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A Theoretical Perspective on Parasite-Host Coevolution with Alternative Modes of Infection

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Abstract

We investigate how natural selection shapes the coevolution of parasitism. We discuss the antagonism fuelled by parasites' necessity to transmit to novel hosts, and host's desire to minimise virulence. In support, we build a mathematical model which considers the epidemiology and life-history trade-offs faced by an obligate microparasite and its host. Our model allows parasites to be transmitted to new hosts via direct contact (horizontally) or from parent to offspring during birth (vertically). We test the hypothesis that vertical transmission causes virulence to diminish in the long run, and contrary to widely accepted views, find that vertical transmission need not result in benign coevolutionary outcomes in general. However, vertical transmission does promotes benign parasitism whenever: it is cheap for the host to retaliate; horizontal transmission saturates quickly; or the intrinsic growth rate of the host population is low.

Summary for Lay Audience

Parasites might seem like the villains, but they are not always necessarily out to get us. Often the damage that they do is a consequence of trying to complete their lifecycle, instead of pure malice. In this thesis we will explore how hosts and parasites coexist, despite their conflicting interests. And how, after many generations, their descendants might have changed to adapt to one another. We use a mathematical model which lets us keep a track of how many hosts are infected, and how many are not. This information is useful for predicting which way natural selection will push the relationship. It is commonly thought that if a parasite can transmit from a mother to her offspring, then the host and parasite will share mutual interests and de-escalate their attack on each other. However, in this paper we will show that the situation is more complicated, and depends on the compromises that both parties face, as well as what each has to gain.

Keywords: infectious disease, pathogen, transmission, game theory, adaptive dynamics, Nash equilibrium

Co-Authorship Statement

Chapter 2 will be revised for publication. It will be submitted as a research article authored by GNS, Francisco Ubeda (Royal Holloway, University of London), and Geoff Wild, in that order. GNS and GW developed the research problem in consultation with FU. GNS developed the model and analysis with input from GW, and GNS wrote Chapter 2 with input from GW.

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Chapter 1

Motivation and Background

1.1 Parasitism

This thesis is an investigation into the coevolution of parasitism. We will begin in Chapter 1 by briefly introducing the field of parasitology, discussing the recent history and innovations which have occurred there, as well as the over-arching open questions which exist today. Throughout we take an evolutionary perspective, by considering the selective forces which act to shape and maintain the phenomenon that exists around us. In Chapter 2 the focus of our attention will be towards the significance that parent-to-offspring transmission of a parasite (termed "vertical transmission") has on the coevolution of long-standing host/parasite symbiosis. We demonstrate how the epidemiological and selective consequences of this mode of transmission alter the degree of antagonism between the host and parasite over evolutionary time. In order to make substantive predictions we will develop a mathematical model of a population of hosts susceptible to a microscopic pathogen. We determine the coevolved optimum levels of a pair of phenotypic traits, one of which is controlled by the host and the other by the parasite. We will test, and challenge, the widely-held claim that vertical transmission acts to align the evolutionary interests of host and parasite and so leads to relatively benign interactions between them. Looking forward to Chapter 3, we will reflect on the assumptions inherent in our model as well as the scope to which it applies. We will take time to discuss alternative modelling frameworks which are available, and can be used in concert to provide a holistic view. Finally, we will speculate on some potential lines of future research which broadly encompass the topic of emerging infectious human diseases, paying particular attention to the dynamics of virulence following zoonotic spillover events.

In the natural world parasitism is a ubiquitous symbiotic strategy which spans every taxon of life and even extends beyond organisms considered to be alive [69]. Parasitism is defined here as any symbiotic relationship in which an organism of a given species – the parasite – is committed to exploiting, and in so reducing the evolutionary fitness of a second organism – the host – which is typically a member of a different species. We shall, throughout the course of this chapter, begin to unpack some of the concepts included here, and try to set them rigorous foundations.

The mathematical underpinning of the evolution of parasite population dynamics can be traced back to the work of Anderson and May [6, 7, 60]. They explored how the impact

and dependency that parasites have on host survival can act to regulate the density of a host population; suppressing host numbers when there are many, but taking less when there are few. The effect they demonstrated dampened fluctuations and, over time, meant the population stabilised to a steady state. This idea was pivotal as it showed theoretically that microscopic organisms can have a significant effect at the population level. Moreover, it hinted that parasites can act to mediate the other interactions of the host. A good example of this comes from the island of St. Maarten, where two species of Anolis lizard (*Anolis gingivinus* and *Anolis wattsi*) are found. These two lizards do not often interact directly, however they still compete over their common food source. The result of this contest is that the more competitive species, *A. gingivinus*, is more abundant and usually excludes the other from where it forages. However, there are places on the island where the two coexist, and the reason for this is due in part to a microscopic, protozoan parasite called *Plasmodium azurophilum*. The parasite happens to only significantly infect the more competitive lizard, frequently inducing symptoms of the disease malaria, and in so reducing its competitive advantage. The places St Maarten where the two lizards coexist are those in which the usually dominant species faces a high prevalence of malaria [82]. In effect the parasite is shaping the geographic distribution and competitive ability of its host. Figure 1.1 illustrates the interactions between each of the four species.

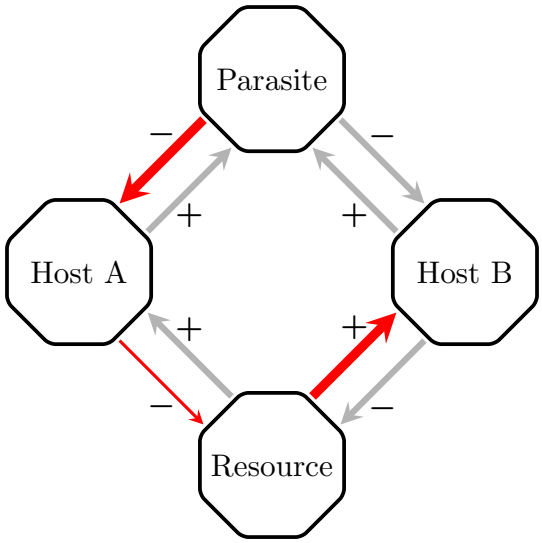

Figure 1.1: The interactions of a small ecosystem, demonstrating how parasites can mediate other interactions. The critical interactions are shown in red. By adversely affecting host A more so than host B, the parasite reduces the competitive ability of host A. In the example given in the text this resulted in cohabitation of the hosts.

In this example it would be quite a far stretch to imagine that the parasite had its own interests at heart when it mediated coexistence in the way that it did - but never say never. There are an abundance of scenarios however, in which parasites leverage what is going on outside of their host to their own selective advantage. And this all comes down to the reasons a parasite depends on its host. Generally, things that a host can provide include: a protective and stable shelter; nutrition [41]; outsourcing of reproduction [46] and parental care [12]; dispersal to new habitats [90]; and transmission to new hosts. We find transmission particularly interesting

(and will discuss it in more detail in Chapter 2) because it is a part of the life cycle of parasites which they are usually, at least in the obligate parasites, unable to complete autonomously. This idea is best understood through another example, and none seems more illustrative than that of a behavioural manipulator like the flatworm (*Euhaplorchis californiensis*).

At one stage of their marvellously intricate life cycle, a sexually mature flatworm needs to transmit to its definitive avian host in order to produce larvae. The challenge faced by the flatworm is that it is currently embedded in the brain of an intermediate host, usually a fish or crustacean. For the flatworm though this is no issue, as it has the ability to influence its host's behaviour. By altering the brain chemistry of its host the flatworm can make the host behave more conspicuously towards avian predators. This manipulation means that the host is more likely to be consumed, worm and all. Thus, the flatworm acts to increase its potential for transmission. In contrast to the malaria parasite in the previous example, the flatworm gains an advantage by mediating the interactions of other species. A mixture of empirical and computational studies have found that flatworm manipulation is highly adapted and that infection can result in a 10- to 30- fold increase in predation of its host [51]. Now, not all flatworms are born with the same ability to manipulate. However those that do more effectively are more likely to be transmitted, and so, more likely to reproduce. Their traits are more likely to be inherited, so that in future generations flatworms with the ability to manipulate will make up a larger proportion of the whole population. The trait is said to be favoured by selection.

In the definition of parasitism our understanding of what constitutes an organism, both of the host and parasite, can be taken in a broad sense. There is certainly some amount of disagreement between fields, particularly between ecology and medicine, as to what is designated as a parasite. The Centers for Disease Control and Prevention includes protozoa, helminths, and ectoparasites in its definition [34], whereas evolutionary ecologists often take a more general definition which also include viruses, bacteria and other protists [69]. We subscribe to the latter definition here. While the distinction may just be a matter of accounting, it has a significant effect on the perception of global health statistics. If the causative agents of disease and mortality are not consistently classified then the significance of parasites to human health, agriculture and economy could be severely under-represented. For example, a paper from 2007 quotes the diarrhoeal disease amoebiasis, which is caused by the protozoan *Entamoeba histolytica* as "the third leading cause of parasitic disease worldwide" [40]. However, this is only true when taking the more restricted definition of parasitism. In this thesis, since we are concerned with transmission, we will focus our attention on endoparasites - those that live inside of their hosts.[1]

Parasitology is of deep consequence to many facets of the biological sciences. From the diseases that parasites cause [97, 71] to their effect on global ecosystems [42, 58], parasites are a pivotal and often overlooked part of our understanding of ecology. Our knowledge of the diversity of parasite species is severely under-developed when compared with the organisms which they call home [77], and we are only just beginning to appreciate their stabilising effect on the ecosystem and in food webs [53]. We have already seen examples of how parasites can influence interactions among hosts, and these kinds of effects have consequences at larger scales. The high degree of connectedness between species in an ecosystem, as well as the

[1] Although I am compelled to point out that the worlds largest single organism, *Armillaria ostoyae*, is a parasitic fungus.

abundance of species which lead a parasitic lifestyle – estimated to be around 30% of named species [61] – means that the effect of parasite-mediated interactions can cascade across the whole ecosystem. This realisation only gained recognition by community ecologists in the 1990s, amidst a plea from parasitologists to include parasites in food webs [59]. In challenging our bias towards macroscopic organisms, we have come to find that parasitism significantly effects properties of trophic network topology which are used as indicators of a robust ecosystem [53].

1.2 Virulence

It might seem obvious that the pathogenic (disease-producing) quality of a parasite is in some sense harmful, what we call *virulent*, to the host. But how should we go about quantifying this harm? How would we compare the virulence inflicted by the flatworm in the previous example, to the parasitic Cuckoo (*Cuculus canorus*) in Figure 1.2? In the early generations after a parasite infects a novel host, it is unlikely that either host or parasite will be particularly well-suited to one another. Their interaction will be prone to a degree of inefficiency which manifests itself as virulence. In Chapter 1 and 2 we will disregard this kind of virulence and focus our attention on longstanding host-parasite relations, so that selection has had time to act, and equilibriate [21]. We will return to novel host-parasite interactions in Chapter 3.

Figure 1.2: A Common cuckoo (*Cuculus canorus*) tricks a Wren (*Troglodytes troglodytes*) into feeding it. The cuckoo is one of many avian brood parasites that shirk parental investment by laying their eggs in the nest of other species. Wrens have developed countermeasures to avoid parasitism, such as teaching their developing embryos a vocal passcode at the early stages of incubation. Hatchlings which sing this passcode trigger the parents to feed them [49]. © [J.C.Salvadores] /Adobe Stock.

While the theory of fitness and its rigorous underpinning in mathematics is well-developed (see [27, 38, 104] for the formative work by Fisher, Haldane and Wright respectively), linking this to empirical data still poses a major challenge in evolutionary biology [63]. One way to indirectly measure fitness is to consider it as the product of two components: longevity and

fecundity. Then, we may say an organism becomes more fit by (i) increasing the time it spends producing offspring (ii) increasing the rate of production and quality of its offspring. Any trait exhibited by the organism that has a net positive effect on its fitness will gain a selective advantage and become more prevalent in the population. Ideally, an organism would strive to maximise both of these components, but in reality a compromise must be made.

Returning to the question of how to properly define the harm inflicted by a parasite, we may now formally define the virulence as the net reduction in host fitness due to infection. Furthermore, we may make our definition of parasite more succinct: parasites are the beneficiaries of long-lasting, virulent interactions. It is important again to distinguish this ecological definition from that typically considered in medicine; an organism can be pathogenic and cause disease, yet by some means increase the net fitness of its host, and so not be considered a parasite.

Now that we have defined virulence the first question to ask is: why be virulent at all? Given that parasites, often obligately, depend on their hosts, what maintains virulence? This is a question which puzzled parasitologists in the 19th and 20th centuries [3]. They hypothesised that virulence was a maladaptation and, by extension, that all parasitism would eventually evolve towards commensalism and even mutualism. Certainly the fitness of a parasite is in some way tied to its host [94]. However we now understand that parasites want to complete their life cycle by creating new infections, and those that most aggressively exploit their host will be at a selective advantage over competing strains. Virulence can provide parasites with the resources they need to transmit or, as was the case for the behavioural-manipulating *E. californiensis*, induce a response in the host which increases transmission.

1.3 Coevolution

Since the choices that parasites make affect the fitness of their host, it is natural to expect that hosts with a better defence or tolerance to this virulence will gain a evolutionary advantage over their fellow hosts. This reciprocal feedback of adaptation and counter-adaptation between host and parasite drives them to coevolve. Throughout a wide variety of host-parasite systems there is significant phenomenological evidence of coevolution [103]. The archetypal case study follows the inoculation of European rabbits with the virus *Leporipoxvirus myxoma* as a means of pest control. At the time, European rabbits were spreading invasively and depleting rangeland in Australia, following their introduction by British colonialists in the mid 19th century. The myxoma virus was naturally occurring in a different species of rabbit native to South America called (*Sylvilagus brasiliensis*). In this species it only caused innocuous symptoms, however, infection in European rabbits led to the highly lethal disease myxomatosis [48]. What followed has been described as “one of the greatest natural experiments in evolution”. [25]

For theoreticians modelling evolutionary dynamics, a typical simplifying assumption is that the rate at which hosts acquire mutations is considerably slower than that of their parasites. The upshot is that modellers may justifiably neglect the evolutionary response of the host and only have to consider the parasite. This assumption is well-founded in many scenarios, since it is often the case that parasites may exist in much larger number and have a lower generation time than that of their host, and so are expected to accumulate mutations quicker. However, the general applicability of this assumption has come under question for numerous reasons. Firstly, the rate at which mutations occur is itself an adaptive trait which evolves due to selection. This

is relevant particularly in non-constant and fluctuating environments such as those imposed by antagonistic coevolution [65]. Experimental support for this was found in a laboratory population of the bacteria *Pseudomonas fluorescens* which, when infected with viral phage Φ2, evolved 10- to 100-fold increases in mutation rate [73]. Secondly, not all mutations effect the fitness of an organism. In one experiment it was shown that the overall rate of nucleotide substitution in ectoparasitic lice was approximately ten times higher than that of their rodent host [37]. However, much of this disparity (but certainly not all) was due to synonymous parasite mutations which have a selectively neutral effect and therefore have no fitness consequences. Finally, it has been proposed that since hosts typically rely on sexual reproduction more so than their parasites, novel resistance genotypes can be acquired through recombination and segregation [22, 39, 50].

Reciprocal to the idea that virulence accentuates coevolution is the often under-appreciated notion that virulence itself is a coevolved, symbiotic phenotype. Indeed, a significant stumbling-block to our understanding of virulence is due to neglecting the response of the host, which may in part be on account of the classical emphasis on the parasite as the 'disease-causing' agent [70]. The response of the host may well be negligible in the limited situation in which the parasite is of small effect, when the cost for the hosts to resist the infection is out-weighed by the cost of infection itself. However this simple accounting is rarely the case in a system as complex and general as an immune system. Indeed the harmful component and symptoms of many infections, stem from host immunopathology [35]. Cytokine storms are a notable example in which a hypersensitive innate immune response follows from viral respiratory infections such as influenza and coronavirus [92]. In light of these observations, in Chapter 2 we will propose a coevolutionary model of parasitism which accounts for the adaptive immune response as well as exploitation by the parasite.

1.4 Transmission

The dependency that parasites have on transmission makes it an imperative aspect of disease control. Epidemiologists are not only interested in suppressing the effective dispersal of parasites, but also aiding the contagious spread of attenuated vaccines in a population. Another study of *Pseudomonas fluorescens* and its viral parasite phage Φ2 demonstrated that coevolution resulted in increased genetic divergence of the phage. This was correlated with the range of hosts which Φ2 was able to infect, suggesting that genes which influenced transmissibility evolved rapidly [74]. As we have seen, the routes by which a parasite transmits between hosts can be incredibly intricate, perhaps involving intermediate hosts as reservoirs in which to replicate, or vectors of transmission. These routes are not fixed in a given parasite and vary after a parasite shifts between host species. Simian immunodeficiency virus is genetically very similar to HIV in humans, however its pattern of infection in mandrills (*Mandrillus sphinx*) was shown to involve maternal transmission via social behaviour, which is not a significant route in humans [28]. Despite the extensive study of HIV phylogeny, studies are yet to determine whether genetic changes between the parasite species can account for these differing routes [8].

Independently of the physical route in which a parasite transmits, we may classify the type of transmission into just one of two modes: vertical or horizontal. A major challenge currently faced by epidemiologists is in determining how each transmission *mode* advances the spread

of an infectious species. Transmission is described as vertical whenever it occurs between a parent and its offspring. This mode is typically thought of as concomitant with the birth of a new offspring, however it can also occur postnatally, for instance when a mother breastfeeds. Vertical transmission has been observed in a diverse range of taxa and is not restricted to microscopic pathogens [84]. The other mode of transmission is horizontal, and encompasses all other routes in which the genetic relatedness of the transmitter and recipient are no greater than that which we expect by randomly sampling two hosts from the population. This mode includes routes such as sexually transmitted infections or contagious spreading. Phylogenetic studies have demonstrated how the modes in which a parasite and other symbionts spread is adaptive and has evolved numerous times [75, 68].

A further possibility is that a parasite species can evolve a combination of both strategies, known as mixed-mode transmission [20]. Since each mode has different epidemiological consequences, it can benefit a parasite to be able to utilise both. Mixed-mode transmission can extend the range of ecological scenarios in which a parasite may persist or enable a higher endemic prevalence. Support for this comes from the Rift Valley fever virus which, though mainly transmitted horizontally in its mosquito vector, is thought to be maintained during unfavourable times by transovarial vertical transmission [24]. Figure 1.3 illustrates the outcome of a simple mathematical model with asexual reproduction (adapted from [54]) demonstrating how horizontal transmission can ignite an epidemic and vertical transmission can maintain it.

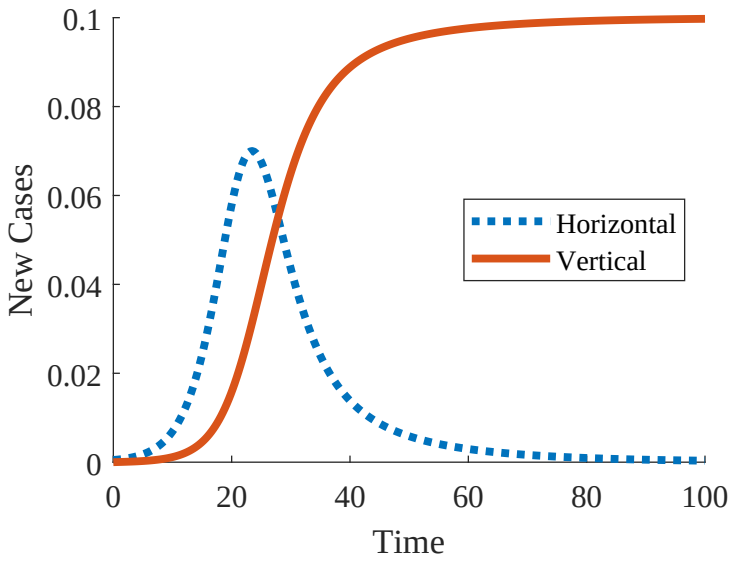

Figure 1.3: Incidence of new cases via horizontal and vertical transmission throughout the course of a simulated epidemic. Initially horizontal transmission is favoured. Since the population starts out almost entirely uninfected, there is a rise in horizontal cases. This produces the necessary infected individuals required for vertical transmission. As the number of susceptibles depletes, so too does the incidence of horizontal transmission. Now vertical transmission is favoured.

Since horizontal transmission depends on the density of susceptible hosts it is most prevalent when there is a plentiful supply, such as at the outset of an epidemic. Vertical transmission on the other hand only indirectly depends on host density. A rise in cases owing to horizon-

tal transmission allows vertical transmission to occur, which unlike horizontal transmission is independent of the density of susceptible hosts. As the epidemic continues there becomes a point when the susceptible hosts which fuelled horizontal transmission begins to deplete, and the balance of significance moves towards vertical infections. Eventually, the new births in the population are balanced by the intrinsic and disease-induced deaths, and the population size equilibrates. In this example, if we only observed the incidence of each mode of infection in the endemic phase (large time), we might unjustly decide that horizontal transmission is insignificant to the equilibrium prevalence. It was however, influential during the outbreak phase in establishing an infective population which would go on to fuel vertical transmission.

It is conceivable that, by opting for a particular mode of transmission, a parasite might inhibit or exclude the other mode of transmission, thus creating a trade-off between the two. For example, bacteriophage are able to either integrate into their host bacteria's chromosome and reproduce vertically, or remain as a free phage, reproducing horizontally via lysis [79]. This trade-off however, need not be true in general. Ebert suggests that a positive correlation between vertical and horizontal transmission is expected when both modes depend on the same physical route [20]. In viscous populations, where individuals do not disperse far from their place of birth, this is exceedingly common, since closely related hosts are liable to be near to their relatives. In these cases the usual routes of horizontal transmission such as contagious spread, have a high chance of also infecting offspring. Furthermore, there is certainly a precedence for no trade-off in the theoretic literature [54].

It is now widely accepted in the scientific literature that vertical transmission inevitably leads virulence to decrease so that the interactions between host and parasite are relatively benign [55, 95, 81, 20, 23]. In Chapter 2, we will test this claim by proposing a mathematical model of mixed mode transmission in which we can track the evolution of virulence. As well as finding supporting evidence for this conventional wisdom, we also demonstrate a number ways in which an increase in vertical transmission leads to a more antagonistic relationship between host and parasite.

In order to support these claims in Chapter 2 we will employ an adaptive dynamics approach. We will take a moment now to briefly overview what this entails. Firstly, we consider the epidemiology of a population of parasitised hosts, described by a system of ordinary differential equations. In order to assess how the host and parasite coevolve, we must allow the system to equilibrate, before structurally perturbing it. What this means biologically is that we have introduced a new, similar and rare mutant parasite. Then, by devising a measure of fitness for the mutant parasite, we may track the evolutionary progress of it and the resident population. We can make a similar structural perturbation to incorporate a mutant host and so track the evolution of its immune response. The coevolved outcome is then a resident population that resists invasion by any mutant parasite or mutant host. We will defer much of the mathematical analysis to the appendix A and try to keep the chapter oriented towards a biologist's perspective. In Chapter 3, we will critically access the model presented in Chapter 2 and conjecture on some avenues of future research. We will conclude with a brief outline of one of the major challenges faced by evolutionary biologists today.

Chapter 2

Host-Parasite Coevolution with Alternative Modes of Transmission

2.1 Introduction

To achieve success a parasite must exploit its host effectively. This means that a host infected with a parasite loses fitness. However, the degree to which hosts are harmed varies, even in the absence of interventions. Smallpox, for instance, killed 300 million people in the 20th century [44], whereas there are no reported cases of death due to the common cold (rhinovirus) [23]. Understanding how such variety has evolved is of crucial importance not only to human health [32], but also to agriculture [62], and even the structure and function of ecosystems [52].

Efforts to understand how selection shapes the virulent effects of parasitism have demonstrated that numerous factors can influence evolutionary outcomes. For example, vector-borne parasites tend to be more debilitating and more lethal than directly transmitted ones, because directly transmitted parasites rely heavily on host mobility to create new infections [23]. Similarly, co-infection can exacerbate disease severity by ramping up within-host competition and modulating immune response [36, 18, 29]. Yet another factor known to affect the evolution of virulence is mode of transmission [20, 72], and it is this factor to which we turn our attention in this thesis. Generally speaking parasite transmission can be partitioned into two modes, vertical and horizontal. The former occurs when a parasite is passed from host parent to its offspring via any number of routes, including across the placenta, through breast milk and even through the germline [67]. The latter mode encompasses everything else.

Theory has repeatedly predicted that vertical transmission leads to evolution of benign parasites [55, 95, 26]. The prediction stems from the notion that vertical transmission provides a parasite with cause to be interested in host success to a greater degree. Reduced virulence is then thought to be an expression of the parasite's heightened interest in its host. Because this idea is intuitively appealing, it has motivated much empirical work [88, 91, 45] and has become well ingrained in the literature [11, 87, 31, 30]. However, empirical support is equivocal in that (i) there exist many examples of highly virulent, vertically transmitted Microsporidia (see [54]) (ii) reductions in virulence do not always occur with increasing prominence of vertical transmission (e.g. [31]), (iii) timescales on which reductions in virulence owing to vertical transmission might occur do not necessarily allow for a coevolutionary response from the host

(e.g. [88]) and (iv) observed reductions in virulence might well be a consequence of reduced horizontal transmission, or reduced reliance on horizontal transmission, rather than vertical transmission itself (e.g. [10, 9]). Overall this raises the question of whether benign host-parasite interactions are an inevitable consequence of vertical transmission.

Our goal in this paper is to explore the effect of vertical transmission on the virulence of host-parasite interactions from a theoretical perspective. In particular, we aim to address whether vertical transmission indeed leads to benign host-parasite associations. Because virulence is often the net effect of parasite and host traits in combination [21], we adopt a coevolutionary modelling framework. By considering coevolution we also distinguish ourselves form previous theoretical work on vertical transmission and pathogenesis [55, 95, 26].

Our analysis reveals that the efficacy of vertical transmission does affect the coevolutionarily optimum traits exhibited by parasites and their hosts, but that increased opportunity for vertical transmission need not always align evolutionary interests. Instead, we find that the eventual fate of the host and parasite, and the antagonism between them, is dependent on a number of parameters related to their ecology and life-history. Furthermore, despite allowing host and parasite to condition their traits based on the origin of their infection, we find that they do not act on this information at the outcome of coevolution.

2.2 Model

2.2.1 Ecological Dynamics

Consider a population comprised of individuals that can play host to an infectious microparasite. Let $S = S(t)$ denote the number of host individuals not infected by the parasite at time t. Although they are not currently infected, these hosts are susceptible to infection in the future. Let $I = I(t)$ denote the total number of hosts infected by the parasite at time t. In addition to being infected, these hosts are also infectious and so are able to transmit the parasite to their susceptible counterparts. Transmission can occur either vertically (from parent to newborn offspring) or horizontally (through social contact with non-relatives). We track hosts that have acquired infections vertically separately from those that acquired infections horizontally. Let $I_V = I_V(t)$ and $I_H = I_H(t)$ denote the number of infectives, at time t, that arose via a vertical and horizontal transmission event respectively, so that $I = I_V + I_H$.

The numbers of individuals in each category vary because of deaths, recovery (death of parasite), births and disease transmission (birth of parasite). All individuals suffer a background mortality at a constant per-capita rate of μ. Infectives suffer an additional parasite-induced mortality at per-capita rate α_V when they arose vertically and at α_H when they arose horizontally. Infectives also clear their parasites at per capita rate γ_V when the infection was acquired vertically and γ_H when acquired horizontally. We recategorise infectives as susceptible once they clear their infection. In other words we assume that infection does not confer immunity.

Susceptible individuals give birth to new susceptibles at a constant per-capita rate b_S. Infective individuals also give birth, but do so at a rate that can vary and which may produce either susceptible or infective offspring. We allow infected hosts to invest in clearing their parasite (we only consider the adaptive immune system) and assume that this diverts resources away from reproduction. Increasing immune function inhibits an infected host's ability to produce

Table 2.1: Glossary of notation.

Notation	Explanation
S	Number of uninfected, susceptible hosts.
I	Number of hosts infected with a micro-parasite.
I_V, I_H	Number of hosts infected via vertical and horizontal transmission. ($I = I_V + I_H$)
$\bar{S}, \bar{I}, \bar{I}_V, \bar{I}_H$	Number of each at ecological equilibrium.
b_S	Per-capita rate at which susceptible hosts give birth.
μ	Per-capita background mortality rate.
α	Per-capita rate of parasite-induced mortality among infected hosts.
α^m	Per-capita rate of parasite-induced mortality of a mutant parasite.
β	Rate constant associated with horizontal transmission of infections (eventually a function of α).
n	Exponent of parasite trade-off $\beta(\alpha)$, measuring how easy horizontal transmission is to the parasite.
γ	Per-capita rate at which hosts clear their infection.
γ^m	Per-capita rate at which mutant hosts clear their infection.
b_I	Per-capita rate at which infected hosts give birth (eventually a function of γ).
λ	Coefficient of host trade-off $b_I(\gamma)$, measuring the cost of immune function to the host.
$\alpha_{\text{br}}(\gamma)$	Parasite population-level best response to host trait.
$\gamma_{\text{br}}(\alpha)$	Host population-level best response to parasite trait.

new offspring. Therefore, we take the birth rate of infectives, b_I, as a decreasing function of the clearance rate. To reflect this we write $b_I = b_I(\gamma_X)$ with $b_I'(\gamma_X) \leq 0$, for $X = H, V$. When an infective host gives birth it transmits its infection with probability v, adding to the number of vertically arising hosts. With probability $1 - v$ the infective host does not transmit its parasite, and so the newborn joins the susceptibles. In this model we assume v is the same for both vertically and horizontally acquired infections. Finally, new horizontally acquired infections occur at a rate $\beta(\alpha_V)I_V + \beta(\alpha_H)I_H$, per susceptible. We call $\beta(\alpha_X)$ the (horizontal) transmissibility and assume, as the notation suggests, that it is a function of the additional mortality induced by an infection of type $X = V, H$. Moreover, to increase its transmissibility a parasite needs to inflict a greater mortality on its hosts, hence $\beta'(\alpha_X) > 0$ [1]. We interpret this trade-off as an inherent cost to the host because its resources are being diverted to the parasite.

The information above leads to dynamics that are illustrated in Figure 2.1 and captured by the system of differential equations presented in Appendix (A.1).

The dynamics eventually reach a steady state where all three categories of host are endemic, $S = \bar{S}$, $I_V = \bar{I}_V$ and $I_H = \bar{I}_H$, provided three technical constraints are met. The first constraint is $b_S > \mu$, and tells us that the population of hosts avoids extinction in the absence of the parasite. Equivalently the first constraint says that the average susceptible makes a positive

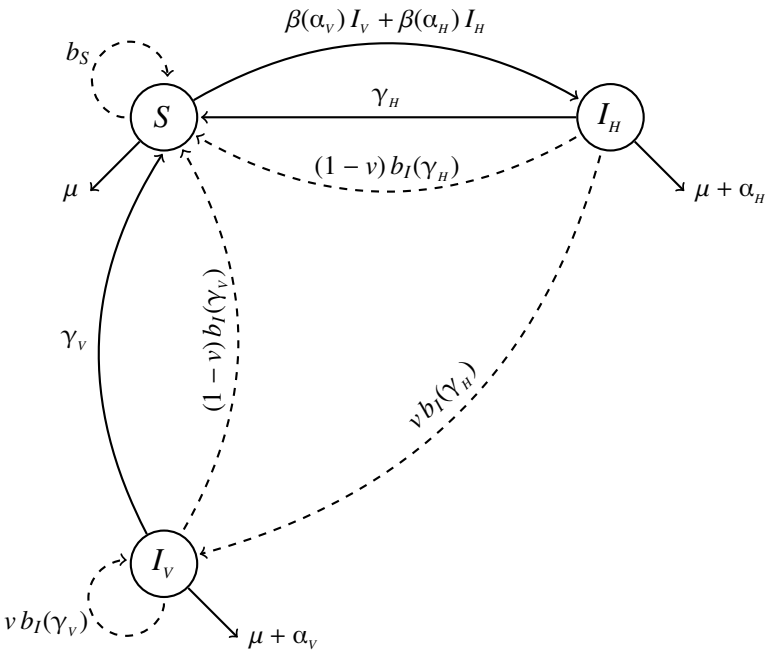

Figure 2.1: The transition of hosts between the possible states of infection S, I_V, I_H. Solid arrows represent reassignment from one state to another, were as broken arrows indicate births.

contribution to the total population size. The positive contribution must be counter-balanced with losses elsewhere if equilibrium is to be maintained. This leads to our second constraint: $b_I(\gamma_H) < \mu + \alpha_H$ or $b_I(\gamma_V) < \mu + \alpha_V$. Finally, the third is $\mu + \alpha_V + \gamma_V - v\, b_I(\gamma_V) > 0$, which says that vertical acquired infections alone are insufficient to maintain that category in the long term.

2.2.2 Coevolutionary Dynamics

In this section, we model the coevolutionary process as a simultaneous-move game between a focal parasite and its host. The parasite's goal in the game is to find an induced mortality rate (α_V or α_H) which maximises its own fitness at ecological equilibrium given its host's clearance rate (γ_V or γ_H). We can interpret this as the parasite's best response to its host. For its part, the host's aim is to find the level of clearance that maximises its own fitness at ecological equilibrium, given the parasite's induced mortality. This is the host's best response to its parasite. The result of the game is a mutual best response, or Nash equilibrium, and it is this that we take as the endpoint of the coevolutionary process.

As described in the supporting material A.2.1, the Nash equilibrium traits of a vertically

acquired parasite and its host, α_v^* and γ_v^* respectively, satisfy the following pair of equations,

$$\beta'(\alpha_v) = \frac{\beta(\alpha_v)}{\mu + \alpha_v + \gamma_v - v\, b_I(\gamma_v)}, \tag{2.1a}$$

$$b_I'(\gamma_v) = \frac{b_I(\gamma_v) - (\mu + \alpha_v)}{(\mu + \alpha_v)(1 - v) + \gamma_v}. \tag{2.1b}$$

We may interpret these conditions geometrically, as depicted in Figure 2.2. If we hold the parasite evolutionarily fixed and consider the evolution of only the host, or vice versa, then the effect of vertical transmission becomes straightforward. Figure 2.2a suggests that when there is vertical transmission the parasite will evolve lower levels of induced mortality. This more benign evolutionary outcome is due to a tighter connection between parasite's success and the long-term success of its host. Moreover, Figure 2.2b suggests that if we fix the level of the parasite-induced mortality then increasing vertical transmission will incentivise the host to invest more in clearance. Of course, vertical transmission implies some offspring are infected and so of a lower quality. By increasing clearance the host produces fewer, but higher quality, descendants, and a more aggressive evolutionary outcome is the result.

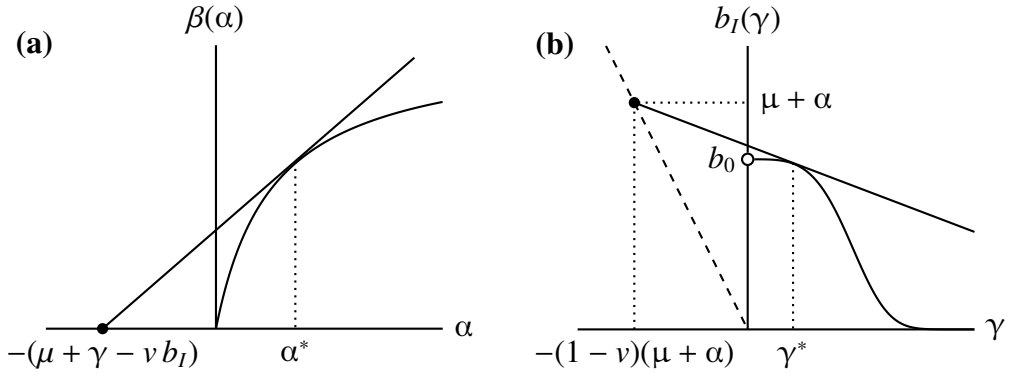

Figure 2.2: (a) The Nash equilibrium trait of a parasite α^* is represented geometrically as the horizontal component of the point at which the tangent to the graph of $\beta(\alpha)$ passes through $(-(\mu + \gamma - vb_I(\gamma), 0)$. The fact that $\beta''(\alpha) < 0$ implies that α^* is evolutionarily stable. The value of α^* is reduced when, all else being equal, we (i) increase the vertical transmission rate v, (ii) decrease the clearance rate of the host γ, or (iii) decrease the background mortality rate of the host μ. (b) The equivalent construction for the host. The equilibrium recovery rate γ^* is reduced when, all else being equal, we decrease the rate of (i) vertical transmission, v, (ii) parasite-induced mortality, α, or (iii) background mortality μ.

A similar derivation (see Appendix A.2) leads to conditions which are satisfied by the Nash

equilibrium traits of a horizontally acquired parasite and its host, α_H^* and γ_H^* respectively,

$$\beta'(\alpha_H) = \frac{\beta(\alpha_H) + v\, b_I(\gamma_H)\beta'(\alpha_V)}{\mu + \alpha_H + \gamma_H}, \tag{2.2a}$$

$$b_I'(\gamma_H) = \frac{1}{\mu + \alpha_H + \gamma_H}\left(b_I(\gamma_H) - \frac{(\mu + \alpha_H)(\mu + \alpha_V + \gamma_V - v\, b_I(\gamma_V))}{(\mu + \alpha_V)(1 - v) + \gamma_V}\right). \tag{2.2b}$$

Through some algebraic manipulation (shown in Appendix A.2.3) it can be shown that equations (2.1) and (2.2) are simultaneously satisfied when the vertical and horizontal traits of both host and parasite coincide, so that the same geometric construction applies to the horizontal traits. This suggests that the current model is not sufficiently powerful to allow for conditional behaviour and addressing this is a topic of future work. From now on we omit subscripts ($\alpha = \alpha_V = \alpha_H$ and $\gamma = \gamma_V = \gamma_H$).

The conflicting agendas of the host and parasite can be reconciled by determining the strategies from which neither player gains a benefit from deviating. This is precisely when the parasite's best response to its host coincides with the best response of its host. Mathematically we accomplish this by recognising that equations (2.1) implicitly define a players best response to their opponent as functions: $\alpha_{\text{br}}(\gamma)$ for the parasite and $\gamma_{\text{br}}(\alpha)$ for the host. Then, we may identify candidate host and parasite traits that emerge as a result of coevolution as the α^{**} and γ^{**} that satisfy the following system of equations,

$$\alpha^{**} = \alpha_{\text{br}}(\gamma^{**}), \tag{2.3a}$$

$$\gamma^{**} = \gamma_{\text{br}}(\alpha^{**}). \tag{2.3b}$$

Geometrically, this means that α^{**} and γ^{**} are the coordinates of the point of intersection between the graphs of the best-response functions (Figure 2.3). The candidate intersection point is then a Nash equilibrium whenever,

$$\alpha_{\text{br}}'(\gamma^{**})\,\gamma_{\text{br}}'(\alpha^{**}) < 1. \tag{2.4}$$

This same geometric interpretation allows us to conclude that α^{**} and γ^{**} is in fact a Nash equilibrium whenever α_{br} has a shallower slope than γ_{br} at the point of intersection. In Appendix A.5 we show that the Nash equilibrium (α^{**}, γ^{**}) is also stable in other ways familiar to evolutionary biology.

To proceed we assume functional forms for the transmissibility $\beta(\alpha)$ and birth rate of infectives $b_I(\gamma)$. The functions must meet the criteria of the life history trade-offs faced by the host and parasite $b_I{}'(\gamma) \leq 0, \beta'(\alpha) > 0$, and, as is shown in Appendix A.5, ensure evolutionary stability, $b_I{}''(\gamma) < 0, \beta''(\alpha) < 0$. We take the simple functions,

$$b_I(\gamma) = b_S - \lambda\gamma^2 \qquad \text{with} \quad 0 < b_S < \mu + \alpha,\ \lambda > 0, \tag{2.5a}$$

$$\beta(\alpha) = \alpha^n \qquad \text{with} \quad 0 < n < 1. \tag{2.5b}$$

Here $\lambda > 0$ reflects the cost the host pays to mount an adaptive immune response. The parabolic function used to simulate the host trade-off places a cap on the rate of host clearance above which the birth rate of infectives becomes negative, and so, unrealistic. This approximation

is acceptable to us however, since we do not lose predictive power. Whenever γ is this high, Figure 2.2b allows us to predict that the host will have already begun to indefinitely escalate its clearance rate.

In the trade-off faced by the parasite, n captures the proportional gains in horizontal transmission achieved through increases in induced mortality; specifically a 1% increase in α results in an n% increase in β. Now these are specified, we determine the best response that a host or parasite has to a given trait of its opponent (equations A.19). Some typical configurations of the best response curves are plotted in Figure 2.3.

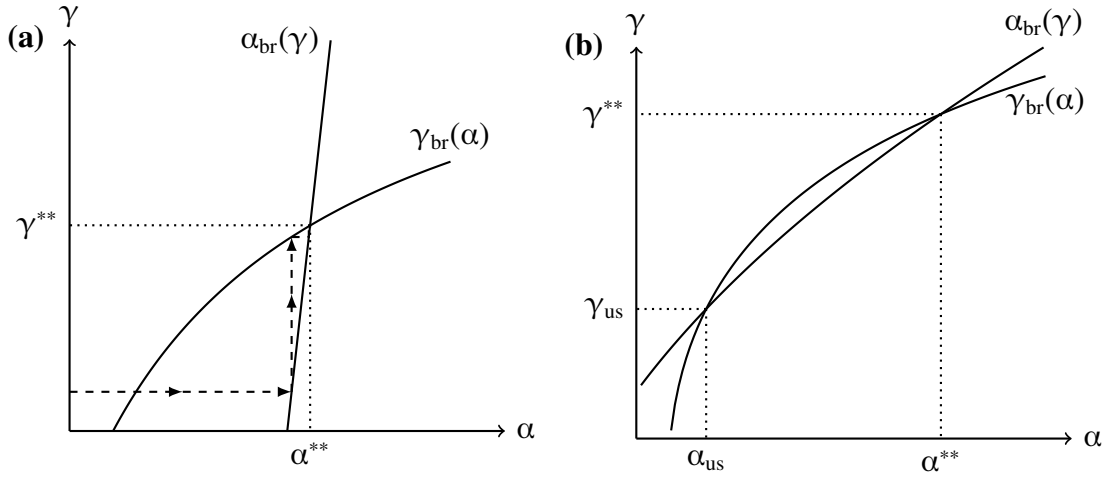

Figure 2.3: (a) The coevolutionary process can lead to positive levels of parasite-induced mortality α^{**} and host recovery γ^{**}. This outcome can be visualized as the intersection of the best-response curves $\alpha_{br}(\gamma)$ and $\gamma_{br}(\alpha)$. (b) A second intersection point, with lower values of induced mortality and clearance rate, can exist in the positive quadrant, however this point is unstable and so acts as a threshold.

The existence and position of the intersection points, and hence the Nash equilibrium, depend on the ecological parameters and shape of the trade-offs imposed. In particular we find that the cost to the host to uptake an immune response, λ, the transmission exponent, n, and the efficacy of vertical transmission, v, change the qualitative result of coevolution.

2.3 Results

2.3.1 Special Cases

In the cases where vertical transmission is either absent or entirely effective ($v = 0$ or $v = 1$ respectively) we can obtain analytic solutions to the coevolutionary process. When there is no possibility of vertical transmission ($v = 0$) we find that $\alpha^{**} = \alpha_0^{**}$ and $\gamma^{**} = \gamma_0^{**}$ where,

$$\alpha_0^{**} = \frac{(2\lambda\mu + 1)\, n + \sqrt{(2\lambda\mu + 1)^2 - (1 - n^2)\,(4\lambda b_S + 1)}}{2\lambda\,(1 - n^2)/n} \tag{2.6a}$$

$$\gamma_0^{**} = \frac{1 - n}{n}\,\alpha_0^{**} - \mu \tag{2.6b}$$

in keeping with equation (A.19a). Note also that previous authors [14] do not report the expression α_0^{**} provided above, but the result coincides with their predictions.

Perfect vertical transmission is not uncommon in parasites, with the proportion of offspring infected reaching 100% in some reported cases [99, 91]. When $v = 1$ the best-response functions potentially intersect twice. Candidate points of intersection are characterised by host traits $\gamma^{**} = \gamma_1^{**}$ and $\gamma^{**} = \gamma_2^{**}$ where,

$$\gamma_1^{**} = \frac{n - \sqrt{8\lambda(b_S - \mu)(n - 1/2) + n^2}}{4(1/2 - n)\lambda}, \tag{2.7a}$$

$$\gamma_2^{**} = \frac{n + \sqrt{8\lambda(b_S - \mu)(n - 1/2) + n^2}}{4(1/2 - n)\lambda}. \tag{2.7b}$$

Then, $\alpha_{\mathrm{br}}(\gamma_1^{**})$ or $\alpha_{\mathrm{br}}(\gamma_2^{**})$ give the corresponding parasite trait.

Of our two candidates, only $(\alpha_{\mathrm{br}}(\gamma_2^{**}), \gamma_2^{**})$ meets the stability condition (2.4) which ensures it is a Nash equilibrium when it exists. Numerical results suggest that the Nash equilibrium with $v = 1$ is escalated compared with the $v = 0$ case, in that $\alpha_{\mathrm{br}}(\gamma_0^{**}) < \alpha_{\mathrm{br}}(\gamma_2^{**})$ and $\gamma_0^{**} < \gamma_2^{**}$.

Whilst the other candidate $(\alpha_{\mathrm{br}}(\gamma_1^{**}), \gamma_1^{**})$ is not a Nash equilibrium, and will not be the endpoint of the coevolutionary process, it is still of interest. When it exists, this candidate acts as a threshold between mutually de-escalating to a benign state and an escalated outcome (the Nash equilibrium or run-away escalation). It is important to note that, like previous work [96], we find that mutual de-escalation can destabilise the ecological equilibrium between host and parasite. (Whether this happens depends sensitively on the initial trait values and the shape of the best response functions.) Ecological destabilisation occurs because we require a positive parasite-induced mortality to regulate host density. Despite the destabilisation of the equilibrium the model still signals the possibility of a benign outcome.

Figure 2.4 illustrates three regions of parameter space each supporting a distinct coevolutionary outcome for the case $v = 1$. In the first region the Nash equilibrium $(\alpha_{\mathrm{br}}(\gamma_2^{**}), \gamma_2^{**})$ exists alongside the threshold pair $(\alpha_{\mathrm{br}}(\gamma_1^{**}), \gamma_1^{**})$. Below the threshold host and parasite are predicted to coevolve to the aforementioned benign state (Figure 2.4, region A). In the second region neither of the candidate intersection points exist and the only predicted outcome is a benign state (Figure 2.4, region B). In the third region only $(\alpha_{\mathrm{br}}(\gamma_1^{**}), \gamma_1^{**})$ exists and separates run-away escalation from the benign state (Figure 2.4, region C).

The parasite's best response to its host, $\alpha_{\mathrm{br}}(\gamma)$ becomes more antagonistic as it gets proportionally more transmissibility for a given proportional increase in induced mortality (increased n). As a result the coevolutionary outcome becomes more antagonistic as well. This is reflected in the order, with respect to the horizontal axis, of the three regions identified in Figure 2.4. For small values of n the most prominent region is B in which the only predicted outcome is a benign interaction. As n grows, region A gains prominence and an escalated outcome, in the form of a Nash equilibrium, appears alongside the benign outcome. As n is increased beyond $1/2$, the Nash equilibrium is replaced by run-away escalation.

De-escalation is made more likely by two properties of the host population, the cost of immune response, λ, and the intrinsic growth rate $b_S - \mu$. This is first reflected by the ordering of regions A and B of Figure 2.4 with respect to the vertical axis. For small values of λ immune function is cheap and so region A, with its escalated Nash equilibrium, is prominent. As λ increases, the cost of immune response becomes more expensive for the host and so

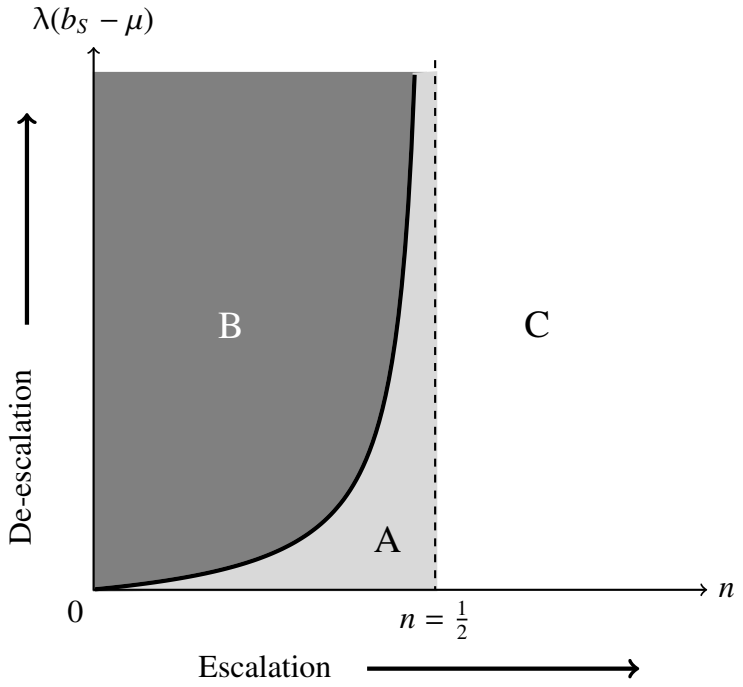

Figure 2.4: Parameter space for the case $v = 1$. Region A is defined by $8\lambda(b_S - \mu)(n - 1/2) + n^2 \geq 0$ and $n < 1/2$. In this case the smaller intersection point acts as a threshold between de-escalation and escalating to the Nash equilibrium. B) De-escalation of host and parasite traits. C) Threshold separates de-escalation from unbounded escalation.

the de-escalation in region B become more dominant. When the intrinsic growth rate is low the host's immune response is more readily triggered by parasite induced mortality, and the parasite values vertical transmission to a smaller degree. Taken together a more sensitive host and a less interested parasite, set the stage for an escalated outcome and this is reflected in the increased prominence of region A near the bottom of Figure 2.4. By contrast, a larger intrinsic growth rate sees a more tolerant host and a parasite more interested in its host, so that region B is most prominent at the top of 2.4.

The effect of λ, $b_S - \mu$ and n is also reflected in the outcomes associated with region C in Figure 2.4. Recall that in this region, only the threshold, which separates mutual de-escalation from run-away escalation, exists. Numerical results not shown indicate that a rise in either the cost of immune response or the intrinsic growth rate of the host, or a decline in n, increases the threshold and so promotes mutual de-escalation.

2.3.2 Generic Results

In this section we explore model predictions when the efficacy of vertical transmission v takes values between the two extremes studied in the previous section. As the reader will see, our exploration of the intermediate cases, $0 < v < 1$, is numerical and leads us to make essentially the same qualitative predictions supported by the exact expressions above. When we allow the efficacy of vertical transmission to take intermediate values ($0 < v < 1$) we again find a Nash equilibrium pair – now denoted $(\alpha^{**}, \gamma^{**})$ – and a threshold pair – now denoted $(\alpha_{us}, \gamma_{us})$. The

respective position of each pair varies as we change the efficacy of vertical transmission v, in a manner that depends on – among other things – the cost of immune function, λ.

When cost of immune function is low (λ small), increasing the efficacy of vertical transmission v always raises the Nash equilibrium level of host clearance. Though the increase in host immune function is sometimes met with a decrease in the Nash-equilibrium parasite trait, α^{**}, any such reduction disappears as v rises further. Indeed, when host immune function is cheap, persistent increases in v always eventually lead to an increase in the Nash-equilibrium level of parasite-induced mortality (Figures 2.5a and 2.6). The result is a consequence of the fact that increased vertical transmission always reduces the quality of offspring a host produces. When immune function is cheap, an infected host can mitigate the reduction in offspring quality by investing more in clearance. This eventually makes the duration of infection so low, and reduces the birth rate to such a point that the parasite has no choice but to invest more heavily in creating new horizontal infections. The ultimate consequence, here, is the mutual aggravation of host and parasite hostilities. If v continues to increase whilst cost is low then the result will be runaway escalation.

When cost is high (λ large), the effect of changing v can be split into two cases. In the first case, v is small and always leads to reduced parasite-induced mortality as v grows. Provided v remains small, its continued growth results in an eventual reduction in host clearance (Figures 2.5b and 2.6). Here, the price of immune function is so high that an infected host has no choice but to tolerate its parasite and reduce its level of clearance. This leads to longer infections, increased births among infected hosts, and ultimately incentivises more benign parasites. As we increase v further, the Nash equilibrium and threshold coalesce and disappear, and in this scenario we find mutual de-escalation. This sub-threshold region of de-escalation is also made larger by increasing λ. The Nash equilibrium and threshold eventually re-appears for larger values of v, but when they do the effect of v switches. Now, cost λ is high but so too is the efficacy of vertical transmission. In fact, v is so high and low-quality offspring so numerous that an infected host is willing to invest more heavily in eliminating its parasite, despite the cost. Mutual escalation and possibly an arms race then follow. We do not observe a scenario in which the host trait at the Nash equilibrium is decreasing whilst the parasite's is increasing.

In the generic case, the effect of the other parameters agrees with those discussed for perfect vertical transmission ($v = 1$). Changing either the transmission exponent, n, or the intrinsic growth rate, $b_S - \mu$, has a two-fold effect on escalation. If n is increased or $b_S - \mu$ decreased then the Nash equilibrium becomes more aggravated and, because the threshold declines, also becomes a more likely outcome of the coevolutionary process. Figure 2.7 demonstrates how the host and parasite can become more discordant as their individual interests change. In this case, it is no longer feasible that increased vertical transmission can mutual de-escalate the Nash equilibrium (no blue curves).

2.3.3 Virulence

In order to address if vertical transmission influences selection for more benign parasites we need to examine the detrimental effect of parasitism on host fitness. The term virulence is used to describe these effects and can be measured in numerous ways [78, 3]. Table 2.2 provides details of four measures of virulence common to theory. It is important to note that, as described in Chapter 1, the fitness decrease due to infection is the correct measure of virulence, were as

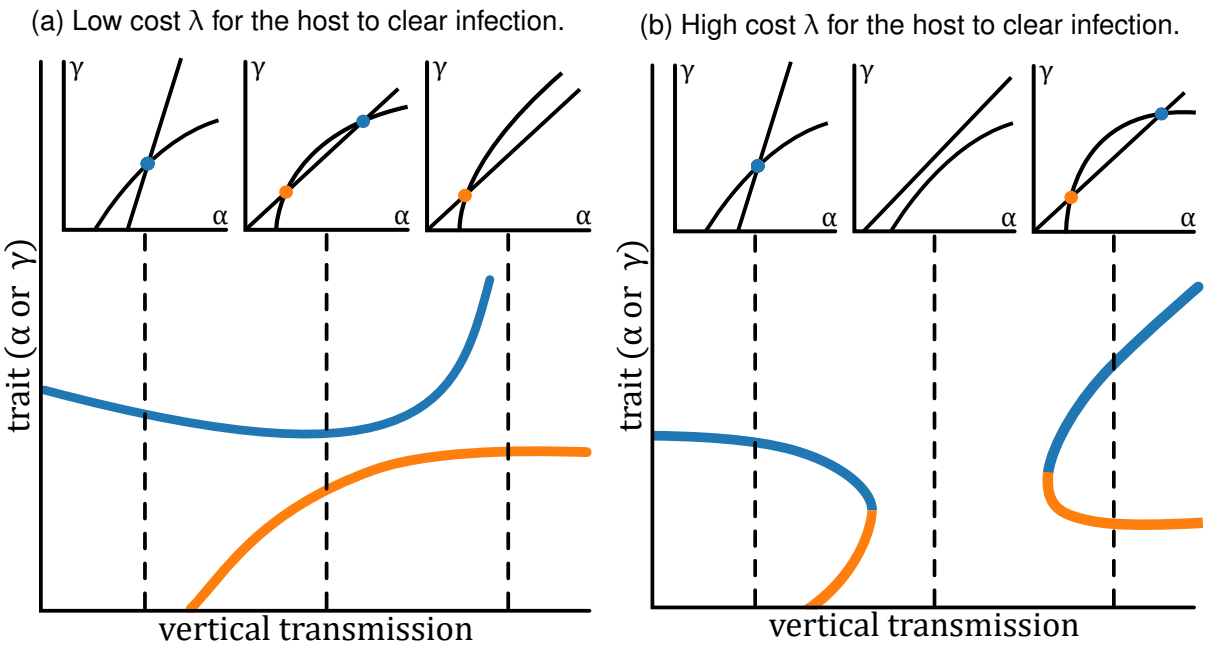

Figure 2.5: Both of the intersection points move as the efficacy of vertical transmission v is varied. The inset graphs show the corresponding best response curves. The larger trait value (blue) is the Nash equilibrium and the smaller (orange) is the threshold. The cost to the host, λ, partitions the behaviour so that either (a) the Nash equilibrium and threshold vary smoothly for all v, or (b) they coalesce and disappear for intermediate levels of v.

the others should be thought of as proxies.

Table 2.2: Measures of virulence used to describe the harmful effects of parasitism on the host.

Virulence Measure		Equation	Description
(I)	Induced mortality	α	Parasite induced mortality.
(II)	Case mortality	$\frac{\alpha}{\mu+\alpha+\gamma}$	Likelihood of death once infected.
(III)	Conditional case mortality	$\frac{\alpha}{\alpha+\gamma}$	Likelihood of death due to disease once infected.
(IV)	Fitness decrease	$\frac{\mu+\alpha+b_I(\gamma)}{\mu+\alpha+\gamma-v\,b_I(\gamma)}$	Decrease in reproductive success due to infection.

Up to now we have used the coevolved parasite-induced mortality, α, and clearance rate, γ, to describe the antagonism between host and parasite. While α and γ are easily accessible to theoreticians, in reality, their affect may be hard to distinguish from background mortality and disease tolerance. To account for this, case mortality (II) or case mortality conditional on not dying of natural causes (III) are often used. These measures incorporate the reaction of the host and, in doing so, change the predicted coevolutionary outcomes drastically [13]. A further complexity arises when parasites can transmit vertically. When hosts can produce offspring of variable quality, the parasite has consequence on the fecundity, as well as survival,

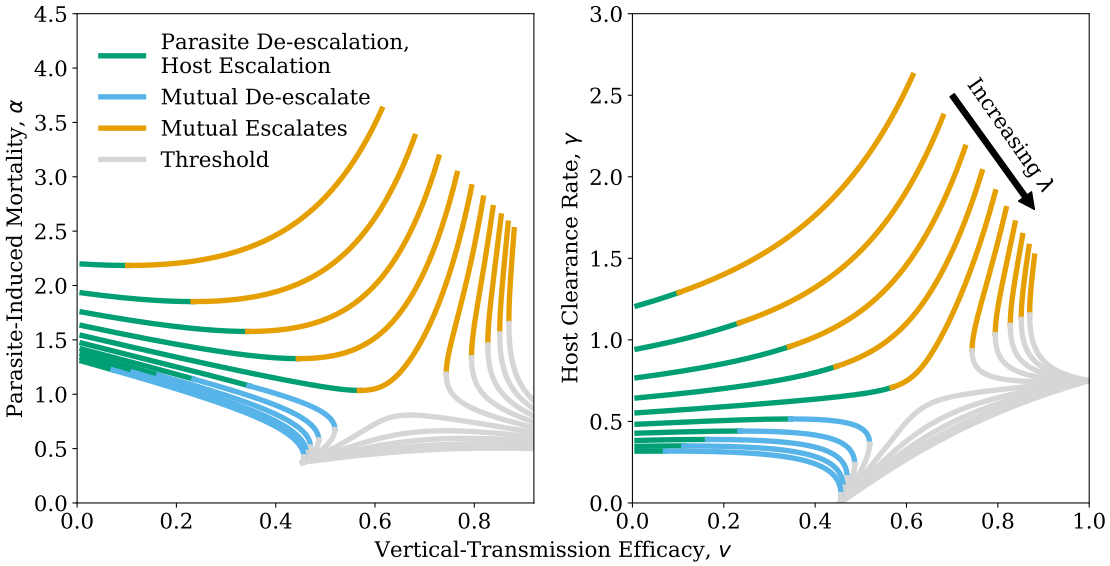

Figure 2.6: Nash-equilibrium trait values (colour) and threshold trait values (grey) for parasite (left) and host (right), as the probability of vertical transmission v varies. Colours, as elaborated in the key, describe whether parasite and host traits are coordinated as v changes. Each line corresponds to a different value of λ (ranging linearly between 0.2 and 0.6).

of its host. In Appendix A.2.2 we calculate the fitness of an infected host in a way which is considerate of the transmission mode and the life-history trade-off faced by the host, and in doing so determine what we propose is the most general measure of virulence in this system: the fitness decrease due to infection (IV). Figure 2.8 depicts the measures of virulence we have discussed, and how they change with the efficacy of vertical transmission, v, and cost of immune function, λ. Measures (I), (II), and (IV) generally have the same qualitative response to changes in the parameters. However we do find that the proxies of fitness (I, II and indeed γ) can be seen to decrease when in fact the true measure of virulence (IV) is increasing. This should act as a caution to experimentalists when measuring proxies of virulence. Increasing λ and $b_S - \mu$ or decreasing n acts to lower virulence. The response of each measure to changes in the efficacy of vertical transmission is also often the same, however there are always exceptions to this, in which any two given measures have the opposite response to the same change. Of the four virulence measures, conditional case mortality (III) stands out as an anomaly. Firstly, its relationship with the cost of immune function and intrinsic growth rate are non-monotonic, so can flip from positive to negative - a result observed in part by Day [13]. Secondly, it takes its highest values (approaching 100% probability of eventual death due to infection) when the parasite induces its minimum level of mortality and consequently the host shows little effort to clear it (α and γ low).

Finally, at Nash equilibrium we find that as the proportion of infections which arose vertically increases, case mortality decreases drastically (Figure 2.9), independently of the cost to the host λ and the intrinsic growth rate $b_S - \mu$. This result extends a previous finding that case mortality takes the constant value n when there is no vertical transmission [14]. Indeed,

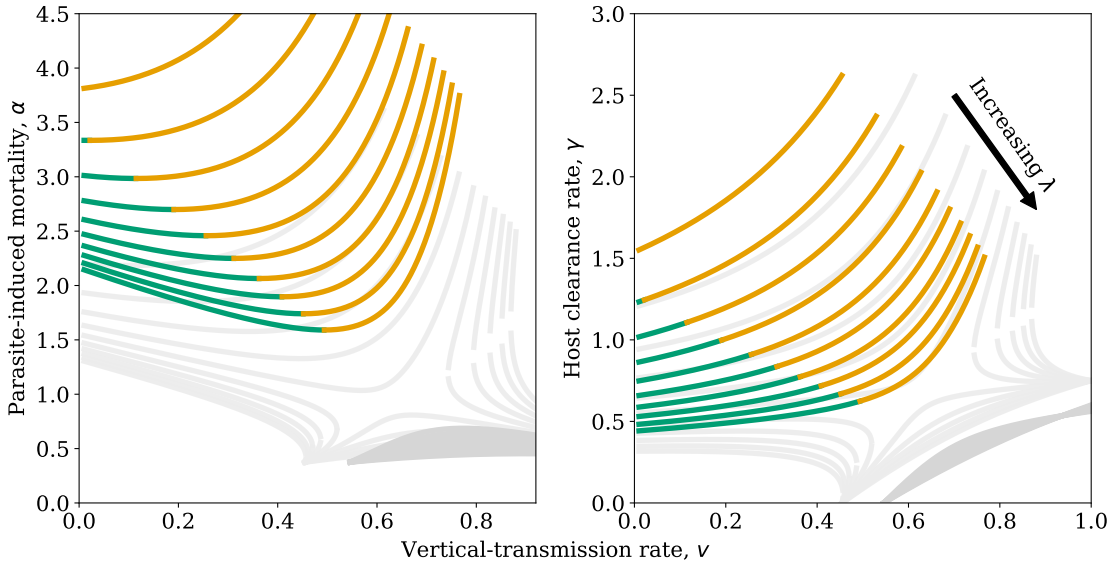

Figure 2.7: Greater proportional gains through horizontal transmission (larger n) raises the Nash equilibrium and decreases the threshold, as compared to Figure 2.6 which is plotted faintly below. Decreasing the intrinsic growth rate $b_S - \mu$ is not shown, but leads to the same qualitative result.

we can recover the the same result by substituting our expression for α_0^{**} and γ_0^{**} in (2.6) into the equation for case mortality. This strong linear relationship is indicative that perhaps the proportion of infections which arose vertically is a better measure than v for the amount of vertical transmission.

2.4 Discussion

In this paper we investigate how vertical transmission affects the coevolution of a parasite and its host. To this end, we extended an existing mathematical model of parasitism [14] by allowing opportunities for vertical transmission to occur alongside the more familiar horizontal ones. We found that the origin of infection – whether it was acquired horizontally or vertically – does not inform the optimal strategy of host and parasite. This finding allowed us to simplify our investigation substantially and study only a single pair of co-evolving traits.

We also found that while the efficacy of vertical transmission influences the co-evolutionary outcomes for both host and parasite, it does not inevitably lead to more benign associations between them; nor does it inevitably lead to a reduction in virulence. Our predictions, here, offer a stark contrast to the prevailing notion that vertical transmission improves disease outcomes by aligning the interests of host and parasite [55, 11, 23, 95]. Our co-evolutionary perspective is undoubtedly the reason for the difference, as previous discussions on the role of vertical transmission treat the host as a fixed feature of the parasite's environment. Of course, in a strict sense, neglecting the possibility of host evolution is not reasonable, but it is certainly not a bad approximation when host-parasite relationships are relatively new and host evolution is substantially outpaced by evolution of the parasite. For long-standing host-parasite relationships,

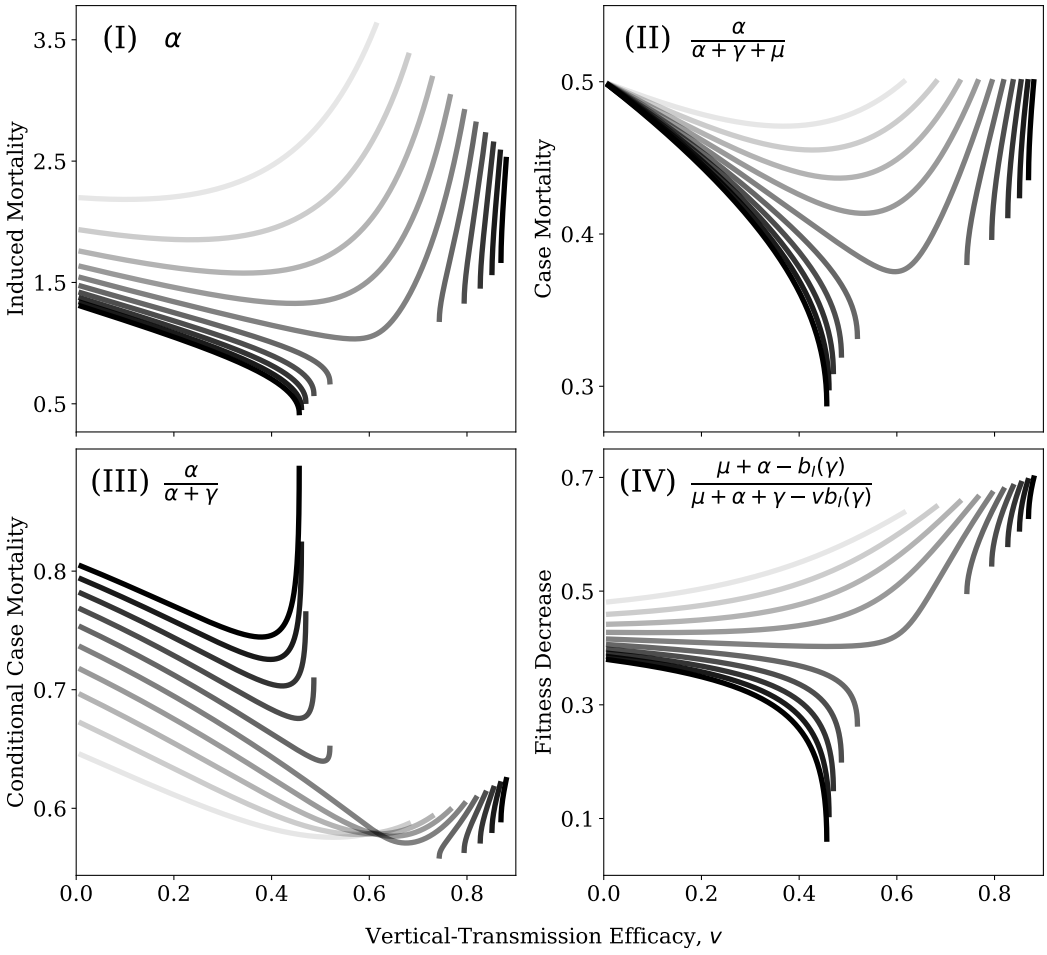

Figure 2.8: The relationship between four measures of virulence and the efficacy of vertical transmission. Darker lines indicate a higher cost to the host to clear the infection.

or for those situations in which host parasite traits evolve at comparable rates, we contend that vertical transmission can lead to more aggressive host and parasite interactions.

Although we cannot be guaranteed that vertical transmission leads to benign associations between hosts and parasites, we can still expect relatively benign outcomes in certain circumstances. Specifically, we find that benign outcomes are promoted as (i) the host immune response becomes more costly, (ii) as the intrinsic rate of increase of the host population rises, and (iii) as the horizontal-transmission benefits of host exploitation decrease. The first of these three makes sense from the host's perspective: if a host cannot afford to rid itself of a parasite, then reduced effort toward that end is prudent because it elicits an in-kind response from the parasite. The host, in that case, is making the best of a bad situation. This is also the reason why we never predict that the host will reduce its investment in clearance whilst the parasite is ramping up its induced mortality — the parasite always de-escalates first. The second and third effects, together, make sense for the parasite, because they reflect the potential for new infections to spread through vertical and horizontal transmission modes, respectively. Vertical transmission is dependant on host reproduction, and so it is more profitable to the parasite in

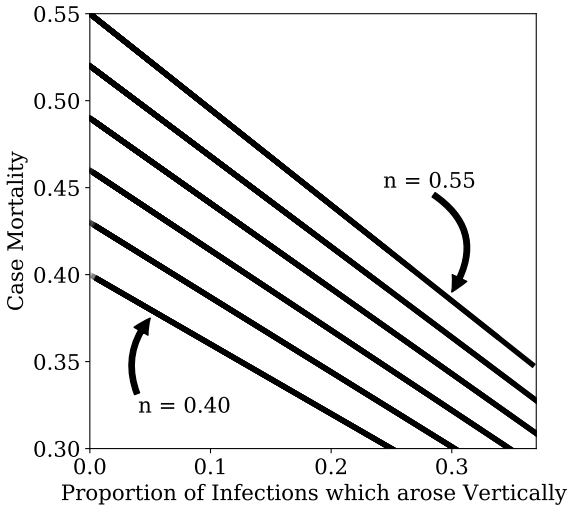

Figure 2.9: Case mortality decreases as the proportion of infections which are vertically acquired increases, independent of the cost of host immune function. Each curve corresponds to a different value of n.

those host populations with a greater intrinsic ability to reproduce. In such a population, a parasite should certainly invest less in traits that negatively impact the fitness of its host. For its part, horizontal transmission, as we have modelled it, necessitates a reduction in host survival. Consequently, the horizontal mode of transmission naturally becomes less attractive when the transmission benefits of induced host mortality accrue at a slower rate.

We found a negative relationship between the proportion of vertically to horizontally acquired infections and case mortality, which is robust to changes in the ecological conditions and life history of the parasite. This negative relationship is interesting because it suggests that the relative number of vertically acquired infections — not the efficacy of vertical transmission itself — offers an indirect indication of the severity of disease outcomes. On the face of it, this finding seems in contrast to the previously held notion, dicussed by Frank [30] and Lipsitch et al. [54], that the relative incidence of each transmission mode cannot inform us about virulence. However, Lipsitch's observation was made in the edge case in which, at ecological equilibrium, all hosts were vertically infected. The relative incidence of each type of infection, in this case, is itself uninformative (comparable to a ratio of 0 to 1). Furthermore, Frank's argument conflates the efficacy of each mode with its incidence, which are distinctly different quantities. In fact, in our model we see the highest incidence of vertically infected hosts when the efficacy of vertical transmission is intermediate.

Like other authors [54, 55, 95], we do not assume vertical transmission trades off against horizontal transmission. Nevertheless, our results do expose a tension, of sorts, between these two transmission modes. De-escalated outcomes tend to be associated with a higher proportion of vertically transmitted infections, whereas the reverse is true for escalated outcomes. This pattern agrees with studies that demonstrate reduced virulence when horizontal parasite transmission is limited experimentally [10, 9]. Furthermore, in keeping with the comments we made in the Introduction, the pattern suggests that experimental reductions in virulence can be due to reduced efficacy of horizontal transmission alone. Where some authors point to small

numbers of susceptible individuals as being a hallmark of the de-escalated outcomes connected to vertical transmission [30], we would simply say that it is the prohibitive economics of horizontal transmission – especially when compared to the potential for vertical transmission – that is the more fundamental factor. As an aside, we add that there are certainly parasites that must trade increased success through one mode of transmission for decreased success in the other. An obvious example are lysogenic bacteriophages that transmit vertically by incorporating themselves into host genomes and abandoning efforts to lyse their host spread horizontally [93]. Our work may see limited application to systems like these.

Our conclusions are limited by a number of simplifying choices we made in the construction of the model. Firstly, the ecological setting we use does not allow the host population to self-regulate its density. Instead, it is the parasite's induced mortality which dampens host growth and brings about a steady state. The same assumption appears in previous work [14, 96]. It means that in scenarios in which the parasite is pacified, we lose the stability of the ecological equilibrium which underpinned the evolution and essentially our model can no longer make predictions about coevolution. Strictly speaking, then, the non-equilibrium outcomes predicted by our model are more accurately viewed as flags indicating the high potential for these outcomes to occur. Similar flags appear in other areas of evolutionary theory; for example, the use of so-called evolutionary branching points to inform us of the likelihood of ecological speciation [33].

A second assumption which our model is sensitive to is the specific functional forms assumed in the life-history trade-offs faced by the host and parasite. Whilst there is continued debate over the existence and shortcomings of these trade-offs [1, 3], here we are (merely) concerned that our progress was made possible because of the tractable functions we used. We were unable to make analytic or computational progress when we considered different functional forms which could be justified as more biologically realistic. For example the quadratic equation used to model the birth rate of infectives has the obvious flaw of being negative for large enough investment by the host in clearance. A more appropriate function would have the birth rate remain positive but tail off as host clearance increased (see 2.2b). However, a more realistic form, which takes this into account, does not provide any more predictive power. This is because as the function tails off, we lose the conditions which ensured the singular strategies are evolutionary attractors. We can however say that, in this case, it becomes marginally cheaper for the host to clear the infection. We expect this to fuel a runaway escalation of the host's clearance, to which the parasite follows in-kind.

Another assumption implicit in the model is that parasites do not have to inflict harm on their host in order to access the vertical transmission pathway. Certainly, there is a precedence for this assumption [95, 54, 55] and we believe it is well-justified. Whereas horizontal transmission typically depends on some form of pathogen-induced response from the host (such as sneezing or diarrhea), vertical transmission relies on the host's existing (uninfected) behaviour (i.e. birth). Because the parasite is not required to alter the host's behaviour in order to vertically transmit we suspect that selection will favour inconspicuous vertical transmission. While there is undoubtedly some inherent cost imposed on the host from, say, the parasite crossing the placenta, we expect that, since it is not in the parasite's interest to provoke an immune response here, the effect will be small.

Our analysis found that the origin of infection need not inform the evolutionarily optimal strategies of both host and parasite. However, the question remains as to whether this must

necessarily be the end point of evolution, or, whether there is the possibility of phenotypic plasticity. We speculate that the reason we do not capture conditional behaviour is perhaps due to the asymptotic amount of time that an individual host or parasite can expect to stay in each infective compartment. Whilst it is possible for a host to be infected horizontally an arbitrary number of times, if a host is ever vertically infected (i.e. born infected), once it leaves that compartment, through clearance or death, it itself will never return. In this light, when a host is deciding on its vertical trait value, it might well be considering what it can expect after its vertical infection.

This work has shown that the 'vertical implies benign' hypothesis, which is commonplace amongst theoreticians and empiricists alike, does not fully capture the complexity of the coevolution of parasitic transmission modes. Our caution to anyone who assumes this hypothesis is to (i) remember that coevolution is the rule and not the exception in long-standing symbiosis, and that consigning the host to a fixed role in evolution requires justification (ii) consider carefully which measures of virulence are appropriate in the system under consideration.

Chapter 3

Critical Evaluation and Topics for Future Work

We will begin this chapter with a discussion of the scope of the model proposed in Chapter 2, as well as the modelling choices which we believe pose the largest limitations, and the approaches which can provide an alternative perspective. We are fortunate that there is an extensive body of literature on the evolution of virulence, particularly with respect to transmission, which we can use as a counterpoint to our discussion.

From my perspective, the simplification which may have the largest ramifications is that we presume that mutations are rare, so that either the resident populations are monomorphic or instead we consider an averaged population. This has numerous consequences which are relevant to transmission and the evolution of virulence. For example, though our work in Chapter 2 put emphasis on the association between vertical transmission and birth, a possibly more elementary aspect of each mode might be the effect that each has on parasite strain diversity. A host lineage which faces purely vertical transmission contends with mutants which arose within that lineage. Vice versa, parasites which horizontally transmit cannot expect such similar successive conditions. It would be interesting to see the effect of this degree of certainty that both parties have under vertical transmission, and how that varies as horizontal transmission is introduced. What this amounts to is viewing horizontal and vertical transmission as extremes on a spectrum of relatedness, as opposed to the usual dichotomy. Vertical transmission is equivalent to low variance in relatedness between successive generations, and as horizontal transmission is introduced, the variance increases. While the effect of this variance on the coevolution remains unclear [89], it is at least strong enough to discern in the genome of both organisms. Indeed, Ebert discusses how population genetics can pinpoint certain combinations of inter-specific alleles which occur together more likely than chance. One of many thing which geneticists can do with this information, what is called linkage disequilibrium, is to infer the historic modes of transmission that a parasite lineage took.

Another way in which parasite diversity can increase within the host is through multiple infections. These can stem from parasite strain diversification within the host, or due to separate infection events of co-circulating strains. Our model did not allow for multiple infections by either of these means. Firstly, our assumption that mutants where rare and defined by a monomorphic phenotype prevented within-host diversification. And secondly, implicit in our epidemiological model is the assumption that infection inferred immunity to further infection,

preventing multiple infections. Models exist which can account for either new strains displacing the old (super-infection), or strains existing simultaneously (co-infection) [2]. In these cases a variety of outcomes are possible, two of which we will touch on now.

Firstly, there is the possibility is that multiple co-infecting strains can compete; perhaps due to their aggregated effect on the immune system or over a limited resource (exploitation competition). One model of malaria demonstrated how competition for a limited resource of red blood cells could favour strains with high viral load, yet the same transmissibility. By refraining from developing transmission stages and exploiting the red blood cells, these strains could out-compete those that favoured transmission [66]. Crucially, high viral load is suggested to increase the burden on the host and so be positively correlated with virulence. Thus, this competition meant that virulent strains prospered without actually benefiting from increased transmission. This hints at the possibility of reducing virulence by limiting the possibility of resource-mediated competition or cross-reactive immune response within the host. The priority would then be preventing strains which depend on the same host resources from co-infecting. This idea runs counter to the philosophy behind public-health policies, [105], whose aim is to inhibit the overall transmission of a parasite. Instead it allows the parasite to transmit freely, but without the virulent costs to the host. In sum, multiple infections can increase virulence.

Contrastingly, co-infection can have the opposing effect on virulence, by enable cooperation between strains. An example of this comes from bacteria that produce siderophore, a molecule which enables uptake of iron into their cells. Iron uptake is used for growth and to increase viral load, so is correlated with virulence. Siderophore production is costly and is available even to those that do not invest in producing it (a public good). Therefore, bacteria which 'cheat', and do not produce siderophore, gain a fitness advantages by using without paying the cost of production. Kin-selection theory tells us that as the degree of relatedness amongst co-infecting bacteria decreases so too does their investment in one another. This leads to a decrease in cooperation, and subsequently the overall level of siderophore production diminishes [102].

Our analysis and computational results in Chapter 2 were sensitive to the specific functions used to model the life-history trade-offs faced by the host and parasite. While we were not able to make good progress with alternative functions, it might be of benefit to explore further. It is not unheard of that alternative trade-offs can overturn results. In fact, this was precisely what happened in a subsequent study of co-infection and public goods. By assuming a saturating transmission–virulence trade-off, as opposed to a linear one, Alizon et al. found that they could reverse the predictions discussed above [4]. Future work could also explore trade-offs between different parameters. For instance, as well as enabling transmission, virulence could evolve as a means to avoid detection by the immune system [11]. Therefore, one could posit a trade-off between induced-mortality and host clearance.

So far, we have discussed the possibility of multiple parasites, but yet another consideration is systems of multiple hosts. Parasites can be generalists, capable of persisting in multiple species endemically. As demonstrated in Chapter 1, they can have significant ecological effect via the interactions of other species. I believe there is a lot of value to understanding parasites at the community level and their effect on ecosystems, especially in light of human's determination to control and extinguish them. Therefore, I consider the evolution of multi-host systems a fruitful avenue of future research. Spillover, the infection into novel hosts, presents parasites with an unparalleled opportunity to proliferate into an untapped resource. In humans, there

were at least 335 emerging infectious diseases which commenced between 1940 and 2004, of which 60% were zoonotic - jumping the species gap between non-human animals and humans [47]. The six most deadly pandemics in human history were caused by zoonoses [56]. So naturally we ask: what factors precede a host shift and, in particular, promote the conception of a zoonotic spillover? What policies can public health authorities leverage in order to the prevent, manage and mitigate spillover? And finally, when can we expect emerging infectious diseases to decrease in severity over time, and what can be done to increase the chance of this outcome?

In order to address at least a brief outline of how one might proceed in modelling emerging infectious human diseases, it is helpful to partition the process of a zoonotic spillover event into discrete phases such as (i) the dynamics in the donor host population (ii) the interface between the donor and novel host (iii) the epidemic phase in which human to human transmission is impossible (iv) the epidemic phase in which it is. We will conclude this thesis with a discussion of the challenges faced by modellers at the first three of these phases. The fourth phase marks the establishment of the parasite in the host population so has already been covered in detail in the previous chapters.

The first step in identifying a host switch is to determine the species which are most liable to act as a donor to humans. Following the response to spillovers, we rarely have complete information on the donor species. For example, the origin of hepatitis C (*Hepacivirus hepacivirus C*) in humans is still unclear [100]. This stems in part from the lack of data we have on wildlife diseases in natural conditions. Information which would be beneficial includes: which species have a history of zoonosis; whether specific phylogenic or physiological properties aid fixation in humans; and which species are likely to have persistent contact with humans. A large share of the zoonotic spillover events since 1940 are due to non-wildlife, such as livestock and domestic animals. One report estimates that nearly 50% of the zoonotic diseases that emerged in humans since 1940 were associated with agricultural drivers [80]. Furthermore, current agricultural practices and methods for dealing with pests are influencing the evolution of virulence. This could also have knock-on effects for spillover. The practice of culling, for example, has been implicated in the increase in virulence observed in avian influenza circulating in ducks [83]. This has led to a call for more empirical work investigating the role of mortality in shaping virulence evolution [11]. This is consistent with our own findings that an increase in background mortality (what was called μ in Chapter 2) leads to more escalated coevolutionary outcomes.

In order to access the force of infection at the interface between the donor species and humans, we need to understand different components of the disease ecology in the donor. Factors such as donor-host density, disease prevalence, within-host viral load, and shedding rate all combined in determining the effective dose at the interface. When a parasite can build up in a population, the donor species is said to act as a reservoir. This is one place in which the approach taken in Chapter 2 is applicable. We found that a combination of high cost to the host to clear the infection and an intermediate efficacy of vertical transmission led to the highest number of infective hosts at ecological equilibrium. In this case the virulence (taken as induced mortality, case mortality or fitness reduction) was low, which matches observations in some natural populations of donors. For example, the bacterium *Yersinia pestis* is asymptomatic in marmots and other rodents [64], but spilt over into humans and went on to cause the second plague pandemic in central Eurasia [86]. The question of whether we consistently see spillovers

preceded by benign interactions in the donor species remains to be answered. One might also ask how the level of virulence in the reservoir affects the virulence in the recipient? This is a question that has been addressed. To quantify the change in mortality rate and infectivity following a host shift, one study cross-infected 48 Drosophilidae species with Drosophila C virus. They found that both mortality rate and viral load changed significantly in the new host and that hosts within the same clade as one another reacted similarly. However, they found no correlation between the genetic distance from the donor species and the level of mortality [57]. This suggests that, event within a taxonomic family, the link between genetic relatedness and virulence to the same pathogen is very complex.

Anthropogenic changes to the environment are shaping our interactions with other species [101]. More so than ever, we are forcing wild populations to cohabit in densely populated urban areas and increasing the prevalence of vectors of transmission. Understanding the potential mechanisms of transmission at the interface between species is of crucial importance. One literature survey suggests that there is a deficiency in research which directly incorporates spillover transmission into models of emerging infectious disease [56]. As was mentioned in Chapter 1, the physical routes of transmission within a given host-parasite system can be numerous and variable. Antonovics et al. suggests that changes in both the mode and route of transmission in bacteria need not stem from *de novo* mutations, and instead that bacteria maintain the genetic capability of expressing multiple modes of transmission [8]. This makes the challenge of discerning spillover routes even greater. The progress of molecular genetics and comparative genomics, however, can offer insight [98, 20].

When a parasite first 'accidentally' infects a novel host, the pair will be relatively maladapted to one another. Immunopathology may be expressed more so in these early cases, where selection has had little time to act [35]. That being said, our immune system is capable of handling a huge variety of novel infections regularly, so that the majority of infections go unnoticed [23]. Nevertheless, with each new contact there is a further opportunity for parasites to adapt and evade detection. During the initial stages of spillover, a human population might still represent an evolutionary dead-end for the parasite, if transmission between humans cannot be maintained. This does not mean an epidemic is impossible though, since a large enough force of infection at the interface can maintain the prevalence in humans. The concept of the basic reproductive number is helpful to introduce here. It is defined as the expected number of secondary infections generated by a single case in an otherwise susceptible population [5]. Importantly here, there are two basic reproduction numbers to consider: one in the donor species, and one in the recipient human population. A parasite can be highly prevalent in a human population even if the basic reproduction number in humans is less than one. In this case, infectious lineages in humans quickly stutter out, but prevalence can be maintained if new spillovers from the donor species are frequent.

The penultimate phase in the emergence of a infectious disease, before a parasite can maintain human-to-human transmission, is an exceptionally transient period where the timescales on which epidemiological and evolutionary dynamics occur are of comparable magnitude. In this phase a foundational assumption of adaptive dynamics, that the resident population is near a demographic attractor whenever mutation occurs, does not hold. However, alternative methods which allow us to consider transitory dynamics exist. The approaches developed by Day and colleagues may prove invaluable. These methods are either based on single-trait quantitative genetics [17], or reformulate multi-strain compartmental models in terms of Price's equa-

tion [15, 16]. These approaches have not been extended to consider coevolutionary dynamics, however the potential to incorporate evolution of the host genotype exists. Another factor to consider when modelling the epidemiology of spillover events is the demographic stochasticity introduced by the initially small number of short-lived infections. Multi-type branching processes have previously been used to study spillover and can be coupled to standard compartmental models to account for stochasticity [85].

3.1 Personal Reflections

Against a backdrop of drug-resistant bacteria and global pandemics, it is becoming increasing clear that evolutionary biology will have a duty to public health and environmental science. Our reliance on intensive agricultural practices is shaping a new domain in which parasites evolve, and our focus on short-term economic losses may be pushing pathogens to spread faster and become more virulent [62]. This thesis has taught me a lot; only a minute fraction of the knowledge we humans have compounded in evolutionary biology. Yet the thing I will take away most from this process is a sense of the scope of our ignorance. History is marred by epidemics that we did not know we were going to cause. Notable examples include: the African rinderpest epizootic which led to famine in sub-Saharan Africa, caused by the import of cattle [76]; the European myxomavirus outbreak, released by a landowner trying to keep rabbits off of his property [19]; and the multiple pandemic of the Americas during the 16^{th} century, which were inadvertently imported by European colonialists, and which have been estimated to have killed over 20 million people [43].

There is still so much more to know, and it appears vital to know it. I feel a responsibility to better understand and protect biodiversity, to make sustainable choices for the climate, and to foster a resilient ecosystem. My intention is that, through research and the understanding it gleams, I may inform our perspectives, the work of future scholars and our policies on conservation. In the future, if we are going to make sustainable ecological choices, we must know the evolutionary consequences of our actions.

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Appendix A

Appendices

A.1 Ecological Stability

A.1.1 Conditional

We can use the following system of differential equations to capture the dynamics of the conditional model described above:

$$\begin{aligned} S' &= (b_S - \mu)\,S - (\beta(\alpha_V)\,I_V + \beta(\alpha_H)\,I_H)\,S \\ &\quad + (\gamma_V + (1-v)\,b_I(\gamma_V))I_V + (\gamma_H + (1-v)\,b_I(\gamma_H))I_H \\ I_V' &= v\,b_I(\gamma_V)\,I_V + v\,b_I(\gamma_H)\,I_H - (\mu + \alpha_V + \gamma_V)\,I_V \\ I_H' &= (\beta(\alpha_V)\,I_V + \beta(\alpha_H)\,I_H)\,S - (\mu + \alpha_H + \gamma_H)\,I_H \end{aligned} \tag{A.1}$$

We can find a positive equilibrium solution to the system of differential equations in (A.1), where

$$S = \bar{S} \triangleq \frac{(\mu + \alpha_H + \gamma_H)(\mu + \alpha_V + \gamma_V - v\,b_I(\gamma_V))}{\beta(\alpha_H)(\mu + \alpha_V + \gamma_V - v\,b_I(\gamma_V)) + \beta(\alpha_V)\,v\,b_I(\gamma_H)}$$

$$I_V = \bar{I}_V \triangleq \frac{\bar{S}\,(b_S - \mu)\,v\,b_I(\gamma_H)}{(\mu + \alpha_V + \gamma_V - v\,b_I(\gamma_V))(\mu + \alpha_H - b_I(\gamma_H)) + v\,b_I(\gamma_H)(\mu + \alpha_V - b_I(\gamma_V))}$$

$$I_H = \bar{I}_H \triangleq \frac{\bar{S}\,(b_S - \mu)(\mu + \alpha_V + \gamma_V - v\,b_I(\gamma_V))}{(\mu + \alpha_V + \gamma_V - v\,b_I(\gamma_V))(\mu + \alpha_H - b_I(\gamma_H)) + v\,b_I(\gamma_H)(\mu + \alpha_V - b_I(\gamma_V))}$$

The positive equilibrium is locally asymptotically stable whenever the eigenvalues of

$$J = \begin{bmatrix} (b_S - \mu) - (\beta(\alpha_V)\,\bar{I}_V + \beta(\alpha_H)\,\bar{I}_H) & -\beta(\alpha_V)\,\bar{S} + \gamma_V + (1-v)\,b_I(\gamma_V) & -\beta(\alpha_H)\,\bar{S} + \gamma_H + (1-v)\,b_I(\gamma_H) \\ 0 & v\,b_I(\gamma_V) - (\mu + \alpha_V + \gamma_V) & v\,b_I(\gamma_H) \\ \beta(\alpha_V)\,\bar{I}_V + \beta(\alpha_H)\,\bar{I}_H & \beta(\alpha_V)\,\bar{S} & \beta(\alpha_H)\,\bar{S} - (\mu + \alpha_H + \gamma_H) \end{bmatrix} \tag{A.2}$$

have negative real part. Supplementary computations in Listings A.1 indicate that this is indeed the case for all parameters of interest.

A.1.2 Unconditional

We can use the following system of differential equations to capture the dynamics of the unconditional model described above:

$$\begin{aligned} S' &= b_S\, S + (1-v)\, b_I(\gamma)\, I - \beta(\alpha)\, S\, I - \mu\, S + \gamma\, I, \\ I' &= v\, b_I(\gamma)\, I + \beta(\alpha)\, S\, I - (\mu + \alpha + \gamma) I \end{aligned} \tag{A.3}$$

If the number of susceptible individuals is equal to

$$\bar{S} = \frac{\mu + \gamma + \alpha - v\, b_I(\gamma)}{\beta(\alpha)}$$

and the number of infected individuals is equal to

$$\bar{I} = \frac{b_S - \mu}{\mu + \alpha - b_I(\gamma)} \frac{\mu + \gamma + \alpha - v\, b_I(\gamma)}{\beta(\alpha)},$$

then the population size is at equilibrium and parasitic infections are endemic. This equilibrium can be shown to be locally asymptotically stable. The local asymptotic stability of the equilibrium state of the unconditional model can be determined by considering the Jacobian matrix arising from (A.3),

$$\begin{aligned} J &= \begin{bmatrix} b_S - (\beta\bar{I} + \mu) & (1-v)\, b_I + \gamma - \beta\bar{S} \\ \beta\, \bar{I} & v\, b_I + \beta\bar{S} - (\mu + \gamma + \alpha) \end{bmatrix} \\ &= \begin{bmatrix} -(b_S - \mu)\frac{(1-v)b_I + \gamma}{\mu - b_I} & -(\mu + \alpha - b_I) \\ \beta\bar{I} & 0 \end{bmatrix}. \end{aligned}$$

Because (i) the trace of J is negative, and (ii) the determinant of J is positive, we can conclude that $\bar{S}$ and $\bar{I}$ are locally asymptotically stable.

A.2 Invasion Fitness

In this Appendix, we describe the fitness of an individual parasite and that of an individual host, at the equilibrium, $\bar{S}, \bar{I}_v, \bar{I}_H$. We define fitness in terms of the long-term success of an individual's lineage. If an individual's descendants represent a portion of an equilibrium population that is growing, then that individual and its traits will be said to be favoured by selection. By contrast, if an individual's descendants represent a portion of an equilibrium population that is shrinking, then the individual and its traits will be disfavoured by selection. Though we set our calculations up slightly differently, they are formally equivalent to those from a typical invasion analysis. For convenience we suppress the dependence that the ecological equilibrium has on the resident trait values.

A.2.1 Parasite fitness

Fix attention on a single parasite lineage which is rare and possesses a mutation which effects a slight change in the rate at which members of the lineage induce mortality in their host. We

let J_X^m be the number of hosts infected either vertically or horizontally (respectively $X = V, H$) by these mutants, and denote the corresponding mutated induced mortality rates by α_X^m. The dynamics of this mutant lineage when the resident population are at equilibrium are governed by,

$$\frac{d}{dt}\begin{bmatrix} J_V^m \\ J_H^m \end{bmatrix} = \begin{bmatrix} \nu\, b_I(\gamma_V) & \nu\, b_I(\gamma_H) \\ -(\mu+\alpha_V^m+\gamma_V) & \beta(\alpha_H^m)\,\bar{S} \\ \beta(\alpha_V^m)\,\bar{S} & -(\mu+\alpha_H^m+\gamma_H) \end{bmatrix}\begin{bmatrix} J_V^m \\ J_H^m \end{bmatrix} \tag{A.4}$$

The coefficient matrix in (A.4) is quasi-positive and so has a dominant eigenvalue. We choose to split the coefficient matrix into those rates representing secondary infections and those of existing infections as such,

$$\frac{d}{dt}\begin{bmatrix} J_V^m \\ J_H^m \end{bmatrix} = (F - V)\begin{bmatrix} J_V^m \\ J_H^m \end{bmatrix},$$

for

$$F = \begin{bmatrix} 0 & 0 \\ \beta(\alpha_V^m)\,\bar{S} & \beta(\alpha_H^m)\,\bar{S} \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \mu + \alpha_V^m + \gamma_V - \nu\, b_I(\gamma_V) & -\nu\, b_I(\gamma_H) \\ 0 & \mu + \alpha_H^m + \gamma_H. \end{bmatrix}$$

Implicit in our choice of F is the convention that we start counting a new lineage at a horizontal transmission event, and that vertical transmission represents fission of the same lineage. The inverse of V represents the expected time spent by each type of infection in each infectious class,

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu+\alpha_V^m+\gamma_V-\nu\, b_I(\gamma_V)} & \frac{\nu\, b_I(\gamma_H)}{\mu+\alpha_H^m+\gamma_H}\frac{1}{\mu+\alpha_V^m+\gamma_V-\nu\, b_I(\gamma_V)} \\ 0 & \frac{1}{\mu+\alpha_H^m+\gamma_H} \end{bmatrix} \tag{A.5}$$

The entries in (A.5) make intuitive sense since (i) by convention, a parasite lineage observed in the vertical compartment cannot transition into the horizontal (ii) a parasite observed in the vertical compartment is expected to remain their for $1/(\mu + \alpha_H^m + \gamma_H)$ time units, during which it will fission into $\nu\, b_I(\gamma_H)$ copies every time unit. Each new vertically acquired parasite in the lineage will spend an average of $1/(\mu+\alpha_V^m+\gamma_V-\nu\, b_I(\gamma_V))$ time unit in the vertical compartment, hence the $(1, 2)$ component.

The next generation matrix FV^{-1} is lower triangular with one zero eigenvalue, so that the spectral radius is precisely the element in the $(2, 2)$ position, given by:

$$\rho\left(FV^{-1}\right) = \underset{H\to H}{\frac{\beta(\alpha_H^m)\,\bar{S}}{\mu + \alpha_H^m + \gamma_H}} + \underset{H\to V}{\left(\frac{\nu\, b_I(\gamma_H)}{\mu + \alpha_H^m + \gamma_H}\right)} \underset{V\to H}{\left(\frac{\beta(\alpha_V^m)\,\bar{S}}{\mu + \alpha_V^m + \gamma_V - \nu\, b_I(\gamma_V)}\right)} \tag{A.6}$$

Expression (A.6) can be interpreted biologically as the average number of secondary horizontal infections a horizontally infected individual is expected to produce in its life time, by either directly infecting others or indirectly by passing infection vertically onto their offspring who subsequently transmit horizontally. Since the spectral radius controls the stability of the mutant-free equilibrium and so the potential of a rare mutant to invade a resident population, we may identify it as the fitness of a mutant parasite, $W_p := \rho\left(FV^{-1}\right)$. We may say that the

focal parasite lineage is favoured by selection when $W_p > 1$ and disfavoured when $W_p < 1$. As expected, if the focal lineage cannot be distinguished phenotypically from the resident, then $W_p = 1$ and it is neither favoured nor disfavoured by selection.

In order to track how the induced mortality rate varies over an evolutionary timescale, we consider the rate of change of the mutant parasite's fitness with the strategies it employs,

$$\frac{\partial W_p}{\partial \alpha_V^m} = \left(\frac{v\, b_I(\gamma_H)}{\mu + \alpha_H^m + \gamma_H}\right)\left(\frac{\bar{S}}{\mu + \alpha_V^m + \gamma_V - v\, b_I(\gamma_V)}\right)\left(\beta'(\alpha_V^m) - \frac{\beta(\alpha_V^m)}{\mu + \alpha_V^m + \gamma_V - v\, b_I(\gamma_V)}\right) \tag{A.7}$$

$$\frac{\partial W_p}{\partial \alpha_H^m} = \frac{\bar{S}}{\mu + \alpha_H^m + \gamma_H}\left(\beta'(\alpha_H^m) - \frac{\beta(\alpha_H^m)}{\mu + \alpha_H^m + \gamma_H} - \frac{v\, b_I(\gamma_H)}{\mu + \alpha_H^m + \gamma_H}\left(\frac{\beta(\alpha_V^m)}{\mu + \alpha_V^m + \gamma_V - v\, b_I(\gamma_V)}\right)\right) \tag{A.8}$$

The parasite strategies $\tilde{\alpha}_V$ and $\tilde{\alpha}_H$ that simultaneously nullify equations (A.7) and (A.8) are the evolutionarily equilibrium levels,

$$\left.\frac{\partial W_p}{\partial \alpha_V^m}\right|_{\substack{\alpha_V^m = \tilde{\alpha}_V \\ \alpha_H^m = \tilde{\alpha}_H}} = 0 \tag{A.9}$$

$$\left.\frac{\partial W_p}{\partial \alpha_H^m}\right|_{\substack{\alpha_V^m = \tilde{\alpha}_V \\ \alpha_H^m = \tilde{\alpha}_H}} = 0 \tag{A.10}$$

The second technical condition discussed in Section 2.2.1 guarantees that only the last factor of each component of the fitness gradient can change sign, and so it is these that determine the root. Because (A.9) only depends on the induced mortality of vertically infected mutants α_V^m we will solve this equation first. It is from here that the geometric construction in Figure 2.2a, and in turn the parasite best response function detailed in Section A.3, are derived. We then note that condition (A.10) is equivalent to the following,

$$\begin{aligned}\beta'(\alpha_H^m) &= \frac{1}{\mu + \alpha_H^m + \gamma_H}\left(\beta(\alpha_H^m) + \frac{v\, b_I(\gamma_H)\beta(\alpha_V^m)}{\mu + \alpha_V^m + \gamma_V - v\, b_I(\gamma_V)}\right) \\ &= \frac{\beta(\alpha_H^m) + v\, b_I(\gamma_H)\beta'(\alpha_V^m)}{\mu + \alpha_H^m + \gamma_H}.\end{aligned} \tag{A.11}$$

And it is this we substitute our solution into to solve the for the evolutionarily equilibrium level of induced mortality of a horizontally infected mutant α_H^m.

A.2.2 Host Fitness

Now, fix attention on a focal host lineage which we will assume has a rare and slight mutation which affects the rate at which it clears an infection. We write γ_V^m or γ_H^m for either of the strategies this host can employ. The dynamics of this lineage when the resident population is at equilibrium is determined by,

$$\frac{d}{dt}\begin{bmatrix} S^m \\ I_V^m \\ I_H^m \end{bmatrix} = \begin{bmatrix} (b_S - \mu) - (\beta(\alpha_V)\,\bar{I}_V + \beta(\alpha_H)\,\bar{I}_H) & \gamma_V^m + (1-v)b_I(\gamma_V^m) & \gamma_H^m + (1-v)b_I(\gamma_H^m) \\ 0 & v\, b_I(\gamma_V^m) - (\mu + \alpha_V + \gamma_V^m) & v\, b_I(\gamma_H^m) \\ \beta(\alpha_V)\,\bar{I}_V + \beta(\alpha_H)\,\bar{I}_H & 0 & -(\mu + \alpha_H + \gamma_H^m) \end{bmatrix}\begin{bmatrix} S^m \\ I_V^m \\ I_H^m \end{bmatrix} \tag{A.12}$$

The Jacobian matrix in the previous equation is quasi-positive and so has one dominant real eigenvalue. The dominant left eigenvector of the matrix stores the reproductive value of individual hosts: each element is the relative evolutionary weight assigned to the corresponding category of host individual. We may use susceptible hosts as a point of reference by scaling this eigenvector so that susceptible hosts have a fitness of $w_S = 1$. When the mutant is phenotypically indistinguishable from the resident, $\gamma_H^m = \gamma_H$ and $\gamma_V^m = \gamma_V$, the dominant eigenvalue is zero and in this case we find a left eigenvector given by

$$\left[w_S, w_V, w_H\right] = \left[1, \frac{\gamma_V + (1-v)\, b_I(\gamma_V)}{\mu + \alpha_V + \gamma_V - v\, b_I(\gamma_V)}, 1 - \frac{b_s - \mu}{\beta(\alpha_V)\, \bar{I}_V + \beta(\alpha_H)\, \bar{I}_H}\right]$$

Expanding the eigenvalue equation in the first/second column of the Jacobian gives us the expression for vertically/horizontally transmitted host fitness. The final column yields a further relation which we note for later use,

$$(1-v)\, b_I(\gamma_H) w_S + v\, b_I(\gamma_H) w_V = (\mu + \alpha_H + \gamma_H) w_H - \gamma_H. \tag{A.13}$$

The virulence of a particular mode of infection is defined here as the reduction in fitness owing to infection by that mode,

$$p_V = w_S - w_V = \frac{\mu + \alpha_V - b_I(\gamma_V)}{\mu + \alpha_V + \gamma_V - v\, b_I(\gamma_V)} \tag{A.14}$$

$$p_H = w_S - w_H = \frac{b_s - \mu}{\beta(\alpha_V)\, \bar{I}_V + \beta(\alpha_H)\, \bar{I}_H} \tag{A.15}$$

To determine the expected virulence of infection in general, we may then take the average virulence of each mode of infection, weighted by the respective size of that mode at equilibrium,

$$p = \frac{p_V I_V + p_H I_H}{I_V + I_H}.$$

In order to find the host equilibrium conditions, we split the Jacobian matrix in (A.12) into components representing new/secondary infections and transmission of existing infections as such,

$$F = \begin{bmatrix} b_S & (1-v) b_I(\gamma_V^m) & (1-v) b_I(\gamma_H^m) \\ 0 & v b_I(\gamma_V^m) & v\, b_I(\gamma_H^m) \\ 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \mu + \beta(\alpha_V)\, \bar{I}_V + \beta(\alpha_H)\, \bar{I}_H & -\gamma_V^m & -\gamma_H^m \\ 0 & \mu + \alpha_V + \gamma_V^m & 0 \\ -(\beta(\alpha_V)\, \bar{I}_V + \beta(\alpha_H)\, \bar{I}_H) & 0 & \mu + \alpha_H + \gamma_H^m \end{bmatrix}.$$

Once again, the inverse of V represents the average time spent by each type of infection in each class. It is best understood in terms of two of its elements: the expected time a susceptible host will spend in the susceptible compartment, $T_{S|S}$, and the expected time a horizontally infected host spends in the horizontal compartment, $T_{H|H}$. For brevity we will use λ to denote the force of infection $\beta(\alpha_V)\, \bar{I}_V + \beta(\alpha_H)\, \bar{I}_H$. Imagine the focal host lineage is susceptible when

we observe it. After spending an average time of $1/(\mu+\lambda)$ it will either die or, with probability $\lambda/(\mu+\lambda)$, become infected by a horizontally acquired parasite. In the latter case there is a possibility, $\gamma_H^m/(\mu+\alpha_H+\gamma_H^m)$, that the host will clear the infection and return to the susceptible compartment to spend more time susceptible. Therefore, the expected time a susceptible host will spend in the susceptible compartment satisfies,

$$T_{S|S} = \frac{1}{\mu+\lambda} + \frac{\lambda}{\mu+\lambda}\left(\frac{\gamma_H^m}{\mu+\alpha_H+\gamma_H^m}\right)T_{S|S}$$

which we rearrange to obtain the explicit expression,

$$T_{S|S} = \frac{\mu+\alpha_H+\gamma_H^m}{(\mu+\lambda)(\mu+\alpha_H+\gamma_H^m)-\lambda\gamma_H^m}.$$

A similar line of reasoning also holds for a focal host lineage that we initially observe in the horizontal compartment, leading to the following expression for the expected time a horizontally infected host will spend in the horizontal compartment during its life,

$$T_{H|H} = \frac{1}{\mu+\alpha_H+\gamma_H^m} + \left(\frac{\gamma_H^m}{\mu+\alpha_H+\gamma_H^m}\right)\frac{\lambda}{\mu+\lambda}T_{H|H},$$

which we may rearrange as

$$T_{H|H} = \frac{\mu+\lambda}{(\mu+\lambda)(\mu+\alpha_H+\gamma_H^m)-\lambda\gamma_H^m}.$$

With these two quantities, the average time a host initially in state j spends in state i is given by the $(i,j)^{th}$ entry of the following matrix,

$$V^{-1} = \begin{bmatrix} T_{S|S} & \frac{\gamma_V^m}{\mu+\alpha_V+\gamma_V^m}T_{S|S} & \frac{\gamma_H^m}{\mu+\alpha_H+\gamma_H^m}T_{S|S} \\ 0 & \frac{1}{\mu+\alpha_V+\gamma_V^m} & 0 \\ \frac{\lambda}{\mu+\lambda}T_{H|H} & \frac{\gamma_V^m}{\mu+\alpha_V+\gamma_V^m}\frac{\lambda}{\mu+\lambda}T_{H|H} & T_{H|H} \end{bmatrix}$$

Then, the bottom row of the next generation matrix FV^{-1} is zero, and so the non-zero eigenvalues are determined by the submatrix formed by deleting the third row and column. If we let τ and δ denote the trace and determinant of this submatrix respectively, then the dominant eigenvalue, denoted by W_h to reflect its interpretation as the fitness of a mutant host, satisfies the equation,

$$W_h^2 - \tau W_h + \delta = 0 \tag{A.16}$$

We may implicitly differentiate to give,

$$2W_h' - \tau' W_h - \tau W_h' - \delta' = 0$$

where $'$ denotes differentiation with respect to either γ_V^m or γ_H^m. When the phenotype of the mutant coincides with that of the resident population the mutants fitness is also the same as the residents, $W_h = 1$, and in this scenario we find that,

$$W_h' = \frac{\tau'-\delta'}{2-\tau}. \tag{A.17}$$

The vertical trait for which both components of the fitness gradient are zero is again the evolutionarily equilibrium strategy. The component of the gradient in the direction of the clearance rate of a vertically infected mutant ($'$ denoting differentiation w.r.t γ_V^m) was found in the Maple script `Host_Fitness.mw` to satisfy,

$$\begin{aligned} b_I'(\gamma_V) &= \frac{b_I(\gamma_V)}{\mu+\alpha_V+\gamma_V} - \frac{\mu+\alpha_V}{\mu+\alpha_V+\gamma_V}\frac{\lambda b_I(\gamma_H)}{(\mu+\alpha_H+\gamma_H)(\mu+\lambda-b_S)-\lambda\gamma_H} \\ &= \frac{b_I(\gamma_V)}{\mu+\alpha_V+\gamma_V} - \frac{\mu+\alpha_V}{\mu+\alpha_V+\gamma_V}\frac{\lambda b_I(\gamma_H)}{\lambda((\mu+\alpha_H+\gamma_H)w_H-\gamma_H)} \end{aligned}$$

At this point we use equation (A.13).

$$\begin{aligned} &= \frac{b_I(\gamma_V)}{\mu+\alpha_V+\gamma_V} - \frac{\mu+\alpha_V}{\mu+\alpha_V+\gamma_V}\frac{\lambda b_I(\gamma_H)}{\lambda((1-v)\,b_I(\gamma_H)+v\,b_I(\gamma_H)w_V)} \\ &= \frac{b_I(\gamma_V)}{\mu+\alpha_V+\gamma_V} - \frac{\mu+\alpha_V}{\mu+\alpha_V+\gamma_V}\frac{1}{1-v+vw_V} \\ &= \frac{b_I(\gamma_V)}{\mu+\alpha_V+\gamma_V} - \frac{\mu+\alpha_V}{\mu+\alpha_V+\gamma_V}\frac{\mu+\alpha_V+\gamma_V-vb_I(\gamma_V)}{(\mu+\alpha_V)(1-v)+\gamma_V} \\ &= \frac{b_I(\gamma_V)-(\mu+\alpha_V)}{(\mu+\alpha_V)(1-v)+\gamma_V} \end{aligned}$$

To derive the equilibrium condition for a horizontally infected host we leverage the fact that, assuming that there are vertical infections at the stable age distribution, the fitness gradient is proportional to (and so shares the same roots as) the product of the reproductive value, element-wise differentiated Jacobian and stable class distribution,

$$\begin{aligned} \left.\frac{\partial W_h}{\partial \gamma_H^m}\right|_{\gamma_H^m=\gamma_H} &= \vec{w}\left.\frac{\partial J}{\partial \gamma_H^m}\right|_{\gamma_H^m=\gamma_H}\vec{r_J} \\ &= \vec{w}\begin{bmatrix} 0 & 0 & 1+(1-v)b_I'(\gamma_H) \\ 0 & 0 & vb_I'(\gamma_H) \\ 0 & 0 & -1 \end{bmatrix}\vec{r_J}. \end{aligned}$$

Note that the elements of the matrix are differentiated with respect to the mutant arguments and then evaluated when the mutant trait coincides with the resident.

$$= (1+(1-v)b_I'(\gamma_H)+w_V v b_I'(\gamma_H)-w_H)\bar{S}$$

Using (A.13) enables us to express the equilibrium condition for a horizontally infected host as,

$$b_I'(\gamma_H) = \frac{1}{\mu+\alpha_H+\gamma_H}\left(b_I(\gamma_H) - \frac{\mu+\alpha_H}{1-v+vw_V}\right) \tag{A.18}$$

Which upon substituting in w_V and rearranging, yields condition (2.2b) from the main text.

A.2.3 Coevolution of Unconditional traits

While the epidemiological model allows host and parasite traits to differ depending on the origin of infection, subsequent derivations of evolutionary dynamics show that unconditional trait expression is a valid coevolved outcome. Mathematically, we show that system (2.2) simplifies to system (2.1) when $\alpha_V = \alpha_H = \alpha$ and $\gamma_V = \gamma_H = \gamma$. Firstly,

$$\beta'(\alpha) = \frac{\beta(\alpha) + v\, b_I(\gamma)\beta'(\alpha)}{\mu + \alpha + \gamma} \quad \Longrightarrow \quad (\mu + \alpha + \gamma)\beta'(\alpha) = \beta(\alpha) + v\, b_I(\gamma)\beta'(\alpha)$$
$$\Longrightarrow \quad (\mu + \alpha + \gamma - v\, b_I(\gamma))\beta'(\alpha) = \beta(\alpha) \quad \Longrightarrow \quad \beta'(\alpha) = \frac{\beta(\alpha)}{\mu + \alpha + \gamma - v\, b_I(\gamma)}.$$

And then secondly,

$$\begin{aligned} b_I'(\gamma) &= \frac{1}{\mu + \alpha + \gamma}\left(b_I(\gamma) - \frac{(\mu + \alpha)(\mu + \alpha + \gamma - v\, b_I(\gamma))}{(\mu + \alpha)(1 - v) + \gamma}\right) \\ &= \frac{1}{\mu + \alpha + \gamma}\left(\frac{b_I(\gamma)((\mu + \alpha)(1 - v) + \gamma) - (\mu + \alpha)(\mu + \alpha + \gamma - v\, b_I(\gamma))}{(\mu + \alpha)(1 - v) + \gamma}\right) \\ &= \frac{1}{\mu + \alpha + \gamma}\left(\frac{b_I(\gamma)(\mu + \alpha + \gamma) - (\mu + \alpha)(\mu + \alpha + \gamma)}{(\mu + \alpha)(1 - v) + \gamma}\right) \\ &= \frac{b_I(\gamma) - (\mu + \alpha)}{(\mu + \alpha)(1 - v) + \gamma}. \end{aligned}$$

A.3 Best Response

To proceed we assume functional forms for both the birth rate of infectives, b_I, and transmissibility β. As discussed in the text we posit that β to be an increasing function of parasite-induce mortality α. A simple function which meet this condition is one in which the parasite sees diminishing returns in transmissibility for inducing mortality on the host, $\beta(\alpha) = \alpha^n$, with $0 < n < 1$. Lower values of the exponent n indicate greater diminishing returns on a parasite's investment in reducing host mortality - it becomes marginally more expensive to detriment a host's mortality. Similarly, we take b_I as a decreasing function of host clearance, $b_I(\gamma) = b_S - \lambda\gamma^2$ for $0 < b_S < \mu + \alpha$ and $\lambda > 0$, the cost to the host to clear the parasite. The form of $b_I(\gamma)$ ensures that host recovery tends to a stable equilibrium over time.

As the notation suggests, the equilibrium host recovery rate is also considered to be its population-level best response to the average level of parasite-induced mortality, α. It is worth noting that, when there is no vertical transmission, v is equal to 0 and we recover the result presented previously [14].

$$\alpha_{\text{br}}(\gamma) = \frac{n}{1 - n}\left(\mu + \gamma - v\left(b_S - \lambda\gamma^2\right)\right), \tag{A.19a}$$

$$\gamma_{\text{br}}(\alpha) = -(1 - v)(\mu + \alpha) + \sqrt{(1 - v)^2(\mu + \alpha)^2 + \frac{\mu + \alpha - b_S}{\lambda}}. \tag{A.19b}$$

A.4 Numerics

We are concerned with numerically computing the equilibrium point $(\alpha^{**}, \gamma^{**})$ of the best response system given in (2.3). While an iterative scheme could find the equilibrium, we found our algorithm to be more robust numerically when the problem was translated into a root-finding problem. This is possible because γ_{br} is easily invertible,

$$\gamma_{\text{br}}^{-1}(\gamma) = \frac{\lambda\gamma^2 + 2\lambda\gamma(1-v)\mu + b_S - \mu}{1 - 2\lambda\gamma(1-v)}$$

We may compose equation (2.3b) with the inverse,

$$\gamma_{\text{br}}^{-1}(\gamma) = \gamma_{\text{br}}^{-1}(\gamma_{\text{br}}(\alpha)) = \alpha$$

Then we may use equation (2.3a) to eliminate α and rearrange to find the intersection of the best response functions which are also the roots of,

$$\alpha_{\text{br}}(\gamma) - \gamma_{\text{br}}^{-1}(\gamma) = \frac{n}{1-n}\left(\mu + \gamma - v\left(b_S - \lambda\gamma^2\right)\right) - \frac{\lambda\gamma^2 + 2\lambda\gamma(1-v)\mu + b_S - \mu}{1 - 2\lambda\gamma(1-v)}$$

Since we are only concerned with the roots, we may combine the right-hand side into one fraction and neglect the denominator. After some algebra, the equilibrium point $(\alpha^{**}, \gamma^{**})$ of the best response system is found to satisfy,

$$\frac{n}{1-n}\left(\mu + \gamma - v\left(b_S - \lambda\gamma^2\right)\right)(1 - 2\lambda\gamma(1-v)) - (\lambda\gamma^2 + 2\lambda\gamma(1-v)\mu + b_S - \mu) = 0$$

The coefficients of this cubic polynomial in γ where extracted in the Maple script `inverse1.mw` and programmed into the Python notebook `Host_Parasite_Coevolution.ipynb`. In that notebook, we swept over a range of parameters and used the numpy routine 'roots' to determine all three (possibly complex) roots. When those roots are real and positive, the most-positive corresponds to the stable equilibrium value of γ and the second most-positive is the threshold. The third is irrelevant and neglected. Once the solution to the vertical system has been determined, we may use this to full specify the horizontal system, which was solved numerically using numpy's 'fsolve' routine. All values are then checked against the ecological conditions present in the main text and neglected when the conditions are not met.

A.5 Evolutionary Stability

In Sections A.2.1 and A.2.2 respectively, we derived conditions under which a parasite and host trait would be an singular strategy. In order for these trait values to be evolutionary attractors they must evolutionarily stable strategies (ESS) and convergent stable.

A.5.1 Unconditional

When the host and parasite cannot condition their traits based on the origin of their infection the parasite and host fitnesses collapse from 2 dimensional vector functions to scalar functions

W_p, W_h respectively, where

$$W_p(\alpha, \alpha^m) = \beta(\alpha^m)\bar{S}(\alpha) - (\alpha^m + \mu + \gamma), \tag{A.20a}$$

$$W_h(\gamma, \gamma^m) = (b_S - \mu)(\gamma^m + \mu + \alpha - v\, b_I(\gamma^m)) - \beta(\alpha)\,\bar{I}(\alpha)\,(\mu + \alpha - b_I(\gamma^m)). \tag{A.20b}$$

The fitness gradients are then,

$$\frac{\partial W_p}{\partial \alpha^m} = \beta'(\alpha^m)\bar{S}(\alpha) - 1, \tag{A.21}$$

$$\frac{\partial W_h}{\partial \gamma^m} = (b_S - \mu)(1 - v\, b_I'(\gamma^m)) + \beta\,\bar{I}\, b_I'(\gamma^m). \tag{A.22}$$

Selection on each trait is at equilibrium when the fitness gradient is zero when evaluated at the mutant-free equilibrium,

$$\left.\frac{\partial W_p}{\partial \alpha^m}\right|_{\alpha^m=\alpha} = 0 \qquad \text{and} \qquad \left.\frac{\partial W_h}{\partial \gamma^m}\right|_{\gamma^m=\gamma} = 0. \tag{A.23}$$

We will label traits which satisfy these conditions α^* and γ^* respectively. These traits are evolutionary singular strategies whenever they are maximums of the fitness landscape, which for

$$\frac{\partial}{\partial \alpha^m}\left(\frac{\partial W_p}{\partial \alpha^m}\right) = \beta''(\alpha^m)\bar{S}(\alpha) \tag{A.24}$$

$$\frac{\partial}{\partial \gamma^m}\left(\frac{\partial W_h}{\partial \gamma^m}\right) = \Big(\beta(\alpha)\bar{I}(\alpha) + (b_S - \mu)v\Big)\, b_I''(\gamma^m) \tag{A.25}$$

$$= \left(\frac{(\mu + \alpha)(1 - v) + \gamma}{\mu + \alpha - b_I(\gamma)}\right) b_I''(\gamma^m)(b_S - \mu) \tag{A.26}$$

requires

$$\left.\frac{\partial}{\partial \alpha^m}\left(\frac{\partial W_p}{\partial \alpha^m}\right)\right|_{\alpha^m=\alpha=\alpha^*} < 0 \qquad \text{and} \qquad \left.\frac{\partial}{\partial \gamma^m}\left(\frac{\partial W_h}{\partial \gamma^m}\right)\right|_{\gamma^m=\gamma=\gamma^*} < 0. \tag{A.27}$$

Because of the decelerating life history trade-offs face by both host and parasite, and because of an ecological condition from the main text, both inequalities in the previous line are guaranteed and so α^* and γ^* are ESS whenever they exist.

In order for these traits to be an evolutionary attractor they must also satisfy the condition of convergence stability. Since the second order derivatives,

$$\frac{\partial}{\partial \alpha}\left(\frac{\partial W_p}{\partial \alpha^m}\right) = \beta'(\alpha^m)\frac{\partial \bar{S}(\alpha)}{\partial \alpha} \tag{A.28}$$

$$= \beta'(\alpha^m)(\beta(\alpha) - \beta'(\alpha)(\mu + \gamma + \alpha)) \tag{A.29}$$

$$\frac{\partial}{\partial \gamma}\left(\frac{\partial W_h}{\partial \gamma^m}\right) = \beta(\alpha)\, b_I'(\gamma^m)\frac{\partial \bar{I}(\alpha)}{\partial \gamma} \tag{A.30}$$

$$= \frac{b_I'(\gamma^m)(b_S - \mu)}{(\mu + \alpha - b_I(\gamma))^2}\Big(\mu + \alpha - b_I(\gamma) + b_I'(\gamma)(\gamma + (1 - v)(\mu + \alpha))\Big) \tag{A.31}$$

are both zero at the equilibrium, in the unconditional model ESS implies convergence stable.

A.5.2 Conditional

In the Maple code listed in Figure A.0 we calculate the Hessian matrix of the parasite fitness at the singular strategy as,

$$H_p = \left[\begin{matrix} \partial^2_{\alpha_V^m} W_p & \partial_{\alpha_V^m,\alpha_H^m} W_p \\ \partial_{\alpha_H^m,\alpha_V^m} W_p & \partial^2_{\alpha_H^m} W_p \end{matrix}\right]\Bigg|_{\substack{\alpha_V^m=\alpha_V=\alpha_V^* \\ \alpha_H^m=\alpha_H=\alpha_H^*}}$$
$$= \begin{bmatrix} \frac{\beta''(\alpha_V^*)\nu b_I(\gamma_H)\bar{S}}{(\mu+\alpha_H^*+\gamma_H)(\mu+\alpha_V^*+\gamma_V-\nu\, b_I(\gamma_V))} & 0 \\ 0 & \frac{\beta''(\alpha_H^*)\bar{S}}{\mu+\alpha_H^*+\gamma_H} \end{bmatrix}. \tag{A.32}$$

Because the Hessian matrix is real and triangular its eigenvalues are the diagonal components, which are negative given that transmissibility is a decelerating function. Therefore, the Hessian is negative definite and we can conclude that the singular strategy of the parasite is ESS whenever it exists. Further, in the same Maple script, we find that the Jacobian of the fitness gradient, given by,

$$J_p = \left[\begin{matrix} \partial_{\alpha_V^m,\alpha_V} W_p & \partial_{\alpha_V^m,\alpha_H} W_p \\ \partial_{\alpha_H^m,\alpha_V} W_p & \partial_{\alpha_H^m,\alpha_H} W_p \end{matrix}\right]\Bigg|_{\substack{\alpha_V^m=\alpha_V=\alpha_V^* \\ \alpha_H^m=\alpha_H=\alpha_H^*}} \tag{A.33}$$

is identical to the Hessian in (A.32) at the singular strategy. Therefore we may conclude that the singular strategy of the parasite is convergent stable whenever it exists, and furthermore, that it is an evolutionary attractor whenever it exists.

We were unable to show that the singular strategy of the parasite in the conditional model is an evolutionary attractor.

A.6 Code

```
import matplotlib.pyplot as plt
import matplotlib.patheffects as pe
from numpy import *
import csv
from scipy.optimize import fsolve
import scipy.linalg as la
import itertools

def bi(g,l,bS):
  # Birth rate of infectives
  return bS - l*g**2

def beta(a,m,n):
  return m*a**n

def gbr(a,l,n,v,u,bS):
  # Host's best response g
  return -(1-v)*(u+a) + ( ((1-v)*(u+a))**2 + (u+a-bS)/l )**.5
```

```
19
20 def abr(g,l,n,v,u,bS):
21   # Parasite's  best response alpha
22   return (u + g - v*bi(g,l,bS))*n/(1 - n)
23
24 def abr_boundary(n,v,u,bS):
25   return (u - v*bS)*n/(1 - n)
26
27 # ECOLOGICAL EQUILIBRIUM
28
29 def SbarUN(a,g,l,v,u,bS,m,n):
30   # (Unconditional Model) Numerator of the number of suseptible hosts at
       equilibrium
31   return (u + a + g - v*bi(g,l,bS))/beta(a,m,n)
32
33 def IbarUN(a,g,l,v,u,bS,m,n):
34   # (Unconditional Model) Denominator of the number of infective hosts at
       equilibrium
35   return (bS-u)*SbarUN(a,g,l,v,u,bS,m,n)/(u + a - bi(g,l,bS))
36
37 def Sbar(aH,aV,gH,gV,l,v,u,bS,m,n):
38   # (Conditional Model)
39   numerator = (u+aH+gH)*(u+aV+gV-v*bi(gV,l,bS))
40   denominator = beta(aH,m,n)*(u+aV+gV-v*bi(gV,l,bS))+beta(aV,m,n)*v*bi(gH,l
       ,bS)
41   return numerator/denominator
42
43 def IVbar(aH,aV,gH,gV,l,v,u,bS,m,n):
44   # (Conditional Model)
45   numerator = Sbar(aH,aV,gH,gV,l,v,u,bS,m,n)*(bS-u)*v*bi(gH,l,bS)
46   denominator = (u+aV+gV-v*bi(gV,l,bS))*(u+aH-bi(gH,l,bS)) + v*bi(gH,l,bS)
       *(u+aV-bi(gV,l,bS))
47   return numerator/denominator
48
49 def IHbar(aH,aV,gH,gV,l,v,u,bS,m,n):
50   # (Conditional Model)
51   numerator = Sbar(aH,aV,gH,gV,l,v,u,bS,m,n)*(bS-u)*(u+aV+gV-v*bi(gV,l,bS))
52   denominator = (u+aV+gV-v*bi(gV,l,bS))*(u+aH-bi(gH,l,bS)) + v*bi(gH,l,bS)
       *(u+aV-bi(gV,l,bS))
53   return numerator/denominator
54
55 def constraint2(a,g,l,u,bS):
56   return u + a - bi(g,l,bS)
57
58 def constraint3(a,g,l,v,u,bS):
59   return u + a + g - v*bi(g,l,bS)
60
61 def Jacobian(aH,aV,gH,gV,l,v,u,bS,m,n):
62   # Returns a negative value when ecological equilibrium of the conditional
       model is locally asymptotically stable.
63   IV = IVbar(aH,aV,gH,gV,l,v,u,bS,m,n)
64   IH = IHbar(aH,aV,gH,gV,l,v,u,bS,m,n)
65   S  =  Sbar(aH,aV,gH,gV,l,v,u,bS,m,n)
66   bV = bi(gV,l,bS)
```

```
  bH = bi(gH,l,bS)
  BV = beta(aV,m,n)
  BH = beta(aH,m,n)
  FoI = BV*IV+BH*IH

  J = array([[bS-u-FoI,-BV*S+gV+(1-v)*bV,-BH*S+gH+(1-v)*bH],[0,v*bV-(u+aV+
    gV),v*bH],[FoI,BV*S,BH*S-(u+aH+gH)]])
  eigenvals,_ = la.eig(J)

  return int(all(real(eigenvals)<0))-.5

def Horizontal_System(vars,parameters):
  aH, gH = vars
  n, l, v, aV, gV, bS, u, m = parameters
  IV = IVbar(aH,aV,gH,gV,l,v,u,bS,m,n)
  IH = IHbar(aH,aV,gH,gV,l,v,u,bS,m,n)
  FoI = beta(aV,m,n)*IV+beta(aH,m,n)*IH
  bpV = m*n*aV**(n-1)
  wV = ( gV+(1-v)*bi(gV,l,bS) )/( u+aV+gV-v*bi(gV,l,bS) )

  eq1 = m*n*aH**(n-1) -  (m*aH**n + v*bi(gH,l,bS)*bpV)/(u+aH+gH)
  eq2 = -2*l*gH       -bi(gH,l,bS)/(u+aH+gH+FoI*(u+aH)/(u-bS))

  return [eq1, eq2]

# Toggle to True if you would like to output a .csv file
save_to_file = True

# Biological Parameters
bS      = 1.375
u       = 1
m       = 1
nvals   = arange(.4,.58,.03)
nvals = [.5]
lambdas = linspace(.2,.6,10)
vvals   = arange(0.01,1,0.001)      # for a quick look
vvals   = arange(0.01,1,0.00001)  # for fine-grained view (longer runtime).

names = array(['alpha', 'bI', 'C2i', 'C3', 'C4', 'S', 'I', 'Jacobian'])

param_dim = (len(lambdas), len(nvals), len(vvals))

# UNCONDITIONAL MODEL

if save_to_file:
  f = open('Unconditional_outfile.csv', 'w')
  writer = csv.writer(f)
  writer.writerow([
    'bS','u','m','n','l','v',
    'alpha','gamma',
    'flags','S','I','virulence','case mortality',
    'a unstable','g unstable'
  ])

```

```
# Initialise arrays to assign later
alpha_st           = full(param_dim, nan) # vertical induced mortality (stable)
gamma_st           = full(param_dim, nan) # vertical clearance rate (stable)

flags              = empty(param_dim,dtype='U100') # Ecological contraint not met
flags_b            = empty(param_dim,dtype='U100') # Ecological contraint not met

Sbar_vals          = full(param_dim, nan) # long-run level of susceptibles
Ibar_vals          = full(param_dim, nan) # long-run level of infectives

virulence          = full(param_dim, nan) # virulence

case_mortality     = full(param_dim, nan) # case mortality
case_mortality2    = full(param_dim, nan) # virulence

alpha_un           = full(param_dim, nan) # vertical induced mortality (Threshold)
gamma_un           = full(param_dim, nan) # vertical clearance rate (Threshold)

alpha_bound        = full(param_dim, nan) # boundary outcome

constraint2_vals   = full(param_dim, nan)
constraint3_vals   = full(param_dim, nan)

incidence_ratio    = full(param_dim, nan)
proportion_vert    = full(param_dim, nan)

# Loop through parameters
for (i, j, k) in itertools.product(range(len(nvals)),range(len(vvals)),range(len(lambdas))):
  flag = ''
  n = nvals[i]
  v = vvals[j]
  l = lambdas[k]

  # Coefficients of the cubic whose roots coincide
  # with the gammaV coordinate of the fixed points.
  # (Found in Maple)
  p = [2*l*l*(v-1)*v*n/(1-n),
      (l*v-2*l*(1-v))*n/(1-n)-l,
      (1-2*l*(1-v)*(u-bS*v))*n/(1-n)-2*l*(1-v)*u,
      (u-bS*v)*n/(1-n)+u-bS]

  _ , g_unstable, gamma = sort_complex(roots(p))

  # Ecological checks
  if imag(g_unstable) != 0 or real(g_unstable) < 0:
    gamma_un[k,i,j] = nan
    alpha_un[k,i,j] = nan
```

```
  else:
    gamma_un[k,i,j] = real(g_unstable)
    alpha_un[k,i,j] = abr(real(g_unstable),l,n,v,u,bS)

  if imag(gamma) != 0 or real(gamma) < 0 :
    alpha_st[k,i,j] = nan
    gamma_st[k,i,j] = nan
  else:
    gamma = real(gamma)
    alpha = abr(gamma,l,n,v,u,bS)
    bI    = bi(gamma, l, bS)
    C2i   = constraint2(alpha,gamma,l,u,bS)
    C3    = constraint3(alpha,gamma,l,v,u,bS)
    C4    = alpha+u-bS
    S     = SbarUN(alpha,gamma,l,v,u,bS,m,n)
    I     = IbarUN(alpha,gamma,l,v,u,bS,m,n)
    J     = Jacobian(alpha,alpha,gamma,gamma,l,v,u,bS,m,n)

    if any(array([alpha, bI, C2i, C3, C4, S, I, J]) < 0):
      flags[k,i,j] = ' '.join(names[array([alpha, bI, C2i, C3, C4, S, I, J
   ]) <= 0])
      alpha_st[k,i,j] = nan
      gamma_st[k,i,j] = nan
    else:
      alpha_st[k,i,j] = alpha
      gamma_st[k,i,j] = gamma

      Sbar_vals[k,i,j] = S
      Ibar_vals[k,i,j] = I

      case_mortality[k,i,j] = alpha/(alpha+gamma+u)
      case_mortality2[k,i,j] = alpha/(alpha+gamma)
      virulence[k,i,j] = (u + alpha - bI)/(u + alpha + gamma - v*bI)

      constraint2_vals[k,i,j] = C2i
      constraint3_vals[k,i,j] = C3

      incidence_ratio[k,i,j] = (v*bI)/(u+alpha+gamma-v*bI)
      proportion_vert[k,i,j] = (v*bI)/(u+alpha+gamma)

      alpha_bo = abr(0,l,n,v,u,bS)
      bI       = 2
      C2i      = constraint2(alpha_bo,0,l,u,bS)
      C3       = constraint3(alpha_bo,0,l,v,u,bS)
      S        = SbarUN(alpha_bo,0,l,v,u,bS,m,n)
      I        = IbarUN(alpha_bo,0,l,v,u,bS,m,n)
      if any(array([alpha_bo, C2i, C3, S, I]) < 0):
        alpha_bound[k,i,j] = nan
        flags_b[k,i,j] = ' '.join(names[array([alpha_bo, bI, C2i, C3, C4, S
   , I, J]) <= 0])
      else: alpha_bound[k,i,j] = alpha_bo

  if save_to_file:
    writer.writerow([
```

```
    bS,u,m,n,l,v,
    alpha_st[k,i,j],gamma_st[k,i,j],
    flags[k,i,j],flags_b[k,i,j],Sbar_vals[k,i,j],Ibar_vals[k,i,j],
    virulence[k,i,j],case_mortality[k,i,j],
    alpha_un[k,i,j],gamma_un[k,i,j]
    ])

if save_to_file:
  f.close()
```

Listing A.1: The main Python script which numerically calculates the singular strategies in the unconditional model.

```
> restart : with(linalg) :
> alias(b[V] = b[V](g[V])) : alias(b[H] = b[H](g[H])) :
> F := matrix(3, 3, [b[s], (1 - v)·b[V], (1 - v)·b[H], 0, v·b[V], v·b[H], 0, 0, 0])
```

$$F := \begin{bmatrix} b_s & (1-v)\,b_V & (1-v)\,b_H \\ 0 & v\,b_V & v\,b_H \\ 0 & 0 & 0 \end{bmatrix} \tag{1}$$

```
> Vee := matrix(3, 3, [lambda + u, -g[V], -g[H], 0, a[V] + g[V] + u, 0, -lambda, 0, a[H]
      + g[H] + u])
```

$$Vee := \begin{bmatrix} \lambda + u & -g_V & -g_H \\ 0 & a_V + g_V + u & 0 \\ -\lambda & 0 & a_H + g_H + u \end{bmatrix} \tag{2}$$

```
> J := map( simplify, evalm(F - Vee) )
```

$$J := \begin{bmatrix} b_s - \lambda - u & -(-1+v)\,b_V + g_V & -(-1+v)\,b_H + g_H \\ 0 & v\,b_V - u - a_V - g_V & v\,b_H \\ \lambda & 0 & -a_H - g_H - u \end{bmatrix} \tag{3}$$

```
> Vinv := map(factor, inverse(Vee))
```

$$Vinv := \left[\left[\frac{a_H + g_H + u}{\lambda u + \lambda a_H + u^2 + u a_H + u g_H}, \right.\right. \tag{4}$$

$$\frac{g_V (a_H + g_H + u)}{(a_V + g_V + u)(\lambda u + \lambda a_H + u^2 + u a_H + u g_H)}, \frac{g_H}{\lambda u + \lambda a_H + u^2 + u a_H + u g_H} \Bigg],$$

$$\left[0, \frac{1}{a_V + g_V + u}, 0 \right],$$

$$\left[\frac{\lambda}{\lambda u + \lambda a_H + u^2 + u a_H + u g_H}, \frac{\lambda g_V}{(a_V + g_V + u)(\lambda u + \lambda a_H + u^2 + u a_H + u g_H)}, \right.$$

$$\left. \left. \frac{\lambda + u}{\lambda u + \lambda a_H + u^2 + u a_H + u g_H} \right] \right]$$

Which is written in the main text as : Vinv = $\begin{bmatrix} T_{SS} & \frac{g_V T_{SS}}{a_V + g_V + u} & \frac{g_H T_{SS}}{a_H + g_H + u} \\ 0 & \frac{1}{a_V + g_V + u} & 0 \\ \frac{\lambda T_{HH}}{u+\lambda} & \frac{\lambda g_V T_{HH}}{(a_V + g_V + u)(u+\lambda)} & T_{HH} \end{bmatrix}$

```
> #alias(T[SS] = T[SS](g[H])) : alias(T[HH] = T[HH](g[H])) :
> K := evalm(F&*Vinv)
```

$$K := matrix\left(\left[\left[\frac{b_s\left(a_H+g_H+u\right)}{\lambda u+\lambda a_H+u^2+u a_H+u g_H}+\frac{(1-v)\,b_H\lambda}{\lambda u+\lambda a_H+u^2+u a_H+u g_H},\right.\right.\right. \tag{5}$$
$$\frac{b_s g_V\left(a_H+g_H+u\right)}{\left(a_V+g_V+u\right)\left(\lambda u+\lambda a_H+u^2+u a_H+u g_H\right)}+\frac{(1-v)\,b_V}{a_V+g_V+u}$$
$$\left.+\frac{(1-v)\,b_H\lambda g_V}{\left(a_V+g_V+u\right)\left(\lambda u+\lambda a_H+u^2+u a_H+u g_H\right)},\frac{b_s g_H}{\lambda u+\lambda a_H+u^2+u a_H+u g_H}\right.$$
$$\left.+\frac{(1-v)\,b_H(\lambda+u)}{\lambda u+\lambda a_H+u^2+u a_H+u g_H}\right],\left[\frac{v b_H\lambda}{\lambda u+\lambda a_H+u^2+u a_H+u g_H},\frac{v b_V}{a_V+g_V+u}\right.$$
$$\left.+\frac{v b_H\lambda g_V}{\left(a_V+g_V+u\right)\left(\lambda u+\lambda a_H+u^2+u a_H+u g_H\right)},\frac{v b_H(\lambda+u)}{\lambda u+\lambda a_H+u^2+u a_H+u g_H}\right],$$
$$\left.[0,0,0]\right]\Bigg)$$

```
> subK := submatrix(K, 1..2, 1..2)
```

$$subK := \left[\left[\frac{b_s\left(a_H+g_H+u\right)}{\lambda u+\lambda a_H+u^2+u a_H+u g_H}+\frac{(1-v)\,b_H\lambda}{\lambda u+\lambda a_H+u^2+u a_H+u g_H},\right.\right. \tag{6}$$
$$\frac{b_s g_V\left(a_H+g_H+u\right)}{\left(a_V+g_V+u\right)\left(\lambda u+\lambda a_H+u^2+u a_H+u g_H\right)}+\frac{(1-v)\,b_V}{a_V+g_V+u}$$
$$\left.+\frac{(1-v)\,b_H\lambda g_V}{\left(a_V+g_V+u\right)\left(\lambda u+\lambda a_H+u^2+u a_H+u g_H\right)}\right],$$

$$\left[\frac{v\,b_H\,\lambda}{\lambda u+\lambda a_H+u^2+u a_H+u g_H},\ \frac{v\,b_V}{a_V+g_V+u}+\frac{v\,b_H\,\lambda\,g_V}{\left(a_V+g_V+u\right)\left(\lambda u+\lambda a_H+u^2+u a_H+u g_H\right)}\right]$$

```
> delta := det(subK)
```

$$\delta := \frac{\left(a_H+g_H+u\right) b_s\, v\, b_V}{\left(a_V+g_V+u\right)\left(\lambda u+\lambda a_H+u^2+u a_H+u g_H\right)} \tag{7}$$

```
> tau := subK[1, 1] + subK[2, 2]
```

$$\tau := \frac{b_s\left(a_H+g_H+u\right)}{\lambda u+\lambda a_H+u^2+u a_H+u g_H}+\frac{(1-v)\,b_H\,\lambda}{\lambda u+\lambda a_H+u^2+u a_H+u g_H}+\frac{v\,b_V}{a_V+g_V+u}+\frac{v\,b_H\,\lambda\,g_V}{\left(a_V+g_V+u\right)\left(\lambda u+\lambda a_H+u^2+u a_H+u g_H\right)} \tag{8}$$

```
> eqn := simplify(diff(tau - delta, g[V])) = 0
```

$$eqn := \left(\left(\left(u^2+\left(\lambda+a_H-b_s+g_H\right)u+\left(-b_s+\lambda\right)a_H-b_s g_H\right)\left(a_V+g_V+u\right)\left(\frac{\partial}{\partial g_V}\,b_V\right)+\left(-u^2+\left(-\lambda-a_H+b_s-g_H\right)u+\left(-\lambda+b_s\right)a_H+b_s g_H\right)b_V+\lambda\,b_H\left(u+a_V\right)\right)v\right)\Big/\left(\left(u^2+\left(\lambda+a_H+g_H\right)u+\lambda a_H\right)\left(a_V+g_V+u\right)^2\right)=0 \tag{9}$$

```
> ∂/∂g_V b_V = simplify(solve(eqn, ∂/∂g_V b_V))
```

$$\frac{\partial}{\partial g_V}\,b_V=\frac{\left(u^2+\left(\lambda+a_H-b_s+g_H\right)u+\left(-b_s+\lambda\right)a_H-b_s g_H\right)b_V-\lambda\,b_H\left(u+a_V\right)}{\left(u^2+\left(\lambda+a_H-b_s+g_H\right)u+\left(-b_s+\lambda\right)a_H-b_s g_H\right)\left(a_V+g_V+u\right)} \tag{10}$$

Which is equivalent to

$$\frac{\partial}{\partial g_V}\,b_V=\frac{b_V}{a_V+g_V+u}-\frac{\lambda\,b_H\left(u+a_V\right)}{\left(\left(-b_s+\lambda+u\right)\left(a_H+g_H+u\right)-\lambda\,g_H\right)\left(a_V+g_V+u\right)}$$

Figure A.0: Maple script used to derive the equilibrium conditions for the host.

Paraste fitness is given by:

```
> W[p] := B(aHm)·S(aH, aV)/(u + aHm + gH) + v·b(gH)/(u + aHm + gH) · B(aVm)·S(aH, aV)/(u + aVm + gV − v·b(gV)) :
```

Both components of the fitness gradient are:

```
> diff(W[p], aVm) : WaVm := subs([aVm = aV, aHm = aH], %)
```

$$WaVm := \frac{v\,b(gH)\left(\frac{\mathrm{d}}{\mathrm{d}aV}\,B(aV)\right)S(aH, aV)}{(u + aH + gH)\,(u + aV + gV - v\,b(gV))} - \frac{v\,b(gH)\,B(aV)\,S(aH, aV)}{(u + aH + gH)\,(u + aV + gV - v\,b(gV))^2} \tag{1}$$

```
> diff(W[p], aHm) : WaHm := subs([aVm = aV, aHm = aH], %)
```

$$WaHm := \frac{\left(\frac{\mathrm{d}}{\mathrm{d}aH}\,B(aH)\right)S(aH, aV)}{u + aH + gH} - \frac{B(aH)\,S(aH, aV)}{(u + aH + gH)^2} - \frac{v\,b(gH)\,B(aV)\,S(aH, aV)}{(u + aH + gH)^2\,(u + aV + gV - v\,b(gV))} \tag{2}$$

ESS

The four components of the Hessian, evalutated at the evolutionarily equilibrium levels, are:

```
> diff(W[p], aVm, aVm) : subs([aVm = aV, aHm = aH], %) : H[1, 1] := simplify(%, {WaVm = 0})
```

$$H_{1,1} := \frac{v\,b(gH)\left(\frac{\mathrm{d}^2}{\mathrm{d}aV^2}\,B(aV)\right)S(aH, aV)}{(u + aH + gH)\,(u + aV + gV - v\,b(gV))} \tag{3}$$

```
> diff(W[p], aVm, aHm) : subs([aVm = aV, aHm = aH], %) : H[1, 2] := simplify(%, {WaVm = 0})
```

$$H_{1,2} := 0 \tag{4}$$

```
> diff(W[p], aHm, aVm) : subs([aVm = aV, aHm = aH], %) : H[2, 1] := simplify(%, {WaVm = 0})
```

$$H_{2,1} := 0 \tag{5}$$

```
> diff(W[p], aHm, aHm) : subs([aVm = aV, aHm = aH], %) : H[2, 2] := simplify(%, {WaVm = 0, WaHm = 0})
```

$$H_{2,2} := \frac{\left(\frac{\mathrm{d}^2}{\mathrm{d}aH^2}\,B(aH)\right)S(aH, aV)}{u + aH + gH} \tag{6}$$

Convergence stability

In the appendix B1 we have shown that $WaVm = 0$ is equivalent to $\frac{\mathrm{d}}{\mathrm{d}aV}\,B(aV) = \frac{B(aV)}{u + aV + gV - v\,b(gV)}$ and $WaHm = 0$ is equivalent to $\frac{\mathrm{d}}{\mathrm{d}aH}\,B(aH)$

$= \dfrac{B(aH) + v \cdot b(gH) \cdot \dfrac{d}{daV} B(aV)}{u + aH + gH}$. We use this result here to simplify the Jacobian.

The Jacobian of the parasite fitness gradient at the singular strategy is,

> $diff(WaVm, aV) : J[1, 1] := simplify\left(\%, \left\{ \dfrac{d}{daV} B(aV) = \dfrac{B(aV)}{u + aV + gV - v\, b(gV)} \right\}\right)$

$$J_{1,1} := \frac{v\, b(gH) \left(\dfrac{d^2}{daV^2} B(aV) \right) S(aH, aV)}{(u + aH + gH)\ (u + aV + gV - v\, b(gV))} \tag{7}$$

> $diff(WaVm, aH) : J[1, 2] := simplify\left(\%, \left\{ \dfrac{d}{daV} B(aV) = \dfrac{B(aV)}{u + aV + gV - v\, b(gV)} \right\}\right)$

$$J_{1,2} := 0 \tag{8}$$

> $diff(WaHm, aV) : J[2, 1] := simplify\left(\%, \left\{ \dfrac{d}{daV} B(aV) = \dfrac{B(aV)}{u + aV + gV - v \cdot b(gV)}, \dfrac{d}{daH} B(aH) = \dfrac{B(aH) + v \cdot b(gH) \cdot \dfrac{d}{daV} B(aV)}{u + aH + gH} \right\}\right)$

$$J_{2,1} := 0 \tag{9}$$

> $diff(WaHm, aH) : J[2, 2] := simplify\left(\%, \left\{ \dfrac{d}{daV} B(aV) = \dfrac{B(aV)}{u + aV + gV - v \cdot b(gV)}, \dfrac{d}{daH} B(aH) = \dfrac{B(aH) + v \cdot b(gH) \cdot \dfrac{d}{daV} B(aV)}{u + aH + gH} \right\}\right)$

$$J_{2,2} := \frac{\left(\dfrac{d^2}{daH^2} B(aH) \right) S(aH, aV)}{u + aH + gH} \tag{10}$$

Which is identical to the Hessian above.

Figure A.0: Maple sheet used to prove the parasite traits in the conditional model are ESS and convergent stable.

Ancillary calculations: Coefficients of the cubic.

Formular **(1)** below corresponds to the numerator of the difference between alpha_br and gamma_br_inverse. Maple allows us to rearrange this formular in desending powers and pull off each of the coefficients.

```
cubic_formular := n·(1 − 2· l·(1-v)·y)·(u + y − v·(b − l·y^2)) / (1-n)-(l·y^2 + 2 ·l·(1-v)·u
    ·y + b − u)
```

$$cubic\_formular := \frac{n\,(1-2\,l\,(1-v)\,y)\,(u+y-v\,(-l\,y^2+b))}{1-n} - l\,y^2 - 2\,l\,(1-v)\,u\,y - b + u \quad (1)$$

```
expand(cubic_formular)
```

$$\frac{2\,n\,l^2\,v^2\,y^3}{1-n} - \frac{2\,n\,l^2\,v\,y^3}{1-n} - \frac{2\,n\,b\,l\,v^2\,y}{1-n} + \frac{2\,n\,b\,l\,v\,y}{1-n} + \frac{2\,n\,l\,u\,v\,y}{1-n} + \frac{3\,n\,l\,v\,y^2}{1-n} - \frac{2\,n\,l\,u\,y}{1-n} - \frac{2\,n\,l\,y^2}{1-n} - \frac{n\,b\,v}{1-n} + \frac{n\,u}{1-n} + \frac{n\,y}{1-n} - l\,y^2 + 2\,l\,u\,v\,y - 2\,l\,u\,y - b + u \quad (2)$$

```
collect(cubic_formular, y)
```

$$-\frac{2\,n\,l^2\,(1-v)\,v\,y^3}{1-n} + \left(\frac{n\,v\,l-2\,n\,l\,(1-v)}{1-n} - l\right)y^2 + \left(\frac{n-2\,n\,l\,(1-v)\,(-b\,v+u)}{1-n} - 2\,l\,(1-v)\,u\right)y + \frac{n\,(-b\,v+u)}{1-n} - b + u \quad (3)$$

Third order coefficient

```
coeff(cubic_formular, y, 3)
```

$$-\frac{2\,n\,l^2\,(1-v)\,v}{1-n} \quad (4)$$

Second order coefficient

```
coeff(cubic_formular, y, 2)
```

$$\frac{n\,v\,l-2\,n\,l\,(1-v)}{1-n} - l \quad (5)$$

First order coefficient

```
coeff(cubic_formular, y, 1)
```

$$\frac{n-2\,n\,l\,(1-v)\,(-b\,v+u)}{1-n} - 2\,l\,(1-v)\,u \quad (6)$$

Zeroth order coefficient

```
coeff(cubic_formular, y, 0)
```

$$\frac{n\,(-b\,v+u)}{1-n} - b + u \quad (7)$$

Figure A.1: Maple sheet used to find the coefficients of the cubic whose two largest roots are the hosts component of the threshold value and Nash equilibrium respectively.

Curriculum Vitae

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