The interplay between host community structure and pathogen life-history constraints in driving the evolution of host-range shifts

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Funding information
Yale Institute for Biospheric Studies: NSF, Grant/Award Number: DEB 1354053, DEB 1543920, DEB 1556848 and DEB 1457815; NSF BEACON Center for the Study of Evolution in Action, Grant/Award Number: 13-004443; James S. McDonnell Foundation

Handling Editor: Dana Hawley

Abstract
1. The ability of pathogens and parasites to adaptively exploit novel hosts has contributed to their unparalleled diversification along the tree of life. Moreover, evolved host-range shifts are of particular applied interest – for instance, zoonotic ‘spillovers’ towards humans motivate growing concern about emerging infectious diseases. Thus, identifying the constraints upon, and conditions conducive to, host switching by pathogens is critical to addressing pressing public health and agricultural problems, as well as to understand a major driver of biodiversity.
2. How do processes that structure host communities (such as among-host competition) set the selective context for the evolution of pathogen host ranges, and how do these processes interact with trade-offs constraining the evolution of a pathogen’s ability to exploit its host?
3. Here, we develop a theoretical framework to understand how resource competition among hosts interacts with constraints on pathogen biology in driving host shifts. We characterize how antagonistic pleiotropy in the pathogen’s ability to exploit hosts can counteract ecological selection towards host-range shifts.
4. We find that although the effects of apparent competition on host-range shifts are mediated through the ancestral pathogen’s direct and indirect effects on the entire host community, the effects of exploitative competition on host-range shifts are mediated through exploitative competition’s effect on the previously unexploited host.
5. Finally, we show that even when changes in host community structure create conditions conducive to host switching, a general trade-off between pathogen virulence and burst size can prevent pathogens from evolving seemingly adaptive patterns of host use. We illustrate how these constraints faced by pathogens shape the eco-evolutionary interaction between pathogen evolution and host communities.
6. We discuss how our results inform predictions about the kinds of pathogen lineages likely to exhibit host-range shifts, and the role of apparent versus direct competition in structuring host–pathogen communities over evolutionary time.
1 | INTRODUCTION

Host shifts, which occur when a pathogen of one species can sustain infection and transmission within populations of a novel host species, are extremely common in nature (Tabashnik, 1983; Hafner et al., 1994; Agosta, 2006; Gilbert & Webb, 2007; Hobberg & Brooks, 2008; De Vienne et al., 2013; Longdon, Brockhurst, Russell, Welch, & Jiggins, 2014). Elucidating the drivers of pathogen host-range shifts is key to addressing central questions in ecology and evolutionary biology, both basic and applied. Several medically and agriculturally important infectious disease agents, including emerging pathogens implicated in particularly severe epidemics, such as HIV and the Ebola virus, are believed to have arisen via host shifts from one species to another (reviewed in, e.g., Cleaveland, Laurenson, & Taylor, 2001; Anderson et al., 2004; Jones et al., 2008; Giraud, Gladieux, & Gavrilets, 2010).

Phylogenetic evidence for the distribution of host shifts is not uniform across pathogen lineages, with some clades experiencing rates of host shifts up to an order of magnitude greater than others (De Meeûs, Michalakis, & Renaud, 1998; Karvonen & Seehausen, 2012; Kamiya, O’Dwyer, Nakagawa, & Poulin, 2014). Several ecological and evolutionary processes can explain this diversity of patterns—for instance, gene flow from specialist pathogen demes may prevent local adaptation in sexually reproducing parasites towards exploiting novel hosts (Gandon & Michalakis, 2002), and genetic and environmental costs may constrain host-range shifts under some conditions (Whitlock, 1996; Remold, 2012). This suggests that spatial structuring of pathogen subpopulations or relaxed pleiotropic and environmental constraints may promote the rapid diversification of host ranges (Giraud, 2006; Duffy, Turner, & Burch, 2006). Consequently, gradients across assortative mating, antagonistic pleiotropy (i.e., a mutation favourable for exploiting one host renders exploitation of another host detrimental to fitness), and abiotic factors that drive host–pathogen interactions, such as seasonal infection dynamics (e.g. Lajeunesse & Forbes, 2002; Morgan, Gandon, & Buckling, 2005; Penczykowski, Laine, & Koskella, 2016), may explain variation in host-range shifts across lineages.

The relative availability of hosts in a given environment is a major factor determining whether pathogens can switch hosts (Via, 1990; Kawecki, 1998; Kassen, 2002; Friman, Hiltunen, Laakso, & Kaitala, 2008; Duffy & Turner, 2009). All else being equal, pathogens exploiting a rare host can experience strong selective pressure to exploit a more abundant host. Interspecific competition is a key factor structuring species densities (Gause, 1934), even in the presence of a pathogen, and can affect evolutionary dynamics at higher trophic levels. For instance, a model by Velzen and Etienne (2012) shows that increasing the amount of nutrients available among competing plant species can favour selection for resource generalism among herbivores. Velzen and Etienne (2012) further note how antagonistic pleiotropy can prevent the evolution of generalist herbivores, even when among-host competition may favour the evolution of generalists. These considerations suggest a context-dependent role of inter-host competition in governing the dynamics of host-range shifts by altering the availability of hosts.

To adapt to exploit novel hosts, pathogens must also frequently overcome several genetic trade-offs besides their ability to infect alternative hosts. In particular, many pathogens face severe life-history trade-offs (Susi & Laine, 2013; Keen, 2014) that are critical to driving epidemiological dynamics over both ecological and evolutionary time-scales (Laine & Barrés, 2013; Bull & Lauring, 2014). Because of the central role played by pathogen population dynamics in determining their evolutionary trajectory, such life-history constraints on pathogens are likely to interact with host community structure (e.g. the relative availability of hosts) in governing the evolution of host switching.

Here, we investigate how the interplay between these three factors—antagonistic pleiotropy among infecting host types, life-history constraints on pathogen virulence and transmission, and among-host competition—governs the dynamics of host-range shifts. Because of the nonlinearities inherent in host-pathogen interactions, we develop a mathematical framework to elucidate the ecological and evolutionary dynamics. Our work departs from earlier theoretical work on evolution in multi-host parasites (e.g., Gandon, 2004; Gandon & Day, 2009) in two key respects. First, we evaluate host-range shifts in the presence of diverse scenarios of asymmetric resource competition among hosts. Second, we aim to systematically compare how qualitatively and biologically distinct pathogen life-history constraints mediate the consequences of such asymmetric resource competition for pathogen host-range shifts. Below, we describe our model formulation in greater detail.

2 | MATERIALS AND METHODS

2.1 | Model description

We model two host species competing for a common resource within a given locality (habitat), using a logistic model to describe competitive interactions between hosts. We define $r_j$ as the intrinsic proliferation rate of host species $j$, $d_j$ as the natural death rate of host species $j$ and $a_{jk}$ as the effect of host $k$ on the per capita growth rate of host $j$; thus, $a_{jk}$ represents density-dependent effects on host $j$’s recruitment. We assume that host competition follows Lotka–Volterra dynamics in the absence of the pathogen and that $a_{jk} < a_{jj}$ for $k \neq j$ (and thus that the two host species can...
always coexist absent the pathogen). We consider a model in which a host species $A$ initially vulnerable to the pathogen competes with a novel host species $\nu$ that is initially resistant to the ancestral pathogen strain $\alpha$, but which mutant pathogens may potentially infect; we model up to $\eta$ pathogen strains. Each of the two host species potentially consists of several subpopulations — hosts infected with the pathogen strain $i \in [0, \eta] (A_i, \nu_i)$, and hosts that are not infected ($A_i, \nu_i$). An infection coefficient $\beta_{ij}$ describes the ability of an infectious quantity of pathogens of strain $i$ to encounter and infect a single uninfected host of species $j = A, \nu$; for brevity, we refer to $\beta_{ij}$ as the infection rate for the remainder of the text. Pathogen strain $i$ kills an infected host of species $j$ at a rate $\delta_{ij}$, at which point $b_{ij}$ free-living particles (in units of infectious doses) are released. We assume pathogen virulence results in increased host mortality, and thus refer to $\delta_{ij}$ throughout as the virulence of pathogen strain $i$ on host species $j$. For lytic viruses, $b_{ij}$ can be thought of as the burst size (the number of infectious virions released from each cell upon lysing) of pathogen $i$ infecting host $j$. Other mechanisms such as the release of fungal or bacterial spores from host cadavers (e.g., Feng, Poprawski, & Khachatourians, 1994; Hugh-Jones & Blackburn, 2009) could also describe $b_{ij}$. Nevertheless, for convenience, we refer to $b_{ij}$ throughout as the ‘burst size’. Pathogen particles can also leave their hosts through shedding, and the inflow of new free-living pathogens from infected, living hosts $j$ occurs at a rate $\delta_{ij}$ for each host species $j = A, \nu$. The density of the pathogen strain $i$ during the free-living stage is given by $p_i$ and free-living pathogens are removed from the system at a constant rate $\omega$. Thus, the epidemiological dynamics within a single host population is an $S - I - P$ model, with the free-living pathogen population $p_i$ represented explicitly.

Inside hosts of either species infected with pathogens of strain $i$ ($\nu_i, A_i$), pathogens can mutate from strain $i$ to strain $i'$. Mutant pathogen strain $i'$ competitively displaces pathogen strain $i$ inside an infected host at a rate $\mu_{ii'}$, which we assume is given by $\mu_{ii'} = \frac{1}{|i' - i|}$ for a constant $\mu$, where $|i - i'|$ describes the genetic distance between the two strains. Thus, if strain $i$ is well adapted to host $j$, then the other strain $i'$ is from $i$, the less likely it is that $i'$ will out-compete strain $i$ in host $j$. The intra-host competitive dynamics between pathogen strains is modelled to be sufficiently fast relative to the dynamics of the host–pathogen interaction (e.g. Gandon & Day, 2009). We consider two scenarios. Our analyses begin by considering the invasion of a single mutant pathogen strain M that can exploit either both hosts or only the novel host $\nu$. For this analysis, there are only $\eta = 2$ host trains. We then proceed to consider the case where mutations can result in $\eta = 10$ distinct pathogen strains, each of which varies in their ability to exploit the two hosts. Throughout, we assume the effects of co-infection with different pathogen strains to be negligible. Figure S1 provides a visual summary describing the key processes we model.

The combined ecological and evolutionary dynamics of the interacting susceptible hosts, resistant hosts and pathogen are described by:

$$\frac{dp_i}{dt} = r_i\left(p_i + \sum_{j=1}^{\eta} p_j \right) \left(1 - a_{i,\nu} p_i + \sum_{j=1}^{\eta} \frac{\mu_{i'j}}{\mu_{ii'}} \frac{b_{i'j}}{b_{ij}} \nu_j + \sum_{j=1}^{\eta} A_j \right) - \frac{\nu_i (\sum_{j=1}^{\eta} \beta_{ij} p_j) - d_i p_i}{d_i}$$

$$\frac{dA_i}{dt} = r_i A_i + \sum_{j=1}^{\eta} A_j \left(1 - a_{i,\nu} A_i + \sum_{j=1}^{\eta} A_j - a_{i,\nu} (p_i + \sum_{j=1}^{\eta} \nu_j) \right) - A_i (\sum_{j=1}^{\eta} \beta_{ij} A_j - d_i A_i)$$

$$\frac{d\nu_i}{dt} = \beta_{ij} \nu_i p_i - \delta_{ij} \nu_i - d_{ij} \nu_i + \sum_{j=1}^{\eta} \left(\mu_{j\nu} \nu_j - \mu_{i\nu} \nu_i \right)$$

To compare how different evolutionary and ecological constraints (i.e. trade-offs) affect the evolution of host-range shifts among pathogens, we analysed equation (1) under three different scenarios: (a) a trade-off in the pathogens’ ability to infect hosts (which could arise, for example, when different cellular receptors are used by different viruses for entry), (b) a trade-off in the ability of the pathogen to exploit hosts (i.e. virulence; this could arise, for example, through differential susceptibility to novel toxins in different hosts) and (c) a trade-off between the pathogen burst size and virulence.

Overcoming differential infectivity ($\beta_{ij}$ in our model) is widely understood to be a major challenge for pathogens shifting their host ranges (e.g., Turner & Elena, 2000; Duffy et al., 2006). However, the inability to replicate inside, and hence exploit, alternative hosts can also prevent host-range shifts (as this would render the virulence $\delta_{ij}$ in novel hosts $\approx 0$). Such failed replication could result, for instance, from changes in a virus’s ability to utilize their host’s replication machinery and have little to do with the adsorption mechanism. This scenario can also describe a situation where the pathogen takes longer to produce the same number of particles within the novel host as it produces in the ancestral host.

Finally, we consider a trade-off between the pathogen’s burst size $b_{ij}$ and virulence $\delta_{ij}$. Such a trade-off can result, for instance, if pathogen strains that wait longer to kill their hosts can accumulate and release more infectious particles upon host death (as is found for, e.g., many bacteriophages — Wang, Dykhuijen, & Slobodkin, 1996; Abedon, Hyman, & Thomas, 2003; Bull, 2006; Wang, 2006, and Heineman & Bull, 2007). We note that because the per capita infection rate of hosts $j$, $\beta_{ij} p_j$, is proportional to the density $p_j$ of free-living pathogens, a trade-off between burst size and virulence can also entail a trade-off between virulence and transmission. This is because if the dynamics of free pathogen particles operate on a considerably faster time-scale than the dynamics of the host populations, as is often evoked in traditional epidemic models, the per capita transmission rate from host to host is proportional to $b_{ij}$. Thus, for a given infection coefficient
\( \beta \), pathogen burst size controls the transmission rate. Moreover, for pathogens that do not release infectious particles upon host death (i.e., \( b_j = 0 \) and \( \delta_j, \delta_j > 0 \)), the number of free-living pathogen particles becomes proportional to the number of infected hosts. Pathogens that accelerate host death (and therefore virulence) thereby also remove this source of transmission. Hence, our model incorporates a transmission–virulence trade-off even when burst sizes are zero. As both shedding and release upon host death are part of our model, we can compare how constraints across these distinct modes of transmission contribute to the evolution of host-range shifts.

To describe various shapes these trade-offs can take, we assume that traits \( x \) and \( y \) are subject to a pleiotropic relationship:

\[
y(x) = \frac{e^{-\exp\left(\frac{x}{\tilde{x}}\right)}}{e-1} y_0,
\]

where \( e \) is Euler’s number and \( \tilde{x} \) describes the maximum possible value of \( x \).

Function (2) is attractive for several reasons. First, the parameter \( s_i \) controls the severity, nature and relative nonlinearity of the trade-off. That pathogen trade-offs can take a diversity of functional forms is well documented (reviewed in, e.g., Ewald, 1983; Ebert & Bull, 2003; Alizon, Hurford, Mideo, & Van Baalen, 2009; Bull & Lauring, 2014; Alizon & Michalakis, 2015; Acevedo, Dillemuth, Flick, Faludy, & Elderd, 2019). Function (2) allows us to encapsulate in a single parameter how convex (severe), concave (relaxed) or (approximately) linear the trade-off curve is. A second advantage of function (2) is that the value \( s_i \) can be specified so that the trade-off can operate over some ranges of \( x \) but not others. For example, \( y = y_0 \) if \( s_i \) is chosen to be sufficiently large over a range of values where \( x < \tilde{x} \). Figure S2 shows how the range of values of the trade-off parameter \( s_i \) governs the behaviour of function (2).

### 2.2 Model analyses

We compare how interspecific competition among hosts under each of the three pathogen trade-offs (infectivity, virulence and virulence–burst size) affects the evolution of host-range shifts. We explore the behaviour of model (1) first when evolutionary processes occur at a slower time-scale than ecological processes (Geritz & Gyllenberg, 2005). We characterize when a rare, mutant pathogen strain \( M \) that can exploit both novel and original hosts can invade a resident community at equilibrium consisting of both hosts and an ancestral, specialist pathogen \( a \) exclusively infecting host \( A \). We then evaluate when this pathogen further evolves to exploit only the novel host under alternative trade-off regimes by analysing when a community at equilibrium with a generalist pathogen is invaded by a specialist pathogen of host \( \lambda \). We note that this means that in principle, there could be regions of parameter space where a generalist mutant cannot invade, but, were such a generalist to be at equilibrium, a mutant specializing on the novel host can invade. This may occur, for instance, if the generalist pathogen experiences an Allee effect at low densities, but may have nevertheless reached equilibrium, for example, by overcoming the Allee effect through temporary immigration from another habitat where it is abundant. Finally, we ask when a community at equilibrium with a pathogen specializing on the ancestral host \( A \) is invaded by a mutant pathogen specializing on the novel host \( \nu \). These analyses assume there are \( q = 2 \) pathogen strains in model (1).

We then expand our analysis to the case when ecological and evolutionary dynamics occur on congruent time-scales. Under these conditions, the evolution of the pathogen occurs simultaneously with the population dynamics of resistant and susceptible hosts and the resident, ancestral pathogen strain \( a \). We numerically integrate equation (1) to characterize the change in pathogen genotype composition under the pleiotropic constraints described in Table 1. For these analyses, we assume there are \( q = 10 \) different pathogen strains in our model.

When investigating the evolutionary dynamics under a trade-off between virulence and burst size, it is important to consider a continuum of pathogen strains that confer successively greater degrees of host specificity, rather than a pairwise comparison of resident and mutant strains. This is because both virulence and burst size are often quantitative traits rather than discrete states. We therefore investigated evolutionary dynamics when successive mutations produce several pathogen strains \( i \) that increasingly specialize on once resistant hosts according to their underlying genotype \( g_i \).

To represent this continuum of trait values, we describe the virulence \( \lambda_{ij} \) of pathogen strain \( i \) for novel hosts \( \nu \) to decline with its burst size \( b_{ij} \) in hosts \( \nu \) according to:

\[
\begin{align*}
\lambda_{ij} &= \frac{e^{-\exp\left(\frac{\lambda_{ij}}{\lambda_{a}}\right)}}{e-1} \lambda_{a}, \\
\lambda_{Aij} &= \left(1 - \frac{e^{-\exp\left(\frac{\lambda_{Aij}}{\lambda_{Aa}}\right)}}{e-1}\right) \lambda_{Aa}, \\
b_{ij} &= \frac{e^{-\exp\left(\frac{\lambda_{ij}}{\lambda_{a}}\right)}}{e-1} b_{a}, \\
b_{Aij} &= \frac{e^{-\exp\left(\frac{\lambda_{Aij}}{\lambda_{Aa}}\right)}}{e-1} b_{Aa}.
\end{align*}
\]

where \( s_{c_i} \) characterizes the trade-off in virulence across the two host types, the parameter \( s_{c_i} \) controls the steepness and relative nonlinearity of the virulence–burst size trade-off, and \( g_i \) determines the specificity of the pathogen to a particular host.

We consider the dynamics of \( q = 10 \) strains and set, without loss of generality, \( g_i = 0,1,\ldots,10 \). For moderate levels of the parameters \( s_{c_i} \) this scales specialization of the pathogen strains on a given host species to range from nearly 0 to 1. We assume the initial densities of all pathogen strains except the one that exclusively exploits susceptible hosts (the pathogen strain with \( g_i = 0 \)) are set at zero. Table 1 summarizes the parameters used for our model, and Table 2 summarizes the scope of our analyses.

### 3 RESULTS

#### 3.1 Ecological dynamics occur on a faster time-scale than evolutionary dynamics

When ecological dynamics operate on a much faster time-scale than evolutionary dynamics, the evolution of host-range shifts begins...
with the emergence of a generalist mutant pathogen $M$ in a community of two competing hosts with only one host being exploited by the ancestral pathogen $a$ at equilibrium. We ask how tropism for an ancestral host type could be lost when a generalist mutant arises in this community. The host-shifting process can be further examined by evaluating when a mutant pathogen that can only exploit the new host invades. Throughout the analyses that follow, we focus on the case where there is a single mutation event conferring the ability to exploit different hosts (and thus, evolution is mutation limited).

### 3.1.1 Conditions for the emergence of pathogens in novel hosts

A mutant, generalist pathogen strain $M$ can emerge whenever the number $R_{a,M}$ of secondary infections in a population where no host is infected with the mutant exceeds unity, where

$$R_{a,M} = \frac{\beta_M(d + \lambda_M)(d_A + \lambda_{AM})v_M + \beta_A(d + \lambda_A)(d_M + \lambda_{AM})v_A + \beta_M(d + \lambda_M)v_M + \beta_A(d + \lambda_A)v_A}{(d + \lambda_M)(d_A + \lambda_{AM})(\omega + \beta_Mv_M + \beta_Av_A)}$$

(Appendix S2).

This expression illustrates how competition among hosts, and hence the relative density of the two host types at equilibrium ($v_A^*, v_M^*$), mediates the evolution of host-range shifts. In particular, we can use $R_{a,M}$ to evaluate how the ancestral pathogen's heavy exploitation of only a single host may in fact create the selective conditions favouring host-range shifts. When the previously unexploited host $v_M$ is highly abundant relative to the exploited host, then mutant pathogens with even a modest ability to exploit the novel host (small $\beta_M$) can invade whenever $d_A + \lambda_{AM} < \delta_A + b_A$, where $A$ is the specialist pathogen. Such a result can occur, for instance, if the effect of apparent competition (e.g., Holt, 1977) is strong and the unexploited host can increase to high numbers in the presence of a specialist pathogen constraining its competitor's density. The equilibrium $A_U^*$ of the exploited host when only the ancestral pathogen exploiting host $A$ but not host $v$ is present does not depend on the severity of resource competition. Thus, the expression $R_{a,M}$ highlights how the effect of resource competition on the ability of a generalist pathogen to invade is mediated through the equilibrium density $v_M^*$ of the unexploited host in a community with only the specialist pathogen. An important implication of this result is the following contrast: whereas the effects of apparent competition on expanding host ranges are mediated through the ancestral pathogen's
\begin{table}[h]
\centering
\footnotesize
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{A) Ecological Scenarios. (B) Pathogen Life-History Trade-offs} & \textbf{Time scales} & \textbf{Ecological dynamics faster than evolutionary dynamics} & \textbf{Congruent ecological and evolutionary time-scales} \\
\hline
\textbf{Pathogen mutations} & Generalist or specialist on novel host & Only specialist on novel host & Genotypic gradient of host specificity \\
\hline
\textbf{Among-host competition} & 0 < \alpha_{A,M} \alpha_{A,M} < 1 & Highly asymmetric & Moderately asymmetric & Strong (\alpha_{A,M} = 0.8) & Weak (\alpha_{A,M} = 0.05) \\
\hline
\textbf{Trade-off} & \textbf{Parameter combinations} & \textbf{Biological interpretation} & \textbf{Example systems} \\
\hline
\textbf{Infec}tivity trade-off & \beta_{j,i} \neq \beta_{A,i} or \beta_{j,i} \neq \beta_{A,a} & Mutant pathogen infects different hosts at different rates & Bacteriophage adsorption (Daniels & Wais, 1998), Ebola (Urbanowicz et al., 2016) \\
\hline
\textbf{Virulence trade-off} & \lambda_{i,j} \neq \lambda_{A,i} or \lambda_{j,i} \neq \lambda_{A,a} & The ability of the pathogen to kill its hosts differs across host types & Lyme disease (Levi, Keesing, Holt, Barfield, & Ostfeld, 2016), schistosomes (Webster, Shrivastava, Johnson, & Blair, 2007) \\
\hline
\textbf{Virulence–burst size trade-off} & Virulence trade-off as well as \( b_{A,M} > b_{A,a} \) and \( \lambda_{i,M} < \lambda_{i,a} \) or \( b_{A,M} < b_{A,a} \) and \( \lambda_{i,M} > \lambda_{i,a} \) & The mutant pathogen infects resistant and susceptible hosts at the same rate, but burst sizes and virulences differ and are inversely related to each other & HIV (Fraser, Hollingsworth, Chapman, de Wolf, & Hanage, 2007), protozoan parasites of butterflies (de Roode, Yates, & Altizer, 2008), Bacteriophages (Bull, Badgett, Springman, & Molineux, 2004; Bull, Pfennig, & Wang, 2004) \\
\hline
\end{tabular}
\end{table}

Direct and indirect effects on the host community, the effects of exploitative competition on host-range shifts are mediated only through resource competition's effect on the previously unexploited host.

The expression for \( R_{0,M} \) also shows that a trade-off in pathogen virulence \( \lambda_{i,M} \) and burst size \( b_{A,M} \) can constrain the evolution of host-range shifts even when the previously unexploited host is considerably more abundant than the pathogen's original host and there are no barriers to infecting the novel host. To see this, note \( \beta_{i,M} \neq \beta_{A,M} \) simply scale the effect of the equilibrium densities of the two hosts on the number of secondary infections of the mutant pathogen, and the linear effect of pathogen virulence \( \lambda_{i,M} \) is scaled by the number \( b_{A,M} \) of free-living individuals produced upon killing the host. By contrast, the inverse effect of pathogen virulence on \( R_{0,M} \) is not scaled by the production of free-living particles. Because the host species’ background mortality rates \( d_{i}, d_{A} \) are independent of the pathogen's biology, the ability of pathogens to evolve host-range shifts are ultimately constrained by the pathogen's burst size. This occurs because when the mutant pathogen is extremely virulent, \( R_{0,M} \rightarrow b_{A,M} \lambda_{i,M} + b_{A,a} \lambda_{i,a} \delta_{A,M} \). But if virulence trades off with burst size, then even if the pathogen is extremely virulent, host-range shifts cannot evolve. If highly virulent pathogens suffer low burst sizes, then \( R_{0,M} \rightarrow 0 \). Importantly, this result does not depend on the ability \( \delta_{i,M} - \delta_{A,M} \) of the pathogen to shed propagules during the infectious stage (as, if the pathogen is highly virulent, the infectious stage is necessarily short).

Moreover, all else being equal, even if infectivity in the novel host is minimal (so that \( \beta_{i,M} = 0 \)), a mutant capable of exploiting the previously resistant host \( i \) can evolve if

\[ A_{i}^{M} > \frac{(d_{A} + \lambda_{i,M}) \omega}{\beta_{A,M}(\delta_{A,M} - d_{A} + (b_{A,M} - 1)\lambda_{i,M})}, \] (4)

provided \( \delta_{A,M} > d_{A} + \lambda_{A,M} \) or \( b_{A,M} > (d_{A} + \lambda_{A,M} - \delta_{A,M})/(\lambda_{i,M}) \). In effect, condition (4) illustrates how a large pool of uninfected, ancestral hosts can subsidize the invasion of a mutant pathogen that rarely infects the novel host. If the shedding \( \delta_{A,M} \) of infectious particles by the pathogen is small, this latter inequality illustrates the critical importance of a trade-off between virulence \( \lambda_{i,M} \) of the mutant pathogen strain and its burst size \( b_{A,M} \) in moderating the effect of the relative availability of hosts on the evolution of host shifting.

### 3.1.2 The evolution of specialization on a novel host

Host shifts are also possible when the pathogen specializes on the alternative host \( \nu \). In Appendix S2, we show that the average number \( R_{0,M} \) of secondary infections of a mutant pathogen \( M' \) only exploiting host \( \nu \) is given by

\[ R_{0,M} = \frac{\beta_{M,M}(\delta_{M,M} + b_{M,M} \lambda_{i,M}) \nu_{\nu}^M}{(d_{A} + \lambda_{i,M} \omega + \beta_{A,M} \nu_{\nu}^M)}, \] (5)

where \( \nu_{\nu}^M \) denotes the equilibrium density of uninfected \( \nu \) hosts when an ancestral, generalist pathogen is at equilibrium. We further show in Appendix S2 that equation (5) applies whether the ancestral pathogen is a specialist on host A or a generalist.
As was the case for a generalist pathogen, we find that trade-offs between virulence and progeny production can constrain the evolution of host-range shifts. In particular, when the mutant is highly virulent on its singular host (so that \( \lambda_{A,M} \to \infty \)), \( R_{0,M} \) of the mutant pathogen strain reduces to \( \frac{b_{A,M}^{\gamma_{A}}}{u_{A,M}^{\gamma_{A}}} \). However, when pathogen virulence and burst size are negatively correlated (so that \( \lambda_{A,M} \to \infty \) implies \( b_{A,M} \to 0 \)), then the invasibility requirement \( R_{0,M} > 1 \) becomes harder to satisfy. We further show in Appendix S1 that when hosts are ecologically similar (so that \( r_{A} = r_{\nu} = a_{A,\nu} \) and \( d_{A} = d_{\nu} \)) but differ only in their competitive abilities, then absent trade-offs, a specialist pathogen cannot evolve from a generalist pathogen, and restricted host ranges are never evolutionarily stable. Thus, model (1) predicts pathogen specialization on ecologically similar hosts to be maladaptive.

3.1.3 | How pathogen pleiotropy and host resource competition interact to drive host-range shifts

Next, we seek to describe how trade-offs a pathogen faces interact with interspecific competition among hosts to drive the evolution of host-range shifts. Although the equilibrium density of the unexploited host \( v_{A}^{\nu} \) in a community consisting only of the specialist pathogen can be derived algebraically, its expression is quite complex and does not permit biological interpretation of the effects of host resource competition \( a_{A,\nu} = a_{A,\nu} \) on the invasibility criteria \( R_{0,M} \) or \( R_{0,\nu} \). Thus, we used Mathematica (Wolfram Research Inc. 2009) to numerically evaluate how \( R_{0,M} \) and \( R_{0,\nu} \) depend upon a range of effects of exploitative competition \( 1 > a_{A,\nu} > 0 \).

Figures 1 and 2 illustrate how the extent of exploitative competition and assumptions about the underlying trade-offs in pathogen biology govern the evolution of host-range shifts. These figures are based on two mutation scenarios. First, we assumed that mutations can result in generalist mutants as well as pathogens specializing on the novel hosts (Figure 1). Under this scenario, we assumed that a mutant specializing on the novel host must be evolutionarily preceded by a generalist mutant. When a generalist mutant can evolve, we characterize the host range as expanding; when a mutant specializing on the novel host can evolve from a generalist ancestor, we characterize the host range as contracting. Thus, the host range can both expand and contract when a generalist pathogen can evolve from a pathogen specializing on ancestor host \( A \), and a pathogen specializing on novel host \( \nu \) can subsequently evolve from the generalist (white regions in Figure 1). When a generalist pathogen can evolve from a specialist on host \( A \), but a specialist on host \( \nu \) cannot subsequently evolve from the generalist pathogen, we describe host ranges as only expanding (light grey regions). Conversely, when a specialist on host \( \nu \) can evolve from a generalist pathogen, but a generalist pathogen cannot evolve from an ancestral, specialist pathogen on host \( A \), we characterize host ranges as only contracting (dark grey regions).

Our key result is that different constraints on the pathogen alter how resource competition among hosts drives the evolution of pathogen host-range shifts. When mutant pathogens suffer reduced infectivity (Figure 1a,b), where there is limited competition among hosts (both \( a_{A,\nu}, a_{A,\nu} \) small), both host-range expansion and contraction can result (white regions in Figure 1a,b). However, as the competitive effect \( a_{A,\nu} \) on the novel host increases, the novel host \( \nu \) becomes rarer, and this creates the conditions where although a pathogen specializing on a novel host can evolve away from a generalist ancestor, a mutant generalist pathogen cannot evolve from an ancestral pathogen specializing on host \( A \) (dark grey regions in Figure 1a,b).

By contrast, when the cost of exploiting both hosts is manifested in the pathogen’s virulence (so that although pathogens can infect both host types equally well, they kill either host at only half the efficiency of the ancestral specialist; Figure 1c,d), when the pathogen burst size is small, generalists and specialists on the novel host can emerge whenever the ecological equilibrium with the specialist pathogen is viable (white region, Figure 1c). However, when burst sizes are large, although a generalist mutant can emerge, a pathogen specializing on the novel host cannot readily evolve from a generalist ancestor (light grey region, Figure 1d); only a very strong competitive effect of the ancestral host on the alternative host facilitates eventual specialization on the novel host (white region, Figure 1d).

We further evaluated the situation where a trade-off in pathogen virulence and burst size causes a more virulent generalist to suffer reduced burst sizes, while a less virulent specialist experiences higher burst sizes. For the range of parameter values evaluated, although generalist pathogens exploiting both hosts can emerge (light grey regions, Figure 1e,f), specialization on the novel host cannot evolve except when the competitive effect \( a_{A,\nu} \) of the ancestral host on the alternate host is very large (white and dark grey regions, Figure 1e,f).

Figure 2 presents results for the case where the ancestral pathogen is always assumed to be a specialist on the ancestral host \( A \), and the invading, mutant pathogen is always a specialist on the novel host \( \nu \) (thus, an intermediary generalist pathogen is not required). When there is strong competition from the ancestral host on the alternative host \( (a_{A,\nu} \) large, this can prevent the evolution of host shifts altogether under all trade-off scenarios (Figure 2). Moreover, when the trade-off experienced by the mutant specialist involves reduced infectivity on the novel host, a specialist is less likely to evolve under a wider range of competitive effects \( a_{A,\nu} \) of the ancestral host on the novel host than when the trade-off involves reduced virulence (Figure 2a vs. 2b,c).

To summarize, these contrasts highlight how the strength of selection to exploit a novel host is mediated by trade-offs in the different pathogen life-history traits. For example, when the novel host is rare (as a result of strong interspecific competition – i.e. high values of \( a_{A,\nu} \)) and mutant pathogens suffer reduced infectivity, then even if the pathogen has a high burst size, there will be fewer opportunities to replicate in the new host (e.g. dark grey region in Figures 1a,b and 2). However, when the trade-off involves virulence, then mutant pathogens with lower virulence that are nevertheless able to encounter and infect novel hosts can invade, even if interspecific competition experienced by the novel host is high, particularly if generalist pathogens are already present (light grey regions in Figure 1e,f).
To further assess the effect of the virulence–burst size trade-off, we varied how the trade-off parameter $s_r$ in equation (2) and the virulence of the invader affect the evolution of host-range shifts (Figure 3). We find that the more severe the trade-off between virulence and burst size (smaller trade-off parameter values), the less conducive conditions become to host-range expansion. Even when the mutant pathogen has very high virulence relative to the ancestral pathogen strain, only when the trade-off is more relaxed can host-range expansion evolve. However, when resource competition between hosts is less asymmetric (Figure 3b), host-range expansion can more readily evolve (Figure 3a). The effect of competitive asymmetry is more apparent when mutations only produce pathogens specializing on the alternate host, with host shifts more readily evolving as competitive asymmetry is relaxed (Figure 3c vs. 3d).

### 3.2 Congruent ecological and evolutionary timescales

Our analyses thus far have focused on the case where evolution is mutation limited. In many host–pathogen systems, however, intense selection pressures at both trophic levels can facilitate rapid evolutionary change, causing evolutionary shifts that drive...
ecological processes (Doebeli, 1996; Bohannan & Lenski, 2000; Post & Palkovacs, 2009; Hiltunen & Becks, 2014). We numerically integrated model (1) using the Isoda routine in R (Soetaert, Petzoldt, & Setzer, 2010), assuming pathogen genotypes to lie along a continuum from complete specificity on host A (designated by genotype 1) to complete specificity on host ν (designated by genotype 10). We focus our analyses on two cases: (a) when the host exploited by the ancestral, specialist pathogen is subject to strong competitive pressure from the other (initially) unexploited host, and (b) when the host exploited by the ancestral pathogen experiences weak competitive pressure from the (initially) unexploited host.

3.2.1 Initially vulnerable host subject to strong inter-host competition

We begin our analyses with congruent ecological and evolutionary time-scales by first considering the case where the competitive effect \( \alpha_{A,\nu} \) of the novel host \( \nu \) on host A exploited by the ancestral, specialist pathogen is strong (\( \alpha_{A,\nu} = 0.8 \); Figures 3 and 4). We find that the interplay between host resource competition and the nature and magnitude of the pathogen’s trade-offs governs the extent to which host-range shifts evolve. Figure 3a illustrates the results of our analysis when the only trade-off a pathogen strain experiences is between its infectivities \( \beta_{A} \) of the two hosts \( \nu \) and A, respectively. We find host-range shifts result when both the trade-off between infectivities and the effect of inter-host competition on the novel host are weak (Figure 4a). By contrast, a severe trade-off in infectivities readily constrains the evolution of host-range shifts even when the novel host has a relatively small competitive effect on the originally exploited host (Figure 4a). Broadly similar trends emerge when the pathogen is able to infect both hosts (\( \beta_{A,\nu} = \beta_{A,M} \)), but pathogen strains differ in their relative virulence among host types (Figure 4b).

We next explore when pathogen virulence \( \lambda \) in the two host types is subject to a trade-off, but the burst size \( b_{\nu} \) of the pathogen in a host species inversely depends, in turn, on its virulence in that host. We find that whether a trade-off between pathogen virulence and burst size constrains the evolution of host-range shifts depends on the effect \( \alpha_{A,\nu} \) of inter-host competition on the novel hosts (Figure 4c–e). Mutant pathogen strains that can exploit the novel host do so at the cost of their virulence to the ancestral host; however, if the virulence–burst size trade-off is very strong, they experience high burst sizes in the ancestral host. When novel hosts are rare (large), these pathogens are thus able to benefit from exploiting ancestral hosts, thereby facilitating host-range shifts. By contrast, when novel hosts are more abundant (smaller \( \alpha_{A,\nu} \)), these generalist pathogens remain constrained in their ability to exploit the novel hosts effectively due to their low virulence. The key result is that a transmission–virulence trade-off can constrain host-range shifts when competition on the novel host is lower and the novel host is more abundant—that is despite ecological conditions conducive to host-range shifts (Figure 4c–e).

Because model (1) tracks the dynamics of each pathogen genotype explicitly, we can characterize not only the average pathogen genotype, but also how the interplay between inter-host competition and constraints affect the higher-order moments of the pathogen’s genotypic distribution. In Figure 5, we illustrate how host community ecology and pathogen constraints affect the coefficient of variation among pathogen genotypes. We highlight two results. First, if the trade-off involves a single ecological trait across two hosts, then when competition is weak, low levels

![Figure 2](image-url)

**FIGURE 2** Effect of interspecific competition among hosts on the dynamics of pathogen host-range shifts, but where mutations in the specialist pathogen population exploiting the ancestral host can only result in specialist pathogens on the novel host. In all panels, black regions depict areas of parameter space where the resident equilibrium community is not viable (i.e., not all population densities of the resident community are positive and finite), dark grey regions are where host shifts do not occur, the light grey region is where specialists on the new host can evolve. (a) The mutant pathogen can exploit both hosts, but suffers reduced infectivity for both hosts \( \beta_{A,M} = \beta_{A,A} = 2.5 \times 10^{-2} \) relative to the ancestral pathogen \( \beta_{A,A} = 5 \times 10^{-2} \). (b) The mutant pathogen can infect and exploit both hosts equally well \( \beta_{A,M} = \beta_{A,A} = 5 \times 10^{-2} \), but suffers reduced virulence \( \lambda_{A,M} = \lambda_{A,A} = 10^{-4} \) relative to the ancestral host \( \lambda_{A,A} = 2 \times 10^{-4} \). (c) The trade-off between burst size and virulence results in the mutant pathogen having a higher virulence \( \lambda_{A,M} = 2 \times 10^{-3} \) but lower burst size \( b_{A,M} = 1,000 \) than the ancestral pathogen \( \lambda_{A,A} = 2 \times 10^{-5} \). \( b_{A,A} = 5,000 \). The remaining parameter values are as in Figure 1.
of antagonistic pleiotropy can reduce genetic variation within the pathogen population (Figure 5a,b). Second, the amount of antagonistic pleiotropy across hosts in virulence strongly affects the extent of genetic variability within the pathogen population following a host-range shift (Figure 5c–e). If antagonistic pleiotropy is strong, then genetic variability is retained in the pathogen population even when the virulence-burst size trade-off is strong and the competitive pressure on the new host is high (Figure 5c). By contrast, weakening antagonistic pleiotropy more readily selects for a pathogen population that can only exploit a novel host (Figure 5d,e). Finally, we found that despite differences in the composition of pathogen populations across trade-off strengths and host community ecology, only in the case of antagonistic pleiotropy in infectivity did we detect a substantial effect of variable trade-off strengths and competitive abilities on the long-term density of the novel hosts (Figure S3).

3.2.2 | Initially vulnerable host subject to weak inter-host competition

Next, we assessed the generality of the patterns we found by assuming the competitive effect $\alpha_{A\nu}$ of the new host $\nu$ on the ancestral host $A$ to be weak ($\alpha_{A\nu} = 0.05$). One important consequence of lowering this competitive pressure is that a specialist ancestor pathogen can more readily persist without evolution. Thus, we find that there are large quantitative differences from the case where the competitive effect $\alpha_{A\nu}$ was large (Figures 4–5 vs. 6–7). For instance, when the trade-off between infecting hosts $A$ and $\nu$ is weak, large shifts in host exploitation can only evolve when the competitive effect of the ancestral host on the new host is weak (Figure 6a), and, in contrast to when the competitive effect $\alpha_{A\nu}$ is large, only when the trade-off is also weak (lower right corner of Figures 4a vs. 6a). Moreover, unlike the case for when the competitive effect of the ancestral host is strong, when host-range
Why do some pathogen lineages exhibit broader host ranges than others? One possibility is that some pathogen populations are exposed to more hosts of a particular type in their environment, favouring adaptations to effectively exploit available hosts. When the relative availability of host types is governed by patterns of resource competition, among-host competition can be a major driver of host-range shifts in pathogens. Another possibility is that the severity of trade-offs inherent to the pathogen’s biology can account for differences across lineages. Antagonistic pleiotropy in the traits required to infect or exploit one host or the other appears common (Duffy et al., 2006; Caraco & Wang, 2008; Guyader & Burch, 2008; García-Arenal & Fraile, 2013; Caraco, Yousefi, & Wang, 2015), as are trade-offs between pathogen virulence, burst size and transmissibility (Ebert & Bull, 2003; Alizon & Van Baalen, 2005).

These two possibilities are not mutually exclusive. Here, we have sought to elucidate how the interplay between resource-mediated host competition and constraints inherent to the pathogen’s biology drive host-range shifts. Our results illustrate the centrality of pathogen pleiotropy in governing how host competition affects the evolution of range shifts. When interspecific host competition favours a previously unexploited host, pathogens may be under strong selection to exploit the more abundant host. However, we find trade-offs between pathogen virulence and burst size can mitigate...
the selective advantages for host shifts. Thus, when novel pathogens are first exposed to two closely related host species, as can occur, for example, during biological invasions, a lack of shared evolutionary history can result in no trade-offs in exploiting either host, thereby facilitating host-range shifts.

Under congruent ecological and evolutionary time-scales, our analyses reveal that a strong virulence–burst size trade-off can constrain host-range shifts when relaxed competition on the novel host can increase its density. By contrast, host-range shifts can still evolve when the relevant pathogen trade-offs are linear or concave (and hence more forgiving than when these trade-offs are convex). Furthermore, the interplay between host competition and any single trade-off is mediated by other trade-offs the pathogen faces. We showed that when there is little antagonistic pleiotropy in the pathogen’s virulence across the two host types, then host-range shifts can readily evolve even when the virulence–burst size trade-off is severe and the novel host suffers strong competitive pressure.

Our analyses of higher-order moments of the genotypic distribution within the pathogen population (Figures 5 and 7) also suggest some unanticipated ways in which constraints and host community ecology can interact to drive patterns of host-range shifts. Interestingly, for all scenarios our numerical results indicate the presence of a band across the trade-off parameter’s range at which genetic variation among pathogens is maximized. These results can suggest how likely host-range shifts are to be reversed. In regions of parameter space where pathogen variability is low but host-range shifts are likely to occur, subsequent shifts from the new host back to the old host are less likely than in regions of parameter space where pathogen variability is substantial. Thus, our results provide the first steps towards predicting how pathogens that vary in the strengths of their life-history constraints are likely to diversify differently based on the structure of their host communities.

Explaining and predicting when host-range shifts are likely to evolve among pathogens has broader applications in medicine, agriculture, conservation and public health, particularly in regard to managing emergent pathogens. Our modelling indicates comparative hypotheses that we feel could be fruitfully evaluated across well-studied pathogen lineages of clinical or economic importance (Niebergding & Olivieri, 2007). For instance, our analyses suggest that environments with severe interspecific host competition are conducive to selecting against host switching when the pathogen’s primary constraint is its ability to infect different hosts (upper right corners of Figures 4a and 6a). By contrast, when there is a trade-off between virulence and burst size, host switching can evolve when interspecific competition experienced by the novel host is severe (upper right corner of Figures 4c,d and 6c,d). These results could be tested in a factorial analysis exploring host-range diversification among pathogen lineages that vary in the key constraints, and that may also differ on whether they (or their ancestors) inhabited communities where host competition is either primarily symmetric or asymmetric (but see Jackson, 1999 for the inherent limitations of such an approach). A comparative approach examining host shifts among communities of potentially competing host species that comprise the sylvatic cycle of several emerging pathogens (e.g. primate communities hosting Chikungunya – Althouse et al., 2018) may be especially attractive, and our results could potentially help in prioritizing pathogen lineages and sylvatic host communities for monitoring. A focus on the role of competition in host-range shifts can also be useful in agricultural contexts, where agricultural plant hosts share considerable overlap in resource use as well as pathogens...
(e.g. millet and rice blast – Couch et al., 2005) and where invasive weeds may harbour novel diseases (Anderson et al., 2004). Comparing different life-history constraints among broad groups of plant pathogens may help identify which are prone to evolve to exploit crops, or to develop agricultural practices that mimic regions of asymmetric competition that prevent host shifting.

A further promising application of our theoretical results would be to experimentally manipulate either, or even both, the competitive
environment of hosts and the constraints the pathogen faces. Our qualitative predictions could be assessed by converting the gradients we analysed to an assay. The modelling approach we present could generate quantitative predictions based on observed parameters for model organisms (following approaches in, e.g., Levin, Stewart, & Chao, 1977; Joo et al., 2006; Hyman & Abedon, 2010). System-specific modelling and experimental research into how host ecology and pathogen pleiotropy affect host-range evolution in microcosms such as bacteria–bacteriophage systems will likely have important implications in understanding the structure and composition of microbiome communities (e.g., Manrique et al., 2016). Connecting our model to experimental work in eukaryotic viruses can also provide a more mechanistic understanding of the prerequisites for host stability in medically important viruses, such as vesicular stomatitis virus (e.g., Wasik, Muñoz-Rojas, Okamoto, Miller-Jensen, & Turner, 2016) which is used in oncolytic and anti-HIV therapy (Lichty, Power, Stojdl, & Bell, 2004) as well as in live vaccine development (e.g., Regules et al., 2015). We highlight both comparative and experimental tests of our model as fruitful directions towards elucidating broader patterns of host-range shifts.

ACKNOWLEDGEMENTS

This research was funded with a grant from the Yale Institute for Biospheric Studies, Program in Eco-Evolutionary Interactions and a Chair’s Fellowship from UCLA to K.W.O., NSF Grants DEB 1354053, 1343920 and 1556848 to D.M.P., NSF BEACON Center for the Study of Evolution in Action (No. 13-004443) to P.E.T. and a Complex Systems Scholar Award from the James S. McDonnell Foundation and NSF Grant DEB 1457815 to P.A.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTIONS

K.W.O. and P.A. conceived or designed the work; K.W.O. contributed to model development and analysis and drafted the article; K.W.O., P.A. and P.E.T. critically revised the article; and all authors gave final approval of the version to be published.

DATA AVAILABILITY STATEMENT

This manuscript does not use data.

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How to cite this article: Okamoto KW, Amarasekare P, Post DM, Vasseur DA, Turner PE. The interplay between host community structure and pathogen life-history constraints in driving the evolution of host-range shifts. Funct Ecol. 2019;33:2338–2353. https://doi.org/10.1111/1365-2435.13467