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Interim Report **IR-06-075**

The role of trade-off shapes in the evolution of parasites in spatial host populations: an approximate analytical approach

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Contents

Title: The role of trade-off shapes in the evolution of parasites in spatial host populations: an approximate analytical approach.

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LRH: M. KAMO ET AL.
RRH: TRADE-OFF SHAPE AND EVOLUTION OF VIRULENCE

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Abstract

Given the substantial changes in mixing in many populations, there is considerable interest in the role that spatial structure can play in the evolution of disease. Here we examine the role of different trade-off shapes in the evolution of parasites in a spatially structured host population where infection can occur locally or globally. We develop an approximate adaptive dynamic analytical approach, to examine how the evolutionarily stable (ES) virulence depends not only on the fraction of global infection/transmission but also on the shape of the trade-off between transmission and virulence. Our analysis can successfully predict the ES virulence found previously by simulation of the full system. The analysis confirms that when there is a linear trade-off between transmission and virulence spatial structure may lead to an ES virulence that increases as the proportion of global transmission increases. However, we also show that the ESS disappears above a threshold level of global infection, leading to maximization. In addition just below this threshold, there is the possibility of evolutionary bi-stabilities. When we assume the realistic trade-off between transmission and virulence that results in an ESS in the classical mixed model, we find that spatial structure can increase or

decrease the ES virulence. A relatively high proportion of local infection reduces virulence but intermediate levels can select for higher virulence. Our work not only emphasises the importance of spatial structure to the evolution of parasites, but also makes it clear that situations between the local and the global need to be considered. We also emphasise the key role that the shape of trade-offs plays in evolutionary outcomes.

Key Words: Space, evolution, trade-off shape, approximations, adaptive dynamics, bi-stability.

Introduction

The evolutionary theory of infectious disease is well developed. Classical "mean-field", homogeneous mixing models, in which there is no co- or super-infection, predict that selection will tend to maximise the parasite's epidemiological R_0 (May & Anderson, 1983; Bremermann & Thieme, 1989). R_0 is a key epidemiological characteristic and determines the ability of the disease to spread in a population; it is defined as the average number of secondary infections caused by an average infected host in a susceptible host population (see Anderson & May,1991). In order to maximise R_0, evolution should maximise the transmission rate and minimise virulence and recovery (May & Anderson, 1983; Bremermann & Thieme, 1989). However it is doubtful that the disease behaviour is completely unconstrained, and we therefore generally assumed that there is 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 that lead to increased parasite transmission cause damage to the host (Mackinnon & 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. The game theoretical approach to the evolution of parasites that assumes trade-offs between transmission and virulence, is an established route to predicting the long term evolution of parasites under a number of circumstances (see Lipsitch & Nowak 1995; Frank 1996; Gandon, 1998ab; Day 2001; Gandon et al. 2001; Day, 2002abc; Gandon et al., 2002; Boots & Sasaki, 2003; Day 2003; Day & Burns, 2003; Gandon et al., 2003; Gandon, 2004).

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 useful approach to examining the role of the spatial structure of individual hosts is by using lattice models which are also known as probabilistic cellular automata: PCA (Sato et al., 1994; Rand et al., 1995; Rhodes &

Anderson, 1996; Boots & Sasaki, 1999; Haraguchi & Sasaki, 2000). This approach models the spatial relationships of individuals within a population. 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 the epidemiological R_0 is not maximized when spatial structure is considered because that parasite transmission to neighbouring hosts is constrained. 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. Boots & Sasaki (1999) included both local and global transmission and showed that the ES transmission rate reduced as infection became more local when there is a linear trade-off between transmission rate and virulence. These models, that range between the completely local and the global 'mean-field' are useful in that they allow us to understand over what range of spatial variation these effects are important.

However, these studies are largely based on Monte-Carlo simulations of spatially explicit host-parasite models. The simulations often take a time to reveal

evolutionary trends and sometimes they fail to find the actual evolutionary direction, in particular, when the selection is weak. Recently, Boots et al. (2006) developed a pair approximation technique for examining evolutionary stability, which allows the rapid analysis for the evolution of parasite's traits. In this paper, we consider a spatial SI model in which the pathogen transmission can occur both locally and globally and analyse the evolutionary outcomes by using the approximation technique. Our aims are firstly to more fully understand how evolutionary stable virulence changes as the proportion of global infections are increased by assuming the same linear trade-offs as in Boots & Sasaki (1999). Secondly we wish to examine how different forms of the trade-off 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, where the parasite pays an accelerating cost in terms of virulence from increased transmission. This is likely to be a reasonable assumption in many microparasitic infections and, although rarely studied, there is experimental evidence for this decelerating trade-off in nature (see Mackinnon & Read (2004) for review). In addition, this form of trade-off is commonly assumed in classical

mean field theory since it leads to a finite evolutionarily stable (ES) transmission rate and virulence and may therefore explain the existence of evolutionarily stable non-zero virulence in mixed populations. Here we examine how a decelerating trade-off affects the outcome once there is spatial structure.

Modelling

We, first, mathematically formulate the changes of host densities in time, then analyze evolutionary outcomes using an adaptive dynamics techniques. These results are compared with those from the full Monte-Carlo simulation, which has been the approach of earlier studies (e.g., Boots & Sasaki, 1999). For ease of comparison, 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 neighbouring sites. They are infected by contact with an infected host at a rate β. Transmission can occur 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 neighbouring 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: α). Infected individuals do not reproduce or recover.

The population dynamics on the lattice is described as,

$$\begin{aligned}
\dot{P}_{OO} &= 2[dP_{SO} + (d+\alpha_I)P_{IO} - r(1-\theta)q_{S/OO}P_{OO}], \\
\dot{P}_{SO} &= dP_{SS} + (d+\alpha_I)P_{IS} - dP_{SO} + r(1-\theta)q_{S/OO}P_{OO} \\
&\quad -[r\{\theta + (1-\theta)q_{S/OS}\} + \beta_I\{L\rho_I + (1-L)(1-\theta)q_{I/SO}\}]P_{SO}, \\
\dot{P}_{SS} &= 2[-dP_{SS} + r\{\theta + (1-\theta)q_{S/OS}\}P_{SO} - \beta_I\{L\rho_I + (1-L)(1-\theta)q_{I/SS}\}P_{SS}], \\
\dot{P}_{IO} &= dP_{IS} + (d+\alpha_I)P_{II} - (d+\alpha_I)P_{IO} - r(1-\theta)q_{S/OI}P_{IO} \\
&\quad +\beta_I\{L\rho_I + (1-L)(1-\theta)q_{I/SO}\}P_{SO}, \\
\dot{P}_{IS} &= -dP_{IS} - (d+\alpha_I)P_{IS} - \beta_I[L\rho_I + (1-L)\{\theta + (1-\theta)q_{I/SI}\}]P_{IS} \\
&\quad +r(1-\theta)q_{S/OI}P_{IO} + \beta_I\{L\rho_I + (1-L)(1-\theta)q_{I/SS}\}P_{SS}, \\
\dot{P}_{II} &= -2(d+\alpha_I)P_{II} + 2\beta_I[L\rho_I + (1-L)\{\theta + (1-\theta)q_{I/SI}\}]P_{IS}. \qquad (1)
\end{aligned}$$

where $\dot{x}$ denotes a time derivative of x. The quantity $q_{\sigma/\sigma'\sigma'} = P_{\sigma\sigma'\sigma''} / \rho_{\sigma}$ represents the conditional density of σ in the neighbourhood of σ' site of $\sigma'\sigma''$ pair. Here we denote the transmission rate and virulence of wild type pathogen by β_I and α_I. Throughout this paper, we use ordinary pair approximation (Matsuda et al. 1992), i.e., we approximate the conditional triplet densities by their doublet densities ($q_{\sigma/\sigma'\sigma''} \approx q_{\sigma/\sigma'}$ for any $\sigma,\sigma',\sigma'' \in \{O,S,I\}$). This is less accurate approximation than the other sophisticated ones (e.g., Sato et al. 1994; Keeling 1999), but it is often used to analyse the lattice model in many other ecological context (Harada and Iwasa 1994; Kubo et al, 1996; Nakamaru et al. 1997, 1998; Iwasa et al., 1998; van Baalen and Rand 1998; also see some chapters in Dieckman et al. 2000). We will show later in Discussion that the pair approximation fails to accurately predict the host densities and the ESS virulence, but is good enough to understand the general tendency of the evolutionary outcomes.

The global density of infected host ($\rho_I = P_{I0} + P_{IS} + P_{II}$) changes with time as

$$\dot{\rho}_I = [\beta_I \{L\rho_S + (1-L)q_{S/I}\} - (\alpha_I + d)]\rho_I, \qquad (2)$$

where $\rho_S = P_{S0} + P_{SS} + P_{SI}$ is the global density of susceptible hosts. The definition of parameters and variables are in Table 1 and 2.

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

$$\lambda(J \mid I) = \frac{1}{\rho_J}\frac{d\rho_J}{dt} = \beta_J\{L\hat{\rho}_S + (1-L)\hat{q}^0{}_{S/J}\} - (\alpha_J + d) > 0, \qquad (3)$$

where β_J and α_J are the transmission rate and virulence of the mutant. $\hat{\rho}_S$ denotes the global density of susceptible host at an equilibrium and $\hat{q}^0{}_{S/J}$ is the local density of susceptible host in the neighbourhood of the mutant parasite at a "quasi equilibrium" (Boots & Sasaki 1999; Keeling 1999). In order to obtain the value of $\hat{q}^0{}_{S/J}$, 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, which can be justified during the initial phase of invasion in which the global density of mutant-infected hosts remains small. The changes of these fast variables are approximately described as,

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

$$\dot{q}_{S/J} = -dq_{S/J} + r(1-\theta)q_{S/O}q_{O/J} - \beta_J(1-L)\theta q_{S/J}$$

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

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

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

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

$$\dot{q}_{J/J}=-(d+\alpha_J)q_{J/J}+2\beta_J(1-L)\theta q_{S/J}-\beta_J[L\rho_S+(1-L)q_{S/J}]q_{J/J}. \qquad (4)$$

Note that variables without *J* are at the endemic equilibrium and are constant. We can solve Eqs. (4) numerically to obtain the quasi equilibrium value of $\hat{q}^0{}_{S/J}$ and then calculate the invasibility of mutant strain from Eq. (3). When we repeat the procedure for a various combination of resident and mutant parameters, we can draw pair wise invasibility plots (PIPs). The PIP is a graphical representation of the evolutionary outcomes developed in the adaptive dynamics framework (Geritz et al., 1997, 1998). In the following section, we will analyze the invasibility of mutant strains by drawing PIPs with trade-offs between transmission rate and virulence.

We also carry out full Monte Carlo simulations where we consider a model where each site of the lattice is either empty, occupied by a susceptible, or occupied by an infected. A 100 x 100 regular lattice with a periodic boundary is assumed so that

each site has 4 nearest neighbours. The detail of the simulation has been described elsewhere (see, for example, Boots et al., 2006). In order to produce PIPs by simulation, we first carry out a Monte-Carlo simulation in the absence of mutant strains. After the host densities reach equilibrium, mutation occurs on 10% of the infected hosts, then we continue the simulation. After a long period, if the mutant strain persists in the population, we consider that the invasion has been successful. The number of successful invasions among 20 replicates is represented by a grey scale. For the purposes of this paper the ESS values predicted by the simulation are assumed to be the correct value. Since we use approximations to draw PIPs by our analysis, we might expect this to be less accurate than the simulations.

Results

At first we assume the same linear trade-off relationship assumed in Boots & Sasaki (1999) such that,

$$\beta = 3\alpha \tag{5}$$

and examine how well pair approximations predict the outcome of the Monte-Carlo

simulations. With the linear trade-off, the evolution always leads to higher virulence in well mixed populations (L=1.0); however, as has been reported previously (Boots & Sasaki, 1999; Haraguchi & Sasaki, 2000), there is possibility for an evolutionarily stable (ES) virulence when the population is spatially structured. Figure 1 shows approximate PIPs with L=0.0, 0.3 and 1.0. The PIPs confirm the results obtained in previous studies, with global reproduction, the strains with higher virulence always invade (Fig. 1C), while continuously stable strategies (CSS), defined as the strategies which are both evolutionarily stable and convergence stable, are predicted once there is local transmission (Fig. 1A and B).

From Eq. (2) and Eq. (3), if we assume that the virulence is different between resident (I) and mutant (J) and other parameters are common, the invasion condition can be written as,

$$\left(\frac{1}{R_0(\alpha_I)}-\frac{1}{R_0(\alpha_J)}\right)+(1-L)(\hat{q}^0{}_{S/J}-\hat{q}_{S/I})>0, \qquad (6)$$

R_0 is a basic reproductive ratio. If we assume that virulence between strains are close (say $\alpha_I=\alpha$ and $\alpha_J=\alpha+\Delta\alpha$, $\Delta\alpha$>0), we can define the selection gradient as,

$$D(\alpha)=\Delta(1/R_0)/\Delta\alpha+(1-L)\Delta\hat{q}^0{}_{S/J}/\Delta\alpha. \qquad (7)$$

where

$$\Delta(1/R_0) \equiv \left(\frac{1}{R_0(\alpha_I)} - \frac{1}{R_0(\alpha_J)} \right), \tag{8}$$

$$\Delta \hat{q}^0{}_{S/J} \equiv (\hat{q}^0{}_{S/J} - q_{S/I}). \tag{9}$$

If the absolute value of $D(\alpha)$ is large, selection occurs rapidly and if it is positive, strains with larger virulence can invade. In the limit of $L \to 1$, the invasion condition is the same as that in the well mixed 'mean-field' model. As soon as we have spatial structure (i.e., L<1), the probability of the occurrence of susceptible individuals in the neighbourhood of an infected individual affects the evolution.

When the trade-off is linear, R_0 is a monotonically increasing function of α and hence $\Delta(1/R_0)/\Delta\alpha$ is always positive. Figure 2A shows the dependencies of $\Delta(1/R_0)/\Delta\alpha$ and $\Delta \hat{q}^0{}_{S/J}/\Delta\alpha$ when L=0. $\Delta \hat{q}^0{}_{S/J}/\Delta\alpha$ is negative when a is very small and gradually goes up as α is increased, but remains in negative over the range examined. $D(\alpha)$ is also shown in Fig. 2A. It is positive with small virulence and as virulence is increased, it becomes negative. This indicates that there is an ES virulence. Since $D(\alpha)$ changes its sign from positive to negative as virulence is increased, the ES virulence is locally stable.

The way in which $D(\alpha)$ varies with the proportion of global transmission (L) is shown in Fig. 2B. As is shown in Boots & Sasaki (1999), ESS virulence is increased with larger L. However, when L is beyond a certain threshold value L_C ($0.3 < L_C < 0.4$), $D(\alpha)$ does not become negative for any α. This indicates a disappearance of ES virulence and therefore evolution leads to the highest virulence. The linear trade-off gives small virulence with small L and infinite virulence when L=1.0 as ESS values. When we see changes of the ES value as a function of L, it first gradually goes up, but at some point, the ESS virulence jumps up to the infinite values discontinuously.

Between L =0.3 and 0.4, there is an evolutionary bi-stability. Fig. 2C shows the selection gradient when L =0.35. The selection gradient crosses the horizontal axis twice. Both of these points can be an ESS, but left one (closed circle) is convergence stable and the right one (open circle) is convergence unstable; therefore, if evolution begins at a relatively high value of virulence, the virulence goes toward infinity. If evolution starts with a lower value, it converges to a finite ESS virulence. Figure 3A shows a PIP when L =0.33 which shows an evolutionary bi-stability: there is a finite local CSS virulence, but when the initial virulence of population is greater than a

convergence unstable evolutionary singular point, it evolutionarily diverges towards infinity. The ES virulence disappears as we increase *L*, as a saddle node bifurcation occurs when unstable and stable equilibria collide and disappear (Fig. 3B). If we compare Fig. 3 with Fig. 1, we can understand how ES virulence varies as a function of *L*. The area of bistability depends on the parameters. Figure 4A shows other example of bistability with different trade-off constant (Eq. 5). The evolutionary trajectories of Monte-Carlo Simulation is in Fig. 4B.

It is important to note here that the selection gradient above the unstable ESS value is small. This means that the selection pressure is rather weak and it may therefore be difficult to observe these evolutionary trajectories in Monte-Carlo evolutionary simulations. This is due to the fact that the simulations have both mutation and demographic stochasticity which may swamp the weak selection pressure. Simulation studies, such as Boots & Sasaki (1999), may therefore conclude that there is a continuously increasing ES virulence until we have 100% global infection.

Next we consider the importance of a non-linear trade-off between transmission and virulence such that,

$$\beta = C\log(\alpha + 1) \tag{10}$$

where C is a constant. This monotonically increasing, but decelerating trade-off gives a finite ESS transmission value in completely mixed populations. This form of decelerating trade-off is commonly assumed in mean-field theory and reflects the situation where transmission becomes acceleratingly costly to the parasite in terms of increased virulence. Figure 5 depicts six PIPs with different proportions of global transmission. The three top panels show PIPs drawn analytically. The other three panels are PIPs which are drawn by Monte-Carlo simulations.

In Fig. 5, the two panels on the right indicate the result when the proportion of global transmission is 1 (equivalent to completely mixing). There is an ES virulence around α=0.145 and the two PIPs are almost identical indicating that the approximate analysis is nearly exact in the completely mixed infection case. Note that the case L=1 is not equivalent to completely mixing model, as host reproduction to vacant sites occurs only locally. The two middle panels show the result with intermediate levels of

global infection (L=0.7). Both panels show that the ESS virulence is slightly higher than the one when L=1.0. The final two panels on the left indicate the result with L=0.0. Both panels show that there is an ES virulence and the values are almost the same (i.e., the analytical method predicts the actual ESS well). Boots et al. (2006) have shown that the prediction of ESS virulence using pair approximation failed with completely local model if there is no trade-off between virulence and transmission rate. However, if we assume a trade-off, the pair-approximation predicts the ESS values very well even in the completely local model. Figure 6A shows detailed analysis of the ESS virulence by the pair approximation (lines) and the Monte-Carlo simulations (dots). The analytically predicted ESS is always lower than the results by simulations (Fig. 6A). In Fig. 6B, we investigated the densities of SS and OO pairs. The pair approximation predicts SS pair well; however, the density of OO pair is quite underestimated (this has been already pointed out by Sato et al. 1994). The discrepancy between analysis and simulation may be attributed to this effect.

Disscussion

We have demonstrated again how spatial structure can have a number of important

consequences to the evolution of parasites. By developing an approximate analytical technique in addition to Monte-Carlo simulation, we have been able to gain a number of key insights into the role of spatial structure and trade-off shapes in determining ES transmission and virulence. In addition, we have demonstrated that spatial structure can lead to bi-stability in ES transmission and virulence in a parasite system without acquired immunity. In general, the analysis that we have developed allows a more detailed understanding of the sometimes complex implications of spatial structure.

It is well understood that the evolution of particular fitness traits may be constrained by trade-offs with other life history traits (Roff, 2002). In addition, a key prediction of life-history theory is that the evolution of a particular trait is not just the result of the trade-off but it is also critically dependent on the functional form of the trade-off relationship (Roff, 2002). The recent advent of adaptive dynamical evolutionary theory has further emphasized that it is not only the absolute strength of costs and benefits that are important, but also how these relationships change under different conditions (Geritz et al., 1998; Bowers & White, 2002; Bowers et al., 2005). This adaptive evolutionary theory recognises that trade-off relationships are unlikely to

be exactly linear and that the shape of the relationship is important in determining the ultimate evolutionary outcome. In particular, the way that the costs and benefits vary determines both the convergence stability of the evolutionary system and whether evolutionary branching will occur (Boots & Haraguchi 1999). We have shown that the shapes of trade-offs are also important in spatial models. With a linear trade-off, increased local infection always selects for decreased transmission and virulence. However with a decelerating trade-off, spatial structure can also increase ES transmission and virulence. Highly local transmission does select for lower virulence, but intermediate levels of local interaction lead to the higher transmission and virulence than in a completely mixed population. It is well known that these two trade-off assumptions have very different outcomes in the mean-field: one leads to maximum transmission and virulence while the other selects for an intermediate ES. Our work emphasises that the way in which they interact with spatial structure is also different. It is important, therefore, in this and most likely in other contexts, that assumptions of trade-off shapes are examined before the implications of spatial structure can be completely understood.

The effect of spatial structure on the evolution of parasites can be understood by examining the selection gradient for virulence evolution, $D(\alpha)$ defined in Eq. 6. It is divided into two components. The first term corresponds to the maximization of the basic reproductive ratio, and therefore corresponds to the selection in a conventional mean-field theory. The second term ($dq_{S/I}/d\alpha$), involves the local density of infecteds next to susceptibles and is important due to spatial structure. It is not always possible to maximize these two terms independently. The first term of Eq. 6 is always positive when the trade-off is linear and therefore, always selects for higher virulence. The second term may be negative, particularly at when infection is highly local and therefore may balance this selection pressure. When the trade-off is non-linear (Eq. 10), there is an optimum virulence in the absence of spatial structure and therefore the first term is 0 and the direction of the evolution is determined by the sign of the second term.

A number of studies have previously shown that spatial structure can limit the evolution of transmission without trade-offs (Rand et al., 1995; Haraguchi & Sasaki, 2000; Kamo & Boots, 2004). However, here we have also shown that some degree of local interaction can select for higher rather than lower transmission and virulence. The

maximum ES transmission and virulence is found at intermediate levels of transmission and virulence rather than in the mean-field. This is a key result of this work. Population/spatial structure may lead to the evolution of higher rather than lower transmission and virulence in microparasites. This emphasises the importance of always considering models intermediate between the mean-field and the completely spatial. The vast majority of natural systems are likely to lie somewhere intermediate between the mean-field and the completely local. By only considering the two extremes, many evolutionary models may miss important behaviours.

Evolutionary bi-stability has been previously reported in spatial host parasite models (Read & Keeling, 2003; Boots et al., 2004; van Ballegooijen & Boerlijst, 2004). Bi-stability is important since it may lead to dramatic changes in parasite transmission and virulence（Boots et al. 2004). However in these previous models, it was assumed that the host could develop long lasting immunity to the parasite. Here we have shown it can also occur in the SI context, although the range of mixing over which we have demonstrated it is more restricted.

In this study, we persisted on using the regular lattice. To include the spatial

structures, there are another approaches, such as random graph or scale free networks (see Keeling and Eames 2005 for review). The most different part of our model from these is that there is no variation in connections. The number of connection at each site is always equal as a mean. Recent study showed that the evolutionary outcome is different with different way of connections among sites (Ohtsuki 2006). The evolution of virulence with considering trade-offs on various graphs will be a challenging theme in the future.

There has been considerable interest in the role of spatial structure in ecology and evolution (Keeling 1999; Dieckmann et al., 2000). However, most studies, particularly the evolutionary ones only use Monte-Carlo simulations. The application of our analysis is likely to allow a more complete understanding of the role of spatial structure to the evolution of a wide range of systems. One limitation of our analysis is that we largely rely on pair approximation, and hence the analysis may not be accurate in some scenarios. The pair-approximation works well in our model once we assume trade-offs between transmission and virulence, but the approach has been less successful in other models (see Boots et al, 2006 for a case where the approximation fails). That

said, given the complexity of spatial models, theoretical progress is likely to be much more rapid with the adoption of approximate analytical approaches.

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Tables

Table 1

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

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

Table 2

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

β_x	transmission rate of the strain x
α_x	virulence of the strain x
r	reproduction rate
d	natural death rate
θ	1/z
z	number of the nearest sites (= 4)
L	proportion of global transmission

Figure captions

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 invades strains with lower virulence (the principle of maximizing R_0). When L=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.

Figure 2 A: Dependencies of $\Delta\hat{q}^0{}_{S/J}/\Delta\alpha$ (dashed line) and $\Delta(1/R_0)/\Delta\alpha$ (thin line) when L=0.1 with a linear trade-off. It also shows a selection gradient ($D(\alpha)$: thick line). α which makes $D(\alpha)$ = 0 is an ES virulence. 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 bi-stability. A closed circle shows stable ESS and open circle does unstable ESS. Arrows on the panel indicates the direction of evolution. Parameters are in Fig. 1.

Figure 3 A: a PIP showing evolutionary bi-stability (L=0.33) with linear trade-off. B: a

PIP showing no ES virulence (L=0.37). Parameters are in Fig. 1.

Figure 4 Example of evolutionary bistability with different parameters. A shows a PIP when L=0.33, and B shows evolutionary trajectories of the Mote-Carlo Simulation with L=0.38. Trade-off constant in Eq. (5) is 2.9, and others are in Fig. 1.

Figure 5 PIPs with non-linear trade-off. Top three panels show PIPs 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=0.7. When L=1.0, two PIPs are almost identical. ESS virulence is not monotonically increased as L is increased and is the largest at L=0.6 in the figure. Parameters: r=3, d=0.01, C=5.

Figure 6 A: Comparison between analytically predicted ESS (lines: analysis by selection gradient and by drawing PIPS) and simulations (dots, bar denotes s.d.). When there is a non-linear trade-off. B: Comparison of densities of pairs (gray: OO pair,

brack: SS pair). Although, analysis predicts general tendency, actual amounts are different. Parameters in A are in Fig. 5, in B: r=5, d=0.01, C=5, α=0.144717 (ESS virulence in the mixed model).

Appendix

the selection gradient by rough approximation

Boots & Sasaki (1999) showed that the invasion condition can be written as,

$$\left(\frac{1}{R_0(\alpha_I)}-\frac{1}{R_0(\alpha_J)}\right)+(1-L)(\hat{q}^0{}_{S/J}-\hat{q}_{S/I})>0, \qquad \text{(A1)}$$

where $R_0(\alpha)$ is a basic reproductive ratio as a function of virulence. $\hat{q}^0{}_{S/J}$ and $\hat{q}_{S/I}$ are also functions of virulence. If we assume that a difference of virulence between resident and mutant strains is very small (say $\alpha_J=\alpha_I+\Delta\alpha;\ \Delta\alpha>0$), the first term in Eq. (A1) is

$$\frac{1}{R_0(\alpha+\Delta\alpha)}\approx\frac{1}{R_0(\alpha)}-\Delta\alpha\frac{1}{R_0{}^2(\alpha)}\frac{dR_0(\alpha)}{d\alpha}+[\text{higher terms}]. \qquad \text{(A2)}$$

Here we omit the subscript *I*. If we approximate $\hat{q}^0{}_{S/J}\approx\hat{q}_{S/J}$ (i.e., ignoring the quasi-equilibrium), the second term can be expand as,

$$\hat{q}^0{}_{S/J}\approx\hat{q}_{S/I}+\Delta\alpha\frac{d\hat{q}_{S/I}}{d\alpha}+[\text{higher terms}] \qquad \text{(A3)}$$

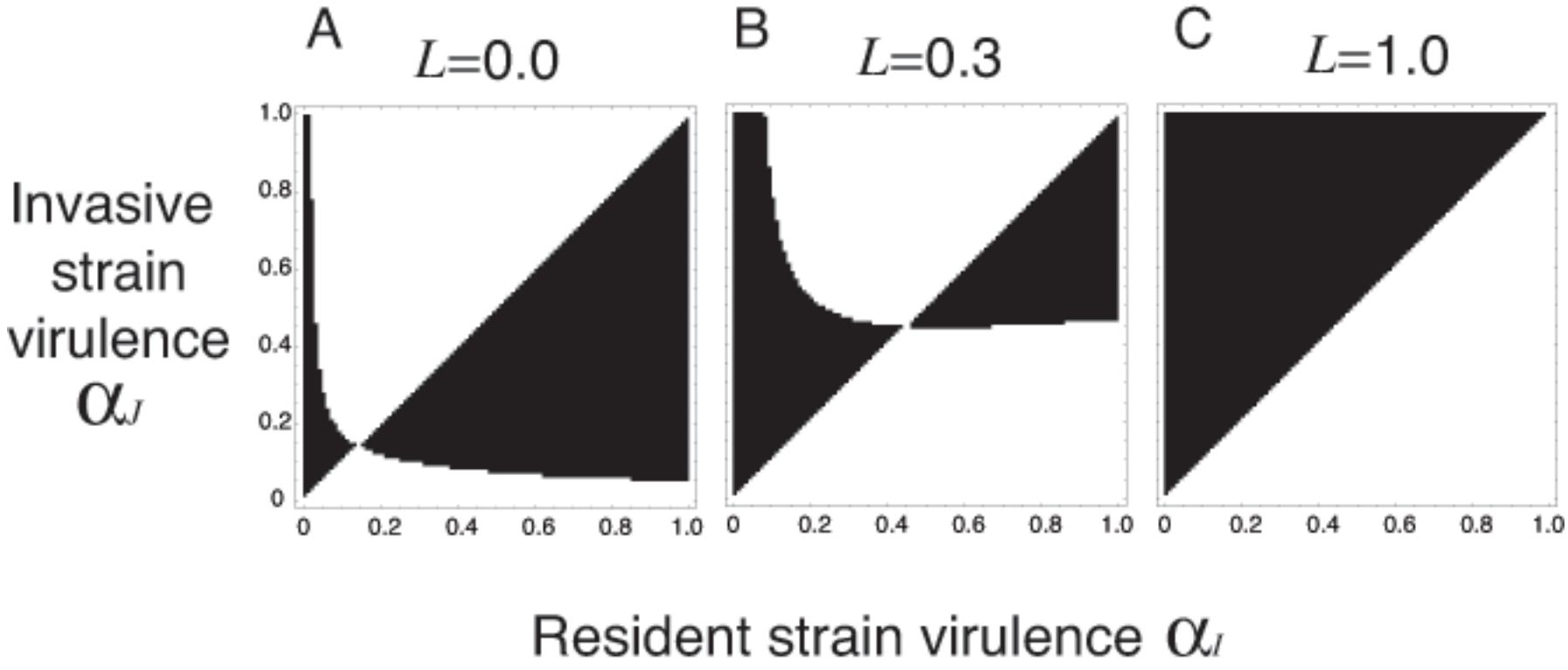
If we ignore the higher terms and combine Eqs. (A1-A3), and dividing both side by $\Delta\alpha$, we have the selection gradient in other form,

$$\frac{1}{R_0{}^2(\alpha)}\frac{dR_0(\alpha)}{d\alpha}+(1-L)\frac{d\hat{q}_{S/I}}{d\alpha}>0. \qquad \text{(A4)}$$

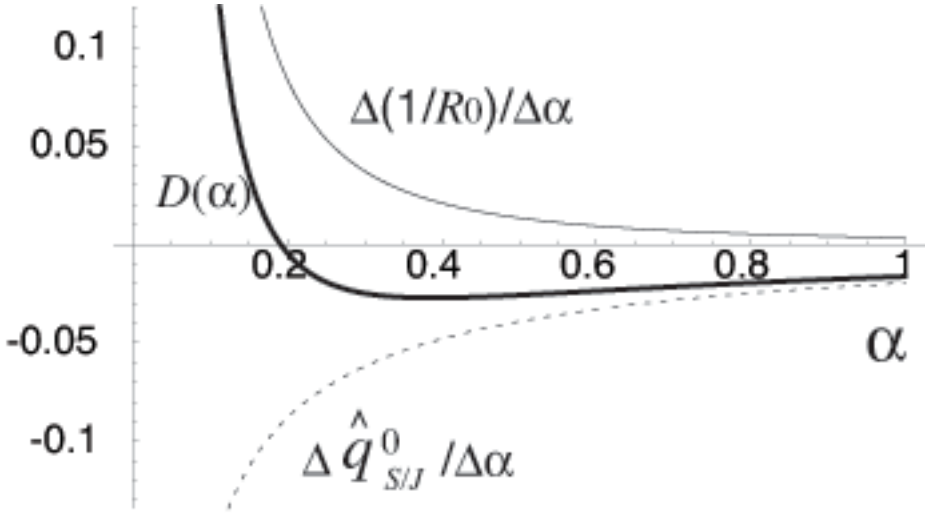
Since we ignore the quasi-equilibrium, this is a very rough approximation and not guaranteed for all the other cases. However, as is in Fig. A1, it shows a general trend of ESS values except L close to 0. When L is close to 0, there is an up-trend of ESS virulence and when L is exactly 0, ESS value is not computed because $D(\alpha)$ is always positive for any α in the range we examined and no ESS is predicted.

Figure caption

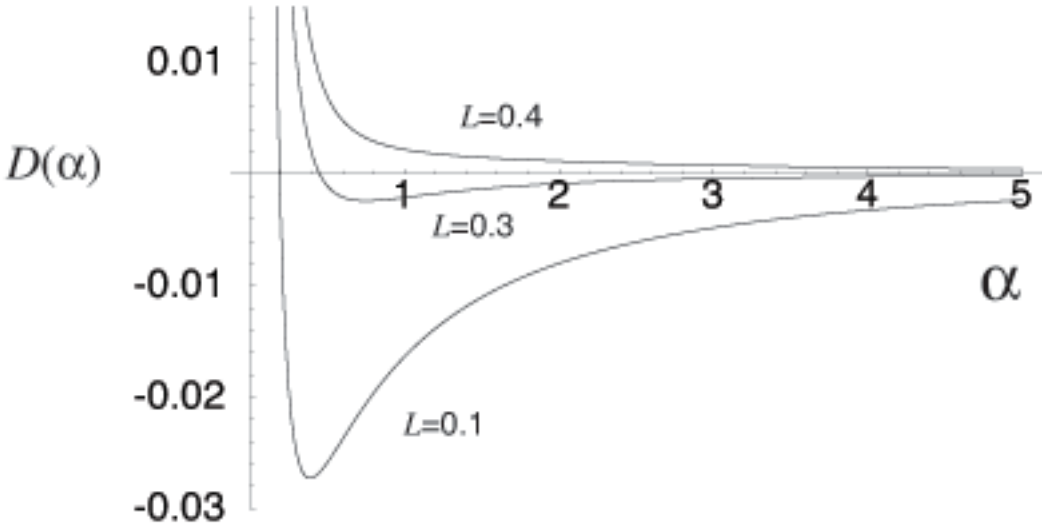
Figure A1. ESS values computed from Eq. (7) and Eq. (A1). The parameters are the same as in Figure 6. Analysis of assuming quasi-equilibrium value has better agreement to the Monte Carlo simulations (dots).


A
L=0.0
B
L=0.3
C
L=1.0
Invasive strain virulence α_J
1.0
0.8
0.6
0.4
0.2
0
0
0.2
0.4
0.6
0.8
1.0
Resident strain virulence α_I

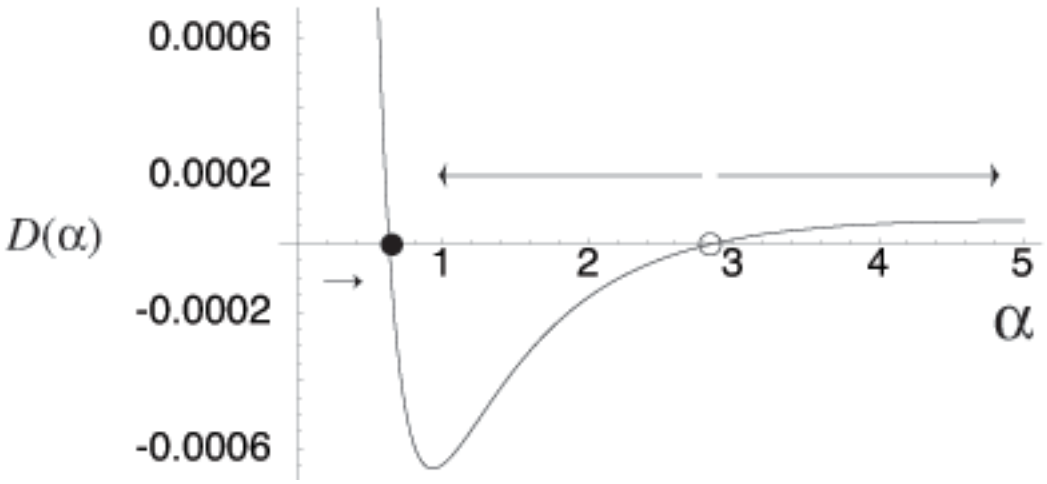
A

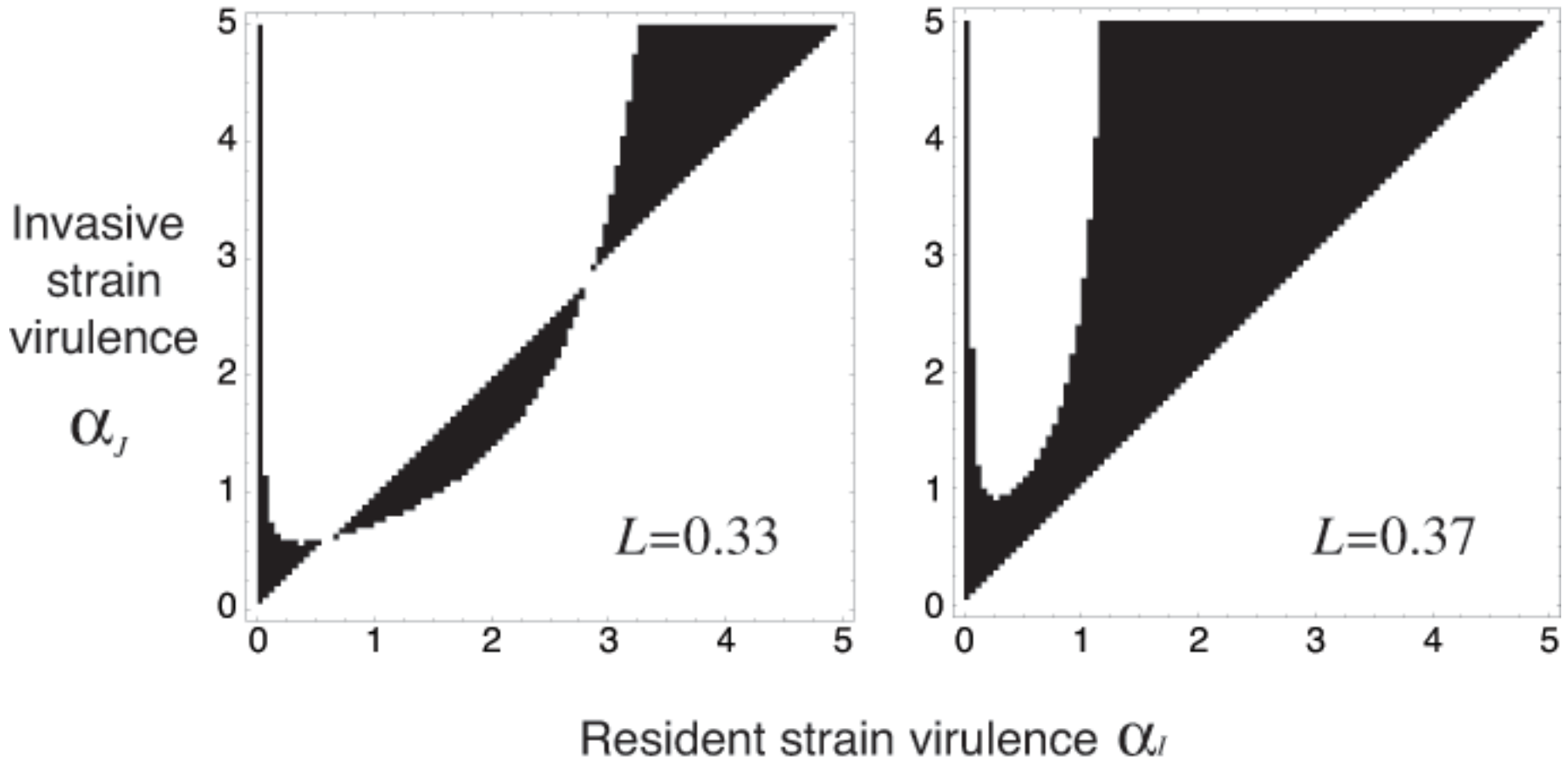

0.1
0.05
-0.05
-0.1
0.2
0.4
0.6
0.8
1
α
D(α)
Δ(1/R0)/Δα
Δ q̂ 0 S/J /Δα

B

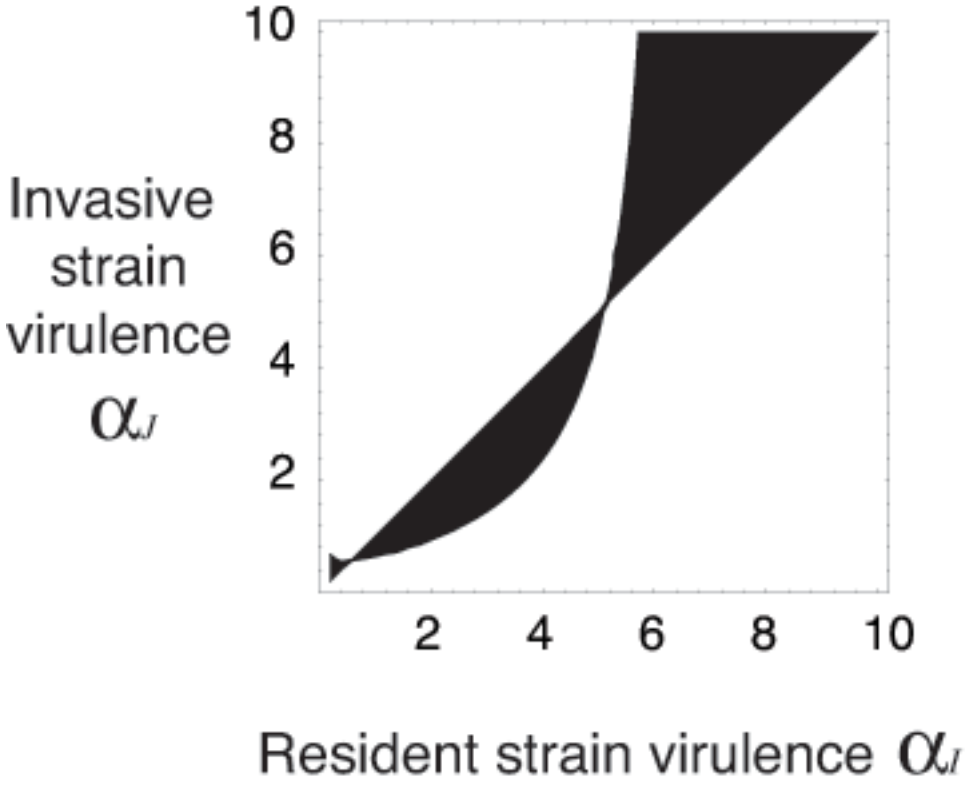

0.01
-0.01
-0.02
-0.03
1
2
3
4
5
α
D(α)
L=0.4
L=0.3
L=0.1

C

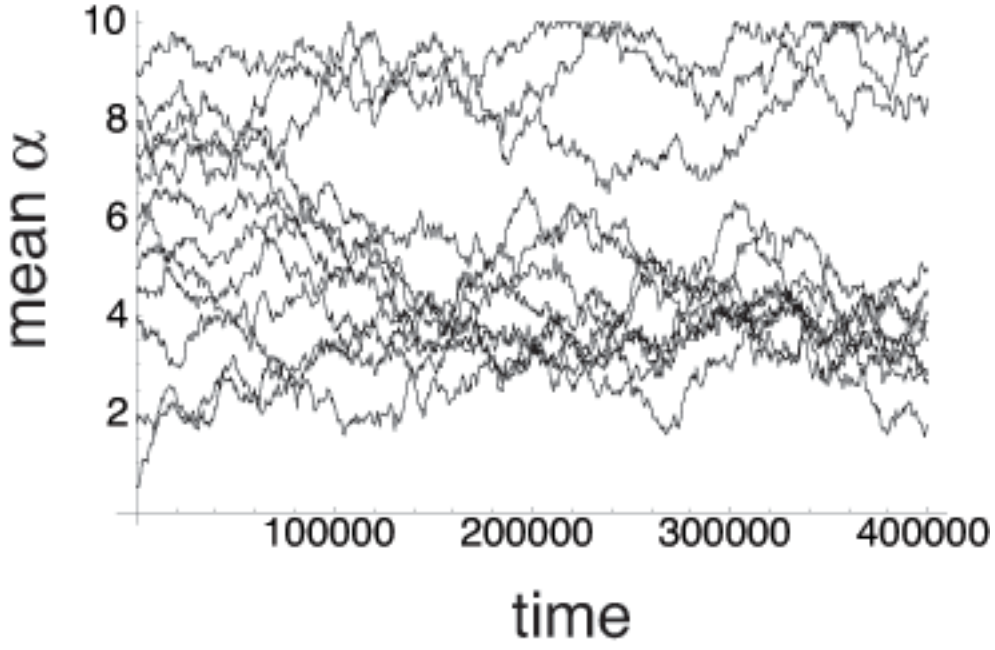

0.0006
0.0002
-0.0002
-0.0006
1
2
3
4
5
α
D(α)


Invasive strain virulence α_J
L=0.33
L=0.37
Resident strain virulence α_I

A


10
8
6
4
2
Invasive strain virulence α_J
2
4
6
8
10
Resident strain virulence α_I

B


10
8
6
4
2
mean α
100000
200000
300000
400000
time

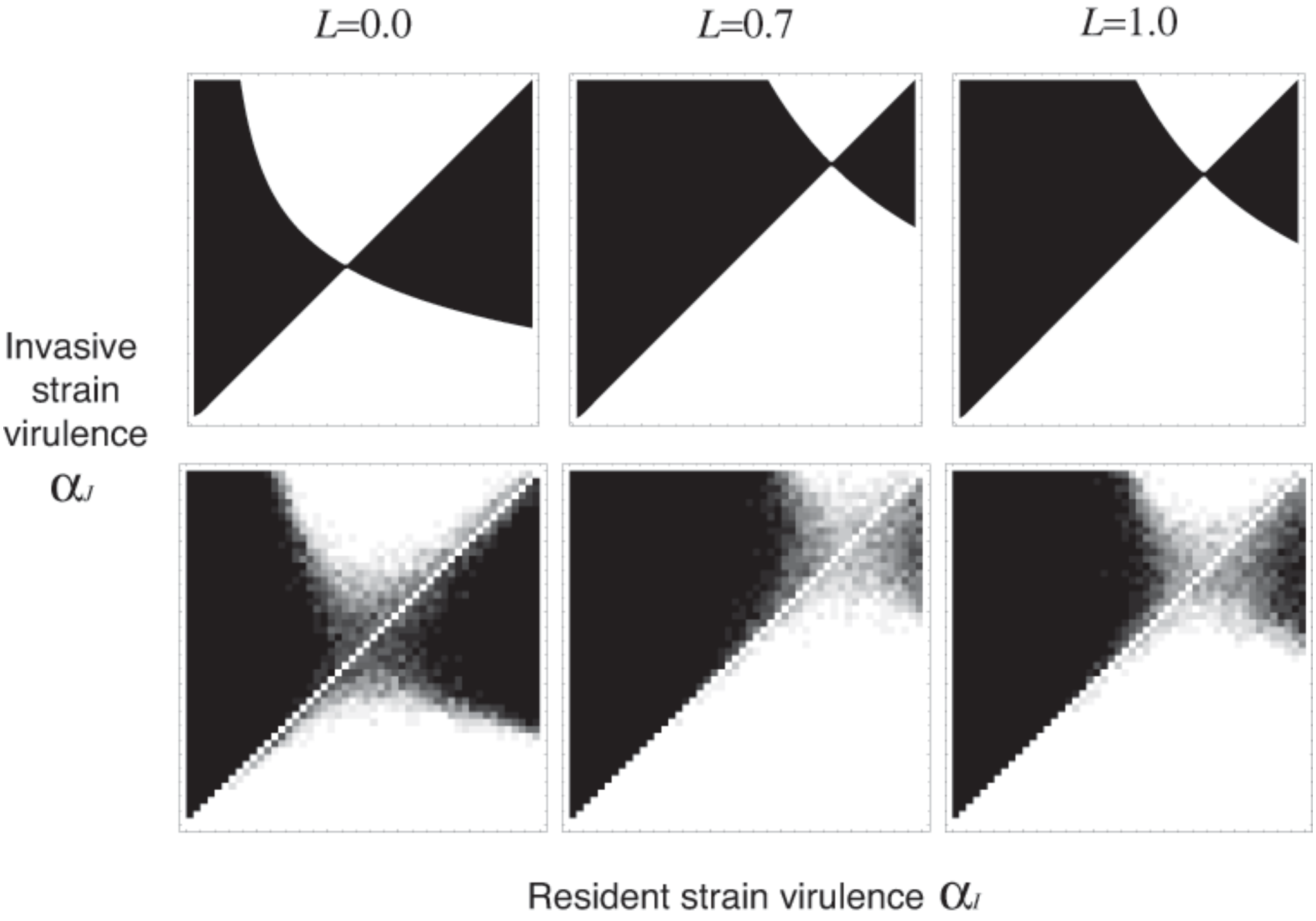
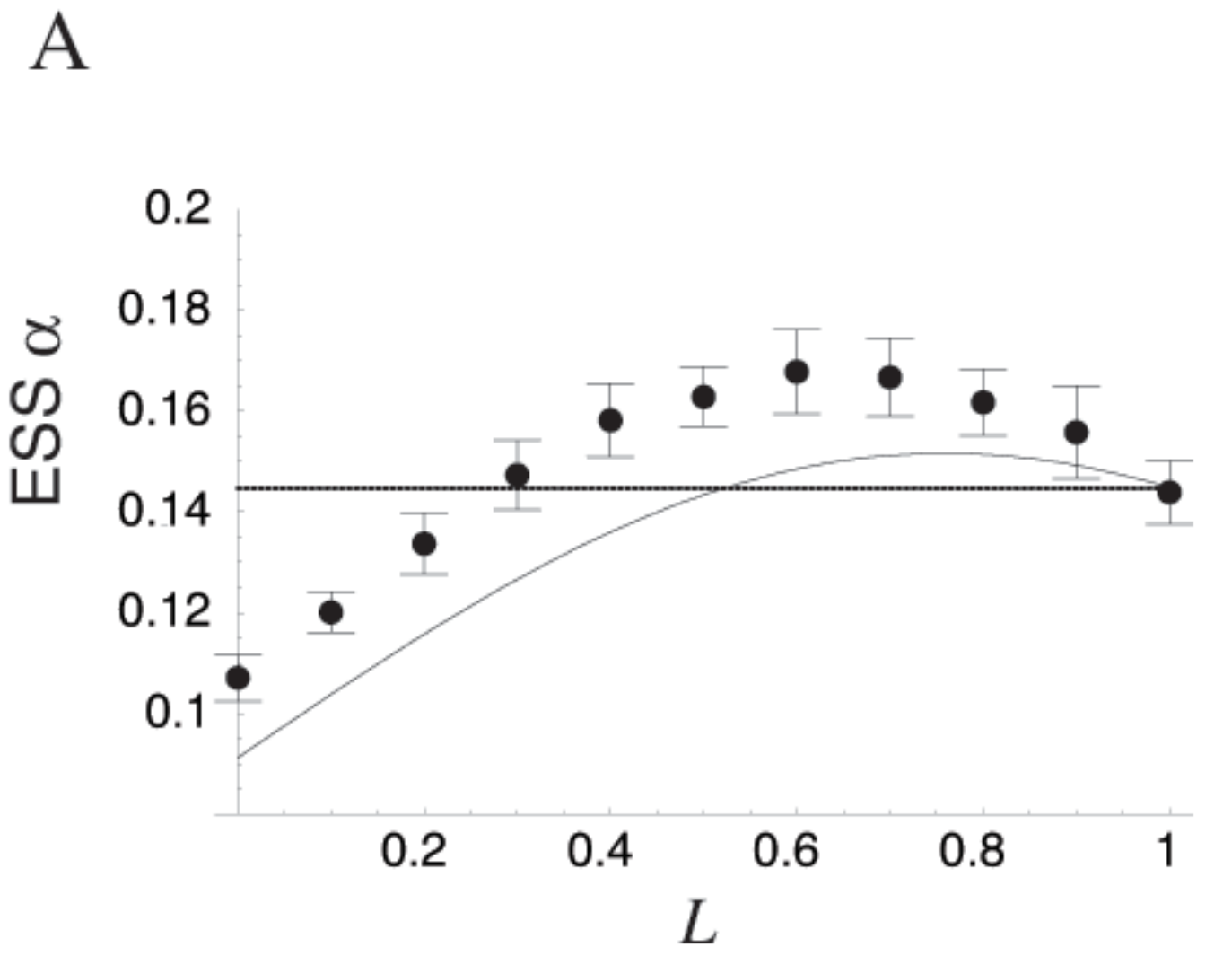
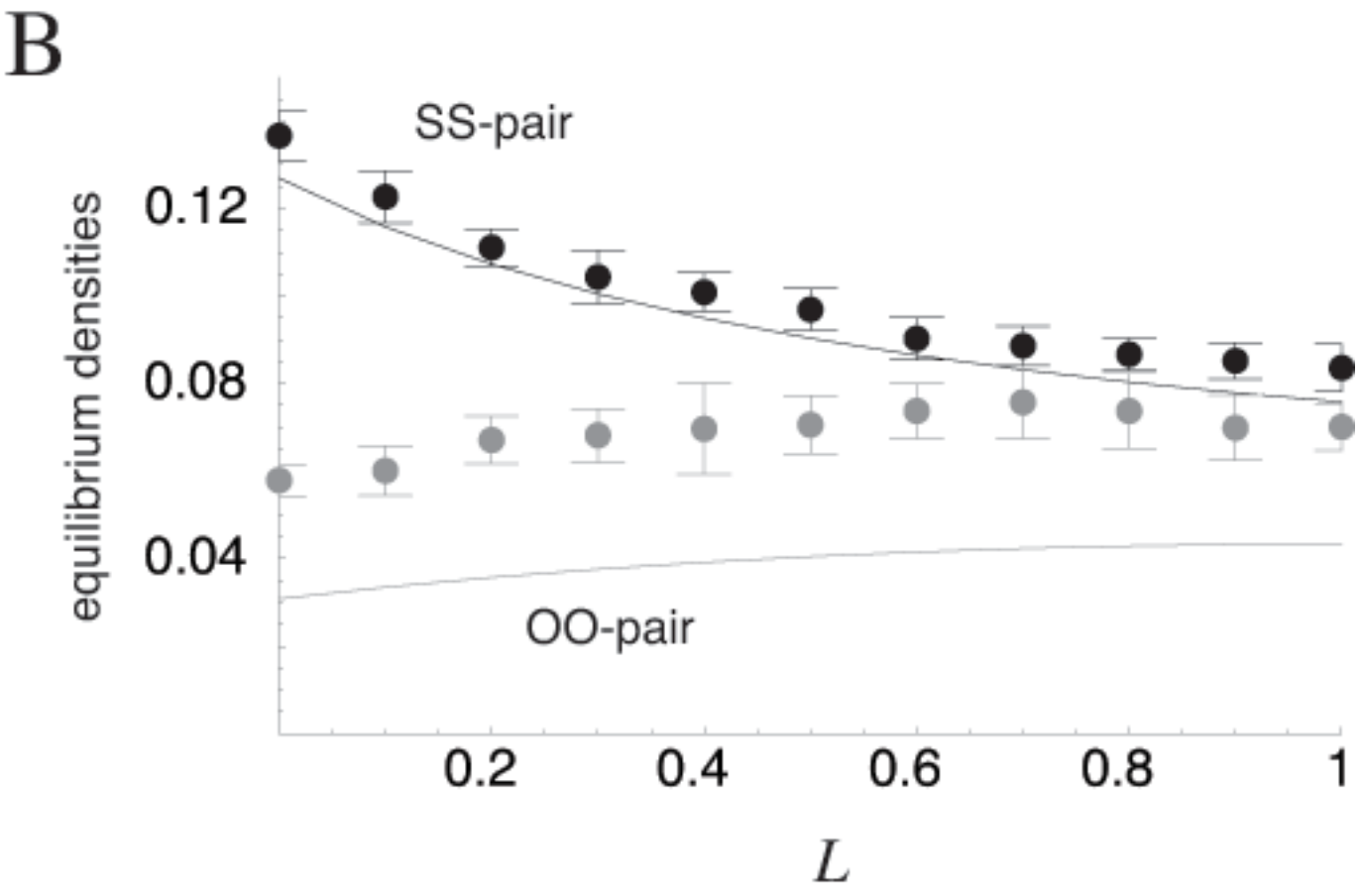
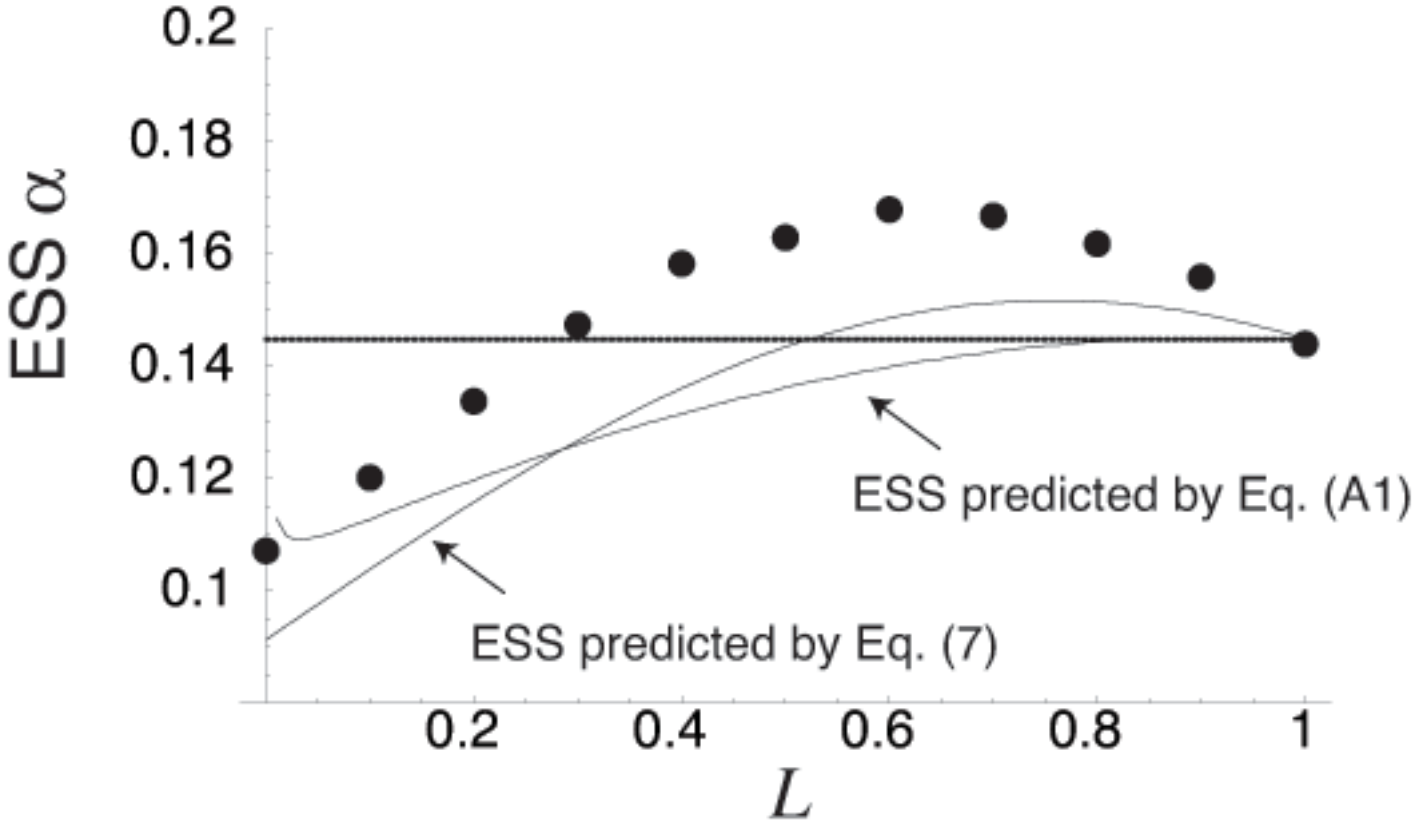

L=0.0
L=0.7
L=1.0
Invasive strain virulence α_J
Resident strain virulence α_I

Figure 6


A
ESS α
0.2
0.18
0.16
0.14
0.12
0.1
0.2
0.4
0.6
0.8
1
L


B
SS-pair
OO-pair
equilibrium densities
0.12
0.08
0.04
0.2
0.4
0.6
0.8
1
L


0.2
0.18
0.16
0.14
0.12
0.1
ESS α
ESS predicted by Eq. (A1)
ESS predicted by Eq. (7)
0.2
0.4
0.6
0.8
1
L