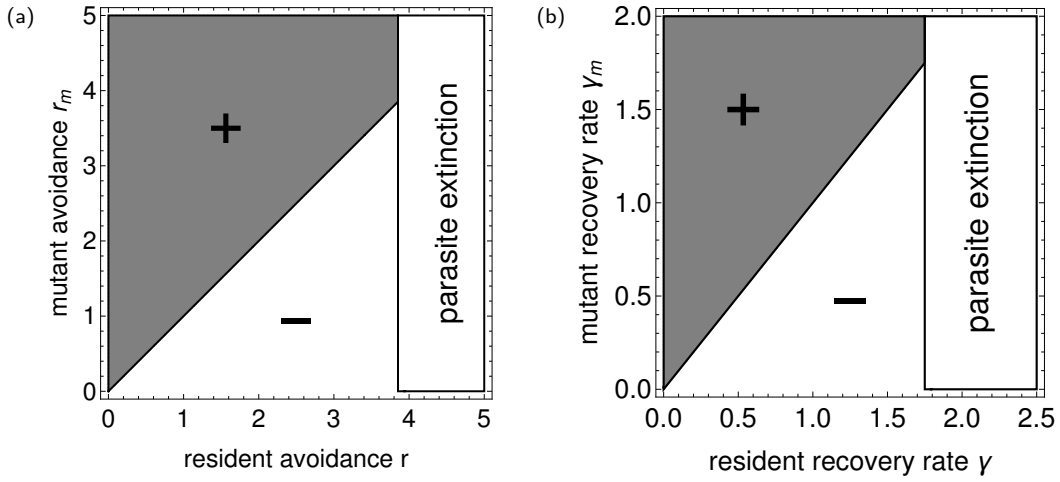

Figure 1: Pairwise invasibility plot for resistance evolution without costs. In (a) the sign of $s_r(r, r_m)$ is plotted in the r-r_m plane under the hypothesis that $a'(r) = 0$. Analogously, (b) shows the sign of $s_\gamma(\gamma, \gamma_m)$ as function of γ and γ_m. In both panels the gray region marks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

gradient is

$$\lim_{\overline{Y}\to 0^+} \frac{\partial s_\gamma}{\partial \gamma_m}\bigg|_{\gamma_m=\gamma} = \Gamma a'(\gamma) < 0 \tag{15}$$

and mutants with lower values of resistance will invade.

It can be shown that R_0 and disease prevalence $\overline{Y}/\left(\overline{X}+\overline{Y}\right)$, with $\overline{X}$ and $\overline{Y}$ defined in (3), are monotonically increasing for decreasing resistance, therefore, the host cannot clear the disease by lowering defence. Notice also that we proved that extinction cannot occur in the deterministic model under the assumption of small mutations. When $\overline{Y}$ is close to 0, extinction could be possible if stochastic effects are taken into account.

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

$$a(r) = a^* - \frac{a'(r^*)^2}{a''(r^*)}\left(1 - e^{\frac{a''(r^*)}{a'(r^*)}(r-r^*)}\right) \tag{16}$$

$$a(\gamma) = a^* - \frac{a'(\gamma^*)^2}{a''(\gamma^*)}\left(1 - e^{\frac{a''(\gamma^*)}{a'(\gamma^*)}(\gamma-\gamma^*)}\right). \tag{17}$$

This choice allows to easily determine the local shape close to a chosen point (r^*, a^*) or (γ^*, a^*) and consequently, by absolute monotonicity, a wide range of global behaviours, e.g.

different steepness or concavity. Specifically, $a'(r^*)$ and $a'(\gamma^*)$ are chosen such that r^* and γ^* are a singular strategy, i.e. the selection gradients in (4)-(5) are equal to zero. Notice that this choice respects the assumption of monotonically increasing costs. We derive the intervals for $a''(r^*)$ and $a''(\gamma^*)$ such that the singular strategies are convergence stable from (11). If r^* and γ^* are convergence stable, parasite extinction is trivially avoided (Fig.2a and Fig.2c). More interestingly, when r^* and γ^* are convergence unstable a second singular strategy close to the boundary necessarily emerges and prevents the disease dying out (Fig.2b and Fig.2d).

3.2. Evolution of tolerance

In the absence of costs, the selection gradient (6) for tolerance is

$$\left.\frac{\partial s_\tau}{\partial \tau_m}\right|_{\tau_m=\tau} = \frac{(\beta - r)\gamma}{\Gamma}\overline{Y} > 0 \tag{18}$$

when the infection is present and null at the extinction boundary. Therefore, the evolutionary dynamics moves towards tolerance maximisation and balance the effect of parasite virulence α. Contrary to the case of resistance, disease prevalence increases when tolerance is selected and parasite extinction does not occur. This can be observed in the simulation in Fig.3, implemented as in Appendix C.

We consider now the case of costly tolerance. In line with what stated for resistance, we assume that investing in tolerant strategies limits the allocation of resources for reproduction. A field study on voles showed evidence for such a trade-off (Jackson et al., 2014; Kutzer and Armitage, 2016) but our general understanding on the mechanisms behind tolerance is still limited. When we consider the costs of tolerance, the trade-off $a(\tau)$ is assumed to be monotonically decreasing with respect to τ. Under this assumption, near the extinction boundary the selection gradient (6) is

$$\lim_{\overline{Y}\to 0^+} \left.\frac{\partial s_\tau}{\partial \tau_m}\right|_{\tau_m} = \tau = \Gamma a'(\tau) < 0, \tag{19}$$

meaning that selection for *lower* tolerance can lead to parasite extinction. Such situations are illustrated in Fig.4a and Fig.4b, in which the sign of $s_\tau(\tau, \tau_m)$ is plotted for different values of both mutant and resident strategies. Compared to the case without costs, the zero

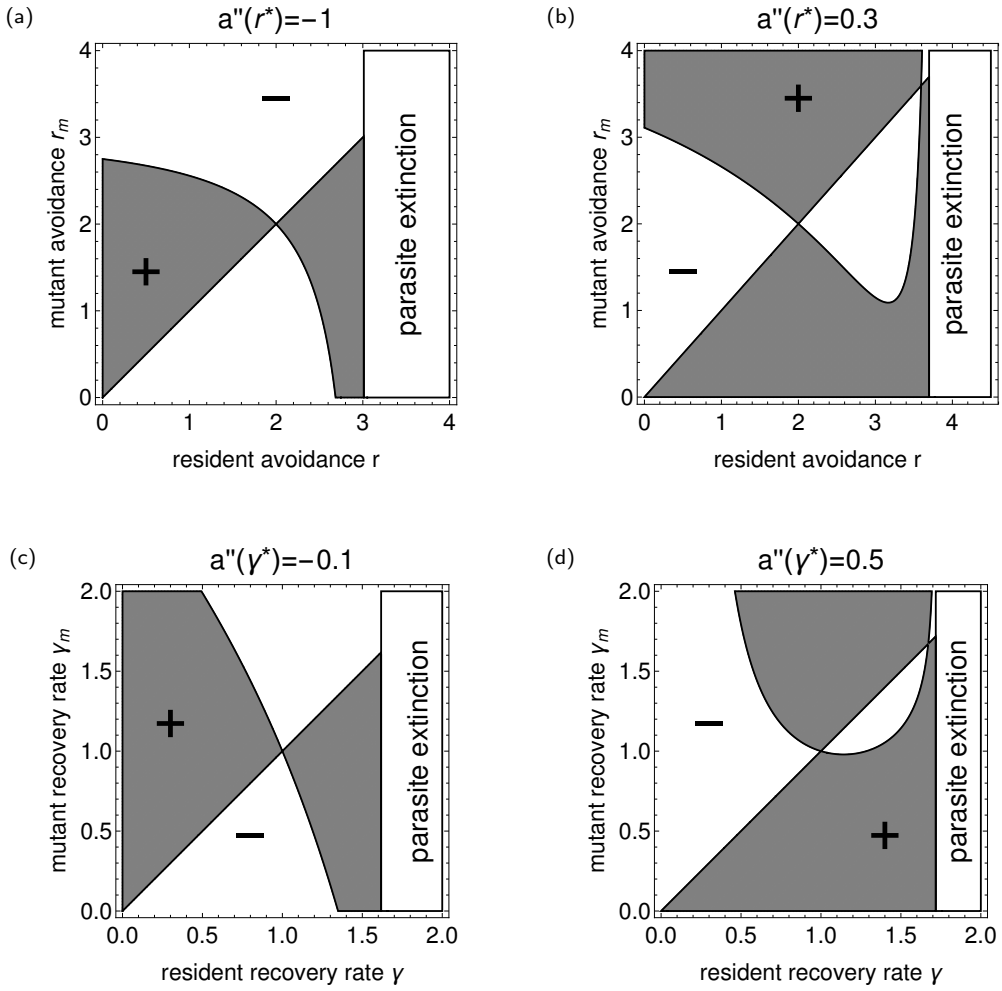

Figure 2: Pairwise invasibility plots for resistance evolution with costs. In (a) and (b) the sign of $s_r(r, r_m)$ is plotted in the r-r_m plane for two different values of the second derivative of the trade-off function $a(r)$ at the singular strategy $r^* = 2$. Similarly, in (c) and (d) the sign of $s_\gamma(\gamma, \gamma_m)$ is plotted for two different values of $a''(\gamma^*)$. In the gray regions the invasion fitness is positive. $\alpha = 1$. In (a) and (b) $\beta^* = 2; a(\beta^*) = 2; a'(\beta^*) = 0.78$. In (c) and (d) $\gamma^* = 1; a(\gamma^*) = 2; a'(\gamma^*) = -0.1$.

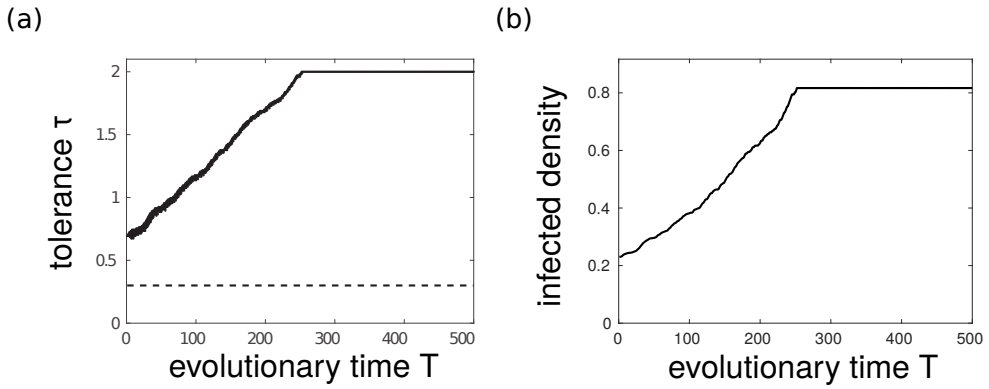

Figure 3: Simulation of the evolution of tolerance in absence of costs (for details see Appendix C). In the left panel, the black region represents the values of τ of the strains present at each iteration and the dashed line the parasite extinction boundary. In the right panel, the continuous curve represents the disease prevalence. $\alpha = 2$.

of the selection gradient that was on the extinction boundary has now entered the region of parasite viability, changing the direction of selection for low $\overline{Y}$.

We investigate now under which conditions on the trade-off function host evolution drives the parasite to extinction by lowering tolerance. As a first condition, we need the parasite to be present in the system, meaning $R_0 > 1$. By rearranging condition (2), we found that it holds when

$$a(\tau) > b + \frac{q(\gamma + b + \alpha)}{\beta - r} - \frac{q}{\beta - r}\tau \tag{20}$$

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

$$a(\tau) = b + \frac{q(\gamma + b + \alpha)}{\beta - r} - \frac{q}{\beta - r}\tau \tag{21}$$

has to have a least one real and positive root for some parameter sets otherwise the parasite is viable for every value of τ. To derive the last condition, we notice that, under the assumption of a decreasing trade-off $a(\tau)$, R_0 can be non monotonous with respect to τ and the parasite can be not viable for both low and high values of tolerance (e.g. in Fig.4a). The selection gradient close to extinction boundary is given in (19) and is negative, therefore, parasite extinction can occur only for lower values of tolerance. Notice that extinction can happen only when parasite prevalence is locally monotonically increasing with respect of τ, so it

decreases as τ decreases. Infection prevalence P is defined as

$$P = \frac{\overline{Y}}{\overline{X} + \overline{Y}} = \frac{q\left(\overline{X}_0 - \overline{X}\right)}{a + \alpha - \tau}. \tag{22}$$

Consequently, the derivative of P with respect of τ is

$$\frac{dP}{d\tau} = \frac{\left(a'(\tau) - q\frac{d\overline{X}}{d\tau}\right)(a(\tau) + \alpha - \tau) - q(a'(\tau) - 1)\left(\overline{X}_0 - \overline{X}\right)}{(a + \alpha - \tau)^2}, \tag{23}$$

which it is positive when

$$a'(\tau) > -\frac{(\beta - r)(a(\tau) - b) + q\,(a(\tau) - b - \gamma)}{(\beta - r)(\alpha - \tau + b) + q\Gamma}. \tag{24}$$

When we evaluate the right-hand side of (24) at (21), we get that the slope of the trade-off evaluated at the boundary has to be more than $-q/\beta$, which is minus the ratio between host internal competition and the parasite transmission coefficient. To summarise, considering a trade-off that satisfies (20) for some τ, parasite extinction is possible when (21) has at least one real and positive root where the slope of the trade-off function is more than $-q/\beta$.

Notice that another consequence of the non-monotony of disease prevalence is that (21) may not have any real and positive roots and the disease does not die out for any values of τ. Due to the trade-off between birth rate and tolerance, if the increase in reproduction is considerable the large susceptible inflow compensates the shortening of the infectious period and the disease persists despite tolerance decreasing.

We can give a graphical representation to the conditions for parasite extinction by plotting the right-hand side of (21), i.e. the thick line in Fig.5. Condition (20) is satisfied if a trade-off function is above the line for some value of τ and condition (21) holds when the trade-off intersects it. Moreover, the slope of the line is $-q/\beta$ and if a trade-off function intersects it with a larger gradient parasite extinction is possible. Choosing the trade-off function

$$a(\tau) = a^* - \frac{a'(\tau^*)^2}{a''(\tau^*)}\left(1 - e^{\frac{a''(\tau^*)}{a'(\tau^*)}(\tau - \tau^*)}\right), \tag{25}$$

in Fig.5 we check if the conditions for extinction hold for different values of $a''(\tau^*)$, namely the value of the second derivative of the trade off function evaluated at τ^*.

Accordingly, the evolutionary outcomes of tolerance evolution can be observed in Fig.4. In the first two panels parasite extinction occurs through reduced tolerance, while in the

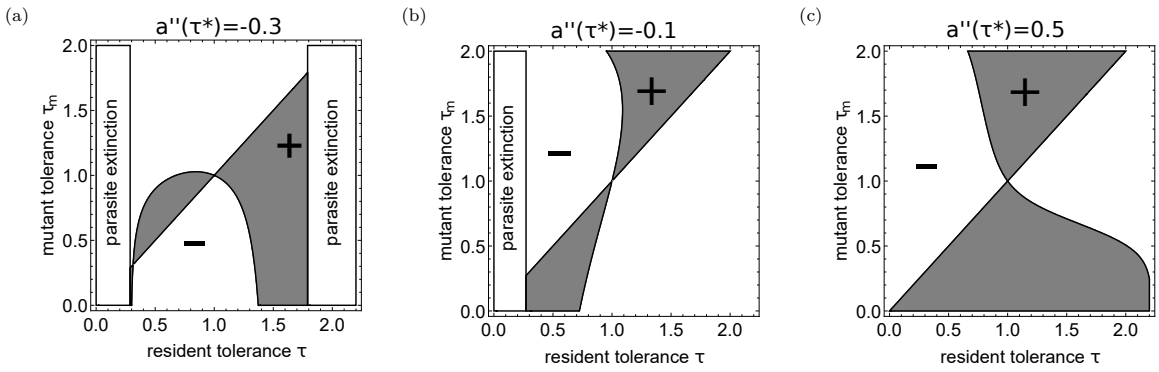

Figure 4: Pairwise invasibility plot for tolerance evolution with costs. In the τ-τ_m plane, $s_\tau(\tau, \tau_m)$ is positive in correspondence with gray regions. The three panels are related to different values of the parameter $a''(\tau^*)$ of the trade-off function $a(\tau)$. $\alpha = 2; \tau^* = 1; a(\tau^*) = 1.5; a'(\tau^*) = -0.049$.

third panel condition (24) is satisfied before evolution reaches the extinction boundary and the disease persists.

It can be noticed that in the first panel of Fig.4, extinction occurs for a narrower range of initial strategies than in the second panel. To quantify the range of initial strategies from which natural selection leads to parasite clearance, we define the basin of attraction of the extinction boundary as the difference between the extinction value of τ that satisfies conditions (20), (21) and (24) and either the closest singular strategy, which is always a repeller, or 0 when there are not positive singular strategies. As it can be seen in Fig.6, extinction can occur for a wide range of choices of trade-off parameters $a'(\tau^*)$ and $a''(\tau^*)$ and different combinations of q and β. Particularly, extinction happens mostly for negative $a''(\tau^*)$, i.e. for increasingly accelerating costs. For low values of $a'(\tau^*)$, the basin of attraction is narrow due to a repeller strategy close to the boundary. When $a'(\tau^*)$ increases the repeller strategy either disappears through a fold bifurcation (black curve in Fig.6) or its value decreases and the basin of attraction increases. Moreover, when q/β increases extinction occurs for a wider range of values with smaller basin of attraction due to a decrease in R_0 and an increase in the steepness of the bold line in Fig.5.

Numerical simulations (performed as in Fig.3),where we relaxed the hypothesis of a timescale separation between evolutionary and ecological time, showed the occurrence of parasite extinction due to tolerance evolution. Furthermore, we questioned whether such

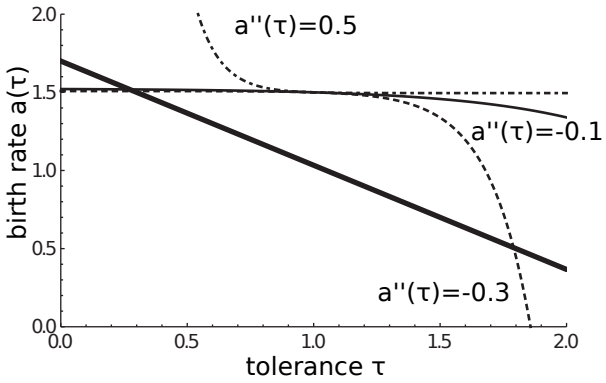

Figure 5: Conditions for parasite extinction. The thick line represents the RHS of (21) and the thin curves are plots of (20) for different values of $a''(\tau^*)$. The parasite population is viable, when $a(\tau)$ is above the thick line, and the extinction boundaries are at the cross between $a(\tau)$ and the thick line. For $a''(\tau^*) = -0.3$ (dashed curve) parasite are not viable for both high and low values of tolerance, for $a''(\tau^*) = -0.1$ (continuous curve) parasite are not viable for low values of tolerance and for $a''(\tau^*) = 0.5$ (dot-and-dashed curve) parasite are always viable. Parasite extinction can occur only for the lower value of τ, since at the lower one the gradient of the trade-off is higher than $-q/\beta$. $\tau^* = 1; a(\tau^*) = 1.5; a'(\alpha^*) = -0.049$.

extinctions could still occur when the parasite is able to co-evolve its virulence strategy and gain faster transmission by increasing virulence. Running numerical simulations of the co-evolution of host tolerance and parasite virulence we found it easy to obtain examples where extinction did still occur (Fig.7a). Depending upon initial values, co-evolution can also lead to parasites avoiding extinction by lowering virulence as in Fig.7b.

4. Discussion

We analysed the possibility for parasite extinction due to the evolution of costly host defence and found that only tolerance can lead to deterministic host-driven parasite extinction. Interestingly, it is by lowering tolerance, and therefore suffering more damaging effects from infection, that eradication of the parasite occurs. To our knowledge, this is the first study to demonstrate this possibility through a dynamic evolutionary process. We have also recovered previously known results that hosts can eradicate the disease by evolving resistance mechanism if costs are not present (Antonovics and Thrall, 1994), but that eradication of

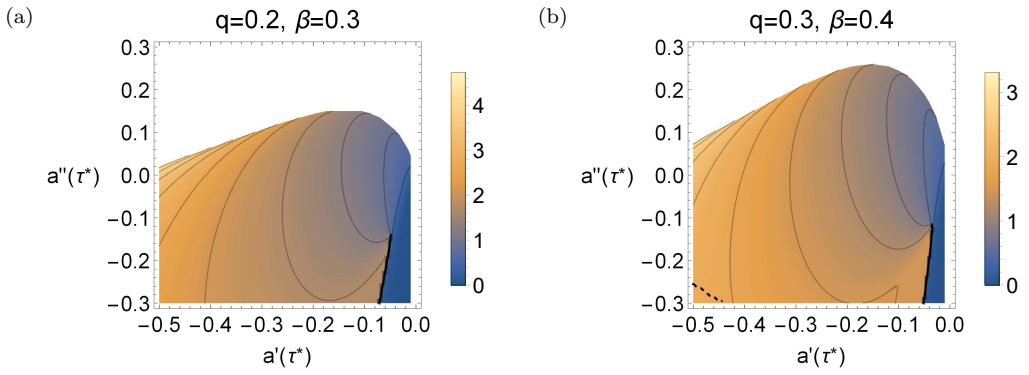

Figure 6: Density plots of the attraction basin of the extinction boundary as function of $a'(\tau^*)$ and $a''(\tau^*)$ for different values of q and β. The basin is measured as the difference between the value of τ that satisfies conditions (20)-(21) and the closest singular strategy, which is an evolutionary repeller. In the white regions, equation (21) does not have a real and positive solution and extinction cannot occur. The continuous black line marks a discontinuity in the basin of attraction due to a fold bifurcation between two singular strategies. Below the dashed curve in the third panel, there are not positive singular strategies and extinction occurs for every initial value of t. $\alpha = 5; \tau^* = 1; a(\tau^*) = 1.5$.

infection is impossible through costly resistance since selection for resistance always vanishes before parasite extinction (Roy and Kirchner, 2000). Our work not only identifies a potential route for host-driven parasite extinction but also further highlights the crucial distinction between resistance and tolerance mechanisms.

An important question that arises is whether such host-driven extinctions are possible in natural systems. Experimental studies of coevolutionary bacteria-phage interactions have found that phage can be driven to extinction through the evolution of host resistance when the pathogen is subjected to some external pressure, for example population bottlenecks (Hesse and Buckling, 2016) or reduced resource availability (Zhang and Buckling, 2016). Interestingly, a similar result has been predicted theoretically by Hoyle et al. (2012), where it was found that the presence of a predator species adds environmental pressure on the parasite that can lead to parasite extinction. Further experimental work is required to determine whether the evolution of tolerance mechanisms can lead to extinction in the absence of external pressures as we have predicted here.

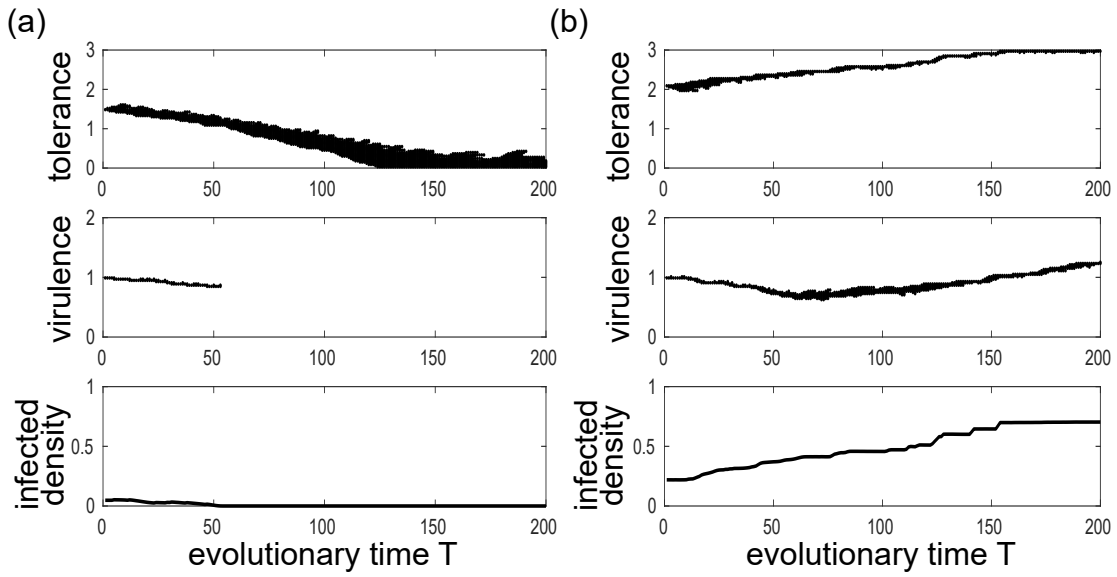

Figure 7: Numerical simulations of host-parasite co-evolution (for details see Appendix C) for two different initial values. Parasite virulence α^P is linked with disease transmission by the function $\beta(\alpha^P) = 0.3 - 0.05\left(1 - e^{-2(\alpha^P - 1)}\right)$. $\alpha^H = 2, \tau^* = 1; a(\tau^*) = 1.5; a'(\tau^*) = -0.049; a''(\tau^*) = -0.1; n_P = 100; n_H = 100$.

Questioning if parasite extinction would be possible requires understanding whether selection could promote the lowering of tolerance in an already tolerant population. A few potential routes can be hypothesized. Firstly, tolerance that has evolved due to exposure to different pathogens in the past could be lost due to different selection pressures from a novel pathogen. Evidence of such a change has been found by Ayres and Schneider (2008), where a single gene was found lowering tolerance in Drosophila according to different microbial challenge. Secondly, the concept of "behavioural tolerance" has been described by Sears et al. (2013) and Adelman and Hawley (2017). In this case organisms may evolve behavioural adaptations to face infection, like anorexia or lethargy, that increase the severity of disease symptoms. Similarly there is the potential for hosts to evolve immunopathological responses (Read et al., 2008; Medzhitov et al., 2012), whereby the host immune response inflicts damage to infected hosts, and can in some sense be seen as the opposite side of the coin to tolerance. There continues to be much interest in exploring tolerance mechanisms across a range of host-pathogen interactions (Råberg, 2014; Kutzer and Armitage, 2016; Soares et al., 2017).

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

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

mortality and increased reproduction, lowered tolerance is still beneficial for the individual's fitness.

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

The gap between the theoretical dichotomy of resistance and tolerance and the complexity of experimental results is still wide. In the theoretical framework, tolerance and resistance are clearly defined as distinct and predicted to lead to different evolutionary consequences. In experimental studies, even when it is possible to distinguish among the two traits it is still challenging to unravel all the implication of their interplay. While some studies found a trade off between tolerance and resistance (Råberg, 2014), others suggest a more complementary dynamics, as tolerance contributes to reducing the effects on tissues caused by resistance mechanisms (Medzhitov et al., 2012; Soares et al., 2017). Filling this gap would be beneficial for both theoretical and experimental development. A better understanding of the mechanisms behind tolerance would improve the reliability of evolutionary models that

in return could facilitate the design of experimental studies. In this sense, the aim of this work is to further highlighted the crucial role that host tolerance may play in host-parasite systems, and as such it is vital that modellers and empiricists identify avenues for further research with closer integration.

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Appendix A Invasion fitness

We give now a quick explanation for the fitness proxy $s_r(r, r_m)$ and analogous arguments hold for $s_\gamma(\gamma, \gamma_m)$ and $s_\tau(\tau, \tau_m)$. Given a resident population of trait r at the demographic equilibrium $\left(\overline{X}, \overline{Y}\right)$, the dynamics for a new mutant strain r_m is

$$\begin{aligned} \frac{dX_m}{dt} &= \left(a(r_m) - b - q\left(\overline{X} + \overline{Y}\right) - (\beta - r_m)\overline{Y}\right) X_m + \gamma Y_m \\ \frac{dY_m}{dt} &= (\beta - r_m)X_m - (\alpha - \tau + b + \gamma)Y_m. \end{aligned} \tag{A1}$$

The underlying assumption is that at the beginning mutant prevalence is low and does not influence the environment set by the resident. The mutant strain can spread if the equilibrium (3) is unstable in the full system, i.e. if the Jacobian matrix with respect to the mutant variables

$$\begin{pmatrix} a(r_m) - b - q(\overline{X} + \overline{Y}) - (\beta - r_m)\overline{Y} & \gamma \\ (\beta - r_m)\overline{Y} & -\Gamma \end{pmatrix} \tag{A2}$$

has at least one eigenvalue with positive real part. Therefore, the mutant fitness is defined as the leading eigenvalue of (A2). Hoyle et al. (2012) proved that the negative of the determinant of (A2) has equivalent sign of the leading eigenvalue and thus it can be used as fitness proxy.

Appendix B Impact of fertility under infection

We show here that even when hosts reproduce while infected, parasite extinction through tolerance evolution can still occur. We assume that the reproduction rate of infected indi-

viduals is reduced by a coefficient f. Considering this hypothesis, the model is

$$\begin{aligned}\frac{dX}{dt} &= a\,(X+fY) - bX - q(X+Y)(X+fY) + (\beta - r)XY + \gamma Y \\ \frac{dY}{dt} &= (\beta - r)XY - (\alpha - \tau + b + \gamma)Y.\end{aligned} \tag{B1}$$

The dynamics of (B1) differs from the one of (1) as it can show more than one internal equilibrium. Here, we assume that the dynamics reaches a stable internal equilibrium $\left(\overline{X}, \overline{Y}\right)$, leaving the details to a more deepened study. The invasion fitness for a mutant strategy with tolerance t_m, calculated as in Appendix A, is:

$$\begin{aligned}s_\tau(\tau, \tau_m) =&(\alpha - \tau_m + b + \gamma)\left[a(\tau_m) - b - q\left(\overline{X} + \overline{Y}\right) - (\beta - r)\overline{Y}\right] \\ &+ (\beta - r)\overline{Y}\left[\gamma + af - qf\left(\overline{X} - \overline{Y}\right)\right].\end{aligned} \tag{B2}$$

Consequently, the selection gradient is

$$\left.\frac{\partial s_\tau(\tau, \tau_m)}{\partial \tau_m}\right|_{\tau_m = \tau} = -\left[a(\tau) - b - q\left(\overline{X} + \overline{Y}\right) - (\beta - r)\right] + a'(\tau)(\alpha - \tau + b + \gamma), \tag{B3}$$

which, taking the limit at the extinction boundary, becomes

$$\lim_{\substack{\overline{Y}\to 0 \\ \overline{X}\to \overline{X}_0}} \left.\frac{\partial s_\tau(\tau, \tau_m)}{\partial \tau_m}\right|_{\tau_m = \tau} = a'(\tau)(\alpha - \tau + b + \gamma) < 0 \tag{B4}$$

as the reproduction rate is decreasing with respect of τ. Equation (B4) shows that the selection gradient at the extinction boundary for low level of tolerance points towards the region of parasite extinction. Therefore, parasite extinction due to tolerance minimisation occurs also when infected individuals can reproduce. In fact, PIP (not shown) realised as in Fig.4 show a qualitatively similar behaviour as in Fig.4 for different values of f between 0 and 1.

Appendix C Numerical simulations

To perform numerical simulations we followed a method similar to Hoyle et al. (2012). For tolerance evolution, we set a system for 200 possible host strain values of τ and initialised as non zero the initial condition for a random strain. At every step the system is solved for a fixed time that is not long enough for the population dynamics to reach the dynamical equilibrium. In this way it can be relaxed the hypothesis of time-scale separation between

ecological and evolutionary dynamics. Strains with frequency less than 0.1% are then removed from the system and a new mutant close to the most frequent strain is introduced randomly. Moreover, the parasite is removed from the system when its prevalence drops under 0.01%. Similarly, to simulate co-evolution between host tolerance (τ) and parasite virulence (α_P) at every step we solve the system

$$\begin{aligned}\frac{dX_i}{dt} =& a\left(\tau_i\right) X_i - q\left(\sum_i^{n_H}\sum_j^{n_P} Y_{ij} + \sum_i^{n_P} X_i\right) X_i - X_i \sum_{i=1}^{n_H}\sum_{j=1}^{n_P} \beta\left(\alpha_j^P\right) Y_{ij} \\ &+ \gamma \sum_{j=1}^{n_P} Y_{ij}, \quad i = 1, \ldots, n_H \\ \frac{dY_{ij}}{dt} =& \beta\left(\alpha_j^P\right) Y_{ij} X_i - \left((\alpha^H - \tau_i)\alpha_j^P + b + \gamma\right) Y_{ij}, \quad i = 1, \ldots, n_H \quad j = 1, \ldots, n_P,\end{aligned} \tag{C1}$$

where X_i is the density of the host population with tolerance strain t_i and Y_{ij} is the density of infected with tolerance strain t_i from the parasite strain α_j^P. The parameter α^H has been introduced to avoid that the term for infected mortality becomes positive. The number of host strains is n_H and the number of parasite strains is n_P, $a(\tau_i)$ is defined as in (25), $\beta(\alpha_j^P)$ is a monotonously increasing function (e.g. Fig.7) and the others parameters have same interpretation as in (1). After a fixed time, populations with frequency under 0.1% are set to zero and a new mutant strain is introduced randomly with same probability of being a new host or a new parasite.

References

Adelman, J.S., Hawley, D.M., 2017. Tolerance of infection: A role for animal behavior, potential immune mechanisms, and consequences for parasite transmission. Hormones and Behavior 88, 79–86. URL: http://www.sciencedirect.com/science/article/pii/S0018506X16302963, doi:10.1016/j.yhbeh.2016.10.013.

Anderson, R.M., May, R.M., 1981. The Population Dynamics of Microparasites and Their Invertebrate Hosts. Philosophical Transactions of the Royal Society of London B: Biological Sciences 291, 451–524. URL: http://rstb.royalsocietypublishing.org/content/291/1054/451, doi:10.1098/rstb.1981.0005.

Antonovics, J., Thrall, P.H., 1994. The Cost of Resistance and the Maintenance of Genetic Polymorphism in Host-Pathogen Systems. Proceedings of the Royal Society of London B: Biological Sciences 257, 105–110. URL: http://rspb.royalsocietypublishing.org/content/257/1349/105, doi:10.1098/rspb.1994.0101.

Ayres, J.S., Schneider, D.S., 2008. A Signaling Protease Required for Melanization in Drosophila Affects Resistance and Tolerance of Infections. PLoS Biology 6. URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2596860/, doi:10.1371/journal.pbio.0060305.

van Baalen, M., 1998. Coevolution of Recovery Ability and Virulence. Proceedings: Biological Sciences 265, 317–325. URL: https://www.jstor.org/stable/50837.

Bartlett, L.J., Wilfert, L., Boots, M., 2018. A genotypic trade-off between constitutive resistance to viral infection and host growth rate 72, 2749–2757. URL: https://onlinelibrary.wiley.com/doi/abs/10.1111/evo.13623, doi:10.1111/evo.13623.

Best, A., White, A., Boots, M., 2008. Maintenance of host variation in tolerance to pathogens and parasites. Proceedings of the National Academy of Sciences 105, 20786–20791. URL: http://www.pnas.org/content/105/52/20786, doi:10.1073/pnas.0809558105.

Best, A., White, A., Boots, M., 2009. The Implications of Coevolutionary Dynamics to Host-Parasite Interactions. The American Naturalist 173, 779–791. URL: http://www.journals.uchicago.edu/doi/abs/10.1086/598494, doi:10.1086/598494.

Best, A., White, A., Boots, M., 2014. The Coevolutionary Implications of Host Tolerance. Evolution 68, 1426–1435. URL: http://onlinelibrary.wiley.com/doi/10.1111/evo.12368/abstract, doi:10.1111/evo.12368.

Boldin, B., Kisdi, É., 2016. Evolutionary suicide through a non-catastrophic bifurcation: adaptive dynamics of pathogens with frequency-

dependent transmission. Journal of Mathematical Biology 72, 1101–1124. URL: https://link.springer.com/article/10.1007/s00285-015-0945-5, doi:10.1007/s00285-015-0945-5.

Boots, M., 2008. Fight or learn to live with the consequences? Trends in Ecology & Evolution 23, 248–250. URL: http://www.sciencedirect.com/science/article/pii/S0169534708000943, doi:10.1016/j.tree.2008.01.006.

Boots, M., Begon, M., 1993. Trade-Offs with Resistance to a Granulosis Virus in the Indian Meal Moth, Examined by a Laboratory Evolution Experiment. Functional Ecology 7, 528–534. URL: http://www.jstor.org/stable/2390128, doi:10.2307/2390128.

Boots, M., Best, A., Miller, M.R., White, A., 2009. The role of ecological feedbacks in the evolution of host defence: what does theory tell us? Philosophical Transactions of the Royal Society of London B: Biological Sciences 364, 27–36. URL: http://rstb.royalsocietypublishing.org/content/364/1513/27, doi:10.1098/rstb.2008.0160.

Boots, M., Bowers, R., 1999. Three Mechanisms of Host Resistance to Microparasites-Avoidance, Recovery and Tolerance-Show Different Evolutionary Dynamics. Journal of Theoretical Biology 201, 13–23. URL: http://www.sciencedirect.com/science/article/pii/S0022519399910093, doi:10.1006/jtbi.1999.1009.

Boots, M., Haraguchi, Y., 1999. The Evolution of Costly Resistance in Host-Parasite Systems. The American Naturalist 153, 359–370. URL: http://www.journals.uchicago.edu/doi/abs/10.1086/303181, doi:10.1086/303181.

Bowers, R.G., Boots, M., Begon, M., 1994. Life-History Trade-Offs and the Evolution of Pathogen Resistance: Competition between Host Strains. Proceedings of the Royal Society of London B: Biological Sciences 257, 247–253. URL: http://rspb.royalsocietypublishing.org/content/257/1350/247, doi:10.1098/rspb.1994.0122.

Caldwell, R.M., Schafer, J.F., Compton, L.E., Patterson, F.L., 1958. Tolerance to Cereal Leaf Rusts. Science 128, 714–715. URL: http://science.sciencemag.org/content/128/3326/714, doi:10.1126/science.128.3326.714.

Chahroudi, A., Bosinger, S.E., Vanderford, T.H., Paiardini, M., Silvestri, G., 2012. Natural SIV Hosts: Showing AIDS the Door. Science 335, 1188–1193. URL: http://science.sciencemag.org/content/335/6073/1188, doi:10.1126/science.1217550.

Clarke, D.D., 1986. Tolerance of parasites and disease in plants and its significance in host-parasite interactions. Advances in plant pathology URL: http://agris.fao.org/agris-search/search.do?recordID=US201302064119.

Dieckmann, U., Law, R., 1996. The dynamical theory of coevolution: a derivation from stochastic ecological processes. Journal of Mathematical Biology 34, 579–612. URL: http://link.springer.com/article/10.1007/BF02409751, doi:10.1007/BF02409751.

Ferrière, R., Dieckmann, U., Couvet, D., 2009. Evolutionary conservation biology. Digitally printed version (pbk. re-issue) ed., Cambridge University Press, Cambridge, UK.

Geritz, S.a.H., Kisdi, É., Meszéna, G., Metz, J.a.J., 1998. Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. Evolutionary Ecology 12, 35–57. URL: http://link.springer.com/article/10.1023/A:1006554906681, doi:10.1023/A:1006554906681.

Gómez, P., Bennie, J., Gaston, K.J., Buckling, A., 2015. The Impact of Resource Availability on Bacterial Resistance to Phages in Soil. PLOS ONE 10, e0123752. URL: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0123752, doi:10.1371/journal.pone.0123752.

Hardin, G., 1968. The Tragedy of the Commons. Science 162, 1243–1248. URL: http://science.sciencemag.org/content/162/3859/1243, doi:10.1126/science.162.3859.1243.

Hart, B.L., 1990. Behavioral adaptations to pathogens and parasites: Five strategies. Neuroscience & Biobehavioral Reviews 14, 273–294. URL: http://www.sciencedirect.com/science/article/pii/S0149763405800387, doi:10.1016/S0149-7634(05)80038-7.

Hesse, E., Buckling, A., 2016. Host population bottlenecks drive parasite extinction during antagonistic coevolution. Evolution 70, 235–240. URL: http://onlinelibrary.wiley.com/doi/10.1111/evo.12837/abstract, doi:10.1111/evo.12837.

Hoyle, A., Best, A., Bowers, R.G., 2012. Evolution of host resistance towards pathogen exclusion: the role of predators. Evolutionary Ecology Research 14, 125–146. URL: http://www.evolutionary-ecology.com/abstracts/v14/2723.html.

Hoyle, A., Bowers, R.G., White, A., Boots, M., 2008. The influence of trade-off shape on evolutionary behaviour in classical ecological scenarios. Journal of Theoretical Biology 250, 498–511. URL: http://www.sciencedirect.com/science/article/pii/S002251930700495X, doi:10.1016/j.jtbi.2007.10.009.

Jackson, J.A., Hall, A.J., Friberg, I.M., Ralli, C., Lowe, A., Zawadzka, M., Turner, A.K., Stewart, A., Birtles, R.J., Paterson, S., Bradley, J.E., Begon, M., 2014. An Immunological Marker of Tolerance to Infection in Wild Rodents. PLoS Biology 12. URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4086718/, doi:10.1371/journal.pbio.1001901.

Kraaijeveld, A.R., Godfray, H.C.J., 1997. Trade-off between parasitoid resistance and larval competitive ability in Drosophila melanogaster. Nature 389, 278–280. URL: http://www.nature.com/nature/journal/v389/n6648/full/389278a0.html, doi:10.1038/38483.

Kutzer, M.A.M., Armitage, S.A.O., 2016. Maximising fitness in the face of parasites: a review of host tolerance. Zoology 119, 281–289. URL:

https://www.sciencedirect.com/science/article/pii/S0944200616300368, doi:10.1016/j.zool.2016.05.011.

Little, T.J., Shuker, D.M., Colegrave, N., Day, T., Graham, A.L., 2010. The Coevolution of Virulence: Tolerance in Perspective. PLOS Pathogens 6, e1001006. URL: http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1001006, doi:10.1371/journal.ppat.1001006.

Malo, D., Skamene, E., 1994. Genetic control of host resistance to infection. Trends in Genetics 10, 365–371. URL: http://www.sciencedirect.com/science/article/pii/0168952594901333, doi:10.1016/0168-9525(94)90133-3.

Marrow, P., Dieckmann, U., Law, R., 1996. Evolutionary dynamics of predator-prey systems: an ecological perspective. Journal of Mathematical Biology 34, 556–578. URL: http://link.springer.com/article/10.1007/BF02409750, doi:10.1007/BF02409750.

Matsuda, H., Abrams, P.A., 1994. Timid Consumers: Self-Extinction Due to Adaptive Change in Foraging and Anti-predator Effort. Theoretical Population Biology 45, 76–91. URL: http://www.sciencedirect.com/science/article/pii/S0040580984710045, doi:10.1006/tpbi.1994.1004.

Mealor, M.A., Boots, M., 2006. An indirect approach to imply trade-off shapes: population level patterns in resistance suggest a decreasingly costly resistance mechanism in a model insect system. Journal of Evolutionary Biology 19, 326–330. URL: http://onlinelibrary.wiley.com/doi/10.1111/j.1420-9101.2005.01031.x/abstract, doi:10.1111/j.1420-9101.2005.01031.x.

Medzhitov, R., Schneider, D.S., Soares, M.P., 2012. Disease Tolerance as a Defense Strategy. Science 335, 936–941. URL: http://science.sciencemag.org/content/335/6071/936, doi:10.1126/science.1214935.

Metz, J.A.J., Nisbet, R.M., Geritz, S.A.H., 1992. How should we define 'fitness' for general ecological scenarios? Trends in Ecology & Evolution 7, 198–202.

URL: http://www.sciencedirect.com/science/article/pii/016953479290073K, doi:10.1016/0169-5347(92)90073-K.

Miller, M.R., White, A., Boots, M., 2005. The evolution of host resistance: Tolerance and control as distinct strategies. Journal of Theoretical Biology 236, 198–207. URL: http://www.sciencedirect.com/science/article/pii/S0022519305000949, doi:10.1016/j.jtbi.2005.03.005.

Miller, M.R., White, A., Boots, M., 2006. The Evolution of Parasites in Response to Tolerance in Their Hosts: The Good, the Bad, and Apparent Commensalism. Evolution 60, 945–956. URL: http://onlinelibrary.wiley.com/doi/10.1111/j.0014-3820.2006.tb01173.x/abstract, doi:10.1111/j.0014-3820.2006.tb01173.x.

Miller, M.R., White, A., Boots, M., 2007. Host Life Span and the Evolution of Resistance Characteristics. Evolution 61, 2–14. URL: http://onlinelibrary.wiley.com/doi/10.1111/j.1558-5646.2007.00001.x/abstract, doi:10.1111/j.1558-5646.2007.00001.x.

Parvinen, K., 2005. Evolutionary suicide. Acta Biotheoretica 53, 241–264. URL: https://link.springer.com/article/10.1007/s10441-005-2531-5, doi:10.1007/s10441-005-2531-5.

Parvinen, K., Dieckmann, U., 2018. Environmental dimensionality. Journal of Theoretical Biology URL: http://www.sciencedirect.com/science/article/pii/S002251931830122X, doi:10.1016/j.jtbi.2018.03.008.

Råberg, L., 2014. How to Live with the Enemy: Understanding Tolerance to Parasites. PLOS Biology 12, e1001989. URL: http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1001989, doi:10.1371/journal.pbio.1001989.

589 Råberg, L., Graham, A.L., Read, A.F., 2009. Decomposing health: tol-
590 erance and resistance to parasites in animals. Philosophical Transac-
591 tions of the Royal Society of London B: Biological Sciences 364, 37–49.
592 URL: http://rstb.royalsocietypublishing.org/content/364/1513/37,
593 doi:10.1098/rstb.2008.0184.

594 Råberg, L., Sim, D., Read, A.F., 2007. Disentangling Genetic Variation
595 for Resistance and Tolerance to Infectious Diseases in Animals. Science
596 318, 812–814. URL: http://science.sciencemag.org/content/318/5851/812,
597 doi:10.1126/science.1148526.

598 Read, A.F., Graham, A.L., Råberg, L., 2008. Animal De-
599 fenses against Infectious Agents: Is Damage Control More Impor-
600 tant Than Pathogen Control. PLOS Biology 6, e1000004. URL:
601 http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000004,
602 doi:10.1371/journal.pbio.1000004.

603 Regoes, R.R., McLaren, P.J., Battegay, M., Bernasconi, E., Calmy, A.,
604 Günthard, H.F., Hoffmann, M., Rauch, A., Telenti, A., Fellay, J., 2014.
605 Disentangling Human Tolerance and Resistance Against HIV. PLoS Biol-
606 ogy 12. URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4165755/,
607 doi:10.1371/journal.pbio.1001951.

608 Restif, O., Koella, J.C., 2003. Shared Control of Epidemiological Traits in a Coevolution-
609 ary Model of Host-Parasite Interactions. The American Naturalist 161, 827–836. URL:
610 http://www.journals.uchicago.edu/doi/abs/10.1086/375171, doi:10.1086/375171.

611 Roy, B.A., Kirchner, J.W., 2000. Evolutionary Dynamics of
612 Pathogen Resistance and Tolerance. Evolution 54, 51–63. URL:
613 http://onlinelibrary.wiley.com/doi/10.1111/j.0014-3820.2000.tb00007.x/abstract,
614 doi:10.1111/j.0014-3820.2000.tb00007.x.

615 Sears, B.F., Rohr, J.R., Allen, J.E., Martin, L.B., 2011. The economy of in-
616 flammation: when is less more? Trends in Parasitology 27, 382–387. URL:

http://www.sciencedirect.com/science/article/pii/S1471492211000961, doi:10.1016/j.pt.2011.05.004.

Sears, B.F., Snyder, P.W., Rohr, J.R., 2013. Infection deflection: hosts control parasite location with behaviour to improve tolerance. Proceedings of the Royal Society of London B: Biological Sciences 280, 20130759. URL: http://rspb.royalsocietypublishing.org/content/280/1762/20130759, doi:10.1098/rspb.2013.0759.

Simms, E.L., 2000. Defining tolerance as a norm of reaction. Evolutionary Ecology 14, 563–570. URL: https://link.springer.com/article/10.1023/A:1010956716539, doi:10.1023/A:1010956716539.

Simms, E.L., Triplett, J., 1994. Costs and Benefits of Plant Responses to Disease: Resistance and Tolerance. Evolution 48, 1973–1985. URL: http://www.jstor.org/stable/2410521, doi:10.2307/2410521.

Soares, M.P., Teixeira, L., Moita, L.F., 2017. Disease tolerance and immunity in host protection against infection. Nature Reviews Immunology 17, 83–96. URL: https://www.nature.com/nri/journal/v17/n2/full/nri.2016.136.html, doi:10.1038/nri.2016.136.

Stearns, S.C., 1992. Stearns, Stephen C., 1992. The Evolution of Life Histories. Oxford University Press. URL: http://onlinelibrary.wiley.com/doi/10.1046/j.1420-9101.1993.6020304.x/abstract.

van Tienderen, P.H., de Jong, G., 1986. Sex ratio under the haystack model: Polymorphism may occur. Journal of Theoretical Biology 122, 69–81. URL: http://www.sciencedirect.com/science/article/pii/S0022519386802259, doi:10.1016/S0022-5193(86)80225-9.

Woolhouse, M.E.J., Webster, J.P., Domingo, E., Charlesworth, B., Levin, B.R., 2002. Biological and biomedical implications of the co-evolution of pathogens and their hosts. Nature Genetics 32, 569–577. URL:

https://www.nature.com/ng/journal/v32/n4/full/ng1202-569.html, doi:10.1038/ng1202-569.

Wright, R.C.T., Brockhurst, M.A., Harrison, E., 2016. Ecological conditions determine extinction risk in co-evolving bacteria-phage populations. BMC Evolutionary Biology 16, 227. URL: http://dx.doi.org/10.1186/s12862-016-0808-8, doi:10.1186/s12862-016-0808-8.

Zhang, Q.G., Buckling, A., 2011. Antagonistic coevolution limits population persistence of a virus in a thermally deteriorating environment. Ecology Letters 14, 282–288. URL: http://onlinelibrary.wiley.com/doi/10.1111/j.1461-0248.2010.01586.x/abstract, doi:10.1111/j.1461-0248.2010.01586.x.

Zhang, Q.G., Buckling, A., 2016. Resource-dependent antagonistic coevolution leads to a new paradox of enrichment. Ecology 97, 1319–1328. URL: http://onlinelibrary.wiley.com/doi/10.1890/15-1408.1/abstract, doi:10.1890/15-1408.1.