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**Interim Report** **IR-07-061**

# The Role of Trade-Off Shapes in the Evolution and Coexistence of Virulence in Spatial Host-Parasite Interactions: An Approximate Adaptive Dynamical Approach

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## Contents

**Title**: The role of trade-off shapes in the evolution and coexistence of virulence in spatial host-parasite interactions: An approximate adaptive dynamical approach.

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**Abstract**

We propose a new analysis for the evolution of virulence of pathogen in a spatially structured host population where each site of a regular lattice is either occupied by a susceptible or by an infected, or is empty. We assume that reproduction by susceptible individuals occurs locally but infection by a contact of susceptible and infected hosts occurs either locally or globally with a certain proportion. We examine by combining Monte-Carlo simulation and adaptive dynamics approach, how the evolutionarily stable (ESS) virulence depends on the fraction of global infection/transmission and the trade-off between transmission and virulence in the model investigated by Boots and Sasaki (1999). Our analysis developed in this paper can successfully predicted the ESS virulence found in the previous papers, and reveals followings: [1] With a linear trade-off, as is reported by previous studies, there is an ESS virulence when the proportion of global infection is small. We newly find that, if we increase the proportion, the ESS disappears when the proportion exceeds a certain threshold value, and proportions just below the threshold, there are evolutionary bi-stabilities. [2] With a non-linear trade-off, there can be no monomorphic ESS; instead, the evolutionary competition between many parasite genotypes differing in their virulence gives rise to

an evolutionarily stable coalition of pathogen strains with markedly different virulence (dimorphic ESS virulence) with a middle proportion of global transmission. These analytical results well illustrate the results by Monte-Carlo simulations. Since coexistence and evolutionary bistability are not impossible in the model we investigate in this paper, these are apparently derived by the effect of spatial structure. (280 words)

**Key Words:** model of epidemiology, spatially structured model, evolution of virulence, trade-off between virulence and transmission rate, adaptive dynamics, coexistence and evolutionary bistability.

## Introduction

What determines the level of virulence in nature has been one of the central topics in the theories on the evolution of pathogens. Conventional wisdom has it that parasites should evolve to be harmless to their hosts and hence nonzero virulence seen in nature is regarded as a maladaptation (see May and Anderson 1983 for references, [is this a proper ref to cite?]**)**. The heart of this idea was a group selection argument that the parasite should evolve for the benefit of the parasite species. Modern theory of the evolution of parasites is based more on individual selection (MK: repetition, removed). More specifically, with classical mean-field (homogeneous mixing) assumption and no co-infection or super-infection to an already infected host, the theory predict that either high or low virulence can evolve depending on the trade-off between virulence and transmission rate/recovery rate (May and Anderson 1983; Bremermann and Thieme 1989) [-- Bremermann and Thieme is not the paper to be cited here -- it's on the maintenance of host polymorphism with many strains of parasite with matching allele model. -- Am I correct?]. $R_0$ is the most important epidemiological measure that characterizes the ability of an infectious disease to spread in host population; defined as

the average number of secondary infections caused by an average infected host in a susceptible host population (see Anderson 1991)[--repeatition, maybe I should remove the earlier one… (MK: done)]. It depends on the rate of infection and the duration of the infectious period. The infectious period is governed by the rate at which an infected individual either recovers or dies, and hence virulence, the increased death rate due to infection, affects $R_0$. Although there are a number of different definitions for 'virulence' in the literature of infectious diseases, the increased death rate due to infection is defined as virulence in the context of evolutionary ecology and epidemiology. This definition immediately leads to a general tendency that lower parasite virulence is selected for, if there is no trade-off, because reducing host death rate will increases the infectious period and hence does $R_0$ (May and Anderson 1983; Bremermann and Thieme 1989)[-- again, should B & T be cited here?].

In order to maximise $R_0$, evolution should maximise the transmission rate and minimise virulence and recovery (May and Anderson 1983; Bremermann and Thieme 1989). However it is doubtful that the disease behaviour is completely unconstrained, and we

therefore expect there to be a trade-off from the point of view of the parasite between transmission and virulence. Higher transmission can only be 'bought' at the expense of higher virulence as the processes of producing of the necessary amounts of parasite transmission cause damage to the host (Mackinnon and Read 1999). If transmission is increasingly costly in terms of virulence, models predict the evolution of a finite transmission rate and virulence, otherwise evolution will maximise transmission and virulence; in both cases maximising $R_0$. This analysis is by no means always applicable to all circumstances. For example, superinfection of parasites (Sasaki and Iwasa 1991; Frank 1992; May and Nowak 1994; Nowak and May 1994) leads to a higher ESS virulence because the intra-host competition among strains favors a more virulent parasite than that maximizes the basic reproductive number. The virulence evolved in expanding population has also been shown to be larger than that in constant populations (Lenski and May 1995).

General evolutionary theory assumes that the host population is completely mixed and that therefore any individual is as likely to infect any one individual as any another. The

assumption of homogeneous mixing in host populations ignores the fact that certain individuals are more likely to contact and therefore infect others. The inclusion of such spatial/social structure into host-parasite models has shown that this more realistic assumption about the structure of host populations has dramatic implications to the evolution of the parasite. A successful approach to examining the role of the spatial structure of individual hosts is by using lattice models (also called probabilistic cellular automata PCA)(Sato, Matsuda et al. 1994; Rand, Keeling et al. 1995; Rhodes and Anderson 1996; Boots and Sasaki 1999; Haraguchi and Sasaki 2000). This approach examines the fundamental spatial relationships of individuals within populations and uses biologically realistic and quantifiable parameters. There is now a body of theoretical work that shows how important spatial structure is to the evolution of parasites (reviewed in Boots et al 2006). For example, Haraguchi & Sasaki (2000) showed that $R_0$ is not maximized when spatial structure is considered because that parasite transmission rate is constrained. Boots & Sasaki (1999) included both local and global transmission and showed that the ES transmission rate reduced as infection became more local. This effect on transmission is a result of a form of 'self shading'

where parasite strains with lower transmission rates gain an advantage in terms of an increased chance of susceptible individuals being next to infected ones and therefore available for infection.

The current theory assumes either no trade-off between transmission and virulence or a linear relationship (Haraguchi & Sasaki 2000, Boots & Sasaki 1999). In both cases, mean-field theory predicts the evolution of maximum transmission rate. The spatial models show that local interactions can constrain the evolution of the transmission rate. Here we will extend the spatial evolutionary theory by examining how different assumptions concerning the trade-off between transmission and virulence affect the evolution of parasites in spatially structured populations. In particular we will examine the role of spatial structure when there is a non-linear trade-off between transmission and virulence so that they would both be constrained without population structure. We ask whether there are important effects of local interactions on parasites that are constrained by the trade-off between transmission and virulence.

Another key result from the simple mean-field models that lead to the maximization of

$R_0$ (Anderson & May 1993) is that coexistence among pathogens is not possible. This can be proved very easily. Assume that a resident strain ($w$) is in equilibrium. An invasion coefficient of mutant strain ($m$) is defined by a difference in the basic reproductive ratio defined as,

$$R_0 = \frac{\beta}{(\alpha + \gamma + \mu)}, \tag{1}$$

where $\beta$, $\alpha$, $\gamma$ and $\mu$ are transmission rate, virulence, recovery rate and natural mortality of the host respectively. Then the fitness of the rare mutant is defined as

$$s_w(m) = R_0(m) - R_0(w) \tag{2}$$

where $R_0(i)$ is a basic reproductive ratio of a strain $i$ ($i \in \{w, m\}$). A given singular point ($w^*$) satisfies,

$$\frac{\partial s_w(w^*)}{\partial m} = 0. \tag{3}$$

The second order partial derivatives of Eq. (1) are,

$$\frac{\partial^2 s_w(w^*)}{\partial w^2} = \left[ -\frac{\partial^2 R_0(w^*)}{\partial w^2} \right]_{m=w=w^*} \tag{4}$$

and

$$\frac{\partial^2 s_w(w^*)}{\partial m^2} = \left[ \frac{\partial^2 R_0(w^*)}{\partial m^2} \right]_{m=w=w^*}. \tag{5}$$

Then following relationship is always satisfied in the completely mixed model.

$$\frac{\partial^2 s_w(w^*)}{\partial m^2} = -\frac{\partial^2 s_w(w^*)}{\partial w^2} \qquad (6)$$

Geritz et al. (1997, 1998) showed that evolutionary branching occurs when $\partial^2 s_w / \partial m^2 > \partial^2 s_w / \partial w^2$. Obviously, Eqs. (6) cannot satisfy the condition, implying that the evolutionary branching is impossible. The condition for the coexistence between two strains is $\partial^2 s_w / \partial m^2 > -\partial^2 s_w / \partial w^2$, and this is also impossible; hence, coexistence is not possible.

Our second purpose is to examine whether spatial structure and local interactions can lead to coexistence between parasite strains. Boots and Sasaki (1999) showed that there were in theory the possibility of coexistence in the spatial model, but did not examine it in detail. This paper will examine whether spatial structure leads to coexistence in detail.

Previous theory has relied on Monte Carlo simulation of spatially explicit host-parasite models. Here we use pair approximation techniques in addition to MonteCarlo simulation. The advantage of approximation techniques is that they allow the rapid

analysis of the behaviour of the model, that can then be checked by simulation of the full system. This approach has been successful in ecological host-parasite models (Sato et al. 1994, Haraguchi & Sasaki 2000, Boots and Sasaki 2000). Pair approximations have however failed to predict the ES parasite transmission rates of completely local host-parasite models (Boots et al 2006), but we show here how they can predict evolutionary outcomes well if there is some degree of global interactions.

**Modelling**

We, first, mathematically formulate the population dynamics of hosts changing in time, and then analyze evolutionary outcomes using an adaptive dynamics techniques. These results are compared to those by Monte-Carlo simulations which are mainly used in previous studies (e.g., Boots and Sasaki 1999). Followings are procedures of two methods.

*Mathematical formulation: pair densities*

We follow the model by Boots & Sasaki (1999) by considering a regular network of sites, each of which contains one of a single susceptible individual ($S$), an infected

individual (*I*) and empty (*O*). Susceptible individuals reproduce at a rate *r* into the nearest neighboring sites. They are infected by contact with an infected host at a rate $\beta$. Transmission can occurs both locally and globally. When the transmission occurs globally, a susceptible individual contacts an infected host which is chosen randomly from one of the sites in the lattice. When the transmission is local, it has a contact to the nearest neighboring cell. Global transmission occurs a certain proportion denoted by *L* ($0 \le L \le 1$). The natural death rate of individuals is *d*, and infected hosts have an increased mortality due to infection (virulence: $\alpha$). Infected individuals do not reproduce and they do not recover.

The population dynamics on the lattice is described as,

$$\dot{P}_{OO} = 2[-r(1-\theta)q_{S/OO}P_{OO} + (d+\alpha_I)P_{IO} + dP_{SO}],$$

$$\dot{P}_{SO} = r(1-\theta)q_{S/OO}P_{OO} - dP_{SO} + dP_{SS} + (d+\alpha_I)P_{IS}$$

$$-[r\{\theta + (1-\theta)q_{S/OS}\} + \beta_I\{(1-L)(1-\theta)q_{I/SO} + L\rho_I)\}]P_{SO},$$

$$\dot{P}_{SS} = 2[r\{\theta + (1-\theta)q_{S/OS}\}P_{SO} - dP_{SS} - \beta_I\{(1-L)(1-\theta)q_{I/SO} + L\rho_I)\}P_{SO}],$$

$$\dot{P}_{IO} = -r(1-\theta)q_{S/OI}P_{IO} - (d+\alpha_I)P_{IO} + (d+\alpha_I)P_{II} + dP_{IS}$$

$$+\beta_I\{(1-L)(1-\theta)q_{I/SO} + L\rho_I)\}P_{SO},$$

$$\dot{P}_{IS} = -dP_{IS} - (d+\alpha_I)P_{IS} - \beta_I[(1-L)\{\theta + (1-\theta)q_{I/SO}\} + L\rho_I]P_{SO}$$

$$+r(1-\theta)q_{S/OI}P_{IO} + \beta_I[(1-L)(1-\theta)q_{I/SS} + L\rho_I)]P_{SS},$$

$$\dot{P}_{II} = -2(d+\alpha_I)P_{II} + 2\beta_I[(1-L)\{\theta + (1-\theta)q_{I/SI}\} + L\rho_I)]P_{IS}. \quad (7)$$

where $\dot{x}$ denotes a time derivative of $x$. The global density of infected host ($\rho_I$) exactly changes in time as,

$$\dot{\rho}_I = [\beta_I\{L\rho_S + (1-L)q_{S/I}\} - (\alpha_I + d)]\rho_I. \quad (8)$$

Definition of parameters and variables are in Table 1 and Table 2.

A mutant strain (*J*) can invade into a population at an endemic equilibrium with resident strain (*I*), if

$$\lambda(J \mid I) = \frac{1}{\rho_J}\frac{d\rho_J}{dt} = \beta_J\{L\hat{\rho}_S + (1-L)\hat{q}^0{}_{S/J}\} - (\alpha_J + d) > 0, \qquad (9)$$

where $\beta_J$ and $\alpha_J$ are the transmission rate and virulence of the mutant. $\hat{\rho}_S$ denotes the global density of susceptible host at the equilibrium and $\hat{q}^0{}_{S/J}$ is the local density of susceptible host in the neighborhood of the mutant parasite at a "quasi equilibrium". Recently, Boots et al. (2006) developed an analytical method to obtain the value of $\hat{q}^0{}_{S/J}$. We assumed that the conditional densities in the nearest neighborhood of a rare mutant strain change much faster than the global density of the resident strain. Those fast variables are approximately described as,

$$\begin{aligned}\dot{q}_{O/J} &= (d+\alpha_J)q_{J/J} + (d+\alpha_I)q_{I/J} + dq_{S/J} - r(1-\theta)q_{S/O}q_{O/J} \\ &\quad + \beta_J[L\rho_S(q_{O/S} - q_{O/J}) - (1-L)\{(q_{O/J} - (1-\theta)q_{O/S}\}q_{S/J}],\end{aligned}$$

$$\begin{aligned}\dot{q}_{S/J} &= -dq_{S/J} + r(1-\theta)q_{S/O}q_{O/J} - \beta_J(1-L)\theta q_{S/J} \\ &\quad - \beta_J[L\rho_S + (1-L)q_{S/J}]q_{S/J} + \beta_J[L\rho_S + (1-L)(1-\theta)q_{S/J}]q_{S/S}\end{aligned}$$

$$-\beta_I[L\rho_I + (1-L)(1-\theta)q_{I/S}]q_{S/J},$$

$$\dot{q}_{I/J} = -(d+\alpha_I)q_{I/J} - \beta_J[L\rho_S + (1-L)q_{S/J}]q_{I/J}$$

$$+\beta_J[L\rho_S + (1-L)(1-\theta)q_{S/J}]q_{I/S} + \beta_I[L\rho_I + (1-L)(1-\theta)q_{I/S}]q_{S/J},$$

$$\dot{q}_{J/J} = -(d+\alpha_J)q_{J/J} + 2\beta_J(1-L)\theta q_{S/J} - \beta_J[L\rho_I + (1-L)q_{S/J}]q_{J/J}. \qquad (10)$$

Note that variables without *J* are at the endemic equilibrium and are constant. We can solve Eq. 10 numerically to obtain the quasi equilibrium value of $\hat{q}^0_{S/J}$ and then calculate the invisibility of mutant strain from Eq. (9). When we repeat the procedure for a various combination of resident and mutant parameters, we can draw pair wise invadability plots (PIPs). The PIP is a graphical representation of the evolutionary outcomes developed in the adaptive dynamical framework (Geritz et al 1997, 1998). In the following section, we will analyze the invadability of mutant strains by drawing PIPs with trade-offs between transmission rate and virulence.

*Monte-Carlo simulations*

In the simulation, we consider a model where each site of the lattice is either empty, occupied by a susceptible, or occupied by an infected. A 100×100 regular lattice with a periodic boundary is assumed so that each site has 4 nearest neighbors. The state of the $x$-th site in the lattice at time $t$ is denoted by $\sigma_x(t) \in \{0, S, I\}$, where the state 0, $S$, and $I$ indicate respectively that the site is empty, occupied by a susceptible, and occupied by an infected host. When we consider the evolution of parasites, we introduce the state $I_j$ which indicates that the site is occupied by an individual that infected by the $j$-th strain of parasite. A continuous time Markov process was defined by specifying the transition probability of each site in a unit time interval. The state of the $x$-th site changes by

(i) the mortality of a susceptible individual:

$S \rightarrow 0$, at rate $d$;

(ii) the mortality of an infected individual:

$I \rightarrow 0$, at rate $\alpha$;

(iii) the reproduction of susceptible individuals:

$0 \rightarrow S$, at rate $r\, n_x(S)/z$;

(iv) infection:

$S \rightarrow I$, at rate $\beta\, n_x(I)/z$;

where $n_x(\sigma)$ represents the number of sites with the state $\sigma$ in the nearest neighbor of the $x$-th site, and $z$ is the number of nearest neighbor sites ($z$=4 for a regular lattice).

In order to draw PIPs by simulation, we first carry out a Monte-Carlo simulation with a monomorphic population. After the host densities reach equilibrium, small numbers of the resident strains mutate. Then simulation is continued. After a sufficiently long time, if the mutant strains persist in the population, we defined that the invasion is successful.

For the purposes of this paper we will consider that ESS values predicted by the simulation are actual value. Since we use approximations to draw PIPs by analysis, we might expect that the analysis is less accurate than the simulations.

**Results**

At first, we assume the same linear trade-off relationship assumed in Boots and Sasaki

(1999) such that,

$$\beta = 3\alpha \tag{11}$$

and examine how well pair approximations predict the outcome of the Monte-Carlo simulations. With the linear trade-off, the evolution always prefers higher virulence in well mixed populations ($L$=1.0); however, as is reported (Boots and Sasaki 1999; Haraguchi and Sasaki 2000), there is an evolutionary stable virulence when the population is spatially structured. Figure 1 shows three PIPs with L=0.0, 0.3 and 1.0. When L=1.0, the PIP predicts that mutant strains with larger virulence can always invade. However, with smaller proportions (L=0.0 and 0.3), PIPs show that there is an ESS virulence, which has been reported by previous studies. These results show that our analysis works very well when there is a trade-off.

In this study, we examine a non-linear trade-off between transmission and virulence such that,

$$\beta = C\log(\alpha + 1) \tag{12}$$

where $C$ is a constant. This monotonically increasing, but decelerating trade-off gives a finite ESS transmission value in completely mixed populations. Figure 2 depicts six

PIPs with different proportions of global transmission. Top three panels show PIPs by analysis, and bottom three panels show those by Monte-Carlo simulations. For the simulation, we take 20 replicates and number of invasion successions is shown in gray scale. Black indicates that mutants invade 20 times, and white indicates that mutants fail to invade 20 times. The two panels on the very right indicate the result when the proportion of global transmission is 1 (completely mixed model). A top panel is a result by analysis, and the bottom one is by simulations. As is expected, there is an ESS virulence and with the parameter (see a caption of the figure for parameters), the ESS value is about 0.2. These two panels are almost identical because we do not consider spatial structure at all in the PIPs (and hence no pair-approximation).

Two panels in the middle indicate the results with L=0.6. Both PIPs by analysis (top) and simulation (bottom) show that there is an ESS virulence, although predicted values are slightly different. The other two panels on the very left indicate the results with $L$=0.0. The two panels also show that there is an ESS virulence and the values are almost the same (i.e., the analytical method predicts the actual ESS well). Boots et al.

(2006) showed that the analysis failed with completely local model without trade-off between virulence and transmission rate; however, if we assume a trade-off (regardless of linear or non-linear), the analysis predicts the ESS values well.

In all cases in Figure 1 and 2, the ESS virulence is different depending on the proportion of global transmission ($L$). With the linear trade-off, ESS virulence is the smallest when L=0.0. When L=0.3, the ESS value is a bit higher, and it eventually becomes infinity when L=1.0. Contrary, with a non-linear trade-off (Fig. 3), the ESS values is the highest with L=0.6 and is smaller if we increase and decrease the proportion of global transmission.

**Coexistence – mutual invadability**

In this section we will examine the possibility of coexistence in the spatial model. In Figure 2, we produced a PIP with the proportion of the global transmission at 0.6 (middle top in Fig. 2). We depict the invadability of mutant strain into a population at an endemic equilibrium with resident strain. We can then draw a PIP to examine the

invadability of resident strain into a population at an endemic equilibrium with the mutant strain. If there is an area where rare mutants and rare residents can invade each other, there will be the possibility of coexistence.

Figure 3A illustrates a mutually invadable area when $L$=0.6 obtained analytically. There are three different regions. White indicates that the resident and mutant cannot invade each other. In this figure, this color is observed on the diagonal line, where the parameters of resident and mutant are exactly the same, i.e., the invasion condition (Eq. 9) is exactly zero. Gray indicates that one strain can invade into the population, but the other cannot. Black area indicates that both strains can invade each other. In this area, the two strains can coexist.

When we decrease $L$, the black area is reduced, and a new white area appears (Fig. 2B, $L$=0.3). In this white are, rare strains cannot invade into the population; hence, the system shows a bistability. Depending on the initial condition of the simulation, one of the strains dominates the population. The white area becomes larger when we decrease $L$ more. When L=0, the area for coexistence completely disappears (Fig. 2C,

$L$=0.0), and hence the area for bistability become large.

Figure 4 shows time series data of the densities of infected hosts resulted from Monte-Carlo simulation. We start the simulation with a population with monomorphic strain. After the transient period is over, we introduce a mutant strain which has a different virulence (the timing of mutant introduction is defined as time 0 in the figure). As is expected from the numerical analysis, two strains are maintained in the population indicating that these two strains coexist. A snapshot at the end of the simulation is in Figure 4.

Boots & Sasaki (1999) showed that coexistence is possible when the following condition is satisfied.

$$\frac{1}{R_{0I}} - (1-L)q_{S/I} = \frac{1}{R_{0J}} - (1-L)q_{S/J} = L\rho_S \qquad (13)$$

where $R_{0I}$ and $R_{0J}$ are basic reproductive ratio of resident and mutant strain respectively. We computed all values in Eq. 13 from Fig. 4 to confirm if the condition is satisfied or not. The results are in Table 3.

**Discussion**

We have shown coexistence of two pathogenic strains. These two strains are not

possible in the complete mixing model, but if we consider spatial structure, then coexistence becomes possible.

The dependency of ESS virulence to the proportion of global transmission ($L$) is different in the two trade-offs. When the trade-off is linear, if we increase $L$, the ESS virulence goes up (see Fig. 1). When the trade-off is non-linear, the ESS virulence is the largest with middle $L$ ($L$=0.6). The dependency of ESS virulence is different in the linear and non-linear trade-off.

From the invasion condition, Eq. 9, if the virulence of resident and mutant strain is very close, a selection gradient is computed as,

$$D(\alpha) = \frac{1}{R_0^{\,2}} \frac{dR_0}{d\alpha} + (1-L)\frac{dq_{S/I}}{d\alpha}. \qquad (14)$$

If $D(\alpha)$ is positive, a strain with larger virulence can invade. If it is negative, conversely, a strain with smaller virulence can invade. In the limit of $L \to 1$, the invasion condition is the same as that of well mixed model. If we consider the spatial structure (i.e., L<1), the probability of having susceptible individuals at the

neighborhood of infected individual ($q_{S/I}$) affects the direction of evolution.

When the trade-off is linear, $R_0$ is a monotonically increasing function of $\alpha$ is always positive; hence, the first term in Eq. (14) always has an effect to increase virulence. Figure 6A shows the dependencies of $dR_0/d\alpha$ and $dq_{S/I}/d\alpha$ as a function of $\alpha$ when $L$=0. We computed $dq_{S/I}/d\alpha$ numerically using Eq. (7). It is a monotonically increasing function of $\alpha$ and is always negative; therefore, the second term in Eq. (14) always has an effect to reduce virulence. The selection gradient is determined by the sum of these two terms, and if there is a $\alpha^*$ which satisfies $D(\alpha^*)$=0, it can be an ESS virulence. $D(\alpha)$ is also shown in Fig. 6A (gray line). When virulence is increased, it is decreased and becomes 0, and here there is an ESS. This ESS virulence is evolutionarily stable because it changes its sign from positive to negative as virulence is increased. If we increase the virulence more, it is reduced for a while and then increased. In this case when L=0.0, $D(\alpha)$ asymptotically goes to 0, and never becomes positive again.

$D(\alpha)$ with other proportion of global transmission ($L$) are shown in Figure 6B. As is

shown in Boots and Sasaki (1999), ESS virulence is increased with larger $L$. However, when $L$ is beyond a certain threshold value (between 0.3 - 0.4), $D(\alpha)$ does not become negative for any $\alpha$. This indicates that there is no ESS and evolution always prefers larger virulence.

Between $L$=0.3 and 0.4, there is an evolutionary bistability. Figure 6C shows the selection gradient when $L$=0.35. The Selection gradient crosses the horizontal axis twice. These two points can be ESS, but left one (closed circle) is stable and the right one (open circle) is unstable; therefore, if evolution starts with larger value than the unstable ESS values, virulence goes toward infinity. If evolution starts with smaller value, it converges to the stable ESS value. Evolutionary bistability has been also found by Boots et al. (2004). Such an evolutionary scenario may exist more than we expect when we consider spatial structure.

We must note here that the selection gradient, $D(\alpha)$, is very small when virulence is large. This means that the selection pressure is weak; therefore, it may be difficult to

observe evolutionary of virulence cleary by Monte-Carlo simulations because of couple of agents which befog the weak selection, such as selection mutaiton balance and demographic stochastisity.

If we apply the analysis when the link between transmission and virulence is non-linear trade (Eq. 11), we can predict the ESS virulence and we confirmed that ESS values are the largest with middle $L$.

The effect of spatial structures has been widely studied recently; however, most studies are by Monte-Carlo simulations. Such previous results would be fully understood if we apply our analysis. One problem of our analysis is that we largely rely on the pair approximation, and hence the analysis becomes less accurate when the local interaction is very strong. The pair-approximation is good in our model in which we assume trade-offs among parameters; however, the goodness is not guaranteed in other models (see Boots et al. (2006) for a case of failure).

We have discussed coexistence and bistability in this paper. As we see in the introduction, neither of them is not possible in the completely mixed population. These phenomenon are purely attributed to the effect of the spatial structure. The most important parameter to understand the evolution in the spatially structured population is $q_{S/I}$, the amount of susceptible individuals around an infected individual. This value is, obviously, not independent from the rate for reproduction. We can expect that the rate itself has some effects on the evolution of virulence. Throughout this paper, we assume the reproduction rate is a constant and reproduction is done completely locally. If we allow susceptible individuals to reproduce globally, there could be a different outcome on the evolution (Boots and Sasaki 2000). They found that global reproduction increase the ESS virulence. If we increase a reproduction rate, is virulence increased? Since the reproduction rate has been thought to be not an important parameter on the evolution of virulence in the completely mixed populations (with fixed total density), potential effect of the reproduction has not been well studied. This would be our future study.

**Figure Legend**

Figure 1 Three PIPs drawn analytically with different proportions of global transmission. when L=1 (C), there is no ESS and strains with larger virulence always win (the principle of maximizing $R_0$). When L=0.0 (A) and L=0.3 (B), PIPs predict that there is an ESS virulence. The ESS virulence is the smallest with L=0, and is the largest when L=1.0. Parameters: $r$=3, $d$=0.01, $C$=3.

Figure 2 PIPs with non-linear trade-off. Top three panels show the PIP by analysis, and bottom three by simulations. In all cases, there is an ESS virulence. Generally, PIPs by analysis and simulations are similar; however, the discrepancy is the largest when L=0.6. When L=1.0, two PIPs are almost identical. ESS virulence is not monotonically increased as L is increased. It is the largest at L=0.6 in the figure. The effect of L on the ESS virulence is different from the one in Figure 1 where alpha is an increasing function of L. Parameters: $r$=5, $d$=0.01, $C$=15.

Figure 3 Information of invadability. Black indicates mutually invadable (coexistence),

gray indicates that either one of the strains can invade but the other cannot, white indicates that both cannot invade each other (bistability). Parameters are in Figure 2.

Figure 4. An example of coexistence. Gray line indicates the global density of mutant and black line indicates that of residents. Mutants are introduced at time 0. Virulence of residents is 0.8 and that for mutants is 0.22. Other parameters are in Fig. 2. A snapshot at the end of the simulation (time 3000) is in Figure 4.

Figure 5. A snapshot at the end of the simulation in Figure 4. White, light gray, dark gray and black indicate a site occupied by a susceptible individual, an empty site, a site occupied by resident strain and by mutant strain respectively. Conditional probabilities, $q_{S/I}$ and $q_{S/J}$ are in Table 3.

Figure 6 A: Dependencies of $dq_{S/I}/d\alpha$ (dashed line) and $(dR_0/d\alpha)/R_0^2$ (solid line) when L=0.1 with a linear trade-off. These are denoted by $q_{S/I}'$ and $R_0'/R_0^2$ in the panel. It also shows a selection gradient ($D$ ($\alpha$): gray line). There is an ESS virulence where $D$ ($\alpha$) = 0. B: selection gradients with other $L$. When L=0.4, the ESS disappears.

C: selection gradient when L=0.35. $D$ ($\alpha$) becomes 0 twice.; hence it shows a bistability.

A closed circle shows stable ESS and open circle does unstable ESS. Arrows on the panel indicates the direction of evolution.

**TABLES**

Table 1

Variables. $x,y,z \in \{O,S,I,J\}$.

| | |
|---|---|
| $P_{xy}$ | probability that a randomly chosen pair of nearest neighbor sites has state *x*-*y* |
| $\rho_x$ | global density of *x* |
| $q_{x/y}$ | conditional probability that a randomly chosen *y* site has a *x* site at its nearest neighbor |
| $q_{x/yz}$ | conditional probability that a randomly chosen *y*-*z* pair has a *x* site at its nearest neighbor. This variable is approximated by $q_{x/y}$ in our analysis (ordinal pair approximation ; Sato et al. 1994) |

Table 2

Parameters. $x \in \{I,J\}$

| | |
|---|---|
| $\beta_x$ | transmission rate of the strain $x$ |
| $\alpha_x$ | virulence of the strain $x$ |
| $r$ | reproduction rate |
| $d$ | natural death rate |
| $\theta$ | $1/z$ |
| $z$ | number of the nearest sites (= 4) |
| $L$ | proportion of global transmission |

Table 3

Values in Eq. 13 computed from the snapshot in Figure 4.

| L | $q_{S/I}$ | $q_{S/J}$ | $\rho_S$ | $\frac{1}{R_{0I}} - (1-L)q_{S/I}$ | $\frac{1}{R_{0J}} - (1-L)q_{S/J}$ |
|---|---|---|---|---|---|
| 0.6 | 0.070 | 0.113 | 0.067 | 0.0490 | 0.0467 |