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The impact of resource quality on the evolution of virulence in spatially heterogeneous environments

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ABSTRACT

Understanding the drivers of parasite evolution and in particular disease virulence remains a major focus of evolutionary theory. Here, we examine the role of resource quality and in particular spatial environmental heterogeneity in the distribution of these resources on the evolution of virulence. There may be direct effects of resources on host susceptibility and pathogenicity alongside effects on reproduction that indirectly impact host-parasite population dynamics. Therefore, we assume that high resource quality may lead to both increased host reproduction and/or increased disease resistance. In completely mixed populations there is no effect of resource quality on the outcome of disease evolution. However, when there are local interactions higher resource quality generally selects for higher virulence/transmission for both linear and saturating transmission-virulence trade-off assumptions. The exception is that in castrators (i.e., infected hosts have no reproduction), higher virulence is selected for both low and high resource qualities at mixed local and global infection. Heterogeneity in the distribution of environment resources only has an effect on the outcome in castrators where random distributions generally select for higher virulence. Overall, our results further underline the importance of considering spatial structure in order to understand evolutionary processes.

1. INTRODUCTION

The evolution of parasites is of clear importance to human, agricultural and wildlife populations, and as a consequence the evolution of virulence theory is particularly well developed (Anderson and May, 1992; Best et al., 2011; Boots and Sasaki, 1999; Bremermann and Pickering, 1983; Dieckmann et al., 2002; Getz and Pickering, 1983; Laine, 2007; Rand et al., 1995). A key theoretical result is that host's spatial structure profoundly influences the evolution of parasites, with local infection selecting for lower virulence and rates of transmission (Boots and Sasaki, 2000; Boots and Mealor, 2007; Haraguchi and Sasaki, 2000; Kamo et al., 2007; Lion and Boots, 2010; Lion and Gandon, 2015; Rand et al., 1995). In these models, spatial structure arises naturally due to the local transmission and reproduction of hosts within a spatially homogenous environment. However, the environment in reality also typically varies in space and time, and this heterogeneity in environmental quality may directly impact host spatial structure and the outcome of the epidemic (Becks and Agrawal, 2010; de Roode et al., 2008; Mostowy and Engelstadter, 2011; Penczykowski et al., 2014; Restif and Kaltz, 2006; Wolinska and King, 2009). In addition, environmental quality may directly play an important role in host-parasite interactions, impacting host defence, parasite transmission and virulence (Cornet et al., 2014; Tack et al., 2014). One of the major theoretical challenges that remains therefore, is to explore how parasites adapt to hosts in environment with spatially heterogeneous resources.

Empirical and theoretical studies have shown that resource quality has the potential to impact host-parasite interactions in a number of ways. Resource quality can impact individual host immune function such that high resources lead to high resistance to infection (Boots, 2011; Forde et al., 2008; Hall et al., 2009; Lopez-Pascua and Buckling, 2008; Lopez-Pascua et al., 2014; Penczykowski et al., 2014). Generally, environmental stress should be associated with higher levels of virulence because decreased host immunity function in poor resources enhances pathogeniticity (Ferguson and Read, 2002; Hall et al., 2009; Jokela et al., 1999; Restif and Kaltz, 2006). However, it should also be noted that there might be indirect impacts of variation in host resource quality, where higher resources lead to higher host reproduction and abundance and then will further increase encounter rates between hosts and parasites (Anderson and May, 1992; Hall et al., 2009; Lopez-Pascua et al., 2014). Therefore, increased resource availability may transform benign microbial communities into virulent ones (Mckenzie and Townsend, 2007; Wedekind et al., 2010). As such, parasite fitness

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is likely to be directly and indirectly impacted by resource quality, and we therefore need a theoretical framework to tease apart the various roles of resources to the evolution of parasites.

Classic evolutionary epidemiology theory examines the evolutionary dynamics of parasites assuming well-mixed populations (Anderson and May, 1979, 1991; Boots and Haraguchi, 1999; Bowers et al., 1994). Theoretical models assuming completely mixed host populations ("mean-field" approximation) have predicted that parasites will evolve to infinite transmission and minimum virulence with no relationship between transmission and virulence (Anderson and May, 1992; Bremermann and Pickering, 1983; Dieckmann et al., 2002; Lenski and May, 1994; Lion and van Baalen, 2008). Recent theoretical works have shown the importance of spatially structured host populations on the evolution of parasites and indicated that an evolutionary stable transmission rate can exist despite no transmission-virulence trade-off (Haraguchi and Sasaki, 2000; Keeling, 1999; Lion and Boots, 2010; Messinger and Ostling, 2013; O'Keefe and Antonovics, 2002). Generally, parasites will evolve lower transmission rates and therefore potentially lower virulence when infections occur locally (Boots and Sasaki, 1999; Haraguchi and Sasaki, 2000; O'Keefe, 2005; Rand et al., 1995). Spatially heterogeneous environments are also fundamental for evolutionary dynamics and the maintenance of diversity in host-parasite interactions (Byers, 2005; Jousimo et al., 2014; Tack et al., 2014; Thrall and Burdon, 1997, 2002; Thrall et al., 2012). These previous works mainly assume homogenous environments in which the spatial heterogeneity emerges naturally from host-parasite interactions, but there is a lack of theoretical consideration for how parasite's evolution is expected to occur when the environment itself is heterogeneous (e.g., host resource quality varies spatially).

Here, our aim is to understand the evolutionary behavior of parasites in hosts on spatially structured heterogeneous resource environments. For generality, we consider a simple host-pathogen/parasite model, with resource-mediated host reproduction and parasite transmission. We start by examining the evolutionary dynamics of parasites in non-spatially structured host population ("mean-field" approximation), in comparison with the spatial models. Second, we use pair approximation (i.e., constructing ordinary differential equations for global and local densities of single and neighbouring pairs of habitat patches that change over time) to explore how the virulence evolution changes with resource quality in spatially homogeneous environments. Pair approximation has been successfully applied in a wide range of ecological, epidemiological, and evolutionary systems (Hiebeler, 2000; Hui and MeGeoch, 2007; Iwasa, 2000; Matsuda et al., 1992; Su et al., 2009b; Webb et al., 2013). We finally build a spatially explicit stochastic model to examine how spatial heterogeneity of habitat resources drives the outcome of virulence evolution.

2. Methods

We explore a classical host-parasite interaction in a lattice-structured environment where each patch can be either empty (denoted by O) or occupied by a susceptible (S) or infected (I) individual. Individuals consume the resources of patches where each patch k has a fixed resource quality R_k ($k = 1, \ldots, N \times N$). In a homogenous resource environment, all patches have the same value of R, with variations in R resulting in a heterogeneous environment (Okuyama, 2008). For homogenous resource environments, mean-field and pair approximations can work well for describing host-parasite evolutionary dynamics accurately. The heterogeneous model makes the mathematical analysis complex and therefore we rely on spatially stochastic simulations to analyze these cases.

Susceptible host individuals reproduce at rate r (which depends on their resource consumption) into neighbouring empty patches (Boots and Sasaki, 1999; Kamo et al., 2007; Webb et al., 2013). As in many species (e.g., *Daphnia*), reproduction rate increases with resource quality but then slows as resource quality becomes high (Hall et al., 2007). Then, we assume that the rate of host reproduction depends on the resource quality according to an exponential function: $r = r_{\max}(1 - \exp(-\eta_r R))$, where parameter $r_{\max}$ is the maximum reproduction rate with available abundant resource, η_r is a constant that controls the efficiency of resource used by the host population. Disease-associated reductions in fecundity can occur with reproduction from infected individuals taking place at a fractional rate, denoted by rf ($f \in [0, 1]$), where castrator ($f = 0$) indicates parasites prevent the infected hosts reproduction. Changes in resource quality can modify the condition of hosts, which may in term affect their susceptibility for parasites (Anderson and May, 1992; Daniels et al., 2013; Hall et al., 2009; Penczykowski et al., 2014). High-quality resources may reduce susceptibility through direct effects on immunity or general improved condition (Babin et al., 2010; Boots, 2010; Penczykowski et al., 2014; Venesky et al., 2012). Then, we further assume another similar form as resource-mediated reproduction rate, between transmission rate and resource quality,$\beta = \beta_{\max} \exp(-\eta_\beta R)$, where $\beta_{\max}$ is the maximum infection rate with available abundant resource, η_β is a constant reflecting the efficiency of the feedback process. The natural death rate of host individuals is d, and infected hosts have an increased mortality due to parasitic infection (virulence α).

Parasitic infection happens through the contact of infected and susceptible host individuals locally at neighbouring patches ($z = 4$) and globally at patches chosen at random (G denotes the proportion of global infection where $0 \le G \le 1$, Fig. 1). We assume that virulence is a cost to parasite transmission since higher within host growth rate leads to both higher transmission and more damage leading to a higher host death rate (Best et al., 2011; Boots and Sasaki, 1999; Haraguchi and Sasaki, 2000; Messinger and Ostling, 2013). Thus, in the case that infected host can reproduce ($0 < f \le 1$), increasing transmission rate is probably relatively more costly than in the case with castrator ($f = 0$). Here, the functional forms of the transmission-virulence trade-off are either taken as linear for $\beta_{\max} = 3\alpha$ or saturating for $\beta_{\max} = 5\log(\alpha + 1)$ (Kamo et al., 2007; Webb et al., 2013). There are a number of parasite's strains ($t = 1, \ldots, n$) that differ in their intrinsic transmission rate ($\beta_{\max}$) (the rate of causing infection) and have correlated changes in the virulence. Evolution occurs through small mutations (in any single time-step mutation to the neighbourhood strain with the next high or next low transmission rate can occur, Appendix S1, S2).

2.1. Mean-field approximation

Before analyzing the viscous system, we first consider the equivalent non-spatially structured mixed ("mean-field") model for compar-

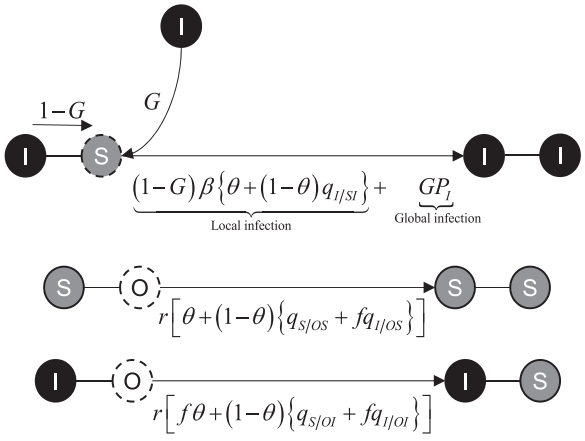

Fig. 1. Diagram for host reproduction and parasite infection process with possible pair state and their transition probability. A susceptible individual can be infected from a nearest-neighbor ($z = 4$) at probability $1 - G$ and globally from a distant patch at G. β, r, and f represents the transmission rate, reproduction rate and infected fecundity, respectively.

ison. The mean-field model only consider the global densities of host and parasite population, P_S, P_I.

$$P'_S = r(P_S + fP_I)(1 - P_S - P_I) - dP_S - \beta P_S P_I \tag{1}$$

$$P'_I = -(d + \alpha_I)P_I + \beta P_S P_I \tag{2}$$

2.2. Pair approximation

Based on the rules described above, a pair approximation model can be constructed. Let the global density $P_{\sigma'}(t)$ ($\sigma' \in \{S, I, O\}$) denote the probability that a randomly chosen patch is in the state σ' at time t. Doublet density $P_{\sigma'\sigma''}$ is the probability that a randomly chosen pair of two neighbouring patches is in state $\sigma'\sigma''$. Local density $q_{\sigma''/\sigma'}$ is the conditional probability that a randomly chosen neighbor of a patch in state σ'' is in state σ', and $q_{\sigma'/\sigma''\sigma'''}$ is the conditional probability that a randomly chosen neighbor of the σ'' patch in a $\sigma''\sigma'''$ pair is in state σ' (σ'', σ''' $\in \{S, I, O\}$). The pair approximation model then yields the following differential equations:

$$P'_{OO} = -2r(1 - \theta)P_{OO}\{q_{S/OO} + fq_{I/OO}\} + 2dP_{SO} + 2(d + \alpha)P_{IO} \tag{4}$$

$$P'_{SS} = 2rP_{SO}[\theta + (1 - \theta)\{q_{S/OS} + fq_{I/OS}\}] - 2dP_{SS} - 2\beta\{GP_I + (1 - G)(1 - \theta)q_{I/SS}\}P_{SS} \tag{5}$$

$$P'_{II} = -2(d + \alpha)P_{II} + 2\beta[GP_I + (1 - G)\{\theta + (1 - \theta)q_{I/SI}\}]P_{IS} \tag{6}$$

$$P'_{SO} = -dP_{SO} - \beta[GP_I + (1 - G)(1 - \theta)q_{I/SO}]P_{SO} - rP_{SO}[\theta + (1 - \theta)\{q_{S/OS} + fq_{I/OS}\}] + dP_{SS} + (d + \alpha)P_{IS} + r(1 - \theta)P_{OO}\{q_{S/OO} + fq_{I/OO}\} \tag{7}$$

$$P'_{IO} = -(d + \alpha)P_{IO} + \beta[GP_I + (1 - G)(1 - \theta)q_{I/SO}]P_{SO} + dP_{IS} + (d + \alpha)P_{II} - rP_{IO}[f\theta + (1 - \theta)\{q_{S/OI} + fq_{I/OI}\}] \tag{8}$$

$$P'_{IS} = -(2d + \alpha)P_{IS} + \beta\{GP_I + (1 - G)(1 - \theta)q_{I/SS}\}P_{SS} + rP_{IO}[f\theta + (1 - \theta)\{q_{S/OI} + fq_{I/OI}\}] - \beta[GP_I + (1 - G)\{\theta + (1 - \theta)q_{I/SI}\}]P_{IS} \tag{9}$$

where $\theta = 1/z$ (z is the number of nearest neighbouring patches). According to the following constraints $P_{\sigma'\sigma''} = P_{\sigma'}q_{\sigma''/\sigma'} = P_{\sigma''\sigma'} = P_{\sigma''}q_{\sigma'/\sigma''}$, $P_{\sigma'} = \sum_{\sigma''} P_{\sigma'\sigma''}$, $\sum_{\sigma''} q_{\sigma''/\sigma'} = 1$ and $P_O + P_S + P_I = 1$, we can derive the dynamics of local densities (P_{SO}, P_{IO}, P_{OO}). Furthermore, because triplet densities in pair approximation method are substituted by pair densities (i.e. $q_{\sigma'/\sigma''\sigma'''} \approx q_{\sigma'/\sigma''}$) (Boots and Sasaki, 1999; Iwasa, 2000; Matsuda et al., 1992), there are only five independent variables namely P_S, P_I, P_{SS}, P_{II}, P_{IS}. All the other singlet and doublet probabilities can be calculated from these five variables.

3. Evolutionary invasion analysis

We now consider a rare mutant parasite strain denoted by subscript j, which invades an endemic host-parasite population with resident strain i. The invasion condition is given by:

$$\lambda(I_j|I_i) = \frac{P'_{I_j}}{P_{I_j}} = -(d + \alpha_j) + \beta_j\left[(1 - G)\hat{q}_{S/I_j} + G\hat{P}_S\right] \tag{10}$$

where α_i, α_j are the virulence of the resident and mutant parasite strains, and β_i, β_j ($\beta_t = \beta_{t\,\max}\exp(-\eta_\beta R)$, $t = i, j$) are the transmission rate of the resident and mutant strains, respectively. $\hat{P}_S$ denotes the equilibrium density for resident susceptible individuals at the endemic stationary state based on Eqs. (4)–(9), and $\hat{q}_{S/I_j}$ is the quasi-equilibrium density of susceptible individuals in the neighbourhood of the invading mutant (Boots and Sasaki, 1999; Kamo et al., 2007; Messinger and Ostling, 2013; Webb et al., 2013). To derive $\hat{q}_{S/I_j}$ we assume that the conditional densities in the nearest neighbourhood of a rare mutant strain change much faster than the global density of the resident strain, so that all the resident densities without a j are given by their endemic values (based on Eqs. (4)–(9)) and the quantities P_{I_j}, $q_{I_j/O}$, $q_{I_j/S}$ are small. The changes of these fast variables are approximately described as

$$\begin{aligned} q'_{S/I_j} = {} & -\beta_i q_{S/I_j}\{GP_{I_i} + (1 - G)(1 - \theta)q_{I_i/S}\} \\ & + rq_{O/I_j}[\theta f + (1 - \theta)\{q_{S/O} + fq_{I_i/O}\}] - dq_{S/I_j} - \beta_j q_{S/I_j}(1 - G)\theta \\ & + \beta_j\left\{GP_{SS} + (1 - G)(1 - \theta)q_{S/I_j}q_{S/S}\right\} \\ & - \beta_j q_{S/I_j}\left[GP_S + (1 - G)q_{S/I_j}\right] \end{aligned} \tag{11}$$

$$\begin{aligned} q'_{I_i/I_j} = {} & -(d + \alpha_i)q_{I_i/I_j} + \beta_i q_{S/I_j}\{(1 - G)(1 - \theta)q_{I_i/S} + GP_{I_i}\} \\ & - \beta_j q_{I_i/I_j}[GP_S + (1 - G)q_{S/I_i}] + \beta_j\left[GP_{I_iS} + (1 - G)(1 - \theta)q_{S/I_j}q_{I_i/S}\right] \end{aligned} \tag{12}$$

$$\begin{aligned} q'_{O/I_j} = {} & -rq_{O/I_j}[\theta f + (1 - \theta)\{q_{S/O} + fq_{I_i/O}\}] + dq_{S/I_j} + (d + \alpha_i)q_{I_i/I_j} \\ & + (d + \alpha_j)q_{I_j/I_j} + \beta_j GP_S\left(q_{O/S} - q_{O/I_j}\right) \\ & - \beta_j(1 - G)q_{S/I_j}\left\{q_{O/I_j} - (1 - \theta)q_{O/S}\right\} \end{aligned} \tag{13}$$

We can now determine the invasibility of the mutant strain j from Eq. (10), by equating the right-hand sides of (11)–(13) to zero, and substituting for the positive equilibrium value $\hat{q}_{S/I_j}$ in (10). If $\lambda(I_j|I_i)$ is positive, then the mutant j can invade.

3.1. Spatially stochastic simulation model

Spatially stochastic simulations were designed to check the validity and robustness of the pair approximation, and also allow us to make predictions on the epidemiological and evolutionary consequences of heterogeneous environments. Habitat resources with spatially structured heterogeneity were generated using the mid-point displacement algorithm (Hiebeler and Morin, 2007; Su et al., 2015; With, 1997), and a binary environment was created by assigning a fraction (h) of patches with high resource and fraction ($1 - h$) of patches has low resource level. To compare with homogenous resource environment, the qualities of high and low resource were always set to fixed values ($R_{high} = 3$, $R_{low} = 0.1$), where the spatial distribution of high/low resource patches can form the heterogeneous environment. Both the proportion of high resource habitat (h) and the degree of spatial autocorrelation of the fractal environment (measured by the roughness constant, H) were varied to create an array of complex heterogeneous resource structures. High clustering parameter H represents a strong spatial autocorrelation, which indicates a high probability that a randomly chosen neighbor of high/low resource quality patch is also found high/low (Su et al., 2009a). The detail of the simulations is described in the Appendix S1.

4. Results

The selection derivative indicates the sensitivity of the per capita growth rate of a species to a change in the trait value (Dieckmann and Law, 1996; Kamo et al., 2007). It is a measure of the selection pressure generated by the environment through the ecological interactions (Marrow et al., 1992). The change in value of the selection derivative function can be defined as (Appendix S2)

$$D(\alpha) = \underbrace{\Delta(1/R_0)/\Delta\alpha}_{\text{Basicreproductiverate}} + \underbrace{(1 - G)\Delta q_{S/I_j}/\Delta\alpha}_{\text{Localdensity}} \tag{13}$$

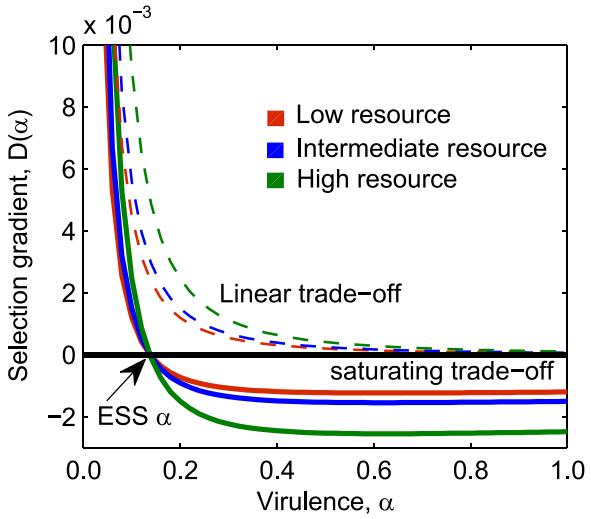

Fig. 2. Selection gradient are predicted in the non-spatial model as resource-mediated effects on both host reproduction and parasite transmission ($r\&\beta$). There is no ESS virulence under linear transmission-virulence trade-off (dashed line). ESS virulence can exist under saturating trade-off (solid line), but the virulence values are not affected by resource quality. Large absolute of $D(\alpha)$ indicates that selection pressures are promoted by the high resource qualities. High resource quality is $R = 3$, intermediate resource quality $R = 1$ and low resource quality $R = 0.1$. Other parameters: $r_{max} = 3$, $d = 0.01$, $\eta_r = 0.6$, $\eta_\beta = 0.25$, $f = 0$.

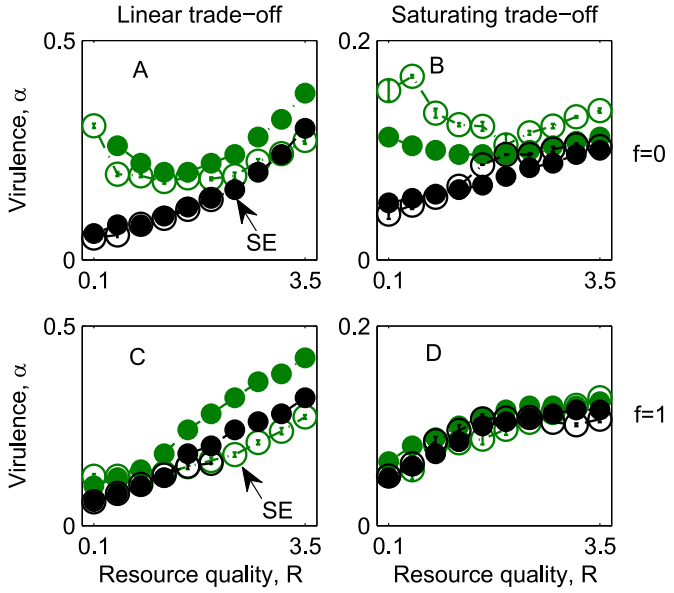

Fig. 3. ESS Virulence plotted against homogenous resource quality evaluated by adaptive dynamics based on pair approximation (solid dots, analysis by selection gradient) and simulations based on spatially stochastic model (circle dots, bar denotes s.d. of ten simulations). Above the threshold of resource quality, the evolution of virulence disappears due to stochastic extinction ('SE') of infected hosts (Fig. 3A, C). f represents the disease-associated reductions in fecundity ($f = 0$ indicates that the infected hosts have no reproduction and $f = 1$ represents the infected hosts can reproduce at rate r). The maximum virulence is fixed at 1, the mutation rate is 0.015 and the lattice size is 256 × 256 in the simulations. Parameters: local infection for $G = 0$ (black dots), mixed infection for $G = 0.2$ (green dots), $r_{max} = 3, d = 0.01, \eta_r = 0.6, \eta_\beta = 0.25, z = 4$.

In the "mean-field" approximation, the selection derivative can be simplified by $\Delta(1/R_0)/\Delta\alpha$. Consequently, this factor determines the direction of adaptive change and also the selected strength of pathogen virulence (Kamo et al., 2007). If the absolute value of selection derivative is large, selection occurs rapidly. If it is positive, strains with higher virulence will be advantageous in the vicinity of the resident trait value.

4.1. Evolution without spatial structure in hosts

Fig. 2 shows results of the "meanfield" approximation under different homogeneous resource distributions. Note that, under all resource qualities, virulence will be maximized by evolution with the linear trade-off (Fig. 2). However, for a saturating functional form, transmission becomes increasingly costly in terms of virulence and therefore there is an evolutionarily stable (ESS) virulence in completely mixed populations (Fig. 2). The way in which absolute value of $D(\alpha)$ varies with different resource environments indicates that the selection pressures are promoted by the high resource qualities under both trade-offs (Fig. 2, Eq. S3). Because $D(\alpha)$ has no term of host reproduction ($\exp(-\eta_r R)$) and also its sign is not influenced by resource-mediated transmission ($\exp(-\eta_\beta R)$), resource quality has no effect on the ESS virulence when resource mediates host reproduction or/and parasite transmission in a completely mixed population. However, evolution to the ESS virulence will be faster at higher resource quality as resource-mediated only parasite transmission (β-only) or both host reproduction and parasite transmission ($r\&\beta$) (Appendix S2).

4.2. Spatial structure in hosts but homogeneous resource

Full evolutionary analyses of homogeneous resource environments from pair approximation showed that host's spatial structure and the various components of host-parasite traits mediated by resource quality can influence the parasite's evolution (Fig. 3). The first point to emphasize is that there exists an ESS virulence with the linear trade-off in spatially structured host-parasite system, which is in contrast with the "mean-field" results (Fig. 3). To better grasp the effect of resource quality on the parasite's evolution in spatially structured host interactions, we track selection under infection occurring locally ($G = 0$) and mixed locally and globally ($G = 0.2$) (Fig. 3). Under completely local infection, whether the disease is castrating ($f = 0$) or not ($f = 1$), there is selection for higher virulence with increasing of resource quality under both trade-offs (Fig. 3). When there is a combination of local and global infection, we found the same pattern when disease does not impact the infected host's fecundity ($f = 1$). However, the resource-mediated effect was more complex for castrators ($f = 0$), where both extreme poor and rich resources can select the higher virulence (Fig. 3A, B). In the supporting information, we further showed that the result which parasites should be more prudent at intermediated resource qualities is general for a range of infected fecundity f with both linear and saturating trade-offs between transmission and virulence (Fig. S1).

To better explore this variation in the parasite's evolution with homogeneous resource environments, we tease apart the various roles of resource-mediated traits in selection on the parasite (Fig. S2, S3). Under completely local infection, both resource-mediated host reproduction (r-only) and parasite transmission (β-only) shows that there is a selection for high virulence with resource quality at disease-associated reductions in fecundity ($f = 0$) (Fig. S2A). The result also holds at there is no reduction in infected fecundity (Fig. S2C). When there is a combination of local and global infection, resource-mediated host reproduction and parasite transmission have different effects on underlying virulence evolution (Fig. S2B, D). When resources mediate host reproduction (r-only), we found that virulence decreases with increasing resource quality. In contrast, when resources mediate transmission only (β-only), we found that virulence increases with increasing resource quality. The combination of these two scenarios contribute to the complex effects that more virulent parasite strains are selected at extreme resource environments (relatively poor or rich resources) when resource-mediated both traits ($r\&\beta$) and intermediate host's spatial structures (Fig. 3; Fig. S2B). However, when there is no

reduction in fecundity, the effect of resources on resistance dominates such that virulence increases with resource quality when both traits are dependent on resources (Fig. S2D). Equivalent results are found in saturating trade-off (Fig. S3), which suggests that these effects are robust to trade-off shape.

To check the insights that we gained from pair approximation, we used stochastic simulation to compare the evolution of virulence predicted by pair approximation. The simulations generally show that pair approximation predicts ESS values well (Fig. 3). Pair approximation assumes infinite virulence while stochastic simulation assumes the virulence of parasite strains has a range between minimum and maximum values, which may lead to some discrepancy in ESS virulence. Particularly, under completely local infection and linear trade-off between transmission and virulence, there is a threshold of resource quality above which the evolution of virulence disappears (i.e., no evolution towards increasing virulence) due to stochastic extinction of infected hosts (Fig. 3A, C; Fig. S4). Completely local infection combined with high virulence (disease-induced mortality increasing with resource quality) could prevent the survivability of parasite in stochastic simulation. In contrast to linear trade-off between transmission and virulence, low virulence in saturating trade-off keeps the persistence of parasite, but the proportion of infected hosts is very small (Fig. 3B, D; Fig. S4). Meanwhile, at the epidemiological level, we find generally that resource quality of homogeneous habitat can strongly affect the disease dynamics: parasite transmission will be inhibited as facing extreme habitat quality (Fig. S4).

4.3. Spatially heterogeneous resource

Heterogeneity in resource distribution can be due to differences in patch quality and the spatial configuration of poor and rich resource patches. We first examined how the evolution of virulence changes with different spatial distributions (random and fractal patterns with $H = 0, 0.5$). Effects of heterogeneous resource distributions on the mean/ESS virulence are relatively obvious when infected hosts have no reproduction ($f = 0$) (Figs. 4 and 5; Fig. S5, S6). Random distributions of resources favor the evolution of higher virulence when the resource effects are mediated through reproduction in castrators. Taking r-only scenario as an example, the above results are robust across different fractions of low to high resource quality, and also hold at the saturating trade-off (Fig. 6; Fig. S7). As infected host reproduces, random distribution can select for lower virulence, but the difference between ESS virulence among various resource distributions is less pronounced (Fig. 5; Fig. S6). When the quality of high (R_{high}) and low (R_{low}) resources are fixed, the average resource quality

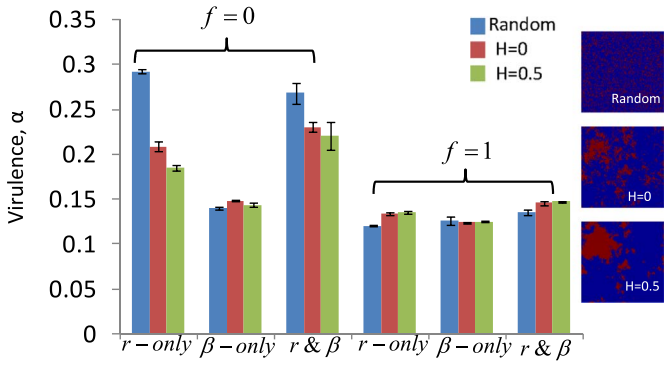

Fig. 4. Mean virulence (ESS) plotted against heterogeneous resource distribution based on spatially stochastic model with linear trade-off. Red in heterogeneous landscapes indicates high resource level ($R_{high} = 3$) and blue represents low resource level ($R_{low} = 0.1$). The terms 'r-only', 'β-only' and '$r\&\beta$' represent resource-mediated effects on only host reproduction, only parasite transmission and both host reproduction and parasite transmission, respectively. Error bars show standard deviation. Parameters: $h = 0.2$, $G = 0.2$, and other parameters are as in Fig. 3.

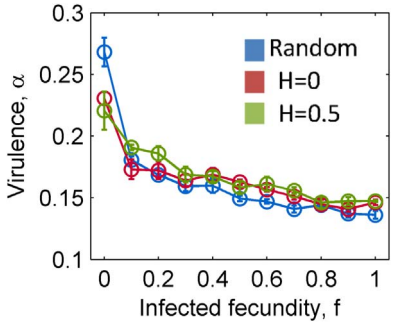

Fig. 5. Effects of infected fecundity f on the ESS/mean virulence based on spatially stochastic model as resource-mediated both host reproduction and parasite transmission with linear trade-off. Parameters are the same with Fig. 4.

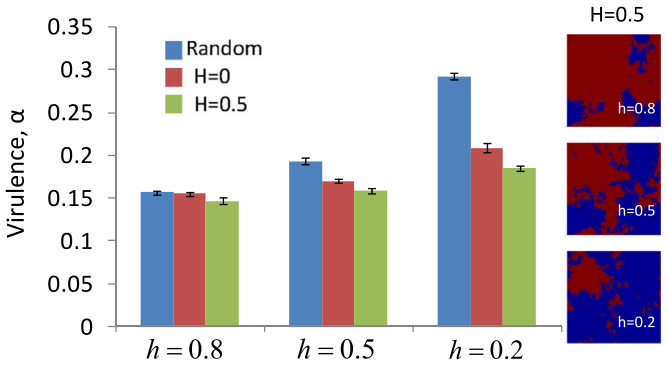

Fig. 6. Mean virulence of random resource pattern and fractal configuration ($H = 0, 0.5$) within various proportions of high resource ($h = 0.2, h = 0.5, h = 0.8$) with resource-mediated host reproduction and castrating disease ($f = 0$). Other parameters as in Fig. 4.

$R_{high}h + R_{low}(1 - h)$ always increases with h. As predicted in homogeneous resource environments (Fig. S2B; Fig. S3B), high levels of average resource in heterogeneous environments also can select for low ESS virulence in r-only scenario with mixed of local and global infection (Fig. 6; Fig. S7).

5. Discussion

Although a large number of studies have explored the effects of spatial structure of host populations on parasite evolution, to our knowledge this is the first theoretical examination of resource quality and heterogeneous distribution in virulence evolution of the spatial structured host-parasite interactions. Resource quality can clearly have a number of impacts on hosts that in turn influence their interactions with their infectious diseases (Hall et al., 2009; Penczykowski et al., 2014). By focusing on the resource-mediated susceptibility to infection and host reproduction, our results here highlight the importance of resource quality and heterogeneous distribution on the evolution of virulence. A spatially structured host-parasite model showed that resource quality could have influence on ESS virulence, which is contrasted to completely mixed populations that assume individuals interact equally with all others. As such, a novel result here has emphasized that variation in resource quality can generate variation in selection for virulence across landscapes, but only when host's spatial structure is taken into account. Our results further emphasize the importance of spatial structure (completely local infection, mixed local and global infection) in evolutionary processes, which is consistent with previous results that completely local infection favors low virulence (Berngruber et al., 2015; Boots and Sasaki, 1999; Boots and Mealor, 2007; Lion and van Baalen, 2008; Wild et al., 2009).

Resource quality has the potential to be a major driver of host-parasite evolution both due to its direct effect on host susceptibility to

infections and indirectly through its impact on host reproduction (Hall et al., 2009; Penczykowski et al., 2014; Restif and Kaltz, 2006; Wolinska and King, 2009). As the host population is completely mixed, resource quality has no effect on ESS virulence under both linear and saturating transmission-virulence trade-offs, because resource quality only influences the selection strength but the sign of selective gradient is not dependent on the quality of environmental resource (Appendix S2). This is true whether resource quality mediates resistance against parasite or reproductive rate of host population. The result also confirms the previous study which showed that host reproduction rate is not predicted to influence pathogen evolution under the "mean-field" approximation (Messinger and Ostling, 2013), but also expands that ESS virulence is influenced by resource-mediated host reproduction and/or resistance in a spatial context. Thus, a more complete theory of parasite's evolution considering the influence of host's spatial structure predicts that variation in disease transmission and virulence may arise from differences in the resource quality.

The relationship between virulence evolution and resource quality in host-parasite interactions depends on the spatial structure of host population and the different components of resource-mediated life-history traits. Our main results showed that in populations with a mixed structure of global and local infection, resource mediated susceptibility effects remain consistent in selecting for higher transmission/virulence at higher resource quality, while the effects of resource-mediated reproduction are more nuanced (Fig. S2, S3). These different effects induced our central result, which is that parasites should be expected to be more "prudent" (lower virulence) when resource quality is intermediate for a range of infected fecundity (Fig. 3A, B; Fig. S1). Previous results showed that lower resource quality indicating lower host reproduction and higher parasite transmission, may result in the small abundance of host population, which in turn inhibits the evolution of virulence (Frank, 1996; Galvani, 2003; Messinger and Ostling, 2013). However, our analysis reveals that a very low resource quality could select for a high parasite's virulence as mixed local and global infection via the following related process: the mixed spatial structure in host population (i.e., mixed local and global infection) provides more opportunities for parasites transmission, while both castrator of disease and a low resource-mediated reproduction rate induce a low host's density in the extremely poor resource, leading effectively to a parasite 'resource limitation'. Thus, it is possible that higher virulence reflects the host's difficulty to cope with infection and the strong infectivity may benefit the survival of parasites.

In our models, completely local infection favors the evolution of lower virulence (i.e., using pair approximation or stochastic simulation, ESS virulence under completely local infection is lower than that under the mixed local and global infection), which reflects the general theoretical expectation that parasites should select for more prudent host exploitation strategies with host's spatial structure. This is consistent with the idea of "self shading" by infected hosts where the spread of faster transmitting parasites is impeded by the rapid depletion of the local supply of susceptible hosts, and results from a combination of evolutionary and ecological correlations (Berngruber et al., 2015; Boots and Sasaki, 1999; Boots et al., 2004; Boots and Mealor, 2007; Messinger and Ostling, 2013). Most importantly, our models suggest that higher resource quality can stimulate local host availability and reduce "self-shading", resulting in a higher ESS virulence with completely local infection. Although completely local infection yielded fewer infected host's individuals by stunting the parasite dispersal, high-quality resource can increase host reproduction and increase the abundance of local susceptible hosts (Penczykowski et al., 2014). Therefore, our results suggest that the more abundant host population can reduce the effect of "self shading" and thus induce parasite selecting for more virulent parasite strain (Fig. 3).

It is clear that natural environments are typically heterogeneous with resources in particular neither continuous or randomly distributed across the landscape (Hiebeler, 2000; Hiebeler and Morin, 2007; Su et al., 2009b, 2015). This spatially heterogeneous structured resource environment may play an important role in the feedback loop between ecology and evolution and thereby impose a selective pressure on the evolution of pathogens and parasites (Hiebeler, 2000; Lion and van Baalen, 2008). However, we found little effect on the evolution of virulence among various heterogeneous resource distributions under this parameters combination, except when the infected host has no reproduction, which implies that the effects of variation in resource patterns should be further explored in host-parasite's evolution.

Spatial structure can alter ecological and evolutionary dynamics in host-parasite interactions through various processes (Lion and van Baalen, 2008). First, it can arise from the intrinsic ecological dynamics such as spatially structured host populations (i.e., hosts distribution and their clustering degree). Second, it can result from the external variations of environment, such as resource quality and its heterogeneity in distribution patterns. Although spatially heterogeneous resource distributions are well recognized factors in ecology and evolutionary, systematic exploration of this axis in evolution of host-parasite systems has only recently begun (Hiebeler, 2000; Jousimo et al., 2014; Su et al., 2009b; Tack et al., 2014). Moreover, acquired immunity can alter the relationship between local infection and effect of "self-shading", which induces local infection selecting for higher virulence (Webb et al., 2013). To what extent will the "self-shading" hold when there is acquired immunity in various resource qualities and heterogeneous resource distributions is valuable to further research.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtbi.2016.12.017.

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