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Multispecies interactions and the community context of the evolution of virulence

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Pairwise host–parasite relationships are typically embedded in broader networks of ecological interactions, which have the potential to shape parasite evolutionary trajectories. Understanding this 'community context' of pathogen evolution is vital for wildlife, agricultural and human systems alike, as pathogens typically infect more than one host—and these hosts may have independent ecological relationships. Here, we introduce an eco-evolutionary model examining ecological feedback across a range of host–host interactions. Specifically, we analyse a model of the evolution of virulence of a parasite infecting two hosts exhibiting competitive, mutualistic or exploitative relationships. We first find that parasite specialism is necessary for inter-host interactions to impact parasite evolution. Furthermore, we find generally that increasing competition between hosts leads to higher shared parasite virulence while increasing mutualism leads to lower virulence. In exploitative host–host interactions, the particular form of parasite specialization is critical—for instance, specialization in terms of onward transmission, host tolerance or intra-host pathogen growth rate lead to distinct evolutionary outcomes under the same host–host interactions. Our work provides testable hypotheses for multi-host disease systems, predicts how changing interaction networks may impact virulence evolution and broadly demonstrates the importance of looking beyond pairwise relationships to understand evolution in realistic community contexts.

1. Introduction

Parasitic lifestyles are ubiquitous, and the wider importance of infectious diseases to human health, agriculture and natural systems is clear [1–4]. As a consequence, there is a large body of theoretical work focused on understanding the evolution of pathogen virulence [5–8]. Consistent with their pervasiveness, host–parasite interactions in nature have not evolved in isolation, but rather in complex webs of species interactions. Multi-host parasites, or those that can infect and transmit onward from more than one host, are the norm, not the exception [9]—they dominate infections in wildlife communities [10,11], and of course many human pathogens are zoonotic [12,13]. However, the evolutionary consequences of these multi-host interactions on pathogen evolution have only rarely been considered [14], and there is a lack of theory focused on how host interactions will interact with epidemiological processes to affect virulence evolution [5,15,16].

It has been shown that multi-host parasite fitness typically varies across hosts [14], with theory proposing that parasites should evolve optimal virulence on their highest-quality hosts [17]. The most obvious (though often difficult to determine) metrics for host quality are tied to the mechanisms

of infection and transmission. If a pathogen performs well on one host and poorly on another, the difference could be attributed to a greater susceptibility of one host to initial infection, a higher intra-host pathogen growth rate, a greater efficiency of production of pathogen propagules for onward transmission, a lower death rate due to infection (i.e. tolerance), or a mixture of these mechanisms [18–21]. The precise reasons for fitness variation and subsequent evolutionary consequences are not so easily determined, however, as host quality is a product of not only underlying biology but also host population dynamics [22]. For example, a host that is more susceptible to a parasite may experience a reduction in population size, which in turn impacts parasite numbers—as well as the population sizes of other hosts through interspecific interactions.

We therefore need to consider the tangled web of interactions in which a parasite's hosts are embedded since host population dynamics are readily impacted by non-parasitic ecological interactions, as has been demonstrated in micro- and macroorganism systems [23–26]. It is clear that such complex eco-evolutionary feedback may have important implications for the evolution of virulence [27], but we have little understanding of how interactions between different hosts in multi-host infectious disease systems impact parasite evolution.

To date, there is a large body of theoretical and empirical work on the disease ecology and evolution in pairwise one-host–one-parasite relationships [5,28,29]. Multi-host systems have been explored in the context of population dynamics and epidemiology, where the consequences of varying inter-host versus intra-host disease transmission and the trade-offs between virulence in different hosts have been considered [17,30,31]. Interspecies transmission and intrinsic host mortality have been identified as key determinants of multi-host parasite evolution [14,17,32], but other forms of interspecies interactions have been ignored. Given the importance of disease spillover in multi-host, multi-parasite systems [33–35], the question of which host communities may favour the evolution of high parasite virulence is critical. Recent work has begun to explore parasite evolution in more complex ecological contexts, such as hyperparasitism [36,37] and multi-parasite assemblages [38,39], and has called for further exploration of the consequences of inter-host interactions on shared parasites [40], but our theoretical understanding of the evolution of parasites in a realistic community context remains limited.

Here, our goal is to develop a theoretical foundation for predicting the evolutionary trajectories of multi-host parasites over a range of different interspecific host interactions. Hosts with many types of relationships have long been known to share parasites, and advances in phylogenetic analyses continue to reveal overlaps. For example, avian malaria is shared in competing native Hawaiian honeycreepers and introduced birds [41], canine distemper virus is shared in the predator/prey pair of Amur tigers/domestic dogs [42], and recent advances in cross-kingdom viral infections have identified a shared virus in orchids and their mutualistic mycorrhizal fungi [43]. We therefore develop a two-host, one-parasite model to investigate our central question of how parasite virulence evolves under host–host interactions ranging from competition and mutualism to exploitation, when parasites vary in their degree of host specialism. To paint a more complete picture of how these evolutionary trajectories are influenced by the degree to which a parasite specializes in one of several hosts, we explore the interaction of host–host relationships with distinct mechanisms that give rise to variation in parasite performance across their hosts. We show that the inter-host interaction is critical to the evolution of multi-host parasites.

2. Methods

(a) Two-host, one-parasite model framework

We modify a standard SIS model for one-host and one-parasite, extending to two hosts and one shared parasite. Hosts are capable of both intra-host and inter-host disease transmission. The dynamics of susceptible, S_i, and infected, I_i, hosts of type $i = 1$ and 2 are described by the following set of equations:

$$\frac{dS_1}{dt} = b(1 - qN_1)S_1 - dS_1 + r_{12}N_2S_1 - \beta_{S1}\beta_{T1}S_1I_1 - \beta_{S1}\beta_{T2}S_1I_2 + \gamma I_1 \tag{2.1}$$

$$\frac{dI_1}{dt} = \beta_{S1}\beta_{T1}S_1I_1 + \beta_{S1}\beta_{T2}S_1I_2 - \gamma I_1 - (d + \alpha_1)I_1 \tag{2.2}$$

$$\frac{dS_2}{dt} = b(1 - qN_2)S_2 - dS_2 + r_{21}N_1S_2 - \beta_{S2}\beta_{T2}S_2I_2 - \beta_{S2}\beta_{T1}S_2I_1 + \gamma I_2 \tag{2.3}$$

$$\frac{dI_2}{dt} = \beta_{S2}\beta_{T2}S_2I_2 + \beta_{S2}\beta_{T1}S_2I_1 - \gamma I_2 - (d + \alpha_2)I_2\,. \tag{2.4}$$

The parameters in the model are defined in table 1 and a schematic of the model system is shown in figure 1. Host–host interactions are reflected in the $r_{ij}N_jS_i$ terms in the model, which increase or decrease the host birth rate. Although infected individuals are assumed not to reproduce, both susceptible and infected hosts of type j contribute to host–host interactions with susceptible hosts of type i. To focus on the impact of host–host interactions, we assume that the following parameters are the same in both hosts: birth ($b_1 = b_2 = b$), death ($d_1 = d_2 = d$), crowding ($q_1 = q_2 = q$) and recovery ($\gamma_1 = \gamma_2 = \gamma$). The terms α_i represent the disease-induced mortality rate, or virulence, for host type i. We draw attention to the various β terms utilized. In order to explore different mechanisms by which parasites could vary in performance on each host (explained further in §3), we expand the 'typical' β found in SI models to the product $\beta = \beta_{Si}\beta_{Tj}$, where β_{Si} is controlled by the host and represents a scaling factor that determines the susceptibility of host i. β_{Tj} is the transmission component controlled by the parasite. We note that work on multi-host parasites often includes a β_{ij} term that reflects differences between inter-host and intra-host contact rates. In our work, we set equal inter-host and intra-host contact rates, as we sought to isolate the impacts of host–host interactions. Such a

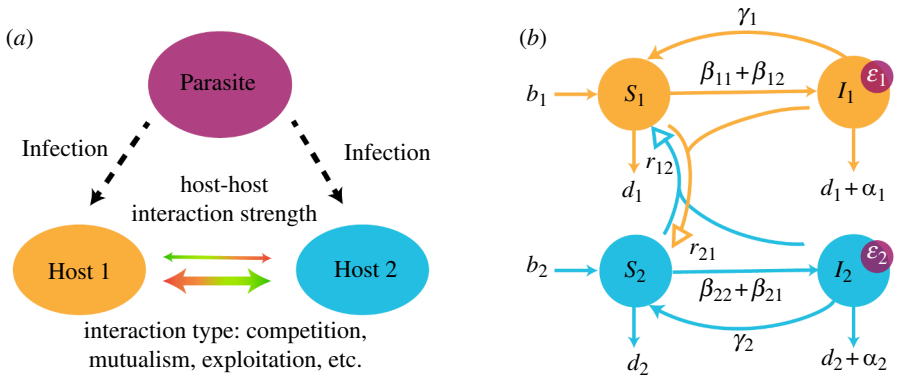

Figure 1. A schematic diagram of the model of the two-host, one-parasite system represented in equations (2.1–2.4). (*a*) The key interactions we model: the simultaneous inter-host- and intra-host-type infection dynamics of a shared parasite and the ecological feedback generated by inter-host interactions of varying strengths and types. (*b*) The formal flow chart diagram for the model is shown. Arrows with solid arrowheads indicate the movement of individual hosts between susceptible (*S*) and infected (*I*) compartments through the processes of birth, death, infection and recovery. Arrows with empty arrowheads do not indicate movement between host classes, but rather the impact (r_{ij}) of host type j on the susceptible class of host type i. β_{ij} terms represent the composite transmission coefficient $\beta_{Si}\beta_{Tj}$; b_i and d_i are the natural birth and death rates of host type i, respectively; α_i and γ_i are the disease-induced death rate and recovery rate in host type i, respectively; ϵ_i is the parasite growth rate in host type i.

Table 1. Descriptions of model parameters.

symbol	meaning
N_i	total hosts of type i
S_i	susceptible hosts of type i
I_i	infected hosts of type i
b_i	natural birth rate of host type i
d_i	natural death rate of host type i
q_i	susceptibility to intraspecific crowding
ϵ_i	parasite growth rate in host type i
α_i	parasite virulence (increased host mortality)
β_{Si}	susceptibility of host type i,
β_{Ti}	onward transmission from host type i
γ_i	recovery rate of host type i
r_{ij}	impact of host j on host i (interaction)

term thus becomes another scaling factor that is incorporated (identically) into the β_{Si} term, and for clarity, we do not explicitly include it in the model.

Previous work often assumes a trade-off between virulence and transmission, in that $\beta = f(\alpha)$. In our breakdown of β into two parts, only β_{Tj} maintains a functional relationship with another parasite-related parameter. Furthermore, we decouple the traditional fixed relationship between α and β and explicitly incorporate ϵ, the parasite intra-host growth rate, setting the positive trade-off relationships between parasite growth rate, transmission and host mortality accordingly [28,44]: $\alpha_i = f(\epsilon_i)$ and $\beta_{Ti} = c\epsilon_i^{\gamma}$, where c is a constant and $\gamma < 1$. For the former, in many cases, this is a direct relationship of $\alpha_i = \epsilon_i$ (thus preserving the same concave $\beta = f(\alpha)$ trade-off shape in previous work [45]), but see figure 2 for the cases when differential parasite performance between the two hosts requires us to deviate from this precedent.

(b) Analytical and numerical techniques

We use the techniques of adaptive dynamics [46–49] to determine the evolutionary stable level of virulence. These techniques assume that rare individuals arise from a homogeneous resident population via small mutations away from that resident strategy. The success of the rare mutant depends on its invasion fitness in the resident population (i.e. a positive initial growth rate for the mutant type in the resident population means the mutant strategy could, over time, coexist with or displace the resident strategy). As a consequence of our choice of trade-off, the population will evolve, through a process of sequential mutation, along its local fitness gradient until it reaches an evolutionarily stable strategy.

To represent the dynamics of hosts infected with the mutant parasites strain I_{iM}, we add two equations to the system of equations 2.1–2.4 as follows:

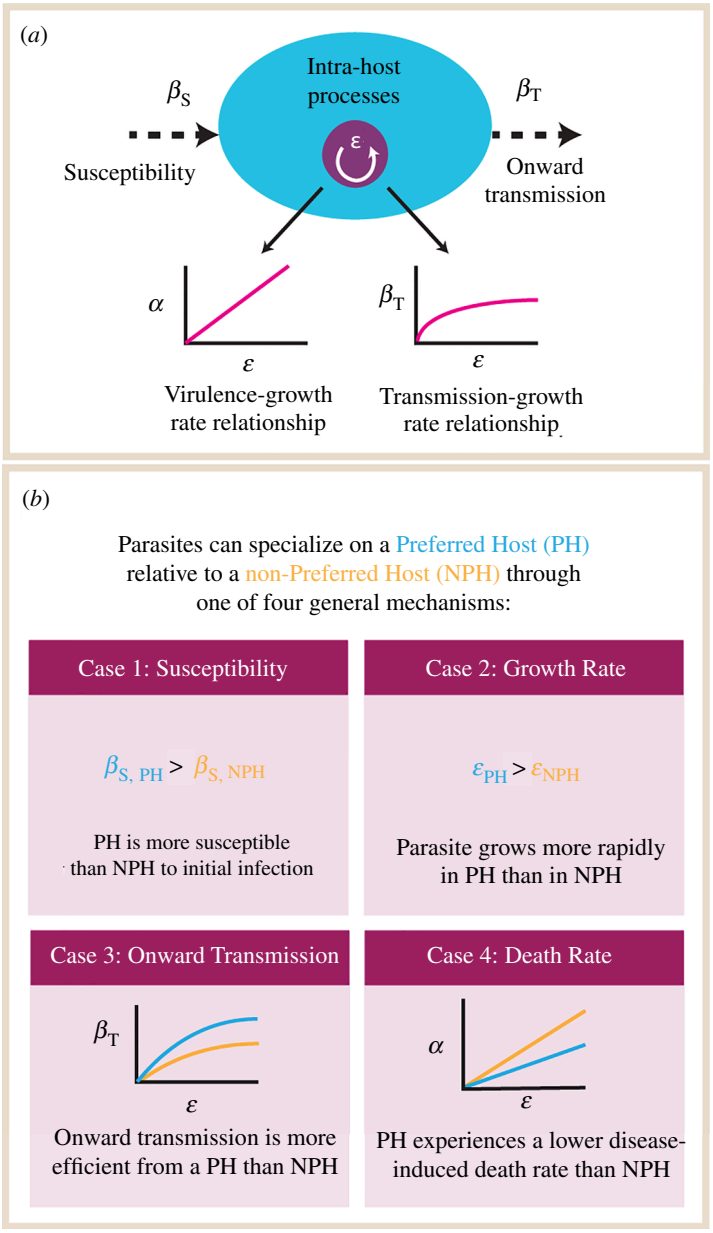

Figure 2. Mathematical representations of various mechanisms of parasite specialism. (*a*) Illustration of how we can break down the biology encompassed by a standard β transmission term into separate processes: a contact rate between hosts (not shown), susceptibility to an initial infection after contact (β_S), intra-host parasite growth and replication (ε) and finally onward transmission of parasite propagules (β_T). (*b*) Illustration of how we can use this detail to mathematically represent four different ways in which a parasite may specialize on one of its two hosts. The curves depicted in cases 3 and 4 are predicated on standard assumptions that more aggressive parasite growth translates to greater harm done to the host (higher virulence α) and that the relationship between growth rate/virulence and onward transmission is saturating.

$$\frac{dI_{1M}}{dt} = \beta_{S1M}\beta_{T1M}S_1I_{1M} + \beta_{S1M}\beta_{T2M}S_1I_{2M} - \gamma I_{1M} - (d + \alpha_{1M})I_{1M} \tag{2.5}$$

$$\frac{dI_{2M}}{dt} = \beta_{S2M}\beta_{T2M}S_2I_{2M} + \beta_{S2M}\beta_{T1M}S_2I_{1M} - \gamma I_{2M} - (d + \alpha_{2M})I_{2M}\,. \tag{2.6}$$

Therefore, hosts can be infected with the resident or mutant parasite strain (though not both simultaneously). The full resident and mutant equations are shown in the supplementary information (electronic supplementary material, section S1).

To determine when invasion will occur, we analyse the eigenvalues of the Jacobian of the resident and mutant systems. In the absence of the mutant parasite, we assume the resident system is at a stable equilibrium, $(\widehat{S_1}, \widehat{I_1}, \widehat{S_2}, \widehat{I_2})$. To examine whether the mutant can invade, we determine the largest eigenvalue of the Jacobian at $(\widehat{S_1}, \widehat{I_1}, \widehat{S_2}, \widehat{I_2}, 0, 0)$. For a mutant invasion to occur, the resident-only equilibrium must be unstable, so we seek conditions where the system has a positive, real eigenvalue. It can be shown (see electronic supplementary material, section S1) that the mutant parasite strain can invade if the following condition holds:

$$\Gamma_{2M}\beta_{S1M}\beta_{T1M}\widehat{S_1} + \Gamma_{1M}\beta_{S2M}\beta_{T2M}\widehat{S_2} - \Gamma_{1M}\Gamma_{2M} > 0, \tag{2.7}$$

where $\Gamma_{1M} = (d + \gamma + \alpha_{1M})$ and $\Gamma_{2M} = (d + \gamma + \alpha_{2M})$. We use this fitness expression, with numerically determined values for the resident host populations $(\widehat{S_1}, \widehat{S_2})$ to construct pairwise invasion plots (PIPs) [46] (such as those in figure 3) that allow us to

determine the evolutionarily stable (ES) parasite virulence in a range of host–host interaction contexts. Each point in figures 4–6 represents the ES virulence (determined from a PIP) for a particular parasite strategy and host–host interaction.

3. Results

We began by testing the simplest system: two hosts with identical life history parameters (birth, natural death, crowding) and identical disease burdens (specifically, identical values of $\epsilon, \widehat{\beta}, \alpha$), but with varying ecological relationships to one another. We find that shared parasite systems in which the parasite is a pure generalist (defined here as a parasite that has an identical infection and disease characteristics in both hosts) do not yield different ES virulence values, even when the sign and magnitude of host–host interactions are varied. We therefore have a very general result that the nature of the interactions between hosts in multi-host parasite system has no impact on the evolution of a pure generalist parasite. We show an analytical proof of this result in the supplementary information (see electronic supplementary material, section S2).

We now include host specialism in the parasite, which reflects the observations in natural systems of multi-host parasites unevenly impacting their hosts—squirrelpox virus (SQPV) in grey and red squirrels (much higher virulence in and transmission between red squirrels) [50], canine distemper virus (CDV) in a range of carnivores (varying from up to 100% mortality in ferrets to 'silent' epidemics in lions only identified by serological investigations) [51], and parasitic nematodes in *Drosophila* (ranging in overall susceptibility and average parasite loads per fly species) [21] are several examples. Our definition of host types here can also allow for subdivision at a smaller level than species—even different host genotypes (with corresponding differences in parasite resistance or infection-induced mortality) could be considered distinct types [52]. For the remainder of the paper, we will use specialism to refer to differential performance on hosts (not whether a parasite can infect a host or not).

In figure 2, we outline four different potential mechanisms of parasite specialism and how they are modelled in our system. We distinguish between a PH and a non-preferred host (NPH) based on which host the parasite would be described as performing 'better'. Importantly, we note that this does not denote a deliberate host choice on the part of the parasite.

In case 1, the parasite's PH is more susceptible to infection than its NPH. In case 2, the parasite's PH sustains a more rapid parasite growth rate (and thus a higher virulence and rate of onward transmission due to the dependence of the latter two on the former). In case 3, for a given intra-host growth rate, the parasite transmits onward more effectively from its PH. In case 4, for a given intra-host growth rate, the parasite causes less damage to its PH. Though we take the opportunity to use our theoretical model to examine these components separately, in natural host–parasite systems, they may be correlated. In particular, the host immune landscape could facilitate these correlations; for example, rabbits infected with the immunosuppressive poxvirus myxoma have enhanced susceptibility to a separate nematode parasite and also maintain high loads of transmissible nematodes for longer periods of time [53].

For each of the four specialism cases, we determined ES virulence for a range of host–host relationships, which we break down into two categories in the following sections: reciprocal and non-reciprocal interactions. Reciprocal interactions are defined as those with matching signs, therefore falling along a sliding scale of mutualism +/+ to competition −/−. Non-reciprocal interactions are defined as those with opposite signs, in that there is an antagonist (exploiter) that benefits and a subject of antagonism (exploitee) that suffers in the presence of the other host. We note that while the model could be further modified to explicitly capture a predator-prey or other multi-trophic level relationship between hosts (e.g. by including prey handling time or life history parameters reflecting biomass conversion), at present, it captures a wider array of non-reciprocal interactions and we therefore use the exploiter/exploitee designations.

(a) Reciprocal interactions

We began by analysing reciprocal host–host interactions of equal strength. When host–host interactions shifted ES virulence, they consistently followed a pattern of stronger mutualism leading to lower parasite virulence, and stronger competition leading to higher parasite virulence. Importantly, the four mechanisms of specialism did not lead to identical shifts in ES virulence. The cases in which the parasite reduced excess death in the PH and in which it grew more rapidly in the PH both led to significant shifts in virulence as interactions changed from competitive to mutualistic scenarios (figure 4*b*,*d*), with virulence evolving to the highest levels under strongly competitive interactions and decreasing as the interaction progressed towards mutualistic interactions.

The case in which susceptibility was the only distinguishing factor between hosts did not show any shifts in ES virulence as host interactions changed, nor did the case in which onward transmission was more efficient in the PH (figure 4*a*,*c*). The mathematical underpinnings of these two instances of independence between host–host relationship and pathogen virulence did differ. When the pathogen's PH was more susceptible to infection (case 1), the equilibrium populations of the PH and NPH were unequal, but the condition for mutant invasion was independent of host densities (see electronic supplementary material, section S2). When the pathogen had higher onward transmission on its PH (case 3), by contrast, the equilibrium populations of each host type remained equal in size, and it was therefore unsurprising that there was no variation in ES virulence of their shared pathogen.

We further examined reciprocal host–host interactions where the interaction strengths were not equal, as this is more relevant for ecological scenarios where the interspecific interaction are unlikely to be the same between two species (figure 5). As previously stated, under case 1: Susceptibility specialism, the ES virulence is independent of host interactions (figure 5*a*). For case 2 (growth rate specialism), ES virulence decreases as the NPH becomes a weaker competitor against the PH or

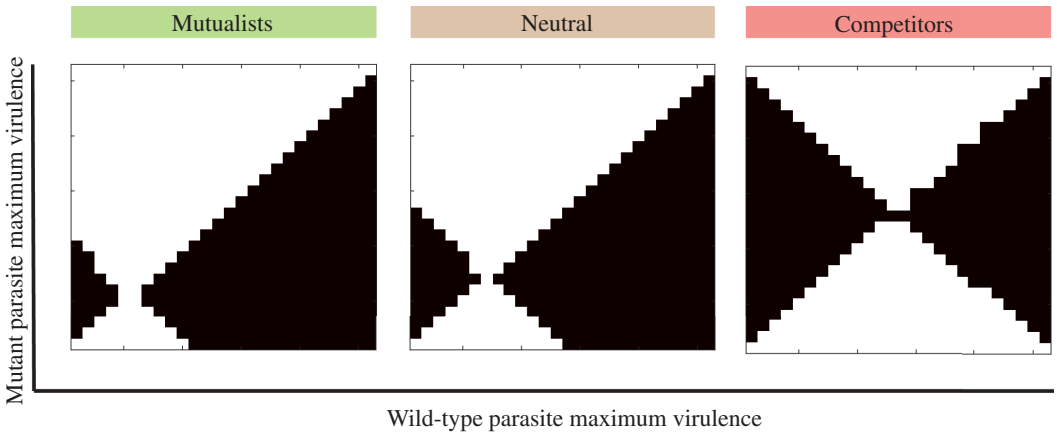

Figure 3. Pairwise invasibility plots that show the evolutionarily stable strategy for parasite virulence (ES virulence) on the backdrop of three different relationships between its two hosts: mutualists, neutral (no interaction beyond parasite transmission) and competitors. The points are continuously stable. Black regions show a pair of resident and mutant parasite strategies in which the mutant will be able to invade the wild-type resident population, and white regions show a pair in which the resident parasite will be able to outcompete the mutant. These analyses were performed for the case in which the parasite exhibits a higher growth rate in its preferred host (PH) than its non-preferred host (NPH; case 2 specialism). The maximum virulence is thus the virulence realized on the PH due to the relationship between growth rate and virulence described in §2. Parameter values for all simulations can be found in electronic supplementary material, section S3.

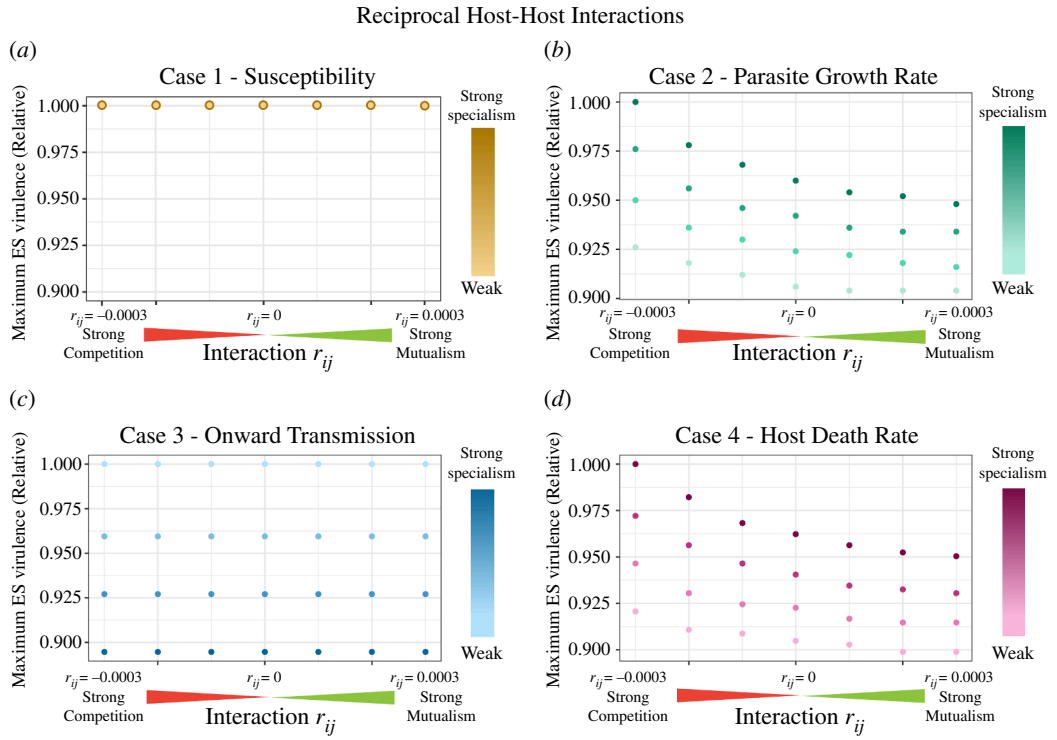

Figure 4. ES virulence for parasites of two reciprocally interacting hosts. In all the interactions tested here, the two host interaction parameters were equal: $r_{ij} = r_{ji}$. Reciprocal host interactions ranged from strong competition ($r_{ij} = r_{ji} = -0.0003$) to strong mutualism ($r_{ij} = r_{ji} = 0.0003$). We tested the range of host interactions on the backdrop of four different mechanisms of parasite specialism (cases 1–4, panels (*a–d*), respectively). In addition, four degrees of parasite specialism (ranging from strong to weak) were tested for each mechanism—strong specialism meant there was a large difference in parasite performance on each host type. The maximum ES virulence refers to the greater realized virulence when realized virulence differs between host types (as occurs for cases 2 and 4 specialism). Because we do not compare magnitudes of ES virulence between cases, only within cases, we plot relative ES virulence (scaled from the highest value for a given specialism case). For the case 1 plot, the degree of parasite specialism did not impact the ES virulence; thus, each point actually reflects four that are superimposed. For the exact parameter values for the degree of specialism, see electronic supplementary material, section S3.

a more generous mutualist to the PH (figure 5*b*). Conversely, for case 3 (onward transmission specialism) and case 4 (death rate specialism), ES virulence increases as the NPH become a weaker competitor or a more generous mutualist to the PH. For case 3, the ranges of ES virulence for unequal competition or mutualism overlap with one another. For example, the scenario in which the NPH is a stronger competitor than the PH will actually result in a parasite with lower ES virulence than the scenario in which the NPH is a less-generous mutualist (see electronic supplementary material, figure S4.2, for absolute ES virulence values). This is unlike reciprocal, unequal strength relationships under cases 2 and 4 specialism (figure 5*b*,*d*). For these, mutualistic relationships, even unbalanced ones, tended to result in lower parasite virulence than competitive ones. Thus, in case 3, it is the relative relationship between hosts, rather than absolute sign that is most significant in predicting shared pathogen virulence.

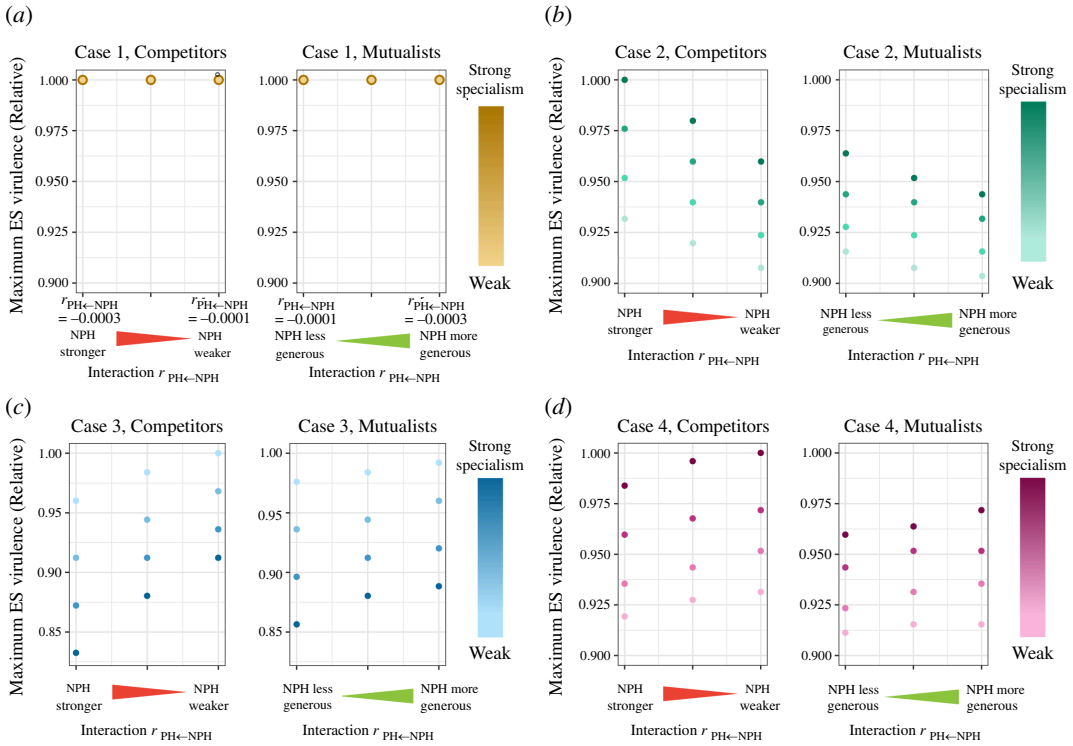

Figure 5. ES virulence for parasites of two reciprocally, but asymmetrically, interacting hosts. In each of the interactions tested here, the host interaction parameters had the same sign. The impact of the PH on the NPH was held constant ($r_{NPH \leftarrow PH} = 0.0002$ for the mutualism panels and $r_{NPH \leftarrow PH} = 0.0002$ for the competition panels). The horizontal axes then indicate the strength of the impact of the NPH on the PH ($0.0001 < |r_{PH \leftarrow NPH}| < 0.0003$; illustrated by the wedges), with resulting imbalances in the inter-host relationship noted. For example, when the NPH has a larger positive (negative) impact on the PH than the positive (negative) impact of the PH on the NPH, the NPH is necessarily a more generous mutualist (stronger competitor). Exact tick mark values are noted for the case 1 panels and are the same for all other cases. We tested the host–host interactions on the backdrop of four different mechanisms of parasite specialism (cases 1–4, panels (*a–d*), respectively) and for four degrees of parasite specialism (ranging from strong to weak) per mechanism. The maximum ES virulence refers to the greater realized virulence when realized virulence differs between host types (as occurs for cases 2 and 4 specialism). For the case 1 plot, the degree of parasite specialism did not impact the ES virulence thus each point reflects four that are superimposed. For the exact parameter values for the degree of specialism, see electronic supplementary material, section S3.

(b) Non-reciprocal interactions

In a non-reciprocal (+/−) host–host interaction, knowledge of the mechanism of parasite specialism was necessary to predict the direction of virulence evolution. For case 3, in which onward transmission was more efficient from the PH, or in case 4, in which excess death was reduced in the PH, higher virulence evolved when the exploiter was the PH and the exploitee was the NPH (figure 6*c,d*). In contrast, for case 2, in which the parasite grew more rapidly in the PH, higher virulence evolved when the exploitee was the PH, and the exploiter was the NPH (figure 6*b*). Figure 6 shows results for equal strength, non-reciprocal interactions, but the trends also hold for unequal strength, non-reciprocal interactions (see electronic supplementary material, figure S4.4). The case in which susceptibility differed between hosts once again did not show any shifts in ES virulence (figure 6*a*).

When comparing the absolute ES virulence values between the reciprocal and non-reciprocal host relationships, the 'extremes' of parasite virulence were selected for in non-reciprocal host relationship scenarios (see electronic supplementary material, figures S4.1-4, for absolute ES virulence values). For example, in case 2 (growth rate specialism), the virulence selected for when the PH is the exploiter was *lower* than the virulence selected for when the PH and NPH are mutualists, and the virulence when the PH is exploited is *higher* than the virulence when the PH and NPH are competitors.

(c) Impacts of the strength of parasite specialism

In addition to examining the role of host–host interactions, we assessed the interaction of host–host interactions with the strength of specialism (figures 4–6). Regardless of whether we considered reciprocal or non-reciprocal relationships of equal or unequal strengths, case 2 and case 4 saw the evolution of higher virulence as disparities between parasite performance on its PH vs NPH grew stronger. In contrast—with similar interaction types and strengths of interaction—case 3 showed the opposite trend: stronger specialization on the PH resulted in the evolution of lower virulence.

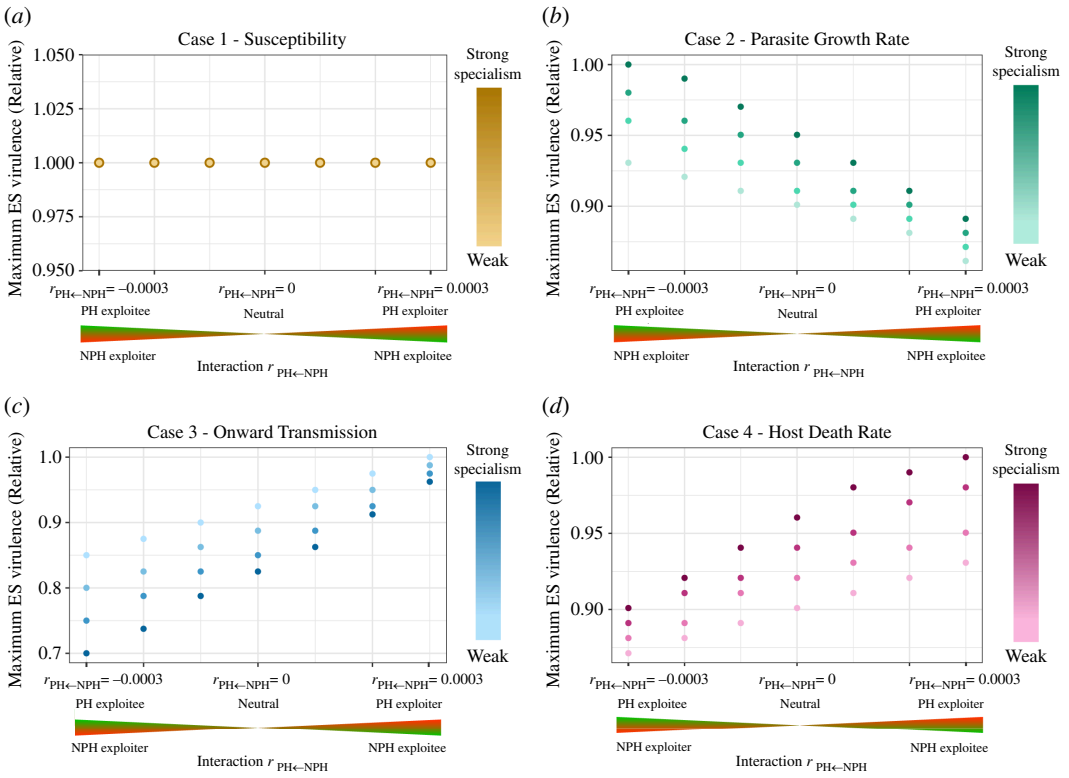

Figure 6. ES virulence for parasites of two non-reciprocally interacting hosts. In all the interactions tested here the two host interaction parameters had opposing signs: $r_{ij} = -r_{ji}$. The horizontal axis indicates the impact of the NPH on the PH. The left half of each case panel, for example, represents interactions in which the NPH exploits the PH: $r_{PH \leftarrow NPH} < 0$ (red wedge) and $r_{NPH \leftarrow PH} > 0$ (green wedge). We tested host–host interactions ranging from neutrality ($|r_{ij}| = |r_{ji}| = 0$) to strong exploitation ($|r_{ij}| = |r_{ji}| = 0.0003$). We tested these interactions on the backdrop of four different mechanisms of parasite specialism (cases 1–4, panels (*a–d*), respectively) and for four degrees of parasite specialism (ranging from strong to weak) per mechanism. The maximum ES virulence refers to the greater realized virulence when realized virulence differs between host types (as occurs for cases 2 and 4 specialism). Because we do not compare magnitudes of ES virulence between cases, only within cases, we plot relative ES virulence (scaled from the highest value for a given specialism case). For the case 1 plot, the degree of parasite specialism did not impact the ES virulence; thus, each point reflects four that are superimposed. For the exact parameter values for the degree of specialism, see electronic supplementary material, section S3.

4. Discussion

With a suite of models we have demonstrated the importance of the community context of multiple hosts with different interspecific interactions to the evolution of pathogen virulence. We have shown that parasite specialism is critical to the outcome, with the evolution of purely generalist parasites unaffected by the nature of the ecological interaction between their hosts. Furthermore, the strength of specialism has a direct impact on the ES virulence, alongside the degree of asymmetry of the host interaction and the fundamental nature of the interaction. Taken as a whole, our work emphasizes the importance of species interactions in determining the evolution of parasite virulence, and moreover emphasizes the community context of evolutionary outcomes. Moving beyond the simple host–parasite evolutionary models to include more realistic multispecies interactions is, therefore, an important aim for understanding the drivers of virulence in nature.

We can summarize the key impacts on virulence evolution in a shared parasite system as three fundamental factors: the strength of specialism on each host, the relative ecological relationship between hosts, and whether relationships could be classified as competitive or mutualistic. First, increasing the strength of specialism monotonically shifted ES virulence, regardless of host–host interactions. Second, extremes of virulence were evolved in contexts where hosts had a large relative difference in their impacts on one another—for example, in cases of exploitation that was strongly beneficial for the exploiter and strongly detrimental to the exploitee. Third, in general, mutualistic relationships (even unbalanced ones) are selected for lower shared parasite virulence than competitive relationships. Along with these commonalities, different mechanisms of parasite specialism differed in the direction of the relationship between the strength of specialism and virulence and in the direction of virulence evolution as we moved from a scenario where a PH was exploited to where it was the exploiter. Here, we explain how the outcomes of each case tie back to a unifying principle, most clearly illustrated by the exploiter/exploitee host–host relationship.

In general, the parasite/pathogen is competing with the exploiter for the exploitee resource, so it will evolve to be able to consume that resource more rapidly (and, thus, will cause more damage to the host) when the exploitee resource is relatively more threatened. We will break this trend down case by case. The case of reduced excess death on the PH (case 4) is the most straightforward. Higher virulence evolves when the exploiter is the PH because the exploitee, as the NPH, thus has higher disease-induced death. The case of more rapid growth in the PH (case 2) is also fairly intuitive. Higher virulence evolves when

the exploitee is the PH since, due to the trade-off between parasite growth rate and virulence, higher parasite growth rate in the exploitee will directly lead to higher excess death.

The case in which there is increased onward transmission from the PH (case 3) is slightly more complex and requires consideration of feedback between parasite generations. Importantly, hosts that share 'case 3' parasites share the same burden of infection (i.e. the same susceptibility to infection from an existing pool of parasites and the same likelihood of death from infection). They differ only in how heavily their infection contributes to the common pool of parasite propagules. When, for example, a shared parasite produces more propagules for transmission on the exploitee, the exploiter's negative impacts on the exploitee lessens relative competition for the exploitee resource because the parasite will have lower reproduction rates on the more available, non-preferred exploiter host. In the opposite case, exploitation strengthens competition because the parasite has a higher reproduction rate on the more available, preferred exploiting host. Thus, higher virulence evolves when the exploiter is the PH.

These same trends from explicitly non-reciprocal host relationships hold when considering imbalanced, yet reciprocal, relationships. For example, consider a mutualistic host–host relationship with case 2 (figure 5*b*). In this scenario, higher virulence evolves when the PH is more generous (i.e. closer to an exploitee than an exploiter) than when it is less generous than its mutualistic partner.

Furthermore, this same principle of relative host scarcity can explain commonalities in the observed trends along the competition to mutualism axis in case 2 and case 4, where the interaction of host–parasite biology with host–host ecology yield similar shifts in host frequencies that drive parasite evolution. Differences in parasite performance on each host type lead to the more heavily-burdened host sustaining a lower population density, even in the absence of host–host interactions. Mutualistic interactions buffer the effects of infection, yielding higher, and more importantly, more evenly distributed host densities than the case in which hosts do not interact beyond disease transmission (see electronic supplementary material, section S3.3). Increasing competition, on the other hand, creates a 'pile-on' effect, driving a further skew in population density, with the host facing a higher disease burden becoming scarce relative to its competitor. The competitor, in turn, can maintain an equilibrium population at a greater density than it does in the absence of host–host interactions (see electronic supplementary material, section S3.3). In effect, this creates a relatively more threatened 'exploitee' resource, even though individual hosts have equal competitive abilities.

The relationship between the strength of specialism and the evolution of virulence is similarly explained by competition for hosts—if stronger specialism directly exacerbates the competition for quality hosts, higher virulence will evolve, and vice versa. In general, stronger specialism results in a reduction in the average quality of the host pool (e.g. consider the extreme case in which a parasite can only infect one of the two hosts—this parasite would see the pool of the two types as inferior to a parasite who could equally parasitize both). In case 2 (growth rate specialism) and case 4 (death rate specialism), this reduction in 'average' host quality directly strengthens competition for infecting the remaining pool of quality hosts, and thus higher virulence evolves when there is a strong difference in parasite performance on each host. Unlike in case 2 or case 4, stronger case 3 (onward transmission) specialism does not restrict the number of hosts that will support rapid growth or longer infectious periods. For case 3 specialism, we consider the consequences of infection to understand trends in ES virulence (the trends are reversed in case 3 compared with cases 2 and 4) where it is *weaker* specialism that exacerbates competition for hosts. A virus that exhibits weaker (case 3) specialism will generate relatively more propagules for onward transmission, and there will thus be more competition among viral lineages for seeding initial infections.

The consideration of host–host interactions in our model draws attention to scenarios in which previous work from one-host, one-parasite systems holds, and in which it does not. One interesting deviation is the role of host availability. High host availability is expected to select for higher virulence [54], and host scarcity for lower virulence. This is exemplified by the self-shading effect in spatial models, in which lower virulence is selected for when parasites would otherwise over-exploit their limited pool of neighbouring hosts [6,55]. Once feedback of ecological relationships between multiple hosts is incorporated, however, this expectation does not appear to hold. In our model, a mutualistic relationship supports higher host populations than does competition (see electronic supplementary material, section S3.3), but competition selects for higher ES virulence for the shared parasite.

There are also fruitful comparisons to draw to multi-host work that focused on intra-host versus inter-host transmission and host life history parameters. Gandon [17] established that parasites should evolve virulence that is optimal on their prime host (i.e. one that is present at high frequency and supports high parasite reproduction). When prime hosts are also more resistant, higher virulence is expected to evolve. Case 4 specialism, where the mechanism of specialism is a more resistant, tolerant host, demonstrates nicely how the impacts of host interactions on population dynamics can be incorporated into existing theory. In this case, parasite growth rates and reproduction are equivalent on both hosts, so class reproductive values will be primarily based on the relative proportion of hosts. Host–host relationships in which the more resistant PH is also 'prime' due to its higher frequency, such as in competition or as a direct exploiter, lead to the evolution of higher virulence (figures 4*d* and 6*d*). Thus, we demonstrate that feedback from hosts' ecological relationships can influence the evolutionary trajectories of their shared parasites in ways previously achieved via a trade-off between resistance and host birth rate [17]. However, it is not the full story; case 3 (onward transmission specialism) shows that when we have a more complex network of host–host relationships, the effect may not hold for non-tolerance-based definitions of resistance. In this case, higher virulence is selected when the *less* resistant host (producing more propagules) is more abundant.

It is interesting to understand why case 1 specialism, in which the parasite's PH was more susceptible to initial infection than its NPH, did not show dependence of ES virulence on either host–host relationships or on the degree of specialism. Mathematically (see electronic supplementary material, section S2), when we allowed a range of appropriate host populations to come to ecological equilibrium, their relative proportions were such that the condition for invasion (and thus, the ultimate ES virulence

we would expect the system to evolve towards) was unchanged. Biologically, this model considers one-sided evolution of a parasite and not co-evolution of the host—and case 1 specialism is the only one of the four mechanisms that is independent of the parasite growth rate. Nevertheless, preliminary numerical simulations show that the time required for the invasion of a mutant parasite differs among competing, cooperating and exploitative hosts (see electronic supplementary material, figure S5.1). There are times when the shared parasite system instead resembles a two-host, two-parasite system, suggesting that non-equilibrium parasite evolution in a community of hosts differing only in susceptibility is still an ecologically interesting system. In particular, some multi-host pathogens (e.g. rabies [56]) are known to produce variants that eventually become associated with distinct hosts.

More nuanced, system-specific biological details should be considered in future work. For example, given that our work assumed a particular static mechanism of specialism, it would be interesting to examine the outcomes in a host–parasite coevolutionary context, where the degree of specialism and generalism in the parasite can evolve [57]. Models in which we relax the assumption that only the susceptible class of individuals are impacted by host–host interactions should also be considered. Our model assumes that host–host interactions result in modified birth rates within the susceptible host class and that infected individuals do not reproduce. These assumptions are less likely to hold true for chronic infections in which infected individuals are also expected to reproduce. Future work could extend our framework into situations where we expect host–host interactions to have differential effects on birth rates from the infected and susceptible hosts, or in which host–host interactions influence the duration or lethality of infection.

In a world in flux, it is becoming more important than ever to characterize and predict the consequences of multi-host pathogens. Climate change [58,59], deforestation and shifts in land usage [60], and a more interconnected globe [61,62] are all changing the strength and type of species interactions in existing communities, and are exposing pathogens to potential new hosts. Hosts with shared parasites are at the forefront of challenges in disease management; disease-mediated invasions can reshape competition between native and invasive species [3], and zoonotic disease poses significant threats to human health [63]. A combination of both future theory and empirical work is essential for predicting virulence evolution after spillover to new hosts or in response to shifts in the host–host interactions themselves. Real ecological communities are, of course, more complex than the triads we study here, and it remains to be seen whether the principles carry over to larger host–parasite assemblages—though recent work in bottom-up predictions of community assembly [64] are cause for hope that complicated ecological network processes can be predicted by considering subunits of the complex system. Quantifying host–host interactions and the precise mechanisms of infection and transmission in a particular disease system is no small task, but it is our hope that integrating community ecology into epidemiological models will allow for better predictions of virulence evolution in a changing world.

Ethics. This work did not require ethical approval from a human subject or animal welfare committee.

Data accessibility. All data and code can be accessed at [65].

Supplementary material is available online [66].

Declaration of AI use. We have not used AI-assisted technologies in creating this article.

Authors' contributions. C.E.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology; A.W.: formal analysis, funding acquisition, methodology; M.B.: conceptualization, funding acquisition, methodology, supervision.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

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