

On multiple infections by parasites with complex life cycles

Phuong L. Nguyen [†] and Chaitanya S. Gokhale ^{‡†,*} 

[†] Department of Biology, University of Fribourg,

Chemin du musée 15, Switzerland

[‡]Max Planck Institute for Evolutionary Biology, Department of Theoretical Biology

August-Thienemann-Straße 2, 24306 Plön, Germany

^{*}Center for Computational and Theoretical Biology, University of Würzburg,

Klara-Oppenheimer Weg, 32, 97074, Würzburg, Germany

[†]linh.phuong.nguyen@evobio.eu

[‡]chaitanya.gokhale@uni-wuerzburg.de

1 **Abstract:** Host manipulation is a common strategy of parasites with complex
2 life cycle. It directly affects predator-prey dynamics in trophically transmitted
3 parasites. Theoretical studies suggest that predation-enhancing manipulation of-
4 ten decimates the prey population, making parasites prone to extinction. Host
5 manipulation, however, can also reduce predation due to conflicting interests
6 when multiple parasites infect a host, which is often neglected in theoretical stud-
7 ies. Misaligned interests of coinfecting parasites can occur due to limited carrying
8 capacity or parasitoid developmental stage. Including this realistic complexity in
9 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 manipulation and reproduction parameters. Our
12 study highlights the necessity of, and provides the means for, incorporating the
13 reality of multiple parasites and their multi-trophic life cycles into the theory of
14 parasite ecology.

15 Introduction

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

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

42 of the intermediate host being eaten by a non-host predator, given that the initial predation
43 risk is sufficiently low. ~~These models, however, lack~~

44 Most studies mentioned above have not explicitly considered a crucial aspect of parasite
45 dynamics ~~;~~ multiple infections (Kalbe et al., 2002)

46 ~~Typical studies do not consider multiple infections, a phenomenon that is the i.e. the~~
47 presence of multiple individual parasites within a single host. Multiple infections are a norm
48 rather than an exception in parasitism. ~~Multiple infections~~ They result in the coinfection of
49 more than one parasite inside a host, which may alter the manipulative outcomes (figure 1).
50 An alignment of interest between coinfecting parasites may enhance manipulation, while a
51 conflict of interest may reduce the manipulative effect. Indeed, Hafer and Milinski (2015)
52 showed that copepods infected by two cestode parasites reduce the activity of copepods
53 when both parasites are at the same noninfectious stage, i.e. both parasites are not ready to
54 transmit. Thus, the reduction in mobility is suggested to reduce the predation rate by the
55 definitive hosts. When two infectious parasites infect the copepods, the copepods' activity
56 increases, and so does the predation risk for the copepod. However, when the copepods
57 are infected by one infectious and one noninfectious parasite, their interests clash, and one
58 parasite win~~over the other~~.

59 Theoretical work that considers multiple infections often focuses on the evolution of viru-
60 lence (van Baalen and Sabelis, 1995; Alizon et al., 2013; Alizon and van Baalen, 2008; Choisy
61 and de Roode, 2010; Alizon, 2012). ~~They show multiple infections can increase virulence~~
62 ~~(van Baalen and Sabelis, 1995; Choisy and de Roode, 2010). Evolutionary branching of a~~
63 ~~less virulent and a hypervirulent parasite can occur when considering within-host dynamics~~
64 ~~(Alizon and van Baalen, 2008), and a reduction in virulence is possible if parasites are co-transmitted~~
65 ~~(Alizon, 2012). These studies also involve host manipulation to a certain extent, as it~~
66 ~~can affect transmission rates, even though they do not explicitly consider the trait. Host~~
67 ~~manipulation,~~ while host manipulation in trophically transmitted parasites receives less atten-
68 tion. ~~Although manipulation correlates with the transmission rate in trophically transmitted~~



Figure 1: Who is in control?. Schistocephalus eggs, which overwinter at the bottom of bodies of water, hatch into microscopically ~~small~~ tiny 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~~ reaching the third larval stage and ~~grow significantly~~ 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~~ decisions pertaining to investment in manipulation and growth. And indeed, a stickleback can be infected by numerous tapeworms, as shown above by Martin Kalbe.

69 ~~parasites and infectious diseases~~ Even though host manipulation and virulence both correlate
 70 with parasite transmission, there are ~~differences~~ subtle differences, such that virulence implies
 71 an addition to the natural mortality rate of the infected host, whereas manipulation links to
 72 the immediate death of the intermediate host due to predation. Host manipulation ~~influences~~
 73 ~~the predation rate~~ in trophically transmitted parasites, ~~predominantly affecting~~ therefore, not
 74 only affects the intermediate host population but also the entire predator-prey dynamics.
 75 Theoretical studies ~~on host manipulation in trophically transmitted parasites with multiple~~
 76 ~~infections are rare~~ (Parker et al., 2003; Vickery and Poulin, 2009). ~~Moreover, they do not~~

~~consider the prey-predator~~ regarding host manipulation rarely consider multiple infections.
 Studies incorporating this feature neglect the predator-prey dynamics, which will likely have
 important feedback on the evolution of host manipulation . ~~A few studies considering the~~
~~prey-predator dynamics do not incorporate multiple infections~~ (Rogawa et al., 2018; Iritani and Sato, 2018; Hader
 . ~~More importantly, they~~ (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; Haderler and Freedman, 1989; Fenton and Rands, 2018).
 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 a 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 hosts~~ life cycle 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 defini-
 tive 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.~~
~~predator-prey-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 and Results

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

125 following system of equations, firstly for the intermediate host as,

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

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

139 For the definitive hosts, we have,

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

140 where $B(D_s, D_w, D_{ww}, I_s, I_w, I_{ww})$ represents the birth rate of definitive hosts. The birth
141 rates depend on the density of both intermediate and definitive hosts, infected or uninfected.

142 The force of infection that corresponds respectively to singly infected intermediate host (I_w)
 143 and doubly infected intermediate hosts (I_{ww}) is denoted respectively by $\lambda_w = h(\rho + \beta_w)I_w$
 144 and $\lambda_{ww} = h(\rho + \beta_{ww})I_{ww}$, where ρ is the baseline predation rate, i.e. the basic constitutive
 145 level of predation, and h is the probability that the parasite successfully establishes inside
 146 the host. ~~If there is no~~ Without manipulation, that is, $\beta_w = \beta_{ww} = 0$, the parasite is still
 147 transmitted via the ~~based line predation~~ baseline predation ρ . The dynamics of the free-living
 148 parasites in the environment are then given by ~~—~~

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

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

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

160 Results

161 **Basic reproduction ratio R_0 of the parasites**

162 The basic reproduction ratio R_0 (or basic reproduction number as often used in epidemiology)
 163 indicates parasite fitness. It can be understood as the expected number of offspring a parasite
 164 produces during its lifetime when introduced to a susceptible host population. We calculate

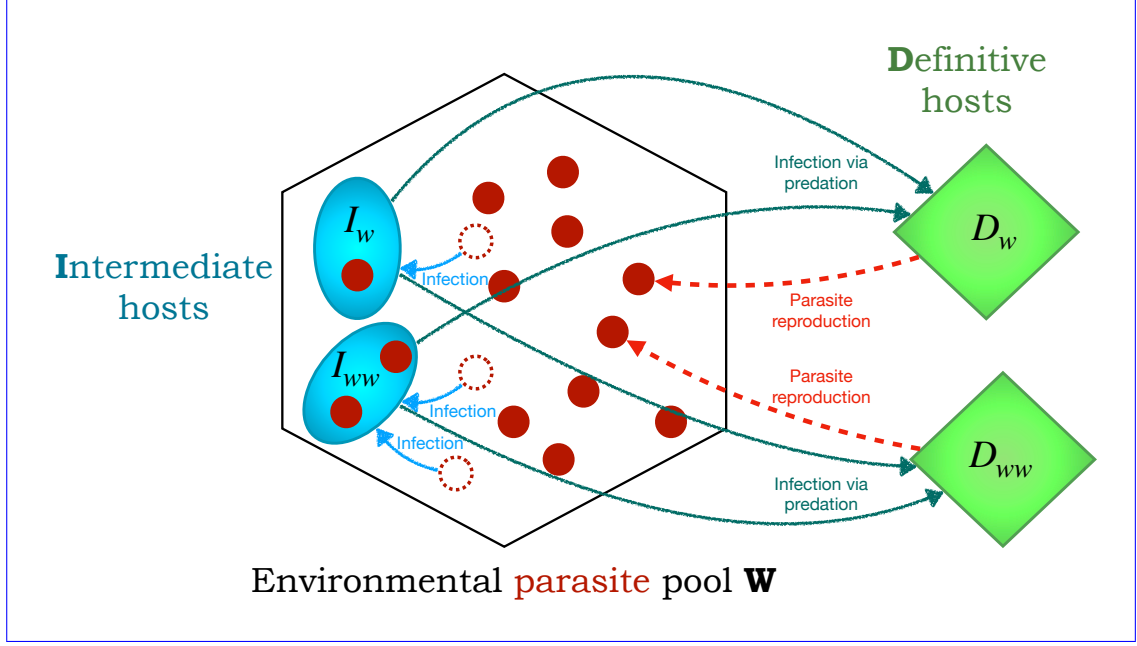


Figure 2: Schematic of the model. Blue ovals represent the intermediate host compartment, while the green diamonds represent the definitive host compartment, and the transparent definitive hosts. The hexagon represents the parasite pool compartment, with the red circles illustrating the free-living individual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

the basic reproduction ratio R_0 using the next-generation method (Diekmann et al., 1990, 2009; Hurford et al., 2010) (See SI1 for details).

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

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

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

170 to the double infections route, in which the focal parasite co-transmits with another par-
 171 asite into a susceptible intermediate host, then co-transmits into a susceptible definitive
 172 host and reproduces. Here, parasites are so rare that only co-transmission matters and the
 173 compartments with sequential infections are ~~therefore~~ neglected. The second component
 174 corresponds to the single infection route, wherein the focal parasite infects a susceptible
 175 intermediate host via single or double infections. The parasite then transmits alone into the
 176 susceptible definitive host and eventually reproduces.

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

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

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

192 is at the baseline value ρ .

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

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

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

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

206 Birth function of intermediate hosts

207 The simplest form of the prey's birth rate is a linear function, in which case the ~~disease-free~~
208 disease-free equilibrium is always unstable. In particular, it has a cyclic behaviour because,
209 at this equilibrium, the jacobian matrix of the system (1, 2, 3) always has two pure imaginary
210 eigenvalues (see SI2). This follows from the Lotka-Volterra system using linear functions for
211 prey birth and predation (Lotka, 1920). Since the disease-free dynamics is cyclic, it is difficult
212 to analyse the spread of a parasite using the basic reproduction ratio, which is evaluated when
213 the disease-free state is stable. Here, $R_0 > 1$ happens when γ , the transmission rate from
214 the environment to intermediate hosts, and the reproduction rates f_w, f_{ww} are ~~significantly~~

215 ~~large (the specific mathematical conditions can be found~~ quite large (as compared to the
 216 ~~theoretical threshold shown by the mathematical conditions~~ in SI3). However, even when this
 217 condition is satisfied, the parasite may not be able to spread and persist in cyclic susceptible
 218 host dynamics (Figure SI1). This result agrees with the conclusion in (Ripa and Dieckmann,
 219 2013), which suggests that it is difficult for a mutant to invade a cyclic resident population.
 220 In our case, it is not the invasion of a mutant in a resident population but the invasion of
 221 a parasite in a cyclic disease-free host population; the argument, however, remains valid in
 222 both cases. This issue deserves a more thorough investigation, which is out of the scope of
 223 this article. Here, we choose a non-linear birth function of the intermediate hosts to obtain
 224 a stable ~~disease-circulation~~ disease-free state and focus on the effect of host manipulation
 225 on the ecological dynamics (Figure 3).

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

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

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

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

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

233 When a parasite appears in the disease-free equilibrium, it spreads if its reproduction ratio
 234 $R_0 > 1$ (Figure 3C, D). Since the expression is complicated, we could ~~not only~~ obtain ana-
 235 lytical solutions for this inequality ~~without with~~ assumptions. We assume the same parasite
 236 virulence, $\alpha_w = \alpha_{ww}$, $\sigma_w = \sigma_{ww}$, 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 ~~as~~ compared to in single infections, whereas $\epsilon \leq 1$, reproduction in double infections is ~~depressed~~ 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 (~~its value is nearly 40 times greater than other parameters~~) Figure 4A. ~~For instance, in the parameter set used to generate Figure (4B, to spread in the predator-prey 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 ~~many~~ 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~~ The parasite population can reach a stable equilibrium in the bistable region 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. In that case, the

system is in a bistable state where intermediate cooperation in host manipulation leads to a bistable system state. Within cannot guarantee a single equilibrium (Hatched area Figure 5 Left). In the bistable region, the basic reproduction ratio can be less than one, suggesting implying that the parasite cannot spread when its manipulative values are within this area of weak manipulation when coinfecting. with manipulative values within this range, i.e. weak manipulation ability, cannot spread. When the system encounters bistability, the parasite population risks extinction if there is a disturbance in the community. In the following parts, we will explore scenarios where bistability may occur.

~~Co-infecting~~ Besides manipulation, 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. $f_{ww} > f_w$ (upper part of the horizontal line in Figure 5 Right). Likewise, they can compete for resources, so reproduction in double infection is depressed as compared to in single infection suppressed compared to single infection (lower part of the horizontal line in Figure 5 Right). 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 suppressed-enhanced range in reproduction. If parasites are This results in four scenarios of parameter combinations: i, parasites sabotage manipulation but have enhanced reproduction – manipulative incoordination (top left quadrant in Figure 5 Right), ii, parasites cooperate to increase manipulation and enhance reproduction – coordination (top right quadrant in Figure 5 Right), iii, parasites cooperate in manipulation but suppress reproduction – reproductive incoordination (bottom right quadrant in Figure 5 Right), and iv, parasites sabotage manipulation and suppress reproduction – discordance (bottom left quadrant in Figure 5 Right).

If coinfecting parasites are discordant, i.e. uncooperative in manipulations and shows depressed show suppressed reproduction, they cannot persist (Figure 5). In contrast, if On the other extreme, where they are highly cooperative in manipulation and show enhanced reproduction (i.e. $\beta_{ww}/\beta_w \rightarrow \infty$ and $f_{ww}/f_w \rightarrow \infty$), an extreme level of coordination,

290 there is a guaranteed single equilibrium for parasite existence.

291 ~~For~~ Note that this happens at the combination of $\beta_{ww}/\beta_w \rightarrow \infty$ and $f_{ww}/f_w \rightarrow \infty$, a
292 scenario that is rather impossible in reality. Very often, we expect intermediate levels of
293 coordination ~~in reproduction and manipulation, where~~ a bistable area could occur (top left
294 quadrant in Figure 5 at $f_w = (37, 37.5)$). However, the size of this area is sensitive to the
295 value of reproduction and manipulation in a single infection. In particular, higher values
296 of these two parameters reduce the bistability area ~~; whereas larger values increase the~~
297 ~~bistability area (Figure 5~~ to the point that sufficiently large reproduction in single infection
298 ~~can guarantee single equilibrium when parasites coordinate (top left quadrant in Figure 5~~
299 ~~Left at $f_w = (38)$, Figure SI.1). 2).~~ In contrast, slightly reducing values of reproduction
300 ~~and manipulative cooperation~~ increase the bistability area. If the parasites sabotage
301 each other, the system is highly prone to bistability and only has a single equilibrium when
302 reproduction is especially enhanced (left side of vertical line in Figure 5 Left). Interestingly,
303 sufficiently high reproduction enhancement leads to bistability (i.e. f_{ww} is at least four times
304 f_w), and ~~depressed reproduction~~ reproductive incoordination, i.e. ~~depressed reproduction~~
305 ~~and manipulative cooperation~~, always leads to a single equilibrium of the system (Figure
306 54A, and bottom right quadrant in Figure 5 Left). While a single equilibrium guarantees the
307 existence of a parasite population, bistability indicates that a disturbance of the system may
308 likely lead to the extinction of the parasite population. This suggests that the benefits of
309 coordination in reproduction and manipulation are context-dependent. Coordinating ~~holds~~
310 ~~an advantage if there are~~ is advantageous if no significant tradeoffs and ~~if~~ reproduction or
311 manipulation in single infections are large enough.

312 ~~Co-transmission probability~~ We now explore the effect of co-transmission probability on
313 the bistability of the system (Figure 6). First, extinction is more likely with varying levels of
314 ~~co-transmission~~ from the parasite pool to intermediate ~~hosts~~ host p has the opposite effect
315 ~~on the bistable area compared to~~ compared to varying levels of co-transmission probability
316 ~~q from intermediate hosts to intermediate hosts (Figure 6).~~ In particular, when the parasite

~~sabotages the manipulation, increasing from intermediate host to definitive host q . For~~
~~exceptionally high level of cooperation and not very small values of both p enlarges and q ,~~
~~the predator-prey-parasite system will always persist with one stable equilibrium. However,~~
~~limitations and trade-offs are often unavoidable, and such high values of cooperation may be~~
~~impossible, putting the system in the parameter space where bistability likely occurs. When~~
~~the parasite sabotages manipulation, the bistable area , whereas increasing decreases with~~
~~increasing p and q reduces it. In contrast, when- . However, this bistable area disappears with~~
~~high values of q but not with high values of p . When parasites cooperate in manipulation,~~
~~reducing p decreases the bistable area while almost always lead to bistability where as re-~~
~~ducing 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. can lead~~
~~to single equilibrium if cooperation is sufficiently large. Bistability indicates vulnerability to~~
~~disturbance, suggesting that and so cooperation in manipulation may be beneficial when q ,~~
~~the co-transmission from the pool to the intermediate host increases intermediate host to the~~
~~definitive host decreases. However, cooperation in manipulation may still harm the popula-~~
~~tion when with reducing p , the co-transmission from the intermediate host to the definitive~~
~~host increases parasite pool to intermediate host.~~

Discussion & Conclusion

Host manipulation is a ubiquitous phenomenon suggested to affect the ~~prey-predator~~ predator-prey
 dynamics in trophically transmitted parasites. In particular, manipulation of infected inter-
 mediate 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

343 is larger than one, it is estimated at the predator and prey's unstable equilibrium (or cyclic
344 equilibrium). Thus, when the density of the prey and predator is at the minimum value of
345 the cycle, the "effective" R_0 of the parasite can be smaller than one. Another interesting
346 result is that the reproduction value is much larger than other parameter values, such as
347 the per capita reproduction rate of the intermediate host. This result is likely due to the
348 introduction of a free-living parasitic pool. Our model shows that in making the system more
349 realistic, we also obtain a more realistic quantitative value for parasitic reproduction.

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

362 ~~In our~~ Another study on host manipulation, Iritani and Sato (2018), showed that manipulative
363 parasites persist if they switch from suppressing to boosting predation rate. This theoretical
364 work modelled the ability to change the manipulative strategy of a single parasite inside
365 a host, which can be equal to introducing the developmental state of a parasite, where a
366 suppressed predation rate protects the parasites that are not ready to transmit. That is
367 why decreasing manipulative ability is beneficial and prevents parasite extinction. In our
368 model, sabotaging manipulation also reduces manipulative ability, which only reduces the
369 basic reproduction ratio R_0 and makes the system bistable, exposing the parasite to the risk

370 of extinction. This result contrasts with Iritani and Sato (2018) because in our model, the
371 parasite cannot switch its manipulative strategy, and sabotage decreases the transmission
372 rate from intermediate to definitive host and does not benefit the parasite in any way.

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

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

391 Finally, our study focuses on the ecological dynamics of the a trophically transmitted para-
392 site. However, investigating the evolution of host manipulation is a natural extension beyond
393 the scope of a single manuscript, given the complexities that arise in the ecological dynamics
394 itself. Studying the evolution of host manipulation, considering the between two host species.
395 In nature, parasites with complex life cycles can have more than two hosts. However,
396 our model of a single intermediate host species can already provide enough complexity to

397 discuss the relationship between transmission and manipulation. Here, we introduce more
 398 realistic features compared to previous models, such as a free-living parasite pool , ~~calls~~
 399 ~~for thorough analyses, which could be a standalone study. For example, we would need to~~
 400 ~~include differences between the traits of the multiple parasites and hence the~~ and multiple
 401 infections, regardless of some simplifications, such as multiple infections being limited to at
 402 most two parasites. In this way, we can obtain analytical results of the reproduction ratio and
 403 mathematical expressions for the existing condition of the parasite. Our model serves as a
 404 groundwork for future exploration into more complex and realistic systems, where numerical
 405 simulation may be the only possible approach. Moreover, the results of our ecological model
 406 ~~becomes more complex than presented in this study. The combinatorics and orderings of~~
 407 ~~sequential infections will then become important. In addition, the occurrence of bistability in~~
 408 ~~our model suggests that~~ are a baseline for further investigation of the evolution of host ma-
 409 nipulation ~~may drive the parasite to extinction simply because of the rarity of the mutant and~~
 410 ~~the Allee effect as per Adaptive dynamics approaches. The coinfecting parasites can increase~~
 411 ~~manipulation and enhance reproduction freely if there exist no tradeoffs. Nevertheless, our~~
 412 ~~model shows that the benefits of this strategy are context-dependent, making it suboptimal~~
 413 ~~in certain cases. Evolutionary dynamics would therefore depend on the tradeoff between~~
 414 ~~host manipulation and other traits of the parasites, such as reproduction, virulence, and~~
 415 ~~survivorship in the parasite pool , to list a few. This extension deserves thorough analysis,~~
 416 ~~and we will treat it as a separate matter,~~ where introducing the parasite pool may create
 417 interesting eco-evolutionary feedbacks to the system.

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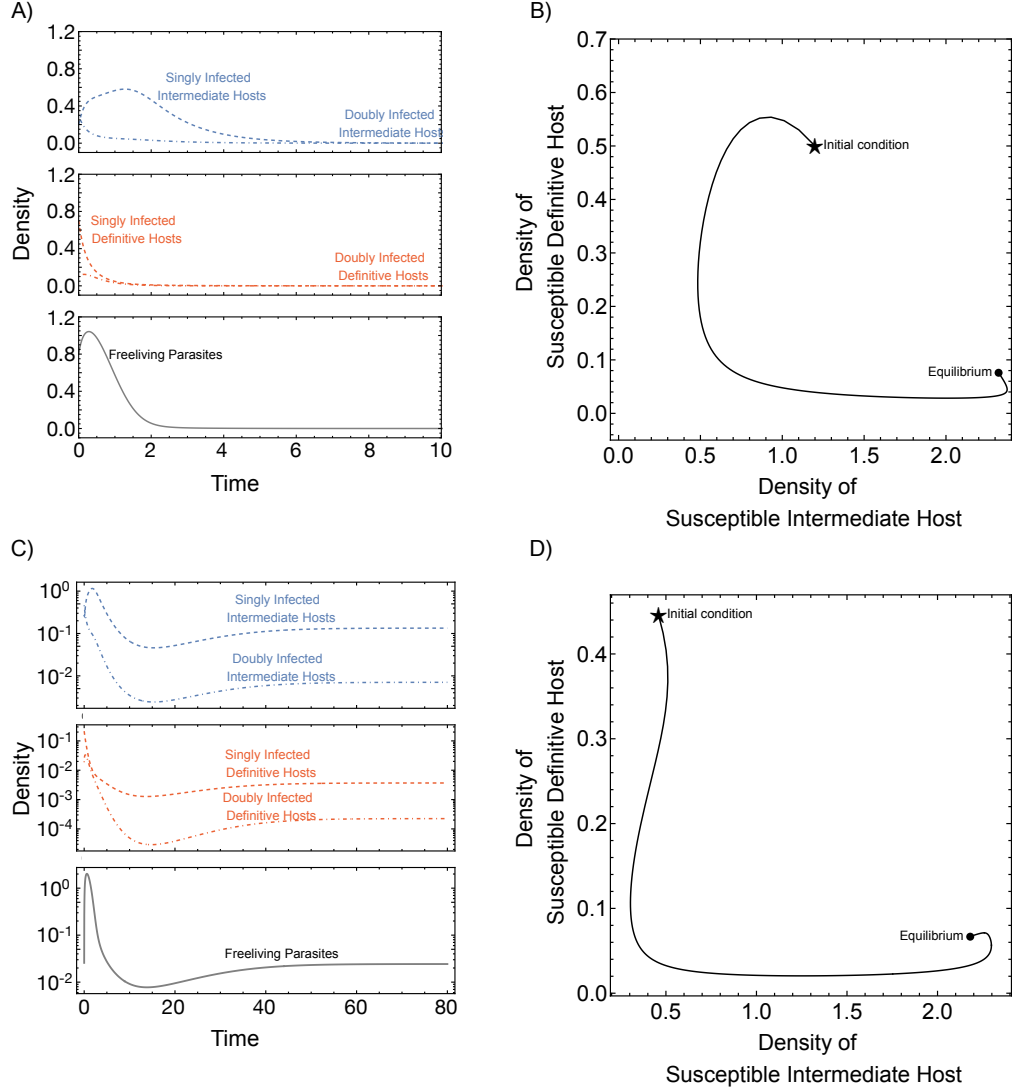


Figure 3: Ecological dynamics of the predator-prey-parasite system. A, B) Disease-free equilibrium where Ecological trajectories of infected hosts and free-living parasite when parasites cannot persist. C, D) Disease-stable equilibrium. Solid gray line indicate the density-Phase plane of free-living parasites, blue lines indicate infected susceptible intermediate hosts while red lines indicate infected and definitive hosts under disease free scenario. Dashed lines indicate singly C) Ecological trajectories of infected hosts while dot-dashed lines indicate doubly 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 $f_w = f_{ww} = 45$

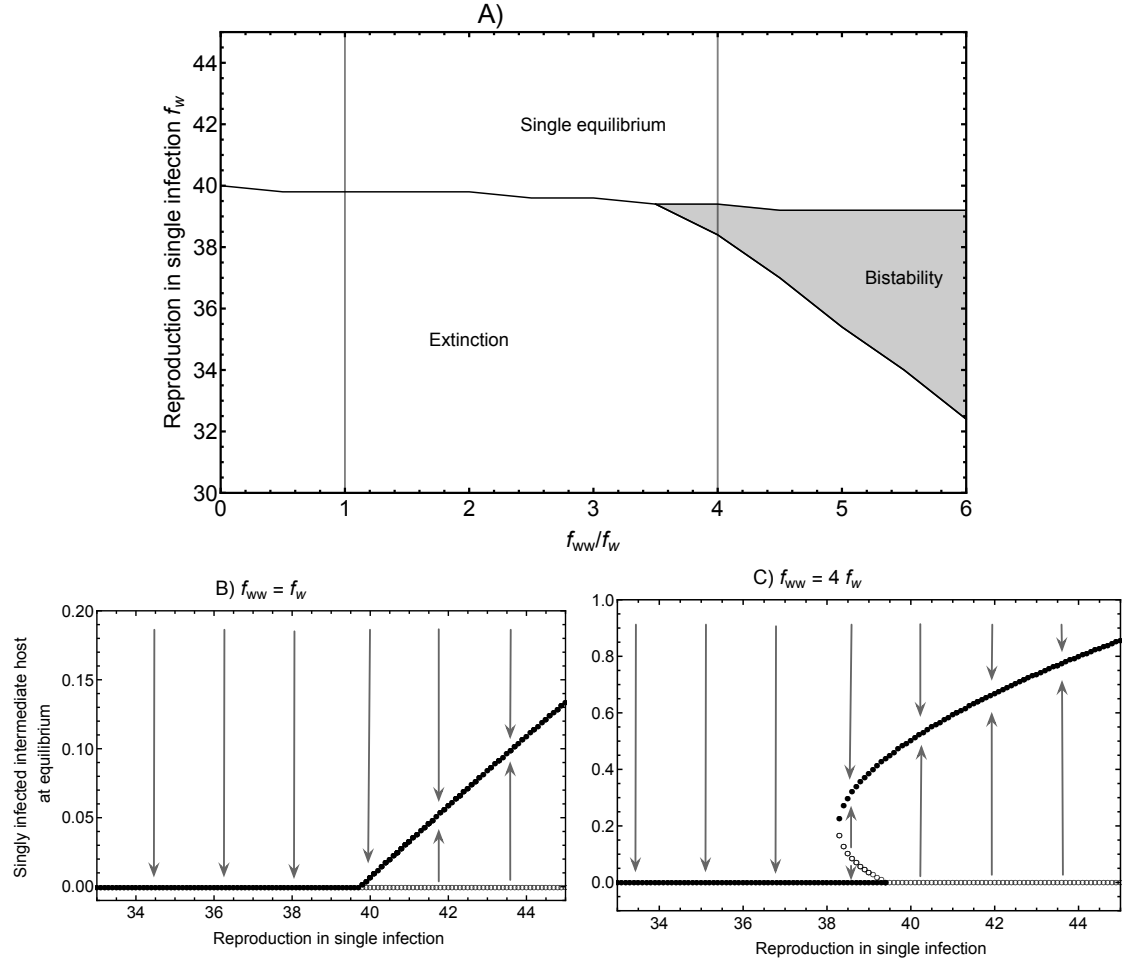


Figure 4: ~~Effect of parasite reproduction on the ecological dynamics~~Effect of parasite reproduction on the ecological dynamics. A) Enhanced reproduction in double infection leads to bistability, B, C) Density of singly infected host at equilibrium when reproduction of parasites are the same in singly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

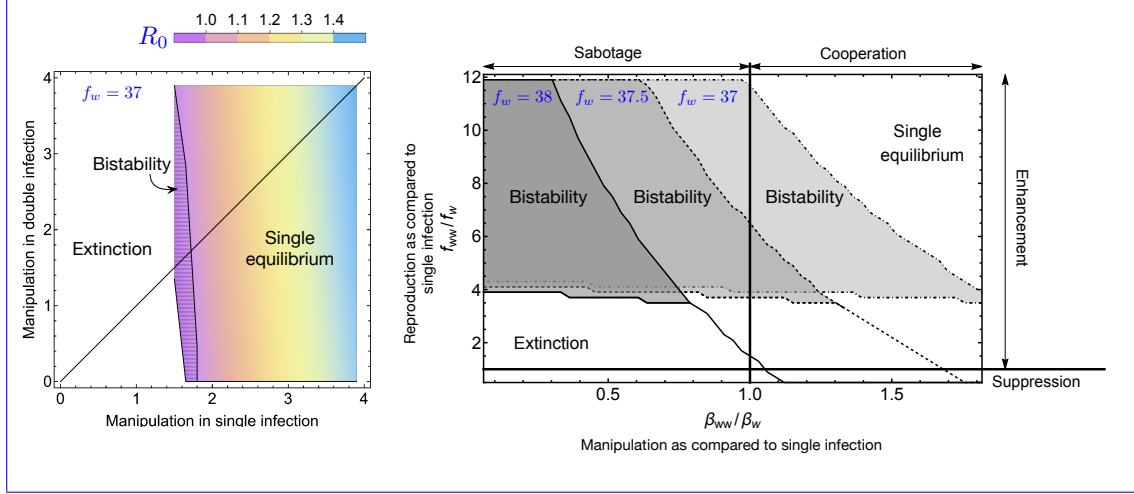


Figure 5: Effect of manipulation and reproduction on bistability. Left: R_0 values increase with more efficient manipulation in ~~both~~ single and double infection. ~~Hatched~~ The hatched area indicates the bistable region. As manipulation in single infection increases, the system only has one stable equilibrium. On the black line, the manipulation level is ~~indifference~~ equal between single ~~infection~~ and double infection ($\beta_w = \beta_{ww}$). In the upper triangular area, parasites cooperate, and in the lower triangular area, parasites sabotage. Right: Changes ~~of~~ in the bistability area (shaded areas) ~~with respect to~~ concerning different reproduction rates in single infection (different boundary styles). Manipulation and reproduction ~~is indifference~~ levels are equal between single ~~infection~~ and double infection on the vertical and horizontal lines ~~respectively~~. On the left side of the vertical line, $\beta_{ww} > \beta_w$, indicating cooperation, whereas on the right side of the vertical line, $\beta_{ww} < \beta_w$, indicating sabotage. On the upper part of the horizontal line, $f_{ww} > f_w$, indicating enhanced reproduction, whereas, on the lower part of the horizontal line, $f_{ww} < f_w$, indicating suppressed reproduction. Common parameter: $\rho = 1.2$, $d = 0.9$, $r = 2.5$, $\gamma = 2.9$, $\alpha_w = 0$, $\alpha_{ww} = 0$, $p = 0.05$, $c = 1.4$, $\mu = 3.9$, $\sigma_w = 0$, $\sigma_{ww} = 0$, $q = 0.05$, $\delta = 0.9$, $k = 0.26$, $\beta_w = 1.65$, $h = 0.6$.

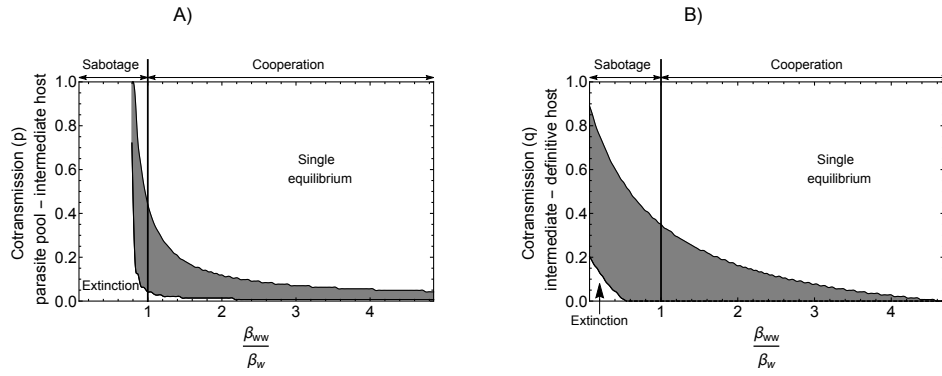


Figure 6: Left: Effect of cotransmission from parasite pool to intermediate host. Right: Effect of cotransmission from intermediate to definitive host. On the left side of the vertical line, $\beta_{ww} > \beta_w$, indicating cooperation, whereas on the right side of the vertical line, $\beta_{ww} < \beta_w$, indicating sabotage. Common parameters: $\rho = 1.2$, $d = 0.9$, $r = 2.5$, $\gamma = 2.9$, $\alpha_w = 0$, $\alpha_{ww} = 0$, $p = 0.05$, $c = 1.4$, $\mu = 3.9$, $\sigma_w = 0$, $\sigma_{ww} = 0$, $q = 0.05$, $\delta = 0.9$, $k = 0.26$, $\epsilon = 4.5$, $\beta_w = 1.45$, $f_w = 38$, $h = 0.6$.