

1           **Abstract:** Host manipulation is a common strategy of parasites with complex  
2       life cycles. 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**

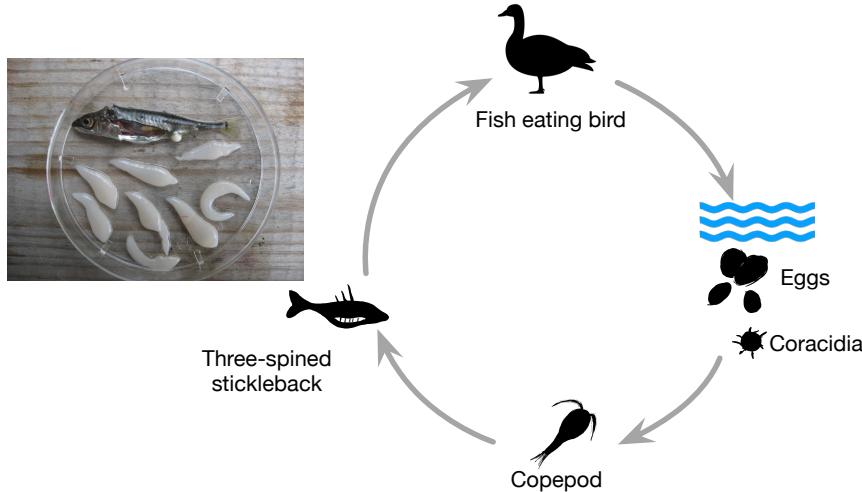
16 Parasites infect life on earth ubiquitously, and many of these parasites have complex life cycles  
17 (Zimmer, 2001). While a complex life cycle can be defined as abrupt ontogenetic changes in  
18 morphology and ecology (Benesh, 2016), it typically involves numerous host species that  
19 a parasite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

54 Theoretical work that considers multiple infections often focuses on the evolution of viru-  
55 lence (van Baalen and Sabelis, 1995; Alizon et al., 2013; Alizon and van Baalen, 2008; Choisy  
56 and de Roode, 2010; Alizon, 2012), while host manipulation in trophically transmitted par-  
57 asites receives less attention. Even though host manipulation and virulence correlate with  
58 parasite transmission, there are subtle differences, such that virulence implies an addition to  
59 the natural mortality rate of the infected host, whereas manipulation links to the immediate  
60 death of the intermediate host due to predation. Host manipulation in trophically transmitted  
61 parasites, therefore, strongly affects the entire predator-prey dynamics. Theoretical studies  
62 regarding host manipulation rarely consider multiple infections. Studies incorporating this  
63 feature neglect the predator-prey dynamics, which will likely have important feedback on the  
64 evolution of host manipulation (Parker et al., 2003; Vickery and Poulin, 2009). Moreover,  
65 these models assume that transmission from definitive hosts to intermediate hosts is due to  
66 direct contact between the two types of hosts (Rogawa et al., 2018; Hadeler and Freedman,  
67 1989; Fenton and Rands, 2006). This is often not the case in nature, as parasites are re-  
68 leased from the definitive hosts into the environment. Transmission thus happens only when

Specific example of a parasite with a complex lifecycle



**Figure 1: Who is in control?** Schistocephalus eggs hatch into microscopically tiny swimming larvae. These larvae are eaten by copepods, 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 presence of multiple parasites in the same host can lead to competition and strategic decisions about investment in manipulation and growth. Indeed, a stickleback can be infected by numerous parasites, all vying for control, as shown and photographed by Martin Kalbe ([Kalbe et al., 2002](#)). While this is a specific example of a parasite with a complex life cycle, our model abstracts the concept to generic multi-host life cycles with an environmental component.

69 intermediate hosts have contact with this free-living parasite pool. The inclusion of this free-  
 70 living stage could have a profound effect on the dynamics of the whole predator-prey-parasite  
 71 system.

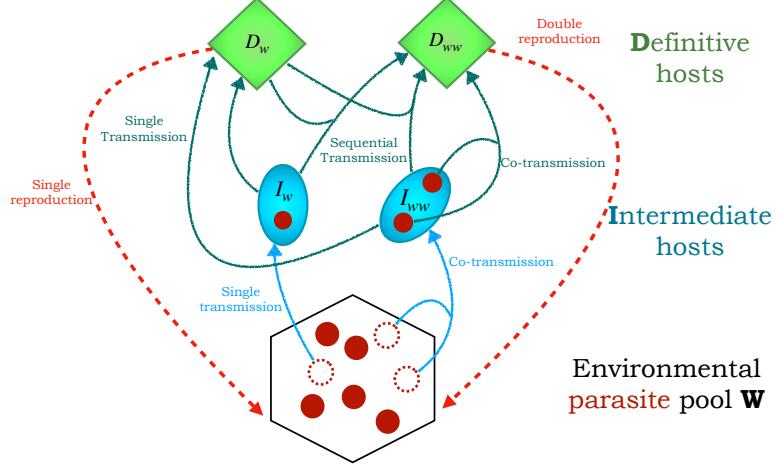
72 Our study addresses the gap in the theoretical work on host manipulation in trophically  
 73 transmitted parasites. We include multiple infections of the same parasite species and con-  
 74 sider the dynamics of the free-living parasite pool. Our compartment model helps illustrate  
 75 a parasite's complex life cycle with two host species: an intermediate host preyed upon  
 76 by a definitive host. Transmission from the intermediate host to the definitive host occurs  
 77 when predation on infected intermediate hosts happens. Reproduction only happens in the

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

## 88 Model

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

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

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

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

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

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

132 For the definitive hosts, we have,

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

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

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

143 where  $f_w$  and  $f_{ww}$  are the reproduction rates of parasites in single and double infection,  
 144 respectively, and parasites die naturally at a rate  $\delta$ .

145 Here, we focus on manipulation that enhances transmission from intermediate hosts to  
 146 definitive hosts; we thus simplify the transmission from the parasite pool to intermediate  
 147 hosts so that no sequential infection occurs. This assumption is motivated because the  
 148 prey's life cycle is often shorter than the predator's. A prey likely encounters the free-living  
 149 parasite pool once and then dies due to predation, making sequential transmission less likely  
 150 at this state. Sequential infection can happen when parasites transmit from intermediate  
 151 hosts to definitive hosts. Therefore, a singly infected definitive host can be further infected  
 152 by another parasite if it consumes infected intermediate hosts.

## 153 Basic reproduction ratio $R_0$ of the parasites

154 The basic reproduction ratio  $R_0$  (or basic reproduction number as often used in epidemiology)  
 155 indicates parasite fitness. It can be understood as the expected number of offspring a parasite

**Table 1:** Description of variables and parameters

Parameters and Variables	Description	Dimensionality
$I_i$	Density of intermediate hosts that are susceptible $i = s$ , singly infected $i = w$ , or doubly infected $i = ww$	$[I_i]t^{-1}$
$D_i$	Density of definitive hosts that are susceptible $i = s$ , singly infected $i = w$ , or doubly infected $i = ww$	$[D_i]t^{-1}$
$W$	Density of parasites released from definitive hosts into the environment	$[W]t^{-1}$
$r$	Reproduction rate of intermediate host	$t^{-1}$
$k$	Competition coefficient	$[I_i]^{-1}$
$d$	Natural death rate of intermediate hosts	$t^{-1}$
$\alpha_i$	Additional death rate of intermediate hosts due to infection by a single parasite ( $i = w$ ) or two parasites ( $i = ww$ )	$t^{-1}$
$p$	Probability that two parasites co-transmit from the environment to an intermediate host	dimensionless
$\gamma$	Transmission rate of parasites in the environment to intermediate hosts	$[W]^{-1}t^{-1}$
$\rho$	Baseline capture rate	$[I_i]^{-1}t^{-1}$
$c$	Coefficient of energy conversion into new definitive host	dimensionless
$\mu$	Natural death rate of definitive hosts	$t^{-1}$
$\sigma_i$	Additional death rate of definitive hosts due to infection by a single parasite ( $i = w$ ) or two parasites ( $i = ww$ )	$t^{-1}$
$\sigma_i$	Additional death rate of the hosts due to being infected by a single parasite ( $i = w$ ) or two parasites ( $i = ww$ )	$t^{-1}$
$q$	Probability that two parasites co-transmit from intermediate hosts to definitive hosts	dimensionless
$\beta_i$	Transmission rate of parasites from intermediate hosts to definitive hosts	$[I_i]^{-1}t^{-1}$
$f_i$	Reproduction rate of parasites in singly infected definitive hosts ( $i = w$ ) or doubly infected hosts ( $i = ww$ )	$t^{-1}$
$\delta$	Natural death rate of parasites in the environment	$t^{-1}$
$h$	Probability that the parasites successfully established inside the definitive host	dimensionless

\*  $[I_i]$ ,  $[D_i]$ , and  $[W]$  have the same unit (*individual area<sup>-1</sup>*)

<sup>156</sup> produces during its lifetime when introduced to a susceptible host population. We calculate

<sup>157</sup> the basic reproduction ratio  $R_0$  using the next-generation method (Diekmann et al., 1990,

158 2009; Hurford et al., 2010) (See SI1 for details).

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

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

169 If  $R_0 > 1$ , a parasite spreads when introduced into the disease-free equilibrium of prey and  
 170 predator. Intuitively, the higher the density of susceptible intermediate and definitive hosts,  
 171 the larger the value of  $R_0$  as the infection reservoir is more extensive. In contrast, regardless  
 172 of the explicit form of the predation function, the higher the predation rate  $P_w$  and  $P_{ww}$ , the  
 173 lower the value of  $R_0$  given the smaller reservoir of intermediate hosts. The effect of host  
 174 manipulation on the value of  $R_0$  is more complex; as host manipulation becomes efficient,  
 175 the transmission rate from the intermediate host to the definitive host increases, but so does  
 176 the predation rate. A higher predation rate results in a smaller intermediate host reservoir  
 177 for the parasites to infect. To understand the effect of manipulation on parasites' fitness  
 178 and the system's ecological dynamics, we next specify the predation functions. We consider

179 linear functions for predation to begin with,

$$P_s(D_{total}) = \rho D_{total}$$

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

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

180 where  $\rho$  is the baseline capture rate of the predator on the prey. If an intermediate host is  
181 infected, it is captured by the definitive hosts with rate  $\rho + \beta_w$  if it is singly infected and with  
182 rate  $\rho + \beta_{ww}$  if it is doubly infected. Zero values for  $\beta_w$  and  $\beta_{ww}$  suggest no manipulation,  
183 and predation is at the baseline value  $\rho$ .

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

$$B(D_{total}, I_{total}) = \rho c D_{total} I_{total}$$

185 where  $c$  is the efficiency of converting prey into predator's offspring. It is important to note  
186 that host manipulation affects population dynamics via its influence on the predation rate,  
187 not the physiological aspect of the definitive host, i.e., the predator. The birth rate of the  
188 predators thus depends on the capture rate, but it is not affected by host manipulation; to  
189 our best knowledge, there is no supporting evidence to consider otherwise.

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

196 **Birth function of intermediate hosts**

197 The simplest form of the prey's birth rate is a linear function, in which case the disease-free  
198 equilibrium is always in a cyclic regime (see SI 2). This follows from the Lotka-Volterra  
199 system using linear functions for prey birth and predation ([Lotka, 1920](#)). Since the disease-  
200 free dynamics is cyclic, it is difficult to analyse the spread of a parasite using the basic  
201 reproduction ratio, which is evaluated when the disease-free state is stable. Here,  $R_0 > 1$   
202 happens when  $\gamma$ , the transmission rate from the environment to intermediate hosts, and the  
203 reproduction rates  $f_w, f_{ww}$  are quite large (as compared to the theoretical threshold shown  
204 by the mathematical conditions in SI 3). However, even when this condition is satisfied, the  
205 parasite may not be able to spread and persist in cyclic susceptible host dynamics (Figure  
206 SI.1). This result agrees with the conclusion in ([Ripa and Dieckmann, 2013](#)), which suggests  
207 that it is difficult for a mutant to invade a cyclic resident population. In our case, it is not  
208 the invasion of a mutant in a resident population but the invasion of a parasite in a cyclic  
209 disease-free host population; the argument, however, remains valid in both cases. This issue  
210 deserves a more thorough investigation, which is out of the scope of this article. Therefore,  
211 we choose a non-linear birth function of the intermediate hosts to obtain a stable disease-free  
212 state and focus on the effect of host manipulation on the ecological dynamics (Figure 3).

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

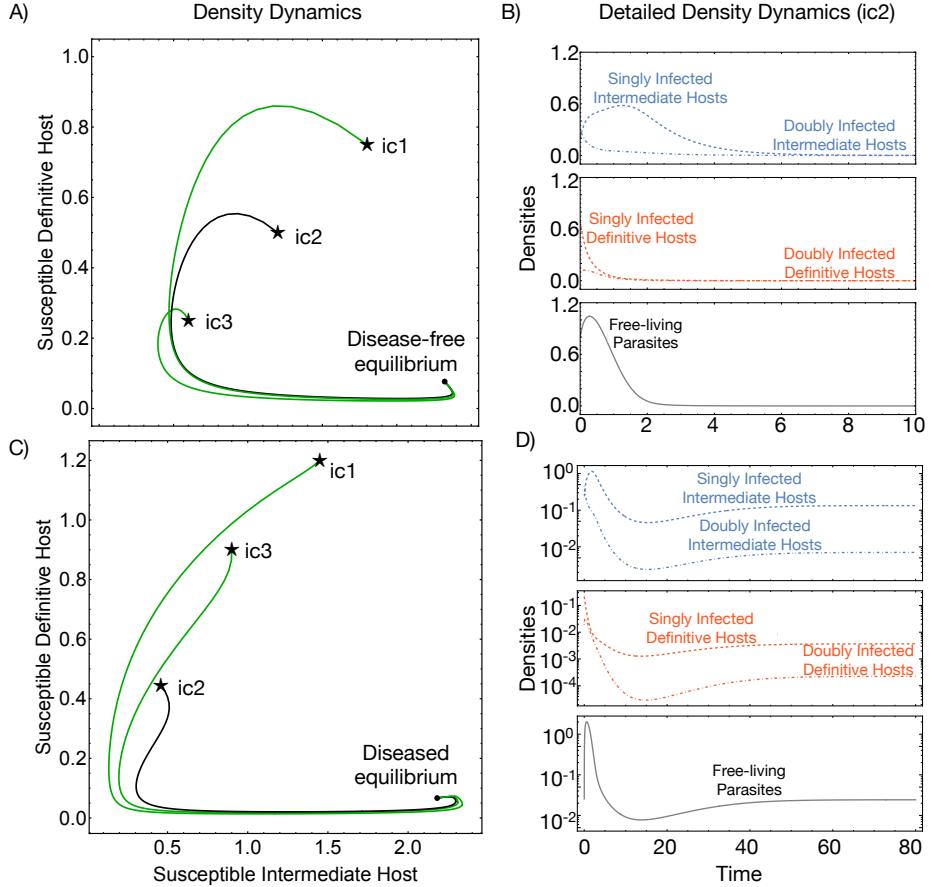
$$R(I_{total}) = rI_{total}(1 - kI_{total})$$

214 where  $r$  is the intrinsic growth rate of the intermediate hosts, and  $k$  is the intraspecific  
215 competition coefficient. The disease-free equilibrium is as follows,

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

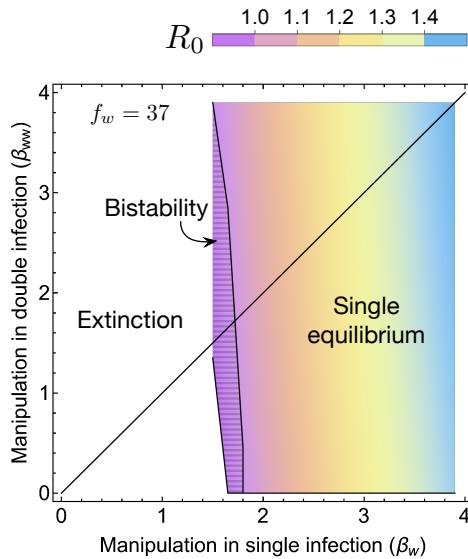
216 This equilibrium is positive and stable if components of the parasite, such as reproduction

and transmission, are sufficiently small; details of the condition can be found in section SI 4.  
 Here, as the reproduction and transmission values of the parasite are not sufficient, it goes extinct (Figure 3A, B), leaving the predator-prey dynamics attaining equilibrium (Figure 3C, D)



**Figure 3: Ecological dynamics of the predator-prey-parasite system.** On the left, we show the density dynamics of the susceptible intermediate and definitive hosts at different initial conditions (ic1, ic2, and ic3). The detailed dynamics of infected compartments are further shown for specific initial conditions (ic2), including the free-living parasite dynamics. A-B) A case of 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 has the same parameter values except for higher host manipulation  $\beta_w = \beta_{ww} = 4.5$  and parasite reproduction  $f_w = f_{ww} = 45$

221 When a parasite appears in the disease-free equilibrium, it spreads if its reproduction ratio  
 222  $R_0 > 1$  (Figure 4). Since the expression is complicated, we could only obtain analytical  
 223 solutions for this inequality with assumptions. We assume the same parasite virulence,  
 224  $\alpha_w = \alpha_{ww}$ ,  $\sigma_w = \sigma_{ww}$ , and reproduction in double infection as a linear function concerning  
 225 reproduction in single infections,  $f_{ww} = \epsilon f_w$ . When  $\epsilon > 1$ , reproduction in double infections  
 226 is enhanced compared to in single infections, whereas for  $\epsilon \leq 1$ , it is suppressed or equal to  
 227 reproduction in single infections. We found that the parasite can establish if its reproduction  
 228 value in a single infection  $f_w$  is more significant than a threshold (Figure 5, see section SI 5  
 229 and Eq. (SI.19)).



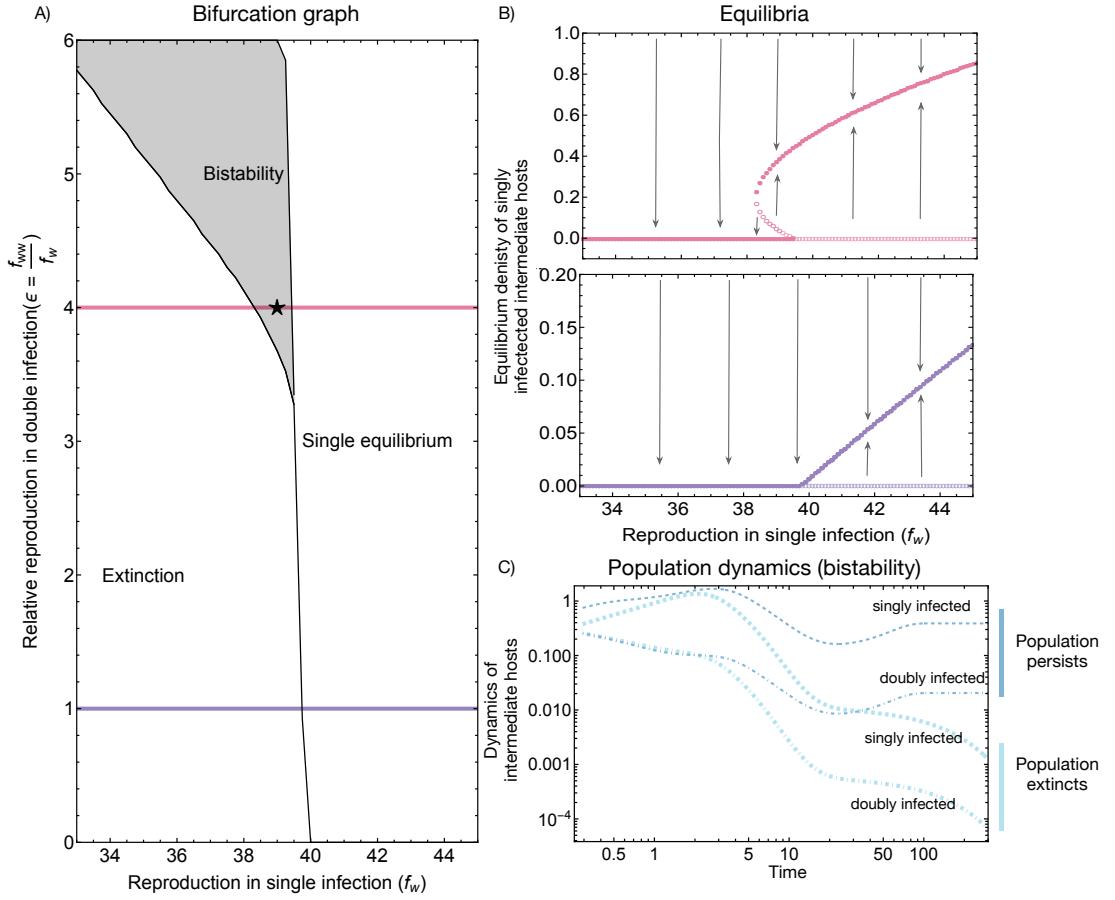
**Figure 4: Effect of manipulation in single and double infections on the reproduction ratio  $R_0$ .**  $R_0$  values increase with more efficient manipulation in single and double infection. The hatched area indicates the bistable region. As manipulation in single infection increases, the system only 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:  $\rho = 1.2$ ,  $d = 0.9$ ,  $r = 2.5$ ,  $\gamma = 2.9$ ,  $\alpha_w = 0$ ,  $\alpha_{ww} = 0$ ,  $p = 0.05$ ,  $c = 1.4$ ,  $\mu = 3.9$ ,  $\sigma_w = 0$ ,  $\sigma_{ww} = 0$ ,  $q = 0.05$ ,  $\delta = 0.9$ ,  $k = 0.26$ ,  $f_w = 37$ ,  $\epsilon = 4.5$ ,  $h = 0.6$ .

230 Our numerical results show that the parasite reproduction is substantial compared to  
 231 other parameters (Figure 5A). For instance, in the parameter set used to generate Figure

5, 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 should  
release many offspring into the environment to persist. Interestingly, bistability occurs if  
the reproduction rate of the parasite in double infections is enhanced. 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 contrast, if only a few parasites are introduced into the  
disease-free populations, or if sufficient disturbance occurs when the parasite population is  
already established, the parasite population could go extinct (Figure 5C).

#### 243 **The effect of host manipulation on ecological dynamics**

244 Host manipulation can be cooperative; two parasites increase the predation rate on interme-  
245 diate hosts, or  $\beta_{ww} > \beta_w$  (Hafer and Milinski, 2015). However, it can also be uncooperative;  
246 the predation rate on doubly-infected intermediate hosts is lower than that on singly-infected  
247 ones or  $\beta_{ww} < \beta_w$  (Hafer and Milinski, 2015). Cooperation in parasite manipulation increases  
248 the parasite's basic reproduction ratio  $R_0$ , but the manipulation in a single infection substan-  
249 tially affects the value of  $R_0$  (Figure 4, see section SI 6 for analytical results). Intuitively,  
250 if the manipulation in a single infection is minor, there is not enough transmission, and the  
251 parasite goes extinct. However, we could suppose that the ability to manipulate the host in  
252 a single infection is enough for the parasite population to escape extinction. In that case,  
253 the system is in a bistable state where intermediate cooperation in host manipulation cannot  
254 guarantee a single equilibrium (Hatched area Figure 4). In the bistable region, the basic  
255 reproduction ratio can be less than one, implying that the parasite with manipulative values  
256 within this range, i.e. weak manipulation ability, cannot spread. This is due to the Allee  
257 effect (Stephens et al., 1999) where the parasite spreads and persists if, initially, there are



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

258 sufficient parasites in the free-living pool as well as in the intermediate and definitive hosts.  
259 On the contrary, if the initial populations of parasites are insufficient, the parasite will perish  
260 (Figure SI.2). In addition, when the system encounters bistability, the parasite population

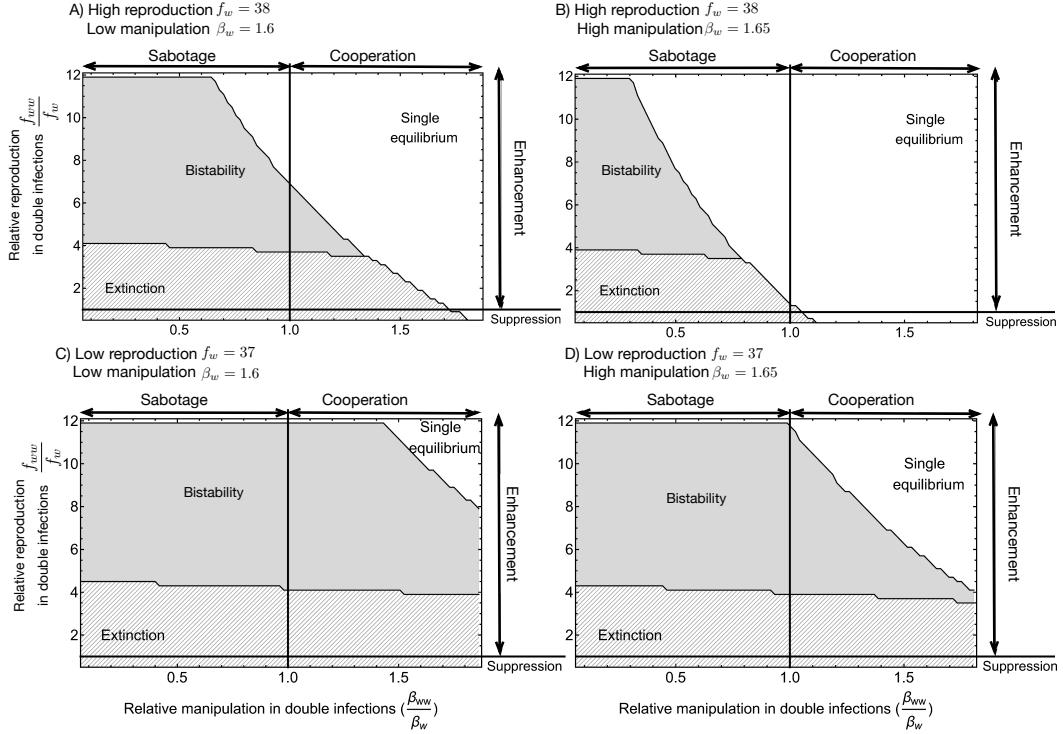
261 risks extinction if there is a disturbance in the community. In the following parts, we will  
262 explore scenarios where bistability may occur.

263 Besides manipulation, co-infecting parasites can influence each other in different life his-  
264 tory traits. Parasites can have an enhanced reproduction rate in coinfections, i.e.  $f_{ww} > f_w$   
265 (upper part of the horizontal line in all panels Figure 6). Likewise, they can compete for re-  
266 sources, so reproduction in double infection is suppressed compared to single infection (lower  
267 parts of the horizontal lines in all panels Figure 6). Without any assumption on the link be-  
268 tween manipulative ability and reproduction, and a linear relationship between manipulation  
269 in single and double infections, we explore all possible combinations of cooperation-sabotage  
270 range in manipulation and suppressed-enhanced range in reproduction. This results in four  
271 scenarios of parameter combinations: i, parasites sabotage manipulation but have enhanced  
272 reproduction – manipulative incoordination (top left quadrants in all panels Figure 6), ii,  
273 parasites cooperate to increase manipulation and enhance reproduction – coordination (top  
274 right quadrants in all panels Figure 6), iii, parasites cooperate in manipulation but suppress  
275 reproduction – reproductive incoordination (bottom right quadrants in all panels Figure 6),  
276 and iv, parasites sabotage manipulation and suppress reproduction – discordance (bottom  
277 left quadrants in all panels Figure 6).

278 If coinfecting parasites are discordant, i.e. uncooperative in manipulations and show sup-  
279 pressed reproduction, they cannot persist (bottom left quadrants Figure 6A-D). On the other  
280 extreme, where they are highly cooperative in manipulation and show enhanced reproduction,  
281 i.e., an extreme level of coordination, there is a guaranteed single equilibrium for parasite  
282 existence (top right quadrants Figure 6A-D). Note that this happens at the combination  
283 of  $\beta_{ww}/\beta_w \rightarrow \infty$  and  $f_{ww}/f_w \rightarrow \infty$ , a scenario that is rather impossible in reality. We  
284 often expect intermediate levels of coordination where a bistable area could occur (top right  
285 quadrant in Figure 6A, C, D). However, the size of this area is sensitive to the value of  
286 reproduction and manipulation in a single infection. In particular, higher values of these  
287 two parameters reduce the bistability area so that sufficiently large reproduction in a single

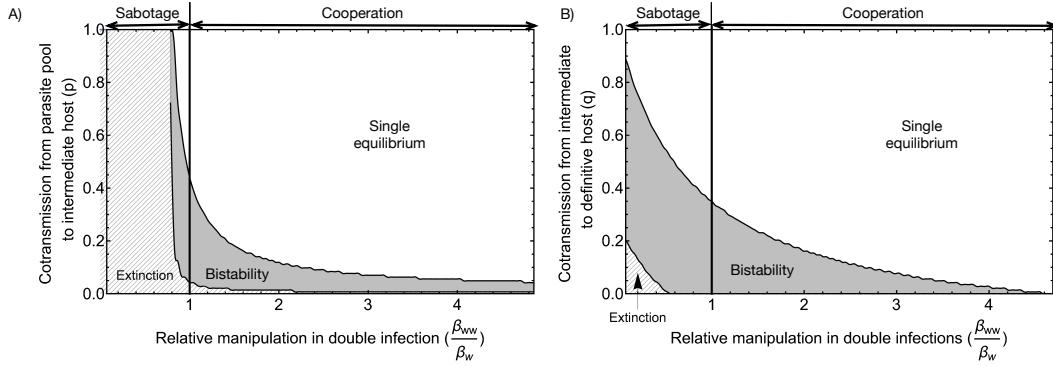
infection can guarantee single equilibrium when parasites coordinate (Figure 6 B, D). In contrast, slightly reducing values of either reproduction or manipulation in a single infection increases the bistability area (Figure 6A, C, D). If the parasites sabotage each other, the system is highly prone to bistability and only has a single equilibrium when reproduction is enhanced. Interestingly, reproductive incoordination, with depressed reproduction and sufficient manipulative cooperation, always leads to a single equilibrium of the system (bottom right quadrants Figure 6, note that if we extend the relative manipulation in Figure C and D, we also obtain single equilibrium in this area). 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 levels of cooperation and intermediate 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 disappears with high values of  $q$  but not with high values of  $p$ . When parasites cooperate in manipulation, reducing  $p$  almost always leads to bistability, whereas reducing  $q$  can lead to a single equilibrium if cooperation is sufficiently large. Bistability indicates vulnerability to disturbance, so 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



**Figure 6: Effect of manipulation and reproduction on bistability.** The bistability area (shaded areas) reduces as the reproduction rate ( $f_w$ ) and manipulation ( $\beta_w$ ) in a single infection increases. Reproduction in single infection decreases from the upper panels (A, B) to the lower panels (C, D), while manipulation in single infection increases from the left panels (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:  $\rho = 1.2$ ,  $d = 0.9$ ,  $r = 2.5$ ,  $\gamma = 2.9$ ,  $\alpha_w = 0$ ,  $\alpha_{ww} = 0$ ,  $p = 0.05$ ,  $c = 1.4$ ,  $\mu = 3.9$ ,  $\sigma_w = 0$ ,  $\sigma_{ww} = 0$ ,  $q = 0.05$ ,  $\delta = 0.9$ ,  $k = 0.26$ ,  $\beta_w = 1.65$ ,  $h = 0.6$ .

315 the population by reducing  $p$ , the co-transmission from the parasite pool to the intermediate  
 316 host.



**Figure 7:** A) Effect of cotransmission from parasite pool to intermediate host. B) Effect of 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:  $\rho = 1.2$ ,  $d = 0.9$ ,  $r = 2.5$ ,  $\gamma = 2.9$ ,  $\alpha_w = 0$ ,  $\alpha_{ww} = 0$ ,  $p = 0.05$ ,  $c = 1.4$ ,  $\mu = 3.9$ ,  $\sigma_w = 0$ ,  $\sigma_{ww} = 0$ ,  $q = 0.05$ ,  $\delta = 0.9$ ,  $k = 0.26$ ,  $\epsilon = 4.5$ ,  $\beta_w = 1.45$ ,  $f_w = 38$ ,  $h = 0.6$ .

## 317 Discussion & Conclusion

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

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

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

344 Another study on host manipulation, [Iritani and Sato \(2018\)](#), showed that manipulative  
345 parasites persist if they switch from suppressing to boosting predation rate. This theoretical  
346 work modelled the ability to change the manipulative strategy of a single parasite inside  
347 a host, which can be equal to introducing the developmental state of a parasite, where a  
348 suppressed predation rate protects the parasites that are not ready to transmit. That is  
349 why decreasing manipulative ability is beneficial and prevents parasite extinction. In our  
350 model, sabotaging manipulation also reduces manipulative ability, which only reduces the  
351 basic reproduction ratio  $R_0$  and makes the system bistable, exposing the parasite to the risk  
352 of extinction. This result contrasts with [Iritani and Sato \(2018\)](#) because in our model, the  
353 parasite cannot switch its manipulative strategy, and sabotage decreases the transmission  
354 rate from intermediate to definitive host and does not benefit the parasite in any way.

355 In our study, population dynamics exhibit bistability under certain circumstances. This  
356 is very likely due to the introduction of co-transmission, which has been shown to result in  
357 bistable population dynamics in plant virus [Allen et al. \(2019\)](#) and infectious diseases [Gao  
et al. \(2016\)](#). In this bistability region, if the system is disturbed (e.g. migration of the

359 intermediate or definitive hosts or predation of intermediate hosts by other predators), then  
360 the density of the infected hosts may crash, leading to parasite extinction. The bistability  
361 region widens as parasites show enhanced reproduction but sabotage manipulation. This  
362 extension is because the density of the doubly infected hosts is always much smaller than  
363 the singly infected hosts, limited by sequential transmission and a small probability of co-  
364 transmission. If manipulation in a single infection is insufficient, then the transmission of  
365 the parasites depends mainly on the doubly infected hosts, which is rare. So, extinction is  
366 possible if manipulation in double infections is low.

367 Our study specifically focuses on the ecological dynamics of a trophically transmitted  
368 parasite between two host species. In nature, parasites with complex life cycles can have more  
369 than two hosts. However, our model of a single intermediate host species already includes  
370 enough complexity to discuss the relationship between transmission and manipulation. In  
371 addition, we consider multiple infections of the same parasite species. Although, in nature,  
372 a host can be co-infected by multiple parasites of the same or different species, the results  
373 of our model stay valid as the key aspect in host manipulation is the alignment or conflict of  
374 interest between co-infecting parasites. Here, we introduce more realistic features compared  
375 to previous models, such as a free-living parasite pool and multiple infections, regardless  
376 of some simplifications, such as multiple infections being limited to at most two parasites.  
377 Thus, we can obtain analytical results of the reproduction ratio and mathematical expressions  
378 for the existing condition of the parasite.

379 Our model serves as a groundwork for future exploration into more complex and real-  
380 istic systems, where numerical simulation may be the only possible approach. Given that  
381 few studies considered measuring different parameters of trophically transmitted parasites  
382 ([Seppälä et al., 2004](#); [Gopko et al., 2015](#)), our model calls for additional empirical work to  
383 measure relevant parameters, especially those from the parasite's perspective. For instance,  
384 comparing the reproduction rate of parasites in single versus multiple infections (parameters  
385  $f_w$  and  $f_{ww}$ ) sheds light on parasite cooperation in definitive hosts. Studying the distribu-

tion of parasites in the environment (the variable  $W$ ) informs us about feeding strategies and reflects the distribution of parasites within intermediate hosts. Finally, comparing host condition (parameters  $\alpha_w$ ,  $\alpha_{ww}$ ,  $\sigma_w$ , and  $\sigma_{ww}$ ) between no infection, single and multiple infections illustrates the magnitude of parasite virulence. Although parasite virulence has been quantified in some studies, none have examined differences between single and multiple infections. Eventually, the results of our ecological model are a baseline for further investigation of the evolution of host manipulation, where introducing the parasite pool may create interesting eco-evolutionary feedback to the system.

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