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# A fully coupled, mechanistic model for infectious disease dynamics in a metapopulation: Movement and epidemic duration

M. Jesse [a,*], P. Ezanno [b,c], S. Davis [a], J.A.P. Heesterbeek [a]

[a] Faculty of Veterinary Medicine, Utrecht University, Yalelaan 7, 3584 CL Utrecht, The Netherlands
[b] INRA, UMR1300 Bio-agression, Epidémiologie et Analyse de Risques, BP 40706, F-44307 Nantes, France
[c] ENVN, UMR1300 Bio-agression, Epidémiologie et Analyse de Risques, BP 40706, F-44307 Nantes, France

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ABSTRACT

The drive to understand the invasion, spread and fade out of infectious disease in structured populations has produced a variety of mathematical models for pathogen dynamics in metapopulations. Very rarely are these models fully coupled, by which we mean that the spread of an infection within a subpopulation affects the transmission between subpopulations and vice versa. It is also rare that these models are accessible to biologists, in the sense that all parameters have a clear biological meaning and the biological assumptions are explained. Here we present an accessible model that is fully coupled without being an individual-based model. We use the model to show that the duration of an epidemic has a highly non-linear relationship with the movement rate between subpopulations, with a peak in epidemic duration appearing at small movement rates and a global maximum at large movement rates. Intuitively, the first peak is due to asynchrony in the dynamics of infection between subpopulations; we confirm this intuition and also show the peak coincides with successful invasion of the infection into most subpopulations. The global maximum at relatively large movement rates occurs because then the infectious agent perceives the metapopulation as if it is a single well-mixed population wherein the effective population size is greater than the critical community size.



## 1. Introduction

A metapopulation is a group of subpopulations, each with their own dynamics, but connected by movement of individuals (Leibold et al., 2004). Understanding how such population structure affects the invasion, spread and persistence of infectious disease is of high importance for public health and wildlife management authorities (Grenfell and Harwood, 1997) and consequently the problem has received and continues to receive considerable attention (Cross et al., 2005; Hagenaars et al., 2004; Keeling and Rohani, 2002; Lloyd and Jansen, 2004). We briefly review some of the methodological aspects of the models used by these and other authors and then present a simple, accessible stochastic metapopulation model in which the spread of an infectious disease within a subpopulation is fully coupled to the dynamics of transmission between subpopulations. By fully coupled we mean that the course of epidemics within subpopulations is affected by the movement of individuals to and from subpopulations, and the probability that a migrant is infectious (i.e. that transmission between subpopulations occurs) depends on the course of the epidemic in the subpopulation from which the migrant came.

Metapopulation infection models can be clearly divided into those that classify whole subpopulations as infectious, susceptible or recovered (Gog et al., 2002; Hess, 1996; McCallum and Dobson, 2002), and those that model the dynamics of infection within each group (Cross et al., 2005; Hess, 1996; Keeling and Gilligan, 2000; Park et al., 2002). The first approach ignores the rise and fall of prevalence within a patch over time and neglects variation between infected subpopulations arising from the stochastic nature of epidemics in finite populations. The critical assumption of these patch-based epidemic models then is that when the infection arrives in a new patch it very quickly, relative to the movement dynamics, reaches an infected quasi-stationary state and so all infected patches are identically and immediately infected with a constant prevalence, i.e. the two processes of infection and movements between patches do not occur on the same time scale. The advantage of such an assumption is tractability, and analytic results can often be obtained (Hagenaars et al., 2004; Hess, 1996). There are infectious disease systems where the progress of an infection in a subpopulation is relatively predictable and so the critical assumption of the patch-based approach is arguably appropriate. One such example is

* Corresponding author. Tel.: +31 30 253 6487; fax: +31 30 252 1887.
*E-mail addresses:* M.Jesse@uu.nl (M. Jesse), ezanno@vet-nantes.fr (P. Ezanno), S.A.Davis@uu.nl (S. Davis), j.a.p.heesterbeek@uu.nl (J.A.P. Heesterbeek).

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foot-and-mouth disease where on average 90% of the animals in a herd become infected in less than a week after a primary infection occurs (Le Menach et al., 2005). That is, in each infected subpopulation prevalence rises predictably and rapidly to ~90%. Other examples, where the prevalence of an infection rises rapidly within a week, are the spreading of *campylobacter* in broiler flocks (Van Gerwe et al., 2005) and the spreading of highly pathogenic avian influenza in chicken flocks (Tiensin et al., 2007).

The second class of models explicitly describe the course of an infection within a subpopulation. This creates two levels of complexity and hence these models are usually simulation models and their behaviour must be understood by running large numbers of simulations to determine the typical or average outcome (Cross et al., 2005).

Another, useful way of dividing metapopulation models is by the way transmission between subpopulations is modelled. It is frequently modelled phenomenologically (Hagenaars et al., 2004; Keeling and Rohani, 2002; Park et al., 2002) by which is meant that the presence of infectious individuals in one subpopulation leads to positive forces of infection on individuals in surrounding subpopulations but exactly *how* transmission between subpopulations occurs is not further specified. A common alternative to modelling transmission phenomenologically is to model mechanistically the movement of hosts between subpopulations so that transmission between subpopulations only occurs when an infectious host from one subpopulation moves to another (Cross et al., 2005; Keeling and Rohani, 2002). Such an approach is frequently used in genetics, for example with the structured deme model (Comins et al., 1979), which is also mechanistic in the sense that the spread of new genes occurs when individuals explicitly move between patches.

Metapopulations are defined on networks which can be classified as spatially implicit or explicit. Each node corresponds to either an individual (Rhodes and Anderson, 1996) or a subpopulation (Cross et al., 2005; Park et al., 2002). In spatially implicit networks, all patches are connected to each other, so each individual can move from one patch to any other patch (Hagenaars et al., 2004). For spatially explicit networks an adjacency matrix can be used to describe which patches are connected to each other—they are, for example, defined on lattices (Cross et al., 2005; Park et al., 2002).

The objective of the present study is twofold. First we set out an accessible model for the spread of pathogens in a metapopulation of hosts, in which the between-patch movement rate of hosts is free to vary from one extreme to the other (for example, there is no requirement that this needs to be slow relative to the rates of transmission and recovery). We model transmission mechanistically and while this choice excludes application of the model to disease agents that are air-borne or vector-borne, it does result in a model for which all parameters have a clear biological interpretation (for example, a parameter representing the strength of coupling between subpopulations is not required). The model is not individual based, rather, it models the numbers of individuals in each class (susceptible, infectious or recovered) in each subpopulation, though one such class within a subpopulation could well consist of a single individual. Our second objective is to present new results on the relationship between the duration of infection in the metapopulation as a whole (beginning with a single infectious individual in a single subpopulation) and the rate of movement of hosts between patches. Our motivation here is to understand how infectious disease dynamics change when the host population is viewed as being structured into many smaller, connected subpopulations. Additionally, there is a direct link with the control of infectious disease by considering a common response to an outbreak: reduction of the movement of hosts. This is particularly valid for infectious diseases of livestock (http://ec.europa.eu/food/animal/diseases/controlmeasures/index_en.htm).

## 2. Model

In the model the host population is divided into subpopulations, each inhabiting a patch in the landscape. At least initially, there are no unoccupied patches. The patches in the model are identical in the sense that the patch carrying capacity, demographic parameters, infection parameters and movement rates of individuals are the same for all patches (Table 1). Births are locally density dependent, meaning that the birth rate in a patch depends on the number of individuals in that patch but not on the numbers of individuals in other patches.

Like the island model of Hess (1996), the between-patch contact structure in this model is such that individuals can move from any patch to any other patch. We consider the relatively simple case where transmission is mechanistic and each individual takes on one of three infection states: susceptible ($S$), infectious ($I$) and recovered/immune to the infection ($R$). Individuals do not lose immunity but eventually die and are replaced by susceptibles.

### 2.1. Within-patch dynamics

The within-patch infection process is a discrete version of the classical stochastic SIR model (Diekmann and Heesterbeek, 2000), where $S_x(t)$, $I_x(t)$ and $R_x(t)$ denote the number of individuals per infection state in patch $x$, at time $t$. The total number of individuals in patch $x$ at time $t$ is given by $N_x(t)$. Events occur successively in the interval $[t, t+1)$ in the order of birth, death, infection, recovery and movement. Such an order is of course artificial because all of these processes are continuous. However, in a discrete model such as this it is necessary to impose an order of events so that probabilities of dying or recovering are consistently applied to the correct numbers of individuals. We now describe how these events are modelled, following the same order as they occur in the model.

The number of births in patch $x$ at time $t$ is represented by the random variable $\mathbf{B}(N_x,t)$ and follows a Poisson distribution:

$$\mathbf{B}(N_x,t) \sim Poi\left[\max\left(0; bN_x(t)\left(1-\frac{N_x(t)}{K}\right)\right)\right]$$

where $b$ represents a maximum birth rate and $K$ the carrying capacity of a single patch.

The expression for the birth probability is the same as the logistic model for population growth. It represents a situation in which each patch has enough resources for $K$ individuals; if the population size exceeds $K$ the birth probability drops to zero.

After the event of birth all individuals except newborns have a chance to die, such that the number of deaths in a patch follows a series of binomial distributions. In this case, the probability of dying is independent of the infection state and this is what is

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

| Parameter | Value | Definition |
|---|---|---|
| $P$ | 100 | Number of patches |
| $K$ | 10 | Patches carrying capacity |
| $b$ | 0.02 | Birth rate per week |
| $\mu$ | 0.001 | Natural mortality rate per week |
| $m$ | [0, 0.1] | Movement rate per week |
| $\beta$ | 1 | Infection rate per week |
| $\gamma$ | 0.05 | Recovery rate per week |

reflected here. More explicitly, three random variables can be written down, representing separately the number of susceptible, infectious and recovered individuals that die in patch $x$ over the time interval $[t, t+1)$:

$$\mathbf{D}(S_x,t)\sim Bin[S_x(t),\mu]$$
$$\mathbf{D}(I_x,t)\sim Bin[I_x(t),\mu]$$
$$\mathbf{D}(R_x,t)\sim Bin[R_x(t),\mu]$$

where $\mu$ is the natural mortality rate. Here, we assume no infection-related mortality. Note that $S_x(t)$ is the number of susceptible individuals in patch $x$ at time $t$, which does not include the newborns appearing in the time interval $[t, t+1)$.

It is assumed that newborns appearing in the time interval $[t, t+1)$ cannot be infected in the same time interval, just as they cannot die. The number of susceptible individuals in patch $x$ that become infected in the time interval $[t, t+1)$ is again modelled as a random variable:

$$\mathbf{Inf}(S_x,t)\sim Bin\left[S_x(t)-\mathbf{D}(S_x,t),1-\exp\left(-\frac{\beta(I_x(t)-\mathbf{D}(I_x,t))}{N_x(t)-\mathbf{D}(S_x,t)-\mathbf{D}(I_x,t)-\mathbf{D}(R_x,t)}\right)\right]$$

where $\beta$ is the transmission rate in a frequency-dependent infection process. The probability of success in the binomial distribution is one minus the probability of avoiding infection. Since in the imposed order of events infection occurs after mortality, the number of individuals per state in a patch at this point is the number of individuals at the beginning of the time step, i.e. at time $t$, minus the number that died.

Infectious individuals (that have been infectious for at least one time step) may recover. The numbers that do recover are also assumed to follow a binomial distribution:

$$\mathbf{Rec}(I_x,t)\sim Bin[I_x(t)-\mathbf{D}(I_x,t),\gamma]$$

where $\gamma$ is the recovery rate.

### 2.2. Between-patch dynamics

So far we have constructed a set of random variables that represent the demographic and infection processes occurring within the various patches. The final step is to model the movements of individuals between patches that might allow an infectious agent to spread through the metapopulation.

We denote the number of patches in the metapopulation by $P$. Taking into account the individuals that have died, recently became infected or just recovered, the numbers of susceptible, infectious and recovered individuals in patch $x$ that *may* move to another patch during the time interval $(t, t+1)$ are, respectively, $S_x(t)-\mathbf{D}(S_x,t)-\mathbf{Inf}(S_x,t)$, $I_x(t)-\mathbf{D}(I_x,t)+\mathbf{Inf}(S_x,t)-\mathbf{Rec}(I_x,t)$ and $R_x(t)-\mathbf{D}(R_x,t)+\mathbf{Rec}(I_x,t)$. Note that the number of susceptible individuals that may move to another patch does not include newborn individuals.

The numbers of susceptible, infectious and recovered individuals that move away from patch $x$ at the end of the time interval $[t, t+1)$ are given by the set of random variables:

$$\mathbf{M}_{out}(S_x,t)\sim Bin[S_x(t)-\mathbf{D}(S_x,t)-\mathbf{Inf}(S_x,t),m]$$
$$\mathbf{M}_{out}(I_x,t)\sim Bin[I_x(t)-\mathbf{D}(I_x,t)+\mathbf{Inf}(S_x,t)-\mathbf{Rec}(I_x,t),m]$$
$$\mathbf{M}_{out}(R_x,t)\sim Bin[R_x(t)-\mathbf{D}(R_x,t)+\mathbf{Rec}(I_x,t),m]$$

where $m$ is the movement rate during a single time step. This probability is, for simplicity, assumed to be the same regardless of the state of an individual or the number of individuals in the patch. It is assumed that all movements take place instantly and successfully, meaning that no mortality or infection takes place during movement. The total number of moving individuals is then distributed randomly over all the patches, i.e. this distribution is multinomial with probability $1/P$ to arrive in any particular patch. Note that it is possible for a migrant to arrive in the same patch it has just left.

Now let $\mathbf{M}^Z_{in}(x,t)$ be the set of random variables denoting the number of individuals in infection state $Z\in\{S, I, R\}$ that arrive in patch $x$ at the end of the interval $[t, t+1)$.

With this final piece of notation we can write down a complete set of stochastic difference equations for the system:

$$\begin{aligned}S_x(t+1) &= S_x(t)-\mathbf{D}(S_x,t)-\mathbf{Inf}(S_x,t)+\mathbf{B}(N_x,t)\\ &\quad-\mathbf{M}_{out}(S_x,t)+\mathbf{M}^S_{in}(x,t)\\ I_x(t+1) &= I_x(t)-\mathbf{D}(I_x,t)+\mathbf{Inf}(S_x,t)-\mathbf{Rec}(I_x,t)\\ &\quad-\mathbf{M}_{out}(I_x,t)+\mathbf{M}^I_{in}(x,t)\\ R_x(t+1) &= R_x(t)-\mathbf{D}(R_x,t)+\mathbf{Rec}(I_x,t)\\ &\quad-\mathbf{M}_{out}(R_x,t)+\mathbf{M}^R_{in}(x,t).\end{aligned}$$

## 3. Initial conditions, outputs and global model behaviour

The infection and demographic processes in the model are stochastic and hence there can be large variation between runs of the model even though the sets of parameter values are identical. This is particularly relevant when the patch size (or rather, the carrying capacity of the patches) is small. The set of stochastic difference equations described in the previous section were simulated for a wide range of parameter values. The programme code we used to do this, written in Fortran, is provided as Supplementary Material. The number of time steps for each simulation was set to 520 where one time step denotes 1 week. At time $t=1$ one infectious individual is introduced into one patch in a completely susceptible metapopulation.

We arbitrarily define the infectious agent to be endemic when it is still present in the metapopulation after 520 time steps, which corresponds to 10 years. For the calculation of the median epidemic duration at least 500 simulations for 100 different movement rates at the interval [0, 0.1] were run for a given set of parameters. Because the time step is a week, a movement rate of 0.01 means that one individual moves once per 100 weeks and this translates to an average of four out of 10 individuals in a patch leaving over 1 year (if $x\sim Bin\,(10, 1-0.99^{52})$, then $E[x]=0.41$). The maximal movement rate (0.1) corresponds to one movement per individual once every 10 weeks, i.e. it is highly likely that all individuals will have left a patch within a period of 1 year.

The qualitative behaviour of the model is, in broad terms, not unlike that of a simple SIR model for a single large population: the infectious agent may (i) not spread at all in the initial patch, (ii) spread in the initial patch, but not between patches, (iii) spread within and between patches and then fade out or (iv) spread within and between patches and persist in the metapopulation. We will refer to the first two outcomes as 'no outbreak' or 'immediate extinction'. In the situation where the infection spreads between patches (situations (iii) and (iv)) we speak of 'an epidemic'. However, whether an infectious agent spreads at all and whether it persists once it does spread, is, in addition to the values of the infection parameters, influenced by the rate of movement between patches. These movements determine the extent to which the infectious agent 'perceives' the spatially structured nature of its host population (Cross et al., 2005).

## 4. Epidemic duration, synchrony during invasion and between-patch movements

We focus here on the relation between the movement rate between patches and the duration of infection presence in the

metapopulation as a whole. Our model is for a directly transmitted, innocuous infection that is transported between subpopulations by movement of individuals.

### 4.1. Basic pattern

We explored the dynamics of the model in several ways and summarized the results in Figs. 1–4. In Fig. 1, the median of the epidemic duration is shown together with the first and third quartile to indicate the variation in epidemic duration between simulations; for most movement rates this variation is quite high. A striking result is the non-linear response of the median epidemic duration to the movement rate between patches (Fig. 1). Initially the epidemic duration increases rapidly with the movement rate but changes abruptly such that a peak in the duration of the epidemic appears at relatively small movement rates. It then decreases for intermediate values of the movement rate until the movement rates become large enough such that the third quartile jumps to values larger than the simulation time, i.e. the increase of the curve is caused by the endemic behaviour that is possible for large movement rates. However, the infection was never observed to persist in a single patch, because the carrying capacity of a patch is always set to values presumably far lower than what is required for this.

### 4.2. Maxima in epidemic duration

We now consider more closely the first peak. The number of patches that are infected at least once are shown in Fig. 2 (dotted line), together with the curve representing median epidemic

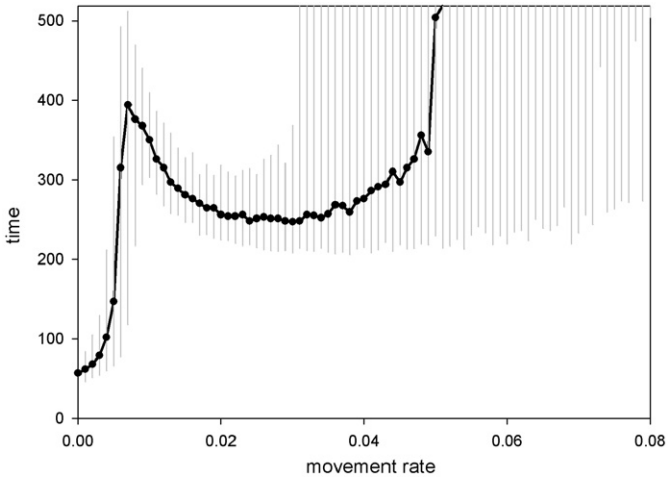


**Fig. 1.** The dependence of the epidemic duration in weeks on the movement rate, with bars indicating the first and third quartile. The default parameter values $P = 100$, $K = 10$, $\beta = 1$, $\gamma = 0.05$, $b = 0.02$ and $\mu = 0.001$ are used. The results are of 500 simulations.

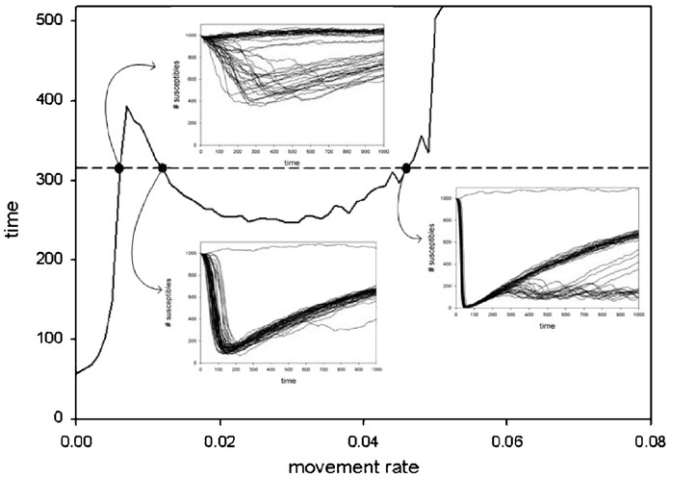


**Fig. 3.** The dependence of the median epidemic duration on the movement rate with insets showing the different behaviour of three movement rates (0.006, 0.012 and 0.046) with the same median epidemic duration of 315 weeks. For these rates the total number of susceptible individuals in the metapopulation is given over 1000 time steps for 50 simulations. The default parameter values $P = 100$, $K = 10$, $\beta = 1$, $\gamma = 0.05$, $b = 0.02$ and $\mu = 0.001$ are used.

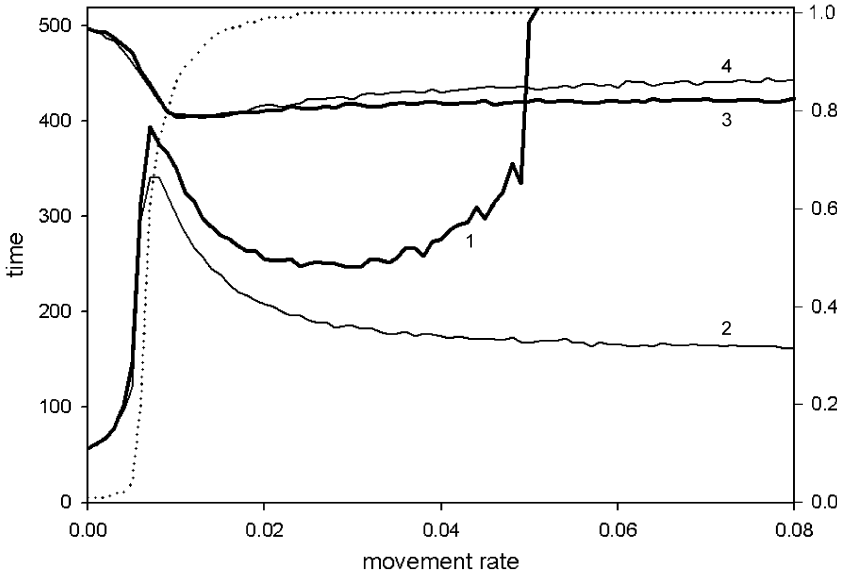


**Fig. 2.** The dependence of the epidemic duration in weeks with the default parameters $b = 0.02$ and $\mu = 0.001$ (line 1) and with $b = \mu = 0$ (line 2), of the between-patch prevalence correlation coefficient with the default parameters $b = 0.02$ and $\mu = 0.001$ (line 3) and with $b = \mu = 0$ (line 4) and of the proportion of patches that have been infected at least once with the default parameters (dotted line) on the movement rate. The other default parameter values $P = 100$, $K = 10$, $\beta = 1$ and $\gamma = 0.05$ are used. The results are the median values of at least 250 simulations.

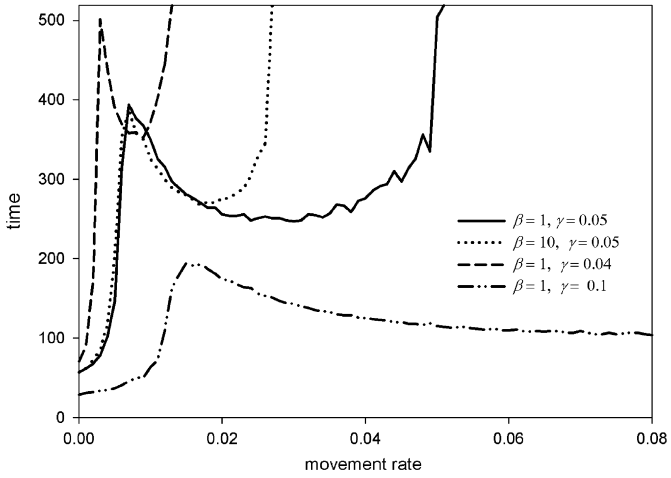


**Fig. 4.** The dependence of the epidemic duration in weeks on the movement rate for transmission rate $\beta = 1$ (default) and $\beta = 10$ and recovery rates $\gamma = 0.04$, $\gamma = 0.05$ (default) and $\gamma = 0.1$. The other default parameter values $P = 100$, $K = 10$, $b = 0.02$ and $\mu = 0.001$ are used. The graphs are the median values of 500 simulations.

duration, and we see that the rapid increase leading to the first peak coincides with a similar increase in the number of patches that become infected at least once. So for small movement rates, an infectious individual moving to another patch has a large probability to arrive in a patch with a completely susceptible subpopulation and transmit the infection. However, there is also a high probability at small movement rates that infectious individuals recover before they move, so that at the scale of the metapopulation the epidemic tends to be short-lived. Indeed, even though a typical epidemic is short-lived at small movement rates, the median number of infectious individuals per infected patch is higher than for large movement rates (results not shown). At movement rates larger than that producing the first peak in epidemic duration almost all patches are infected (Fig. 2).

At a large movement rate the global maximum (where endemic behaviour begins to occur) is reached. For these movement rates a typical infectious individual will visit several patches during its infectious period. This is particularly important just after the first epidemic when very few infectious individuals remain (the vast majority of the population having reached the recovered state). At this point their frequent movement increases the probabilities of meeting the few susceptible individuals that have either just entered the population (births) or have so far escaped infection. This mixing enables the infectious disease to persist in the metapopulation.

In order to better understand the second peak and global maximum in epidemic duration, we recalculated the median epidemic durations, but this time set the birth and mortality rates to zero (line 2 in Fig. 2). This means there is no population turnover, and hence no new susceptible individuals are introduced at any time step. For this situation the second increase in epidemic duration disappears and there is a single global maximum at small movement rates; this shows that the arrival of new susceptible individuals is a necessary condition for endemic behaviour.

### 4.3. The effect of the movement rate

As an aid to interpreting our results on epidemic duration, we show in Fig. 3 more detailed simulation results for three movement rates that produce the *same* median epidemic duration. The rates are 0.006, 0.012 and 0.046, all of which have a median epidemic duration of 315 time steps (i.e. 6 years). These rates represent that one individual moves once per 160, 83 or 22 weeks, respectively. One difference for these three movement rates is the number of patches that become infected at least once during the time the infection is present in the metapopulation of 100 patches. For the smallest movement rate, around 21 patches will have been infected at least once, for the middle rate 91 patches, and for the largest rate every patch (dotted line in Fig. 2). Perhaps more informative is the total number of susceptible individuals in the metapopulation over time for the three different movement rates. These curves reveal that the model exhibits three kinds of behaviour: (i) there is immediate extinction of the infection, i.e. there is no outbreak, (ii) there is one epidemic followed by fade out, and (iii) there are several consecutive epidemics and the infection persists in the metapopulation. At the small movement rate (0.006) two kinds of behaviour are possible: immediate extinction or a single epidemic. After the peak at movement rate 0.012, immediate extinction occurs less often and single epidemics become the rule. At the largest movement rate (0.046) both immediate extinction and single epidemics are still possible, but there are also simulations where several consecutive epidemics occur. Furthermore, as the movement rate increases, the minimum number of susceptible individuals during an epidemic decreases and is reached at an earlier time step (Fig. 3). At this point, where only a few susceptible individuals are left, fade out can occur, which gives smaller epidemic durations. Also, the time it takes the infection to reach a particular patch becomes shorter and synchrony in the infection dynamics in the separate patches emerges.

Not only the minimum number of susceptible individuals, but also the period during which a patch is uninterruptedly infected, decreases with increasing movement rates (result not shown). This is because of a stronger coupling between patches for increasing movement rates such that epidemics occur locally faster.

### 4.4. Synchrony

We confirm the argument in the preceding paragraph by measuring synchrony in the infection dynamics of the patches. We also note that synchrony between patches increases the probability of global extinction of the infection. The between-patch prevalence correlation (Hagenaars et al., 2004), $C$, is calculated, which is a measure of the synchrony between the different patches:

$$C = \frac{2/P(P-1)\sum_{i-1}^{P}\sum_{j=1}^{i-1}\langle S_i(t)S_j(t)\rangle - 1/P^2\left(\sum_{i=1}^{P}\langle S_i(t)\rangle\right)^2}{1/P\sum_{i=1}^{P}\langle S_i(t)^2\rangle - 1/P^2\left(\sum_{i=1}^{P}\langle S_i(t)\rangle\right)^2}.$$

We examined the synchrony between the susceptible individuals, rather than the infectious individuals (Hagenaars et al., 2004), in the patches, because the numbers of infected individuals can be very small (simulations begin with only one infected individual in the metapopulation). The correlation coefficient was calculated for 250 simulations at each movement rate (lines 3 and 4 in Fig. 2), where $\langle \cdot \rangle$ is the time-average over the first 250 time steps of the simulation and the number of runs. We took the first 250 time steps, because the first epidemic takes place within these time steps and this is where the effect of synchrony plays a large role.

The minimum of the between-patch prevalence correlation coincides roughly with the peak in epidemic duration. After this minimum, the correlation coefficient increases again, albeit slowly at the scale shown in Fig. 2. Also shown is the correlation coefficient for the model without population turnover (line 4 in

Fig. 2), which increases somewhat faster compared to simulation results from the model with population turnover (line 3 in Fig. 2); without population turnover there is no rise in susceptible individuals causing endemic behaviour and thus there is more synchrony between the patches for larger movement rates.

### 4.5. Robustness

The non-linear response of the median epidemic duration to increasing movement rate is not restricted to a small part of parameter space, but also occurs for other values of the recovery and transmission rates (Fig. 4). The recovery rate has a large impact on the spread of the infection through the metapopulation: a smaller recovery rate (i.e. a longer infectious period) results in penetration of the infection in the metapopulation at smaller movement rates, because an infectious individual has more time to infect susceptibles. For larger recovery rates, relative to the demographic rates, the endemic behaviour occurs at larger movement rates and finally disappears from the system, leaving only one maximum in median epidemic duration at small movement rates. Intuitively this can be understood as follows: a larger recovery rate yields a shorter infectious period and in this period an infectious individual has to infect enough susceptible individuals to sustain the infectious disease in the metapopulation. This becomes more difficult for larger recovery rates and eventually impossible, resulting in the disappearance of the endemic behaviour.

Furthermore, a larger transmission rate influences neither the spread of the infection nor the median epidemic duration at small movement rates. For larger movement rates, a larger transmission rate does influence the epidemic duration. This is probably because after the first epidemic there are only a few susceptible individuals left, but an infectious individual has to meet a susceptible in order to pass on the infection and ensure that the infection does not fade out. At a large movement rate, an infectious individual can visit more patches which increases the probability of meeting susceptible individuals. However, an infectious individual not only has to meet them, but infect them as well. For a higher transmission rate, the probability of actually infecting, and therefore sustaining the infection in the metapopulation, increases, resulting in a larger median epidemic duration. This observed effect, however, may be due to the small patch sizes used here.

The median epidemic duration for a different number of patches shows (result not shown) that there is a critical community size (Bartlett, 1957; Grenfell and Harwood, 1997) above which the infection will persist in the metapopulation and below which the infection will disappear. For a certain movement rate increasing the number of patches, but not the total population size, can cause the endemic behaviour to disappear.

## 5. Discussion

We have presented a model for the dynamics of an infectious disease in a metapopulation that is fully coupled but not individual based. Patch-based epidemic models assume that if a patch becomes infected, it reaches an equilibrium state immediately such that individuals arriving later (or leaving the patch later) do not influence the course of the infection within the patch. For large subpopulations, or if the rate of movements is much slower than the transmission rate, then this may be an appropriate simplification. However, it is an uncomfortable simplification. In reality there will be variation among subpopulations in what happens once a single infectious individual arrives. Patch-based epidemic models also ignore some of the potential effects of host movements. For example, the frequent arrival of susceptible individuals into an infected patch may extend the infection in that patch in the same way as host turnover does. Models representing the within-patch infection dynamics explicitly account for the effect of additional introductions into a given patch on the probability of infection persistence in this patch. The disadvantage is that analytic results are no longer possible and one can only establish the mean behaviour of the model for a small part of the parameter space. It is hence difficult to use such models to draw general conclusions about the dynamics of infectious disease in metapopulations.

In the proposed approach, the within-patch infection dynamics of an infectious agent is represented and we have chosen a SIR-type model for this. The model can be adapted (e.g. to SI or SIS models) and can be extended to include, for example, higher mortality or smaller movement rates among infectious individuals compared to uninfected. In a first approach, movements were defined as random between patches, with all patches being equally likely destinations, similar to the island model of Hess (1996). In many wildlife metapopulations, movement will not be to a random patch. For example, if movements are related to the dispersal behaviour of maturing animals then there may be a tendency to avoid neighbouring patches (e.g. male cats; Fromont et al., 2003). Another example is phocine distemper virus in the North Sea population (Swinton et al., 1998); this infection causes mortality in harbour seals. The infection is transmitted directly and appears to spread from one subpopulation to another through the movements of individuals. In this example the infectious agent does not persist, at least not in the North Sea harbour seal population. If data are available on animal movements (e.g. in domestic cattle; Ezanno et al. (2006) and Kao et al. (2007)) it is possible to define a specific metapopulation structure. An adjacency matrix can be used to describe such a structure, for instance when not all patches are (equally) connected to each other (Keeling and Eames, 2005).

Empirical studies that address the effect of population structure on the dynamics of infectious agents appear to be rare. One exception is the study by Lopez et al. (2005) on the spread of an ectoparasitic mite in a metapopulation of flour beetles. Interestingly, the experimental system studied was fully coupled (movement of hosts was imposed at weekly intervals whereas the time taken to reach local equilibrium within a patch was around 30 days) and transmission was mechanistic (spread of the parasite was entirely dependent on movements of infectious hosts). Lopez et al. (2005) did not study the effect of movement rate on epidemic duration (there were no epidemics as such and they were concerned largely with the endemic prevalence of the parasite) but, in agreement with our results and those of other theoretical studies, they found that host movement had a large impact on the proportion of infected patches.

We show that the median epidemic duration does not increase monotonically with movement rates and that this is not restricted to a small range of parameter values. In fact, the relationship is highly non-linear. This contradicts some of the results of other modelling studies on the persistence of infectious disease in metapopulations, stating that persistence is always improved by increasing movement between patches (Hagenaars et al., 2004; Lindholm and Britton, 2007). However, care must be taken when comparing the results of studies of persistence as persistence can be defined in several ways. Both Hagenaars et al. (2004) and Lindholm and Britton (2007) measure persistence as the expected time to extinction (of the infectious agent) when all patches were infected at the beginning of the simulations and all patches were assumed to be at the quasi-equilibrium state, representing an endemic infection of the metapopulation. This is quite different to introducing the infection into a fully susceptible metapopulation

with a single infectious individual and then noting when the infection dies out and to looking at the number of patches that have been infected at least once (Cross et al., 2005). That is, we studied the transient infection period, during which many early extinctions occur and this is qualitatively different to studying the extinction of infectious disease from an endemic state or studying if the infectious disease has invaded all the patches in the metapopulation.

Hagenaars et al. (2004) also looked at the fade-out fraction as a measure of persistence in a situation where an infection starts with a single infectious individual, but there the infection can later be reintroduced from an external source. Park et al. (2002) is another study of persistence of infectious disease in structured host populations. They model the force of infection on susceptible individuals in a patch phenomenologically and found a non-linear relation between the median epidemic duration and the patch size. The patch size was shown to directly relate to the probability of transit of the infection between patches and Park et al. (2002) suggest that the peak in epidemic duration is a consequence of when and how often transit of the infection occurs. They suggest lower median extinction times for the largest patch sizes are due to more rapid transit of the infection, because increasing the patch size increases the force of infection from infected patches (in their phenomenological model the force of infection is proportional to the number of infectious individuals). Our results are easier to grasp in the sense that only the rate of movement is varied and hence we have shown that simply increasing movements of individuals between patches can first cause an increase in the median epidemic duration, then a decrease and then going to an endemic state.

The theory of metapopulation persistence, where the persistence of populations is considered as a balance between colonization and local extinction, and the persistence of an infectious agent in a metapopulation are closely related (Grenfell and Harwood, 1997; Hanski, 1999): the process of colonization corresponds to the establishment of the infection into a completely susceptible patch in epidemiological models and local extinction corresponds to the death or recovery of hosts (Grenfell and Harwood, 1997; Hanski, 1999). In metapopulation persistence, persistence occurs at intermediate levels of coupling (Lande et al., 1998). According to Hanski (1999) this is due to asynchrony of the dynamics between patches: moving individuals can reoccupy a patch to prevent extinction (the so-called 'rescue effect').

Persistence of an infectious disease in a structured population has been studied by several authors. Keeling (2000) showed that the probability of global extinction of an infectious disease has a minimum at intermediate levels of coupling, which can be explained by asynchrony between patches (Hagenaars et al., 2004), wherein moving infectious individuals can reintroduce the infectious agent into a patch that had no infectious individuals. This is only possible at relatively small movement rates after which the patches become highly synchronized. We also show that asynchrony between patches is the driving force for the peak in epidemic duration for small movement rate.

Persistence is further studied in ecological models like predator–prey interactions in a metapopulation (Leibold et al., 2004; Sabelis et al., 2005), where the persistence of both the predators and the prey in a metacommunity is examined. These models show resemblance to epidemiological models (Earn et al., 1998) in the sense that the prey are the susceptible individuals, the predators are the infectious individuals and the dispersal of the predators corresponds to the spread of an infection. In the simple predator–prey models, where predators can cause local extinction of prey, it has been shown that persistence of both species is only possible at intermediate dispersal rates (Leibold et al., 2004). This is in contrast to our result that persistence is only possible at larger movement rates.

Our results are possibly more relevant to outbreak management than studies of extinction of infection from an endemic state or studies in which patch size is varied. For example, if for an infectious disease in livestock a peak in the median epidemic duration is expected, then it is useful for health authorities to understand that restricting movement of animals between farms or holdings may not reduce the epidemic duration, although the number of farms or holdings that suffer from the infection is reduced. That is, a possible outcome of intervention is that the total number of infectious individuals is reduced, but not the duration of the epidemic.

At relatively large movement rates, the model predicts that endemic behaviour is possible. That is, rather than a single epidemic the first wave of infection is followed by several others. At these movement rates the infectious agent may 'perceive' the metapopulation as if it is one large population. For several consecutive epidemics to occur, a critical community size (Bartlett, 1957; Grenfell and Harwood, 1997) is needed such that the number of new susceptible individuals replacing older, recovered individuals is high enough to prevent extinction. At large movement rates, the infectious agent must therefore 'experience' or 'perceive' the metapopulation as if it is effectively larger than the critical community size. We emphasise, that whether several consecutive epidemics actually occur at these movement rates, also depends on the number of patches the population is divided into, while keeping the total population size constant; an individual will 'experience' a metapopulation consisting of a few large patches as a larger population than one consisting of many small patches. In the case of epidemics on a lattice, where each node represents an individual rather than a subpopulation, it has been concluded that for persistence both a population size threshold and a population mixing threshold must exist (Rhodes and Anderson, 1996). It would be useful to assess how the population size experienced by an individual is related to the actual total population size, the patch size and the movement rate.

We have proposed a relatively generic model to represent the infection dynamics of a metapopulation composed of patches connected by explicit individual movements. The effect of population structure on epidemic duration is one of several topics that fall under the more general concern about how spatial heterogeneity affects the dynamics and fate of infectious disease. Numerous modelling approaches have been suggested to study these questions and while analytic progress can be made with simpler models we would also suggest that the results of fully coupled models are an important contribution.

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## Appendix A. Supporting Information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtbi.2008.05.038.

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