Double Trouble : Multiple infections and the coevolution of virulence-resistance in structured host-parasite populations.

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DOI not yet assigned

Abstract

Parasite evolution is expected to modulate selective pressures acting upon host, and alter its response to infection. In such a context, parasite competition seems be a key variable for the evolutionary dynamics and epidemic features. We develop a nested coevolutionary model of host resistance and parasite virulence. From individual-based traits, we define a within-host model and derive from the within-host equilibrium the main epidemiological features of interest -transmission, virulence, recovery-. We use this first model to build an adaptive dynamics model in order to assess the joint evolution of the parasite virulence and host resistance. We compared the coevolutionarily stable states predicted by the model under different competition regimes, including single infections (preemption), superinfection (dominance) and coinfections (mixed). We find that parasite virulence under coinfections evolved towards higher values than under superinfections, while the opposite trend was observed for host resistance. The local coexistence of parasites enables a kin selection effects that reduce both virulence and the subsequent host response. We showed that the magnitude of multiple infections effects varies with the ecological context, and that the coevolutionary outcomes deviate from simple optimization of persistence depending on the degree of spatial coupling of hosts.

Keywords: multiple infections, virulence, resistance, epidemiology, kin selection, metapopulation

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Introduction

The study of host-parasite coevolution is of major interest in a wide variety of scientific fields including agronomy, conservation biology and human or animal health. The antagonistic interaction between parasites and their hosts leads to complex eco-evolutionary feedback loops. Assessing how evolutionary forces shape and are shaped by environmental or physiological mechanisms is thus a difficult task. Since the seminal work of May and Anderson, 1979, there has been numerous tentatives of drawing a mathematical picture of the evolution of host-parasite interactions. Particularly, a strong effort has been dedicated to the study of coevolution in attack-defense traits. There is increasing theoretical and empirical support showing that the coevolution of parasite virulence and host resistance are crucial determinants of the ecology and evolution of infectious diseases (Best et al., 2009, Restif and Koella, 2003, Carval and Ferriere, 2010, Kada and Lion, 2015 for the theory;Webster et al., 2004, Lefèvre et al., 2007, Frickel et al., 2016 for the empirical part). One important feature of infections is that hosts are often infected with multiple parasite strains that -at least transiently- coexist in the host (*e.g.*Susi et al., 2015). Multiple infections, and more specifically within-host competition, are known to shape evolutionary dynamics De Roode et al., 2005 and can therefore induce conflicting levels of selection (reviewed in Mideo et al., 2008,Cressler et al., 2016). However, such phenomena remain poorly accounted for in theoretical studies, especially in a coevolutionary framework.

Amongst epidemiologcal models analyzing the evolution of virulence, most -if not all- rely on phenomenological assumptions to resolve within-host competition dynamics. From our litterature survey, three main approaches are traditionally used. The first is to neglect multiple infections altogether: infected hosts are prevented from being infected by new strains. Thus, competition is assumed to be ruled exclusively by the colonization of new susceptible individuals at the between-host scale. A second approach relies on the superinfection assumption, in which competition between two coinfecting strains is instantaneously resolved by the exclusion of the less competitive one Kada and Lion, 2015,Nowak and May, 1994 . The underlying hypothesis is that parasite strains respect a strict competitive hierarchy. While this hypothesis may hold when competitive differences are strong, it is however unlikely for multiple infections with genetically close strains. A third approach is to explicitly allow strains to coexist within a host May and Nowak, 1995, Mosquera and Adler, 1998. Alizon & Van Baalen Alizon and Baalen, 2008 presented a multiple-infection model in which coinfections emerge as an outcome of within-host dynamics. Their model include mixed regimes of competition because a strain with a competitive advantage will slowly displace its competitor, but might not succeed to fully replace the other during the infectious time. One of their main findings was that allowing for transient coexistence of competing strains promotes evolutionary branching of virulence when coinfections are frequent. This result comes from the induction of heterogeneity in hosts to be infected and an emerging sort of competition-colonization trade-off.

Multiple infections in epidemiology share conceptual similarities with community ecology, the host-parasite system being considered as a two-species community. Competition for new susceptibles in single-infection models acts in a very similar way to preemptive competition in metapopulations models (*i.e* the resident status of a strain preclude further competitive replacement by another,*e.g.* Levins and Culver, 1971). Superinfection models, on the other hand, describe competitive rules that are very similar to the ones defining the competition-colonization trade-off modelHastings, 1980 Tilman, 1994 from Levins seminal formalism Levins, 1969. In

such cases, better competitors instantaneoulsy displace the poor ones, such that competition acts through strict dominance. More recently, it has been shown that allowing for mixed regimes of competition has several implications for eco-evolutionary dynamics, for exemple by altering the likelihood of species coexistence at a regional scale Calcagno et al., 2006. In particular, coexistence of species or strains at the regional scale should be favored when fitness is not completely determined by the colonization process -*i.e.* the transmission to suceptible hosts, in an epidemiological context-. The integration of mixed regimes of competition in multiple infections thus appears to be a relevant feature to include in coevolutionary studies.

The importance of multiple infections may not be without consequences for the way hosts respond to parasite infections. In particular, the host resistance to infections appears to be a good candidate for driving parasite evolution in the context of multiple infections. When seen as an avoidance mechanism, resistance reduces the transmission rate, and thus the likelihood of multiple infections Boots and Haraguchi, 1999. When seen as a clearance mechanism, it reduces the infectious period Baalen, 1998. These phenomena are expected to determine the nature of competition between strains during multiple infections, due to a shift in the balance between preemptive and dominance effects. There is thus a need to incorporate multiple infections and detailed within-host interactions processes in a coevolutionary framework. However, despite notable theoretical advances in host-parasite evolution, such mechanisms remain poorly included. Particularly, the potential feedback of multiple infections in host response to parasite evolution remains to our knowledge, unexplored.

Here, we build on the existing theory of metapopulation ecology to build a nested model to study the coevolution of host resistance and parasite virulence. From individual-based traits, we define a within-host model including parasite growth and host-induced parasite attrition. Then, using a time-scale separation argument, we derive from the within-host equilibrium the main epidemiological features of interest (transmission, virulence, recovery) and use them to construct a between-host epidemiological model. Our results are derived assuming trade-offs between parasite replication and virulence, and the host resistance and fecundity. Using the now classical toolbox of adaptive dynamics Geritz et al., 1998, we first provide an overview of the evolutionary outcomes resulting from the evolution of either the host or the parasite. Then we consider the coevolution of both partners, and determine how strain competition and host response drive selection upon host resistance, and parasite virulence.

The model

SIS epidemiological model

Our starting point is the classic susceptible-infected-susceptible (SIS) model Kermack and McKendrick, 1927. We first clarify the link between the SIS model and metapopulation models. Because parasites view the host population as a well-mixed metapopulation of fully connected patches, we follow the usual approach from metapopulation ecology and track the dynamics of the fractions of patch states. Here, each patch can be empty (0) or occupied by a single susceptible (S) or infected host (I). Assuming no density dependence on mortality and a constant number of usable "patches" for hosts (which enforces a negative density-dependence on birth rate), the demographic and epidemiological dynamics of the host is given as:

$$\begin{aligned} \frac{\mathrm{d}p_S}{\mathrm{d}t} &= [b_S p_S + b_I p_I]\, p_0 - d p_S - \beta p_I p_S + \tau p_I \\ \frac{\mathrm{d}p_I}{\mathrm{d}t} &= [\beta p_S - (d + \alpha + \tau)]\, p_I \end{aligned} \tag{1}$$

where p_x is the fraction of patches in state x. Note that our model reduces to two equations because the patch frequencies sum to 1 ($p_S + p_I + p_0 = 1$). Susceptible (resp. infected) hosts reproduce at rate b_S (resp. b_I), and give birth to susceptible newborns, which can only develop into adults if they find an empty patch p_0. Both susceptible and infected hosts have a background mortality rate d. Infected hosts have an additional mortality rate (virulence) α, and can recover at rate τ. Finally, transmission occurs at rate β.

The model has two non-trivial equilibria: a disease-free equilibrium in the form ($\tilde{p}_0 = \frac{d}{b_s}$, $\tilde{p}_s = 1 - \frac{d}{b_s}$, $\tilde{p}_I = 0$), and an endemic equilibrium (p_0^*, p_S^*, p_I^*). For the endemic equilibrium to exist, the following condition is required:

$$R_0 = \frac{\beta \tilde{p_S}}{d + \alpha + \tau} > 1 \tag{2}$$

where R_0 is the basic reproduction number of the parasite Diekmann et al., 1990. It is useful to notice that R_0 is here equivalent to the number of successful dispersers produced by an initial parasite infecting a host "R_m" Ajar, 2003, Metz and Gyllenberg, 2001, Massol et al., 2009 in the absence of evolution.

Within-host model

Following Alizon and Baalen, 2005, we derive the epidemic traits from within-host interactions. We introduce a model of within-host parasite growth which tracks the dynamics of within-host parasite density, X:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = (r_0\theta - r_1 X)X - (\mu + m + \gamma\sigma)X \tag{3}$$

Parasites replicate at rate $r_0\theta$, where r_0 is the maximum replication rate and θ the parasite strategy of host exploitation, which takes values between 0 and 1. We assume that within-host replication is density-dependent, with strength r_1. Parasite emigrate from their host at rate m and die at rate $\mu + \gamma\sigma$, where μ refers to background parasite mortality and $\gamma\sigma$ is the host resistance level. γ is a theoretical maximum for resistance, and σ is the investment trait, with values between 0 and 1. The within-host dynamics have two possible outcomes: either the parasite becomes extinct ($\tilde{X} = 0$), or its density stabilises at an equilibrium parasite load :

$$X^*(\theta, \sigma) = \frac{r_0\theta - \mu - m - \gamma\sigma}{r_1} \tag{4}$$

Bridging the scales

System (1) describes a well-mixed population. However, from the parasite perspective, the host population can be seen as a set of discrete pacthes linked through the dispersal of parasite propagules. Our SIS model can therefore describe the colonization-extinction dynamics of local parasite populations Levins, 1969, the metapopulation dynamics of which are given by eqn.(3). For system (1) to remain consistent, we assume that within-host dynamics is fast compared to the processes that put an end to infection (*i.e.* host mortality, recovery and virulence). This requires

that the rate at which eq.(3) shifts from equilibrium $\tilde{X}$ to $X^*(\theta, \sigma)$ exceeds the inverse of the total infectious period, which can be mathematically translated into :

$$r_0\theta - (\mu + m + \gamma\sigma) \gg d + \alpha + \tau \tag{5}$$

Epidemiological traits

We assume that the fecundity of infected hosts, b_I, the transmission rate β, the recovery rate τ and the virulence α depend on two underlying traits: (1) the host's investment into defence σ, and (2) the parasite's investment in host exploitation θ. Specifically, we assume that the epidemic traits expressed in infected hosts are under the shared control of both partners, and note :

$$\beta = \beta(X^*)$$
$$\alpha = \alpha(X^*)$$
$$\tau = \tau(X^*)$$

We assume that the dependance of epidemic features to host and parasite individual traits occurs through the within-host equilibrium load. Assuming that transmission is a linear increasing function of the equilibrium load, we define :

$$\beta(X^*) = cX^*(\theta, \sigma) \tag{6}$$

where $c = m(1 - \rho)$ is the rate of successful dispersal of parasite propagule, with m the rate at which propagules leave their host, and ρ a dispersal cost that represents the fraction of emigrating propagules lost during dispersal.

We also assume virulence and recovery to be functions of traits through equilibrium load. We generically define the functions $\alpha(\theta, \sigma)$ and $\tau(\theta, \sigma)$ in the following way:

$$u(\theta, \sigma) = u_0 f_u(\tilde{X}(\theta, \sigma)) \tag{7}$$

where $u \in \{\alpha, \tau\}$, and u_0 is a theoretical maximum for the epidemiological trait α (resp. τ). The trade-off function f_α (resp. f_τ) is assumed to be an increasing (resp. decreasing) function of the parasite load. A complete description of the functions used is given in appendix C. In addition, a table summarising parameter notations and interpretations is provided in appendix A.

Furthermore, we assume that host defense is costly and leads to a reduced fecundity of infected hosts, that is :

$$b_S = b(0) = b_0$$
$$b_I = b(\sigma)$$

where $b(\sigma)$ is a decreasing function of σ. Note that this implicitly assumes that the constitutive costs of resistance are negligible, but its induced costs are not.

Resistance in our model acts in two ways: as an avoidance mechanism (*i.e.* causing a reduction in disease transmission), and as a clearance mechanism (*i.e.* causing an increase in host recovery, and/or a decrease in virulence). Both transmission and virulence are assumed to be increasing functions of the within-host replication rate, which has received strong empirical support Acevedo et al., 2019. Because both traits depend on the parasite's strategy θ, our model also incorporates the classic virulence-transmission trade-off: an increase in transmission can only be bought at the expanse of a reduced infectious period Alizon et al., 2009.

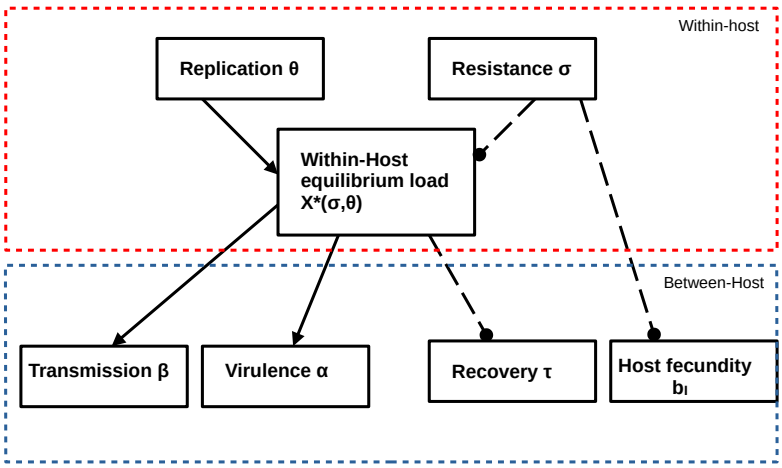


Figure 1 – Schematic view of interactions between resistance and exploitation traits, and their consequences on equilibrium density $X^*(\theta, \sigma)$ and associated epidemiological parameters. Solid arrows refers to up-regulation links (when the origin quantity increases, it induces an increase in the terminal quantity). Dashed lines with black circles refers to inhibition links (when the origin quantity increases, it induces a decrease in the terminal quantity). The red square delimits processes acting at the within-host level, while the blue square delimits between-host processes.

Host evolution

We first describe the outcome of host resistance evolution. In this section, we assume that parasite investment in replication θ is fixed, and write $X^*(\theta, \sigma) = X^*(\sigma)$.

Host and parasite coexistence.

For an endemic equilibrium of the disease to exist, we require that the equilibrium of system (3) also exists and is positive, which holds if :

$$\frac{\mu + m + \gamma\sigma}{r_0} < \theta \text{ or equivalently } \sigma \leq \frac{r_0\theta - (\mu + m)}{\gamma} \tag{8}$$

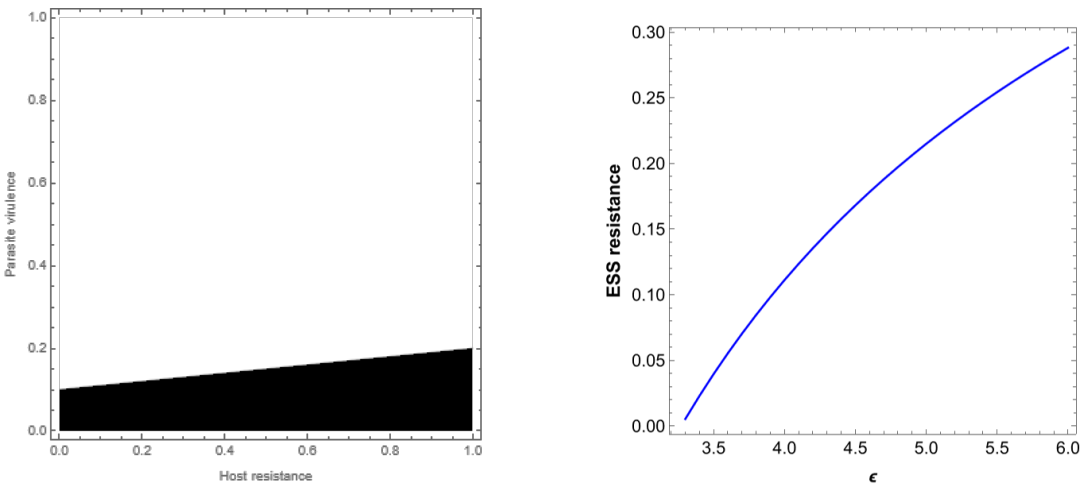
In addition, we also require that the number of secondary infections following the initial invasion of the disease-free equilibrium by a single parasite (the epidemiological R_0) is above one. Note that this implies that the within-host equilibrium load exists and is positive.

From (8), it follows that in absence of host response, parasite growth is only determined by $r_0\theta - (\mu + m)$. It also ensues that a parasite that do not sufficiently invest in virulence is unviable, as shown in figure (2a). For σ constrained on [0,1], the host is able to drive its parasite towards local extinction when :

$$\frac{r_0\theta - (\mu + m)}{\gamma} \leq \sigma \leq 1 \tag{9}$$

From (9), it appears that only a sufficiently slow-growing parasite can be driven to extinction by the host. It also means that setting $\frac{r_0\theta-(\mu+m)}{\gamma} \geq 1$ ensures that no host-driven extinction is achievable. From now, we will restrict our analysis to the set of cases in which the host is always unable to eradicate its parasite, whatever its level of resistance. However, an overview of cases where the host evolution can drive the parasite towards extinction is presented in appendix (B).

Invasion Fitness.



(a) (b)

Figure 2 – (a) Phase diagram describing the parasite domain of existence. White areas reprensent the cases where the hosts and parasite always coexist, while black areas represent the set of cases where the host can drive its parasite towards extinction. (b) CSS strategy of host investment in resistance according to the shape of the trade-off functions between hosts resistance and fecundity. Fixed parameter values for figures a-d were set to :$b_0 = 0.8, = 0.5, \alpha_0 = 1, r_0 = 10, \theta = 0.8, r_1 = 0.04, \rho = 0.9, \gamma_0 = 1, d_0 = 0.05, \tau_0 = 1, \delta = 3, \kappa = 1, d = 0.5$

We consider the fate of a rare mutant host with investment σ_m invading a resident host population with investment σ at its endemic equilibrium. We define the invasion fitness as the initial growth rate of the mutant in the equilibrium resident population Geritz et al., 1998. For structured populations, a proxy for the invasion growth rate is obtained using the next-generation theorem Diekmann et al., 1990; Hurford et al., 2010; Otto and Day, 2007. Denoting quantities that depends on the mutant trait by a subscript m, this yields (see appendix D for the complete derivation) :

$$W_h = \frac{b_0\Psi_m + b_m\beta p_I^*}{d\Psi_m + (d+\alpha_m)\beta p_I^*} p_0^* \tag{10}$$

where $\Psi_m = d + \alpha_m + \tau_m$, such that $1/\Psi_m$ is the average infectious period of a mutant host.

Eq.(10) is similar to eq.(A7) in Kada & Lion (2015) Kada and Lion, 2015 or eq.(6) in Restiff & Koella (2003) Restif and Koella, 2003, with some noticeable differences. First, mutant fitness relies on the infectious period not only through the recovery rate, but also parasite virulence. Second, the force of infection βp_I^* also depends on the host trait. Third, the birth rate of susceptible individuals does not depend on the investment in resistance, as we assume its costs come by mounting an immune response. It is then straightforward to see that in the absence of the parasite (*i.e.* in a disease-free population or when the host can drive its parasite to extinction), resistance becomes a neutral trait (see appendix B). As only infected individuals pay the costs of resistance, parasite presence is needed for resistance to be under selection.

Singular strategies.

Let our parameters be constrained to always verify condition (2). Setting $r_0\theta - (\mu + m) > \gamma$ ensures that no infected host can get rid of the parasite, whatever its level of resistance. We study the fixed points of the adaptive dynamics by solving for σ values for which $\frac{\partial W_h}{\partial \sigma_m}\Big|_{\sigma_m=\sigma} = 0$.

Evolutionary stability is studied through the second derivatives of the fitness function. A strategy is said *evolutionarily stable* (ESS) if the second partial derivative of the fitness function with respect to the mutant trait is negative Geritz et al., 1998. In addition, if the derivative of the fitness gradient evaluated at the singular strategy is negative, the strategy is said to be *convergence stable*, which ensures that it is a locally attracting point. A strategy that is both evolutionarily stable and convergence stable is thus an endpoint of the evolutionary dynamics and is termed as a *continuously stable strategy* (CSS). A strategy that is neither evolutionarily stable nor convergence stable is therefore an evolutionary repellor.

We analyzed how the shape of the trade-off function between resistance and fecundity affects the existence of singular states. Figure (2b) shows that our model allows us to recover some results from Best et al., 2009, Boots and Haraguchi, 1999. That is, a CSS is found for a sufficiently concave trade-off function between σ and $b(\sigma)$. Biologically, this means that an evolutionarily stable investment in resistance occurs only when the subsequent physiological costs are accelerating. When the costs are moderately decelerating, the evolutionarily singular point is a repellor that lies outside of the parameters region that is biologically relevant. In such a case, selection drives resistance towards zero investment. When the costs a strongly decelerating, the repellor then appears and selection drives resistance towards an all-or-nothing strategy, depending on the initial conditions. Pairwise invasibility plots for decelerating costs are presented in appendix A.

When a CSS level of investment exists, it increases with the acceleration of cost (Fig.2b). In such a case, higher investment levels can be reached without paying an excessive cost, as $b'(\sigma)$ decreases for low σ. Unlike previously cited studies, we found no evidence for evolutionary branching depending on the shape of the trade-off function. This is easily explained by the assumption made on the distribution of resistance costs. Indeed, host fitness is determined by a single environmental variable (p_I), which prevents branching Lion and Metz, 2018. This constrasts with the work of Best et al., 2009, Boots and Haraguchi, 1999, where the consideration of constitutive costs of immunity leads the host fitness to be affected by the densities of both susceptible and infected individuals.

Parasite evolution

We analyse the evolutionary dynamics of parasite investment. We assume that the host investment in resistance is not subject to selection, such that σ is arbitrarily fixed and we write $X^*(\theta, \sigma) = X^*(\theta)$.

Due to the metapopulation structure of the parasite, it is not possible anymore to define fitness as the initial growth rate of a mutant invader in a given patch. We therefore use as a fitness measure the average lifetime population success R_m, Metz and Gyllenberg, 2001, Ajar, 2003, following the methods initially described in Jansen and Vitalis, 2007 and Pillai et al., 2012.

Competition dynamics in coinfected hosts.

We consider the the fate of a mutant parasite with trait θ_m and load X_m^* during its early stage of invasion. This implies considering reinvasion dynamics of strains. These reinvasions can occur when the mutant invades a patch already occupied by the resident parasite, or conversely when it is reinvaded by the resident while alone in a host.

The dynamics of the mutant frequency in a shared patch is described by (see appendix E for details on the derivation)

$$\frac{df}{dt} = \Delta_s f(1-f) \tag{11}$$

with competition acting through the differential replication of the two strains, *i.e.* through the quantity $\Delta_s = r_0(\theta' - \theta)$. After reinvasion, each strain will produce dispersers until extinction or competitive exclusion occurs. When extinction is likely to occur before exclusion, even a less competitive strain will benefit from having been the first to colonize a new host, which enables preemptive effects in competition. We thus have to explicitely account for the transient replacement dynamics of the strains. Equation (11) can be solved in closed form and yields :

$$f^{\phi}(t) = \frac{\phi}{\phi + (1-\phi)\exp^{-t\Delta_s}} \tag{12}$$

where ϕ refers to the initial frequency of the mutant in a particular coinfection scenario. Note that by definition, $f^{\phi}(t) = \phi$ when $\Delta s = 0$. We define two initial conditions of interest: $\phi_{rm} = \frac{1}{X^*+1}$, the initial mutant frequency after it re-invades a resident host and $\phi_{mr} = \frac{X_m^*}{X_m^*+1}$ the initial mutant frequency after being re-invaded by a resident.

By definition, a strain at its own equilibrium has a null net growth rate. As our model assume density-dependence acting on natality, an invading mutant whose replication is close to the resident has a low birth rate. Competitive exclusion should therefore be a slow process. We thus assume that the total density of parasite in a coinfected host reaches a quasi-equilibrium value, that is slowly changing trough the frequency dynamics of strains, given by:

$$Y^{\phi}(t) = X_m^* f^{\phi}(t) + X^*(1 - f^{\phi}(t)) \tag{13}$$

Doing so, virulence and recovery in coinfected hosts now depends on the quasi-equilibrium parasite load. It allows us to define the inverse of the average infectious period during coinfections as :

$$\psi^{\phi}(t) = d + \alpha^{\phi}(t) + \tau^{\phi}(t) \tag{14}$$

where $\alpha^{\phi}(t)$ and $\tau^{\phi}(t)$ are now functions of of the quasi-equilibrium load Y^{ϕ} (eq.13). Studying the dynamics of coinfection leads us to look at the number of strains received by the host at equilibrium. A host can theoretically be reinvaded withtout limitations. However, in order to keep the model analytically tractable, we assume that during its lifespan hosts suffer at most two infections events. This assumption has already been used in the context of virulence evolution Baalen and Sabelis, 1995, or dispersal evolution Jansen and Vitalis, 2007. Disentangling the number of infections at one strain equilibrium is achieved by extending system (1) into :

$$\begin{aligned}
\frac{\mathrm{d}p_S}{\mathrm{d}t} &= [b_S p_S + b_I(p_1+p_2)]\, p_0 - dp_S - \beta(p_1+p_2)p_S + \tau(p_1+p_2) \\
\frac{\mathrm{d}p_1}{\mathrm{d}t} &= \beta(p_1+p_2)p_S - [\beta(p_1+p_2) - (d+\alpha+\tau)]\, p_1 \\
\frac{\mathrm{d}p_2}{\mathrm{d}t} &= \beta(p_1+p_2)p_1 - (d+\alpha+\tau)p_2
\end{aligned} \tag{15}$$

where p_1 and p_2 refer to the number of hosts that have received one or two parasite invasions, respectively. Setting $p_1 + p_2 = p_I$ allows us to recover system (1). Solving system (15) equilibria

now allows to break down the endemic equilibrium in the form $p_0 = p_0^*$, $p_s = p_s^*$, $p_1 = p_1^*$, $p_2 = p_2^*$, with $p_1^* + p_2^* = p_I^*$.

Invasion fitness.

We follow the number of successful emigrants produced by a rare focal mutant landing in a given host. This number is equal to the sum of emigrants produced in each of the different hosts states (susceptible or infected) in which the mutant can appear, weighted by the time spent in each of those states Massol et al., 2009. We consider the set of fates a mutant invader can experience. If the mutant lands in a susceptible host p_s^*, it will produce $\beta_m = cX_m^*$ dispersers per unit of time until the infection ends or the host is reinvaded. Such reinvasion will happen with probability $\frac{\beta p_I^*}{\beta p_I^* + \Psi_m}$. Subsequently, the mutant will produce additional dispersers until competitive exclusion occurs or infection ends.

Noting $F^\phi(t)$ the amount of dispersers produced after a given reinvasion, we have :

$$F^\phi(t) = cY^\phi(t) f^\phi(t) \exp^{-\int_0^t \psi_\phi(s)ds} \tag{16}$$

Here $cY^\phi(t)f^\phi(t)$ denotes the number of mutants dispersers produced at time t, and $\exp^{-\int_0^t \psi_\phi(s)ds}$ is a survival function that describes the probability that the infection has not ended until t. Thus, $\int_0^\infty F^{\phi_{mr}}(t)\mathrm{d}t$ dispersers are produced when the mutant is reinvaded by the resident. Similarly, a mutant landing in an already infected host p_1^* will produce $\int_0^\infty F^{\phi_{rm}}(t)\mathrm{d}t$ dispersers over the lifespan of its host. Dropping the dependency on the resident trait for notational convenience, and denoting dependencies on the mutant by a subscript m, we put all scenarii together and obtain the parasite fitness function :

$$W_p = cp_S^* \left[\frac{X_m^*}{\beta p_I^* + \Psi_m} + \frac{\beta p_I^*}{\beta p_I^* + \Psi_m} \int_0^\infty F_m^{\phi_{mr}}(t)\mathrm{d}t \right] + cp_1^* \int_0^\infty F_m^{\phi_{rm}}(t)\mathrm{d}t \tag{17}$$

In the absence of multiple infections (*i.e.* with $cp_I^* = cp_1^* = 0$), parasite fitness reduces to :

$$W_p = \frac{\beta p_S^*}{\Psi_m} = \frac{R_{0m}}{R_0} \tag{18}$$

which is the classic expression for parasite fitness in the SIR model. The evolutionary behaviour of this model has been extensively studied. It this case, selection drives parasite virulence towards R_0 maximization.

Fitness gradient.

The complete derivation of the fitness gradient is described in appendix (F). Dropping the dependency on traits to avoid notational clutter, it leads to the following expression :

$$\begin{aligned} \frac{\partial W_p}{\partial \theta_m}\Big|_{\theta_m=\theta} =& \frac{\Psi}{\beta p_I^* + \Psi} \left[\frac{1}{X^*} \frac{\mathrm{d}X_m^*}{\mathrm{d}\theta_m}\Big|_{\theta_m=\theta} - \frac{1}{\beta p_I^* + \Psi} \frac{\mathrm{d}\Psi_m}{\mathrm{d}\theta_m}\Big|_{\theta_m=\theta} \right] \\ &+ \frac{\beta p_I^*}{\beta p_I^* + \Psi} \left[-\frac{1}{\beta p_I^* + \Psi} \phi_{mr} \frac{\mathrm{d}\Psi_m}{\mathrm{d}\theta_m}\Big|_{\theta_m=\theta} \right. \\ &\left. + \left(\frac{1}{X^*} \frac{\partial X_m^*}{\partial \theta_m}\Big|_{\theta_m=\theta} - \frac{1}{\Psi} \frac{\mathrm{d}\Psi_m}{\mathrm{d}\theta_m}\Big|_{\theta_m=\theta} \right) \left(R - \frac{p_1^*}{p_2^*} \bar{R} \right) + r_0 \frac{p_I^*}{p_2^*} \bar{R} \frac{1}{\Psi} \right] \end{aligned} \tag{19}$$

Where R and $\bar{R}$ are the relatedness and unrelatedness measures in metapopulation, the derivation of which is described in appendix (F).

In the absence of multiple infections (*i.e.* when putting $cp_I^* = 0$), eq. (19) reduces to a simpler form :

$$\frac{\partial W_p}{\partial \theta_m}\Big|_{\theta_m=\theta} = \frac{\frac{d\beta_m}{\partial \theta_m} p_s^*}{\Psi} - \frac{\beta p_S^* \frac{\mathrm{d}\Psi_m}{\mathrm{d}\theta_m}}{\Psi^2} = \frac{1}{R_0}\frac{\partial R_0(\theta_m)}{\partial \theta_m}\Big|_{\theta_m=\theta} \tag{20}$$

Note that this is, as expected, equal to the selection gradient obtained from differentiating eq.(18). Without multiple infections, competition is only driven by preemption (*i.e.* the competition for new susceptibles). We then retrieve classic results from the single-population epidemiology, such that selection obeys the R_0 optimization principle Lion and Metz, 2018.

Eq. (19) can be partially understood in such terms. Terms on the first line have an interpretation analogous to eq. (20), and correspond to changes in R_0 considering reinvasions can occur. The first term between brackets describes the fitness gain of a higher replication when colonizing a susceptible host. The second term reflects the change in fitness due to an alteration of the infectious period. These terms are weighted by the probability that the infection ends before a secondary infection has occured. On the second line, the term in factor denotes the probability of occurence of a secondary infection. The first term between brackets is the fitness change due to the alteration of the infectious period followed by the introduction of a second strain.

Terms in the third line reflect the additional selective pressures induced by the consideration of within-host dynamics. Interestingly, the within-host component can be interpreted in terms of kin structure. The first term in $\bar{R}$ shows the fitness loss through competition with the other strain. This term is accompanied by a term in R that is always of opposite sign and reflect how a change in within-host density or duration of infection would also benefit to the production of dispersed relatives. Thus, if selection favors higher levels of virulence due to the competitive advantage conferred by a higher replication rate, this effect should be dampened by a kin selection effect. The last term between brackets that depends on $\bar{R}$ is always positive, such that increased virulence has always an advantage when multiple infections are allowed for. Our model also considers that any invasion is successful but that less competitive strains are slowly excluded. Thus, there is always an advantage -even small- for any strain to be able to invade an already infected host.

The limit case of pure dominance competition (*i.e.* close or equal to a superinfection framework) is a bit more difficult to mimic on the basis of equation (19). In order to adress it, preemptive effects in infected hosts must become negligible. This would correspond to infinitely long infectious periods, or strong competitive differences between strains. The first case would force crucial epidemiological parameters (virulence and recovery) to also become negligible, which would compromise the evolutionary analysis. The second case would interfere with the quasi-equilibrium assumption used to derive our fitness equation. Consequently, the derivation of pure dominance competition from (19) require additional assumptions. If one assumes that within-host competitive exclusion occurs instantaneously, restricting the number of invasions is not necessary anymore. Then, eq.(17) drastically simplifies and gives the parasite invasion fitness under the superinfection framework :

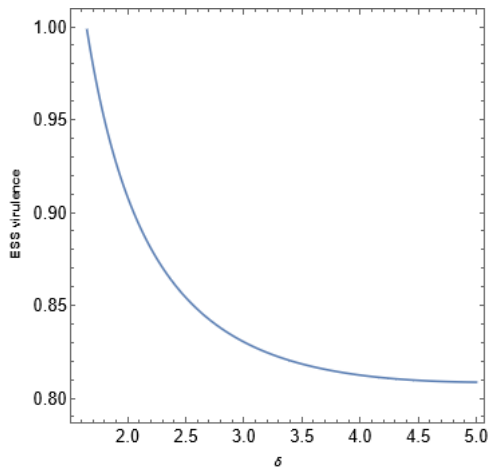


Figure 3 – CSS Parasite virulence as a function of trade-off shape between virulence and replication, with θ left as a variable and σ set to 0.5. Other parameters were fixed to $b_0 = 0.8, \mu = 0.5, \alpha = 1, r_0 = 10, r_1 = 0.04, \rho = 0.9, \gamma_0 = 1, d_0 = 0.05, \tau = 0.5, \delta = 0.8, \kappa = 1, d = 0.5$

$$W_p^s = \frac{\beta_m p_I^*}{\Psi_m + \beta p_I^*} + \frac{\beta_m p_S^*}{\Psi_m + \beta p_I^*} \tag{21}$$

which, in the absence of the shared control of epidemiological traits, is equivalent to eq.(A3) in [Kada & Lion] with their superinfection efficiency parameter equal to one. In such a case, the fitness gradient becomes

$$\frac{\partial W_p^s}{\partial \theta_m}\Big|_{\theta_m=\theta} = \left[p_S^* + p_I^*\right]\left[\frac{1}{\Psi + \beta p_I^*}\frac{d\beta_m}{d\theta_m} - \frac{\beta_m}{(\Psi + \beta p_I^*)^2}\frac{d\Psi_m}{d\theta_m}\right] \tag{22}$$

Regardless of the framework considered (*i.e.* superinfection or coinfection), the fitness of a mutant parasite is always determined by both its R_0 and its within-host competitive ability. This has already been found in several theoretical works Kada and Lion, 2015, Baalen, 1998, Nowak and May, 1994,Alizon et al., 2013, Alizon and Baalen, 2008 and has been shown to generally select for higher virulence. We find that the same effect occurs in our model, as competition is determined by the growth rate, which is an increasing function of virulence.

Existence of singular strategies.

Evolutionarily singular strategies are given by studying the set of θ that cause equation (19) to vanish. Figure (3) shows that we found that an evolutionarily stable investment in virulence exists *iff* the trade-off between replication and virulence is sufficiently convex. Otherwise, investment in virulence is always pushed towards its maximal value. Biologically speaking, this means that an intermediate evolutionarily stable investment is possible only when the costs of virulence are accelerating.

Coevolution

We now extend our framework to coevolutionary dynamics. We first constrain the trade-off curvatures such that an evolutionarily stable strategy exists for both species when evolving alone. The potential endpoints of host and parasite coevolutionary dynamics (co-CSS strategies) are found by studying values that cause both host and parasite gradients to vanish. ESS-stability

and convergence stability were assessed using criterions detailed in Best et al., 2009, Appendix I.

The standalone evolutionary analysis of host resistance and parasite virulence (see eqs. (10), (19)) revealed that the force of infection and the infectious period are important drivers of within-host competition. The force of infection determines the prevalences in the host population, and thus the likelihood of multiple infections. The infectious period determines the time allowed to strain competition when multiple infections occurs. Shortened infectious period should thus enhance the part of preemption in parasite fitness, while long infectious period should elicit dominance competition. We therefore choose to focus our coevolutionary analysis on model parameters that are the more susceptible to affect those epidemiological features, and compared the coevolutionary outcomes under the coinfection and superinfection models.

Dominance competition strenghtens selection towards virulent parasites and well-defended hosts.

Figures (4, 6, 7) shows that the coevolutionary dynamics exhibits one single co-CSS.

Our first result is that both host resistance and parasite virulence are selected towards higher levels in the superinfection model than in the coinfection model. This can easily be explained by the absence of preemption effects in superinfections. As dominance competition takes a larger place in parasite fitness under superinfections, higher virulence levels are selected for. Allowing for preemptive effects by considering the local coexistence of strains (*i.e.* coinfections) leads to lower levels of investment in virulence. In addition, we have also shown (see section 4) that coinfections induce the emergence of a relatedness effect that is expected to counteract competition effects, thus dampening selection towards high virulence. The host generally respond to the higher parasite investment observed in superinfections by investing more in resistance, in order to counteract the deleterious consequences of infection.

Inducible defense creates an epidemiological feedback that determines host resistance.

The force of infection in our model is mainly driven by the parasite dispersal rate m. When parasite dispersal is close to the population viability boundaries (respectively low or high enough), the force of infection is weak. While parasite levels of investment remain high across a wide range of dispersal values, host investment is more variable (fig 4). As a general result, we find that the host investment in resistance and the force of infection follow an inverse pattern. When the parasite dispersal is low, the host then shows relatively high investment in resistance. In such a case, the disease is rare in the population and hosts are infected at high loads. As the damages induced by the parasite are consequent, but the costs of resistance only paid by a few individuals, investment in resistance is favored. In addition, when the parasite dispersal is low, the opportunities of multiple infections are scarce, and both the coinfection and superinfection models tend to be close to the single-infection model and give similar results.

When dispersal is driven towards the upper viability boundary, the force of infection is low due to the cost of dispersal. Few hosts are infected, with small within-host parasite densities. The host investment in resistance is then favored as a way to control the effects of infection, resulting in even higher recovery rates and lesser mortality risks.

When parasite dispersal is intermediate, the force of infection is maximal. In such a case, the opportunities of multiple infections are common, and increase the competition for infected hosts. As a large fraction of the host population is infected, the demographic costs of resistance are widely incurred, which selects for lower investment. This is a consequence of our assumption

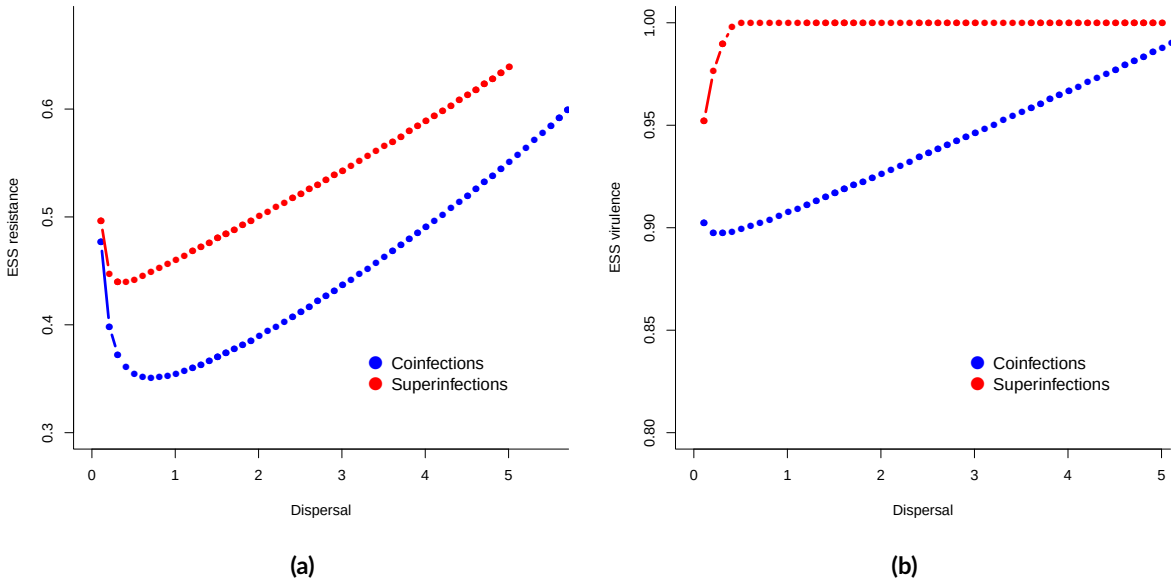


Figure 4 – Coevolutionary singular points as a function of parasite dispersal rate for a) the host resistance and b) the parasite virulence. Red dots refers to results derived from the superinfection model, while blue refers to results derived from the coinfection model. Fixed parameters were set to :$\epsilon = 5$, $b_0 = 0.8$, $\mu = 0.5$, $\alpha_0 = 0.5$, $r_0 = 10$, , $r_1 = 0.04$, $\rho = 0.9$, $\gamma_0 = 1$, $d_0 = 0.05$, $\tau = 1$, $\delta = 5$, $\kappa = 1$

made on the distribution of resistance costs. We assumed that only infected individuals pay the costs of resistance, and considered that the cost acts on host fecundity. Doing so, the infection prevalence creates a negative demographic feedback on host population. Selection on resistance therefore generally leads the host towards less investment when the disease is widespread and sufficiently lethal.

Our assumption on the induced nature of resistance costs also partly conditions the way host and parasite investment respond to changes in the recovery rate. Figure (6) shows that increased recovery select for both higher virulence and resistance, the effect being more important in the superinfection case. This result is fairly common for the parasite (*i.e.* increased recovery has been shown to favor exploitation, *e.g.* Baalen, 1998). Recovery induces a positive demographic feedback on the host population, because individuals returning to the susceptible state do not suffer from virulence and counterparts of resistance. Increasing the baseline recovery mechanically shortens the infection duration, and thus the time during which resistance costs are paid. Increased investment in host resistance is thus selected for, as it results in even shorter infectious period, together with a mitigation of the effects of virulence. A previous study on the nature of immune costs Cressler et al., 2015 showed that investment in inducible defenses should be elicited when the associated costs are cheap, or when the probability of infection is low. Our results thus corroborate previous theory, showing that hosts invest in resistance when the disease is globally rare.

Deviation from R_0 optimization emerges from a competition-colonization trade-off.

The host investment in resistance according to the host background mortality (fig. 7a) shows a quite intuitive pattern. As the host lifespan diminishes, so does the investment in resistance. An intuitive explanation is that the host fecundity is favored over resistance to infectious agents

in short-lived species Miller et al., 2007. However, the parasite investment seems, at first glance, more counter-intuitive (fig. 7b). While virulence seems favored when the host lifespan is short in the case of coinfections, superinfections show the opposite tendency. Such a result can however be understood in terms of optimization principles.

Simple models of parasite evolution state that virulence should be selected towards values that maximizes the basic reproductive ratio R_0 Lion and Metz, 2018. The addition of complexity (*i.e.* multiple infections and host evolution) is expected to cause deviation from the R_0 optimization principle, as it increases the dimensionality of the environmental feedback loop. We have shown in section (4) that when the parasite evolves alone, virulence should evolve towards higher levels in multiple infection than expected under the single infection scenario, as a result of the accountance of strain competition. Host evolution does not change this expectation (fig 5). However, we also find that the R_0 optimization principle holds in our model when the host or the parasite are driven towards their viability limit. This can be explained by the reduction of the environmental feedback loop, which can be seen as a consequence of a scenario in which trait evolution is driven by ecological persistence. Near to the viability boundary, the occurence of multiple infection tends to be drastically reduced because when infections are scarce, double infections are scarcer. Thus the environmental feedback loop acting on the parasite should tend to be only determined by the number of susceptible individuals.

On the contrary, when both partner exists far from their viability boundary, we have shown that dominance competition has a larger contribution in parasite fitness. Competitive ability in our model is acquired at the cost of an increased virulence, which decreases the within-host persistence time. This particular feature induces the emergence of a competition - colonization trade-off Messinger and Ostling, 2009. Not surprisingly, this trade-off is more intense in the superinfection model than in the coinfection model. As superinfections assumes no preemptive effects in strain competition, this enables a stricter competitive hierarchy in parasite, because competitive exclusion always occurs in infected hosts.

Allowing for some preemption through coinfections only leads to a slight deviation from the R_0 optimization. The addition of preemption implies the local coexistence of strains, because exclusion may have not occured at the end of infection. The weak deviation from single-infection models is thus explained by two features that stem from our coinfection framework : (i) the assumption of weak competitive differences, that mechanically dampen the intensity of dominance competition and (ii) the induction of a kin selection effect which always drives selection on virulence in the opposite direction to competition.

Discussion

Our work aims to bridge the gap existing between the ecology of subdivided populations, and theoretical epidemiology assessing coevolution in "attack-defense" traits when multiple infections are possible. Following an approach initiated by Restif et Koella Restif and Koella, 2003, we built an epidemiological model under a shared control of transmission, virulence and recovery, with parasite load as the main driver of control. In addition, we used a modelling framework anchored in metapopulation ecology to assess parasite evolution in the context of multiple infections, under different regimes of competition.

Our broader result is that parasite competition strongly affects the evolution of host resistance, and determines the host response to the selective pressures induced by the ecological

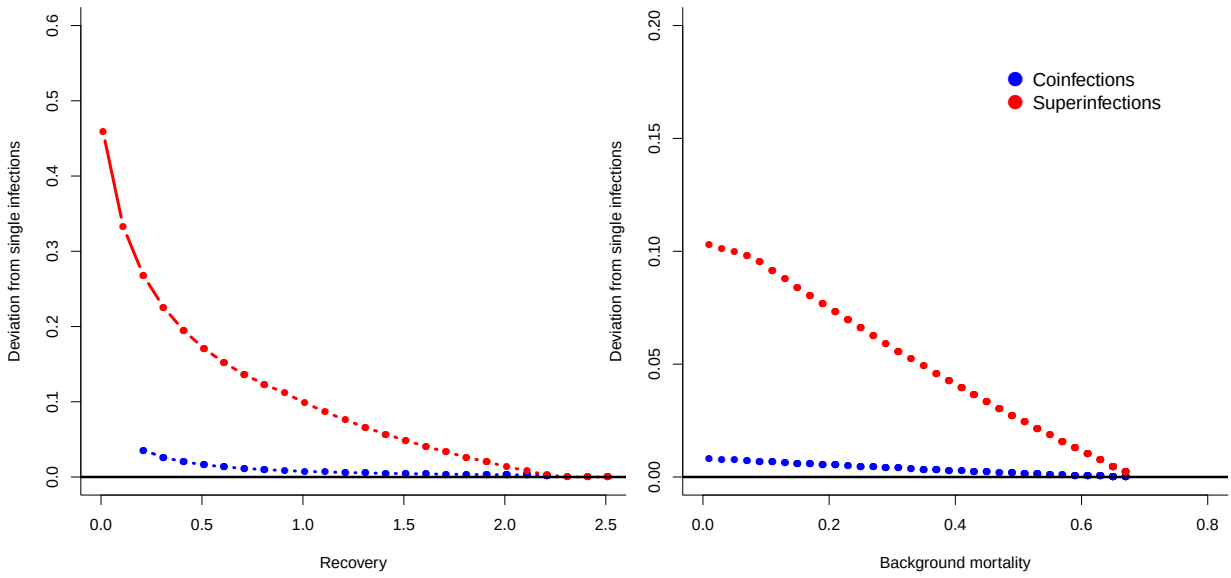


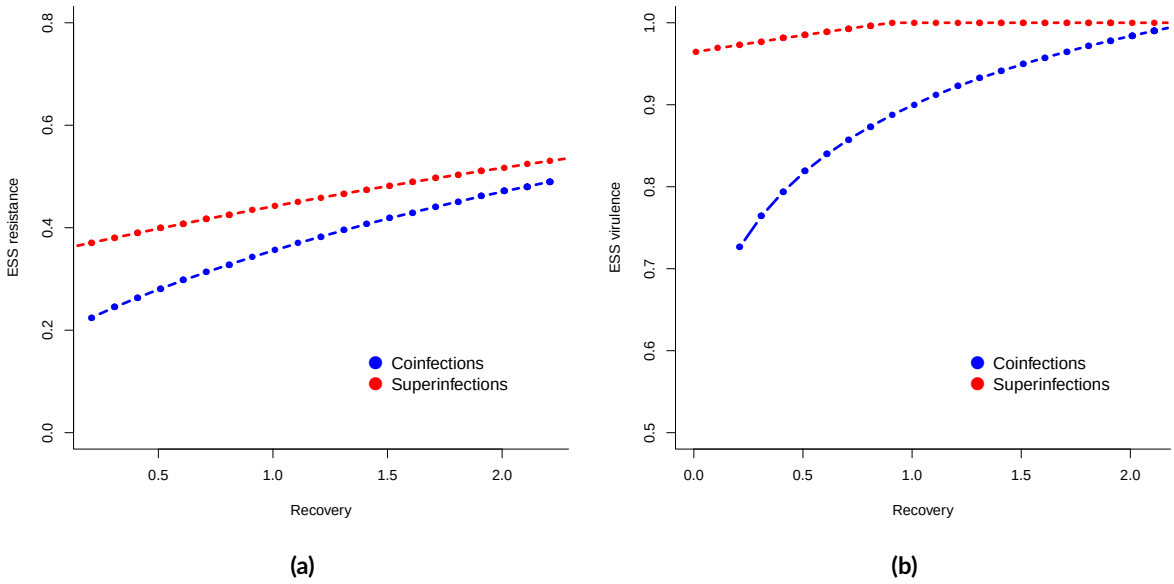
Figure 5 – Deviation between the coevolved R_0 in the coinfection model (blue curve) and superinfection model (red curve) and the R_0 obtained from maximization knowing the host co-singular strategy. Constant parameters were set to $b_0 = 1, \mu = 0.5, r_0 = 10, r_1 = 0.04, \rho = 0.9, d_0 = 0.05, \tau = 1, d_0 = 0.05, \epsilon = 5, \alpha = 1, \gamma_0 = 1, \delta = 5, \kappa = 1$. (a) Deviation is plotted according to the baseline recovery rate τ_0. (b) Deviation is plotted according to the host background mortality d_0

conditions. When strain competition acts mainly through dominance, virulence evolves towards the highest values, and host generally respond by an increased investment in resistance. However, adding preemptive effects in strain competition reduces the overall harm caused by the parasite. Such results are the consequence of two major properties arising from our modelling framework.

First, a competition-colonization (hereafter CC) trade-off emerges from the conflictual selective pressures between the colonization of new susceptibles and the within-host competitiveness Mideo, 2009. The first is expected to maximize the epidemiological R_0, while the second is maximized with replication, at the cost of a reduction in local persistence time Messinger and Ostling, 2009. Such a trade-off is representative of spatially structured populations Tilman, 1994, and emerge in our model from limited dispersal between discrete host patches.

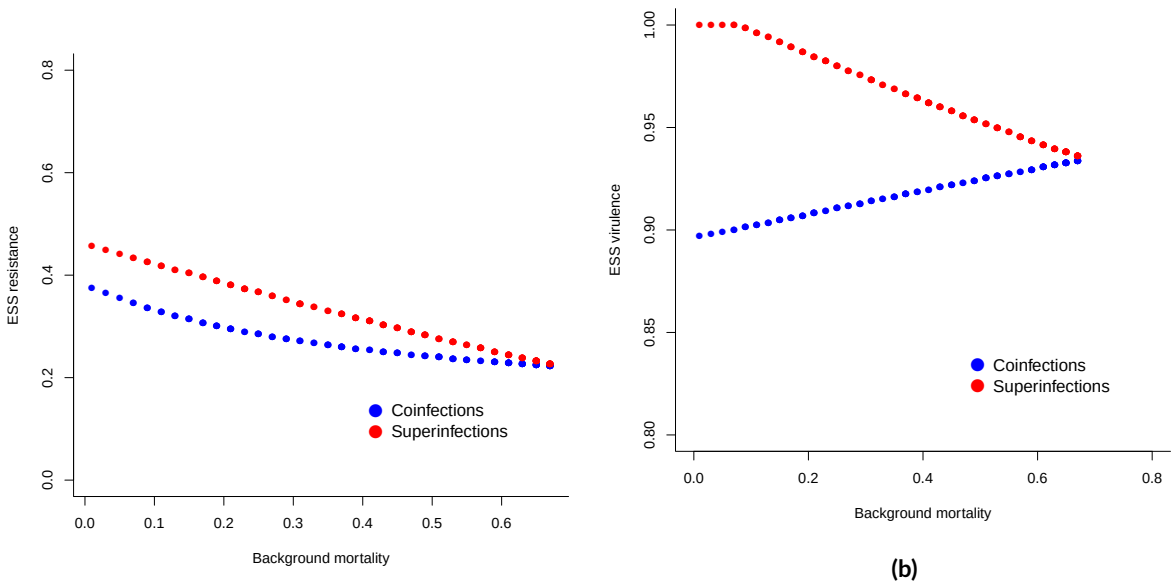
Second, a kin selection effect is induced by the local coexistence of strains, and acts in an opposite sense to competition. Relatedness in coinfecting parasite have been shown to lead to various outcomes according to the nature of exploitation behaviour of individuals Brown et al., 2002 Buckling and Brockhurst, 2008. In our model, virulence is a consequence of collective exploitation of the host patch by the parasite population(s), and depends on both individual traits and the total parasite load. Our work provides consistent results with the idea that when exploitation is limited by the collective action of individuals, relatedness should favor prudent strategies (although it may also depend on the determinism of epidemiological traits and within-host interactions Alizon and Lion, 2011).

A corollary result is that both the CC trade-off and the kin selection effect vary depending on the ecological context. In particular, we have shown that both the parasite transmission success



(a) (b)

Figure 6 – Coevolutionary singular points as a function of host baseline recovery rate for a) the host resistance and b) the parasite virulence. Red lines refers to results derived from the superinfection model, while blue lines refers to results derived from the coinfection model. Fixed parameters were set to :$\epsilon = 5$, $b_0 = 0.8$, $\mu = 0.5$, $\alpha = 1$, $r_0 = 10$, $r_1 = 0.04$, $\rho = 0.9$, $\gamma_0 = 1$, $d_0 = 0.05$, $\delta = 5$, $\kappa = 1$, $d = 0.5$



(a) (b)

Figure 7 – Coevolutionary singular points as a function of host background mortality for a) the host resistance and b) the parasite virulence. Red lines refers to results derived from the superinfection model, while blue lines refers to results derived from the coinfection model. Fixed parameters were set to : $\epsilon = 5$, $b_0 = 0.8$, $\mu = 0.5$, $\alpha = 1$, $r_0 = 10$, $r_1 = 0.04$, $\rho = 0.9$, $\gamma_0 = 1$, $\tau_0 = 1$, $\delta = 5$, $\kappa = 1$, $d = 0.5$

and host demography determine the existence of the CC trade-off. Successful dispersal of parasite propagules can be seen as the degree of coupling between host patches, and reflects the

contact intensity of the host population. Such coupling determines the dimensions of the eco-evolutionary feedback loop acting on the parasite. When the infection is rare, the (eco-to-evo) feedback drives selection towards maximized persistence because transmission occurs mostly from infected to suceptibles. Conversely, widespread parasites cause infected individuals to act as a supplementary ecological niche. This causes deviation from the simple optimization of persistence through the epidemiological R_0, which is a classic result obtained from the study of multiple infections Mosquera and Adler, 1998Alizon and Baalen, 2008 .

We have shown that when coevolution leads to reduced levels of virulence, the host generally responds by a lesser investment in resistance. This can intuitively be explained by the reduction of the damages induced by the parasite. While not exactly surprising, the resulting qualitative patterns of investment put in perspective what is obtained from the single-infection model when the epidemiological traits are under shared control. In the absence of multiple infections, host investment in resistance is expected to reach its maximum for intermediate parasite virulence Restif and Koella, 2003. We did not retrieve this behaviour, and moreover found that both host resistance and parasite virulence decreased in response to increased host mortality, which also contradicts the study conducted by Restif and Koella, 2003. We argue this may result from epidemiological and demographic feedbacks arising from the force of infection $\beta(\sigma,\theta)p_i^*$ and the infectious period $\psi(\sigma,\theta)$, which depends on the distribution of costs.

The force of infection in our model determines prevalences, and thus the magnitude of resistance costs at the host population scale (because only infected individuals suffer from reduced fecundity). Our model predicts that when dominance competition is increased through an increase in the force of infection, both superinfection and coinfection hypotheses state that selection should favor higher virulence and lower resistance. Conversely, we also predict that when preemption increases through the reduction of the infectious period, the parasite virulence is selected to optimize of parasite persistence, while host resistance exhibits contrasted dynamics, depending on the resulting demographic feedback.

When a reduced infectious period has a positive demographic feeback on the host population (*e.g.* by an increase in recovery, which increase the density of susceptible individuals), only the parasite is pushed towards its viability limit. We predict that selection should favor high virulence and resistance. This results from both the shared control of epidemic features, and our assumption on the induced nature of resistance. High resistance allows the host to dampen the deleterious effects of the parasite by reducing both transmission and mortality risks, which is a consequence of the shared control. At the same time, increased resistance enhances the increase of recovery, which has twofold benefits, because a recovered host suffers neither from parasite effects, nor from the costs the resistance. The cost of resistance is thus sufficiently cheap to favor investment Cressler et al., 2015.

When the demographic feedback of a reduced infectious period is negative (*i.e.* by an increase in host mortality), both the host and the parasite are driven towards their viability limit. Selection here leads the traits evolution towards persistence. In the coinfection case, this corresponds to an increase in parasite replication and low (but non-zero) resistance, while in the superinfection case, it leads the parasite to reduce its virulence,because most of the competitive advantage is lost with the opportunities of superinfections. Both behaviors, however, correspond to convergence towards the R_0 optimization principle. High virulence is always counter-selected in these cases, because it induces a direct negative demographic feedback on parasite fitness.

We can hypothesize that the host metapopulation structure also leads to an indirect demographic feedback that can enable selection towards increased resistance and reduced virulence. We considered the host population as a set of patches, some of which are unavailable for the parasite. While neither parasite nor host fitness are sensitive to this assumption in evolution alone (see eqs. 10, 17), this is not the case when coevolving. By increasing its resistance rate, the host induces a demographic pressure due to the costs on its own birth rate. This decreases the amount of patches available for parasite dispersal. Parasites thus experiment virtually enhanced costs of transmission, because ending in a dead-end with higher probability would have an indirect beneficial effect on host fitness. Such a feedback induced by the spatial structure is known to favor lower exploitation levels under a wide range of conditions Boots and Haraguchi, 1999, Lion and Boots, 2010, Messinger and Ostling, 2009. This effect may explain why hosts does not always give up on resisting, and corroborates empirical studies suggesting that a diminished reproductive effort following infection can result from host adaptive strategy Hurd, 2001.

We would like to draw attention on some interesting features of our framework. The fitness equation we derived for the parasite evolution (eq. 17) enables a straightforward link between several theoretical approaches. By considering a well-mixed host population as a set of discrete patches coupled through parasite dispersal, we showed that the measure of the lifetime population success R_m Metz and Gyllenberg, 2001 is equivalent to the reproductive numbers traditionally used in theoretical epidemiology in the absence of multiple infections Lion and Metz, 2018 Almocera et al., 2018. Our nested approach also emphazises the now recognized links between fitness in subdivided populations and inclusive fitness theory Ajar, 2003, as well as the vision of the altruistic nature of virulence-related traits Griffin et al., 2004. Moreover, it provides a natural framework for multiscale modelling and accounting for a variety of local interactions. The links between the different interaction scales, as well as the evolving individual traits, are defined through quantities that are commonly measured in life sciences (*e.g.* parasite load, division rate or clearance rate following phagocytosis by macrophages). We believe our methodological framework could thus help empiricists and theoreticians to design system-specific models and experiments to refine our mechanistic understanding of host-parasite interactions.

Another strength of our model is that the emergence of multi-scale selection as well as demographic feedback are blind to the assumptions made on the cost profile between host and parasite traits (*i.e.* it does not depend on particular trade-off shapes). However, some of our results are expected to be sensitive to several assumptions of our framework.

It is now well-recognized that the choice of the 'take-over' function in multiple infection models can have significant effects on the qualitative outcome of the coevolutionary dynamics, especially relative to the emergence of stable polymorphism Boldin and Diekmann, 2008 Mosquera and Adler, 1998. Our work assumes that any secondary invasion of a host is by definition successful, in the sense where even an invading uncompetitive mutant will be able to produce propagules for a certain time. Such a deterministic behaviour is quite unlikely to occur in natural systems. A natural expansion of our model would account for the early stochastic dynamics of invasion (*e.g.* by defining the probability of multiple infections as a function of competitive traits (see Kada and Lion, 2015, Boldin and Diekmann, 2008 for examples).

Another caveat of our model relies on the assumptions made on the interaction between host defense and parasite growth. We choose a simple model of parasite growth that account

for parasite clearance and derive several mechanisms of avoidance and infection clearance at the host population scale. No possibility of tolerance mechanisms are accounted for. This may have important implications for host and parasite coevolution Carval and Ferriere, 2010, Best et al., 2010 especially in the case of multiple infections. Tolerance is defined in theoretical works as having a positive effect on parasite fitness Carval and Ferriere, 2010, and has been shown to be traded-off with resistance in several systems Salgado-Luarte et al., 2023 Råberg et al., 2007. Recent studies have shown this particular trade-off may strongly affect modes of selection (directional or fluctuating) and alter the possibility of stable coevolutionnary coexistence Singh, 2023. We expect such considerations to greatly affect our results.

The within-host dynamics chosen in our study does not capture the whole diversity of parasite interactions occuring in natural systems, such as production of public goods, or spiteful behaviours Leinweber et al., 2018, Niehus et al., 2017, Bucci et al., 2011, Bashey et al., 2012. Strain competition in our model acts through (i) exploitation competition for the exact same host ressources and (ii) apparent competition against the host's immune system, that can be seen as acting like a generalist predator. However, parasite evolution in our work only account for differences in the intensity of exploitation competition with no possibility to avoid apparent competition. In natural systems, this is achieved through adaptation towards shifts in antigenic determinants that allows new mutant to escape from host immune response Fryer et al., 2010. In spite of these obvious imperfections, we think that the framework used along this paper is readily adaptable to various within-host dynamics.

Most models, ours in first line, use the assumption of equilibrium quantities to derive the main results. The coinfection framework slightly relaxes this assumption by using a quasi-equilibrium to describe variation in parasite density during competition. However, many features of real systems remains hidden by such assumptions. Events of co-transmission, or time heterogeneity in the sequence of invasions by multiple parasites for exemple, would certainly lead to different outcome in competition, subsequently reflecting in the coevolutionary dynamics and associated feedbacks. Empirical evidence for such alterations have been reviewed in Dutt et al., 2022, and can also be suggested by contradictory results obtained by clinical studies Sullivan et al., 2015, Fry et al., 2019. One of the crucial challenges for future theoretical studies assessing how parasite competition would alter coevolutionary dynamics will rely on our ability to adress how the 'age at secondary invasion' affects the outcome of parasite competition.

Fundings

This study is part of the FEEDME project coordinated by O. Kaltz, and has been funded by a grant from the Agence Nationale de la Recherche (NO : ANR-20-CE02-0023) to F. Massol and S. Lion.

Conflict of interest disclosure

The authors declare that they comply with the PCI rule of having no financial conflicts of interest in relation to the content of the article.

Data, script, code, and supplementary information availability

Datas, script, codes and supplementary information are available online (https://doi.org/10.5281/zenodo.12755175).

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