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Two different strategies of host manipulation allow parasites to persist in intermediate–definitive host systems

L. J. DE VRIES & F. VAN LANGEVELDE

Resource Ecology Group, Wageningen University, Wageningen, The Netherlands

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trophic transmission.

Abstract

Trophically transmitted parasites start their development in an intermediate host, before they finish the development in their definitive host when the definitive host preys on the intermediate host. In intermediate–definitive host systems, two strategies of host manipulation have been evolved: increasing the rate of transmission to the definitive host by increasing the chance that the definitive host will prey on the intermediate host, or increasing the lifespan of the parasite in the intermediate host by decreasing the predation chance when the intermediate host is not yet infectious. As the second strategy is less well studied than the first, it is unknown under what conditions each of these strategies is prevailed and evolved. We analysed the effect of both strategies on the presence of parasites in intermediate–definitive host systems with a structured population model. We show that the parasite can increase the parameter space where it can persist in the intermediate–definitive host system using one of these two strategies of host manipulation. We found that when the intermediate host or the definitive host has life-history traits that allow the definitive host to reach large population densities, that is high reproduction rate of the intermediate host or high conversion efficiency of the definitive host (efficiency at which the uninfected definitive host converts caught intermediate hosts into offspring), respectively, evolving manipulation to decrease the predation chance of the intermediate host will be more beneficial than manipulation to increase the predation chance to enhance transmission. Furthermore, manipulation to decrease the predation chance of the intermediate host results in higher population densities of infected intermediate hosts than manipulation that increases the predation chance to enhance transmission. Our study shows that host manipulation in early stages of the parasite development to decrease predation might be a more frequently evolved way of host manipulation than is currently assumed.

Introduction

During the last decades, attention for the effects parasites can have on their hosts has grown, because effects of parasites on the dynamics of the host population can be very large (Price *et al.*, 1986; Minchella & Scott, 1991; Hudson *et al.*, 2002). Consequently, strategies that are evolved, such as how parasites infect their hosts, avoid the immune system and transmit to susceptible hosts, are extensively studied (e.g. Schmid-Hempel, 2011). One way in which parasites influence their host is by manipulating the behaviour, physiology or appearance of their host (Poulin, 2010; Vickery & Poulin, 2010; Schmid-Hempel, 2011). A large number of observations suggest that parasites manipulate the host in their own favour. Often the changes in host behaviour or appearance are subtle, for example changes in the time spent by the host on certain activities (Dianne *et al.*, 2014). However, sometimes the changes can be quite dramatic. For example, the

Correspondence: Lana J. de Vries, Resource Ecology Group, Wageningen University, Droevendaalsesteeg 3a, 6708 PB Wageningen, The Netherlands.
Tel.: +31 (0)317 483509; fax: +31 (0)317 483962;
e-mail: lana.devries@wur.nl

parasitic hairworm *Paragordius tricuspidatus* can manipulate its host, the cricket *Nemobius sylvestris*, in a way that the crickets will jump into the water when the hairworms have become adults. This is a new behaviour for the cricket; healthy individuals would not show this behaviour (Sanchez *et al.*, 2008).

Different ways of host manipulation can be distinguished to increase either the survival chances or the transmission rate of the parasites to the next host (Poulin, 2010; Vickery & Poulin, 2010; Schmid-Hempel, 2011). First, parasites can manipulate their host to go to a habitat more suitable for the parasites or the parasite propagules. Second, they can manipulate their host to protect the parasites after they have left the host, for example when they pupate outside the host. Third, in case of vector-bound parasites, they can manipulate their vector in a way that increases the transmission rate of the parasite, for example by making the vector to visit more hosts. Lastly, two ways of host manipulation can be found in trophically transmitted parasites that have both an intermediate host and a definitive host. The parasites start their development in the intermediate host, and after transmission, they finish their development in their definitive host. At the end, the definitive host can infect the uninfected intermediate host again; often eggs are transmitted via the faeces of the definitive host. Transmission from the intermediate host to the definitive host usually implies predation (Lafferty, 1999; Poulin, 2010; Vickery & Poulin, 2010; Dianne *et al.*, 2011). The two strategies of host manipulation in trophically transmitted parasites both involve manipulation of the intermediate host by increasing either the lifespan of the parasite in the intermediate host or the rate of transmission to the definitive host.

The best known strategy is manipulation of the behaviour or appearance of the intermediate host in order to increase the chance that the definitive host will prey on the intermediate host. The transmission rate from the intermediate host to the definitive host will then be increased (Lafferty, 1999; Poulin, 2010; Vickery & Poulin, 2010). A striking example is the colour change of the abdomen of *Cephalotes atratus* ants, the intermediate host, infected with the nematode *Myrmeconema neatropicum*. The abdomen of these ants changes during the infection from black to deep red. This will increase the predation risk for the ants by the definitive host of the nematode (Poinar & Yanoviak, 2008; Yanoviak *et al.*, 2008).

The second strategy, which is less well studied, is manipulation of the intermediate host by the parasite in order to decrease the predation chance (Hammerschmidt *et al.*, 2009; Dianne *et al.*, 2011; Weinreich *et al.*, 2013). Due to reduction of the predation chance, the lifespan of the parasite in the intermediate host increases to allow for longer growth and development. Only after the parasite completes part of its development, the intermediate host will become infectious to the definitive host (Tierney *et al.*, 1993). During the early developmental stage, it will not be beneficial for the parasites to be consumed by the definitive host or any other predator. Maure *et al.* (2013) argued that this manipulation to reduce predation risk and therefore the mortality of the immature parasites could be interpreted as 'bodyguard manipulation', where manipulated hosts act as bodyguards only during specific phases of the manipulation. They review the diversity of bodyguard manipulation and show that it occurs in several biological systems. For example, when the fresh water amphipod *Gammarus pulex* is infected with the acanthocephalan parasite *Pomphorhynchus laevis*, it shows increased refuge use as long as the infected amphipod is not yet infectious to its fish predators (Dianne *et al.*, 2011). However, research on host manipulation by parasites that decreases the predation chance is limited to date (Maure *et al.*, 2013; Soghigian *et al.*, 2017). Moreover, it is unknown under what conditions each of these two strategies are prevailed and evolved.

In this study, we use a modelling approach to explore under what conditions the two strategies of host manipulation allow trophically transmitted parasites to persist in predator–prey systems: decreasing predation chance early in the development of the parasite, or increasing predation chance to increase the transmission rate of the parasites. The scope of the study is limited to the possible (ecological) consequences of evolving one strategy or another, where we discuss possible selection pressures that could lead to these strategies. Although we acknowledge that these two strategies are not as separated as they are presented here, decreasing predation chances early in the parasite development may be followed by an increase in predation chances to increase the parasite transmission rate (e.g. Médoc & Beisel, 2011), we explore them separately because there is no reason to believe that they are automatically associated. Especially from an evolutionary point of view, the two strategies often require different or even opposite changes in host behaviour or appearance (Parker *et al.*, 2008). Some modelling studies of manipulative parasites with an intermediate and a definitive host have already been done (e.g. Lafferty, 1992; Fenton & Rands, 2006). Lafferty (1992) created a Lotka–Volterra type of model that investigated the energetic costs of parasites on predators. This model was used as a starting point by Fenton & Rands (2006). Fenton and Rands investigated the effect of host manipulation on the population dynamics of intermediate and definitive hosts. In their model, host manipulation increased predation of infected preys. They concluded that host manipulation could enable parasites to persist in the predator–prey system. Fenton & Rands (2006) assumed in their model that after infection, the intermediate host would directly be infectious to the definitive host and parasites would immediately start to manipulate their intermediate host to increase the

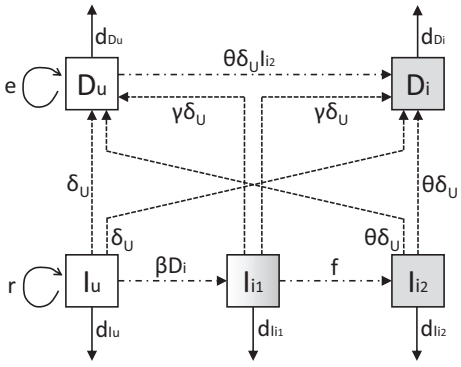

Fig. 1 Schematic diagram of the model with the most important processes. I_U and D_U are the uninfected intermediate host population and the uninfected definitive host population, respectively. I_{I1} and I_{I2} are the infected intermediate host populations, I_{I1} contains parasites of an early developmental stage, whereas I_{I2} contains parasites of an advanced developmental stage. D_I is the infected definitive host population. Predation is shown with dashed arrows, infection with dotted-dashed arrows, and reproduction and death with solid arrows. For further explanation of the parameters of this figure, see the main text.

predation. We added manipulation by the parasite to reduce the predation chance during the early developmental stage.

Model description

The model of Fenton & Rands (2006) is a density dependent model that has an uninfected intermediate host population I_U, an infected intermediate host population I_I, an uninfected definitive host population D_U and an infected definitive host population D_I. To model the manipulation by the parasite to reduce the predation chance during the early developmental stage, the development of the parasite was implemented in the model by splitting the intermediate host population into two groups. The first group consists of recently infected intermediate hosts I_{I1} that contain parasites in an early developmental stage. The second group consists of already longer infected intermediate hosts I_{I2} that contain parasites in an advanced developmental stage. Host manipulation to allow for the development of the parasite decreases the predation rate on I_{I1}, whereas host manipulation to increase the transmission rate of the parasites increases the predation rate on I_{I2}.

The equations of the model describing the rate of change in population densities of I_U, I_{I1}, I_{I2}, D_U and D_I are as follows (see also Fig. 1 and Table 1):

$$\frac{dI_U}{dt} = r_I(1 - q(I_U + I_{I1} + I_{I2}))I_U - (D_U + D_I)\delta_U I_U - \frac{v\lambda D_I I_U}{\mu} \quad (1a)$$

$$\frac{dI_{I1}}{dt} = \frac{v\lambda D_I I_U}{\mu} - (D_U + D_I)\gamma\delta_U I_{I1} - (\gamma m + (1-m))d_{I_{I1}} I_{I1} - fI_{I1} \quad (1b)$$

$$\frac{dI_{I2}}{dt} = fI_{I1} - (D_U + D_I)\theta\delta_U I_{I2} - d_{I_{I2}} I_{I2} \quad (1c)$$

$$\frac{dD_U}{dt} = e\delta_U(I_U + \gamma I_{I1} + \theta I_{I2})D_U - \delta_U\theta I_{I2} D_U - d_{D_U} D_U \quad (1d)$$

$$\frac{dD_I}{dt} = \delta_U\theta I_{I2} D_U - d_{D_I} D_I \quad (1e)$$

The uninfected intermediate host I_U reproduces following a logistic growth curve as described by the first term of eqn 1a, where r_I is the growth rate of I_U at low population density of the total intermediate host population ($I_U + I_{I1} + I_{I2}$), and $q = 1/K$, with K being the carrying capacity for the intermediate host population. Infection of I_U depends on the transmission rate $\beta = \frac{v\lambda}{\mu}$, where λ is the rate at which D_I produces infective stages of the parasite, v is the rate at which I_U ingests infective stages of the parasite, and μ is the death rate of the infective stages of the parasite outside the hosts. Parasite transmission from the definitive host to the intermediate host often goes through the faeces of the definitive host, which contains infective stages of the parasite (Yanoviak *et al.*, 2008; Dianne *et al.*, 2011). The transmission rate β I_U D_I reflects the encounters of the uninfected intermediate host with the (faeces of the) definitive host. We assume that the parasite cannot reproduce outside the intermediate or definitive host.

We assume that the infected hosts I_{I1}, I_{I2} and D_I do not reproduce, that is the parasite has a strong negative effect on fecundity (Hurd, 1998). The rates at which I_U and the infected intermediate hosts I_{I1} and I_{I2} are preyed on depend on the total definitive host population density (D_U + D_I) and on the predation rate of the definitive host δ_U. However, the rate at which the recently infected intermediate host I_{I1}, which contains parasites in an early developmental stage, is preyed on decreases with γ ($0 \leq \gamma \leq 1$). The parameter γ thus describes the decrease in predation on I_{I1} due to host manipulation by parasites in an early stage of their development. The rate at which the infected intermediate host I_{I2}, which contains parasites in an advanced developmental stage, is preyed on increases with θ ($\theta \geq 1$). The parameter θ describes the increase in predation on I_{I2} by the definitive host due to host manipulation by parasites to increase the transmission rate. The parameter f is the rate at which I_{I1} gets infectious and becomes I_{I2}. The death rate of I_{I1} is d_{Ii1}, which includes both natural death causes and death due to predation by other predators than the definitive host. Often host manipulation decreases not only predation by the definitive host, but also predation of other predators, for example, due to parasite manipulation of host behaviour that causes the avoidance of risky situations. For the manipulation strategy by parasites in an early stage

Table 1 Symbols, description of the parameters of the model and their default values.

Parameter	Description [and units]	Parameter value
I_U	Uninfected intermediate host population density [number of individuals per unit area]	0–10
I_{I1}	Recently infected intermediate host population density [number of individuals per unit area]	0–10
I_{I2}	Longer infected intermediate host population density [number of individuals per unit area]	0–10
D_U	Uninfected definitive host population density [number of individuals per unit area]	0–10
D_I	Infected definitive host population density [number of individuals per unit area]	0–10
r_I	Reproduction rate of intermediate host [1/unit of time]	0.03
e	Conversion efficiency of definitive host [–]	0–1
q	$1/K$ [1/number of individuals per unit area], with K being carrying capacity [number of individuals per unit area]	0.1
δ_U	Predation rate of definitive host [1/(unit of time × number of individuals per unit area)]	0.005
β	$\frac{v\lambda}{\mu}$, transmission rate from definitive to intermediate host [1/(unit of time × number of individuals per unit area)]	0.027
λ	Rate of production of infective stages of parasite [1/(unit of time × number of individuals per unit area)]	54
v	Rate at which I_U ingests infective stages of the parasite [1/unit of time]	0.0001
μ	Death rate of infective stages of parasite outside hosts [1/unit of time]	0.2
γ	Decrease in predation on recently infected intermediate hosts [–]	0–1
θ	Increase in predation on longer infected intermediate hosts [–]	1–10
f	Rate at which I_{I1} gets infectious and becomes I_{I2} [1/unit of time]	0.005
m	Fraction of the death rate d_{Ii1} that involves predation by other predators than the definitive host [–]	0.5
d_{Ii1}	Death rate of recently infected intermediate hosts [1/unit of time]	0.01
d_{Ii2}	Death rate of longer infected intermediate hosts [1/unit of time]	0.01
d_{Du}	Death rate of uninfected definitive hosts [1/unit of time]	0.01
d_{Di}	Death rate of infected definitive hosts [1/unit of time]	0.02

of their development, not only predation by the definitive host but also the death rate d_{Ii1} due to other predators will decrease with increasing host manipulation γ (Lagrue *et al.*, 2013). The parameter m describes the fraction of the death rate d_{Ii1} that involves predation by other predators than the definitive host. With increasing m, host manipulation in I_{I1} by the decrease of the predation chance γ will therefore result in a lower death rate d_{Ii1}. The death rate of I_{I2} is d_{Ii2}; we assume that d_{Ii2} is not increased by manipulation of the parasite by θ, as host manipulation that increases predation is most beneficial to the parasite when specifically directed towards the definitive host of the parasite (Parker *et al.*, 2008; Yanoviak *et al.*, 2008; Lagrue *et al.*, 2013). Even if increasing nonhost predation is an unavoidable side effect, we assume that this manipulation may nonetheless yield a net benefit to the parasite, at least up to a point, and hence, we left an effect of θ on predation by nonhost predators out of the model as it would not change the results qualitatively.

The reproduction of the uninfected definitive host D_U depends on the intermediate hosts caught by D_U, which is determined by the total intermediate host population densities (I_U, I_{I1} and I_{I2}), and on the predation rate. The predation rate is determined by δ_U, γ and θ. The parameter e describes the conversion efficiency, which is the efficiency at which D_U converts the caught intermediate hosts into offspring. Infection of D_U depends on the infected intermediate host I_{I2} caught by D_U. The caught I_{I2} depends on the predation rate δ_U and the increased predation on I_{I2} due to host manipulation θ. The death rate of D_U is d_{Du}, whereas the death rate of D_I is d_{Di}.

Model analysis

Effects of two strategies of host manipulation on parasite persistence

To analyse the model behaviour, the equilibria were determined first. Then, the effect of predation increase θ and predation decrease γ on the model behaviour and model outcomes was analysed, followed by the analysis of several other parameters. We could determine the first three model equilibria analytically where the parasite is absent. These model equilibria were equivalent to the model equilibria determined by Fenton and Rands (Table 2). The first equilibrium of the model with all population densities being 0 is an unstable equilibrium. The second equilibrium allows only I_U to stably persist in the system at carrying capacity when $K < \frac{d_{Du}}{\delta_U e}$, whereas population densities of I_{I1}, I_{I2}, D_U and D_I are 0. The third equilibrium with both I_U and D_U larger than 0 is stable when $K > \frac{d_{Du}}{\delta_U e}$ and $\theta < F1$ or $\gamma > F2$ (Table 2). The population density of I_U is $\frac{d_{Di}}{\delta_U e}$ and the population density of D_U is $\frac{r_I(\delta_U e - d_{Di} q)}{{\delta_U}^2 e}$. The population densities of I_{I1}, I_{I2} and D_I are 0. In these three equilibria, the parasite cannot invade. The fourth equilibrium with the parasite being present in the system could not be determined analytically. The numerical model analyses show that population densities of I_U, I_{I1}, I_{I2}, D_U and D_I are all larger than 0. The fourth equilibrium of our model differs from the fourth equilibrium of the model of Fenton and Rands, due to the distinction that we made between I_{I1} and I_{I2}. The fourth equilibrium of our study is stable when $K > \frac{d_{Du}}{\delta_U e}$ and $\theta > F1$ or $\gamma < F2$.

Table 2 The equilibria of the model. The equations for the population densities of equilibria 0, 1 and 2 could be determined analytically. The equations for the population densities of the third equilibrium could not be determined. The requirements for the equilibria 0–2 to be stable are given as well. For equilibrium 3, we found stable values as well as oscillations.

Equilibria	I_U	I_{I1}	I_{I2}	D_U	D_I	Requirements for stability
0	0	0	0	0	0	Always unstable
1	K	0	0	0	0	$K < \frac{d_{Du}}{\delta_U e}$
2	$\frac{d_{Du}}{\delta_U e}$	0	0	$\frac{r_I(\delta_U e - d_{Du} q)}{{\delta_U}^2 e}$	0	$K > \frac{d_{Du}}{\delta_U e}$ & $\theta < F1$ or $\gamma > F2$ (see below for $F1$ and $F2$)
3	> 0	> 0	> 0	> 0	> 0	$K > \frac{d_{Du}}{\delta_U e}$ & $\theta > F1$ or $\gamma < F2$

$$F1 = -\frac{d_{Ii2}\, d_{Di}\, \delta_U\, e\, (\delta_U\, e\, (d_{Ii1} + f + d_{Ii1}\, m\, (\gamma - 1)) + \gamma\, r_I\, (\delta_U\, e - d_{Du}\, q))}{r_I\, (\delta_U\, e - d_{Du}\, q)\, (-\beta\, d_{Du}\, f + d_{Di}\, \delta_U\, e\, (d_{Ii1} + f + d_{Ii1}\, m\, (\gamma - 1)) + d_{Di}\, \gamma\, r_I (\delta_U\, e - d_{Du}\, q))}$$

$$F2 = \frac{d_{Ii2}\, d_{Di}\, {\delta_U}^2\, e^2\, (d_{Ii1}\, m - d_{Ii1} - f) + r_I\, \theta\, (\beta\, d_{Du}\, f + d_{Di}\, \delta_U\, e\, (d_{Ii1}\, m - d_{Ii1} - f))\, (\delta_U\, e - d_{Du}\, q)}{d_{Di}\, (d_{Ii1}\, \delta_U\, e\, m + \delta_U\, e\, r_I - d_{Du}\, q\, r_I)\, (d_{Ii2}\, \delta_U\, e + r_I\, \theta\, (\delta_U\, e - d_{Du}\, q))}$$

A more detailed description of the calculation of the model equilibria and stability requirements can be found in Appendix A.

The parameter regions in which the different equilibria can be found are shown in Fig. 2. Region 1 in Fig. 2 corresponds with equilibrium 1 of Table 2, region 2 with equilibrium 2 and region 3 with equilibrium 3. In region 4, the host populations are oscillating over time. It can be observed that with an increasing degree of host manipulation, which means either a higher value of θ or a lower value of γ, the parasite is more likely to persist in the system, that is regions 3 and 4 together cover a larger part of the parameter space. The effect of manipulation of I_{I2} by θ on the model behaviour as shown in Fig. 2a is similar to the effect observed by Fenton and Rands. Here, at high degree of host manipulation in I_{I2}, which means at high values of manipulation of I_{I2} by θ, the host populations start to show oscillating behaviour, like Fenton and Rands found. However, host manipulation in I_{I1} by decreasing γ seems to involve lower risks of host population oscillation (Fig. 2a–f). When θ is 1, even no oscillation of host populations with decreasing γ is observed (Fig. 2d). Oscillation of the populations increases the risk that one of the populations would go extinct, and this would also cause the extinction of the parasite. When the predation effect decreases for lower values for θ, the oscillations are less likely to occur as the predator population reacts less strongly to changes in the prey population, leading to a stable equilibrium. Also, decreasing value of δ_U leads to a smaller parameter space that the populations oscillate (not shown).

Another difference in model behaviour can be observed when comparing manipulation in I_{I1} with manipulation in I_{I2}. For systems with a definitive host with a high conversion efficiency e, manipulation in I_{I1} increases the parameter space in which the parasite can persist a lot more than manipulation in I_{I2} (Fig. 2g–i). Manipulating both I_{I1} and I_{I2} a little bit can also allow the parasite to persist in the system, that is when evolution would be constrained for the parasite to only manipulate either I_{I1} or I_{I2}. For example, evolution of manipulating I_{I1} by γ may be constrained under certain conditions, say γ cannot go lower than 0.5. Then evolution may result in both predation decrease γ to go down to a value of 0.7 and predation increase θ to go up to a value of 2, which allows the parasite to persist in the system (Fig. 2g).

Effects of other parameters on parasite persistence

When comparing Fig. 3a, b with 3c, d, the effect of increasing the rate f at which I_{I1} gets infectious and becomes I_{I2} can be observed. When this rate f is increased, that is shorten the development time of the parasite in the intermediate host, the parameter space where the parasite can persist increases due to manipulation of I_{I1} by decreasing predation γ or I_{I2} by increasing predation θ (Fig. 3c, d).

Second, reducing the reproduction rate r_I of the uninfected intermediate host I_U decreases the effect that manipulating I_{I1} by γ has on the parameter space for parasite persistence, whereas the effect of manipulation of I_{I2} by θ increases, because manipulating I_{I2} is then also beneficial for definitive hosts with slightly higher conversion efficiencies (Fig. 3e, f). So the reproduction rate influences the parasite under a broader range of conditions to manipulate either I_{I1} or I_{I2}. At higher reproduction rates of the intermediate host, the parasite can occur under a broader range of conditions when manipulating I_{I1} by γ, whereas at lower reproduction rates it is more beneficial to manipulate I_{I2} by θ.

The conversion efficiency e has a comparable effect as the reproduction rate r_I. At higher values of e, the parameter space for parasite persistence is larger due to manipulation of I_{I1} by γ (Fig. 3a, b). Both the effect of the

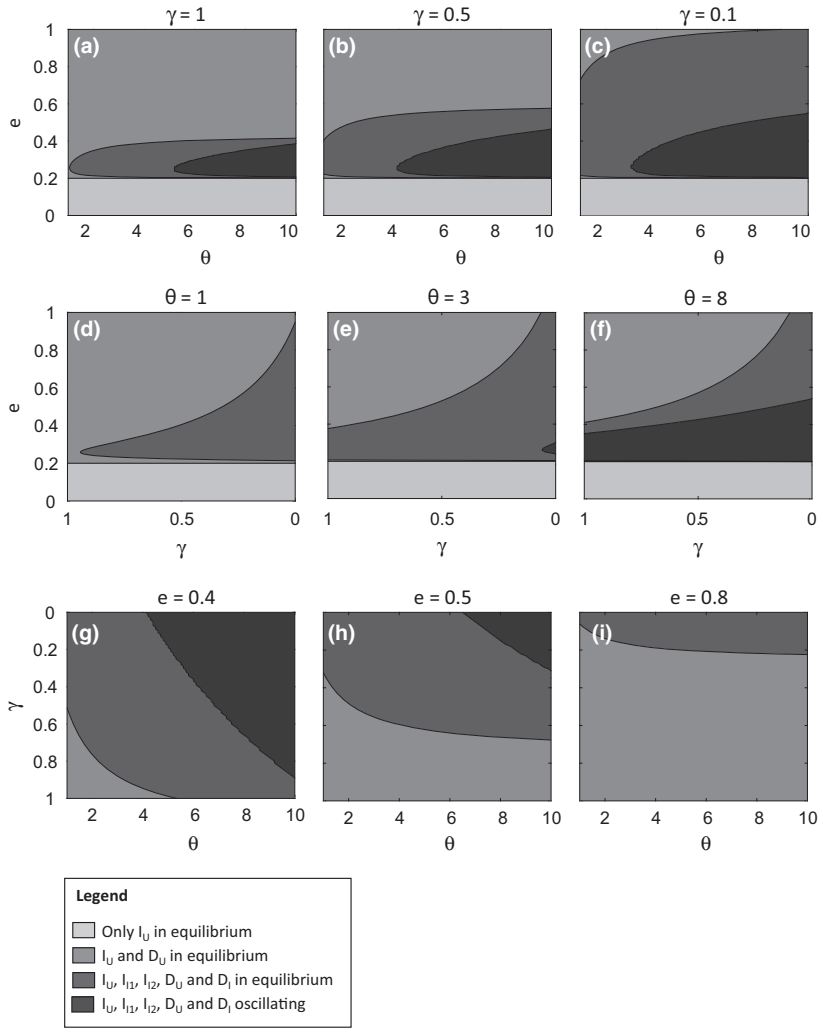

Fig. 2 Model behaviour shown for different values of e, γ and θ. Note the decrease in γ along the x-axis. In the lightest region, only the intermediate host population occurs. In the second lightest region, the intermediate and definitive host populations coexist at equilibrium. In the second darkest region, also the parasite enters the system (Table 2). In the darkest region, when shown, the parasite is still found in the system. However, here the host populations are oscillating over time. The boundary between regions 3 and 4 was determined by extensive numerical simulations. Panels (a–c) show how θ and e affect model behaviour with different values of γ. Panels (d–f) show how γ and e affect model behaviour with different values of θ. Panels (g–i) show how θ and γ affect model behaviour with different values of e. The parameter values used for the graphs are: $r_I = 0.03$, $q = 0.1$, $\delta_U = 0.005$, $\nu = 0.0001$, $\lambda = 54$, $\mu = 0.2$, $f = 0.005$, $m = 0.5$, $d_{Ii1} = 0.01$, $d_{Ii2} = 0.01$, $d_{Du} = 0.01$, $d_{Di} = 0.02$.

reproduction rate r_I and the effect of the conversion efficiency e can be explained by the influence they have on the uninfected definitive host population density D_U. Population density of D_U increases with increasing r_I or e. At higher population density of D_U, the predation of the intermediate hosts will increase. Because of this high predation pressure, decreasing the predation in the early developmental stage of the parasite γ will result in broader conditions for parasite persistence compared to increasing the predation later in its development θ.

Figure 3g, h shows that a decrease in the transmission rate β, for example by a decrease in the production of infective stages λ in the infected definitive host D_I, will decrease the parameter space where a parasite can invade the system. This can be explained by a decrease in the parasite load in the system with a decrease in production of infective stages. Increasing the death rate d_{Di} of D_I has a similar effect as decreasing β (Appendix B). So it will be beneficial for conditions of parasite persistence to increase the production of infective stages and to decrease its lethality to its definitive host, which suggests that the parasite increases its transmission β together with reduction of its damage of the definitive host (i.e. virulence).

Figure 3i, j shows that an increase in the mortality of infected intermediate hosts d_{Ii1} and d_{Ii2} decreases the conditions for parasite persistence in the system. Also, no oscillation is found anymore with manipulation of I_{I2} (Fig. 3i). The decrease in parameter space in which the parasite can persist can be explained by the dependence of the parasite on the survival of its intermediate host. It is not beneficial to the parasite to increase the mortality of its host before it is transmitted.

Figure 3l shows that the conditions for parasite persistence with manipulation of I_{I1} by γ decrease slightly with decreasing value of m, the fraction of the death rate d_{Ii1} that involves predation by other predators than the definitive host. This means that the range of influence of γ is larger when γ also decreases predation from other predators than the definitive host. The parameter

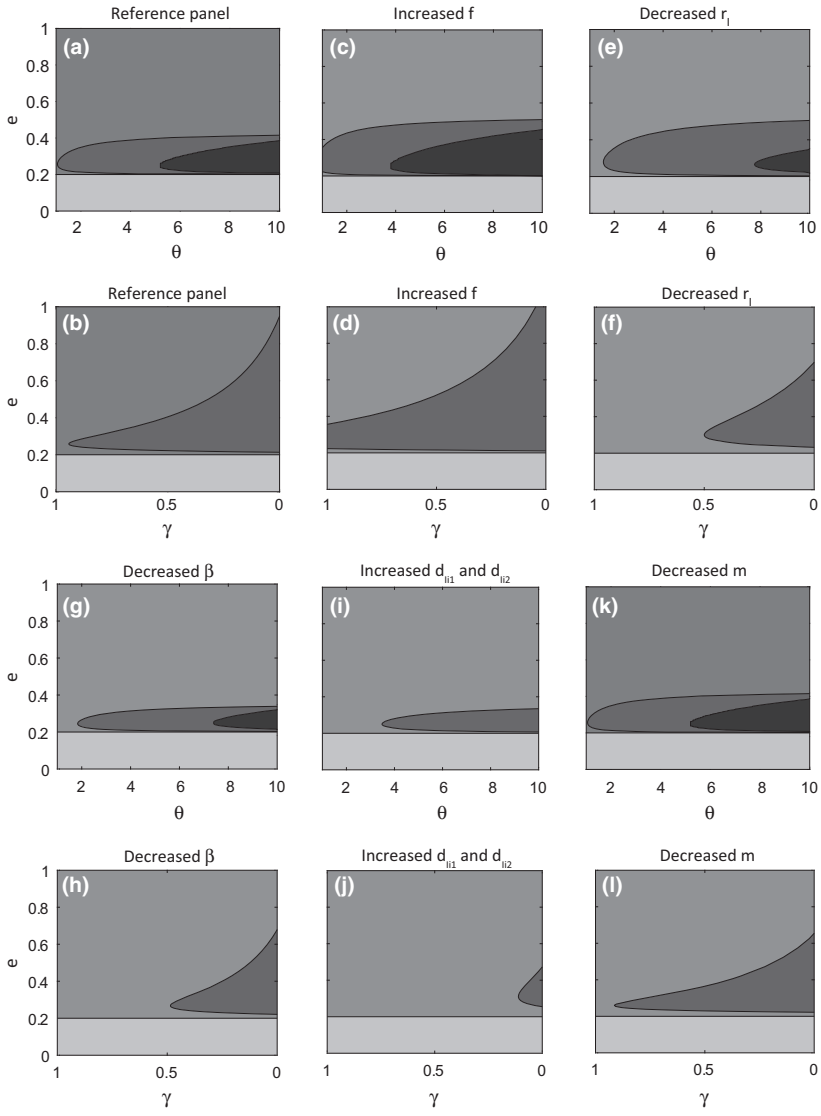

Fig. 3 The effect of some parameters on the model behaviour. The regions are similar as in Fig. 2. Panels (a, b) are the references and show the model behaviour with similar parameter values as in Fig. 2. In panels (c, d), the rate at which the parasite becomes infectious to the definitive host is increased, $f = 0.007$. In panels (e, f), the growth rate of I_U is decreased, $r_I = 0.015$. In panels (g, h), the transmission rate β is decreased, $\lambda = 40$. In (i, j), the mortality of infected intermediate hosts is increased, $d_{Ii1} = 0.02$ and $d_{Ii2} = 0.02$. In (k, l), the death rate of I_{I1} will be less influenced by γ, $m = 0.1$. The parameter values used for the graphs are as follows: $r_I = 0.03$, $q = 0.1$, $\delta_U = 0.005$, $v = 0.0001$, $\lambda = 54$, $\mu = 0.2$, $f = 0.005$, $m = 0.5$, $d_{Ii1} = 0.01$, $d_{Ii2} = 0.01$, $d_{Du} = 0.01$, $d_{Di} = 0.02$, $\gamma = 1$ (panels a, c, e, g, i, k) and $\theta = 1$ (panels b, d, f, h, j, l).

space where the parasite can persist increases when the parasite targets not only its definitive host when decreasing predation, but also decreases predation by other predators. However, when manipulating I_{I2} by θ, no effect of m is observed (Fig. 3k), as m only increases the effect of manipulation in I_{I1}.

Consequences for population densities

The density of I_U increases with an increase in host manipulation of I_{I1} by γ (Fig. 4a). This increase can be explained by the decrease in predation pressure due to the decrease in total definitive host population density ($D_U + D_I$) (Fig. 4d, e). An increase in manipulation of I_{I1} by decreasing predation γ (Fig. 4a–e) results obviously in an increase in the density of I_{I1} as manipulation reduces its predation. The consequences are an increase in I_{I2} and therefore an increase in the density of infected definitive hosts D_I. This increased infection causes a decrease in the density of uninfected predators D_U. However, with even higher degree of manipulation of I_{I1} by γ, the density of infected predators D_I decreases. This decrease can be explained by the decrease in population density of D_U decreasing the amount of definitive hosts that can get infected (Fig. 4d). This negative effect on population density of D_I outweighs the effect of the increase in the density of infected prey on population density of D_I at this point, as can be observed in Fig. 4f (plotting $I_{I2} \times D_U$ helps to illustrate how I_{I2} and D_U together affect population density of D_I).

The density of I_U increases with an increase in host manipulation of I_{I2} by θ (Fig. 4g). This increase can be explained by the decrease in total predation pressure, due to the decrease in the total definitive host population density ($D_U + D_I$) (Fig. 4j, k). The increase in manipulation of I_{I2} by θ results first in an increase in I_{I1}, I_{I2} and D_I, and then in a decrease with further

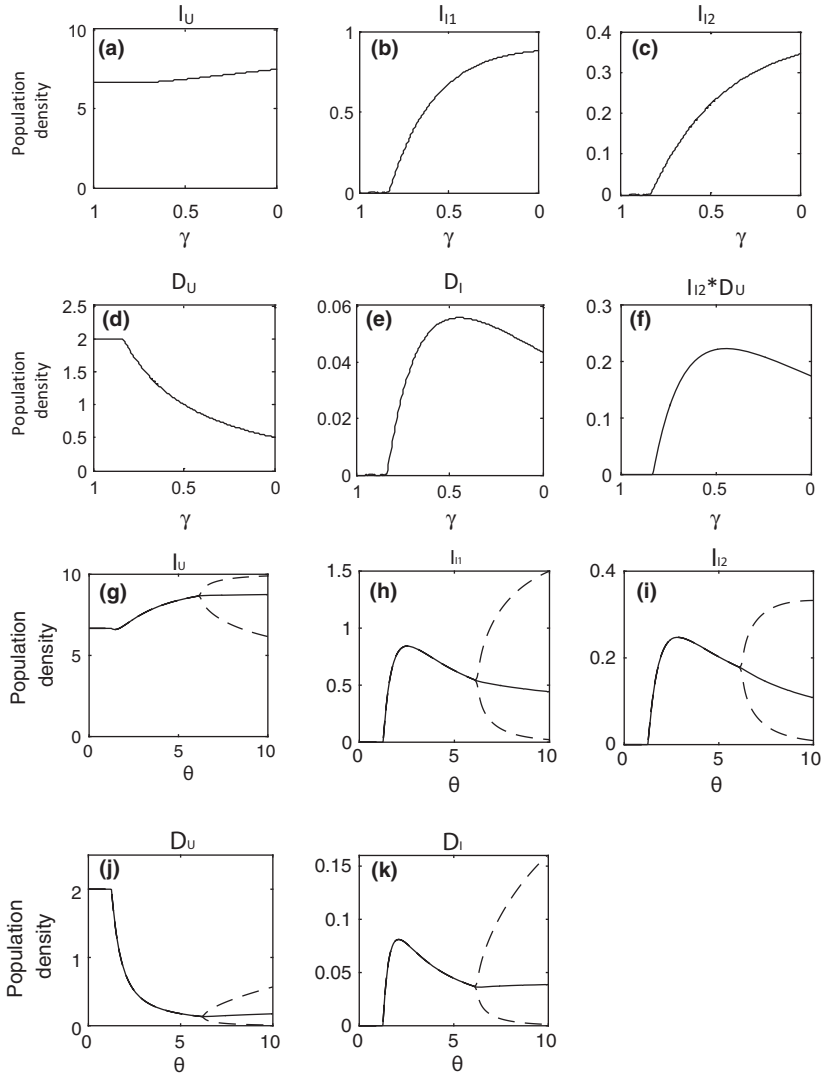

Fig. 4 Population densities of I_U, I_{I1}, I_{I2}, D_U and D_I in equilibrium shown by the solid lines. The dashed lines indicate when the populations start to oscillate and they show the maximum and the minimum population densities while oscillating. When the oscillations occur, the solid line is the mean population density over time. Panels (a–e) show the effect of γ on the population densities I_U, I_{I1}, I_{I2}, D_U and D_I, respectively ($\theta = 1$). Panel (f) shows the effect of γ on $I_{I2} \times D_U$, to illustrate the combined effect of I_{I2} and D_U on population density of D_I ($\theta = 1$). Panels (g–k) show the effect of θ on the population densities I_U, I_{I1}, I_{I2}, D_U and D_I, respectively ($\gamma = 1$). The parameter values used for the graphs are as follows: $r_I = 0.03$, $q = 0.1$, $\delta_U = 0.005$, $v = 0.0001$, $\lambda = 54$, $\mu = 0.2$, $f = 0.005$, $m = 0.5$, $e = 0.3$, $d_{Ii1} = 0.01$, $d_{Ii2} = 0.01$, $d_{Du} = 0.01$, $d_{Di} = 0.02$.

increase in θ (Fig. 4h, i, k). First, host manipulation that increases predation by θ facilitates the presence of the parasite in the system, which causes infected host population densities to increase. Later, the high degree of host manipulation in I_{I2} by θ leads to a high removal rate of I_{I2}, leading to a decline in population densities of I_{I1}, I_{I2} and D_I and at a certain point also to oscillation of the populations. With increasing manipulation of I_{I2} by θ, the population density of D_U decreases. The first steep decrease in D_U can be explained by the increase in I_{I2}. The later decrease in D_U, when I_{I2} is decreasing due to predation, can be explained by the transfer of D_U to D_I when preying more and more on the infected intermediate host I_{I2} with the increasing degree of manipulation by θ.

We found for all our results that changing the values of the parameters did not lead to changes in the qualitative behaviour of the model.

Discussion

Parasites are able to manipulate their hosts in different ways, often by increasing their transmission rate or survival (Poulin, 2010; Schmid-Hempel, 2011). In the intermediate–definitive host system as investigated in this paper, increasing the transmission rate by increasing predation by the definitive host is the most well-known way trophically transmitted parasites manipulate their host (Poulin, 2010). Relatively few researches have been performed to date on host manipulation by parasites that decrease the predation early in their development (Maure *et al.*, 2013; Soghigian *et al.*, 2017). This could indicate that parasites have evolved this strategy infrequently. However, behaviour that decreases predation, like decreased activity and increased sheltering, is in most cases more difficult to measure than behaviour that increases predation

(Parker *et al.*, 2008; Dianne *et al.*, 2014). As prey usually try to avoid being predated on, predation avoidance behaviour will easily be overlooked when studying host manipulation. Another reason why this predation suppression is rarely observed was postulated by Parker *et al.* (2008): suppression may be more costly to the parasite. The model outcomes of this study suggest that manipulation in the early developmental stage of the parasite can be as beneficial to the parasite as manipulation later in the development, in terms of the conditions where the parasite can persist in the system. Moreover, manipulation to decrease the predation chance of the intermediate host results in higher population densities of infected intermediate hosts (I_{I1} and I_{I2}) than manipulation that increases the predation chance to enhance transmission (see Fig. 4).

Another advantage of manipulating to decrease host predation in the early developmental stage is that the risk of destabilizing the host populations by oscillations is low, whereas host manipulation later in the development to increase predation involves higher risks of destabilization of the host populations (Fenton & Rands, 2006). Furthermore, Parker *et al.* (2008) argued that host manipulation by parasites that decreases predation early in the development of the parasite evolves more easily in an intermediate–definitive host system than manipulation increasing their transmission rate does, as manipulation in the early stage to decrease predation is less limited to a specific predator. It is beneficial to the parasite to decrease predation in general during this stage (Lagrue *et al.*, 2013), whereas later in its development it is beneficial to the parasite to direct its manipulation specifically towards its definitive host (such as in the example of the colour change of the abdomen of *C. atratus* ants, Yanoviak *et al.*, 2008). This is more costly to the parasite.

Although we indicated some advantages of host manipulation early in the development of the parasite to decrease predation, more factors influence the effect of the two manipulation strategies of the parasite on the conditions for its persistence. For example, the definitive host can act as selection pressure for either of these strategies, depending on its population density. When the intermediate host or the definitive host have life-history traits that allow the definitive host to reach large population densities, that is high reproduction rate of the intermediate host or high conversion efficiency of the definitive host, respectively, evolving manipulation to decrease predation in the early developmental stage of the parasite will be more beneficial for the conditions of parasite persistence than to increase predation later in its development. We show that in a system with a large definitive host population density, which puts a large predation pressure on the intermediate host, decreasing the predation early in its development results in a larger parameter space for persistence of the parasite than increasing predation later in its development. Also, our study suggests that when the definitive host population density is small and transmission possibilities are more limiting to the parasite, it is beneficial to increase the predation later in its development (see also Vervaeke *et al.*, 2006). Other drivers for population density of the definitive host, such as availability of alternative prey and the absence of competing predator species (Hassell & Comins, 1976), will have a similar effect on the benefits of the two strategies of host manipulation. We should take into account that in our model, the definitive host controls the population density of the intermediate host due to strong top-down effects, so an increase in reproduction rate of the intermediate host results in an increase in the population density of the definitive host (cf. Oksanen *et al.*, 1981). However, in natural systems, an increase in reproduction rate of the intermediate host could result in an increase in the population density of the intermediate host with weak or absent top-down control. Then, a reverse effect on the benefits of the two strategies could be expected.

Manipulating the intermediate host to decrease predation early in the development of the parasite becomes more effective when alternative predator species are present, which could change the relative advantage of the two manipulation strategies. When many nonhost predators predate on the intermediate host, we found that it is more beneficial to decrease the predation early in the development of the parasite. This can, for example, be observed for the parasitic acanthocephalan worm *P. laevis*, which uses a couple of fish species as its definitive host, whereas many other fish species prey on its intermediate host *G. pulex* (Hine & Kennedy, 1974). Then predation risk early in the development of the parasite is high. Our model predicts that manipulation early in the development to decrease predation would be most beneficial to this parasite. *Pomphorhynchus laevis* was indeed found to manipulate its intermediate host early in its development to decrease the predation (Dianne *et al.*, 2014).

Parasites can have large effects on species abundance and interactions in food webs (Lafferty *et al.*, 2008). Often the focus is on the negative impacts parasites have on their host populations (Winternitz *et al.*, 2012; Granovitch & Maximovich, 2013). However, our study predicts that parasite manipulation, resulting in either predation decrease γ or increase θ of the intermediate host by the definitive host, can have a positive effect on the intermediate host population density. This is counterintuitive considering the negative effect of the parasite on the fertility of the intermediate host. However, the positive effect can be explained by the negative impact of the parasite on the definitive host population, which leads to decreasing predation pressure on the intermediate host and increases in this way the intermediate host population density.

Parameterization of the model could provide more insight in the expected frequency at which both strategies of host manipulation will be used by parasites in natural systems, especially the reproduction rate of the intermediate host and the conversion efficiency of the

definitive host are relevant for the effect of the two strategies. There is a need for more data on natural systems showing manipulation to decrease predation in the intermediate host. Our model could help to determine in what systems this manipulation strategy can be found, for example when the definitive host population is relatively large or in systems with a relatively high nonhost predator species richness. Some experimental studies have shown parasites use the strategy manipulation to decrease predation in the intermediate host (Hammerschmidt *et al.*, 2009; Weinreich *et al.*, 2013; Dianne *et al.*, 2014), but no field data on this subject were found.

The lack of compelling evidence for host manipulation has prompted some critical reviews (Poulin *et al.*, 1994; Poulin, 2000, 2010; Thomas *et al.*, 2005; Lefèvre & Thomas, 2008). Although few studies report about host manipulation in early stages of the parasite development to decrease predation, our study provides testable hypotheses to investigate possible examples in more detail. Moreover, our study contributes to understanding under what conditions the two studied strategies are prevailed. It suggests that manipulation in early stages of the parasite development to decrease predation might be a more frequently evolved host manipulation strategy than is currently assumed, as the conditions in which the parasite can persist in predator–prey systems as well as population densities of infected intermediate hosts increase with higher degree of manipulation. Finally, our study indicates that life-history and ecological variables may have played an important role in the evolution of manipulation of host behaviour by parasites in intermediate–definitive host systems.

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Conflict of interest

The authors declare no conflict of interests.

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Appendix A

Stability analysis of model

To calculate the equilibria of the model, first the differential equations of the model were set equal to 0 and then solved for I_U, I_{I1}, I_{I2}, D_I and D_U. For simplicity, $\frac{\nu\,\lambda}{\mu}$ was included as β in the analysis. Three equilibria could be determined in this way, whereas the last one could not be solved. The equilibria that could be determined were as follows:

Equilibria	I_U	I_{I1}	I_{I2}	D_U	D_I
0	0	0	0	0	0
1	K	0	0	0	0
2	$\frac{d_{Du}}{\delta_U e}$	0	0	$\frac{r_I\,(\delta_U e - d_{Du} q)}{{\delta_U}^2 e}$	0

Stability of equilibria 0, 1 and 2 could be determined by solving the Jacobian of the system in the absence of the parasite, so with only I_U and D_U populations at equilibrium 2.

$$J_{\text{predator-prey}} = \begin{vmatrix} r_I - 2\,r_I\,q\,I_U & -\delta_U\,I_U \\ -\delta_U\,D_U & \\ e\delta_U\,D_U & e\,\delta_U\,I_U - d_{Du} \end{vmatrix}$$

The determinant and trace of this Jacobian for equilibrium 2 were determined:

$$\text{Determinant} = d_{Du}\,r_I - \frac{r_I\,{d_{Du}}^2\,q}{\delta_U e}$$

$$\text{Trace} = -\frac{d_{Du} q\,r_I}{\delta_U e}$$

Equilibrium 2 is stable when the trace of the Jacobian is smaller than 0 and the determinant of the Jacobian is larger than 0. The trace of the Jacobian is always smaller than 0. However, the determinant will only be larger than 0 when $K > \frac{d_{Du}}{\delta_U e}$ (note that $K = 1/q$). This leads to the requirement $K > \frac{d_{Du}}{\delta_U e}$ for equilibrium 2 to be stable, whereas equilibrium 1 will be stable when $K < \frac{d_{Du}}{\delta_U e}$. Equilibrium 0 is unstable (Table 2).

The fourth equilibrium could not be determined analytically. However, the requirements for this equilibrium to be stable could be determined with the Jacobian of the full model. This was done with the same approach Fenton & Rands (2006) used. To do this, first the Jacobian of the full model at equilibrium 2 was determined based on I_U, D_U, I_{I1}, I_{I2} and D_I:

$$\begin{vmatrix} r_I - 2\,r_I\,q\,I_U & -\delta_U\,I_U & -r_I\,q\,I_U & -r_I\,q\,I_U & -\delta_U\,I_U - \beta\,I_U \\ -\delta_U D_U & & & & \\ e\,\delta_U\,D_U & e\,\delta_U\,I_U - d_{Du} & e\,\delta_U\,\gamma\,D_U & \delta_U\,\theta\,D_U\,(e-1) & 0 \\ 0 & 0 & -D_U\,\gamma\delta_U - f & 0 & \beta\,I_U \\ & & -d_{Ii1}(\gamma m + (1-m)) & & \\ 0 & 0 & f & -\theta\,\delta_U\,D_U - d_{Ii2} & 0 \\ 0 & 0 & 0 & \delta_U\,\theta\,D_U & -d_{Di} \end{vmatrix}$$

The requirement for the predator–prey system to be stable should also still be fulfilled for the equilibrium with presence of the parasite to be stable, $K > \frac{d_{Du}}{\delta_U e}$. However, equilibrium 2 should be unstable to enable the parasite to invade. The stability of equilibrium 2 is determined not only by the upper left part of the Jacobian, but also by the lower right part:

$$\begin{vmatrix} -D_U\,\gamma\,\delta_U - f & 0 & \beta\,I_U \\ -d_{Ii1}(\gamma m + (1-m)) & & \\ f & -\theta\,\delta_U\,D_U - d_{Ii2} & 0 \\ 0 & \delta_U\,\theta\,D_U & -d_{Di} \end{vmatrix}$$

Equilibrium 2 is unstable when the determinant of the lower right part of the Jacobian is smaller than 0 and the trace of the lower right part of the Jacobian is larger than 0.

$$\begin{aligned} \text{Determinant} = \frac{1}{{\delta_U}^2\,e^2}\;(&\beta\,d_{Du}\,f\,r_I\,\theta\,(\delta_U e - d_{Du} q) \\ &- d_{Di}\,(d_{Ii1}\,\delta_U e\,(1 + m\,(\gamma - 1)) \\ &- d_{Du}\,\gamma\,q\,r_I + \delta_U e\,(f + \gamma\,r_I)) \\ &(d_{Ii2}\,\delta_U e + r_I\theta\,(\delta_U e - d_{Du} q))) \end{aligned}$$

$$\begin{aligned} \text{Trace} = {} & d_{Ii1}\,(m - 1 - \gamma\,m) - d_{Ii2} - d_{Di} - f - \gamma\,r_I - r_I\,\theta \\ & + \frac{d_{Du}\,\gamma\,q\,r_I}{\delta_U e} + \frac{d_{Du} q\,r_I\,\theta}{\delta_U e} \end{aligned}$$

From this criterion, it can be derived that the parasite is able to invade in the system when

$$\theta > -\frac{d_{Ii2}\,d_{Di}\,\delta_U\,e\,(\delta_U e\,(d_{Ii1} + f + d_{Ii1}\,m\,(\gamma - 1)) + \gamma\,r_I\,(\delta_U\,e - d_{Du} q))}{r_I\,(\delta_U e - d_{Du} q)\,(-\beta\,d_{Du}\,f + d_{Di}\,\delta_U e\,(d_{Ii1} + f + d_{Ii1}\,m\,(\gamma - 1)) + d_{Di}\,\gamma\,r_I(\delta_U\,e - d_{Du} q))}$$

or

$$\gamma < \frac{d_{Ii2}\,d_{Di}\,{\delta_U}^2\,e^2\,(d_{Ii1}\,m - d_{Ii1} - f) + r_I\,\theta\,(\beta\,d_{Du}\,f + d_{Di}\,\delta_U e\,(d_{Ii1}\,m - d_{Ii1} - f))\,(\delta_U e - d_{Du} q)}{d_{Di}\,(d_{Ii1}\,\delta_U e\,m + \delta_U e\,r_I - d_{Du} q\,r_I)\,(d_{Ii2}\,\delta_U e + r_I\,\theta\,(\delta_U e - d_{Du} q))}$$

Appendix B

Effect of the death rate of infected definitive hosts d_{Di} on the model behaviour for (a) θ and (b) γ. The regions are similar as in Fig. 2. Comparison between Fig. 3a, b shows the effect of increasing d_{Di} on the model behaviour. Similar parameter values are used except for d_{Di} of which the value was increased compared to its value in Fig. 3a, b. See Fig. 2 for explanation of the different regions in the graphs. The parameter values used for the graphs are as follows: $d_{Di} = 0.03$, $r_I = 0.03$, $q = 0.1$, $\delta_U = 0.005$, $v = 0.0001$, $\lambda = 54$, $\mu = 0.2$, $f = 0.005$, $m = 0.5$, $d_{Ii1} = 0.01$, $d_{Ii2} = 0.01$, $d_{Du} = 0.01$, $\gamma = 1$ (a) and $\theta = 1$ (b).