

On multiple infections by parasites with complex life cycles

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Statement of Authorship

Both authors developed the theory.

P.L.N developed and implemented the computational model.

Both authors wrote the manuscript.

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 can be defined as abrupt ontogenetic changes in
18 morphology and ecology (Benesh, 2016), it typically involves numerous host species that a
19 parasite needs to traverse to complete its life cycle. This complex life cycle results in the
20 evolution of various strategies that enable ~~the success of successful~~ parasite transmission
21 from one host species to another. One famous strategy that inspires many science fiction
22 movies and novels is host manipulation, where a parasite can alter ~~the its host's~~ 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
25 with simple life cycles to those with a complex life cycle that involves more than one host
26 species (Hughes et al., 2012; Molyneux and Jefferies, 1986). For instance, sand flies infected
27 by *Leishmania* parasites bite more and take more time for a blood meal from mammals (the
28 definitive host of *Leishmania*) compared to their uninfected counterparts (Rogers and Bates,
29 2007). Copepods infected by cestode parasites are more active and accessible to sticklebacks
30 (the cestodes' definitive hosts) than 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. Hadeler 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 reproduction of
39 the infected definitive host. Seppälä and Jokela (2008) showed that host manipulation could
40 evolve even when it increases the risk of the intermediate host being eaten by a non-host
41 predator, given that the initial predation risk is sufficiently low.

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

55 Theoretical work that considers multiple infections often focuses on the evolution of viru-
56 lence (van Baalen and Sabelis, 1995; Alizon et al., 2013; Alizon and van Baalen, 2008; Choisy
57 and de Roode, 2010; Alizon, 2012), while host manipulation in trophically transmitted par-
58 asites receives less attention. Even though host manipulation and virulence ~~both~~ correlate
59 with parasite transmission, there are subtle differences, such that virulence implies an ad-
60 dition to the natural mortality rate of the infected host, whereas manipulation links to the
61 immediate death of the intermediate host due to predation. Host manipulation in trophically
62 transmitted parasites, therefore, ~~not only affects the intermediate host population but also~~
63 ~~the~~ strongly affects the entire predator-prey dynamics. Theoretical studies regarding host
64 manipulation rarely consider multiple infections. Studies incorporating this feature neglect
65 the predator-prey dynamics, which will likely have important feedback on the evolution of
66 host manipulation (Parker et al., 2003; Vickery and Poulin, 2009). Moreover, these models
67 assume that transmission from definitive hosts to intermediate hosts is due to direct contact
68 between the two types of hosts (Rogawa et al., 2018; Hadeler and Freedman, 1989; Fenton



Figure 1: Who is in control? Who is in control? Schistocephalus eggs, which overwinter at the bottom of bodies of water, hatch into microscopically 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, 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 decisions pertaining to investment in manipulation and growth. And indeed, a stickleback can be infected by numerous tapeworms, all vying for control, as shown above and photographed by Martin Kalbe (Kalbe et al., 2002).

and Rands, 2006). 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 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 definitive hosts. New parasites then

79 enter the environment, where the cycle continues. We focus on the intermediate host manip-
80 ulation, such that the parasite increases the uptake of the intermediate host by the definitive
81 host to increase its transmission rate. We then analyse the effect of host manipulation on
82 the ecological dynamics in the predator-prey-parasite system. We found that sabotage in
83 host manipulation almost always pushes the dynamical system toward bistability, provided
84 the reproduction in a single infection is sufficiently small. The bistable nature suggests that
85 the predator-prey parasite system is finely balanced and susceptible to extinction via ecolog-
86 ical disturbances. Initially surprising, we showed that cooperation in host manipulation and
87 enhanced reproduction in co-infecting parasites is not always beneficial and might expose
88 the parasite population to the risk of extinction.

89 Model

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

96 For simplicity, we assume that hosts can be infected by one (single infection) or, at most,
97 two parasites (double infections). Thus, while I_s and D_s are the susceptible intermediate
98 and definitive hosts, their singly and doubly infected counterparts are denoted by I_w and D_w
99 and I_{ww} and D_{ww} respectively. Our model is, therefore, more relevant to the macroparasitic
100 system. ~~Given that infection occurs~~ Figure (2) illustrates the transmission dynamics, and
101 details of the model's variables and parameters are shown in Table 1. Note that multiple
102 infections in nature often involve more than two parasites. Typically, the number of parasites
103 in multiple infections follows a negative binomial distribution, i.e. most hosts are infected with
104 a few parasites while very few hosts are infected with many parasites (Wilson et al., 1996).

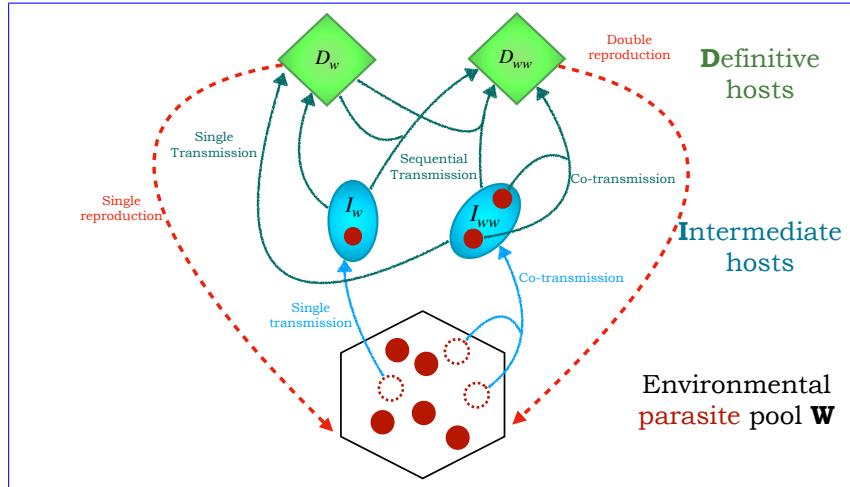


Figure 2: Schematics of the transmission routes. Blue ovals represent the intermediate hosts, while green diamonds represent the definitive hosts. The hexagon represents the parasite pool compartment, with the red circles illustrating the free-living individual parasites. The parasites infect the intermediate hosts singly (I_w) or doubly (I_{ww}) upon encounter between the intermediate hosts and the parasite pool (blue arrows). These intermediate hosts are then predated upon by the definitive hosts (green arrows), 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 (red dashed arrows).

105 However, since we use a compartmental model, enabling binomial distribution would mean
 106 infinitely many differential equations, making it impossible to formulate and analyze the
 107 model. Instead, we focus on another aspect of multiple infections, that is, co-transmission,
 108 which has been shown to affect the evolutionary trajectories of parasites in infectious disease
 109 (Alizon, 2012). Given an infection, the probability that two parasites from the parasite
 110 pool co-transmit to an intermediate host is denoted by p . Thus, $1 - p$ is the probability
 111 that a single parasite enters an intermediate host. When a definitive host consumes an
 112 intermediate host infected by two parasites, there is a probability q that the parasites co-
 113 transmit to the definitive host. With probability $1 - q$, only one parasite successfully transmits.
 114 This formulation assumes that infection always happens when ~~hosts encounter parasites~~.
 115 ~~intermediate hosts encounter free-living parasites and when definitive hosts consume infected~~
 116 ~~intermediate hosts (Figure 2)~~. The dynamics of a complex life cycle parasite that requires

117 two host species is described by the following system of equations, firstly for the intermediate
 118 host as,

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

119 where $R(I_s, I_w, I_{ww})$ represents the birth rate of the intermediate hosts, a function
 120 of both infected and uninfected individuals $I_{total} = I_s + I_w + I_{ww}$. Intermediate hosts die
 121 at a natural rate d , and parasites cause additional mortality rate α_w in single infection and
 122 α_{ww} in double infection. P_s , P_w , P_{ww} are the predation functions of definitive hosts on
 123 susceptible, singly infected and doubly infected intermediate hosts. The predation function
 124 depends on the density of the definitive hosts all definitive hosts $D_{total} = D_s + D_w + D_{ww}$
 125 and the manipulative strategies of parasites in the intermediate hosts. In particular, if a
 126 single parasite infects an intermediate host, the manipulation strategy is β_w . However, if
 127 the intermediate host is co-infected, the manipulation strategy is β_{ww} . In the scope of this
 128 model, we We assume no specific relationship between β_w and β_{ww} to explore all possible
 129 ecological outcomes of the system. The force of infection by parasites in the environment is
 130 denoted by $\eta = \gamma W$, where γ represents the infection rate of free-living parasites. The force
 131 of infection is a term often used in epidemiology, which represents the rate at which a host
 132 gets infected by the parasites. Since parasites can manipulate intermediate and definitive
 133 hosts, whenever we mention host manipulation, it specifically refers to the manipulation in
 134 intermediate hosts, which correlates to the predation rate.

135 For the definitive hosts, we have,

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

136 where $B(D_s, D_w, D_{ww}, I_s, I_w, I_{ww})$ represents the birth rate of definitive
137 hosts. The birth rates depend on the density of both intermediate and definitive hosts,
138 infected or uninfected. The natural mortality rate of definitive hosts is represented by μ ,
139 and parasites induce additional mortality rates σ_w and σ_{ww} in single and double infection,
140 respectively. The force of infection that corresponds respectively to singly infected inter-
141 mediate host (I_w) and doubly infected intermediate hosts (I_{ww}) is denoted respectively by
142 $\lambda_w = h(\rho + \beta_w)I_w$ and $\lambda_{ww} = h(\rho + \beta_{ww})I_{ww}$, where ρ is the baseline predation rate, i.e.
143 the basic constitutive level of predation, and h is the probability that the parasite successfully
144 establishes inside the host. Without manipulation, that is, $\beta_w = \beta_{ww} = 0$, the parasite is
145 still transmitted via the baseline predation ρ . The dynamics of the free-living parasites in
146 the environment are then given by $\underline{\nu}$

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

147 where f_w and f_{ww} are the reproduction rates of parasites in single and double infection,
148 respectively, and parasites die naturally at a rate δ .

149 Here, we focus on manipulation that enhances transmission from intermediate hosts to
150 definitive hosts; we thus simplify the transmission from the parasite pool to intermediate hosts
151 so that no sequential infection occurs. This assumption is motivated given that because the
152 prey life cycle is often shorter than the predator's. A prey likely encounters the free-living
153 parasite pool once and then dies due to predation, making sequential transmission less likely

154 at this state. Sequential infection can happen when parasites transmit from intermediate
 155 hosts to definitive hosts. Therefore, a singly infected definitive host can be further infected by
 156 another parasite if it consumes infected intermediate hosts. ~~Figure (2) illustrates the system's~~
 157 ~~dynamics, and Table (1) contains the different parameters and variables used.~~ ~~Schematic of~~
 158 ~~the model.~~ Blue ovals represent the intermediate hosts, while the green diamonds represent
 159 the definitive hosts. The hexagon represents the parasite pool compartment, with the red
 160 circles illustrating the free-living individual parasites. The parasites infect the intermediate
 161 hosts singly (I_w , top) or doubly (I_{ww} , bottom). These intermediate hosts are then predated
 162 upon by the definitive hosts, thus moving the parasites to the final host (either as D_w or
 163 D_{ww}) where they can reproduce and reenter the free-living stage in the environmental pool
 164 **W.**

165 **Results****Basic reproduction ratio R_0 of the parasites**

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

167 The basic reproduction ratio R_0 (or basic reproduction number as often used in epidemiology)
 168 indicates parasite fitness. It can be understood as the expected number of offspring a parasite
 169 produces during its lifetime when introduced to a susceptible host population. We calculate
 170 the basic reproduction ratio R_0 using the next-generation method (Diekmann et al., 1990,
 171 2009; Hurford et al., 2010) (See SI1 for details).

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

172 where I_s^* and D_s^* are the densities of susceptible intermediate and definitive hosts at the
 173 disease-free equilibrium. Here, the expression of R_0 contains the possible reproduction routes

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

174 of a parasite, which can be via double or single infections. The first component corresponds
 175 to the double infections route, in which the focal parasite co-transmits with another parasite
 176 into a susceptible intermediate host, then co-transmits into a susceptible definitive host and
 177 reproduces. Here, parasites are so rare that only co-transmission matters and the compart-
 178 ments with sequential infections are neglected. The second component corresponds to the
 179 single infection route, wherein the focal parasite infects a susceptible intermediate host via
 180 single or double infections. The parasite then transmits alone into the susceptible definitive

181 host and eventually reproduces.

182 If $R_0 > 1$, a parasite spreads when introduced into the disease-free equilibrium of prey and
183 predator. Intuitively, the higher the density of susceptible intermediate and definitive hosts,
184 the larger the value of R_0 as the infection reservoir is more extensive. In contrast, regardless
185 of the explicit form of the predation function, the higher the predation rate P_w and P_{ww} , the
186 lower the value of R_0 given the smaller reservoir of intermediate hosts. The effect of host
187 manipulation on the value of R_0 is more complex; as host manipulation becomes efficient,
188 the transmission rate from the intermediate host to the definitive host increases, but so does
189 the predation rate. A higher predation rate results in a smaller intermediate host reservoir
190 for the parasites to infect. To understand the effect of manipulation on parasites' fitness
191 and the system's ecological dynamics, we next specify the predation functions. We consider
192 linear functions for predation to begin with,

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

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

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

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

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

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

199 where c is the efficiency of converting prey into predator's offspring, and $I_{total} = I_s + I_w + I_{ww}$

200 ~~is the total density of the intermediate hosts~~. It is important to note that host manipulation
201 affects population dynamics via its influence on the predation rate, not the physiological
202 aspect of the definitive host, i.e., the predator. The birth rate of the predators thus depends
203 on the capture rate, but it is not affected by host manipulation; to our best knowledge, there
204 is no supporting evidence to consider otherwise.

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

211 **Birth function of intermediate hosts**

212 **Birth function of intermediate hosts**

213 The simplest form of the prey's birth rate is a linear function, in which case the disease-
214 free equilibrium is always ~~unstable. In particular, it has a cyclic behaviour because, at this~~
215 ~~equilibrium, the jacobian matrix of the system (1, 2, 3) always has two pure imaginary~~
216 ~~eigenvalues (see SI2 in a cyclic regime (see SI 2)).~~ This follows from the Lotka-Volterra
217 system using linear functions for prey birth and predation (Lotka, 1920). Since the disease-
218 free dynamics is cyclic, it is difficult to analyse the spread of a parasite using the basic
219 reproduction ratio, which is evaluated when the disease-free state is stable. Here, $R_0 > 1$
220 happens when γ , the transmission rate from the environment to intermediate hosts, and the
221 reproduction rates f_w, f_{ww} are quite large (as compared to the theoretical threshold shown
222 by the mathematical conditions in SI3). However, even when this condition is satisfied, the
223 parasite may not be able to spread and persist in cyclic susceptible host dynamics (Figure
224 SI1). This result agrees with the conclusion in (Ripa and Dieckmann, 2013), which suggests

225 that it is difficult for a mutant to invade a cyclic resident population. In our case, it is not the
226 invasion of a mutant in a resident population but the invasion of a parasite in a cyclic disease-
227 free host population; the argument, however, remains valid in both cases. This issue deserves
228 a more thorough investigation, which is out of the scope of this article. ~~Here~~Therefore, we
229 choose a non-linear birth function of the intermediate hosts to obtain a stable disease-free
230 state and focus on the effect of host manipulation on the ecological dynamics (Figure 3).

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

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

232 where k is the intraspecific competition coefficient. The disease-free equilibrium is as follows.3

233

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

234 This equilibrium is positive and stable if components of the parasite, such as reproduction
235 and transmission, are sufficiently small; details of the condition can be found in section SI
236 4. Here, ~~because as~~ reproduction and transmission value of the parasite are not sufficient, it
237 goes extinct (Figure 3AB), leaving the predator-prey dynamics attaining equilibrium (Figure
238 3BC~~D~~)

239 When a parasite appears in the disease-free equilibrium, it spreads if its reproduction
240 ratio $R_0 > 1$ (Figure 3C~~D~~4). Since the expression is complicated, we could only obtain
241 analytical solutions for this inequality with assumptions. We assume the same parasite
242 virulence, $\alpha_w = \alpha_{ww}$, $\sigma_w = \sigma_{ww}$, and reproduction in double infection as a linear function
243 concerning reproduction in single infections, $f_{ww} = \epsilon f_w$. When $\epsilon > 1$, reproduction in double
244 infections is enhanced compared to in single infections, whereas ~~for~~ $\epsilon \leq 1$, ~~reproduction in~~
245 ~~double infections it~~ is suppressed or equal to reproduction in single infections. We found that
246 the parasite can establish if its reproduction value in a single infection f_w is more significant

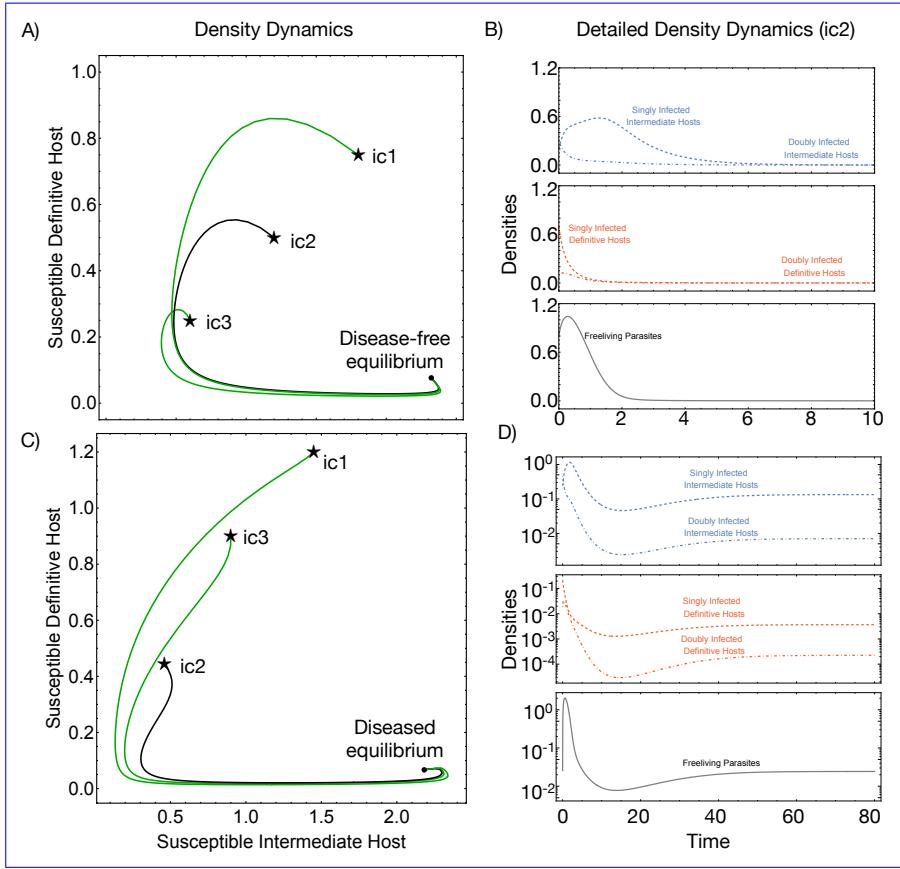


Figure 3: Ecological dynamics of the predator-prey-parasite system. **A)** Ecological trajectories of infected hosts and free-living parasite when parasites cannot persist. On the left, **B)** Phase plane we show the density dynamics of the susceptible intermediate and definitive hosts under disease free scenario. **C**) different initial conditions (ic1, ic2, and ic3). Ecological trajectories. The detailed dynamics of infected hosts and compartments are further shown for specific initial conditions (ic2), including the free-living parasite when parasites persist. **D**) **A-B)** Phase plane A case of susceptible and definitive host under disease circulating scenario a disease-free equilibrium being reached from different initial conditions (ic). **C-D)** A case where the parasite survives. 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 has the same parameter values except for higher host manipulation $\beta_w = \beta_{ww} = 4.5$ and parasite reproduction $f_w = f_{ww} = 45$

247 than a threshold (Figure 5, see section SI 5 and Eq. (SI.19)).

248 Our numerical results show that the parasite reproduction is substantial compared to other

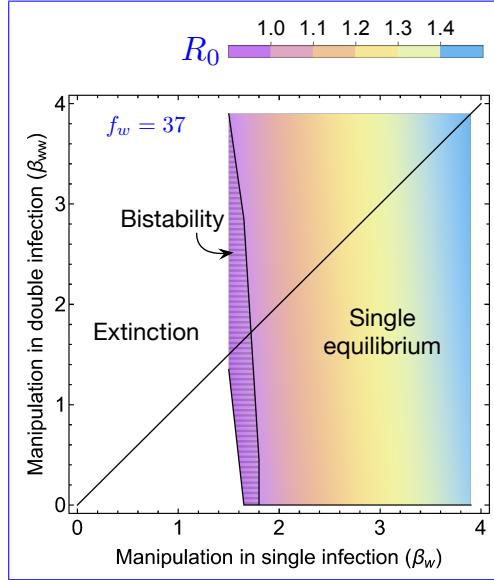


Figure 4: Effect of manipulation in single and double infections on the reproduction ratio R_0 . R_0 values increase with more efficient manipulation in single and double infection. The hatched area indicates the bistable region. As manipulation in single infection increases, the system only has one stable equilibrium. On the black line, the manipulation level is equal between single and double infection ($\beta_w = \beta_{ww}$). In the upper triangular area, parasites cooperate, and in the lower triangular area, parasites sabotage. Common parameter: $\rho = 1.2$, $d = 0.9$, $r = 2.5$, $\gamma = 2.9$, $\alpha_w = 0$, $\alpha_{ww} = 0$, $p = 0.05$, $c = 1.4$, $\mu = 3.9$, $\sigma_w = 0$, $\sigma_{ww} = 0$, $g = 0$.

parameters (Figure 5A). For instance, in the parameter set used to generate Figure 5B, 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 a large amount of~~ should release many offspring into the environment to persist. Interestingly, bistability occurs if the reproduction rate of the parasite in double infections is enhanced (Figure 5A). The parasite population can reach ~~a~~ Bistability suggests that the parasite population is vulnerable to extinction. Specifically, if sufficient parasites are introduced into the disease-free predator-prey populations, the parasite population persists and reaches a stable equilibrium in the bistable region if the initial density is large enough. In contrast, with

260 sufficient disturbance if only a few parasites are introduced into the disease-free populations,
261 or if sufficient disturbance occurs when the parasite population is already established, the
262 parasite population could go extinct (Figure 5C).

263 **The effect of host manipulation on ecological dynamics**

264 Host manipulation can be cooperative; two parasites increase the predation rate on inter-
265 mediate hosts, or $\beta_{ww} > \beta_w$. However, it can also be uncooperative; the predation rate on
266 doubly-infected intermediate hosts is lower than that on singly-infected ones or $\beta_{ww} < \beta_w$.
267 Cooperation in parasite manipulation increases the parasite's basic reproduction ratio R_0 ,
268 but the manipulation in a single infection substantially affects the value of R_0 (Figure 64).
269 Intuitively, if the manipulation in a single infection is minor, there is not enough transmission,
270 and the parasite goes extinct. However, suppose we could suppose that the ability to ma-
271 nipulate the host in a single infection is merely enough for the parasite population to escape
272 extinction. In that case, the system is in a bistable state where intermediate cooperation
273 in host manipulation cannot guarantee a single equilibrium (Hatched area Figure 6 Left4).
274 In the bistable region, the basic reproduction ratio can be less than one, implying that the
275 parasite with manipulative values within this range, i.e. weak manipulation ability, cannot
276 spread. When the system encounters bistability, the parasite population risks extinction if
277 there is a disturbance in the community. In the following parts, we will explore scenarios
278 where bistability may occur.

279 Besides manipulation, co-infecting parasites can influence each other in different life his-
280 tory traits. Parasites can have an enhanced reproduction rate in coinfections, i.e. $f_{ww} > f_w$
281 (upper part of the horizontal line in Figure 6 Right all panels Figure 6). Likewise, they can
282 compete for resources, so reproduction in double infection is suppressed compared to single
283 infection (lower part parts of the horizontal line in Figure 6 Right lines in all panels Figure
284 6). Without any assumption on the relationship link between manipulative ability and re-
285 production, and a linear relationship between manipulation in single and double infections,

we explore all possible combinations of cooperation-sabotage range in manipulation and suppressed-enhanced range in reproduction. This results in four scenarios of parameter combinations: i, parasites sabotage manipulation but have enhanced reproduction – manipulative incoordination (top left ~~quadrant in Figure 6 Right~~quadrants in all panels Figure 6), ii, parasites cooperate to increase manipulation and enhance reproduction – coordination (top right ~~quadrant in Figure 6 Right~~quadrants in all panels Figure 6), iii, parasites cooperate in manipulation but suppress reproduction – reproductive incoordination (bottom right ~~quadrant in Figure 6 Right~~quadrants in all panels Figure 6), and iv, parasites sabotage manipulation and suppress reproduction – discordance (bottom left ~~quadrant in Figure 6 Right~~quadrants in all panels Figure 6).

If coinfecting parasites are discordant, i.e. uncooperative in manipulations and show suppressed reproduction, they cannot persist (Figure 6A-D). On the other extreme, where they are highly cooperative in manipulation and show enhanced reproduction, i.e., an extreme level of coordination, there is a guaranteed single equilibrium for parasite existence. Note that this happens at the combination of $\beta_{ww}/\beta_w \rightarrow \infty$ and $f_{ww}/f_w \rightarrow \infty$, a scenario that is rather impossible in reality. ~~Very often, we~~ We often expect intermediate levels of coordination where a bistable area could occur (top left quadrant in Figure 6 at $f_w = (37, 37.5)$ A, C, D). 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 ~~to the point so~~ that sufficiently large reproduction in a single infection can guarantee single equilibrium when parasites coordinate (~~top left quadrant in Figure 6 Left at $f_w = (38)$, Figure SI.2~~ Figure 6 B). In contrast, slightly reducing values of ~~reproduction and manipulation in single infection increase either reproduction or manipulation in a single infection increases~~ the bistability area (Figure 6A, C, D). If the parasites sabotage each other, the system is highly prone to bistability and only has a single equilibrium when reproduction is ~~especially enhanced(left side of vertical line in Figure 6 Left)enhanced~~. Interestingly, ~~sufficiently high reproduction enhancement leads to bistability (i.e. f_{ww} is at least four times f_w)~~, and re-

productive incoordination, i.e. depressed reproduction and manipulative cooperation, always leads to a single equilibrium of the system (Figure 5A, and bottom right quadrant in Figure 6LeftB, D). 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 no significant tradeoffs and reproduction or manipulation in single infections are large enough.

We now explore the effect of co-transmission probability on the bistability of the system (Figure 7). First, extinction is more likely with varying levels of co-transmission from the parasite pool to the intermediate host, p , compared to varying levels of co-transmission from the intermediate host to the definitive host, q . For exceptionally high levellevels of cooperation and not very small values of bothintermediate values of p 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 decreases with increasing p and q . However, this bistable area disappearsdisappears with high values of q but not with high values of p . When parasites cooperate in manipulation, reducing p almost always lead to bistability where asleads to bistability, whereas reducing q can lead to a single equilibrium if cooperation is sufficiently large. Bistability indicates vulnerability to disturbance, andso cooperation in manipulation may be beneficial when q , the co-transmission from the intermediate host to the definitive host, decreases. However, cooperation in manipulation may still harm the population withby reducing p , the co-transmission from the parasite pool to the intermediate host.

Discussion & Conclusion

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

339 hosts to increase the predation rate of definitive hosts may result in a heavy burden of preda-
340 tors on the intermediate host population. This pressure can make parasites more vulnerable
341 to extinction (Hadeler and Freedman, 1989; Fenton and Rands, 2006).

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

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

363 Another study on host manipulation, Iritani and Sato (2018), showed that manipulative
364 parasites persist if they switch from suppressing to boosting predation rate. This theoretical
365 work modelled the ability to change the manipulative strategy of a single parasite inside

366 a host, which can be equal to introducing the developmental state of a parasite, where a
367 suppressed predation rate protects the parasites that are not ready to transmit. That is
368 why decreasing manipulative ability is beneficial and prevents parasite extinction. In our
369 model, sabotaging manipulation also reduces manipulative ability, which only reduces the
370 basic reproduction ratio R_0 and makes the system bistable, exposing the parasite to the risk
371 of extinction. This result contrasts with [Iritani and Sato \(2018\)](#) because in our model, the
372 parasite cannot switch its manipulative strategy, and sabotage decreases the transmission
373 rate from intermediate to definitive host and does not benefit the parasite in any way.

374 In our study, population dynamics exhibit bistability under certain circumstances. This
375 is very likely due to the introduction of co-transmission, which has been shown to result in
376 bistable population dynamics in plant virus [Allen et al. \(2019\)](#) and infectious diseases [Gao](#)
377 [et al. \(2016\)](#). In this bistability region, if the system is disturbed (e.g. migration of the
378 intermediate or definitive hosts or predation of intermediate hosts by other predators), then
379 the density of the infected hosts may crash, leading to parasite extinction. The bistability
380 region widens as parasites show enhanced reproduction but sabotage manipulation. This
381 extension is because the density of the doubly infected hosts is always much smaller than
382 the singly infected hosts, limited by sequential transmission and a small probability of co-
383 transmission. If manipulation in a single infection is insufficient, then the transmission of
384 the parasites depends mainly on the doubly infected hosts, which is rare. So, extinction is
385 possible if manipulation in double infections is low.

386 Finally, our study focuses on the ecological dynamics of a trophically transmitted parasite
387 between two host species. In nature, parasites with complex life cycles can have more than
388 two hosts. However, our model of a single intermediate host species [can already provide](#)
389 [already includes](#) enough complexity to discuss the relationship between transmission and
390 manipulation. Here, we introduce more realistic features compared to previous models, such
391 as a free-living parasite pool and multiple infections, regardless of some simplifications, such
392 as multiple infections being limited to at most two parasites. In this way, we can obtain

393 analytical results of the reproduction ratio and mathematical expressions for the existing
394 condition of the parasite. Our model serves as a groundwork for future exploration into more
395 complex and realistic systems, where numerical simulation may be the only possible approach.
396 Moreover, the results of our ecological model are a baseline for further investigation of the
397 evolution of host manipulation, where introducing the parasite pool may create interesting
398 eco-evolutionary ~~feedbacks~~feedback to the system.

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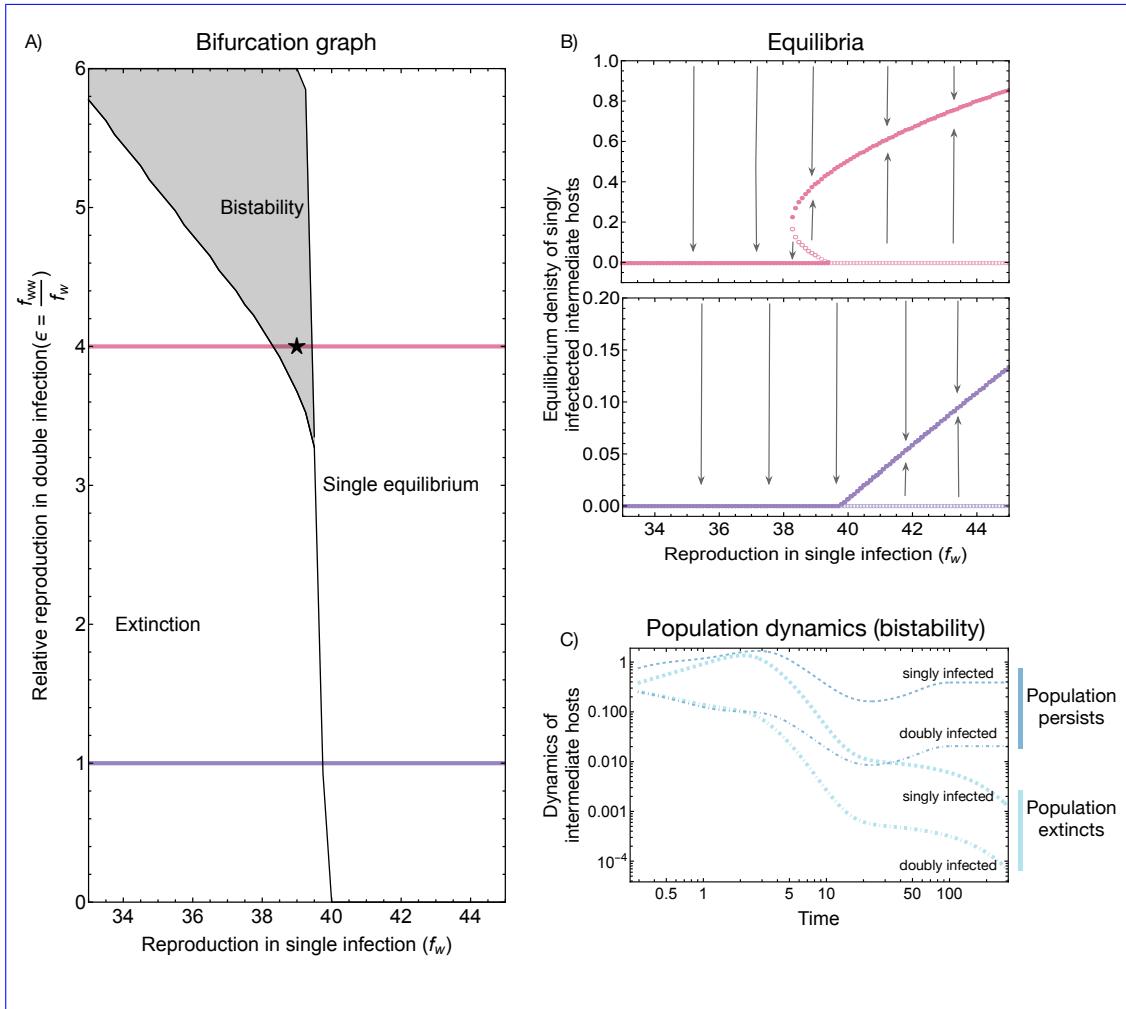


Figure 5: Effect of parasite reproduction on the ecological dynamics. A) Enhanced A bifurcation graph for different reproduction values in single and double infection leads to bistability, infections. B, C) Density Equilibrium density of singly infected intermediate host at equilibrium when reproduction $\epsilon = 4$ when bistability occurs at high values of parasites are the same f_w (in singly and doubly infected hosts $f_{ww} = f_w$ pink), and $\epsilon = 4$ when reproduction only one stable equilibrium exists at high values of parasites f_w (in doubly infected hosts is enhanced four times than those purple). C) Details of the parasite population dynamics in singly the case of bistability shown through the infected intermediate hosts $f_{ww} = 4f_w$. When the parasites start at high density, the parasite population persists, whereas when they start at lower density, they perish. Filled circles indicate stable equilibrium, and open circles indicate unstable equilibrium. Parameter $\rho = 1.2$, $d = 0.9$, $r = 2.5$, $\gamma = 2.9$, $\alpha_w = 0$, $\alpha_{ww} = 0$, $\beta_w = 1.5$, $\beta_{ww} = 1.5$, $p = 0.05$, $c = 1.4$, $\mu = 3.9$, $\sigma_w = 0$, $\sigma_{ww} = 0$, $q = 0.05$, $\delta = 0.9$, $k = 0.26$, $h = 0.6$.

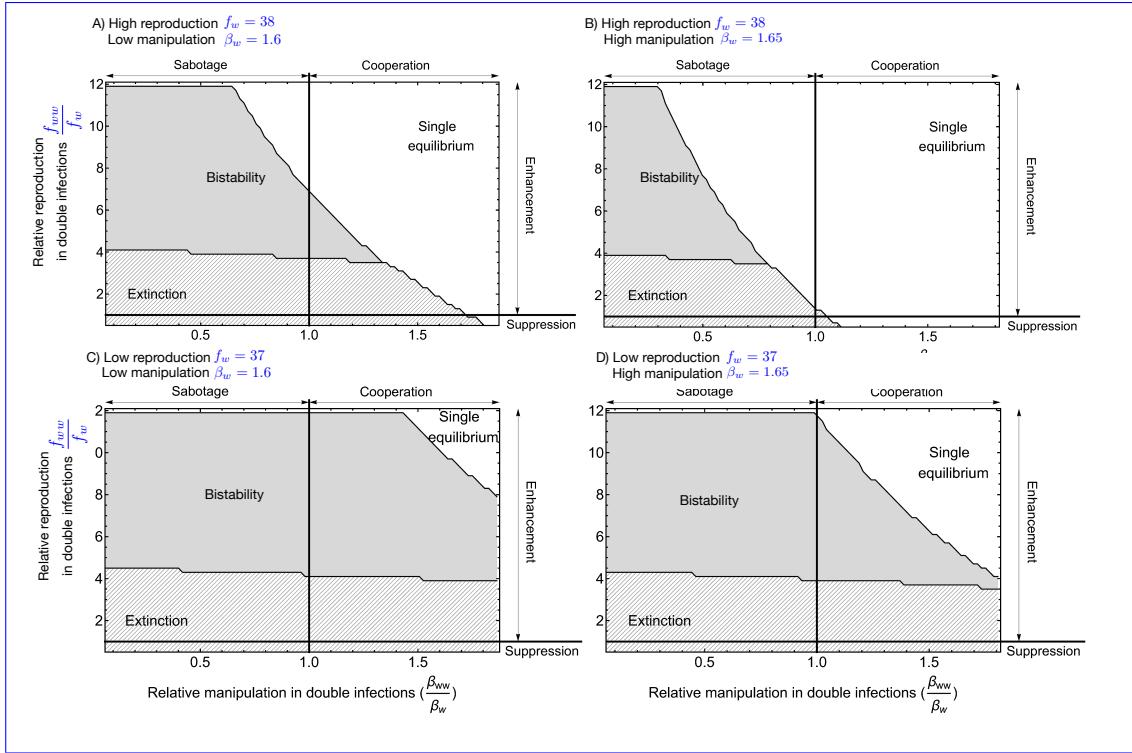


Figure 6: Effect of manipulation and reproduction on bistability. **Left:** R_0 values increase with more efficient manipulation in single and double infection. The hatched bistability area indicates (shaded areas) reduces as the bistable region. As reproduction rate (f_w) and manipulation (β_w) in single infection increases, the system only has one stable equilibrium. On the black line, the manipulation level is equal between Reproduction in single and double infection ($\beta_w = \beta_{ww}$). It decreases from the upper triangular area panels (A, parasites cooperate, and in B) to the lower triangular area, parasites sabotage. **Right:** Changes in the bistability area panels (shaded areas C, D) concerning different reproduction rates while manipulation in single infection increases from the left panels (different boundary styles A, C) to the right panels (B, D). Manipulation and reproduction levels are equal between single and double infection on the vertical and horizontal lines. 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: $\rho = 1.2$, $d = 0.9$, $r = 2.5$, $\gamma = 2.9$, $\alpha_w = 0$, $\alpha_{ww} = 0$, $p = 0.05$, $c = 1.4$, $\mu = 3.9$, $\sigma_w = 0$, $\sigma_{ww} = 0$, $q = 0.05$, $\delta = 0.9$, $k = 0.26$, $\beta_w = 1.65$, $h = 0.6$.

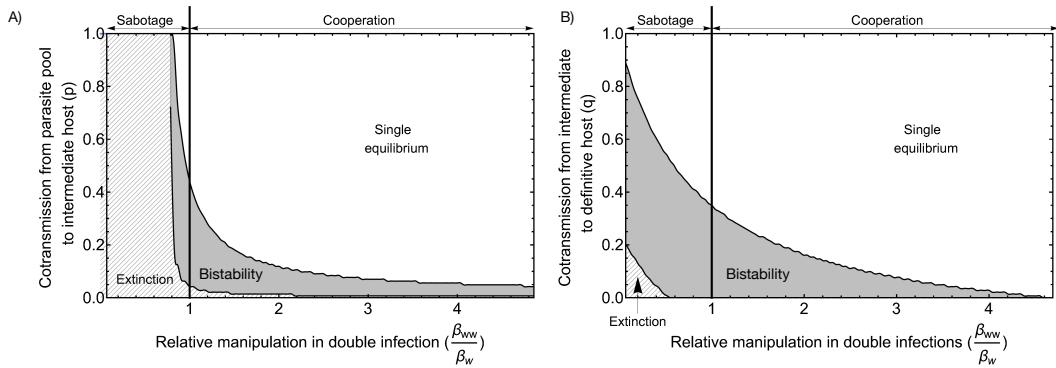


Figure 7: Left: A) Effect of cotransmission from parasite pool to intermediate host. Right: B) Effect of eotransmission-co-transmission from intermediate to the definitive host. On the left side of the vertical line, $\beta_{ww} > \beta_w$, indicating cooperation, whereas on the right side of the vertical line, $\beta_{ww} < \beta_w$, indicating sabotage. Common parameters: $\rho = 1.2$, $d = 0.9$, $r = 2.5$, $\gamma = 2.9$, $\alpha_w = 0$, $\alpha_{ww} = 0$, $p = 0.05$, $c = 1.4$, $\mu = 3.9$, $\sigma_w = 0$, $\sigma_{ww} = 0$, $q = 0.05$, $\delta = 0.9$, $k = 0.26$, $\epsilon = 4.5$, $\beta_w = 1.45$, $f_w = 38$, $h = 0.6$.