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Title: 1

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18 Divide and conquer? Persistence of infectious agents in19 spatial metapopulations of hosts.

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23 Abstract

20 21

22

Persistence of an infectious agent in a population is an important issue in epidemiology. It is assumed that spatially fragmenting a population of hosts increases the probability of persistence of an infectious agent and that movement of hosts between the patches is vital for that. The influence of migration on persistence is however often studied in mean-field models, whereas in reality the actual distance travelled can be limited and influence the movement dynamics. We use a stochastic model, where within- and between-patch dynamics are coupled and movement is modelled explicitly, to show that explicit consideration of movement distance makes the relation between persistence of infectious agents and the metapopulation structure of its hosts less straightforward than previously thought. We show that the probability of persistence is largest at an intermediate movement distance of the host and that spatially fragmenting a population of hosts is not necessarily beneficial for persistence.

24 Key words: stochastic model, migration, movement distance, patch

25 neighbourhood, lattice

26 Introduction

- 27 Once an infectious disease invades a population, it can go extinct immediately,
- 28 fade out after an epidemic or persist in the population. In homogeneously mixing
- 29 populations, infectious agents tend to die out when the host population size is

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30below a critical community size (Bartlett, 1957; Grenfell & Harwood, 1997). 31related to the demographic processes that regulate the inflow of new susceptible 32hosts in the population (Anderson & May, 1992). However, populations are 33 often structured in space and then the situation becomes much more subtle. 34Examples are humans living in cities and towns (Hall et al., 2007), cattle on 35farms (Le Menach et al., 2005; Kao et al., 2007) or wildlife populations, for 36 example the water voles in the U.K. (Telfer et al., 2001), the badgers in the 37 U.K. (Rogers et al., 1998) or the great gerbils in Kazakhstan (Davis et al., 38 2007a). These populations live in a set of spatially separated patches of suitable habitat, connected to each other by migration of the individuals (e.g. travel of 39humans between cities, purchasing and selling of cattle and juvenile migration of 4041wildlife). Each patch moreover, has its own dynamics influenced by the incoming 42and outgoing migrants and by the local conditions. Such a population is called 43a (spatial) metapopulation (Hanski, 1999; Leibold et al., 2004). The patch size measured is the size of the inhabiting population of interest and ranges from 44 very large (e.g. cities, farms), to very small (for example wildlife often lives in 4546small (family)groups).

47The structure of such metapopulations for a given species is distinct from sin-48 gle homogeneously mixing populations, resulting in differences in dynamics and persistence of the species itself, and other species it interacts with. For exam-49ple, infectious disease agents both influence and are influenced by the structure 50and migration of their host (Grenfell & Harwood, 1997). Hanski (1999) showed 5152that, if the total population size is below the critical community size, then spa-53tially fragmenting this population has a positive influence on the ability of an infectious agent to persist and that notably movement of hosts between patches 54is crucial. The latter aspect has received substantial attention in the literature 55(e.g. Swinton et al., 1998; Keeling, 2000; Park et al., 2002; Hagenaars et al., 56 572004; Lindholm & Britton, 2007).

However, there is a much broader range of aspects that influence and control persistence in a metapopulation (Swinton et al., 1998): (i) demographic
aspects: birth and death; (ii) epidemic aspects: length of infectious period and

61the specifics of the transmission process; (iii) spatial aspects: movement distance 62of the host and frequency of migration or length of stay in patches. Notably the 63interaction between these aspects appears to be important, and is not well un-64derstood. Indeed, seemingly new phenomena arise from analysis of real systems 65(Davis et al., 2007b, 2008). In this theoretical paper we aim to contribute to 66 this debate and explore the question: how does the interaction between all the 67 aspects mentioned shape persistence of an infectious disease agent in a spatially 68structured host population with movement modelled explicitly?

69For studying persistence in a metapopulation often a mean-field approxima-70 tion is used (Gog et al., 2002; McCallum & Dobson, 2002; Jesse et al., 2008), 71but here we introduce a (preferred) movement distance of the host: hosts are 72only allowed to migrate to patches within this movement distance. The set of 73patches that can be reached by individual hosts migrating out of a given patch 74within one time step is seen as the neighbourhood of that patch. The effect of the neighbourhood of a patch on persistence has been studied both in an eco-75logical setting (Durrett & Levin, 1994; Hanski & Ovaskainen, 2000; Vuilleumier 76et al., 2007) and in an epidemiological context (Levin & Durrett, 1996; Rhodes 77 78& Anderson, 1996).

79Keeling (2000) pointed out that there are two ways of coupling between subpopulations. The first is based on movement rate of individuals between 80 subpopulations, which is the coupling we use in the present paper. The second 81 82is by using a parameter that describes how much the global average affects 83 the dynamics of a subpopulation. Keeling used the latter way of coupling and 84 concluded that persistence is maximized at intermediate levels of coupling (in the second interpretation), but expects the qualitative behaviour of both ways 85of coupling to be similar. In this paper we show that using a movement rate and 86 in addition a movement distance indeed results in persistence being maximized 87 88 at intermediate levels of coupling.

Here, we take a much broader view by regarding an epidemiological model
with demography, explicit modelling of movement (distance and frequency of
movement) and coupling of between- and within-patch dynamics. Among other

92 results, we show that there can be an optimum for persistence at intermediate 93 neighbourhood size. We explore the reasons behind this and how persistence 94 of an infectious agent is influenced by the demographic, epidemic and spatial 95 parameters. Moreover, we show that, in contrast to what was generally believed, 96 a metapopulation is not necessarily more beneficial for the persistence of an 97 infectious agent compared to a single homogeneously mixing population.

98 Methods

99 Model

100 The model describes a host population divided into subpopulations, each inhab-101iting a patch with suitable habitat (details in Jesse et al., 2008). In contrast to Jesse et al. (2008) we now consider a spatially explicit metapopulation, where 102103 patches are structured in space, in our case on a regular square lattice. At least 104initially there are no unoccupied patches and the patches are identical in the 105sense that all parameter values are the same for all subpopulations. An overview 106of the parameters and their default values used in the numerically studied cases 107is given in Table 1.

In each patch there is homogeneously mixing and SIR-type dynamics occurs, with hosts being in one of the three following states: susceptible (S), infectious (I) or recovered/immune to the infection (R). The infectious disease is transmitted directly and hosts do not lose immunity, but eventually die and are replaced by susceptibles. Births are locally density dependent, meaning that they depend on the number of hosts present in that patch.

-	Parameter	Value	Definition
	P	100	number of patches
	K	10	carrying capacity
	b	0.2	birth rate per week
	μ	0.01	natural mortality rate per week
	m	[0, 1]	movement rate per week
	β	10	transmission rate per week
	γ	0.5	recovery rate per week

Table 1: Definition and default values of the model parameters for numerically studied cases.

Random variable	Distribution	Parameter	Definition
$\mathbf{B}(N_x,t)$	Poisson	$\max[0; bN_x(t)(1-\frac{N_x(t)}{K})]$	# births
$\mathbf{D}(Z_x,t)$	Binomial	μ	# deaths
$\mathbf{Inf}(S_x, t)$	Binomial	$1 - exp(-\frac{\beta I_x(t)}{N_x(t)})$	# infecteds
$\mathbf{Rec}(I_x,t)$	Binomial	γ	# recovereds
$\mathbf{M}_{\mathrm{out}}(Z_x,t)$	Binomial	m	# emigrants
$\mathbf{M}_{\mathrm{in},Z}(x,t)$	Multinomial	1/P	# immigrants

Table 2: The random variables with their distribution and parameters. The state is given explicitly or by Z with $Z \in \{S, I, R\}$.

The model is stochastic and discrete in time, one time step denotes one 114115week, where $S_x(t)$, $I_x(t)$ and $R_x(t)$ denote the number of hosts per infectious 116 state in patch x at time t. The total number of hosts in patch x at time t is 117given by $N_x(t)$. Events occur successively in the interval [t, t+1) in the order of birth, death, infection, recovery and migration. Of course, ordering the events 118 119is artificial, but it is necessary in a discrete model so that in the bookkeeping 120 individual-level events, such as dying or recovering, are taken into account in a 121consistent way. The complete set of stochastic difference equations is given by:

$$\begin{array}{lll} S_x(t+1) &=& S_x(t) - \mathbf{D}(S_x,t) - \mathbf{Inf}(S_x,t) + \mathbf{B}(N_x,t) - \mathbf{M}_{\mathrm{out}}(S_x,t) + \mathbf{M}_{\mathrm{in},S}(x,t) \\ I_x(t+1) &=& I_x(t) - \mathbf{D}(I_x,t) + \mathbf{Inf}(S_x,t) - \mathbf{Rec}(I_x,t) - \mathbf{M}_{\mathrm{out}}(I_x,t) + \mathbf{M}_{\mathrm{in},I}(x,t) \\ R_x(t+1) &=& R_x(t) - \mathbf{D}(R_x,t) + \mathbf{Rec}(I_x,t) - \mathbf{M}_{\mathrm{out}}(R_x,t) + \mathbf{M}_{\mathrm{in},R}(x,t) \end{array}$$

122 The random variables and their distributions (Table 2) are calculated with 123 the number of hosts at that point in the time interval, using the order of the 124 events; for example, the number of newly infected hosts at time interval [t, t+1)125 depends on the number of infectious hosts at time t - 1 minus the number of 126 infectious hosts that died at time t.

127 Structure

128 Above we described the dynamics within each patch, but these patches are con-129 nected to each other via migration of the hosts, which we also model explicitly. 130 Where in Jesse et al. (2008) a mean-field approximation was used, here a finite 131 spatially explicit structure is looked at. The patches to which a host can mi-132 grate, are given by the adjacency matrix A. This adjacency matrix describes

133 the connections between the patches of the metapopulation: if $A_{ij} = 1$ it is 134 possible to move from patch *i* to patch *j*, otherwise $A_{ij} = 0$. We view the 135 metapopulation of patches as being arranged spatially in a finite regular lattice 136 where a node is a patch and where an edge indicates a connection in the above 137 sense. The network is non-directed, which means that if movement is possible 138 from patch *i* to patch *j*, then it is also possible from patch *j* to patch *i*, i.e. 139 $A_{ij} = A_{ji}$.

Of particular interest is the movement distance of the hosts, measured as path length in the lattice. For movement distance d, a host can migrate along at maximum d edges in the regular lattice of patches. The host can, with equal probability, migrate to all patches that can be reached within this number of edges. This movement distance can be seen as the capacity of the host to migrate to patches at that distance. When the movement distance equals 1, hosts can only migrate to their nearest neighbours and when the movement distance is large enough, hosts can move to every patch. The matrix M gives the patches to which a host can move within a movement distance d and has entries such that, for $i \neq j$:

$$M_{ij} = \begin{cases} 1 & \text{if patch } i \text{ and } j \text{ are connected, i.e. } (\sum_d A^d)_{ij} > 0 \\ 0 & \text{otherwise} \end{cases}$$

140 and $M_{ii} = 0$, preventing hosts from migrating back immediately to the patch 141 they just left (i.e. no loops of length 1 are allowed). The matrix M is calculated 142 by means of $\sum_{d} A^{d}$, where A_{ij}^{d} gives the number of paths of length d from patch 143 i to patch j.

144 Simulations

The model is stochastic and hence there can be large variation between runs of the model, even though the set of parameter values is identical. The stochastic difference equations were simulated for a range of parameter values. The program is written in R (package 2.10.1, www.cran.r-project.org). At time t = 1 one infectious host is introduced into one patch in an otherwise completely susceptible metapopulation. For the results the location of this (index) patch, where the

first infectious host is introduced, does not matter. This coincides with findings

151

152of Pautasso & Jeger (2008), when they studied a model with SI-type dynamics 153on a directed network, where each node represents an individual. 154After introduction of this one infectious host in the metapopulation, there 155are four possible situations: the infectious agent may (i) not spread at all in 156the initial patch, (ii) spread in the initial patch, but not between patches (iii) 157spread within and between patches and then fade out or (iv) spread within and 158between patches and (quasi)persist in the metapopulation (Jesse et al., 2008). 159Here, we are interested in the fourth case, persistence in the metapopulation. 160We defined the infectious agent to be persistent in a simulation if it is still present in the population after twice the expected life span of the host. The 161expected life span of a host is $1/\mu$, therefore the simulations were run for $2/\mu$ 162163 time steps. The choice of twice the expected life span is arbitrary, but within 164this number of time steps the infectious agent has survived two generations of 165hosts, and has spread between the patches.

166 The results obtained are from 1000 simulations. This number of simulations 167 per datapoint was chosen such that variation between several runs of 1000 sim-168 ulations for the same set of parameter values is small. Therefore, increasing the 169 number of simulations smoothens the graphs depicting our results, but does not 170 alter or add to conclusions we draw.

171The default parameter values are shown in Table 1. The default death rate 172equals 0.01, meaning that the life span of a host is on average 100 weeks, i.e. a 173host lives around two years. And the default recovery rate equals 0.5, so that 174a host is infectious for on average two weeks. The metapopulation consists of 175100 patches, all with carrying capacity 10. This carrying capacity is chosen 176such that persistence of the infectious agent in a single patch is not possible. In a single homogeneously mixing population of size 1500 around 90% of the 177 178simulations will result in a persisting infection for the default parameter values. 179The metapopulation is arranged on a square 10×10 lattice, with reflective 180boundaries. These boundaries can be considered as natural boundaries such as

181 water or mountains, which cannot be crossed by the host.

182 Results and Conclusions

- 183 In this section we will first present the influence of the spatial aspects on persis-
- 184 tence of infectious agents in the metapopulation. Then the demographical and
- 185 epidemiological aspects will be presented.
- 186 Spatial aspect

In Figure 1a, the influence of the spatial aspects on persistence of the infectious 187188agent are explored. In this figure, contour lines show the fractions of simulations 189with persisting infection as functions of the migration rate and the movement 190 distance of the host. Fixing the movement distance and then increasing the 191 migration rate resulted in a higher fraction of simulations with persisting in-192fection. A higher migration rate means that hosts spend a shorter time in one 193patch and thus change patches more frequently. By changing patches more fre-194 quently, hosts increase the number of contacts with other hosts and therefore 195have a higher probability of finding sufficient susceptible hosts to infect while 196 they are still infectious.

197 Fixing the migration rate and increasing the movement distance shows a 198 maximum in the fraction of simulations with persisting infection at intermediate 199movement distance. This result is also shown in Figure 1b for four different 200 migration rates. Clearly there is a peak at intermediate movement distance, 201except for relatively low migration rates (a migration rate of 0.2 means that a 202host moves once every 5 weeks). The default infectious period is two weeks, so 203at low migration rates the host spends, on average, most of its entire infectious 204period within one patch. Since the patch size is too low for persistence, there is 205 only a very small fraction of simulations showing persistence.

206 Effect of movement distance on patch level

207 As already shown, varying only the movement distance already results in dis-

208 similarities between the fraction of simulations with persisting infection. In

209	order to understand where these dissimilarities come from, we focus on the dif-
210	ferences that occur on patch level. Because the infectious hosts are the key for
211	persistence of the infectious agent in the metapopulation, we focused on some
212	properties of patches with respect to infectious hosts that might be influenced
213	by the movement distance:
214	i) the total number of time steps (not necessarily consecutive) that a patch
215	contains at least one infectious host;
216	ii) the number of times that a patch gets infected, i.e. how often are there
217	transitions from no infectious host in a patch to at least one infectious host
218	in that patch;
219	iii) the total number of infectious hosts per patch, i.e. the sum of the number
220	of infectious hosts at each time step in a patch;
221	iv) the number of consecutive time steps a patch contains an infectious host.
222	Only simulations with persisting infection were taken into account when calcu-
223	lating the above measures. The results are presented as box-and-whisker-plots
224	in Figure 2.
225	It is immediately clear that the medians for movement distance 6 and 14 are
226	approximately the same for all four measures, but that the range differs: the
227	variation between patches for intermediate movement distance is larger than
228	for large movement distance. Movement distance 14 corresponds to a situation
229	where the patches are almost fully connected and the system starts behaving
230	like one single homogeneously mixing population.
231	On average a patch contains 35 out of the 200 time steps $(17.5\%$ of the time)
232	at least one infectious host for low movement distance (Fig. 2a). The average
233	number for the other movement distances is slightly higher. The number of
234	transitions from no infectious hosts in a patch to at least one is the lowest
235	for the low movement distance (median 15 times, Fig. 2b). This might be
236	due to (infectious) hosts returning more often back to a patch they visited
237	just a few time steps ago (fewer patches to choose from). On average the

238total number of infectious hosts per patch is about 1.5 times larger for low 239movement distance (median of 120) than for the other two movement distances 240(Fig. 2c). Because the number of infected patches at each time step is equal 241for all movement distances, the number of infectious hosts in each patch must 242be higher for low movement distance than for the other movement distances. 243Again, this is probably caused by hosts returning more often to a patch they just 244visited at low maximum movement distances. Finally in Figure 2d the median 245number of consecutive time steps a patch is inhabited by infectious hosts is 246shown. Basically, this is just the total number of time steps a patch is infected 247divided by the number of transitions from having no infectious host in a patch 248to having at least one. Here, the low movement distance shows that a patch 249contains at least one infectious host for a longer uninterrupted number of time 250steps.

251With the four measures we looked at, we can conclude that at low movement 252distance, patches are on average longer infected and contain over the whole time 253period more infectious hosts than at large movement distance. This implies that the infectious agent remains within the same area at low movement distance 254255until that area runs too low on available susceptible hosts. At large movement 256distance on the other hand, the infectious agent is more scattered throughout the 257whole metapopulation, patches get (re)infected more often, but it is for a short 258period of time and with only a few infectious hosts. Hence, at low movement 259distance the spreading of the infectious agent occurs more locally and gradually 260 becomes more global when the movement distance increases.

261 Demographical and epidemiological aspects

As mentioned earlier, persistence of an infectious agent is also influenced by demographical and epidemiological aspects. The fraction of simulations with persisting infection is therefore studied as function of each of the four parameters controlling these aspects: birth rate, death rate, transmission rate and recovery rate. The fraction is shown in Figure 3 for three different movement distances, namely 2, 6 and 14, and for a single homogeneously mixing population.

268This single homogeneously mixing population consists of one patch with a 269carrying capacity K of 1000 hosts; the total size of the metapopulation and the 270single population are therefore equal. Moreover, this figure shows how a change 271in a relevant parameter influences the fraction of simulations with persisting 272infection. For all parameters, the fraction of simulations with persisting infection 273is the highest for intermediate movement distance, corresponding to the previous 274result that there is a maximum in the fraction of simulations with persisting 275infection at this movement distance.

276The natural death rate (i.e. not related to the infection) determines the 277life span of a host and influences also, because of the density-dependent birth 278rate, the population turnover: a lower death rate implies a longer life span and 279therefore a slower population turnover; i.e. a slower inflow of new susceptible 280hosts. The life span is used to define when an infectious agent is persistent 281in our set up, so varying the death rate means that the number of time steps 282before an infectious agent is called persistent varies as well. Increasing the death 283rate, i.e. increasing population turnover, has a positive effect on the fraction of simulations with persisting infection (Fig. 3a). At a low death rate, while 284285the speed by which the infectious agent spreads through the whole population 286remains equal, it takes longer for new susceptible hosts to arise. This time gap is 287 more difficult to bridge in a single homogeneously mixing population, where all 288 susceptible hosts are immediately available for contact to the infectious agent. 289Therefore, a low death rate is more beneficial for persistence in a metapopulation 290 than in a single homogeneously mixing population.

291The birth rate in this model is density dependent; a high birth rate implies 292that each subpopulation is around carrying capacity and dead hosts are replaced 293by susceptible new-borns quickly. Hence, increasing the birth rate also increases 294 the fraction of simulations with persisting infection (Fig. 3b). At low birth rate, 295a single homogeneously mixing population is more beneficial for the infectious 296agent, because the few susceptible hosts that are born per unit of time are found 297quickly, while in the metapopulation an infectious host needs time to find the 298susceptible hosts left. When the birth rate is large, susceptible hosts arise faster

and are immediately available for contact with infectious hosts in case of a single homogeneously mixing population. This could mean that the infectious agent 'burns through' the available susceptibles too fast to allow persistence. It is then advantageous for the infectious agent to be in the metapopulation: not all susceptible hosts are immediately available for contact, allowing the infectious agent to persist in the population for a longer time (i.e. the risk of fade out is spread).

306 In Figure 3c the fraction of simulations with persisting infection is shown for 307 various transmission rates. For low transmission rates the fraction of simulations 308 with persisting infection is higher in a metapopulation than in a single homoge-309 neously mixing population, but the opposite holds at high transmission rates. 310In a single homogeneously mixing population an infectious host has immediate access to all susceptible hosts. At high transmission rate, this availability of all 311312susceptibles in a single homogeneously mixing population is beneficial for the 313 infectious agent, because even when there are only a few susceptibles left, there 314is a high probability that they will be contacted. In a metapopulation on the 315other hand, an infectious host needs time to travel to patches where the few 316susceptibles remain, and before successful contact has been made this infectious 317 host may have died or recovered. At low transmission rate, the above situations 318 are reversed.

319 The recovery rate determines the infectious period of a host and Figure 3d 320 shows that the fraction of simulations with persisting infection as a function of 321 recovery rate is hardly influenced by the movement distance of the host. When 322the recovery rate is large, the infectious period is short and, on average, fewer 323infectious hosts leave the patch during the infectious period, making it more 324difficult for the infectious agent to spread to other patches. The movement 325 distance does not have a large influence on this, because the ability to spread is 326 here, in the first instance, mostly determined by the chance to leave the patch 327 at all.

Furthermore, a short infectious period results in a population of many re-covered hosts. In Figure 3d, the fraction of simulations with persisting infection

330 coincides for both the single homogeneously mixing population and a metapop-331ulation where hosts have an intermediate movement distance. However, this 332fraction is very much influenced by the migration rate of the host (not shown). 333 Persistence of the infectious agent is more difficult at low migration rate, because 334 the infectious host does not change patches frequently enough to sustain the in-335 fectious agent. A high migration rate in a metapopulation performs slightly 336 better than a single homogeneously mixing population, because running out of 337 susceptible hosts happens faster in a single population than in a metapopulation. 338 Finally, both the shape of the lattice and the number of patches do not 339 qualitatively change the results (not shown). Reshaping the lattice, for example 340 into 4×25 with the same total population size as the 10×10 case, still gives a peak at the same intermediate movement distance of 6. Interestingly, the 341342 mean distance of one patch to any other patch is for the 4×25 lattice 9.2 343 steps and for the 10×10 lattice 6.6. Increasing the number of patches to, for 344 example, a 12×12 lattice also gives a peak at intermediate movement distance. 345The latter peak occurs at a slightly higher movement distance compared to the 346 above cases, however, the 12×12 case is not directly comparable, because both 347 the total population size and the mean distance from one patch to any other 348 is larger. Thus the size of the lattice does not appear to essentially change the 349 results.

350 Balance

Persistence of an infectious agent in a metapopulation results from a balance
between the spatial, demographical and epidemiological components. We studied the components in isolation above, but now look at their combined effect
(Fig. 4).

Each panel in this figure shows curves leading to the same fraction of simulations with persisting infection ('isopersistence level') as function of the death and the transmission rate. The isopersistence levels are shown for low, intermediate and high movement distance in a metapopulation and for a single homogeneously mixing population and for the four parameter combinations low/high

360 migration rate and low/high birth rate. For all four subfigures the default re-361 covery rate is used, because Figure 3d showed that for the various movement 362distances differences in the fraction of simulations with persisting infection are 363 not strongly affected by the recovery rate. In order to compare situations we 364 used in Figure 4a,c an isopersistence level of 0.3 and in Figure 4b,d a level of 365 0.6. These levels are chosen with use of Figure 3d, where for migration rate 0.4366 the fraction of simulations with persisting infection is around 0.3 at the peak 367 and for migration rate 0.8 around 0.6.

368 At low birth rate the total population size is smaller than at high birth rate, 369 because in the latter situation the population is close to carrying capacity. For 370 low birth rates both the panels with low and high migration rates (Fig. 4a-b) 371show that in a single homogeneously mixing population the isopersistence level 372is achieved at much lower transmission and death rates than in a metapopula-373 tion. In that situation, a single homogeneously mixing population is thus more 374beneficial for the infectious agent than a metapopulation, because at a low birth 375rate susceptible hosts are not replenished at the same rate as at a high birth rate; it takes more time before new susceptible hosts arise. When they do arise 376 377 it is more difficult for an infectious host in a metapopulation to successfully meet 378 this susceptible host, because the infectious host first has to move to a patch 379 with sufficient susceptible individuals within its infectious period. In a single 380 homogeneously mixing population the new susceptible hosts are immediately 381 available for contact.

382 At high birth and low migration rate (Fig. 4c), the isopersistence level for 383 the single homogeneously mixing population and the intermediate movement 384 distance almost coincide. At high transmission rate the isopersistence levels of 385 all situations coincide, because infectious hosts then have successful contacts 386 with more susceptible hosts per unit of time.

At both high birth and high migration rate (Fig. 4d), the differences between
the four cases are very small, especially at a large transmission rate all movement
distances coincide more or less with the single homogeneous mixing population.
All panels in this figure show the same pattern as described in previous

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391 sections: persistence of an infectious agent in a metapopulation is easier accom-392 plished at intermediate movement distance of the host.

393 Discussion

394 In this paper we showed that persistence of an infectious agent in a metapopu-395 lation results from of a balance between spatial, demographical and epidemio-396 logical parameters. We showed on lattices a robust non-linear relation between 397 the fraction of simulations with persisting infection and movement distance of 398 hosts, with this fraction being largest at an intermediate movement distance of 399 the host. Furthermore we showed that dividing a single homogeneously mixing 400population into several smaller populations that are connected to each other, is 401 not necessarily beneficial for the persistence of the infectious agent.

402 The insight we obtain is based on simulations only. While an important 403part of relevant parameter space has been explored, there is considerable addi-404 tional value in providing analytical proof of the observed qualitative phenom-405ena, to obtain robustness of results and deeper understanding. There have been 406 many approaches in the literature where authors have focussed on analytical 407 results concerning infectious disease in spatial metapopulations, and even more 408 concerning single-species populations, predator-prey systems, and notably host-409 parasitoid systems. Mostly these studies concentrate on stability analysis of the 410 trivial equilibrium (i.e. invasion problems, see Jansen & Lloyd, 2000, and refer-411 ences given there) or on providing analytical expressions for the expected time 412to extinction from a quasi-steady state (see Nåsell, 1999; Hagenaars et al., 2004; 413Lindholm & Britton, 2007, and the references given there), as persistence in 414 stochastic models is always temporary (Hanski, 1998; Lloyd-Smith et al., 2005). 415 In discrete-time models it is not possible to determine the quasi-stationary 416 distribution and other measures have to be used; for example, persistence time 417 (Rhodes & Anderson, 1996) or a certain number of time steps the infectious dis-418 ease is present in the metapopulation (Swinton et al., 1998; Vuilleumier et al., 4192007; Jesse et al., 2008; Courcoul & Ezanno, 2010). We focus on persistence 420 (long-term quasi-stability), i.e. we look at the fraction of realisations of the

421 stochastic process persisting for a time beyond a certain minimum (set arbitrar-422 ily by twice the average life span of the host species). We noticed that increasing 423 this minimum did not qualitatively change the results. However, taking twice 424 the life span of the host as measure for persistence for hosts with very short life 425 spans, may lead to a time scale that is too short to speak of persistence.

426In our system we merged a stochastic description with discrete spatial struc-427 ture, with on top of that non-uniform dispersal (due to a maximum movement 428 distance for hosts). This combination did not allow us to obtain analytical re-429 sults, nor does the set-up allow for easy simplified models with only two patches, 430 say, that might be amenable to direct analysis. We can, however, compare to 431 studies where discrete space was studied analytically with different choices for dispersal. Rohani et al. (1996) conclude that, in predator-prey type interac-432433 tion with uniform dispersal, the equilibrium becomes unstable, compared to a 434single homogeneous population, when there is a big difference in the dispersal 435between the two species. We have identical dispersal for our two 'predator-prey 436species' (infected and susceptible individuals, respectively). In our set-up we show, by simulation, differences in persistence, if dispersal is not uniform, but 437438constrained. In the discussion of Rohani et al. (1996), it is argued that the 439equilibrium may destabilise when dispersal is not uniform. Similar equilibrium 440 (in)stability results are discussed analytically by White & White (2005) studying 441 coupled map lattices with integro-differential equations. They show in addition 442 that destabilising influences of dispersal can only occur in "exploiter-victim" 443 type of relationships.

444 In a much simpler model, Funk et al. (2005) study the dynamics of virus par-445ticles in a spatial metapopulation of host cells. This is basically a one-species system because only the virus particles disperse. The dispersal mechanism, 446however, is closer to ours, as dispersal is constrained to be to (eight) nearest 447 448 neighbours only. The analytical results allow a large class of dispersal mech-449anisms to be studied. One of their results is that if dispersal is too fast the 450infection cannot be maintained. Webb et al. (2007) show, for a host-parasite 451system, that highly local systems, i.e. where dispersal is limited, have reduced

452persistence of the infectious agent. Both these observations (Funk et al., 2005; 453Webb et al., 2007) are, although from very different models, in broad agreement 454with our finding of an optimal persistence for intermediate dispersal frequency 455and distance. This is in contrast to results by Hagenaars et al. (2004) who study 456 persistence (measured as time to extinction from a quasi steady state and as 457mean outbreak duration) in a spatial and stochastic SIR set-up similar to ours. 458Their analytical and simulation results show a rather more monotone rise in 459persistence as a function of increasing between-patch contacts. However, there 460 is an important difference with our model: their model has no actual dispersal 461 within the metapopulation, the only migration comes from outside the system, 462and is essentially a model with two levels of contacts (within-patch and with 463individuals in other patches) for individuals that are otherwise fixed in their 464 patch. Together, the above comparisons to related studies lead us to expect 465that our observation of non-monotone persistence as a function of coupling cru-466 cially depends on the physical migration between patches of individuals of at least two types in an "exploiter-victim" relationship, with constraints on the 467468distance over which individuals can migrate within a time step.

469An important characteristic of a metapopulation is that the infectious hosts 470 have to move to find susceptible hosts. At low movement distance infectious hosts encounter a lower number of susceptible hosts than the average host, 471472 because the number of susceptible hosts is depleted by the presence of other 473infectious hosts. These infectious hosts are competing with each other over the 474 available susceptibles and thereby reduce the potential for each one of them to 475transmit the infectious disease to a susceptible (Rhodes & Anderson, 2008). At 476a relatively high migration rate, i.e. with a short sojourn time per patch, a 477host can meet more others than at a low migration rate. An infectious host will therefore have a larger number of contacts with susceptible hosts, because they 478 479visit more patches during their infectious period. Compared to a single homo-480geneously mixing population, hosts in metapopulations can have the advantage 481 that they do not reach all susceptible hosts at the same time, which can improve 482the probability of survival of the infectious agent.

As is also shown by Cross et al. (2005), the relation between migration and recovery is very important for the ability of an infectious agent to persist, because the infectious period determines the time an infectious host has to infect susceptible hosts. And the migration rate is an important determinant of the level of mixing.

488 Regarding movement we studied a wide range of migration rates: from mi-489 grating almost never, to migrating every week. We also assumed that all indi-490viduals experience the same migration rate. In reality there is a lot of difference 491 in movement behaviour among species (Hawkes, 2009). Movement may, for ex-492 ample, be restricted to mainly juveniles leaving their nest to settle elsewhere or 493 to foraging outside the own habitat patch. The first mechanism can be thought of at low migration rates, although there are no age-classes defined in the model. 494495The latter one at high migration rates, where individuals leave their own patch, 496visit another one and then return to their home patch again.

This situation could be even more resembled when the probability to move to a certain patch depends on the distance of that patch with respect to the resident patch. We assumed random dispersal, within the movement distance, but it can also be argued that hosts may have a preference for nearby patches. The influence of a dispersal function, favouring nearby patches, on the persistence of the infectious agent should therefore be studied more carefully.

503In this paper we defined the movement distance by the number of edges 504crossed. Another option would have been using a radial movement distance, 505where individuals can move to all patches within a certain radius around their 506resident patch. However, using a radial movement distance instead, does not 507 affect the results. Durrett & Levin (1994) also concluded that the qualitative 508behaviour is independent of the exact definition of movement distance when 509 they studied interacting particle systems for various definitions of movement 510distance.

511 There have been studies of the effect of the neighbourhood of a patch on the 512 persistence of the infectious agent in a spatially structured population. In an 513 ecological context Vuilleumier et al. (2007) and in an epidemiological context

514Rhodes & Anderson (1996) concluded that increasing the movement distance 515maximises the probability of persistence. They considered patches as the unit 516of study and had many unoccupied patches in the population. Another study 517(Courcoul & Ezanno, 2010) did take within-patch dynamics into account, but 518they also considered indirect transmission. The probability of infection of a sus-519ceptible host in a patch depended then not only on the available infectious hosts 520 in the same patch, but also on the prevalence of the infection in neighbouring 521patches. Courcoul & Ezanno (2010) varied the number of neighbouring patches 522that influence the infection dynamics in a patch, but did not see a peak in the 523fraction of simulations with persisting infection at an intermediate number of 524neighbours. However, due to the different ways persistence can be defined, one 525should be cautious in comparing the various studies.

526The model used in this paper is as simple as possible. For example, it is not 527taken into account that infectious hosts might experience reduced mobility or 528death as a result of the infectious disease. Another assumption is continuous birth, as opposed to seasonal birth, where births occurs in a short period of 529a year, which is often the case in animal populations. Seasonal births reduces 530531the probability of persistence of the infectious agent, because there are fewer 532infectious hosts between epidemics, which increases the probability of fade-out 533due to stochasticity (Grassly & Fraser, 2006). But, each year there is also a burst 534of new susceptible hosts into the population (Altizer et al., 2006), creating the 535possibility of a new epidemic. One of the next steps in exploring the balance 536of the various aspects (spatial, demographical and epidemiological) involved in 537the persistence of an infectious agent would be to include one or more of the 538above mentioned options.

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Figure 1: In *a*) the contour lines mark the area where the combination of the migration rate and the movement distance yield the same minimum fraction of simulations with persisting infection. In *b*) the fraction of simulations with persisting infection is shown with migration rate 0.2 (dotted line), 0.4 (dashed line), 0.6 (solid line) and 0.8 (dot-dashed line). The results are taken from 1000 simulations and the default parameter values are P = 100, K = 10, $\beta = 10$, $\gamma = 0.5$, b = 0.2 and $\mu = 0.01$.



Figure 2: A box-and-whisker-plot, where the thick line denotes the median, the box encloses 50% of the observations and the whiskers show the 2.5 and 97.5 percentile. Panel a) shows the total number of time steps that a patch contains at least one infectious host is shown; panel b) the number of times that a patch gets infected, i.e. the number of transitions from no infectious host in a patch to at least one infectious host; panel c) the total number of infectious hosts per patch and panel d) the number of consecutive time steps a patch contains an infectious host. The results are from 1000 simulations with persisting infection, run till t = 200. The default parameter values are P = 100, K = 10, $\beta = 10$, $\gamma = 0.5$, b = 0.2 and $\mu = 0.01$.



Figure 3: The fraction of simulations with persisting infection for a range of values of four demographical and epidemiological parameters. In each panel, the results (from 1000 simulations) are shown for the movement distance 2 (dashed line), 6 (solid line) and 14 (dotted line) and for a single homogeneously mixing population (grey line). A migration rate of 0.6 is used, and the default parameter values are P = 100, K = 10, $\beta = 10$, $\gamma = 0.5$, b = 0.2 and $\mu = 0.01$.



Figure 4: Curves for parameter combinations leading to the same fraction of simulations with persisting infection, where for panel a) and c) this fraction is 0.3 and for panels b) and d) the fraction is 0.6. The results are for movement distance 2 (dashed line), 6 (solid line) and 14 (dotted line) and for a single homogeneously mixing population (grey line). As migration rates 0.4 (panel a) and c)) and 0.8 (panel b) and d)) are used and birth rate 0.1 (panel a) and b)) and 0.3 (panel c) and d)). The other parameters are set to the default values: P = 100, K = 10 and $\gamma = 0.5$.