On multiple infections by parasites with complex life cycles

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Abstract: Host manipulation is a common strategy of parasites with complex lifecycles. It directly affects predator-prey dynamics in trophically transmitted parasites. Theoretical studies suggest that predation-enhancing manipulation often decimates the prey population, making parasites prone to extinction. Host manipulation, however, can also reduce predation due to conflicting interests when multiple parasites infect a host, often neglected in theoretical studies. Misaligned interests of coinfecting parasites can occur due to limited carrying capacity or parasitoid developmental stage. Including this realistic complexity in a mathematical model, the results depart from previous studies substantially. We show that coinfecting multi-trophic parasites can preserve the predator-prey system and themselves through a combination of manipulation and reproduction parameters. Our study highlights the necessity and provides the means of incorporating the reality of multiple parasites and their multi-trophic life cycles in the theory of parasite ecology.

Introduction

Parasites infect life on earth ubiquitously, and many of these parasites have complex life cycles (Zimmer, 2001). While a complex lifecycle can be defined as abrupt ontogenic changes in morphology and ecology (Benesh, 2016), a complex parasitic lifecycle typically involves numerous hosts that a parasite needs to traverse to complete its life cycle. This complex lifecycle results in the evolution of various strategies that enable the success of parasite transmission from one host to another. One famous strategy that inspires many science fiction movies and novels is host manipulation, where a parasite can alter the morphology and/or behaviour of its host to enhance its transmission to the next host (Hughes et al., 2012). Host manipulation has been shown in many host-parasite systems, from parasites with simple life-cycle to those with complex life-cycle that involves more than one host (Hughes et al., 2012; Molyneux and Jefferies, 1986). For instance, sand flies infected by *Leishmania* parasites bite more and take more time for a blood meal from mammals (the definitive host of *Leishmania*) compared to their uninfected counterparts (Rogers and Bates, 2007). Copepods infected by cestode parasites are more active and accessible to sticklebacks (the definitive hosts of the cestodes) compared to uninfected copepods (Wedekind and Milinski, 1996).

Theoretical studies have long attempted to understand the ecological and evolutionary consequences of host manipulation. Roosien et al. (2013) and Hosack et al. (2008) showed that manipulative parasites could increase the disease prevalence in an epidemic. Gandon (2018) studied the evolution of the manipulative ability of infectious disease parasites, showing different evolutionary outcomes depending on whether the pathogen can control its vector or host. Hadeler and Freedman (1989); Fenton and Rands (2006) and Rogawa et al. (2018) showed that host manipulation could stabilise or destabilise the predator-prey dynamics depending on how manipulation affects the predation response function and the reproduction of the definitive infected host. Seppälä and Jokela (2008) showed that host manipulation could evolve even when it increases the risk of the intermediate host being eaten by a non-host predator, given that the initial predation risk is sufficiently low.

Most studies mentioned above have not explicitly considered a crucial aspect of parasite dynamics – multiple infections (Kalbe et al., 2002) i.e. the presence of multiple individual parasites within a single host. Multiple infections are a norm rather than an exception in parasitism. They result in the coinfection of more than one parasite inside a host, which may alter the manipulative outcomes (figure 1). An alignment of interest between coinfecting parasites may enhance manipulation, while a conflict of interest may reduce the manipulative effect. Indeed, Hafer and Milinski (2015) showed that copepods infected by two cestode parasites reduce the activity of copepods when both parasites are at the same noninfectious stage, i.e. both parasites are not ready to transmit. Thus the reduction in mobility is suggested to reduce the predation rate by the definitive hosts. When two infectious parasites infect the copepods, the copepods' activity increases, and so does the predation risk for the copepod. However, when the copepods are infected by one infectious and one noninfectious parasite, their interests clash, and one parasite wins over the other.

Theoretical work that considers multiple infections often focuses on the evolution of virulence (van Baalen and Sabelis, 1995; Alizon et al., 2013; Alizon and van Baalen, 2008; Choisy and de Roode, 2010; Alizon, 2012), while host manipulation in trophically transmitted parasites receives less attention. Even though host manipulation and virulence both correlates with parasite transmission, there are subtle differences, such that virulence implies an addition to the natural mortality rate of the infected host, while manipulation links to immediate death of the intermediate host due to predation. Host manipulation therefore not only affects the intermediate host population but the entire predator-prey dynamics. Theoretical studies on host manipulation in trophically transmitted parasites rarely consider multiple infections and those that did incorporate this feature neglect the prey-predator dynamics, which will likely have important feedback on the evolution of host manipulation (Parker et al., 2003; Vickery and Poulin, 2009). Moreover, these models assume that transmission from definitive hosts to intermediate hosts is due to direct contact between the two types of hosts (Rogawa et al., 2018; Iritani and Sato, 2018; Hadeler and Freedman, 1989; Fenton and Rands, 2006).

Figure 1: Who is in control?. Schistocephalus eggs, which overwinter at the bottom of bodies of water, hatch into microscopically small swimming larvae. These larvae are eaten by copepods (also known as Cyclops due to its single eye), where they develop to the second larval stage. However, the copepod is only the first intermediate host. The larvae are then eaten by sticklebacks, reaching the third larval stage and growing prominently in size and weight. For the parasite to successfully reach its final host, a warm-blooded animal like a bird, it manipulates its intermediate hosts. The timing is crucial as the chances of success are greatest if the larvae develop in the copepod for 13 to 15 days before entering the stickleback. The presence of multiple parasites in the same host can lead to competition and strategic decision pertaining to investment in manipulation and growth. And indeed a stickleback can be infected by numerous tapeworms as shown above by Martin Kalbe.

This is often not the case in nature, as parasites are released from the definitive hosts into the environment. Transmission thus happens only when intermediate hosts have contact with this free-living parasite pool. The inclusion of this free-living stage could have profound effect on the dynamics of the whole predator-prey-parasite system.

Our study addresses the gap in the theoretical work on host manipulation in trophically transmitted parasites. We include multiple infections and consider the dynamics of the free-living parasite pool. Our compartment model helps illustrate a parasite's complex lifecycle with two host species: an intermediate host preyed upon by a definitive host. Transmission from the intermediate host to the definitive host occurs when predation on infected intermediate hosts happens. Reproduction only happens in the definitive hosts. New parasites then enter the environment, where the cycle continues. We focus on the intermediate host manipulation, such that the parasite increases the uptake of the intermediate host by the definitive host to increase its transmission rate. We then analyse the effect of host manipulation on the ecological dynamics in the prey-predator-parasite system. We found that sabotage in host manipulation almost always pushes the dynamical system toward bistability, provided the reproduction in a single infection is sufficiently small. The bistable nature suggests that the predator-prey parasite system is finely balanced and susceptible to extinction via ecological disturbances. Initially surprising, we showed that cooperation in host manipulation and enhanced reproduction in co-infecting parasites is not always beneficial and might expose the parasite population to the risk of extinction.

Model

Our model concerns the complex lifecycle of a trophically transmitted parasite that requires two hosts: an intermediate host and a definitive host. Reproduction only happens inside the definitive hosts, releasing new parasitic progeny in the environment. An intermediate host can be infected if it encounters this free-living parasite pool. Finally, when a definitive host consumes an infected intermediate host, the definitive host gets infected, and the parasite completes its lifecycle.

For simplicity, we assume that hosts can be infected by one (single infection) or, at most, two parasites (double infections). Thus, while I_s and D_s are the susceptible intermediate and definitive hosts, their singly and doubly infected counterparts are denoted by I_w and D_w and I_{ww} and D_{ww} respectively. Our model is, therefore, more relevant to the macroparasitic system. Given that infection occurs, the probability that two parasites from the parasite pool co-transmit to an intermediate host is denoted by p. Thus $1-p$ is the probability that a single parasite enters an intermediate host. When a definitive host consumes an intermediate host infected by two parasites, there is a probability q that the parasites co-transmit to the definitive host. With probability $1-q$, only one parasite successfully transmits. This formulation assumes that infection always happens when hosts encounter parasites. The dynamics of a complex lifecycle parasite that requires two hosts is described by the following system of equations, firstly for the intermediate host as,

$$\begin{aligned}
\frac{dI_s}{dt} &= R(I_s, I_w, I_{ww}) - dI_s - P_s(D_s, D_w, D_{ww})I_s - \eta I_s \\
\frac{dI_w}{dt} &= (1-p)\eta I_s - (d+\alpha_w)I_w - P_w(D_s, D_w, D_{ww}, \beta_w)I_w \\
\frac{dI_{ww}}{dt} &= p\eta I_s - (d+\alpha_{ww})I_{ww} - P_{ww}(D_s, D_w, D_{ww}, \beta_{ww})I_{ww}
\end{aligned} \tag{1}$$

where $R(I_s, I_w, I_{ww})$ represents the birth rate of the intermediate hosts, a function of both infected and uninfected individuals. $P_s,\ P_w,\ P_{ww}$ are the predation functions of definitive hosts on susceptible, singly infected and doubly infected intermediate hosts. The predation function depends on the density of the definitive hosts and the manipulative strategies of parasites in the intermediate hosts. In particular, if a single parasite infects an intermediate host, the manipulation strategy is β_w. However, if the intermediate host is co-infected, the manipulation strategy is β_{ww}. In the scope of this model, we assume no specific relationship between β_w and β_{ww} to explore all possible ecological outcomes of the system. The force of infection by parasites in the environment, i.e. the rate at which an intermediate host gets infected by free-living parasites, is denoted by $\eta = \gamma W$. Since parasites can manipulate intermediate and definitive hosts, here, whenever we mention host manipulation, it specifically refers to the manipulation in intermediate hosts, which correlates to the predation rate.

For the definitive hosts we have,

$$\begin{aligned}
\frac{dD_s}{dt} &= B(D_s, D_w, D_{ww}, I_s, I_w, I_{ww}) - \mu D_s - (\lambda_{ww} + \lambda_w) D_s \\
\frac{dD_w}{dt} &= (\lambda_w + (1-q)\lambda_{ww}) D_s - (\mu + \sigma_w) D_w - ((1-q)\lambda_{ww} + \lambda_w) D_w \\
\frac{dD_{ww}}{dt} &= q\lambda_{ww} D_s + ((1-q)\lambda_{ww} + \lambda_w) D_w - (\mu + \sigma_{ww}) D_{ww}
\end{aligned} \tag{2}$$

where $B(D_s, D_w, D_{ww}, I_s, I_w, I_{ww})$ represents the birth rate of definitive hosts. The birth rates depend on the density of both intermediate and definitive hosts, infected or uninfected. The force of infection that corresponds respectively to singly infected intermediate host (I_w) and doubly infected intermediate hosts (I_{ww}) is denoted respectively by $\lambda_w = h(\rho + \beta_w)I_w$ and $\lambda_{ww} = h(\rho + \beta_{ww})I_{ww}$, where ρ is the baseline predation rate, i.e. the basic constitutive level of predation, and h is the probability that the parasite successfully establishes inside the host. Without manipulation, that is, $\beta_w = \beta_{ww} = 0$, the parasite is still transmitted via the baseline predation. The dynamics of the free-living parasites in the environment are then given by,

$$\frac{dW}{dt} = f_w D_w + f_{ww} D_{ww} - \delta W - \eta I_s. \tag{3}$$

Definitions of different parameters can be found in Table SI.1.

Here, we focus on manipulation that enhances transmission from intermediate hosts to definitive hosts; we thus simplify the transmission from the parasite pool to intermediate hosts so that no sequential infection occurs. This assumption is motivated given that the prey lifecycle is often shorter than that of the predator. A prey likely encounters the free-living parasite pool once and then dies due to predation, making sequential transmission less likely at this state. Sequential infection can happen when parasites transmit from intermediate hosts to definitive hosts. Therefore, a singly infected definitive host can be further infected by another parasite if it consumes infected intermediate hosts. Figure (2) illustrates the system's dynamics and Table. 1 contains the different parameters and variables used.

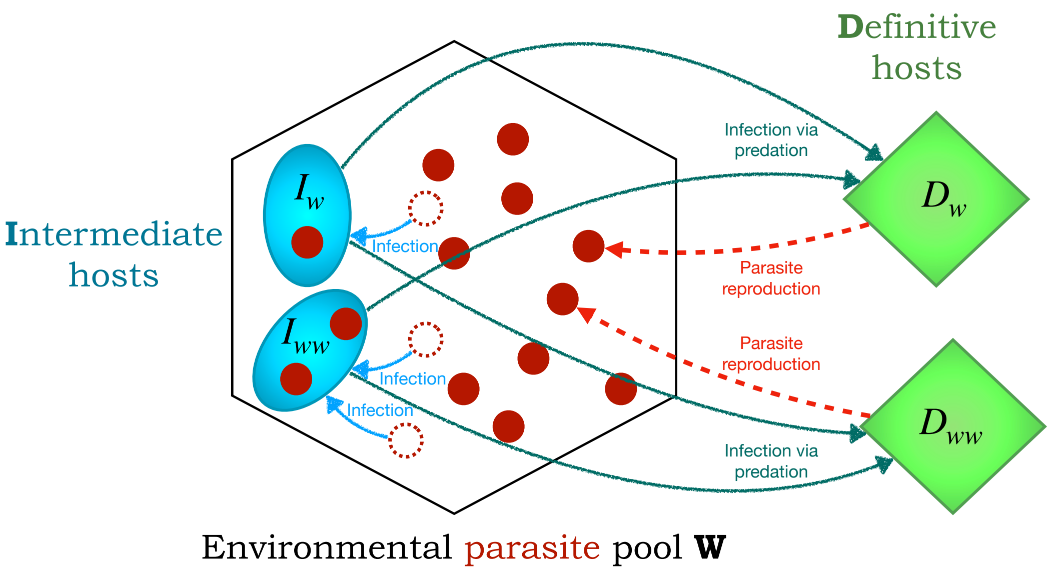

Figure 2: Schematic of the model. Blue ovals represent the intermediate hosts, while the green diamonds represent the definitive hosts. The hexagon represents the parasite pool compartment, with the red circles illustrating the free-living individual parasites. The parasites infect the intermediate hosts singly (I_w, top) or doubly (I_{ww}, bottom). These intermediate hosts are then predated upon by the definitive hosts, thus moving the parasites to the final host (either as D_w or D_{ww}) where they can reproduce and reenter the free-living stage in the environmental pool $\mathbf{W}$.

Results

Basic reproduction ratio R_0 of the parasites

The basic reproduction ratio R_0 (or basic reproduction number as often used in epidemiology) indicates parasite fitness. It can be understood as the expected number of offspring a parasite produces during its lifetime when introduced to a susceptible host population. We calculate the basic reproduction ratio R_0 using the next-generation method (Diekmann et al., 1990,

Table 1: Description of variables and parameters

Parameters and Variables	Description
I_i	Density of intermediate hosts that are susceptible $i = s$, singly infected $i = w$, or doubly infected $i = ww$
D_i	Density of definitive hosts that are susceptible $i = s$, singly infected $i = w$, or doubly infected $i = ww$
W	Density of parasites released from definitive hosts into the environment
d	Natural death rate of intermediate hosts
α_i	Additional death rate of intermediate hosts due to infection by a single parasite ($i = w$) or two parasites ($i = ww$)
p	Probability that two parasites cotransmit from the environment to an intermediate host
γ	Transmission rate of parasites in the environment to intermediate hosts
μ	Natural death rate of definitive hosts
σ_i	Additional death rate of definitive hosts due to infection by a single parasite ($i = w$) or two parasites ($i = ww$)
σ_i	Additional death rate of the hosts due to being infected by a singly parasite ($i = w$) or two parasites ($i = ww$)
q	Probability that two parasites cotransmit from intermediate hosts to definitive hosts
β_i	Transmission rate of parasites from intermediate hosts to definitive hosts
f_i	Reproduction rate of parasites in singly infected definitive hosts ($i = w$) or doubly infected hosts ($i = ww$)
δ	Natural death rate of parasites in the environment
h	Probability that the parasites successfully established inside the definitive host

2009; Hurford et al., 2010) (See SI1 for details).

$$R_0 = \overbrace{\gamma I_s^* \frac{pqh(\rho + \beta_{ww})}{\alpha_{ww} + d + P_{ww}} \frac{D_s^*}{\mu + \sigma_{ww}} \frac{f_{ww}}{\delta + \gamma I_s^*}}^{\texttt{Double infections}} + \\ \underbrace{\gamma I_s^* \left(\frac{(1-p)h(\rho + \beta_w)}{\alpha_w + d + P_w} + \frac{p(1-q)h(\rho + \beta_{ww})}{\alpha_{ww} + d + P_{ww}} \right) \frac{D_s^*}{\mu + \sigma_w} \frac{f_w}{\delta + \gamma I_s^*}}_{\texttt{Single infection}} \tag{4}$$

where I_s^* and D_s^* are the densities of susceptible intermediate and definitive hosts at the disease-free equilibrium. Here, the expression of R_0 contains the possible reproduction routes of a parasite, which can be via double or single infections. The first component corresponds to the double infections route, in which the focal parasite co-transmits with another parasite into a susceptible intermediate host, then co-transmits into a susceptible definitive host and reproduces. Here, parasites are so rare that only co-transmission matters and the compartments with sequential infections are therefore neglected. The second component corresponds to the single infection route, wherein the focal parasite infects a susceptible intermediate host via single or double infections. The parasite then transmits alone into the susceptible definitive host and eventually reproduces.

If $R_0 > 1$, a parasite spreads when introduced into the disease-free equilibrium of prey and predator. Intuitively, the higher the density of susceptible intermediate and definitive hosts, the larger the value of R_0 as the infection reservoir is more extensive. In contrast, regardless of the explicit form of the predation function, the higher the predation rate P_w and P_{ww}, the lower the value of R_0 given the smaller reservoir of intermediate hosts. The effect of host manipulation on the value of R_0 is not so straightforward; as host manipulation becomes efficient, the transmission rate from the intermediate host to the definitive host increases, but so does the predation rate. A higher predation rate results in a smaller intermediate host reservoir available for the parasites to infect. To understand the effect of manipulation on parasites' fitness and the system's ecological dynamics, we next specify the predation functions. We consider linear functions for predation to begin with,

$$P_s(D_s, D_w, D_{ww}) = \rho D_{total}$$

$$P_w(D_s, D_w, D_{ww}, \beta_w) = (\rho + \beta_w) D_{total}$$

$$P_{ww}(D_s, D_w, D_{ww}, \beta_{ww}) = (\rho + \beta_{ww}) D_{total}$$

where $D_{total} = D_s + D_w + D_{ww}$ is the total density of the definitive hosts, and ρ is the baseline capture rate of the predator on the prey. If an intermediate host is infected, it is captured by the definitive hosts with rate $\rho + \beta_w$ if it is singly infected and with rate $\rho + \beta_{ww}$ if it is doubly infected. Zero values for β_w and β_{ww} suggest no manipulation, and predation is at the baseline value ρ.

For simplicity, we also consider a linear function of the birth of definitive hosts

$$B(D_s, D_w, D_{ww}, I_s, I_w, I_{ww}) = \rho c D_{total} I_{total}$$

where c is the efficiency of converting prey into predator's offspring, and $I_{total} = I_s + I_w + I_{ww}$ is the total density of the intermediate hosts. It is important to note that host manipulation affects the population dynamics via its influence on predation rate but not the physiological aspect of the definitive host, i.e. the predator. The birth rate of the predators thus depends on the capture rate, but it is not affected by host manipulation; as to our best knowledge, there is no supporting evidence to consider otherwise.

The explicit form of I_s^* and D_s^*, capturing the predator-prey dynamics, depends on the precise form of all birth and predation functions B, R, P_s, P_w and P_{ww}. But, it does not depend on the manipulation ability or any other parameter of the parasite. Given that the birth rate of the predator and the predation rate are linear functions in prey and predator density, the form of the birth rate R of the prey has a significant effect on the susceptible intermediate and definitive host dynamics.

Birth function of intermediate hosts

The simplest form of the prey's birth rate is a linear function, in which case the disease free equilibrium is always unstable. In particular, it has a cyclic behaviour because, at this equilibrium, the jacobian matrix of the system (1, 2, 3) always has two pure imaginary eigenvalues (see SI2). This follows from the Lotka-Volterra system using linear functions for prey birth and predation (Lotka, 1920). Since the disease-free dynamics is cyclic, it is difficult to analyse the spread of a parasite using the basic reproduction ratio, which is evaluated when the disease-free state is stable. Here, $R_0 > 1$ happens when γ, the transmission rate from the environment to intermediate hosts, and the reproduction rates f_w, f_{ww} are quite large (as compared to the theoretical threshold shown by the mathematical conditions in SI3). However, even when this condition is satisfied, the parasite may not be able to spread and persist in cyclic susceptible host dynamics (Figure SI1). This result agrees with the conclusion in (Ripa and Dieckmann, 2013), which suggests that it is difficult for a mutant to invade a cyclic resident population. In our case, it is not the invasion of a mutant in a resident population but the invasion of a parasite in a cyclic disease-free host population; the argument, however, remains valid in both cases. This issue deserves a more thorough investigation, which is out of the scope of this article. Here, we choose a non-linear birth function of the intermediate hosts to obtain a stable disease circulation state and focus on the effect of host manipulation on the ecological dynamics (Figure 3).

The logistic growth for the non-linear birth function follows by

$$R(I_w, I_s, I_{ww}) = rI_{total}(1 - kI_{total})$$

where k is the intraspecific competition coefficient. The disease-free equilibrium is as follows

$$I_s^* = \frac{\mu}{c\rho} \; ; \; D_s^* = \frac{c\rho(r-d) - k\mu r}{c\rho^2}$$

This equilibrium is positive and stable if components of the parasite, such as reproduction and transmission are sufficiently small, details of the condition can be found in section SI 4. Here, because reproduction and transmission value of the parasite is not sufficient, it goes extinct (Figure 3A), leaving the predator-prey dynamics attaining equilibrium (Figure 3B)

When a parasite appears in the disease-free equilibrium, it spreads if its reproduction ratio $R_0 > 1$ (Figure 3C, D). Since the expression is complicated, we could not obtain analytical solutions for this inequality without assumptions. We assume the same parasite virulence,

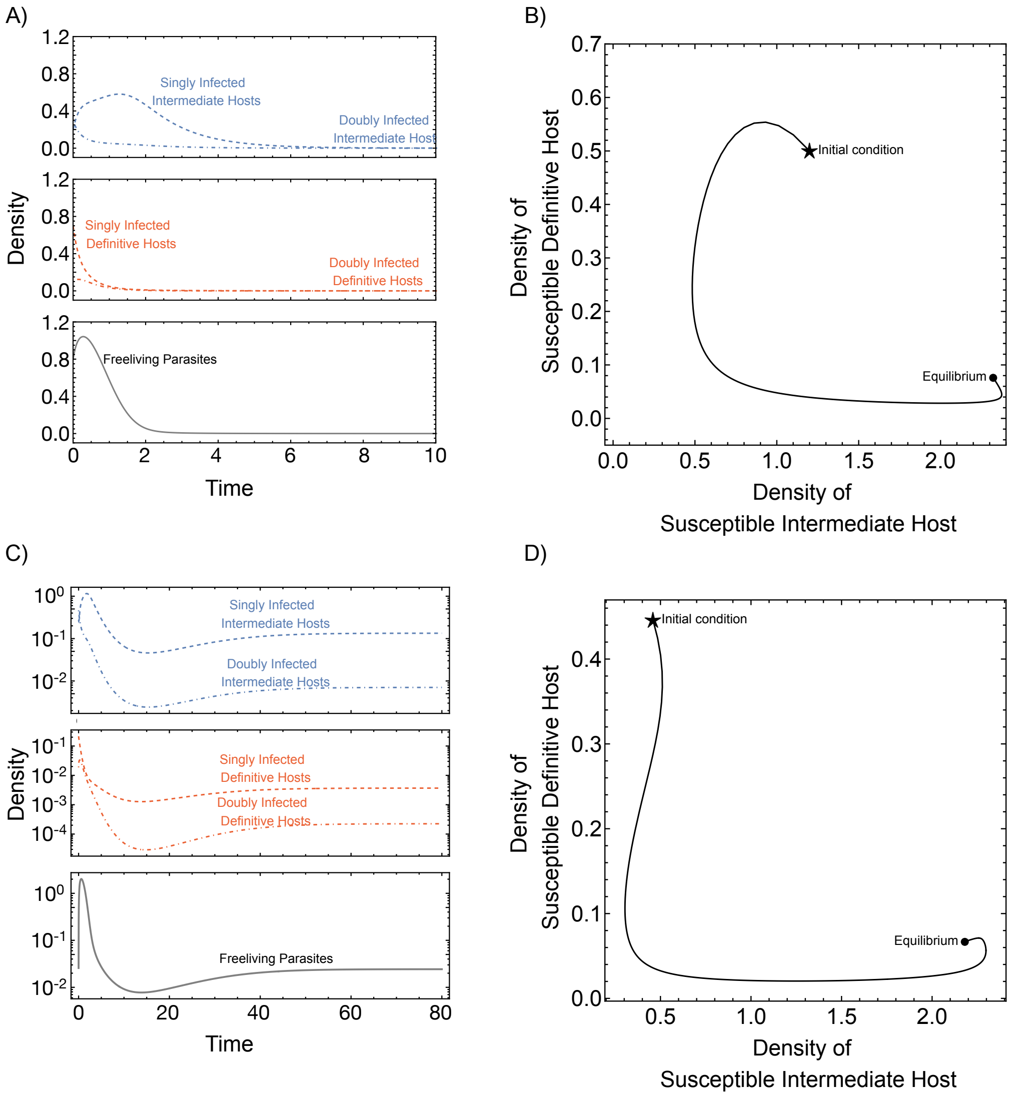

Figure 3: Ecological dynamics of the predator-prey-parasite system. A) Ecological trajectories of infected hosts and free-living parasite when parasites cannot persist, B) Phase plane of susceptible intermediate and definitive hosts under disease free scenario. C) Ecological trajectories of infected hosts and free-living parasite when parasites persist. D) Phase plane of susceptible and definitive host under disease circulating scenario. Parameters for disease free equilibrium $\rho = 1.2,\ d = 0.9,\ r = 2.5,\ \gamma = 2.9, \alpha_w = \alpha_{ww} = 0,\ \beta_w = \beta_{ww} = 1.5,\ p = 0.05,\ c = 1.4,\ \mu = 3.9,\ \sigma_w = \sigma_{ww} = 0,\ q = 0.05,\ f_w = f_{ww} = 7.5,\ \delta = 0.9,\ k = 0.26,\ h = 0.6$. Disease stable equilibrium have the same parameter values except for higher host manipulation $\beta_w = \beta_{ww} = 4.5$ and parasite reproduction $f_w = f_{ww} = 45$

$\alpha_w = \alpha_{ww}$, $\sigma_w = \sigma_{ww}$, and reproduction in double infection as a linear function concerning reproduction in single infections, $f_{ww} = \epsilon f_w$. When $\epsilon > 1$, reproduction in double infections is enhanced compared to in single infections, whereas $\epsilon \leq 1$, reproduction in double infections is suppressed or equal to reproduction in single infections. We found that the parasite can establish if its reproduction value in a single infection f_w is more significant than a threshold (Figure 4, see section SI 5 and Eq. (SI.19)).

Our numerical results show that the parasite reproduction is substantial compared to other parameters (Figure 4A). For instance, in the parameter set used to produce Figure (4B, in order to spread in the prey-predator system, the value of parasite reproduction (f_w) has to be at least 20 times the value of intermediate host reproduction $r = 2.5$, given that both these parameters represent the per capita growth rate of the parasite and the intermediate host population. This observation suggests that trophically transmitted parasites must release a large amount of offspring into the environment to persist. Interestingly, bistability occurs if the reproduction rate of the parasite in double infections is enhanced (Figure 4A). In the bistable region, the parasite population can reach a stable equilibrium if the initial density is large enough. In contrast, with sufficient disturbance, the parasite population could go extinct.

The effect of host manipulation on ecological dynamics

Host manipulation can be cooperative; two parasites increase the predation rate on intermediate hosts, or $\beta_{ww} > \beta_w$. However, it can also be uncooperative; the predation rate on doubly-infected intermediate hosts is lower than that on singly-infected ones or $\beta_{ww} < \beta_w$. Cooperation in parasite manipulation increases the parasite's basic reproduction ratio R_0, but the manipulation in a single infection substantially affects the value of R_0 (Figure 5 Left). Intuitively, if the manipulation in a single infection is minor, there is not enough transmission, and the parasite goes extinct. However, suppose the ability to manipulate the host in a single infection is merely enough for the parasite population to escape extinction.

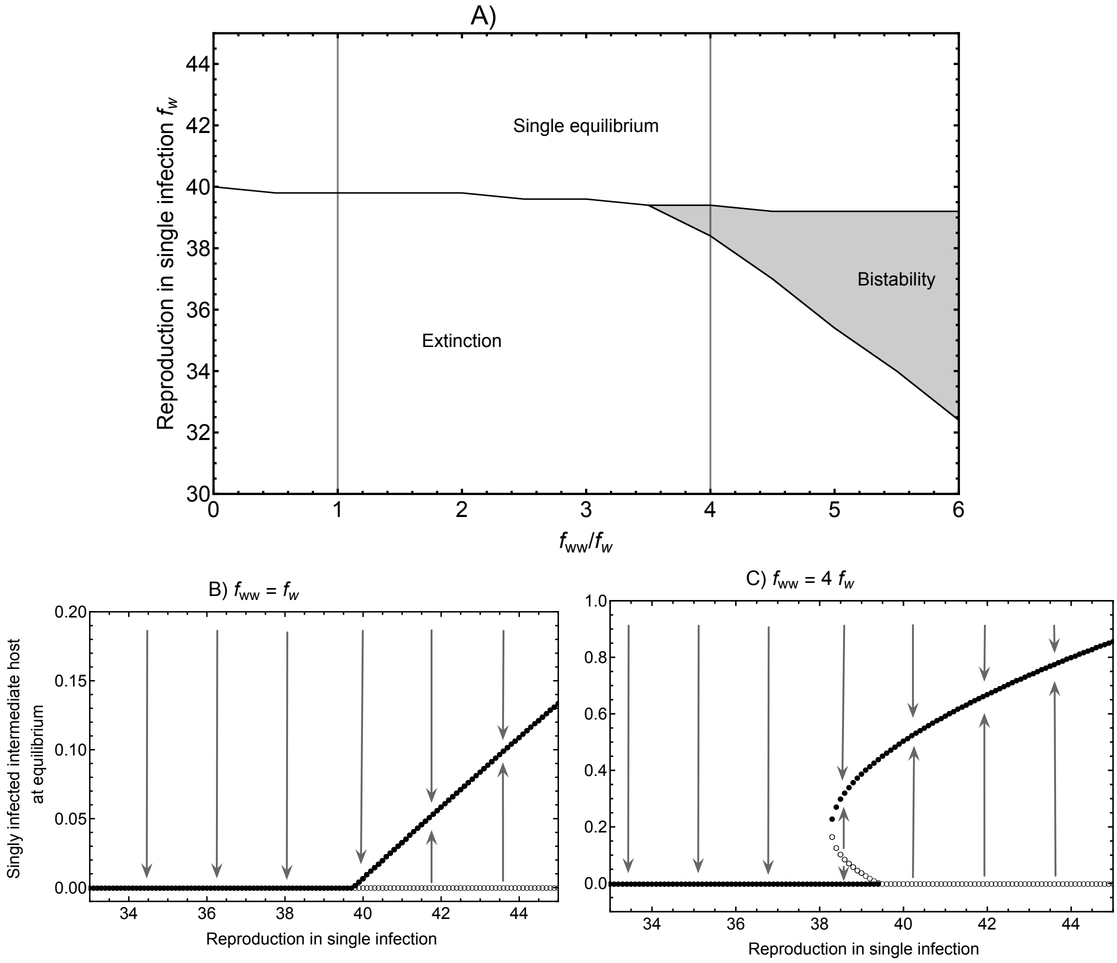

Figure 4: Effect of parasite reproduction on the ecological dynamics. A) Enhanced reproduction in double infection leads to bistability, B, C) Density of singly infected host at equilibrium when reproduction of parasites are the same in singly and doubly infected hosts $f_{ww} = f_w$, and when reproduction of parasites in doubly infected hosts is enhanced four times than those in singly infected hosts $f_{ww} = 4f_w$. Filled circles indicate stable equilibrium and open circles indicate unstable equilibrium. Parameter $\rho = 1.2,\ d = 0.9,\ r = 2.5,\ \gamma = 2.9,\ \alpha_w = 0,\ \alpha_{ww} = 0,\ \beta_w = 1.5,\ \beta_{ww} = 1.5,\ p = 0.05,\ c = 1.4,\ \mu = 3.9,\ \sigma_w = 0,\ \sigma_{ww} = 0,\ q = 0.05,\ \delta = 0.9,\ k = 0.26,\ h = 0.6.$

In that case, cooperation in host manipulation leads to a bistable system state. Within the bistable region, the basic reproduction ratio can be less than one, suggesting that the parasite cannot spread when its manipulative values are within this area of weak manipulation when coinfected.

Co-infecting parasites can influence each other in different life history traits besides manipulation. Parasites can have an enhanced reproduction rate in coinfections, i.e. $f_{ww} > f_w$. Likewise, they can compete for resources, so reproduction in double infection is suppressed compared to single infection. Without any assumption on the relationship between manipulative ability and reproduction, we explore all possible combinations of cooperation-sabotage range in manipulation and depressed-enhanced range in reproduction. If parasites are uncooperative in manipulations and show suppressed reproduction, they cannot persist (Figure 5). In contrast, if they are highly cooperative in manipulation and show enhanced reproduction (i.e. $\beta_{ww}/\beta_w \to \infty$ and $f_{ww}/f_w \to \infty$), there is a guaranteed single equilibrium for parasite existence.

Need to think of this paragraph For intermediate levels of coordination in reproduction and manipulation, a bistable area could occur. However, the size of this area is sensitive to the value of reproduction and manipulation in a single infection. In particular, higher values of these two parameters reduce the bistability area, whereas larger values increase the bistability area (Figure 5, Figure SI.1). If the parasites sabotage each other, the system is highly prone to bistability and only has a single equilibrium when reproduction is especially enhanced. Interestingly, sufficiently high reproduction enhancement leads to bistability (i.e. f_{ww} is at least four times f_w), and depressed reproduction always leads to a single equilibrium of the system (Figure 5). While a single equilibrium guarantees the existence of a parasite population, bistability indicates that a disturbance of the system may likely lead to the extinction of the parasite population. This suggests that the benefits of coordination in reproduction and manipulation are context-dependent. Coordinating is advantageous if there are no significant tradeoffs and reproduction or manipulation in single infections are large enough.

Co-transmission probability from the parasite pool to intermediate hosts p has the opposite effect on the bistable area compared to co-transmission probability q from intermediate hosts to intermediate hosts (Figure 6). In particular, when the parasite sabotages the manipula-

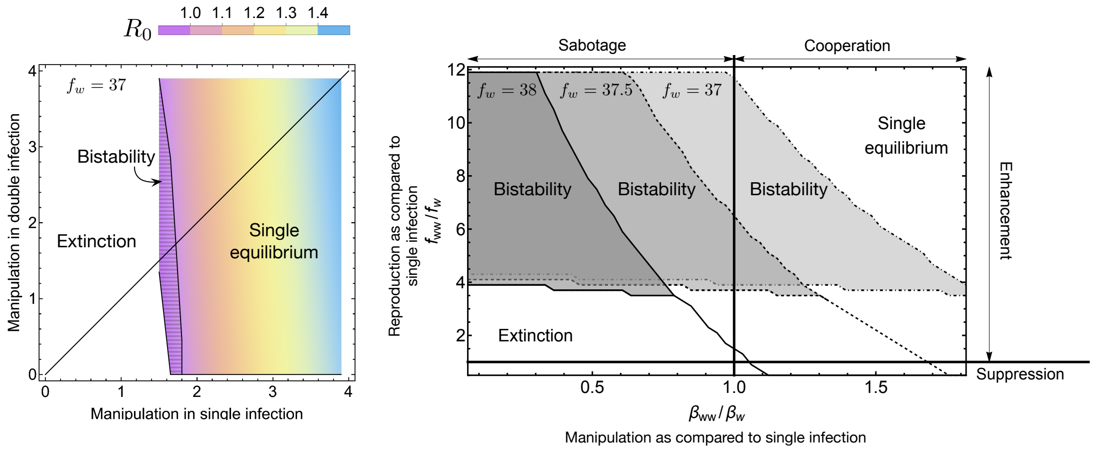

Figure 5: title Left: R_0 values increase with more efficient manipulation in both single and double infection. The hatched area indicates the bistable region. As manipulation in single infection increases, the system only has one stable equilibrium. On the black line, the manipulation level is equal between single and double infection ($\beta_w = \beta_{ww}$). Right: Changes of the bistability area shaded areas) concerning different reproduction rates in single infection (different boundary styles). Manipulation and reproduction levels are equal between single and double infection on the vertical and horizontal lines. Common parameter: $\rho = 1.2,\ d = 0.9,\ r = 2.5,\ \gamma = 2.9,\ \alpha_w = 0,\ \alpha_{ww} = 0,\ p = 0.05,\ c = 1.4,\ \mu = 3.9,\ \sigma_w = 0,\ \sigma_{ww} = 0,\ q = 0.05,\ \delta = 0.9,\ k = 0.26,\ \beta_w = 1.65, h = 0.6$.

tion, increasing p enlarges the bistable area, whereas increasing q reduces it. In contrast, when parasites cooperate in manipulation, reducing p decreases the bistable area while reducing q widens it. If cooperation in manipulation is exceptionally high, the population will always exist with one stable equilibrium regardless of the co-transmission value. However, as there are always limitations and trade-offs, high values may not be possible. Bistability indicates vulnerability to disturbance, suggesting that cooperation in manipulation may be beneficial when the co-transmission from the pool to the intermediate host increases. However, cooperation in manipulation may harm the population when the co-transmission from the intermediate host to the definitive host increases.

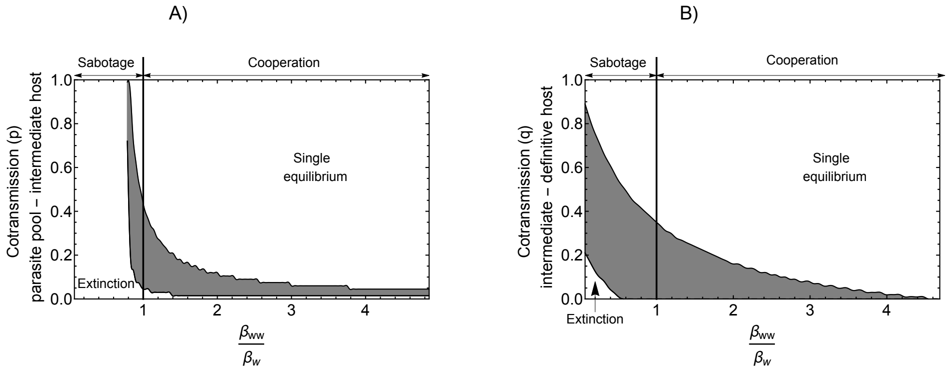

Figure 6: Left: Effect of cotransmission from parasite pool to intermediate host. Right: Effect of cotransmission from intermediate to definitive host. Common parameters: $\rho = 1.2,\ d = 0.9,\ r = 2.5,\ \gamma = 2.9,\ \alpha_w = 0,\ \alpha_{ww} = 0,\ p = 0.05,\ c = 1.4,\ \mu = 3.9,\ \sigma_w = 0,\ \sigma_{ww} = 0,\ q = 0.05,\ \delta = 0.9,\ k = 0.26,\ \epsilon = 4.5,\ \beta_w = 1.45,\ f_w = 38,\ h = 0.6$.

Discussion & Conclusion

Host manipulation is a ubiquitous phenomenon suggested to affect the prey-predator dynamics in trophically transmitted parasites. In particular, manipulation of infected intermediate hosts to increase the predation rate of definitive hosts may result in a heavy burden of predators on the intermediate host population. This pressure can make parasites more vulnerable to extinction (Hadeler and Freedman, 1989; Fenton and Rands, 2006).

Our model shows that parasites cannot spread quickly in a cyclic predator-prey system. This delay is an expected result since even though the parasite's basic reproduction ratio R_0 is larger than one, it is estimated at the predator and prey's unstable equilibrium (or cyclic equilibrium). Thus, when the density of the prey and predator is at the minimum value of the cycle, the "effective" R_0 of the parasite can be smaller than one. Another interesting result is that the reproduction value is much larger than other parameter values. This result is likely due to the introduction of a free-living parasitic pool. Our model shows that in making the system more realistic, we also obtain a more realistic quantitative value for parasitic reproduction.

In the study by Rogawa et al. (2018), a non-manipulative parasite can invade a susceptible prey-predator population and cause the system to cycle. The system stops cycling and approaches a fixed point when the parasite becomes manipulative, and this stability increases with increased manipulation. In our model, non-manipulative parasites cannot persist in the system, and the parasite never leads to cyclic dynamics. These results may contradict with Rogawa et al. (2018), where non-manipulative parasites can still exists via cyclic behaviour. We suggest that the different results may be due to our introduction of a parasite pool and multiple infections, unlike the model of Rogawa et al. (2018). In their system, transmission from the definitive host to the intermediate host was assumed to result from direct contact between the two hosts. Such immediate transmission could directly accelerate the feedback loop between prey and predator. Hence, faster predator-prey dynamics occur, which may lead to cyclic dynamics when parasites are introduced.

In our study, population dynamics exhibit bistability under certain circumstances. This is very likely due to the introduction of co-transmission, which has been shown to result in bistable population dynamics in plant virus Allen et al. (2019) and infectious diseases Gao et al. (2016). In this bistability region, if the system is disturbed (e.g. migration of the intermediate or definitive hosts or predation of intermediate hosts by other predators), then the density of the infected hosts may crash, leading to parasite extinction. The bistability region widens as parasites show enhanced reproduction but sabotage manipulation. This extension is because the density of the doubly infected hosts is always much smaller than the singly infected hosts, limited by sequential transmission and a small probability of co-transmission. If manipulation in a single infection is not sufficient then the transmission of the parasites depends mainly on the doubly infected hosts, which is rare. So, extinction is possible if manipulation in double infections is low.

Iritani and Sato (2018) show that manipulative parasites persist if they can alternate manipulation between boosting and suppressing predation rate. In our model, the parasite cannot switch its manipulative strategy. Sabotaging manipulation reduces the basic reproduction ration R_0 and makes the system bistable, exposing the parasite to the risk of extinction. This result contrasts with Iritani and Sato (2018) because in our model, sabotage decreases transmissmion rate from intermediate to definitive host, and does not benefit the parasite.

Finally, our study focuses on the ecological dynamics of a trophically transmitted parasite between two host species. In nature, parasites with complex life-cycles can have more than two hosts. However, our model consisting of a single intermediate host species can already provide enough complexity to discuss the relationship between transmission and manipulation. However, investigating the evolution of host manipulation is a natural extension beyond the scope of a single manuscript, given the complexities that arise in the ecological dynamics itself. Studying the evolution of host manipulation, considering the free-living parasite pool, calls for thorough analyses, which could be a standalone study. For example, we would need to include differences between the traits of the multiple parasites and hence the ecological model becomes more complex than presented in this study. The combinatorics and orderings of sequential infections wil lthen become important. In addition, the occurrence of bistability in our model suggests that the evolution of host manipulation may drive the parasite to extinction simply because of the rarity of the mutant and the Allee effect as per Adaptive dynamics approaches. The coinfecting parasites can increase manipulation and enhance reproduction freely if there exist no tradeoffs. Nevertheless, our model shows that the benefits of this strategy are context-dependent, making it suboptimal in certain cases. Evolutionary dynamics would therefore depend on the tradeoff between host manipulation and other traits of the parasites, such as reproduction, virulence, and survivorship in the parasite pool, to list a few. This extension deserves thorough analysis, and we will treat it as a separate matter.

References

Alizon, S., 2012. Parasite co-transmission and the evolutionary epidemiology of virulence. Evolution 67:921–933. URL https://doi.org/10.1111/j.1558-5646.2012.01827.x.

Alizon, S. and M. van Baalen, 2008. Multiple infections, immune dynamics, and the evolution of virulence. The American Naturalist 172:E150–E168. URL https://doi.org/10.1086/590958.

Alizon, S., J. C. de Roode, and Y. Michalakis, 2013. Multiple infections and the evolution of virulence. Ecology Letters 16:556–567. URL https://doi.org/10.1111/ele.12076.

Allen, L. J. S., V. A. Bokil, N. J. Cunniffe, F. M. Hamelin, F. M. Hilker, and M. J. Jeger, 2019. Modelling Vector Transmission and Epidemiology of Co-Infecting Plant Viruses. Viruses 11:1153. URL https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6950130/.

van Baalen, M. and M. W. Sabelis, 1995. The dynamics of multiple infection and the evolution of virulence. The American Naturalist 146:881–910. URL https://doi.org/10.1086/285830.

Benesh, D. P., 2016. Autonomy and integration in complex parasite life cycles. Parasitology 143:1824 – 1846.

Choisy, M. and J. C. de Roode, 2010. Mixed infections and the evolution of virulence: Effects of resource competition, parasite plasticity, and impaired host immunity. The American Naturalist 175:E105–E118. URL https://doi.org/10.1086/651587.

Diekmann, O., J. Heesterbeek, and J. Metz, 1990. On the definition and the computation of the basic reproduction ratio r 0 in models for infectious diseases in heterogeneous populations. Journal of Mathematical Biology 28. URL https://doi.org/10.1007/bf00178324.

Diekmann, O., J. A. P. Heesterbeek, and M. G. Roberts, 2009. The construction of next-generation matrices for compartmental epidemic models. Journal of The Royal Society Interface 7:873–885. URL https://doi.org/10.1098/rsif.2009.0386.

Fenton, A. and S. A. Rands, 2006. The impact of parasite manipulation and predator foraging behavior on predator - prey communitites. Ecology 87:2832–2841. URL https://doi.org/10.1890/0012-9658(2006)87[2832:tiopma]2.0.co;2.

Gandon, S., 2018. Evolution and manipulation of vector host choice. The American Naturalist 192:23–34. URL https://doi.org/10.1086/697575.

Gao, D., T. C. Porco, and S. Ruan, 2016. Coinfection dynamics of two diseases in a single host population. Journal of Mathematical Analysis and Applications 442:171–188. URL https://www.sciencedirect.com/science/article/pii/S0022247X16300841.

Hadeler, K. P. and H. I. Freedman, 1989. Predator-prey populations with parasitic infection. Journal of Mathematical Biology 27:609–631. URL https://doi.org/10.1007/bf00276947.

Hafer, N. and M. Milinski, 2015. When parasites disagree: evidence for parasite-induced sabotage of host manipulation. Evolution 69:611 – 620.

Hosack, G. R., P. A. Rossignol, and P. van den Driessche, 2008. The control of vector-borne disease epidemics. Journal of Theoretical Biology 255:16–25. URL https://doi.org/10.1016/j.jtbi.2008.07.033.

Hughes, D. P., J. Brodeur, and F. Thomas, 2012. Host Manipulation by Parasites. Oxford University Press, London, England.

Hurford, A., D. Cownden, and T. Day, 2010. Next-generation tools for evolutionary invasion analyses. Journal of The Royal Society Interface 7:561–571.

Iritani, R. and T. Sato, 2018. Host-manipulation by trophically transmitted parasites: The switcher-paradigm. Trends in Parasitology 34:934–944. URL https://doi.org/10.1016/j.pt.2018.08.005.

Kalbe, M., K. M. Wegner, and T. B. H. Reusch, 2002. Dispersion patterns of parasites in

0+ year three-spined sticklebacks: a cross population comparison. Journal of Fish Biology 60:1529–1542.

Lotka, A. J., 1920. Analytical note on certain rhythmic relations in organic systems. Proceedings of the National Academy of Sciences 6:410–415. URL https://doi.org/10.1073/pnas.6.7.410.

Molyneux, D. H. and D. Jefferies, 1986. Feeding behaviour of pathogen-infected vectors. Parasitology 92:721–736.

Parker, G. A., J. C. Chubb, G. N. Roberts, M. Michaud, and M. Milinski, 2003. Optimal growth strategies of larval helminths in their intermediate hosts. Journal of Evolutionary Biology 16:47–54. URL https://doi.org/10.1046/j.1420-9101.2003.00504.x.

Ripa, J. and U. Dieckmann, 2013. Mutant invasions and adaptive dynamics in variable environments. Evolution 67:1279–1290. URL https://onlinelibrary.wiley.com/doi/abs/10.1111/evo.12046.

Rogawa, A., S. Ogata, and A. Mougi, 2018. Parasite transmission between trophic levels stabilizes predator–prey interaction. Scientific Reports 8. URL https://doi.org/10.1038/s41598-018-30818-7.

Rogers, M. E. and P. A. Bates, 2007. Leishmania manipulation of sand fly feeding behavior results in enhanced transmission. PLoS Pathogens 3:e91. URL https://doi.org/10.1371/journal.ppat.0030091.

Roosien, B. K., R. Gomulkiewicz, L. L. Ingwell, N. A. Bosque-Pérez, D. Rajabaskar, and S. D. Eigenbrode, 2013. Conditional vector preference aids the spread of plant pathogens: Results from a model. Environmental Entomology 42:1299–1308. URL https://doi.org/10.1603/en13062.

Seppälä, O. and J. Jokela, 2008. Host manipulation as a parasite transmission strategy when manipulation is exploited by non-host predators. Biology Letters 4:663–666. URL https://doi.org/10.1098/rsbl.2008.0335.

Vickery, W. L. and R. Poulin, 2009. The evolution of host manipulation by parasites: a game theory analysis. Evolutionary Ecology 24:773–788. URL https://doi.org/10.1007/s10682-009-9334-0.

Wedekind, C. and M. Milinski, 1996. Do three-spined sticklebacks avoid consuming copepods, the first intermediate host of *Schistocephalus solidus*? - an experimental analysis of behavioural resistance. Parasitology 112:371–383. URL https://doi.org/10.1017/s0031182000066609.

Zimmer, C., 2001. Parasite Rex: Inside the Bizarre World of Nature's Most Dangerous Creatures. Atria Books.