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E-Note

Transmission-Recovery Trade-Offs to Study Parasite Evolution

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abstract: Parasite evolution is mainly studied through a trade-off involving host death (i.e., virulence) and transmission. In addition to the lack of evidence, this trade-off largely fails to understand the evolution of sublethal parasite effects. Here, I argue that considering host recovery as a main selection pressure faced by the parasite helps to address these problems and opens new perspectives for the study of parasite evolution. Using an embedded model, I show how a trade-off between transmission and recovery may emerge from within-host dynamics if immune activation is assumed to depend on the parasite's overall growth rate. I also show that the value of the parasite's optimal growth rate strongly depends on the immunological state of the host. Transmission-recovery trade-offs are of particular interest to the study of the evolution of human pathogens because of the use of antipathogen treatments, which strengthens the recovery constraint.

Keywords: recovery, trade-off, virulence, evolution, microparasites, within-host dynamics.

For more than 20 years, studies on the evolution of parasite life-history traits have focused on the evolution of disease-induced mortality, or virulence, because of its obvious public health implications and also because it is the least ambiguous and easiest trait to quantify (Anderson and May 1982; Ewald 1983). The now classical approach is to use the transmission-virulence trade-off hypothesis, which stipulates that more intense parasite host exploitation strategies increase transmission but also virulence at the same time (Ewald 1983; Massad 1987). If the trade-off curve between transmission and virulence is convex (Van Baalen and Sabelis 1995), there exists a parasite evolutionarily stable strategy (ESS; Maynard Smith 1982), which maximizes parasite fitness.

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The evolution of parasite sublethal effects (e.g., anemia, fever, weight loss, sterilization) is difficult to study using the classical framework, where parasite negative effects are solely expressed as host death. In most of the exceptions, the parasite is transmitted vertically, which means host fitness and parasite fitness are linked (O'Keefe and Antonovics 2002; Schjørring and Koella 2003; Bonds 2006). Sublethal effects can also be studied in cases where they affect components of the parasite fitness. For instance, decreasing the host's movements often decreases parasite transmission (Ewald 1994). Also, infection may decrease host intraspecific competitive fitness, which could ultimately increase host death rate, that is, virulence (Bedhomme et al. 2005). Understanding the evolution of sublethal effects is of obvious interest in the case of parasites of humans but also for many other parasites (e.g., agricultural pests). Importantly, using a less restrictive virulence definition could explain the lack of experimental evidence for the trade-off (Lipsitch and Moxon 1997; Ebert and Bull 2003; Alizon and Van Baalen 2005): contrary to theoretical studies, experiments use a wide variety of measures to approximate virulence. Finally, finding a way to address the evolution of sublethal effects without resorting to the transmission-virulence trade-off is important because several parasites (e.g., rhinoviruses, responsible for the common cold) are nonlethal but regularly cause illness that could be considered moderately virulent (see Walther and Ewald 2004 for quantification of the extremely low percentage of mortalities of rhinovirus and respiratory pathogens of humans). More generally, considering recovery as the main selection is also consistent with the fact that most human pathogens kill less than 5% of untreated infected people (P. W. Ewald, personal communication; for an overview of mortality rates, see Ewald 1983, 1991, 1994; Walther and Ewald 2004; Wolfe et al. 2007).

To address these questions, I develop an original approach where recovery is the main selection pressure faced by the parasite. Like virulence, host recovery is a trait that is shared by the host and the parasite. Data show important variations in duration of contagiousness (here assumed to be identical to the duration of the infection, i.e., to the inverse of the recovery): influenza usually lasts several

days, while hepatitis B can last several months and tuberculosis several years (see table S1 in Wolfe et al. 2007). Trade-offs between virulence and recovery have been studied (Anderson and May 1982; Frank 1996), but never has it been suggested that within-host processes could create an evolutionary constraint on the parasite fitness through host recovery. The underlying idea is similar to that of the "classical" trade-off: by increasing its host exploitation strategy, a parasite increases its transmission rate, but it also decreases the duration of the infection. In the following, I develop a theoretical model to illustrate how a transmission-recovery trade-off can emerge from within-host dynamics. I also discuss the epidemiological and evolutionary implications of this new approach.

Several studies have shown the important impact of host recovery on parasite evolution (Van Baalen 1998; Day and Burns 2003), but they consider recovery as an independent parameter. Only in some models with explicit spatial structure does recovery evolve. It is known that the duration of the infectious period affects the spatial spread of a disease if recovered individuals are immune to the disease (Anderson and May 1991; Keeling 1999), but only three studies explicitly mention a trade-off between transmission and recovery. The first study concerns virulence evolution in a spatial graph where such a trade-off is assumed but not analyzed (Van Baalen 2002*a*). The second study shows how a link between transmission and the duration of the infection can emerge at the epidemiological level as a result of spatial structure (van Ballegooijen and Boerlijst 2004). However, the resulting transmission-recovery relationship is linear, and there is no finite optimal strategy for the parasite. Finally, Read and Keeling (2006) develop a spatial embedded model based on a transmission-recovery trade-off where they show that spatial structure can lead to an ESS. The following approach differs from previous studies in two essential ways: first, the trade-off here emerges from within-host dynamics and not from spatial processes; second, I investigate the factors affecting the value of the ESS for the parasite.

Parasite fitness can be estimated with the basic reproduction ratio, R_0 (Anderson and May 1979), which shows that natural selection may favor avirulent parasites with a high transmission rate that cause persistent infections. This is referred to as the "conventional wisdom." Reality is more complex, and if the epidemiological parameters of the parasite (transmission, virulence, and recovery) are linked through trade-off relationships, parasite evolution becomes less obvious (Anderson and May 1982; Ewald 1983). A trade-off relationship between transmission and recovery implies a link between these variables, achieved through the host exploitation strategy of the parasite φ (as a first approximation, φ can be seen as the parasite within-host growth rate). The basic reproduction ratio is then

$$R_0(\varphi) = \frac{\beta(\varphi)}{\mu + \alpha + \gamma(\varphi)} S, \tag{1}$$

where β is the transmission, μ the host natural death rate, α the virulence, γ the recovery, and S the density of susceptible hosts. As shown previously by Van Baalen and Sabelis (1995) in the case of transmission-virulence trade-offs, the conditions to have an ESS imply that the trade-off curve between transmission and recovery is convex. In other words, after a given value of parasite growth rate (the ESS), increasing the growth rate will still increase parasite transmission, but it will also increase host recovery and at a faster rate, thus decreasing parasite fitness.

It is difficult to find clear support for the fact that faster-growing parasite strains face a higher risk of elimination. What classical immunology shows is that the activation of the acquired immune response depends on the density of parasite antigens (Mitchison 1964; Janeway et al. 2001). More precisely, for low antigen densities, no antibodies are produced (a phenomenon known as low-zone tolerance). The antibody response increases linearly after a given antigen density threshold and then saturates (note that antibody response decreases for very high antigen densities). This pattern is even clearer in the case of a secondary encounter with the antigen. Thus, a low antigen density can be a way to escape the acquired immune system. The problem with these data is that it is impossible to disentangle the effect of parasite density from the effect of the growth rate.

Other data could support the main assumption. For instance, Bocharov et al. (2004) find a bell-shaped relationship between the growth rate of the lymphocytic choriomeningitis virus and the peak cytotoxic T-lymphocyte response. More generally, to persist in their host, some viruses (e.g., herpes) enter a stage of latency where they decrease their replication rate until the immune response vanishes (Preston 2000; Janeway et al. 2001). These results support a positive correlation between parasite density and the rapidity and intensity of the immune response, which is likely to be linked to the duration of the infection. These aspects will be further addressed in the "Discussion."

The Model

To better understand the underlying mechanisms that could lead to a trade-off, I develop an embedded model (Ganusov et al. 2002; Gilchrist and Sasaki 2002; André et al. 2003; Alizon and Van Baalen 2005) linking within-host processes to epidemiological functions (here transmission and recovery). I use a model where the immune system always eventually gets rid of the parasite, because here parasite evolution is constrained by host recovery. Also, I assume that parasite

virulence and host death are low compared with recovery and can be neglected. As in most studies (Alizon and van Baalen 2008), I use the Lotka-Volterra prey equation for the variations in parasite density:

$$\frac{dx}{dt} = (\varphi - \sigma y)x, \tag{2}$$

where φ is the parasite growth rate, σ is the efficiency of parasite destruction by the immune system, and x and y are the densities of parasite and immune cells, respectively.

Existing within-host models are much more heterogeneous concerning their modeling of the immune response (Alizon and van Baalen 2008). Here, I use a formulation close to the one used by Gilchrist and Sasaki (2002):

$$\frac{dy}{dt} = c\varphi^b xy, \tag{3}$$

where c is the efficiency of immune activation and b is a constant scaling the effect of parasite growth rate on immune activation. In the following, I will assume that $b = 1$. The originality of this equation is that the activation of the immune cells does not merely depend on the parasite density (x) but on their overall rate of replication (φx). This introduces the idea that it is the replication of the parasites that triggers the immune response. Similar results can be obtained if immune proliferation is a quadratic function of parasite density, but the analysis is more difficult.

It is not possible to solve this dynamical system analytically. However, as I show in "Finding the Immune Cell Density at the End of an Infection" (app. A) using the framework developed by Gilchrist and Sasaki, it is possible to find an approximation of the density of immune cells at the end of an infection.

We now need to link the within-host dynamics to the epidemiological functions (i.e., transmission, recovery, and virulence). In the general case, I will assume that the parasite is avirulent (a case with disease-induced mortality is discussed in "Finding the R_0 for a Virulent Parasite" [app. A]). Note that this does not imply that an increase in parasite growth rate has no deleterious effect on the host; it simply implies that these effects do not affect the fitness of the parasite. For the transmission function, I assume the simplest relationship, that is, the transmission rate at time t, denoted $\beta(\varphi, t)$, is proportional to the number of parasites at this time:

$$\beta(\varphi, t) = ax(\varphi, t), \tag{4}$$

where a is a proportionality constant. For more details on the influence of the transmission function on virulence evolution, see Day (2001), Ganusov and Antia (2003), or Gilchrist and Coombs (2006).

Since there is no disease-induced mortality, the fitness of a parasite (i.e., its R_0) is simply the number of new infections caused by an infected host before recovering:

$$R_0(\varphi) = \int_0^\infty \beta(\varphi, t)dt. \tag{5}$$

Using the analytical approach developed by Gilchrist and Sasaki, I show in "Finding the R_0 for an Avirulent Parasite" (app. A) that the R_0 expression can be simplified into

$$R_0(\varphi) = \frac{a}{c\varphi^b}\ln\left(\frac{\hat{y}(\varphi)}{y_0}\right), \tag{6}$$

where y_0 is the initial density of immune cells and $\hat{y}(\varphi)$ is the density of immune cells at the end of an infection. A similar expression of R_0 is derived in the case of a virulent parasite in "Finding the R_0 for a Virulent Parasite" (app. A).

The last epidemiological function in the model is the recovery rate (γ). It is approximated by the inverse of the duration of the infection, which has to be estimated numerically (see also André and Gandon 2006). Formally, from the parasite's point of view, recovery occurs when contagiousness ends, but here I assume that the recovery of the host and the loss of contagiousness are identical. This is not always the case, particularly for long-lasting infections (for details on the effect of the timing of disease life-history events, see Day 2003).

In this approach, the definition of the epidemiological functions is less arbitrary than in most models involving parasite virulence. Previous models that found an ESS either introduced a lethal parasite density above which the host dies (Antia et al. 1994; Ganusov et al. 2002) or defined a virulence function depending on the within-host densities (Gilchrist and Sasaki 2002; André et al. 2003; Alizon and Van Baalen 2005). Here, the key assumption (the fact that immune activation depends on parasite overall growth rate) is made at the within-host level.

Results

Figure 1 shows parasite fitness as a function of parasite growth rate (φ). There is an ESS with an intermediate value for the parasite because the fitness curve has a maximum. In "Finding the R_0 for a Virulent Parasite" (app. A), I show that this result holds for virulent parasites, even if virulence is proportional to parasite density. This is interesting because such a definition of virulence leads to a linear transmission-virulence trade-off (Alizon and Van

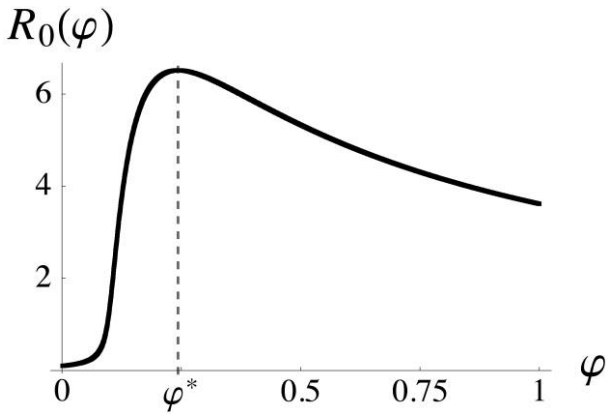

Figure 1: Effect of parasite host exploitation strategy (φ) on parasite fitness. The dashed line indicates the optimal growth rate (φ^*). Parameter values are $\sigma = 1$, $b = 1$, $c = 0.1$, $x_0 = 0.1$, $y_0 = 0.1$, and $a = 0.1$.

Baalen 2005), which means an absence of finite ESS if there is no spatial structure (for further details, see "Case Where Immune Cell Proliferation Depends on Parasite Density" [app. A]).

The underlying process leading to an ESS can be understood in further details by looking at the transmission-recovery trade-off curve, which is the parametric curve $(\gamma(\varphi), \beta(\varphi))$ here obtained by increasing parasite growth rate (φ) from 0 to 1 (fig. 2). The curve shows two distinct patterns (fig. 2). At first, increasing parasite growth rate decreases host recovery without affecting transmission (the horizontal line), which means a zero growth rate is never optimal for the parasite. Then, increasing parasite growth rate leads to the second pattern where both transmission and recovery increase with φ. This part of the curve is convex, implying that recovery increases more rapidly than transmission. As explained above, a convex trade-off curve means that recovery is enough to select for an intermediate ESS value of the parasite.

Similar results can be obtained for any strictly positive value of b (figure not shown). However, the lower the value of b, the higher the ESS value, and at some point the ESS values are so high that they do not make any sense biologically (e.g., if $b < 0.1$, then $\varphi^* > 100$).

Most previous within-host models where parasites always reach a zero density used given initial densities of parasites and lymphocytes (Antia et al. 1994; Ganusov et al. 2002; André et al. 2003). However, these values are likely to vary among hosts, particularly the initial density of lymphocytes, which depends on the life-history events of the host, such as previous infections or vaccination (André and Gandon 2006; Ganusov and Antia 2006). The sensitivity analysis reveals that the ESS value strongly depends on the immunological status of the host (fig. 3*A*): the higher the initial density of lymphocytes, the higher the ESS value. Finally, increasing the infection dose decreases the optimal growth rate (fig. 3*B*), but this effect is much less pronounced than the effect of the host's immunological state.

Discussion

There currently exists a separation between experiments and theory in understanding the evolution of parasite host exploitation strategies. Working with a trade-off between transmission and recovery could help to fill this gap. The importance of recovery to parasite evolution has already been noted, but recovery had never been suggested to be the main constraint on parasite evolution. In current models, the existence of an ESS comes from either an external virulence constraint (Ganusov et al. 2002; Gilchrist and Sasaki 2002; André et al. 2003; Alizon and Van Baalen 2005) or from spatial dynamics (Read and Keeling 2006). Using a within-host model, I show that the assumption that the immune proliferation function depends on the parasite overall growth rate is sufficient to favor parasites with a prudent host exploitation strategy (because recovery increases faster than transmission). This result is true for avirulent parasites, and it holds if virulence is a linear function of parasite density ("Finding the R_0 for a Virulent Parasite" [app. A]). Finally, the value of the parasite ESS strongly depends on the initial immunological state of the host before the infection, which corroborates earlier findings of embedded models of host vaccination (André and Gandon 2006; Ganusov and Antia 2006). Note that the model also shows a slight effect of the parasite infectious dose on the evolution of virulence: the higher the dose, the lower the optimal growth rate. A possible interpretation is that because the parasite has nearly exponential

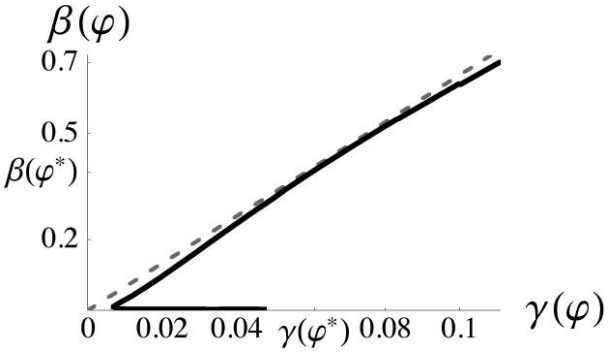

Figure 2: Transmission-recovery trade-off curve. The dashed line shows the tangent of the curve that passes through the origin and that allows one to find the optimal growth rate (φ^*) graphically. Parameter values are as in figure 1, except $y_0 = 1$ (to obtain a figure easier to read).

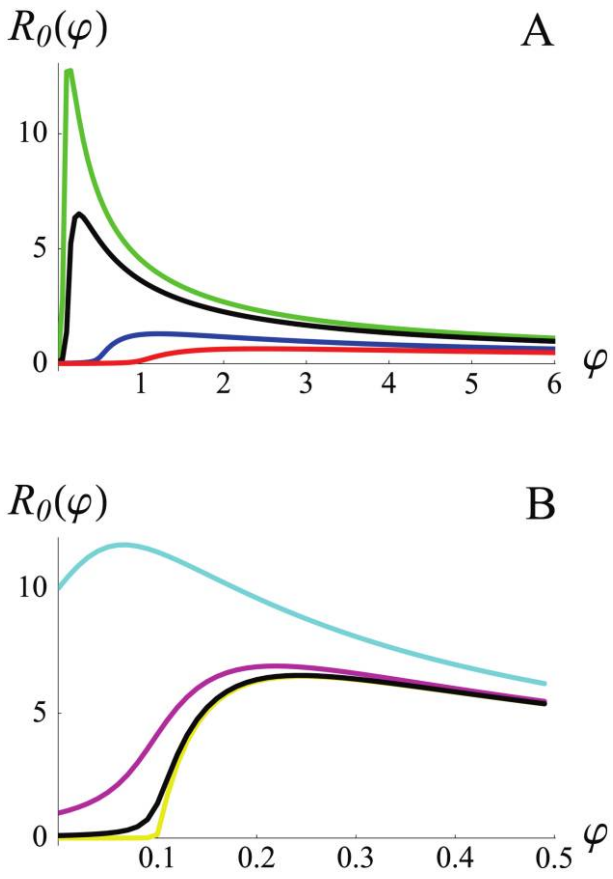

Figure 3: Effect of lymphocyte (*A*) and parasite (*B*) initial density on parasite R_0. In *A*, $x_0 = 0.1$, and in *B*, $y_0 = 0.1$. On the black line, the initial value is 0.1. In *A*, the initial values are 0.05 (*green*), 0.5 (*blue*), and 1 (*red*). In *B*, the initial values are 0.001 (*yellow*), 1 (*pink*), and 10 (*cyan*). Other parameter values are as in figure 1.

growth in the early stages of the infection, increasing the initial dose is likely to decrease the duration of the infection. This result illustrates Schmid-Hempel and Frank's (2007) recent opinion on the evolution of the infective dose and deserves further analysis.

The transmission-recovery trade-off brings new arguments in the intense debate about virulence evolution (Ewald 1994; Ebert and Bull 2003; Alizon and Van Baalen 2005). Considering recovery as the main constraint helps to address two concerns. The first concern is the lack of evidence for a trade-off between virulence and transmission. The second concern is the importance of sublethal virulence effects. A positive correlation between transmission and virulence could come from the fact that both are positively correlated with parasite growth rate. Thus, both lethal and sublethal virulence effects could be seen only as an indirect consequence of parasite growth rate instead of a major constraint shaping parasite evolution.

This model is based on a number of simplifying assumptions that could be relaxed in further studies. The main limitation is common to most embedded models: it concerns the description of the immune response (Alizon and van Baalen 2008). There are many ways to increase the complexity of the model. For instance, different immune proliferation functions can lead to similar results (e.g., if proliferation is a quadratic function of x), but the killing rate itself does seem to be a sufficient constraint to limit parasite growth. Also, the results hold if the proliferation rate is a saturating function of y but not if it is a saturating function of x. This makes sense because in the latter case, at some point the duration of the infection becomes independent of the parasite density, which favors faster replicating strains. However, an increase in the nonlinearity of the immune activation function (the b term) can compensate a saturation in x. Finally, possible improvements could be to model memory cells or to distinguish between the innate and the acquired immune response. This would allow a test of the fact that a parasite must grow enough to overcome the innate immune response but not too much to avoid the triggering of the acquired immune response. Nevertheless, a simple model is sufficient to show how recovery alone can shape the evolution of parasite strategies. Also, contrary to current embedded models, this approach does not require any assumption with regard to how virulence and transmission are related to parasite within-host dynamics. The only assumption concerns the immune activation rate.

The framework developed here is valid for acute infections, but it might not be difficult to apply it to chronic infections. One of the reasons for this limitation is that when the duration of the infection increases, the assumption that the end of the infection and the loss of contagiousness period are identical weakens (see the first section of this article). Chronic infections also introduce another confounding factor, which is that increased host exploitation rate may favor increased persistence without enhanced immunological activation and sometimes even with reduced immunological function. Examples of such exploitation mechanisms include production of antiapoptotic proteins (Strasser et al. 2000), deregulation of telomerase, activation of host cell replication, and immunosuppression (e.g., see Zajac et al. 1998; Schneider-Schaulies and Dittmer 2006). To apply this framework to persistent infections, it would be necessary to take virulence into account in addition to recovery.

From an experimental point of view, even though many studies on parasite evolution attempt to link transmission and virulence, it seems that only one takes host recovery into account (Mackinnon and Read 2003, which is based on chronic infections). The main reason is that there usually is a strong correlation between parasite growth rate and host recovery in experimental studies, since they both

involve the immune response. In most experimental studies, growth rate is measured inside a host, which implies that the stronger the immune response, the lower the measured growth rate of the parasite. Thus, the effect we want to test (higher growth rates lead to more intense and rapid immune responses) is already included in the measure of the growth rate. This problem could be overcome by studying the within-host dynamics of different parasites in immunodepressed hosts and in standard hosts. This way, we could have an idea of the growth rate independent of the immune response. Note that the same argument applies to virulence. As stated by Ewald (1983), infections often occur in populations where hosts have different immunological statuses, and it is not always possible to disentangle a highly virulent parasite from a host with low immune defenses.

There are two mathematical differences between transmission-recovery and transmission-virulence trade-offs. The first difference is that if recovery is the main constraint on the parasite, the trade-off can emerge from simple assumptions on the within-host dynamics and without any external constraint (virulence or spatial structure). The second difference lies in the consequences on the epidemiological dynamics. Among the many studies based on spatial dynamics involving recovery, some do let parasite transmission and host recovery evolve (Read and Keeling 2003; van Ballegooijen and Boerlijst 2004). These studies show that spatial structure leads to an increasing relationship between transmission and recovery. They also find that parasites evolve to increase both their transmission rate and the host recovery rate. An exception is provided by Read and Keeling (2006), who show that spatial dynamics can sometimes lead to an optimal strategy for the parasite. All these studies suggest that developing the epidemiological side of embedded models based on recovery is likely to lead to interesting results.

Finally, this trade-off hypothesis has particular implications regarding antiparasite treatments, because they allow us to recover earlier from infections. Treatments are known to affect parasite resistance, but they could also affect virulence (Gandon et al. 2001; Van Baalen 2002*b*; Alizon and Van Baalen 2005; André and Gandon 2006; Ganusov and Antia 2006). One of the implications of using an approach based on recovery is the importance of the heterogeneity in the immunological state of the hosts, which has a strong influence on the ESS of the parasite (and hence on detrimental effects experienced by the patients). Taking these effects into account would require one to model lymphocyte dynamics in noninfected hosts and to introduce other processes such as immune memory. Introducing these epidemiological details could help to better predict the evolutionary response of parasites to treatments.

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APPENDIX A

The Analytical Approach

Most of the analysis presented was originally developed by Gilchrist and Sasaki (2002). For further details on the analysis, the reader should refer to their article and particularly to appendix B.

Finding the Immune Cell Density at the End of an Infection

We are in a case (similar to the classical Lotka-Volterra predator-prey model) where we cannot solve the dynamical system explicitly, but we can infer most of its properties. The first step is to divide equation (2) by equation (3):

$$\frac{dx}{dy} = \frac{\varphi - \sigma y}{c\varphi^b y}. \tag{A1}$$

We can then separate the variables to integrate this expression:

$$\int c\varphi^b dx = \int \frac{\varphi - \sigma y}{y} dy, \tag{A2}$$

which leads to

$$x(\varphi, t) = \frac{\varphi^{1-b}}{c} \ln\left(y(\varphi, t)\right) - \frac{\sigma}{c\varphi^b} y(\varphi, t) + K, \tag{A3}$$

where K is an integration constant that depends on the initial densities of parasites and lymphocytes:

$$K = x_0 - \frac{\varphi^{1-b}}{c} \ln\left(y_0\right) + \frac{\sigma}{c\varphi^b} y_0. \tag{A4}$$

Overall, we find that

$$x(\varphi, t) = \frac{\varphi^{1-b}}{c} \ln\left(\frac{y(\varphi, t)}{y_0}\right) - \frac{\sigma}{c\varphi^b}\left(y(\varphi, t) - y_0\right) + x_0. \tag{A5}$$

As noticed by Gilchrist and Sasaki,

$$\lim_{t\to+\infty} x(\varphi, t) = 0. \tag{A6}$$

We also know that y will eventually converge toward a finite value $\hat{y}(\varphi)$. From equation (A5), we have

$$0 = \frac{\varphi}{c}\ln\left(\frac{\hat{y}(\varphi)}{y_0}\right) - \frac{\sigma}{c}(\hat{y}(\varphi) - y_0) + x_0. \tag{A7}$$

By solving this equation, we can estimate $\hat{y}$. The problem is that this expression needs to be solved numerically. Note that b does not affect the value of $\hat{y}$.

Finding the R_0 *for an Avirulent Parasite*

If we denote by $\beta(\varphi, \tau)$ the transmission rate of a strain with growth rate φ at time τ, we obtain

$$R_0(\varphi) = \int_0^\infty \beta(\varphi, \tau)d\tau. \tag{A8}$$

Transmission is assumed to be proportional to parasite density, thus

$$\beta(\varphi, \tau) = ax(\varphi, \tau), \tag{A9}$$

where a is a proportionality constant. From equation (3), we know that

$$x = \frac{1}{c\varphi^b y}\frac{dy}{d\tau}. \tag{A10}$$

Equation (A8) then becomes

$$R_0(\varphi) = \int_0^\infty \frac{a}{c\varphi^b y}\frac{dy}{d\tau}d\tau. \tag{A11}$$

This can be simplified into

$$R_0(\varphi) = \frac{a}{c\varphi^b}\int_0^\infty \frac{dy}{y}. \tag{A12}$$

Solving this integral and using the fact that we know the limit of y when t goes to infinity lead to the general expression

$$R_0(\varphi) = \frac{a}{c\varphi^b}\ln\left(\frac{\hat{y}(\varphi)}{y_0}\right). \tag{A13}$$

Note that the density of immune cells at the end of the infection ($\hat{y}(\varphi)$) is the only component of the R_0 that has to be solved numerically.

Finding the R_0 *for a Virulent Parasite*

If we denote by $\sigma(\tau)$ the probability the host is alive at time τ (which is equal to 1 for an avirulent disease), we obtain

$$R_0(\varphi) = \int_0^\infty \beta(\varphi, \tau)\sigma(\varphi, \tau)d\tau. \tag{A14}$$

I here assume that virulence is proportional to parasite density

$$\alpha(\varphi, \tau) = ux(\varphi, \tau), \tag{A15}$$

where u is a proportionality constant. If we ignore the host baseline mortality, the survival probability can be calculated as follows:

$$\frac{d\sigma}{dt} = -\alpha(\varphi, \tau)\sigma, \tag{A16}$$

$$= -ux\sigma. \tag{A17}$$

Using equation (A10), we obtain

$$\frac{d\sigma}{d\tau} = -u\frac{1}{c\varphi^b y}\frac{dy}{d\tau}\sigma, \tag{A18}$$

which, by separating the variables, leads to

$$\frac{d\sigma}{\sigma} = -u\frac{1}{c\varphi^b}\frac{dy}{y}. \tag{A19}$$

As shown by Gilchrist and Sasaki, we find that

$$\sigma(\varphi, \tau) = \left(\frac{y(\varphi, \tau)}{y_0}\right)^{-u/(c\varphi^b)}, \tag{A20}$$

because $\sigma(\varphi, 0) = 1$ and $y(\varphi, 0) = y_0$. Note that the probability $\hat{\sigma}$ a host is still alive at the end of an infection is

$$\hat{\sigma}(\varphi) = \left(\frac{\hat{y}(\varphi)}{y_0}\right)^{-u/(c\varphi^b)}. \tag{A21}$$

If we come back to equation (A14), we can now write

$$R_0(\varphi) = \int_0^\infty ax(\varphi, \tau)\left(\frac{y(\varphi, \tau)}{y_0}\right)^{-u/(c\varphi^b)} d\tau. \tag{A22}$$

Again, using equation (A10), we can get rid of x:

$$R_0(\varphi) = \int_0^\infty a \frac{1}{c\varphi^b y(\varphi, \tau)} \frac{dy}{d\tau} \left(\frac{y(\varphi, \tau)}{y_0} \right)^{-u/(c\varphi^b)} d\tau. \quad \text{(A23)}$$

Solving this integral and using the fact that we know the limit of y when t is infinity lead to the general expression

$$R_0(\varphi) = \frac{a}{u} \left[1 - \left(\frac{\hat{y}(\varphi)}{y_0} \right)^{-u/(c\varphi^b)} \right]. \quad \text{(A24)}$$

In addition to the main equations (here eqq. [2], [3]), the difference between this approach and that of Gilchrist and Sasaki lies in the definition of the virulence function. In their model, virulence is not proportional to parasite density (as it is here) but to the parasite overall replication rate (φx). As shown by other studies (André et al. 2003; Alizon and Van Baalen 2005), such a virulence function creates a constraint on φ and leads to an ESS.

Equation (A24) leads to fitness curves that are similar to figure 1 (fig. B1). Note that the value of u, that is, the virulence of the parasites, has no effect on the value of the ESS.

Case Where Immune Cell Proliferation Depends on Parasite Density

If we use Gilchrist and Sasaki's model but with the virulence function we defined here (eq. [A10]), there is no ESS, and parasites with higher growth rate always invade. In this case, equation (A24) becomes

$$R_0(\varphi) = \frac{a}{u} \left[1 - \left(\frac{\tilde{y}(\varphi)}{y_0} \right)^{-u/c} \right]. \quad \text{(A25)}$$

I here introduce the notation $\tilde{y}$ instead of $\hat{y}$ because Gilchrist and Sasaki use a different equation (3) (see below). With this virulence function, the most fitted parasite strain is the strain that maximizes $\tilde{y}$.

Gilchrist and Sasaki use the following equation for lymphocyte proliferation:

$$\frac{dy}{dt} = cxy. \quad \text{(A26)}$$

This implies that $\tilde{y}$ is the solution of the following equation:

$$\frac{\varphi}{c} \ln \left(\frac{\tilde{y}(\varphi)}{y_0} \right) = \frac{\sigma}{c} (\tilde{y}(\varphi) - y_0) - x_0. \quad \text{(A27)}$$

There is a solution in this system because when y is large enough, the linear function of y increases faster than $\ln(y)$. With this expression, it is easy to see that by increasing φ, we increase the left-hand side, which imposes to increase $\tilde{y}$ in both sides to obtain an equality. Since a parasite should maximize $\tilde{y}$, mutants with a greater value of φ always invade. This corroborates the results shown by Alizon and Van Baalen (2005) for persistent infections.

APPENDIX B

Appendix Figure

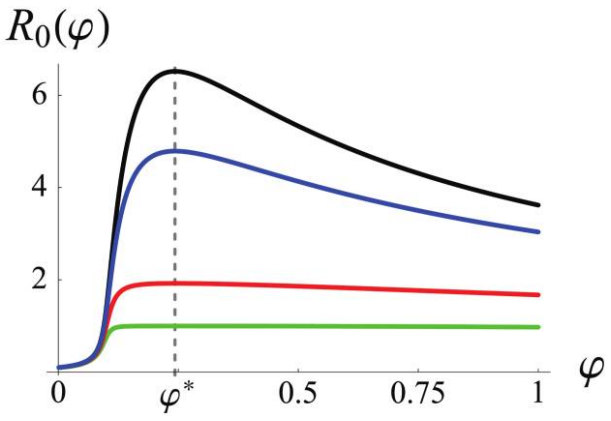

Figure B1: Effect of parasite host exploitation strategy (φ) on the total number of parasites produced for different levels of parasite virulence (u). The dashed line indicates the optimal growth rate (φ^*). The values of u are 0 (*black*), 0.01 (*blue*), 0.05 (*red*), and 0.1 (*green*). Other parameter values are $b = 1$, $\sigma = 1$, $c = 0.1$, $x_0 = 0.1$, $y_0 = 0.1$, and $a = 1$.

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