

On multiple infections by parasites with complex life cycles

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

15 Introduction

16 Parasites infect life on earth ubiquitously, and many of these parasites have complex life
17 cycles (Zimmer, 2001). While a complex lifecycle can be defined as abrupt ontogenic changes
18 in morphology and ecology (Benesh, 2016), a complex parasitic lifecycle typically involves
19 numerous hosts that a parasite needs to traverse to complete its life cycle. This complex
20 lifecycle results in the evolution of various strategies that enable the success of parasite
21 transmission from one host to another. One famous strategy that inspires many science
22 fiction movies and novels is host manipulation, where a parasite can alter the morphology
23 and/or behaviour of its host to enhance its transmission to the next host (Hughes et al.,
24 2012). Host manipulation has been shown in many host-parasite systems, from parasites with
25 simple life-cycle to those with complex life-cycle that involves more than one host (Hughes
26 et al., 2012; Molyneux and Jefferies, 1986). For instance, sand flies infected by *Leishmania*
27 parasites bite more and take more time for a blood meal from mammals (the definitive host of
28 *Leishmania*) compared to their uninfected counterparts (Rogers and Bates, 2007). Copepods
29 infected by cestode parasites are more active and accessible to sticklebacks (the definitive
30 hosts of the cestodes) compared to uninfected copepods (Wedekind and Milinski, 1996).

31 Theoretical studies have long attempted to understand the ecological and evolutionary
32 consequences of host manipulation. Roosien et al. (2013) and Hosack et al. (2008) showed
33 that manipulative parasites could increase the disease prevalence in an epidemic. Gandon
34 (2018) studied the evolution of the manipulative ability of infectious disease parasites, show-
35 ing different evolutionary outcomes depending on whether the pathogen can control its vector
36 or host. Haderler and Freedman (1989); Fenton and Rands (2006) and Rogawa et al. (2018)
37 showed that host manipulation could stabilise or destabilise the predator-prey dynamics de-
38 pending on how manipulation affects the predation response function and the assumption
39 on the fertility of the definitive infected host. Seppälä and Jokela (2008) showed that host
40 manipulation could evolve even when it increases the risk of the intermediate host being
41 eaten by a non-host predator, given that the initial predation risk is sufficiently low. These

models, however, lack a crucial aspect of parasite dynamics, multiple infections (Kalbe et al., 2002)

Typical studies do not consider multiple infections, a phenomenon that is the norm rather than an exception in parasitism. Multiple infections 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; Haderler and Freedman, 1989; Fenton and Rands, 2006).



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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, where they reach the third larval stage and grow significantly 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.

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

73 Our study addresses the gap in the theoretical work on host manipulation in trophically
 74 transmitted parasites. We include multiple infections and consider the dynamics of the free-
 75 living parasite pool. Our compartment model helps illustrate a parasite's complex lifecycle
 76 with two hosts: 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. In contrast to the abovementioned examples, our model consists of a single intermediate host as it already provides enough complexity to discuss between transmission and manipulation. 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). 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

103 host infected by two parasites, there is a probability q that the parasites co-transmit to the
 104 definitive host. With probability $1 - q$, only one parasite successfully transmits. This formu-
 105 lation assumes that infection always happens when hosts encounter parasites. The dynamics
 106 of a complex lifecycle parasite that requires two hosts is described by the following system
 107 of equations, firstly for the intermediate host as,

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

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

120 For the definitive hosts we have,

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

121 where $B(D_s, D_w, D_{ww}, I_s, I_w, I_{ww})$ represents the birth rate of definitive hosts. The birth
122 rates depend on the density of both intermediate and definitive hosts, infected or uninfected.
123 The force of infection that corresponds respectively to singly infected intermediate host (I_w)
124 and doubly infected intermediate hosts (I_{ww}) is denoted respectively by $\lambda_w = h(\rho + \beta_w)I_w$
125 and $\lambda_{ww} = h(\rho + \beta_{ww})I_{ww}$, where ρ is the baseline predation rate and h is the probability
126 that the parasite successfully establishes inside the host. If there is no manipulation, that is,
127 $\beta_w = \beta_{ww} = 0$, the parasite is still transmitted via the based line predation. The dynamics
128 of the free-living parasites in the environment are then given by,

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

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

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

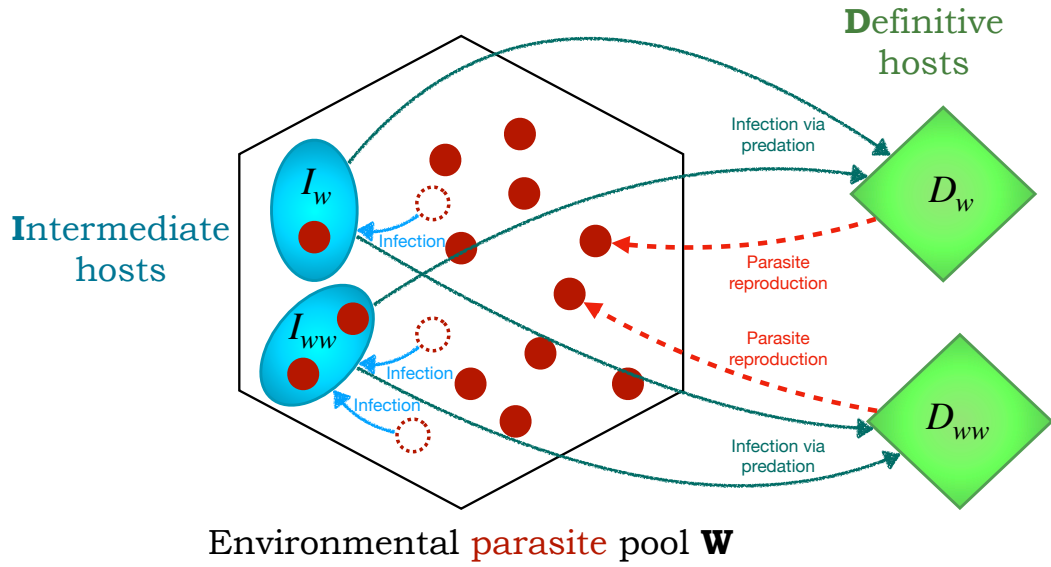


Figure 2: Schematic of the model. Blue ovals represent the intermediate hosts, while the green diamonds represent the definitive hosts. The hexagon represents the parasite pool compartment, with the red circles illustrating the free-living individual parasites. The parasites infect the intermediate hosts 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,

145 2009; Hurford et al., 2010) (See SI1 for details).

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

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

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

166 functions. We consider linear functions for predation to begin with,

$$\begin{aligned} P_s(D_s, D_w, D_{ww}) &= \rho D_{total} \\ P_w(D_s, D_w, D_{ww}, \beta_w) &= (\rho + \beta_w) D_{total} \\ P_{ww}(D_s, D_w, D_{ww}, \beta_{ww}) &= (\rho + \beta_{ww}) D_{total} \end{aligned}$$

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

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

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

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

179 The explicit form of I_s^* and D_s^* , capturing the predator-prey dynamics, depends on the
 180 precise form of all birth and predation functions B, R, P_s, P_w and P_{ww} . But, it does not
 181 depend on the manipulation ability or any other parameter of the parasite. Given that the
 182 birth rate of the predator and the predation rate are linear functions in prey and predator
 183 density, the form of the birth rate R of the prey has a significant effect on the susceptible
 184 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 significantly large (the specific mathematical conditions can be found 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.

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

207 and transmission are sufficiently small, details of the condition can be found in section SI 4.
208 (Figure 3B).

209 When a parasite appears in the disease-free equilibrium, it spreads if its reproduction ratio
210 $R_0 > 1$. Since the expression is complicated, we could not obtain analytical solutions for
211 this inequality without assumptions. We assume the same parasite virulence, $\alpha_w = \alpha_{ww}$,
212 $\sigma_w = \sigma_{ww}$, and reproduction in double infection as a linear function concerning reproduction
213 in single infections, $f_{ww} = \epsilon f_w$. When $\epsilon > 1$, reproduction in double infections is enhanced
214 as compared to in single infections, whereas $\epsilon \leq 1$, reproduction in double infections is
215 depressed or equal to reproduction in single infections. We found that the parasite can
216 establish if its reproduction value in a single infection f_w is more significant than a threshold
217 (Figure 4, see section SI 5 and Eq. (SI.19)).

218 Our numerical results show that the parasite reproduction is substantial compared to other
219 parameters (its value is nearly 40 times greater than other parameters). This observation
220 suggests that trophically transmitted parasites must release many offspring into the environ-
221 ment to persist. Interestingly, bistability occurs if the reproduction rate of the parasite in
222 double infections is enhanced (Figure 4A). In the bistable region, the parasite population can
223 reach a stable equilibrium if the initial density is large enough. In contrast, with sufficient
224 disturbance, the parasite population could go extinct.

225 The effect of host manipulation on ecological dynamics

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

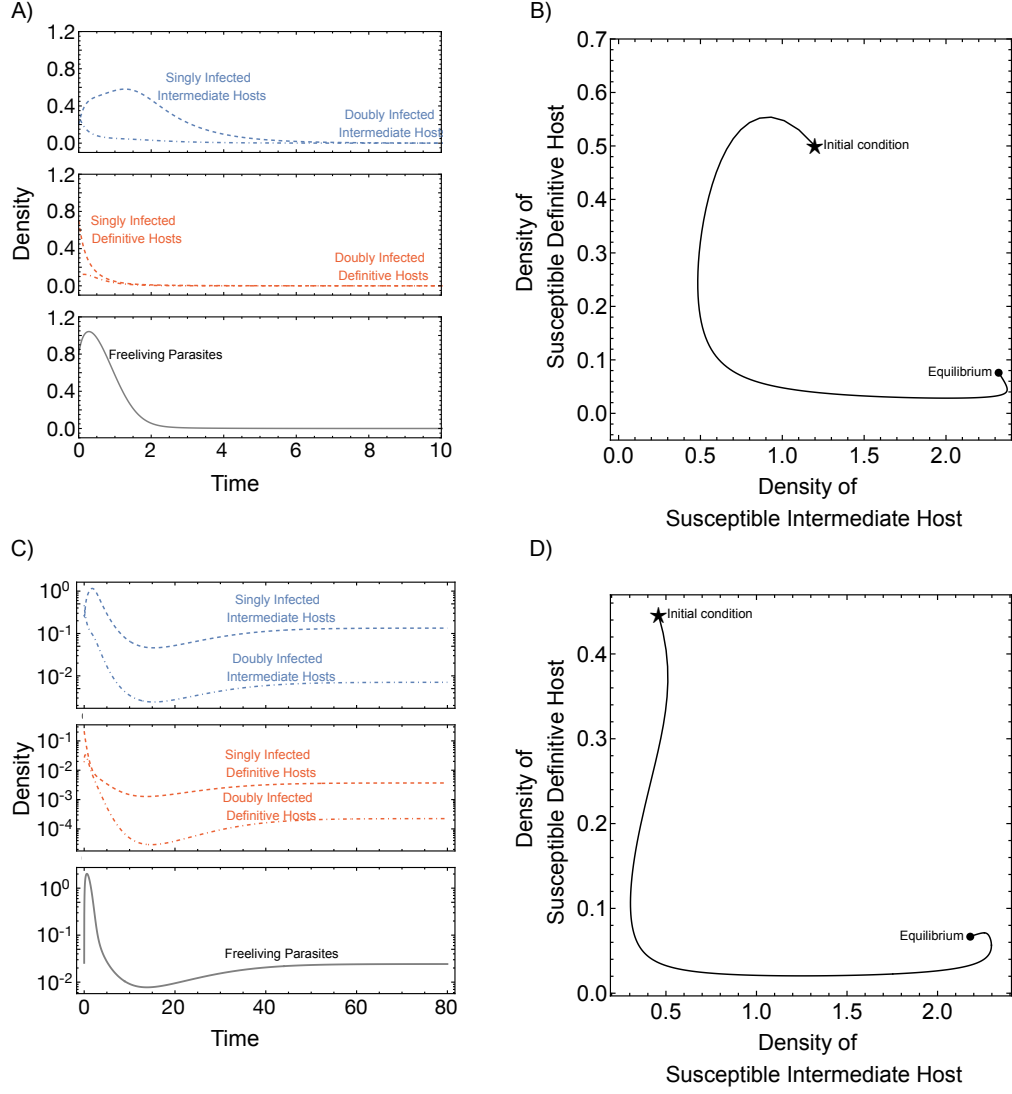


Figure 3: A, B) mention A and B separately and same for C and D Disease-free equilibrium where the parasite cannot persist. C, D) Disease stable equilibrium. Solid gray line indicate the density of free-living parasites, blue lines indicate infected intermediate hosts while red lines indicate infected definitive hosts. Dashed lines indicate singly infected hosts while dot-dashed lines indicate doubly infected hosts. 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 $f_w = f_{ww} = 45$

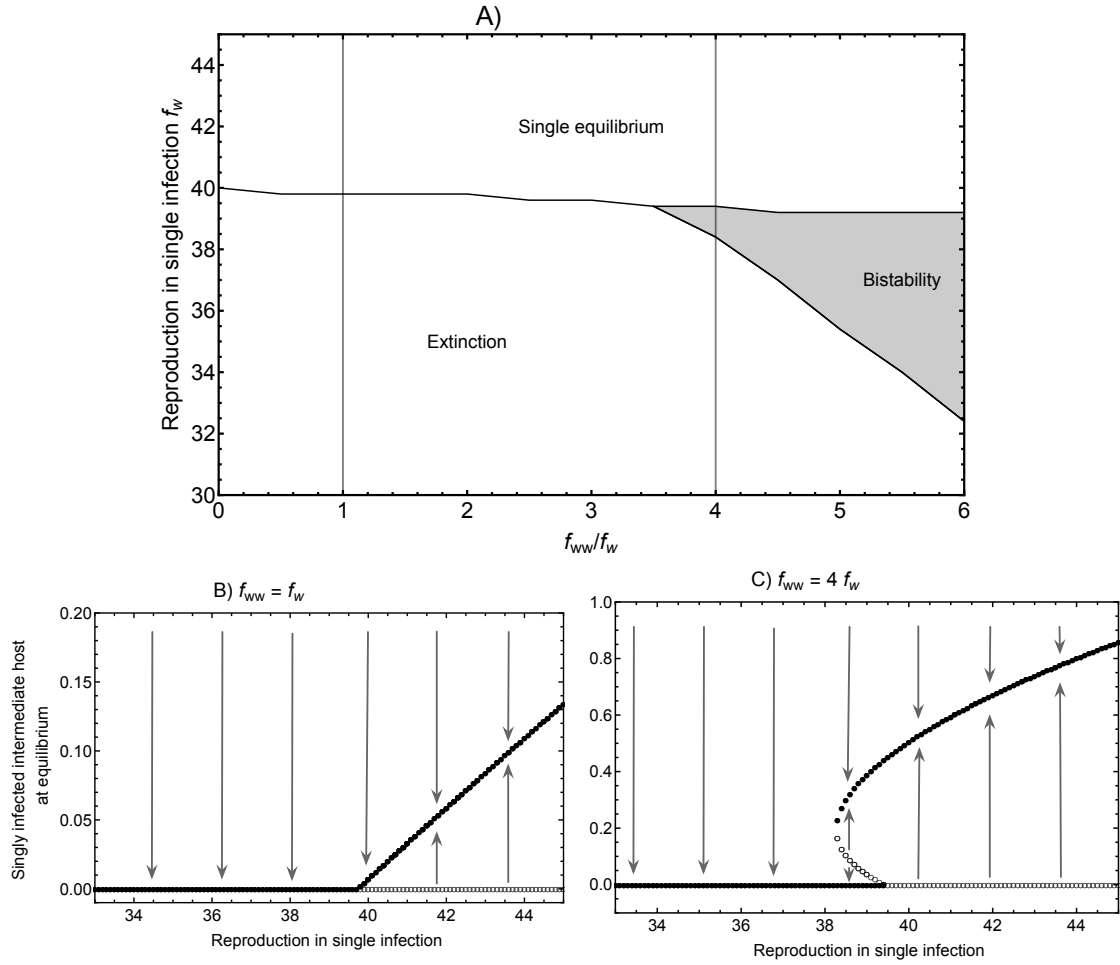


Figure 4: Effect of parasite reproduction on the ecological dynamics. A) Enhanced reproduction in double infection leads to bistability, B, C) Density of singly infected host at equilibrium when reproduction of parasites are the same in singly and doubly infected hosts $f_{ww} = f_w$, and when reproduction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

233 host in a single infection is merely enough for the parasite population to escape extinction.
 234 In that case, cooperation in host manipulation leads to a bistable system state. Within the
 235 bistable region, the basic reproduction ratio can be less than one, suggesting that the parasite
 236 cannot spread when its manipulative values are within this area of weak manipulation when

237 coinfecting.

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

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

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

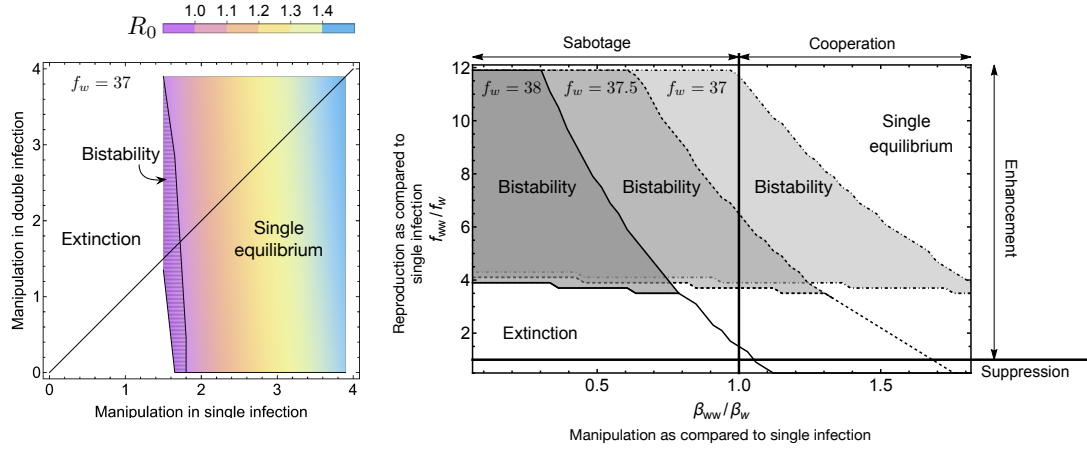


Figure 5: Left: R_0 values increase with more efficient manipulation in both single and double infection. The hatched area indicates the bistable region. As manipulation in single infection increases, the system only has one stable equilibrium. On the black line, the manipulation level is equal between 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.

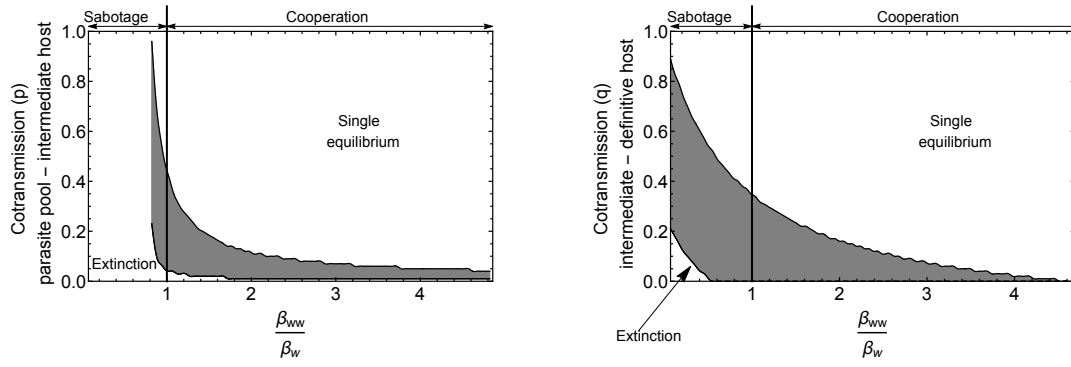


Figure 6: Left: Effect of cotransmission from parasite pool to intermediate host. Right: Effect of cotransmission from intermediate to definitive host. Common parameters: $\rho = 1.2$, $d = 0.9$, $r = 2.5$, $\gamma = 2.9$, $\alpha_w = 0$, $\alpha_{ww} = 0$, $p = 0.05$, $c = 1.4$, $\mu = 3.9$, $\sigma_w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

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 (Haderl 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

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

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

312 Iritani and Sato (2018) show that manipulative parasites persist if they can alternate
313 manipulation between boosting and suppressing predation rate. In our model, the para-
314 site cannot switch its manipulative strategy. Sabotaging manipulation reduces the basic
315 reproduction ratio R_0 and makes the system bistable, exposing the parasite to the risk of

316 extinction. This result contrasts with Iritani and Sato (2018) because in our model, sabotage
317 decreases transmission rate from intermediate to definitive host, and does not benefit the
318 parasite.

319 Finally, our study focuses on the ecological dynamics of the trophically transmitted para-
320 site. However, investigating the evolution of host manipulation is a natural extension beyond
321 the scope of a single manuscript, given the complexities that arise in the ecological dynamics
322 itself. Studying the evolution of host manipulation, considering the free-living parasite pool,
323 calls for thorough analyses, which could be a standalone study. For example, we would need
324 to include differences between the traits of the multiple parasites and hence the ecological
325 model becomes more complex than presented in this study. The combinatorics and orderings
326 of sequential infections will then become important. In addition, the occurrence of bistabil-
327 ity in our model suggests that the evolution of host manipulation may drive the parasite to
328 extinction simply because of the rarity of the mutant and the Allee effect as per Adaptive
329 dynamics approaches. The coinfecting parasites can increase manipulation and enhance re-
330 production freely if there exist no tradeoffs. Nevertheless, our model shows that the benefits
331 of this strategy are context-dependent, making it suboptimal in certain cases. Evolutionary
332 dynamics would therefore depend on the tradeoff between host manipulation and other traits
333 of the parasites, such as reproduction, virulence, and survivorship in the parasite pool, to list
334 a few. This extension deserves thorough analysis, and we will treat it as a separate matter.

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