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The central role of host reproduction in determining the evolution of virulence in spatially structured populations

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ABSTRACT

A substantial body of work has shown that local transmission selects for less acute, 'prudent' parasites that have lower virulence and transmission rates. This is because parasite strains with higher transmission rates 'self-shade' due to a combination of genetic correlations (self: clustered related parasite strains compete for susceptible individuals) and ecological correlations (shade: infected individuals clustering and blocking transmission). However, the interaction of ecological and genetic correlations alongside higher order ecological effects such as patch extinctions means that spatial evolutionary effects can be nuanced; theory has predicted that a relatively small proportion of local infection can select for highest virulence, such that there is a humped relationship between the degree of local infection and the harm that parasites are selected to cause. Here, we examine the separate roles of the interaction scales of reproduction and infection in the context of different degrees of pathogenic castration in determining virulence evolution outcomes. Our key result is that, as long as there is significant reproduction from infected individuals, local infection always selects for lower virulence, and that the prediction that a small proportion of local infection can select for higher virulence only occurs for highly castrating pathogens. The results emphasize the importance of demography for evolutionary outcomes in spatially structured populations, but also show that the core prediction that parasites are prudent in space is reasonable for the vast majority of host-parasite interactions and mixing patterns in nature.

1. Introduction

The evolutionary persistence of pathogens which cause severe host mortality is a key question for evolutionary biologists, more widely motivated by the burden infectious diseases cause for society (Froissart et al., 2010; Jones et al., 2008; Lambrechts and Scott, 2009). Classic theory in much of ecological and evolutionary biology, including work on parasite ecology and evolution, assumes that populations are homogenous; studies assume the 'mean-field' such that populations are completely mixed, and interactions are essentially random. However, real populations are structured, for example simply due to individuals closer in space interacting more often. We know that local interactions leading to strong spatial structuring within populations can impact host and pathogen evolution due to a combination of ecological clustering (infected individuals tend to be near to each other) and genetic clustering (interactions are more likely to occur with related individuals leading to kin selection) (Lion and Boots, 2010). There is a particularly rich body of theory exploring how spatial structure impacts the evolution of parasite virulence (Boots and Sasaki, 1999; Boots, 2000; Haraguchi and Sasaki, 2000; Kamo et al., 2007; Kamo and Boots, 2006; Lion and Boots, 2010; Lion and Gandon, 2015; Rand et al., 1995; Webb et al., 2013a, 2013b, 2007a, 2007b) detailing the compelling result that highly local interactions lead to a lower evolutionarily stable strategy (ESS) virulence when compared to well-mixed systems with 'global' infection. This result can be understood intuitively because parasite strains with higher transmission rates 'self-shade' due to genetic correlations (self) – clustered related parasite strains compete for susceptible individuals – and ecological correlations (shade) - infected individuals clustering and blocking transmission. This observation that spatial mixing selects for higher virulence also has notable empirical support (Boots and Mealor, 2007; Kerr et al., 2006; Szilágyi et al., 2009).

However, more nuanced predictions have also emerged from this theoretical body because the interaction of selective pressures, from ecological and genetic correlations, have different selective

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outcomes when infection occurs both locally and globally (Kamo et al., 2007; Kamo and Boots, 2006). In particular, Kamo et al. (2007) found that when they assumed a classic saturating trade-off between transmission rate and virulence such that there is an optimal level of transmission and virulence in mixed populations (Alizon et al., 2009; Alizon and Michalakis, 2015; Anderson and May, 1982; Ewald, 1993, 1987; Read, 1994) there was still selection for low virulence with high proportions of local transmission, but that a small proportion of local infections can select for higher virulence compared to a fully mixed system (Kamo et al., 2007; Lion and Boots, 2010; Webb et al., 2013b, 2013a). Therefore, as infection changes from completely global to completely local transmission, virulence shows a humped shaped relationship with a peak virulence at intermediate levels of spatial structure, higher than that which maximizes R_0 in the mean-field, and a minimum below the mean field optima once infections are predominantly local (Kamo et al., 2007). It is important to understand how general this result is given that it suggests that spatial structure may increase as well as decrease disease virulence under different circumstances.

Spatial theoretical work has successfully used a coupling of pair-approximations (Matsuda et al., 1992) and adaptive dynamics (Geritz et al., 1998; Mágori et al., 2005) to develop an approximate spatial analytical prediction of evolutionary outcomes (Kamo et al., 2007; Kamo and Boots, 2006; Webb et al., 2013b, 2013a). However, in order to increase analytical tractability, this body of theory makes varied and numerous simplifying assumptions concerning the biology it approximately models. One prevalent assumption across this body of studies is that infected individuals do not reproduce, infection by a parasite is fully castrating (Best et al., 2011; Boots and Sasaki, 1999; Boots, 2000; Haraguchi and Sasaki, 2000; Kamo et al., 2007; Kamo and Boots, 2006; Lion and Gandon, 2015; Webb et al., 2013b, 2013a, 2007a), with few exceptions (Débarre et al., 2012; Webb et al., 2007b). This assumption improves analytical tractability, but a key characteristic of parasites (as opposed to predators) is that infected individuals persist as ecological agents, occupying space and can reproduce (or recover and then reproduce). Webb et al. (2013a), Webb et al. (2013b) showed that recovery reduces the impact of spatial structure on evolutionary outcomes, but reproduction from infected individuals is yet to be examined in the context of virulence evolution and evolutionary theory.

Castration by parasites clearly occurs in real biological systems, where it is typically understood to be an alternative strategy where infected host mortality is lowered but overall host fitness costs still remain very high, often to the parasite's overall benefit (O'Keefe and Antonovics, 2002). Although it is also likely that most parasitic infections reduce host reproduction to some degree, for example in correlation with virulence due to resource theft (Heins et al., 2010); complete castration of infected hosts is relatively rare (but not unknown). The prevalence of assumptions around infected host reproduction in the spatial parasite evolutionary theory therefore needs to be interrogated, and calls to better account for host demography (including reproduction) in this research vein have been previously made (Lion and Boots, 2010; Messinger and Ostling, 2013). Moreover it is important to better understand the linked role that the assumptions about local reproduction may have on parasite evolutionary outcomes. Given the likely impact of local reproduction from infected individuals on both ecological and genetic correlations, there are potentially important implications for the overall evolutionary outcomes.

Here we develop approximate theory to better understand how relaxing this castration assumption impacts the evolutionary outcomes of spatial models of parasite virulence. We adapt established theory to allow infected individuals to reproduce, sacrificing some analytical tractability and numerically solving our pair equations. We test whether previous findings relating spatial structure to virulence evolution are independent of this assumption and begin to explore how potential reproduction by infected individuals (varying degrees of castration) may affect virulence evolution in spatially structured populations.

2. Methods and model descriptions

We construct two models: one to describe the dynamics of a monomorphic resident pathogen strain and one to describe the local dynamics of a rare mutant pathogen strain. We approximate a regular lattice where each site is in state σ, and pairs of sites are in state $\sigma\sigma'$, where $\sigma \in \{0, S, I, J\}$; '0' represents an empty site, 'S' a site with a susceptible host, 'I' a site with a resident-strain infected and infectious host, and 'J' a site with a mutant-strain infected and infectious host. We vary independently the proportion of reproduction and/or infection occurring locally (between neighbouring sites only) and globally (between any two sites). We vary the amount of reproductive potential an infected host represents compared to a susceptible host (we vary degree of castration caused by infection). Parameters are detailed in Table 1.

As P_σ and $P_{\sigma\sigma'}$ represent proportions of sites and proportions of pairs of sites, and $P_{\sigma\sigma'} \equiv P_{\sigma'\sigma}$, the following definitions hold where $\sigma \in \{0, S, I, J\}$

$$\sum_{\sigma} P_\sigma = 1$$

$$\sum_{\sigma} P_{\sigma\sigma} + \sum_{\sigma \neq \sigma'} 2P_{\sigma\sigma'} = 1$$

$$\sum_{\sigma} q_{\sigma|\sigma'} = 1 for \sigma' \in \{0, S, I, J\}$$

$$q_{\sigma|\sigma'} = P_{\sigma\sigma'}/P_{\sigma'}$$

In constructing the models, we approximate conditional probabilities, where $q_{\sigma|\sigma'\sigma''}$ represents the conditional probability of a site being in state σ in the neighbourhood of the σ' site of a $\sigma'\sigma''$ pair. We use an ordinary pair approximation following Matsuda et al. (1992), where $q_{\sigma|\sigma'\sigma''} \approx q_{\sigma|\sigma'}$. This conditional probability that given a focal site is in state σ' it has a neighbor in state σ is defined as $q_{\sigma|\sigma'} = P_{\sigma\sigma'}/P_{\sigma'}$. An illustrative example of this approximation is as follows, where

$$\dot{P}_{II} = 2\left[\beta G_T P_I P_{SI} + \beta(1 - G_T)(\theta + (1 - \theta)q_{I|SI})P_{SI} - (b + \alpha)P_I\right]$$

becomes

$$\dot{P}_{II} = 2[\beta G_T P_I P_{SI} + \beta(1 - G_T)(\theta + (1 - \theta)P_{SI}/P_S)P_{SI} - (b + \alpha)P_I]$$

Table 1
Variables used in ode system models, where $z \in \{I, J\}$ and $\sigma \in \{0, S, I, J\}$.

Variable	Description
a	Reproduction rate
b	Natural mortality (natural death rate)
C	Infected reproduction potential ($0 \leq C \leq 1$)
α_z	Virulence of strain z (additional mortality due to infection by strain z)
β_z	Transmission rate of strain z
θ	Inverse of number of neighbours (=¼ for a regular lattice)
G_R	Proportion of global reproduction
G_T	Proportion of global transmission
P_σ	Proportion of sites in state σ
$P_{\sigma\sigma'}$	Proportion of pairs of nearest-neighbour sites in state $\sigma\sigma'$, where $P_{\sigma\sigma'} \equiv P_{\sigma'\sigma}$
$q_{\sigma\|\sigma'}$	Conditional probability that for a site in state σ' a neighbouring site will be in state σ

Accordingly, the following system of ordinary differential equations describes the endemic state (see Table 1) of a single resident strain, where $\dot{P}_x$ denotes a time derivative of P_X.

$$\dot{P}_0 = (b+\alpha)P_I + bP_S - aG_RP_SP_0 - CaG_RP_IP_0 - a(1-G_R)(P_{S0}/P_0)P_0 - Ca(1-G_R)(P_{I0}/P_0)P_0$$

$$\dot{P}_S = aG_RP_SP_0 + CaG_RP_IP_0 + a(1-G_R)(P_{S0}/P_0)P_0 + Ca(1-G_R) \times (P_{I0}/P_0)P_0 - bP_S - \beta G_TP_IP_S - \beta(1-G_T)(P_{S0}/P_S)P_S$$

$$\dot{P}_I = \beta G_TP_IP_S + \beta(1-G_T)(P_{SI}/P_S)P_S - (b+\alpha)P_I$$

$$\dot{P}_{00} = 2[bP_{S0} + (b+\alpha)P_{I0} - aG_RP_SP_{00} - CaG_RP_IP_{00} - a(1-G_R)(1-\theta)(P_{S0}/P_0)P_{00} - Ca(1-G_R)(1-\theta)(P_{I0}/P_0)P_{00}]$$

$$\dot{P}_{S0} = aG_RP_SP_{00} + CaG_RP_IP_{00} + a(1-G_R)(1-\theta)\left(\frac{P_{S0}}{P_0}\right)P_{00} + Ca(1-G_R)(1-\theta)(P_{I0}/P_0)P_{00} + (b+\alpha)P_{SI} + bP_{SS} - bP_{S0} - aG_RP_SP_{S0} - CaG_RP_IP_{S0} - a(1-G_R)(\theta+(1-\theta)P_{S0}/P_0)P_{S0} - Ca(1-G_R)(1-\theta)(P_{I0}/P_0)P_{S0} - \beta G_TP_IP_{S0} - \beta(1-G_T)(1-\theta)(P_{SI}/P_S)P_{S0}$$

$$\dot{P}_{I0} = \beta(1-G_T)(1-\theta)(P_{SI}/P_S)P_{S0} + \beta G_TP_IP_{S0} + bP_{SI} + (b+\alpha)P_{II} - (b+\alpha)P_{I0} - aG_RP_SP_{I0} - a(1-G_R)(1-\theta)(P_{S0}/P_0)P_{I0} - CaG_RP_IP_{I0} - Ca(1-G_R)(\theta+(1-\theta)P_{I0}/P_0)P_{I0}$$

$$\dot{P}_{SS} = 2[aG_RP_SP_{S0} + CaG_RP_IP_{S0} + a(1-G_R)(\theta+(1-\theta)P_{S0}/P_0)P_{S0} + Ca(1-G_R)(1-\theta)(P_{I0}/P_0)P_{S0} - bP_{SS} - \beta G_TP_IP_{SS} - \beta(1-G_T)(1-\theta)(P_{SI}/P_S)P_{SS}]$$

$$\dot{P}_{SI} = aG_RP_SP_{I0} + CaG_RP_IP_{I0} + a(1-G_R)(1-\theta)(P_{S0}/P_0)P_{I0} + Ca(1-G_R)(\theta+(1-\theta)P_{I0}/P_0)P_{I0} + \beta G_TP_IP_{SS} + \beta(1-G_T)(1-\theta) \times (P_{SI}/P_S)P_{SS} - bP_{SI} - (b+\alpha)P_{SI} - \beta G_TP_IP_{SI} - \beta(1-G_T)(\theta+(1-\theta)P_{SI}/P_S)P_{SI}$$

$$\dot{P}_{II} = 2[\beta G_TP_IP_{SI} + \beta(1-G_T)(\theta+(1-\theta)P_{SI}/P_S)P_{SI} - (b+\alpha)P_I]$$

We assess whether a mutant strain J can invade a resident strain I. We numerically solve the single-resident strain ode system (above) to establish an endemic equilibrium. We then model a mutant strain J which has a different virulence (α_J) and transmission (β_J) to the resident strain, where virulence and transmission are governed by a relationship of the form $\beta = D \cdot \ln(\alpha + 1)$ where D is a positive scalar. Accordingly, β is a saturating function of α, used elsewhere in equivalent theoretical modelling (Hoyle et al., 2008). As has been previously established (Boots and Sasaki, 1999; Lion and Gandon, 2015), strain J is able to invade if $\lambda(J|I) > 0$ where $\lambda(J|I)$ is defined as follows:

$$\lambda(J|I) = \left(\frac{b+\alpha_I}{\beta_I} - \frac{b+\alpha_J}{\beta_J}\right) + (1-G_T)\left(\hat{q}^*_{S|J} - q^*_{S|I}\right)$$

and $q^*_{S|I}$ is the endemic equilibrium density of susceptible sites in the local neighbourhood of an infected individual for the single resident strain. $\hat{q}^*_{S|J}$ is the quasi-equilibrium density of susceptibles in the local neighbourhood of the invading mutant early on in its invasion. The rationale for this quasi-equilibrium approximation has been discussed in previous studies (Boots and Sasaki, 1999; Lion and Gandon, 2015), and justified by the generalisation that early on in a mutant's invasion in a large population it remains globally rare, and so global dynamics change much more slowly from the single-strain endemic equilibrium compared to the dynamics in the local neighbourhood of the invading rare mutant.

Accordingly, we assess the quasi-equilibrium state by approximating all pair densities and conditional probabilities which do not include the rare mutant J as constant values taken from the endemic equilibrium (denoted by a*). We examine the rates of change of $q_{\sigma/J}$ for $\sigma \in \{0, S, I, J\}$ and approximate $P_J \approx 0$. This yields the following system of ordinary differential equations:

$$\dot{q}_{0|J} = bq_{S|J} + (b+\alpha_I)q_{I|J} + (b+\alpha_J)q_{J|J} - aG_RP^*_Sq_{0|J} - CaG_RP^*_Iq_{0|J} - a(1-G_R)(1-\theta)(P^*_{S0}/P^*_0)q_{0|J} - Ca(1-G_R)(1-\theta)(SPI0/P^*_0)q_{0|J} - Ca(1-G_R)\theta q_{0|J} + \beta_J(1-G_T)(1-\theta)(P^*_{S0}/P^*_S)q_{S|J} + \beta_JG_TP^*_{S0} - \beta_J(1-G_T)q_{S|J}q_{0|J} - \beta_JG_TP^*_Sq_{0|J}$$

$$\dot{q}_{S|J} = aG_RP^*_Sq_{0|J} + CaG_RP^*_Iq_{0|J} + a(1-G_R)(1-\theta)(P^*_{S0}/P^*_0)q_{0|J} + Ca(1-G_R)(1-\theta)(P^*_{I0}/P^*_0)q_{0|J} + Ca(1-G_R)\theta q_{0|J} - bq_{S|J} - \beta_IG_TSPIq_{S|J} - \beta_I(1-G_T)(1-\theta)(P^*_{SI}/P^*_S)q_{S|J} + \beta_J(1-G_T)(1-\theta)(P^*_{SS}/P^*_S)q_{S|J} + \beta_JGTP^*_{SS} - \beta_J(1-G_T)\theta q_{S|J} - \beta_J(1-G_T)q_{S|J}q_{S|J} - \beta_JG_TP^*_Sq_{S|J}$$

$$\dot{q}_{I|J} = \beta_IG_TP^*_Iq_{S|J} + \beta_I(1-G_T)(1-\theta)(P^*_{SI}/P^*_S)q_{S|J} - (b+\alpha_I)q_{I|J} + \beta_J(1-GT)(1-\theta)(P^*_{SI}/P^*_S)q_{S|J} + \beta_JG_TP^*_{SI} - \beta_J(1-G_T)q_{S|J}q_{I|J} - \beta_JG_TP^*_Sq_{I|J}$$

$$\dot{q}_{J|J} = 2\beta_J(1-G_T)\theta q_{S|J} - (b+\alpha_J)q_{J|J} - \beta_J(1-G_T)q_{S|J}q_{J|J} - \beta_JG_TP^*_Sq_{J|J}$$

Having numerically solved this ode system, we can substitute $\hat{q}^*_{S|J}$ into the invasion criteria $\lambda(J|I) > 0$ (see above). Using this approach across all values of α we can generate pairwise invasibility plots (PIPs) to assess if any value of α yields an evolutionarily singular strategy (ESS) (Geritz et al., 1998) for a given set of parameters; an example is shown in Fig. 1. We computationally examine

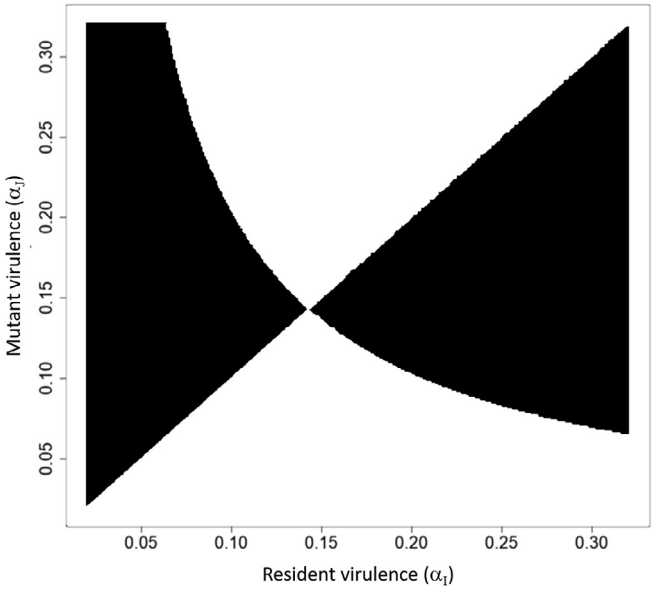

Fig. 1. Example pairwise invasibility plot (PIP) with ESS (and CSS) virulence $\alpha = 0.143$. Parameters values used to generate this plot are $G_T = 0.7$, $G_R = 0.3$, $C = 0.9$, with remaining parameters taken used universally unvaried elsewhere in this study ($a = 5$, $b = 0.01$, $\theta = 1/4$, $D = 5$). For this plot, alpha (α) is approximated to a precision of 0.001. The black contour represents positive growth rate for a mutant strain invading a resident.

these pairwise invasibility plots to extract the approximate ESS values for many parameter combinations. This allows us to compare how changes in ecological parameters affect the ESS virulence (α) for an evolving pathogen. We investigate how altering two spatial parameters (global transmission G_T and global reproduction G_R) and altering infected reproduction (C) affects the ESS virulence of the pathogen, where $0 \leq \{G_T, G_R, C\} \leq 1$.

We compare the results of the numerically solved pair approximated models above to equivalently parameterised stochastic simulations. Simulations were written in C++ based on and informed by previous simulations from Kamo et al. (2007) and other subsequent studies (for example, see supplemental material in Best et al. (2011)). Briefly, the simulation uses an explicit lattice (here, 400 × 400 sites) where ecological processes (birth, infection, and death) occur stochastically and either globally or locally, at rates in part defined by the variable global parameters (G_T, G_R, and C) and the evolution of the pathogen's phenotype (α and β) as above, as well as the real-time ecology of the global and local densities of empty (0), susceptible (S), and infectious (I) sites on the lattice. Simulations were run for 20,000 generations where each generation is taken to be N ecological events where N is the size of the lattice (here, 1.6×10^5); this is consistent with the previous studies we set out to compare our results against. We used a pathogen phenotype resolution of 50 possible α, β pair values and a mutation rate (chance of mutation per new infection) of 0.001. Each parameter combination was run with 10 technical replicates, with our three parameters of interest (G_T, G_R, and C) sampled at a step-resolution of 0.125 (729 unique parameter combinations total, 7290 simulations run).

3. Results

We find that across our range of varied parameters ($0 \leq \{G_T, G_R, C\} \leq 1$), we recover evolutionarily singular strategies in every case, allowing us to characterise how these changing ecological parameters affect ESS virulence. We present here example plots for a subset of parameter value combinations which capture our main findings. Across the study, the stochastic simulations agreed qualitatively with the analytical model, broadly to a very high degree. This suggests that pairwise rather than higher order interactions are critical to the evolutionary outcomes. The ESS virulence values from the simulations were universally higher than those from the analytical model for every parameter combination examined, a phenomenon which has been discussed in detail elsewhere (Webb et al., 2013b).

In Fig. 2 we recover the well-established result that reducing local infection (increased mixing of transmission) increases ESS virulence; the magnitude of this effect is highest when pathogens are strongly castrating (Fig. 2a–d). We further recover that in specific cases, ESS virulence is highest for well-mixed, but not entirely global, infection (see Fig. 2a and compare to Kamo et al. (2007) and others (Lion and Boots, 2010; Webb et al., 2013b)). By varying the strength of castration and the proportion of local reproduction we are now able to examine when we see this 'humped' relationship. We show that the phenomenon of low levels of local transmission leading to higher virulence manifests only when reproduction is almost entirely local and infected individuals almost never reproduce. The hump is lost when there is significant reproductive dispersal or reproduction by infected hosts.

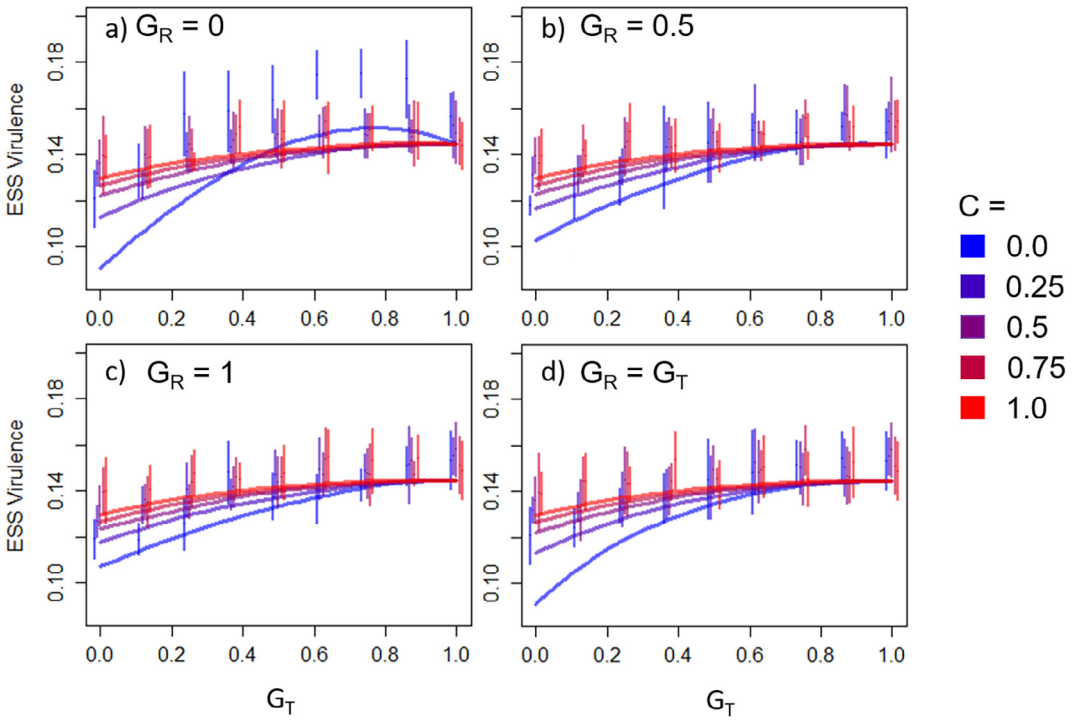

Fig. 2. Example panels showing relationship between degree of spatial structuring of infection process (G_T, x-axis) and ESS parasite virulence (α, y-axis) across five levels of infected reproduction for four reproductive spatial structuring (G_R) scenarios. Where 'C = 0', no infected reproduction is possible (the parasite is fully castrating). Panels a-c show the effect of increasingly mixed infection processes for fully local (a), partially local (b) or fully global (c) reproduction across five castration levels. Panel d) shows the same relationship but in the special instance where reproduction and transmission are a single 'mixing' parameter. Panel a) where C = 0 recovers the characteristic 'humped' result from Kamo et al. (2007) and others (Lion and Boots, 2010; Webb et al., 2013b). Solid curves represent results from the mathematical model above, interpolated between many numerically solved virulence ESS values where alpha (α) is approximated to a precision of 0.00015; vertical bars represent results from the stochastic simulations plotted as mean virulence ± S.E. across replicate simulations. Non-varied parameters used universally unvaried elsewhere in this study (a = 5, b = 0.01, θ = ¼, D = 5).

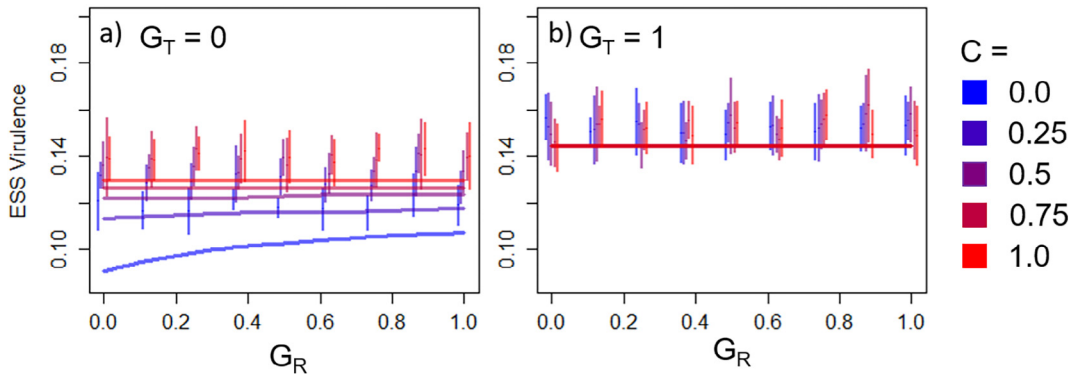

Fig. 3. Example panels showing relationship between degree of spatial structuring of reproduction process (G_R, x-axis) and ESS parasite virulence (α, y-axis) across five levels of infected reproduction (C) for the extreme instances of fully local (a) and fully global (b) transmission scenarios; intermediate G_T scenarios show slow convergence of the sets of relationships in a) to those in b). Solid curves represent results from the mathematical model above, interpolated between many numerically solved virulence ESS values where alpha (α) is approximated to a precision of 0.00015; vertical bars represent results from the stochastic simulations plotted as mean virulence ± S.E. across replicate simulations. Non-varied parameters used universally unvaried elsewhere in this study (a = 5, b = 0.01, θ = ¼, D = 5).

We examine in Fig. 3, in more detail, the effect of decreasing the spatial structuring of reproduction (the effect of increased host reproductive dispersal) on ESS virulence. Increased dispersal generally has a weak effect on ESS virulence with local parasite transmission (as can also be inferred comparing across Fig. 2a–c) unless the pathogen is highly castrating (Fig. 3a). Spatial structuring of reproduction does not by itself influence the evolution of parasite virulence if transmission is global (Fig. 3b). It is interesting to note that in Fig. 3a we show the only instance where our stochastic simulations do not qualitatively mirror the finding of the numerically solved ode systems. This suggests that a major component of the effect of local reproduction on the evolution of virulence in castrating disease may be due to higher order spatial effects such as 'patchiness' that is not captured in pairwise analysis (Webb et al., 2013b). For example, the pair-approximations may underestimating the local densities of hosts experienced by evolving pathogens when host populations are in sparsely distributed dense aggregations resulting from entirely local ecological processes.

We show in Fig. 4 (and as can also be inferred from each panel in Fig. 2) that higher rates of castration select for lower ESS virulence ESS values with local transmission. The magnitude of this effect on changing ESS virulence in the fully local system (Fig. 4a and d) is comparable to that of the effect of reducing spatial structuring of infection (Fig. 2), however the effect strength decreases with only moderate increases in mixing of the system, and any effects of castration on virulence disappear entirely when the system is fully mixed (Fig. 4a–d). Fig. 4b shows again that very high castration of infected individuals can instead lead to the highest ESS virulence when infection is only partly local and reproduction is entirely local. We explore this instance in the Appendix (Fig. A1) – but note here that it is a replotting of the phenomenon of the 'hump' shown in Fig. 2a, recovered from Kamo et al. (2007).

4. Discussion

Our key result is that the important prediction that local infection (increased spatial structuring or reduced system mixing) selects for lower ESS virulence in a pathogen is independent of assumptions of whether infected individuals can reproduce in a 0SI system, increasing its putative biological realism. We show that the 'virulence hump' first predicted by Kamo et al (2007), where virulence first increases before decreasing as infection becomes more local, only manifests when reproduction is local and where there is very little or no reproduction from infected individuals. The prediction of higher virulence than the mean-field with low levels of mixing therefore only applies to highly castrating pathogens in sessile hosts with very local reproduction, as might be present in for instance some anther-smut systems (Bruns et al., 2017). We show that the effect of host reproductive dispersal has very little effect on parasite ESS virulence, with no support for a role in determining parasite evolution if infected individuals are even moderately fecund, or if the infection process isn't entirely local. Finally, we show that castration of infected individuals limits ESS virulence at a magnitude similar to the effect of spatial structuring of transmission, however this is only true for systems with mostly local infection. Therefore reduced fecundity in infected individuals selects for a lower virulence when there is local infection, but in moderately- or well- mixed systems has little or no effect on ESS virulence for a pathogen, in an equivalent way to its role in mean-field theory (Jaenike, 1996; O'Keefe and Antonovics, 2002). Taken as a whole, our results show that parasites and pathogens are typically 'prudent' in space with increasingly local infection selecting for lower virulence (Boots and Sasaki, 1999), and that the size of this effect is sensitive the ecology of host reproduction.

We recover the key qualitative finding as previous work that increasing rates of global transmission select for higher pathogen virulence, and build on this to show that this is still found when relaxing strong assumptions around infected reproduction. In this sense, we find that the core statement that reduced spatial structure selects for increased virulence is applicable to more biologically realistic host ecology. This is crucial for informing evolutionary management of infectious diseases, as in a 'shrinking world' of reduced spatial structure (Hanski, 2005; Janelle, 1973), we may select for hypervirulent pathogen strains with obvious risks for human health, agriculture, and wildlife (Boots and Sasaki, 1999). The phenomena of a virulence 'hump' (Fig. 2), where populations with some small amount of local infection select for more virulent pathogens, has however also been found in multiple theoretical studies (Kamo and Boots, 2006; Lion and Boots, 2010; Webb et al., 2013a). We recover this effect, but show that it only occurs when reproduction is a predominantly local process and mostly from uninfected individuals. This builds on earlier work that highlights the importance of demography in critically determining the evolutionary outcomes in spatial models (Webb et al., 2007a; Lion and Boots, 2010; Messinger and Ostling, 2013). For example, we show that in non-spatial models the evolutionary outcomes are not affected by any assumptions of infected castration, but in spatial models it is critical to the outcome.

We have shown that the humped virulence relationship occurs only when reproduction is predominantly local. It is also favored by low reproduction from infected individuals. This occurs because

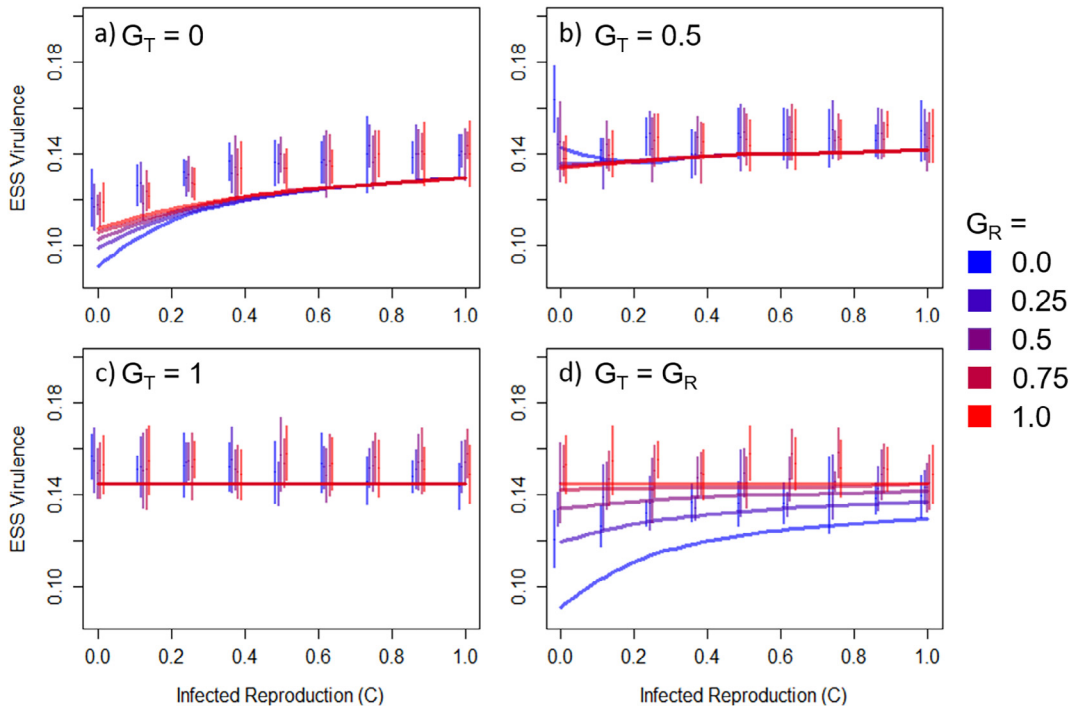

Fig. 4. Example panels showing relationship between infected reproduction ('C', x-axis) and ESS parasite virulence (α, y-axis) across five levels of reproductive spatial structuring (G_R) for four transmission spatial structuring (G_T) scenarios. Note increasing x-axis values relate to lower degrees of castration; C = 0 is the most castrating instance where infected reproduction = 0 (infected individuals cannot reproduce at all). Panels a-c show the effect of reducing castration for fully local (a), partially local (b) or fully global (c) transmission across five spatial structuring of reproduction levels. Panel d) shows the same relationship but in the special instance where reproduction and transmission are a single 'mixing' parameter. Solid curves represent results from the mathematical model, interpolated between many numerically solved virulence ESS values where alpha (α) is approximated to a precision of 0.00015; vertical bars represent results from the stochastic simulations plotted as mean virulence ± S.E. across replicate simulations. Non-varied parameters used universally unvaried elsewhere in this study (a = 5, b = 0.01, θ = ¼, D = 5).

with local reproduction from only susceptible individuals, available hosts are likely to be very patchy. When infection always occurs globally, a pathogen is always able to 'find' available susceptible individuals such that the very patchy nature of their hosts is not relevant. When there is a small amount of local transmission, the highly clumped nature of the susceptible population means that rapid transmission is favored to exploit these clumps efficiently when infection occurs in a new clump. Such reasoning may lead to sub-optimally high rates of resource consumption (virulence) on behalf of the pathogen as described empirically in Kerr et al. (2006). The existence of inter-patch (or approximated, inter-pair) dynamics, which are absent from mean-field or fully-local models, may therefore underpin the elevated-virulence ESS strategy we find (Pohley and Thomas, 1983). Effectively, in the mean field, there is but 'one large patch', and in the fully local system, each pathogen transmits within its own patch in isolation. The former and latter may be predisposed to optimization of virulence strategies, but not the intermediate degrees of long-distance dispersal, whereby invasion of 'foreign-patch' strains mandates higher virulence to more rapidly deplete patches of hosts when encountered and successfully compete for others at a distance. We show that without local reproduction and castration, these patch like processes are not strong enough to lead to increase the ESS virulence above that of the mean-field.

We find that the impact of local transmission on absolute ESS virulence, is very sensitive to whether infected individuals can reproduce (castration) but not especially sensitive to whether reproduction is local (Fig. 2). In particular, the largest impacts on ESS virulence are observed under scenarios with reproduction by exclusively uninfected individuals. This makes sense because limited reproduction from infected individuals in a very local system reduces the local supply of new susceptible individuals next to infected ones and stronger ecological correlations and 'shading' (infecteds are surrounded by infecteds). It is important to note that the strong empirical evidence demonstrating the phenomenon that reduced spatial structure selects for more virulent pathogens (Boots and Mealor, 2007; Kerr et al., 2006; Szilágyi et al., 2009) was found in systems with castrating parasites, where reproduction was not necessarily local. It may be unsurprising therefore, given the empirical challenges associated with empirically demonstrating theoretical predictions of parasite evolution along a trade off (Cressler et al., 2016), that these demonstrations of spatial structure affecting virulence are from systems with no apparent reproduction by infected individuals, where we would expect the strongest effect of transmission structure in determining ESS virulence.

While we find that castration limits virulence in spatially structured systems (Fig. 4), once a moderate degree of mixing occurs, assumptions around castration have diminishing (or, in the case of the mean field, no) effect on ESS virulence. The classic 'mean-field' framework is therefore less dependent on certain assumptions concerning processes of reproduction. For some natural systems, close to well-mixed populations are realistic; for example, certain infectious agents existing in the environment in aquatic systems, such as the well-studied *Daphnia* (Ebert et al., 2004; Jensen et al., 2006) system where known pathogens are indeed castrating, or for increasingly studied marine viruses (Middelboe and Brussaard, 2017). Hopefully, this knowledge of when assumptions around infection and castration are most likely to seriously affect outcomes will help inform more tailored theory for specific infectious disease modelling. Never-the-less, the magnitude of the effect of castration on virulence evolution in highly structured systems is significant (Fig. 4a), this is important given the rich body of work examining how pathogens may use, abuse, or be constrained

by castration in (co-) evolutionary systems (e.g. Ashby and Gupta, 2014; Best et al., 2009; Débarre et al., 2012; Ebert et al., 2004; Hartikainen and Okamura, 2012; Jensen et al., 2006).

We show that local reproduction and local transmission do not have the same impact on the evolution of virulence. Local reproduction only appears to significantly impact virulence evolution when infected individuals do not reproduce (Fig. 3) (Boots, 2000). Biological analogues of such a 'local infection, global dispersal' systems include holometabolous insects, and sessile organisms with dispersing progeny such as many plants or corals. Notably, both corals and plants have been highlighted as areas of interest for the study of the evolution of castrating pathogens (Hartikainen and Okamura, 2012; Vijayan et al., 2017). Overall however, the fact that reproduction distance only matters when the pathogen is castrating arguably simplifies our understanding of 'small worlds' and virulence evolution, in that for most systems where castration is not apparent, only changing the rates of global infection matters to the outcome. This aligns conceptually with some observations made in spatially explicit 0SIR systems in Webb et al. (2007a).

Our theoretical understanding of the evolution of parasites in spatial populations would benefit from further examination of the impact of ecological parameters such as natural mortality and birth rate. In this case, in order to maintain equivalence to previous studies, a 'long-lived' host is modelled. Speculatively, this long-lived host may be driving some of the critical importance of the assumptions around castration. Clearly a clustering of long-lived hosts all infected with a castrating pathogen 'choke out' opportunity for new infections and therefore without a high mortality, no space becomes empty for new susceptible individuals to be born into. Self-shading (Boots, 2000; Messinger and Ostling, 2013) could plausibly be more important for long-lived hosts as they inherently limit demographic turnover. Linked to this is the evidence that parasitic castration selects for more rapid (shorter lived) host life-history strategies (Lafferty and Kuris, 2009), which would increase demographic turnover, making long-lived castrated 'host' potentially rare in nature. Further speculation of these biological underpinnings requires discussion of the limits of the numerical approach used here, as well as better integration with other well studied biological processes using this framework.

Our approach is limited to characterizing evolutionarily stable ESS (in fact continuously stable CSS) points, rather than being able to confirm whether this is also strictly an optimum virulence. We have not attempted a formal examination of the environmental feedbacks (Govaert et al., 2019) in the system using the pair approximation equations, although this may be possible. This analysis would give us a deeper understanding of the fundamental processes that lead to the outcomes that we see. Despite our numerical approximations studying only CSS virulence values (which may or may not be optima, depending on the case at hand), these results should give the expected long term outcome of real-world evolution. This justifies usefulness of the current approach, and maintaining the plausibility of observing these trends in partially-structured empirical systems where both reproductive assumptions are met.

However, there remain gains to be made with theoretical approaches by pursuing closed-form analytical solutions to the ODE system we present here, and characterising the feedback environment in such a way as to also see if the 'hump' solutions are non-optima ESSs. Lion (2017) has recently pointed to the difficulty in incorporating spatial structuring into models which allow for insightful analytical solutions examining environmental feedback in adaptive dynamics approaches to studying the evolutionary ecology of infectious diseases. However, when such gains are made, we expect more insight into competition in patch (pairs) dynamics and long-distance access to new patches or partial-patches at intermediate levels of infection mixing with otherwise local and uninfected constraints on reproduction.

There are, additionally, expansions to be made from a biological perspective on how this theory paradigm is applied to pathogen evolution more broadly. Here, castration is modelled as a phenomenon separate to pathogen phenotype, interpretably determined by different host biology. However, other understandings of castration due to infection should be pursued in future. Maintaining the idea that castration is a host-driven phenomenon, it would be perhaps insightful to positively link castration to virulence. In its simplest form, this link can be understood from resource budgeting (Bonds, 2006) and nutrient theft – increased parasite burden sequesters more nutrients, reducing fecundity and increasingly mortality (Heins et al., 2010). More nuanced interpretations can also be argued, for example the biological phenomena of pariahship (Cremer et al., 2007) where the most visibly infected individuals, exhibiting more virulent symptoms, are avoided by other individuals including mates. While mating is not explicitly modelled here are abundant hermaphroditic species which require sexual reproduction, but do not have individuals categorisable into distinct sexual phenotypes, and are indeed infected by castrating pathogens (Lafferty and Kuris, 2009). We would not therefore forgo biological realism by pursuing a question relating to higher virulence leading to greater castration. It is equally interesting to consider castration as negatively correlated with virulence if we assume that castration and additional mortality are different pathogen strategies (Abbate et al., 2015; Jaenike, 1996; O'Keefe and Antonovics, 2002). Expanding this work to link transmission to both castration and additional mortality would provide insight into when castration is more costly to parasites compared to additional mortality and may raise questions of why we do not appear to observe infection-driven castration more commonly, beyond the selection on hosts to resist or tolerate 'castrating' parasites (Best et al., 2017).

In the context of host evolution, virulence is instead more broadly defined (and correctly so) as a loss of fitness resulting from infection (Abbate et al., 2015). Using this frame of thought, a completely castrating pathogen represents a total loss of fitness to the host, akin to an obligately lethal pathogen. The selection pressure on hosts to resist or tolerate this infection without succumbing to castration is therefore extremely strong (Best et al., 2009). This may account for the relatively low number of castrating pathogens. A clear next goal of spatial evolutionary theory should be to further interrogate the assumptions around reproduction and castration from the standpoint of host evolution. It is tempting to speculate that the castration assumption discussed throughout this manuscript may be much more important in determining evolutionary outcomes for host evolution (see Débarre et al., 2012) and host-parasite co-evolution (O'Keefe and Antonovics, 2002).

Overall, we show how the important finding that the reduced spatial structuring of transmission selects for more virulent pathogens is qualitatively consistent despite assumptions around host castration. Our work emphasizes the importance of host demography and assumptions about reproduction in determining the evolutionary outcomes in spatial host parasite models. Future work should therefore examine the impacts of host life history strategies as well as the epidemiological characteristics of the interaction in determining the role of spatial structure in the evolution of infectious disease.

Author contributions

L.J.B. & M.B. conceptualised the study. M.B. provided guidance for derivation of equations, computational work was undertaken

by L.J.B. L.J.B. drafted the first manuscript with both authors contributing substantially to the final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Evolutionarily Stable Strategy (ESS) values calculated both from numerically solved ordinary differential equation (ode) systems and from stochastic simulations will be deposited in an appropriate data repository upon this manuscript's acceptance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtbi.2021.110717.

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