Journal of Theoretical Biology 376 (2015) 66–73

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Dilution versus facilitation: Impact of connectivity on disease risk in metapopulations

Zheng Y.X. Huang [a,b,c,*], Frank van Langevelde [b], Herbert H.T. Prins [b], Willem F. de Boer [b]

[a] School of Life Sciences, Nanjing Normal University, Wenyuan Road 1, Nanjing 210023, China
[b] Resource Ecology Group, Wageningen University, Droevendaalsesteeg 3a, 6708PB Wageningen, The Netherlands
[c] Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544-1003, USA

HIGHLIGHTS

- We study the effect of connectivity on disease risk in metapopulations.
- We link the diversity–disease relationship to habitat fragmentation.
- Connectivity can have either positive or negative effect on disease risk.
- The net impact of connectivity depends on the facilitation versus dilution effect.
- Different disease risk indicators react differently to changes in connectivity.

ARTICLE INFO

Article history:
Received 1 December 2014
Received in revised form
1 April 2015
Accepted 4 April 2015
Available online 14 April 2015

Keywords:
The diversity-disease relationship
Habitat fragmentation
The competence–extinction relationship
Local extinction
Frequency-dependent transmission

ABSTRACT

Epidemiological studies have suggested that increasing connectivity in metapopulations usually facilitates pathogen transmission. However, these studies focusing on single-host systems usually neglect that increasing connectivity can increase species diversity which might reduce pathogen transmission via the 'dilution effect', a hypothesis whose generality is still disputed. On the other hand, studies investigating the generality of the dilution effect were usually conducted without considering habitat structure, which is surprising as species loss is often driven by habitat fragmentation. Using a simple general model to link fragmentation to the dilution effect, we determined the effect of connectivity on disease risk and explored when the dilution effect can be detected. We showed that landscape structure can largely modify the diversity–disease relationship. The net impact of connectivity on disease risk can be either positive or negative, depending on the relative importance of the facilitation effect (through increasing contact rates among patches) versus the dilution effect (via increasing species richness). We also demonstrated that different risk indices (i.e. infection prevalence and abundance of infected hosts) react differently to increasing connectivity and species richness. Our study may contribute to the current debate on the dilution effect, and a better understanding of the impacts of fragmentation on disease risks.

1. Introduction

The landscape configuration and structure can influence pathogen transmission dynamics by modifying host movements and contact rates (Cross et al., 2005; Hess, 1996; Keeling, 2000). Previous epidemiological studies have suggested that increasing habitat connectivity and host movements in metapopulations usually facilitate disease transmission, allowing a pathogen to successfully invade a metapopulation (Colizza and Vespignani, 2007; Tanaka et al., 2014) and increasing the prevalence and incidence of endemic diseases in metapopulations (Cross et al., 2005; Hess, 1996). However, epidemiological studies usually focused on single-host systems and neglected the effect of habitat structure and connectivity on species diversity and composition in landscape which may also influence host–pathogen interactions. In fact, studies have demonstrated that habitat structure and connectivity are linked to the capacity of a metapopulation and can determine the species diversity and composition in a landscape (Hanski and Ovaskainen, 2000). Therefore, habitat structure and connectivity can also influence pathogen transmission via modifying species composition.

Several studies argued, taking an ecological perspective, that high species richness can reduce the risk of infectious diseases via a

* Corresponding author at: Resource Ecology Group, Wageningen University, Droevendaalsesteeg 3a, 6708PB Wageningen, The Netherlands.
Tel.: +86 13921431410.
E-mail address: zhengyxhuang@gmail.com (Z.Y.X. Huang).

http://dx.doi.org/10.1016/j.jtbi.2015.04.005
0022-5193/

hypothesised 'dilution effect' (Huang et al., 2013b; Keesing et al., 2010; LoGiudice et al., 2003; Ostfeld and Keesing, 2012; Venesky et al., 2013). This dilution effect has been reported in a wide range of infectious diseases, and has attracted much current attention in the context of global biodiversity loss and increased disease emergence (Ostfeld and Keesing, 2012). While the dilution effect hypothesis presents an exciting convergence of public health concern and biodiversity conservation, its generality is still under active debate (Begon, 2008; Randolph and Dobson, 2012; Salkeld et al., 2013; Wood and Lafferty, 2013; Wood et al., 2014). There are several theoretical studies trying to explore the generality of the dilution effect. For example, it has been shown that the probability of the occurrence of the dilution effect may depend on the type of disease transmission (Dobson, 2004; Rudolf and Antonovics, 2005). Specifically, studies found that the dilution effect is more likely to operate in diseases with frequency-dependent transmission (Joseph et al., 2013; Rudolf and Antonovics, 2005); for diseases with density-dependent transmission, high species richness generally increases the risk unless it engenders reduced densities of competent hosts (Rudolf and Antonovics, 2005) or reduce the encounters between parasites or vectors and competent hosts (Keesing et al., 2006). Different indices of disease risk may also react differently to the changes in species richness. Using Preston's distribution as the law of community assemblage, a theoretical study found that high species richness can reduce infection prevalence while the number of total infected hosts in the community increases (2012). However, these studies on the diversity-disease debate were usually conducted in spatially homogeneous environments (but see (Allan et al., 2003)). Considering that species loss is often driven by habitat fragmentation, it is necessary to explore the diversity–disease relationship in fragmented landscapes to get a better understanding of the dilution effect and the role of fragmentation in host–pathogen interactions.

Increasing connectivity can enhance disease risk through facilitating contact rates among individuals, however it may also bring more species in the community, reducing disease risk via the dilution effect. Here, using a simple model, we investigate the effect of habitat connectivity, measured as host migration rate (Hess, 1996), on pathogen transmission in Levins' metapopulations (Levins, 1969). We explored the relative importance of the facilitation versus the dilution effect when connectivity increases. Furthermore, we explored the conditions under which the dilution effect can be expected. The risk of pathogen transmission was measured with three different indices: probability of pathogen invasion to the metapopulation, the mean infection prevalence of the competent host (i.e., the proportion of infected hosts in the whole metapopulation) and the mean number of infectious competent hosts. We first analysed the model behaviour in a single-host system and explored how the facilitation effect operated. We then extended our model to a two-host system, with a competent host species and a low-competence host species, and explored the relative importance of the dilution versus facilitation effect on disease risk.

2. Methods

2.1. Pathogen transmission in the single-host system

We incorporated a classical SIR (susceptible-infectious-recovered) model into Levins' metapopulation model where the hosts were fully mixed in a certain number of identical, environmentally homogenous patches and all patches were equally accessible to the hosts from other patches (Levins, 1969). The model reads as

$$dS_i/dt = bN_i - (\lambda + d)S_i \quad (1)$$

$$dI_i/dt = \lambda S_i - (r + d)I_i \quad (2)$$

$$dR_i/dt = rI_i - dR_i \quad (3)$$

where N_i represented the host population size in patch i, and hosts could be either susceptible (S_i), infected (I_i) or recovered/immune (R_i). The host population increased with logistic growth, which included a constant birth rate b and a density-dependent mortality d within each patch. Host mortality was assumed to be independent of infection status. Infected hosts could be recovered from the infection at a recovery rate r and recovered individuals were immune to the pathogens. We assumed a frequency-dependent transmission, since the dilution effect is more likely to occur in this type of disease (Dobson, 2004; Joseph et al., 2013; Rudolf and Antonovics, 2005). Then, the force of infection λ was determined by intraspecific transmission rate β

$$\lambda = \beta I_i/N_i \quad (4)$$

The population demographic processes and pathogen transmission dynamics were modelled discretely. At each time step, the processes of birth, death, infection, recovery, movement and extinction were modelled sequentially (Hess, 1996; Jesse and Heesterbeek, 2011; Jesse et al., 2008). These processes were also modelled stochastically by describing them as random variables for each step. The number of newly-born individuals followed a Poisson distribution, whereas the number of deaths, infections, and recoveries followed a binomial distribution. Newborns would neither die nor be infected (Jesse and Heesterbeek, 2011; Jesse et al., 2008).

All patches were connected to each other via host movements (Hess, 1996; Jesse et al., 2008). The migration proportion, m, as a measure of connectivity, was used to describe how many individuals left a patch at each time step. The migration proportion therefore represented the movement rates among subpopulations, with a higher value of migration proportion representing a higher frequency of movements (Hess, 1996), which is a characteristic of less fragmented landscapes. This migration proportion was assumed to be the same, regardless of the state of the individuals or the local population size in the patch. The number of emigrants for each patch at each time step also followed a binomial distribution, and all emigrants were distributed randomly over all patches.

In addition, we set a local extinction rate for the local population in each patch at each time step. This extinction rate was the inverse of persistence time, $T_p(i)$, which was a function of population size N_i and carrying capacity K (Hakoyama and Iwasa, 2000)

$$T_p(i) = \frac{N_i K}{N_i + K/a} \quad (5)$$

where a was the adjusting parameter for persistence time. Higher values of a lead to a higher T_p and thus a lower local extinction risk.

2.2. Pathogen transmission in the two-host system

We further extended the above mentioned single-host model to a two-host system including one competent and one low-competence host species. We only used two host species to make the results tractable. Here, we assumed that the low-competence host species had a higher local extinction risk (lower birth rate, b_2 and lower carrying capacity, K_2) than the competent host. The negative competence–extinction relationship can be generated from two alternative mechanisms based on parasite local adaptation theory and life-history theory (Joseph et al., 2013). Parasite local adaptation theory predicts that parasites may evolve to exploit the most common host as a consequence of selective pressure of losing hosts during community disassembly (Joseph et al., 2013). Life-history theory generally suggests that slow-lived species, which are more likely to have lower population densities and are more vulnerable to biodiversity declining due to less investment in reproduction (Cardillo,

2003; Henle et al., 2004), usually invest more in immunological defences and act as less competent hosts for pathogens (Lee et al., 2008; Martin II et al., 2006). Although the relationship between life-history and reservoir competence has been supported in several different diseases (Cronin et al., 2010, 2014; Huang et al., 2013a; Johnson et al., 2012; Previtali et al., 2012), directly using immune-response measures as indication of reservoir competence might be difficult due to the complication of immunity (Randolph and Dobson, 2012). Despite the existing disputes regarding to the life-history theory, the negative competence–extinction relationship has been documented in several disease systems, such as *Ribeiroia ondatrae* (Johnson et al., 2013) and four generalist aphid-vectored pathogens (Lacroix et al., 2014), implying that our assumption about higher extinction risk of low-competence host species may at least be valid for these diseases.

Interspecific transmission between the competent and low-competence hosts was assumed to be symmetrical and was quantified as a scaled average of the intraspecific transmission rates, as set in previous studies (Dobson, 2004; Joseph et al., 2013; Rudolf and Antonovics, 2005)

$$\beta_{12}=\beta_{21} = c\left(\frac{\beta_1+\beta_2}{2}\right) \tag{6}$$

where β_1 and β_2 were the intraspecific transmission rates, while β_{12} and β_{21} were the interspecific transmission rates, and c was a scaling parameter allowing us to adjust the magnitude of the interspecific transmission rates. The force of infection for the competent host, λ_1, was calculated as (Rudolf and Antonovics, 2005)

$$\lambda_1 = \beta_1\frac{I_1}{N_1+N_2}+\beta_{21}\frac{I_2}{N_1+N_2} \tag{7}$$

In this way, λ_1 can be reduced by the mechanism 'transmission interference' due to the lower intraspecific transmission rate of the low-competence host. Besides, the dilution effect can also be caused by two other mechanisms: host regulation where the low-competence host species can reduce the abundance of competent host species by competition or predation, and encounter reduction where the low-competence host is capable of reducing the contact rate among the competent hosts (Keesing et al., 2006). In addition, the low-competence host may also increase the encounter rates among competent hosts, generating an 'encounter augmentation' (Keesing et al., 2006). We simulated all of these scenarios. We modelled host regulation by adding an extra mortality of the competent host in the presence of the low-competence host species, so that the carrying capacity of the competent host K_1' was dependent of the abundance of the low-competence host

$$K_1' = K_1\left(1-\frac{H_2}{q}\right) \tag{8}$$

where q is the 'host regulation parameter' modulating the extent to which the low-competence host population reduces the carrying capacity of the competent host. H_2 is the abundance of the low-competence host. In this way, the mortality of the competent host in the presence of low-competence hosts was

$$d' = \frac{dq}{q-H_2} = b\left(1+\frac{H_2}{q-H_2}\right) \tag{9}$$

The encounter reduction and augmentation were simulated using an 'encounter modification parameter', p, to modulate the extent to which the low-competence host population increase or reduce the force of infection of the competent host, λ_1.

$$\lambda_1' = \beta_1\frac{I_1}{N_1+pN_2}+\beta_{21}\frac{I_2}{N_1+N_2} = \frac{\beta_1(N_1+N_2)}{(N_1+pN_2)}*\frac{I_1}{N_1+N_2}+\beta_{21}\frac{I_2}{N_1+N_2} \tag{10}$$

When the value of p is larger than one, it means that the low-competence host can reduce the encounter rate (and thus transmission rate) among competent hosts, while p smaller than one means that the encounter rate increases with the addition of the low-competence host.

The 'dilution potential', defined as the potential of the additional host to reduce the disease risk of the competent host (LoGiudice et al., 2003), could be determined by the intraspecific transmission rate of the low-competence host β_2, the scaling parameter c and the parameters p and/or q. A higher dilution potential corresponds with a lower value of β_2, c, q and/or a higher value of p. We varied these parameters to investigate the relative importance of the dilution effect triggered by the low-competence host with different dilution potentials. Details for all parameters are provided in Table 1. For reasons of simplicity, the migration proportions for the low-competence and competent hosts were assumed to be similar. However, relaxing this assumption will not qualitatively affect our conclusions (see Section 3 and Appendix Fig. A.2).

2.3. Model analyses

The carrying capacity of a patch was set at 100 for the competent host, which was large enough for the infection to become endemic after the pathogen successfully invaded the metapopulation. Twenty-five patches in a Levins metapopulation were used in the simulations (we found that the number of patches did not change the results qualitatively). We assumed that the time step was two weeks. Therefore, the annual reproduction rate was $1.01^{25}=10.8$ and the death rate for the competent host was 0.05 if the population is at half of the carrying capacity, translating to the mean life expectancy of 40 weeks. The movement rate $m=0.01$ means an average of 22% of individuals in a

Table 1
Description of model parameters and variables. Subscripts 1 and 2 represent the competent and low-competence host species, respectively.

Parameter	Definition	Values
b	Birth rate	$b_1=0.1$; $b_2=0.08$
d	Death rate	$d=bN/K$
β_1	Intraspecific transmission rate for competent host	0.9
β_2	Intraspecific transmission rate for low-competence host	[0.1, 0.9]
$\beta_{12}=\beta_{21}$	Interspecific transmission rate	$c(\beta_1+\beta_2)/2$
c	Interspecific transmission scaling parameter	[0.01, 1]
q	Host regulation parameter	200, 300, 400
p	Encounter modification parameter	0.5, 1, 2
r	Recovery rate	[0.1, 0.3]
K	Patch carrying capacity	$K_1=100$; $K_2=80$
$m_1=m_2$	Migration proportion	[0, 0.05]
a	Local population extinction adjusting parameter	$a_1=5$; $a_2=3$

patch leaving over 1 year (if $x \sim Bin$ (10, $1-0.99^{25}$), then $E[x]=0.22$), whereas the maximum movement rate in our study 0.05 translates to 72% of individuals leaving in one year. We first ran the model without pathogens for 500 time steps to allow the system to reach a quasi-equilibrium. Then, an infectious competent individual was added into a randomly selected occupied patch, and the transmission process was simulated with another 500 time steps so that the populations reached an approximate equilibrium (Appendix Fig. A.1). Since the infection and demographic processes are stochastic and can create large variation among runs of the model, we ran 1000 repetitions for each parameter set (Cross et al., 2005). The mean infection prevalence of the competent host (IPC) and the number of infected competent hosts (NumInfC) were quantified for the simulations with successful pathogen invasion and persisting infection.

We first analysed the model behaviour in a single-host (competent host) system with different recovery rates, and explored how the facilitation effect operated. We then extended our model to a two-host system and explored the relative importance of the dilution and facilitation effects on disease risk under different levels of dilution potential of the low-competence host.

3. Results

3.1. Two scenarios: facilitation effect and dilution effect

Our results for the pathogen transmission with a single-host model under different recovery rates show that the infection could not invade the metapopulation when habitat connectivity was very low (Fig. 1). When the pathogen invaded the metapopulation, the mean infection prevalence and the probability of pathogen invasion showed similar saturating relationships with migration proportion at different recovery rates (Fig. 1), indicating that the facilitative effect of connectivity can only operate within a certain range of connectivity. We defined the facilitation region as the range of the migration proportion where increasing migration proportion increased the infection prevalence. We used moving windows with a window of five steps (0.005), where the infection prevalence increased by less than 2% with an increase of 0.005 in migration proportion to determine the upper threshold for the facilitation range (we found that slightly different criteria did not change the results qualitatively). We used infection prevalence to define the facilitation region because infection prevalence for frequency-dependent transmitted diseases is independent of host density, and thus its increase would only have been caused by increasing contact rates among local populations. The width of the facilitation region was enlarged with increasing recovery rate (shown by the dashed vertical lines in Fig. 1).

The results also showed that the population sizes for competent and low-competence hosts reacted similarly to increasing connectivity (Fig. 2). A higher connectivity threshold was needed for the low-competence host than for the competent host to persist in the metapopulation due to a lower carrying capacity and higher local extinction risk of the low-competence host. When the low-competence hosts began to persist in the system, the dilution effect might start to operate due to various mechanisms (transmission interference, host regulation or encounter reduction). Given that the facilitation region for the competent host depended on the recovery rate, two distinct scenarios became apparent. One scenario was that the facilitation effect and dilution effect overlapped over a gradient of migration proportions (i.e., $r=0.3$, shown as the shaded area in Fig. 2). The other scenario was that the facilitation effect operated at lower values of the migration proportion than the dilution effect (i.e., $r=0.1$, Fig. 2). We explored how disease risks reacted to increasing connectivity with different dilution potentials of the low-competence

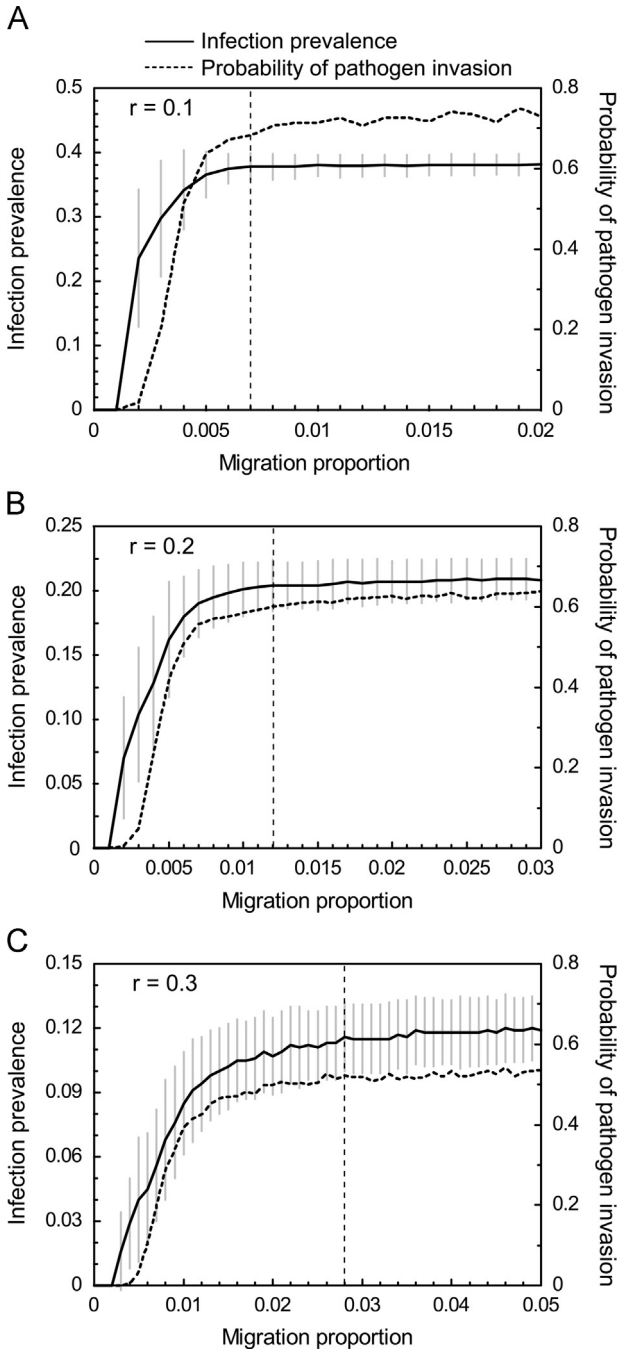

Fig. 1. Changes in the probability of pathogen invasion (dashed curves) and in infection prevalence (solid curves) with increasing migration proportion under different recovery rates: (A) $r=0.1$; (B) $r=0.2$; and (C) $r=0.3$. Grey vertical lines indicate the standard deviation for the infection prevalence, and dashed vertical lines indicate the upper threshold of the facilitation region.

host, varying intra- and interspecific transmission rates (low: $\beta_2=0.1$, $c=0.1$; high: $\beta_2=0.75$, $c=0.75$). We also varied the host regulation parameter and encounter modification parameter to simulate different strength of host regulation (low, $q=400$; intermediate, $q=300$; high, $q=200$) or encounter reduction/augmentation (reduction, $p=2$; augmentation, $p=0.5$). We only investigated the scenario in which the facilitation and dilution effect overlapped, since we focused on the relative importance of these two effects. Here, we considered that relaxing the assumption of similar migration rates between two hosts would not qualitatively affect our results, since it only changed the threshold of connectivity for colonisation of the low-competence host and made the overlap region (the range of

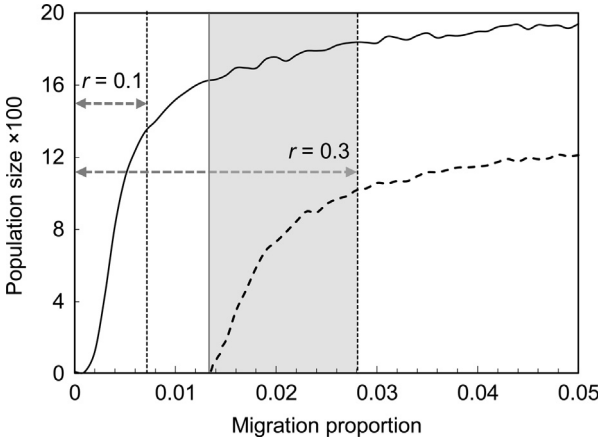

Fig. 2. Changes in the equilibrium population sizes (after 500 time steps) of the two hosts (dashed curve: low-competence host; solid curve: competent host) with increasing migration proportion. The grey dashed arrows indicate the facilitation region under different recovery rates (taken from Fig. 1) and the shaded area refers to the overlap region where both a dilution and a facilitation effect operate under the condition that the recovery rate $r=0.3$. The dilution effect operates when the low-competence hosts invade the system.

connectivity where both a facilitation and a dilution effect operate) move over the gradient of connectivity (see Appendix Fig. A.2).

3.2. Dilution versus facilitation in a two-host system

We first explored the scenario when only transmission interference operated ($p=1$, $q=+\infty$). When the dilution effect and the facilitation effect overlapped ($r=0.3$) and the low-competence host had lower intra- and interspecific transmission rates ($\beta_2=0.1$, $c=0.1$, Fig. 3A), the number of infected competent hosts (NumInfC) and the infection prevalence of the competent host (IPC) showed similar patterns. They first increased with migration proportion because of the facilitation effect, and then decreased due to the dilution effect to relatively stable levels. Hence, in the overlap region (where both the facilitation and the dilution effect operate), the facilitation effect was outweighed by the dilution effect. However, when the low-competence host had higher intra- and interspecific transmission rates ($\beta_2=0.75$, $c=0.75$) different disease risk indicators showed different reactions in the overlap region (Fig. 3B). The NumInfC increased, whereas the IPC remained relatively stable, indicating the dilution effect roughly balanced by the facilitation effect. We then varied the intra- and interspecific transmission rates of the low-competence host (different combinations of c and β_2) to investigate the net effect of connectivity on disease risk, i.e., whether disease risk indicators increased or not in the overlap region where the facilitation and the dilution effect overlapped (Fig. 4A). Our results showed that lower intra- and interspecific transmission rates (low values for β_2 and/or c) were required for NumInfC to decrease than for IPC, indicating that it would be more likely to detect a negative effect of connectivity when using infection prevalence as the disease indicator in this situation.

When we added the host regulation mechanism and increased its extent, lower dilution potentials were required to allow the number of infected competent hosts (NumInfC) to decrease in the overlap region (Fig. 4B). When the competition was strong enough (q was smaller than 200), connectivity always had a negative effect on NumInfC. However, the infection prevalence of the competent host (IPC) only changed slightly (Fig A.3) with increasing extent of competition, as we used a frequency-dependent transmission which is independent of host abundance. Therefore, which risk indicator (prevalence or abundance of infection) is more likely to have a negative relationship with connectivity depends on the strength of competition when host regulation operates. We then

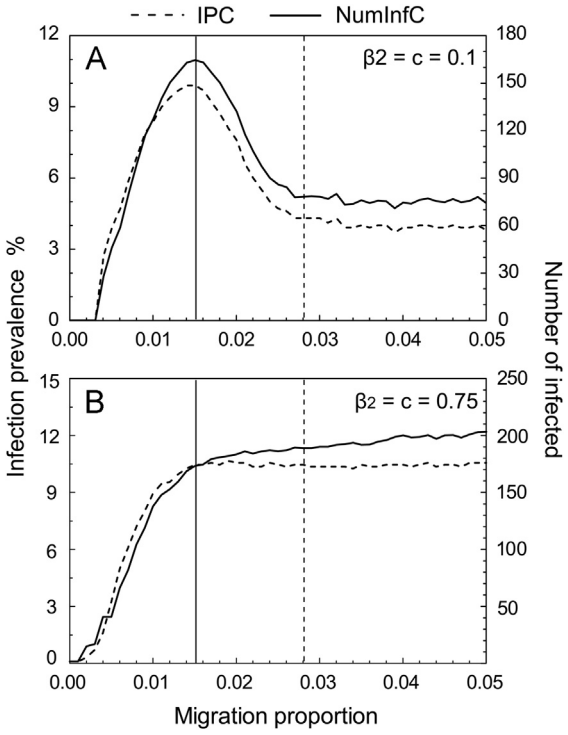

Fig. 3. Changes in the infection prevalence of the competent host (IPC, dashed curves) and number of infected competent hosts (NumInfC, solid curves) with increasing migration proportion when only the transmission interference operates. Dashed vertical lines indicate the upper threshold of the facilitation region (see Fig. 1), while the solid vertical lines indicate the start of the dilution effect (see Fig. 2). (A) Dilution overweighs facilitation ($\beta_2=c=0.1$). (B) Dilution roughly balanced by facilitation ($\beta_2=c=0.75$).

investigated the relative importance of the facilitation versus dilution effect in the condition of 'encounter modification'. Compared with IPC, a lower dilution potential of the low-competence host (higher values for β_2 and/or c) was always required for the NumInfC to keep stable in the overlap region (Fig. 4C) due to the increased population size of the competent host. Therefore, when either the encounter reduction or the encounter augmentation operates, it will always be more likely to detect a negative effect of connectivity when using IPC than using NumInfC.

4. Discussion

4.1. Results from the single-host system

Our results from the single-host system showed that the infection could not invade the metapopulation when habitat connectivity was very low (Fig. 1). This because at low connectivity infected individuals cannot move frequently enough and thus have very low probabilities of arriving in a fully susceptible patch and spreading the pathogen within their infection periods. Then, the infection prevalence increased within a certain range of migration proportion to a relative stable value (Fig. 1). This is because infectious individuals did not move frequently at low migration proportions, i.e. in a highly fragmented landscape, and thus could not encounter enough susceptible individuals and spread the pathogen, especially when there are many recovered and immune individuals and limited susceptibles. The infection prevalence was high when the metapopulation acted more like a homogeneous population at high migration proportions, which resulted in immediately access of susceptible individuals for infected individuals. A higher recovery rate led to a larger facilitation region as a higher recovery rate means shorter

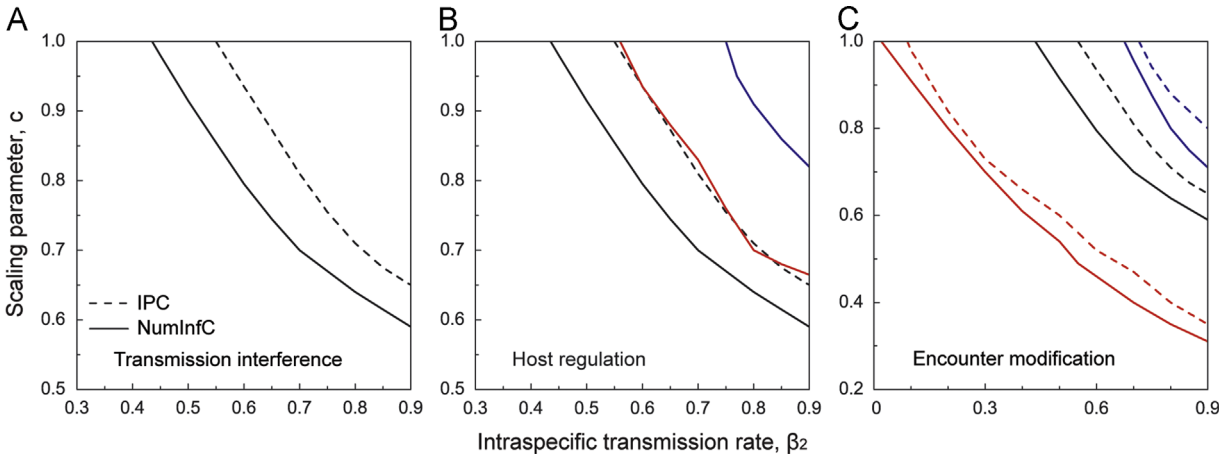

Fig. 4. Thresholds for the combination of the intraspecific transmission rate for the competent host (β_2) and the interspecific transmission scaling parameter (c) under which the disease risk indicators decreases in the overlap region. The infection prevalence of the competent host (IPC, dashed curves) or the number of infected competent hosts (NumInfC, solid curves) increased in the upper-right regions (lower dilution potential). (A) Under the condition of transmission interference ($p=1$, $q=+\infty$). (B) Under different strength of host regulation (black=no competition; red=low; blue=intermediate). (C) Under the mechanism 'encounter modification' (black=no modification; red=encounter augmentation; blue=encounter reduction).

infection periods, and high infection prevalence could only be achieved when infectious individuals moved more frequently to encounter susceptible individuals within their infection period.

4.2. Dilution versus facilitation

Human-induced habitat fragmentation plays an important role in species loss (Fahrig, 2003), and in turn can modify disease dynamics (Keesing et al., 2006; Ostfeld and Keesing, 2012). Some studies have shown increased disease risk in fragmented habitats with decreasing species richness (Allan et al., 2003; Brownstein et al., 2005; Johnson et al., 2013), providing supporting evidence for the dilution effect. Others, however, have not found such a relationship (Young et al., 2013), and argued that habitat fragmentation has a more complex and ambiguous role in pathogen transmission (Estrada-Peña et al., 2014; Wood and Lafferty, 2013). Our modelling study demonstrates that these apparent contradictions for the effects of habitat fragmentation can be understood, and suggests that both dilution and facilitation effects can operate with increasing habitat connectivity. Our study also shows that whether disease risk decreases or not depends on the dilution potential of the low-competence host. In addition, different disease risk indicators (the prevalence and number of infections) respond differently to changes in connectivity. Which risk indicator is more likely to have a negative relationship with connectivity depends on the mechanism of the dilution effect and its strength.

Our results show that disease risk in fragmented habitats does not always need to decrease due to the dilution effect when connectivity increases, but can also increase because of a facilitation effect. The net effect of connectivity reflects the relative importance of the dilution versus the facilitation effect. This result about spread of pathogens in fragmented habitat might partly explain the current contradictions about whether the dilution effect exists or not. For example, a recent study showed that a higher risk of chytridiomycosis, caused by the chytrid fungus *Batrachochytrium dendrobatidis*, was found in less fragmented landscapes with higher amphibian species richness (Becker and Zamudio, 2011), whereas experimental studies on this emerging amphibian disease suggested a dilution effect where increased species richness reduced the disease risk (Becker et al., 2014; Searle et al., 2011). We show in this study that facilitation and dilution might occur simultaneously in fragmented habitat. Although the dilution effect is expected to operate under high levels of species richness (with less fragmentation), this effect could be outweighed by the facilitation effect caused by increasing landscape connectivity. *B. dendrobatidis*, a driver of the global amphibian decline, can heavily infect many amphibian species (Fisher et al., 2009), which leads to low dilution potentials of these host species, so that the facilitation effect might overshadow the dilution effect in habitats with high connectivity and high species richness. However, such a positive diversity–disease relationship in the field might also be caused by the identity effect that some particular disease-prone species may present with increasing species diversity (Becker and Zamudio, 2011; Becker et al., 2014).

In addition, we found that different indicators of disease risk (i.e. the proportion of infected and the number of infected hosts) show different trends over the connectivity gradient in metapopulations, suggesting that connectivity affects these indicators differently. If so, then the detection of a dilution effect becomes more difficult. Many studies reported the dilution effect using infection prevalence as the indicator of disease risk (Allan et al., 2009; Clay et al., 2009; LoGiudice et al., 2003; Schmidt and Ostfeld, 2001; Suzan et al., 2009). However, several studies argued that the density of infected individuals might sometimes be a more direct measure of disease risk (Salkeld et al., 2013; Wood and Lafferty, 2013; Wood et al., 2014), especially for the risk to humans when wildlife–human contacts are density-dependent (Roche et al., 2012). According to our results, if the density of infected individuals is used as the risk indicator instead of the infection prevalence, the negative effect of connectivity might disappear, making the dilution effect harder to detect. This result is consistent to a previous theoretical study which also showed that it would be easier to detect a negative effect of species diversity using the hosts' infection prevalence than using the abundance of infected hosts (Roche et al., 2012). To better understand the determinants of disease risk and the generality of the dilution effect, we recommend reporting both the prevalence and the density of infected individuals.

4.3. Limitations of the model

In the simulation models, we made a number of simplifying assumptions to make the analysis tractable. First, by using the SIR model, we have restricted our focus to diseases that generate lifelong immunity. In many systems, immunity can be non-existent (described as SI model) or only short-lived (described as SIRS model). However, using SI or SIRS model also generates the facilitation and

dilution regions (data are not shown here) and are thus expected not to qualitatively change our results. In addition, we assumed a negative relationship between a species' reservoir competence and its local extinction risk, which is central in the dilution effect hypothesis (Huang et al., 2013a; Joseph et al., 2013; Young et al., 2013). Although this negative relationship, based on life-history theory and parasite local adaptation, has been documented in several studies (see review in Joseph et al., 2013), its generality is still under debate (Joseph et al., 2013; Young et al., 2013). Weak correlations between host reservoir competence and local extinction risk can produce inconsistent effects of host species richness on disease risk (Joseph et al., 2013), which however does not change our conservative conclusion that the dilution effect can be overshadowed by the facilitation effect of connectivity in metapopulations. Also, to compare the relative importance of the dilution against the facilitation effect, we only used two host species, but this framework can be easily extended to systems with more species and we expect that adding more species will not give qualitatively different results.

In our analyses, we assumed a frequency-dependent transmission, which are usually applied to vector-borne or sexually-transmitted diseases (McCallum et al., 2001). However, we did not incorporate the vector into the model due to the complexity of vector behaviour and life cycle, which can largely impact the transmission dynamics and may quantitatively impact our results. For example, the addition of the low-competence host may elevate vector density and cause an amplification effect, making the dilution effect harder to detect. We also assumed that seasonal factors did not influence disease transmission and host demographic variables and the hosts were fully mixed. Relaxing these two assumptions about contact structure and seasonal factors can directly modify susceptible recruitment and transmission patterns (Altizer et al., 2006) and thus might potentially influence our results. Finally, some studies pointed out that higher connectivity, from an evolutionary perspective, may generate a higher genetic diversity within host species, providing a higher variation in host resistance to be selected for, and thus reduce disease risk (Jousimo et al., 2014). Therefore, a natural next step would be to relax these assumptions and incorporate evolutionary perspective to increase our understanding of the roles that connectivity plays in pathogen transmission.

4.4. Conclusions

In general, our study shows that even when a dilution effect operates in a system, the impact of fragmentation on disease risk cannot be easily predicted because connectivity is able to simultaneously trigger a facilitation and a dilution effect. Different disease risk indicators (the prevalence and number of infections) respond differently to changes in connectivity. Which risk indicator is more likely to have a negative relationship with connectivity depends on the mechanism of the dilution effect and its strength. With this finding our study contributes to better understanding when the dilution effect can be found and what impacts habitat fragmentation has on disease risk.

Author contributions

ZYXH conducted simulations and analyses and wrote the first draft of manuscript. WFdB, FvL and HHTP jointly designed the study. All authors reviewed the manuscript.

Acknowledgements

We greatly appreciate the help of Simon Levin and Bryan Grenfell, who provided valuable comments and suggestions on model development. We also thank Chi Xu from Nanjing University, colleagues of the Resource Ecology Group at Wageningen University and members of the Bryan Grenfell laboratory at Princeton University for their useful comments. ZYXH is supported by the Chinese Scholarship Council (No. 2010619023). The authors declare no conflict of interest

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jtbi.2015.04.005.

References

Allan, B.F., Keesing, F., Ostfeld, R.S., 2003. Effect of forest fragmentation on Lyme disease risk. Conserv. Biol. 17, 267–272.
Allan, B.F., Langerhans, R.B., Ryberg, W.A., Landesman, W.J., Griffin, N.W., Katz, R.S., Oberle, B.J., Schutzenhofer, M.R., Smyth, K.N., de St Maurice, A., Clark, L., Crooks, K.R., Hernandez, D.E., McLean, R.G., Ostfeld, R.S., Chase, J.M., 2009. Ecological correlates of risk and incidence of West Nile virus in the United States. Oecologia 158, 699–708.
Altizer, S., Dobson, A., Hosseini, P., Hudson, P., Pascual, M., Rohani, P., 2006. Seasonality and the dynamics of infectious diseases. Ecol. Lett. 9, 467–484.
Becker, C.G., Zamudio, K.R., 2011. Tropical amphibian populations experience higher disease risk in natural habitats. Proc. Natl. Acad. Sci. USA 108, 9893–9898.
Becker, C.G., Rodriguez, D., Toledo, L.F., Longo, A.V., Lambertini, C., Correa, D.T., Leite, D.S., Haddad, C.F.B., Zamudio, K.R., 2014. Partitioning the net effect of host diversity on an emerging amphibian pathogen. Proc. R. Soc. B – Biol. Sci., 281.
Begon, M., 2008. Effects of host diversity on disease dynamics. In: Ostfeld, R., et al. (Eds.), Infectious Disease Ecology: Effects of Ecosystems on Disease and of Disease on Ecosystems. Princeton University Press.
Brownstein, J.S., Skelly, D.K., Holford, T.R., Fish, D., 2005. Forest fragmentation predicts local scale heterogeneity of Lyme disease risk. Oecologia 146, 469–475.
Cardillo, M., 2003. Biological determinants of extinction risk: why are smaller species less vulnerable? Anim. Conserv. 6, 63–69.
Clay, C.A., Lehmer, E.M., Jeor, S.S., Dearing, M.D., 2009. Sin nombre virus and rodent species diversity: a test of the dilution and amplification hypotheses. PLoS One 4, e6767.
Colizza, V., Vespignani, A., 2007. Invasion threshold in heterogeneous metapopulation networks. Phys. Rev. Lett., 99.
Cronin, J.P., Rúa, M.A., Mitchell, C.E., 2014. Why is living fast dangerous? Disentangling the roles of resistance and tolerance of disease. Am. Nat. 184, 172–187.
Cronin, J.P., Welsh, M.E., Dekkers, M.G., Abercrombie, S.T., Mitchell, C.E., 2010. Host physiological phenotype explains pathogen reservoir potential. Ecol. Lett. 13, 1221–1232.
Cross, P.C., Lloyd-Smith, J.O., Johnson, P.L.F., Getz, W.M., 2005. Duelling timescales of host movement and disease recovery determine invasion of disease in structured populations. Ecol. Lett. 8, 587–595.
Dobson, A., 2004. Population dynamics of pathogens with multiple host species. Am. Nat. 164, S64–S78.
Estrada-Peña, A., Ostfeld, R.S., Peterson, A.T., Poulin, R., de la Fuente, J., 2014. Effects of environmental change on zoonotic disease risk: an ecological primer. Trends Parasitol. 30, 205–214.
Fahrig, L., 2003. Effects of habitat fragmentation on biodiversity. Annu. Rev. Ecol. Evol. Syst. 34, 487–515.
Fisher, M.C., Garner, T.W.J., Walker, S.F., 2009. Global emergence of batrachochytrium dendrobatidis and amphibian Chytridiomycosis in space, time, and host. Annu. Rev. Microbiol. 63, 291–310.
Hakoyama, H., Iwasa, Y., 2000. Extinction risk of a density-dependent population estimated from a time series of population size. J. Theor. Biol. 204, 337–359.
Hanski, I., Ovaskainen, O., 2000. The metapopulation capacity of a fragmented landscape. Nature 404, 755–758.
Henle, K., Davies, K.F., Kleyer, M., Margules, C., Settele, J., 2004. Predictors of species sensitivity to fragmentation. Biodivers. Conserv. 13, 207–251.
Hess, G., 1996. Disease in metapopulation models: Implications for conservation. Ecology 77, 1617–1632.
Huang, Z.Y.X., de Boer, W.F., van Langevelde, F., Olson, V., Blackburn, T.M., Prins, H.H.T., 2013a. Species' life-history traits explain interspecific variation in reservoir competence: a possible mechanism underlying the dilution effect. PLoS One 8, e54341.
Huang, Z.Y.X., de Boer, W.F., van Langevelde, F., Xu, C., Ben Jebara, K., Berlingieri, F., Prins, H.H.T., 2013b. Dilution effect in bovine tuberculosis: risk factors for regional disease occurrence in Africa. Proc. R. Soc. B – Biol. Sci. 280, 20130624.
Jesse, M., Heesterbeek, H., 2011. Divide and conquer? Persistence of infectious agents in spatial metapopulations of hosts. J. Theor. Biol. 275, 12–20.
Jesse, M., Ezanno, P., Davis, S., Heesterbeek, J.A.P., 2008. A fully coupled, mechanistic model for infectious disease dynamics in a metapopulation: movement and epidemic duration. J. Theor. Biol. 254, 331–338.
Johnson, P.T.J., Preston, D.L., Hoverman, J.T., Richgels, K.L.D., 2013. Biodiversity decreases disease through predictable changes in host community competence. Nature 494, 230–233.

Johnson, P.T.J., Rohr, J.R., Hoverman, J.T., Kellermanns, E., Bowerman, J., Lunde, K.B., 2012. Living fast and dying of infection: host life history drives interspecific variation in infection and disease risk. Ecol. Lett. 15, 235–242.
Joseph, M.B., Mihaljevic, J.R., Orlofske, S.A., Paull, S.H., 2013. Does life history mediate changing disease risk when communities disassemble. Ecol. Lett. 16, 1405–1412.
Jousimo, J., Tack, A.J.M., Ovaskainen, O., Mononen, T., Susi, H., Tollenaere, C., Laine, A.L., 2014. Ecological and evolutionary effects of fragmentation on infectious disease dynamics. Science 344, 1289–1293.
Keeling, M.J., 2000. Metapopulation moments: coupling, stochasticity and persistence. J. Anim. Ecol. 69, 725–736.
Keesing, F., Holt, R.D., Ostfeld, R.S., 2006. Effects of species diversity on disease risk. Ecol. Lett. 9, 485–498.
Keesing, F., Belden, L.K., Daszak, P., Dobson, A., Harvell, C.D., Holt, R.D., Hudson, P., Jolles, A., Jones, K.E., Mitchell, C.E., Myers, S.S., Bogich, T., Ostfeld, R.S., 2010. Impacts of biodiversity on the emergence and transmission of infectious diseases. Nature 468, 647–652.
Lacroix, C., Jolles, A., Seabloom, E.W., Power, A.G., Mitchell, C.E., Borer, E.T., 2014. Non-random biodiversity loss underlies predictable increases in viral disease prevalence. J. R. Soc. Interface, 11.
Lee, K.A., Wikelski, M., Robinson, W.D., Robinson, T.R., Klasing, K.C., 2008. Constitutive immune defences correlate with life-history variables in tropical birds. J. Anim. Ecol. 77, 356–363.
Levins, R., 1969. Some demographic and genetic consequences of environmental heterogeneity for biological control. Bull. ESA 15, 237–240.
LoGiudice, K., Ostfeld, R.S., Schmidt, K.A., Keesing, F., 2003. The ecology of infectious disease: Effects of host diversity and community composition on Lyme disease risk. Proc. Natl. Acad. Sci. USA 100, 567–571.
Martin II, L.B., Hasselquist, D., Wikelski, M., 2006. Investment in immune defense is linked to pace of life in house sparrows. Oecologia 147, 565–575.
McCallum, H., Barlow, N., Hone, J., 2001. How should pathogen transmission be modelled. Trends Ecol. Evol. 16, 295–300.
Ostfeld, R.S., Keesing, F., 2012. Effects of host diversity on infectious disease. Annu. Rev. Ecol. Evol. Syst. 43, 157–182.
Previtali, M.A., Ostfeld, R.S., Keesing, F., Jolles, A.E., Hanselmann, R., Martin, L.B., 2012. Relationship between pace of life and immune responses in wild rodents. Oikos 121, 1483–1492.
Randolph, S.E., Dobson, A.D.M., 2012. Pangloss revisited: a critique of the dilution effect and the biodiversity-buffers-disease paradigm. Parasitology 139, 847–863.
Roche, B., Dobson, A.P., Guegan, J.F., Rohani, P., 2012. Linking community and disease ecology: the impact of biodiversity on pathogen transmission. Philos. Trans. R. Soc. Lond. Ser. B – Biol. 367, 2807–2813.
Rudolf, V.H.W., Antonovics, J., 2005. Species coexistence and pathogens with frequency-dependent transmission. Am. Nat. 166, 112–118.
Salkeld, D.J., Padgett, K.A., Jones, J.H., 2013. A meta-analysis suggesting that the relationship between biodiversity and risk of zoonotic pathogen transmission is idiosyncratic. Ecol. Lett. 16, 679–686.
Schmidt, K.A., Ostfeld, R.S., 2001. Biodiversity and the dilution effect in disease ecology. Ecology 82, 609–619.
Searle, C.L., Biga, L.M., Spatafora, J.W., Blaustein, A.R., 2011. A dilution effect in the emerging amphibian pathogen Batrachochytrium dendrobatidis. Proc. Natl. Acad. Sci. USA 108, 16322–16326.
Suzan, G., Marce, E., Giermakowski, J.T., Mills, J.N., Ceballos, G., Ostfeld, R.S., Armien, B., Pascale, J.M., Yates, T.L., 2009. Experimental evidence for reduced rodent diversity causing increased hantavirus prevalence. Plos One 4, e5461.
Tanaka, G., Urabe, C., Aihara, K., 2014. Random and targeted interventions for epidemic control in metapopulation models. Sci. Rep., 4.
Venesky, M., Liu, X., Sauer, E., Rohr, J., 2013. Linking manipulative experiments to field data to test the dilution effect. J. Anim. Ecol. 83, 557–565.
Wood, C.L., Lafferty, K.D., 2013. Biodiversity and disease: a synthesis of ecological perspectives on Lyme disease transmission. Trends Ecol. Evol. 28, 239–247.
Wood, C.L., Lafferty, K.D., DeLeo, G., Young, H.S., Hudson, P.J., Kuris, A.M., 2014. Does biodiversity protect humans against infectious disease. Ecology 95, 817–832.
Young, H., Griffin, R.H., Wood, C.L., Nunn, C.L., 2013. Does habitat disturbance increase infectious disease risk for primates? Ecol. Lett. 16, 656–663.