17. METAPOPULATION DYNAMICS OF INFECTIOUS DISEASES

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17.1 INTRODUCTION

John Donne's famous line "No man is an island, entire of itself" has deep resonances for the dynamics of parasites. This is particularly true for microparasitic infections, such as viruses and bacteria, for which each susceptible host is a potential patch of favourable habitat. Propagules from infected "patches" can colonize others, followed by parasitic multiplication and "local" growth of the parasite population. Thus, at the scale of the host population, infectious dynamics bears strong analogies to metapopulation dynamics. Furthermore, host individuals are, more often than not, structured into local populations, within which contact among hosts may be very frequent and between which contacts may be less frequent. In this way, the spatiotemporal dynamics and persistence of parasites are determined at two scales: the *infrapopulation* scale (a local population scale; parasites within hosts) and the *metapopulation* scale (spatial and/or social aggregation of hosts). The spatiotemporal dynamics of infection in human and domestic systems are of particular academic interest because of the wealth of data combined with well-described natural histories.

As a result of the dual spatial scales of regulation, an extended metapopulation paradigm is central to infectious disease dynamics in two important

0-12-323448-4

ways. First, the metapopulation approach can help us understand disease dynamics at the different spatial scales. This topic is the main concern here, we use extensive data sets and realistic dynamic models to discuss the metapopulation dynamics of infectious disease. Second, there are important conceptual insights about the eradication by vaccination of infections to be gained from studies of the persistence of metapopulations (Nee, 1994; Grenfell and Harwood, 1997; Ovaskainen and Grenfell, 2003). This chapter therefore explores two main topics: (i) the analogies between the disciplines of ecology and epidemiology at the metapopulation-level and (ii) how metapopulation theory at a variety of scales can aid our understanding of epidemiological dynamics. We discuss these issues in the face of a set of detailed models and high-resolution space–time data of disease incidence.

Metapopulation-like disease dynamics occur whenever the environment, in this case the population of susceptibles, is sufficiently patchy that isolated clumps of suitable habitat exist. This is always the case at the microscale; each host is an island to be colonized and a resource patch to be depleted. At the macroscale, hosts are usually aggregated in local communities within which transmission is relatively frequent and between which infection spreads at a lower rate. Our dominant focus is on the metapopulation (macro)scale. To illustrate the key issues, we first introduce a simple epidemic model and then use this to illuminate the basic processes in the spatiotemporal dynamics of epidemics. Two distinct modeling scenarios are considered: a fully stochastic metapopulation where the individual level processes within each habitat (or community) are modeled explicitly and a spatially implicit (Levins-type) metapopulation where habitats are classified into a limited set of discrete classes. Both formulations have associated benefits and allow different insights into the dynamic processes in disease spread. We then revisit how metapopulation processes operate at various spatial scales (individual level, local, and regional epidemics). These resultant spatiotemporal dynamics are then illustrated through a series of case studies, which explore diseases metapopulation dynamics at the interface of models and data. We conclude with a section on fruitful areas for future work.

17.2 THE SIR MODEL FOR EPIDEMIC DYNAMICS

We focus here on microparasite infections (mainly viruses and bacteria), where direct reproduction of the pathogen in the host allows us to model disease dynamics by dividing the host population between compartments, classified by their infection status (Anderson and May, 1991). In contrast, macroparasitic helminth infections, where parasite burden matters, are much harder to model spatially (and not considered here), although strong analogies have been found between macroparasite and metapopulation dynamics (Cornell et al., 2000). The most studied microparasite system is the SIR model, where individuals are susceptible (S), infected (I), or recovered (R). This classification holds analogies to the "compartmental" Levins metapopulation models in which patches are classified as either occupied or empty (Chapter 4). As discussed in the next section, the "reversibility" of true metapopulations (such that local patch populations can become extinct, then reestablished by colonization) is a closer match to the SIS dynamics (susceptible–infectious–susceptible, such that

recovered individuals do not possess immunity) associated with many sexually transmitted diseases (Anderson and May, 1991). In the SIR paradigm, susceptible individuals can catch the disease from contact with infected individuals, and infected individuals recover at a given rate, after which time they are assumed to be immune to the disease. This leads to the following set of differential equations:

$$\begin{aligned} \frac{dS}{dt} &= BN - \beta\frac{SI}{N} - dS \\ \frac{dI}{dt} &= \beta\frac{SI}{N} - gI - dI \\ \frac{dR}{dt} &= gI - dR \\ N &= S + I + R \end{aligned} \tag{17.1}$$

where B is the birth rate, d is the natural death rate, β is the transmission rate between infected and susceptible individuals, and g is the recovery rate. Many improvements and variations on this underlying framework have been developed successfully to describe the behavior of particular diseases and hosts (Anderson and May, 1991; Grenfell and Dobson, 1995; Hudson et al., 2002). In essence, Eq. (17.1) predicts a stable equilibrium level of susceptibles and infected, which is reached through a series of damped epidemics.

17.3 THE SPATIAL DIMENSION

Spatial structure and the aggregation of hosts into discrete patches can have dramatic effects on the dynamics of infectious diseases (May and Anderson, 1979; Grenfell and Bolker, 1998). We subdivide these effects into four main groups, which we consider with respect to the dynamics of one large, homogeneously mixed host population versus the dynamics of several smaller, more isolated ones.

Isolation and Coupling: A Simple Two-Patch Model

The most obvious aspect of spatial separation is the isolation of one or more local populations. The degree of isolation is controlled by the coupling between patches. In the absence of coupling, the dynamics in each patch are independent, and as the coupling increases, so does the correlation between them. We generally envisage coupling as the result of the movement of hosts; in such cases it is important to realize that the movement of both susceptibles and infecteds plays an equal role. We also note that two patches can be coupled directly due to the mixing of individuals in a third patch (e.g., people from two outlying towns might meet, and transmit infection, at a nearby large town). As we are concerned primarily with the spread of infection between human communities, we envisage coupling as the result of short duration commuter movements. For other host species, coupling could be generated by

the permanent movement of hosts or simply the movement of pathogens between local populations (Keeling et al., 2001).

A key question for understanding the ensuing spatial dynamics is how to accurately allow for the movement of infection. Consider, first, a metapopulation of just two patches (Keeling and Rohani, 2002). In this model, individuals commute from their home population to the other patch, but return rapidly (Sattenspiel and Dietz, 1995). We label individuals by two subscripts such that S_{ij} are the number of susceptibles currently in patch j, whose home is patch i. We also assume that individuals from patch i commute at rate ρ_i and return at rate τ_i, independent of their infectious state. If we assume frequency-dependent transmission (de Jong et al., 1995; McCallum et al., 2001), then equations for the number of susceptibles and infecteds in each patch are given by

$$\begin{aligned}
\frac{dS_{ii}}{dt} &= bN_{ii} - \beta S_{ii}\frac{I_{ii} + I_{ji}}{N_{ii} + N_{ji}} - dS_{ii} + \tau_i S_{ij} - \rho_i S_{ii} \\
\frac{dI_{ii}}{dt} &= \beta S_{ii}\frac{I_{ii} + I_{ji}}{N_{ii} + N_{ji}} - gI_{ii} - dI_{ii} + \tau_i I_{ij} - \rho_i I_{ii} \\
\frac{dS_{ij}}{dt} &= bN_{ij} - \beta S_{ij}\frac{I_{ij} + I_{jj}}{N_{ij} + N_{jj}} - dS_{ij} - \tau_i S_{ij} + \rho_i S_{ii} \\
\frac{dI_{ij}}{dt} &= \beta S_{ij}\frac{I_{ij} + I_{jj}}{N_{ij} + N_{jj}} - gI_{ij} - dI_{ij} - \tau_i I_{ij} + \rho_i I_{ii}
\end{aligned} \tag{17.2}$$

where $i \neq j$. Here, equations for the recovered class (R_{ii} and R_{ij}) have not been given explicitly, as they can be calculated from the fact that $S + I + R = N$. If we allow the distribution of individuals to equilibrate, then $N_{ii}/N_{ij} = \tau_i/\rho_i$. Now, summing over all individuals whose home is patch i and assuming that time spent away from the home patch is relatively short compared to the disease dynamics, we get

$$\begin{aligned}
\frac{dS_i}{dt} &= bN_i - \beta S_i\left[\sigma_{ii}I_i + \sigma_{ij}I_j\right] - dS_i \\
\frac{dI_i}{dt} &= \beta S_i\left[\sigma_{ii}I_i + \sigma_{ij}I_j\right] - gI_i - dI_i
\end{aligned} \tag{17.3}$$

where σ are the conventional rates of coupling between populations. These are given by

$$\begin{aligned}
\sigma_{ii} &= \frac{(1-\gamma_i)^2}{(1-\gamma_i)N_i + \gamma_j N_j} + \frac{\gamma_i^2}{\gamma_i N_i + (1-\gamma_j)N_j} \\
\sigma_{ij} = \sigma_{ji} &= \frac{(1-\gamma_i)\gamma_j}{(1-\gamma_i)N_i + \gamma_j N_j} + \frac{\gamma_i(1-\gamma_j)}{\gamma_i N_i + (1-\gamma_j)N_j}
\end{aligned} \tag{17.4}$$

where $\gamma_i = \frac{\rho_i}{\tau_i}$ is the ratio of commuting to return rates and as such can be calculated from the expected amount of time an individual from patch i spends away from home $\left(= \frac{\gamma_i}{1+\gamma_i}\right)$. In the much simplified case where the population sizes and movement patterns are equal in both patches,

$$\sigma_{ii} = \frac{\gamma^2 + (1 - \gamma)^2}{N} \qquad \sigma_{ij} = 2\gamma(1 - \gamma) \tag{17.5}$$

The factor of two in σ_{ij} originates because coupling can come from either the movement of susceptibles or the movement of infecteds. Quadratic terms occur due to two individuals with the same home patch meeting in the away patch.

If we assume global coupling, such that commuter movement occurs equally to all other local populations irrespective of distance between them, then the n patch generalization is

$$\begin{aligned} \frac{dS_i}{dt} &= bN_i - \beta S_i\left[(1 - n\sigma)I_i + \sigma\Sigma_{j=1}^{n} I_j\right]/N - dS_i \\ \frac{dI_i}{dt} &= \beta S_i\left[(1 - n\sigma)I_i + \sigma\Sigma_{j=1}^{n} I_j\right]/N - gI_i - dI_i \\ \sigma &= 2\gamma(1 - \gamma). \end{aligned} \tag{17.6}$$

where γ is again the ratio of the rate of commuting to a given patch to the rate of return. The proportion of time spent away from the home patch is now $\frac{n\gamma}{1 + n\gamma}$.

These models [Eqs. (17.3) and (17.6)] illustrate that even the complex mechanistic movement of commuters can generally be expressed as a distributed force of infection from each infected individual across multiple local populations. Thus the complex patterns of human movements can be subsumed into a set of parameters σ, which specify the relative strengths of within-patch to between-patch transmission. These equations (17.3 and 17.6) are identical to those derived when the movement between local populations is permanent immigration rather than short-duration commuter travel (Kot et al., 1996; Smith et al., 2002) and to those formulated when the transmission of infection between different local populations is via wind-borne spread (Bolker, 1999; Park et al., 2001). Therefore, the simple and intuitive method of coupling local populations is applicable to a wide variety of diseases and interaction scenarios.

The aforementioned framework for studying the dynamics of a disease in a spatially structured population is founded on the premise of deterministic interactions and very rapid movement of commuters back to their home patch. Now we consider how this translates into a more realistic stochastic framework, where the population is individual based and events are assumed to occur at random; this is often termed demographic stochasticity. In such a framework, the coupled model [Eq. (17.3)], which has far fewer equations than the full mechanistic model [Eq. (17.2)], is a reliable approximation if the movement rate of individuals between the populations is rapid. However, as the movement rate slows (e.g., if commuters generally spend the entire day or longer away from home), the individual nature of the population plays an ever greater role. If just one individual is infected, then the level of coupling will be influenced greatly by whether that individual commutes. Figure 17.1 shows the distribution of cases caused by a single infectious case in their nonhome patch. Clearly the number of cases produced is highly dependent on whether

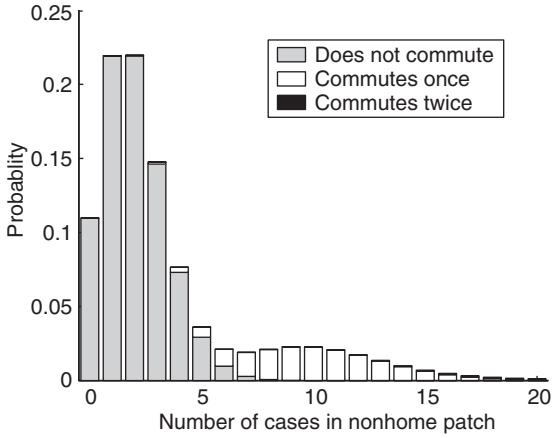

Fig. 17.1 Probability of a single infectious individual causing different numbers of secondary cases in their nonhome patch. If the infectious individual commutes, there is a dramatic shift in the expected number of cases. In this scenario, the infectious period is exactly 3 days, commuters always spend a full day away from home, and the basic reproduction ratio $R_0 = 30$. The susceptible population is considered to be very large.

the infectious person commutes, although even when they remain in their home patch the disease can still spread due to the movement of susceptibles.

In stochastic metapopulation models, therefore, when the level of infection is low and the commuter time is of the same order as the infectious period, we must be very cautious in our use of approximations to the true mechanistic dynamics. The occasional rare event, when the infected individual commutes, can have large repercussions and leads to a far wider range of outcomes than would be expected from a stochastic version of the simple coupling model [Eq. (17.3)].

Stochastic and Seasonal Forcing

The main manifestation of random fluctuations explored in epidemic theory is the impact of demographic stochasticity. As for conventional metapopulations, a major impact of demographic stochasticity is on the extinction rate, here of epidemics in small populations (see next section). However, due to the inherent oscillatory nature of epidemics, *stochastic forcing* of epidemics can give rise to regular or irregular cycles. This issue has strong parallels with the recurrent debate in ecology on the relative impact of noise and deterministic forces on dynamics (e.g., Bjørnstad and Grenfell, 2001). In epidemiology, the interaction between deterministic nonlinearity and forcing has been most studied in terms of the perturbing forces, which may maintain strong recurring epidemics of measles in the prevaccination era; these epidemics are predicted to dampen to an equilibrium by simple deterministic nonseasonal models (May and Anderson, 1991). The seminal work here is by Bartlett (1956, 1957), who showed that both stochastic forcing or the marked seasonality in transmission due to the aggregation of children in schools could excite the measles oscillator into sustained epidemics. In the case of childhood diseases, seasonality appears to play a major role in the maintenance of measles cycles (Schenzle, 1984; Bjørnstad et al., 2002; Grenfell et al., 2002).

In general, most observations and stochastic model results agree that the average number of cases in a population scales linearly with population size ($\bar{I} \propto N$). The variance in the number of cases, however, can be best described by a power law, with an exponent between 1 and 2, [$var(I) \propto N^{2\alpha}$, $\frac{1}{2} \leq \alpha \leq 1$] (Keeling and Grenfell, 1999; Keeling, 2000a). This underlines how large populations have relatively lower standard deviations in the number of cases compared to the mean [$StD(I)/\bar{I} \propto N^{\alpha-1}$] and thus behave more like deterministic systems. These subtleties lead to nontrivial consequences of spatial subdivision of hosts on epidemic dynamics.

Work on whooping cough illustrates the dramatic influence of demographic stochasticity on epidemic dynamics due to the intricate interaction between stochasticity and nonlinearity (Rohani et al., 2000; Keeling et al., 2001; Rohani et al., 2002; see also Rand and Wilson, 1994). As predicted by standard theory, demographic stochasticity becomes increasingly important in small populations because one individual in smaller populations is a comparatively larger fraction of the entire population and therefore each stochastic event represents a relative larger change to the susceptible and infected proportions — one infectious individual in a small village is likely to infect a greater proportion of the population than one infectious individual in a large city. Thus we can illustrate the complex roles of noise on epidemics by considering the stochastic dynamics of whooping cough across a range of host community sizes (Rohani et al., 2000). Small model populations are seen to display 4-yr cycles driven by stochastic resonance at, or close to, their natural frequency, whereas large populations possess more annual dynamics constrained by the deterministic attractor (Fig. 17.2).

We can extend the concept of power-law variances to a metapopulation with n local populations. If the level of coupling between the populations is weak, such that the dynamics are almost independent, then the average number of cases across all local populations is the same as for one large population. For independent populations, the variance of the sum is the sum of the variances; hence, an increase in the number of local populations causes a linear increase in the total variance. However, a similar increase in the population size of one large patch causes a faster than linear rise due to the scaling of the power law. Naively, then, one could be tempted to conjecture that by breaking the habitat into multiple (independent) patches, one would effect a decrease in the relative variability observed in the aggregate dynamics. This is analogous to the statistical averaging discussed as the "portfolio effect" in community ecology (Tilman, 1999). However, in practice, the significant levels of coupling and the complex interactions between nonlinear transmission dynamics and demographic stochasticity mean that no such general assertions are possible. Wilson and Hassell (1997) have shown that such complexities also take place in other host–enemy systems.

Extinctions

One effect of increased stochasticity in small populations is an increased tendency for chance extinctions. This behavior is highlighted in Bartlett's classical work on measles, where the number of fadeouts (or localized extinctions) decreases exponentially with population size (Bartlett, 1957). Bartlett (1957,

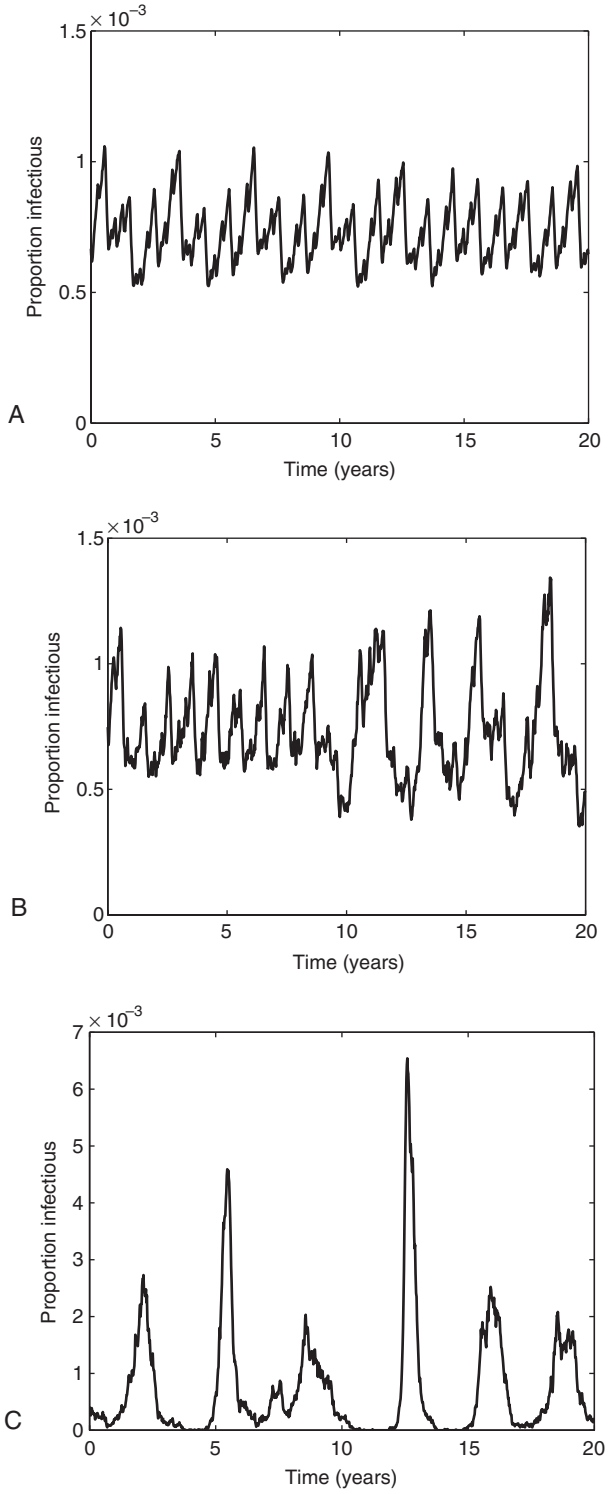

Fig. 17.2 The dynamics of a stochastic SEIR model (which contains a noninfectious incubation or exposed class) for whooping cough for three population sizes (graph A is with a population size of 100,000, graph B is 1 million, and graph C is 10 million). At a population size of 10 million, the dynamics are very close to the deterministic attractor, whereas for populations of 100,000, stochastic forces dominate and 3- to 4-yr epidemic cycles are observed.

1960) identified a critical community size (CCS) for disease persistence, such that above this population size the disease is endemic and is rarely subject to stochastic extinctions. Interestingly, this emergent critical community size is remarkably robust, and similar values of around 300,000 for measles occur for communities in England, the United States, and isolated islands (Bartlett, 1957, 1960; Black, 1966). The CCS is arguably the best empirically documented local extinction threshold in metapopulation biology (Grenfell and Harwood, 1997; Keeling and Grenfell, 1997).

When considering the regional persistence of an infectious disease across several small populations versus one large population, there are conflicting elements. Small isolated populations exhibit more frequent local extinctions than large populations. However, in a metapopulation consisting of many small populations, extinction (or eradication) at national or regional scales requires the concerted collapse of all local epidemics; in contrast, regional eradication, where there is just one large population, only requires a single extinction event. In classic metapopulation models, coupling enhances persistence through local recolonization, but erodes persistence through synchronizing the local dynamics (Chapter 4). For epidemic metapopulations, the relationship between regional persistence and coupling is complex and depends critically on the disease parameters and the demography and movement of the host population. Thus, it is far from obvious whether one large patch or several smaller patches have the greater extinction rate.

The effects of coupling between local populations on global disease eradication have received much attention due to the interesting trade-offs that arise (Keeling, 2000b). If the coupling is very small, then the local populations act independently and there is little or no chance of the disease being reintroduced from another local population; there is no rescue effect. Thus using the language associated with Levins metapopulations, the local populations have a large extinction rate and a very low probability of colonization. If the coupling is very large, then the local populations act like one large homogeneously mixed population and thus stochastic effects may lead the entire metapopulation to extinction. In disease models, heterogeneity plays an important role as low levels of infection allow the susceptible population to recover, which in turns promotes future cases. Between these two extremes persistence of the disease is maximized: there are sufficient amounts of coupling to allow recolonization and sufficient amounts of variability between patches for the metapopulation to absorb stochastic fluctuations.

The global eradication (extinction) of disease metapopulations is obviously a key aim in public health terms. This is generally investigated using computer simulations, as analytical techniques have difficulty dealing with the complexities of spatial heterogeneities and the stochastic dynamics that permeate the problem. Figure 17.3 illustrates the aforementioned principles using extinction probabilities for a spatial SIR epidemic model . When the coupling is very low such that recolonization is rare, local extinctions (at the local population level, Fig. 17.3A) are common, as are global extinctions (at the metapopulation level, Fig. 17.3B). When the coupling is high, local populations rarely go extinct. However, because of the synchrony induced by coupling, rescue effects are less effective as all epidemic declines are aligned and therefore prone to simultaneous local extinctions. Hence the global extinction

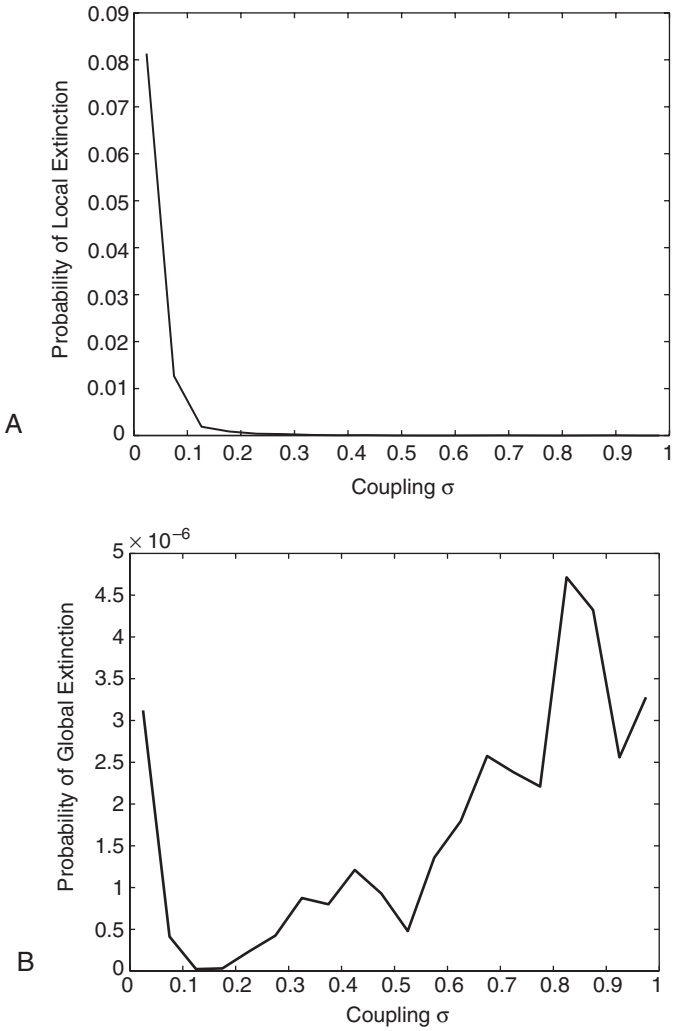

Fig. 17.3 For a stochastic SIR model with 20 coupled local populations, graph A gives the probability of local population level extinctions, whereas graph B is the probability of a global metapopulation level extinction across all 20 local populations. (Infectious period is 13 days, local population size is 30,000, basic reproductive ratio $R_0 = 14$, birth rate is 5.5×10^{-5} per person per day).

probability is again enhanced. There is a clear intermediate minimum for which the disease persistence is the greatest. This compares with the diminished persistence of classic metapopulations when embedded in a correlated landscape (Harrison and Quinn, 1989). It is still an open problem to relate disease characteristics, host demography, and coupling to the extinction risk at the metapopulation scale for a wide range of microparasites (Keeling, 2000b). Changes in coupling between populations due to social changes and ease of long-distance travel have important implications for disease extinction and eradication — this is a major question for the theoretical epidemiology of the future.

Dynamic Heterogeneity

In this context, "heterogeneity" is taken to mean the total degree of variation (or asynchrony) between epidemic dynamics at different locations. This includes variation due to asynchronous timing of epidemics at different locations, as well as heterogeneities in local dynamics due to differences in local host demography. Heterogeneities are thus a fundamental difference between spatial and nonspatial processes. As outlined earlier, heterogeneity is promoted by stochasticity but is reduced by coupling. The level of heterogeneity further depends on the relative and absolute differences in host community size, movement, and demography, as well as subtle characteristics of the transmission dynamics. To better understand the causes and consequences of such heterogeneity, we contrast a range of metapopulation models. The simplest metapopulation model assumes identical demography within each local population, deterministic dynamics and global coupling, so that the interaction is the same between all patches. Under these simplifying assumptions, and even for very low levels of coupling, we generally observe phase locking where the interaction between patches leads to complete synchronization of each local epidemic and zero heterogeneity.

When the internal dynamics are stochastic, the spatial dynamics are more complex. Coupling still acts to synchronize the dynamics by homogenizing the level of infection in each local population. In contrast, stochasticity acts to separate the dynamics as different populations experience different random events. Figure 17.4 shows the correlation in disease incidence between two stochastic local populations for various levels of coupling. When the coupling is low, the two populations are unsynchronized and the correlation is zero; however, as the coupling increases, the stochastic oscillations are increasingly correlated. As seen in Fig. 17.4, the coupling has a greater effect for larger populations (results on populations of more than 10,000 did not differ significantly), which is primarily due to the diminished effect of stochasticity (Grenfell et al., 2002).

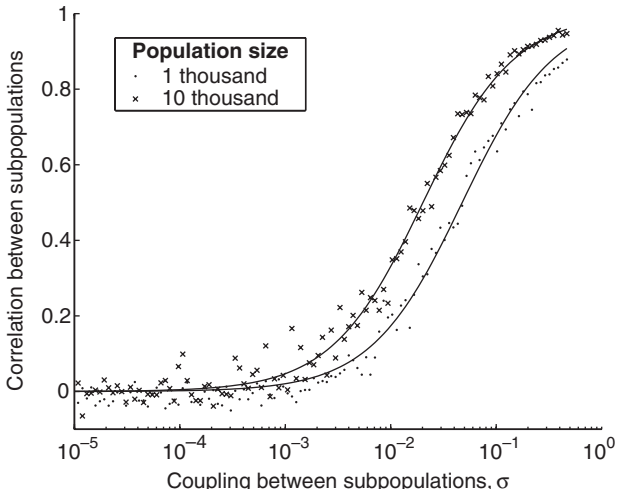

Fig. 17.4 Correlation between disease levels in two stochastic SEIR local populations. Two different population sizes are simulations; 1000 individuals and 10,000 individuals. Fitted curves are of the form $\sigma/(\xi + \sigma)$, which is based on theoretical predictions (Keeling and Rohani, 2002). Disease parameters match those of whooping cough, although seasonal forcing is ignored.

In the presence of seasonal forcing, space–time dynamics are more involved. In general, unforced stochastic epidemics can peak at any time of the year, whereas seasonal forcing usually constrains the epidemic cycle. Therefore, if seasonality tends to force the epidemics into a rigid annual cycle, populations appear partially or fully synchronized without the need for strong coupling — this echoes the operation of the Moran effect in ecology (Moran, 1953; Grenfell et al., 1998). If the epidemic period is multiannual, however, epidemics can become locked out of phase (Henson et al., 1998), as was the case for the 2-yr epidemics of measles in Norwich and London during the 1950s (Grenfell et al., 2001), for which high levels of coupling may be required to regain synchrony. In this latter case, greater levels of stochasticity and weaker attractiveness of the cyclic attractor can also help synchronization as there is a greater chance that a population will switch phases (as indeed happened for the Norwich measles epidemics during the 1960s).

Two other factors influence the synchrony and hence the level of heterogeneity. The first is the presence of inherent differences between the local populations, such as different host reproductive rates. In general, such heterogeneities will act to decorrelate the dynamics, as different populations will obey different underlying models. This was the case for the measles epidemics in Liverpool and Manchester during the prevaccination era during which the higher birth rates in Liverpool led to annual epidemics (Finkenstädt et al., 1998; Grenfell et al., 2002). Heterogeneities in the size of local host populations may have contrasting effects. The presence of one large population may act to synchronize the behavior of many surrounding small populations; in such a scenario of mainland–island epidemic metapopulation, coupling to the large population is a main synchronizing force across the whole metapopulation (Grenfell et al., 2001; see also Fig. 17.10). Local, rather than global, coupling may furthermore lead to epidemic traveling waves, although strong seasonal forcing can again counteract this. Such epidemic waves are a common feature of many spatially explicit models of natural–enemy interactions (rabies, bubonic plague, parasitoid–host systems) and have been confirmed in both ecological and epidemiological systems (Nobel, 1974; Grenfell et al., 2001; Ranta et al., 1997; Smith et al., 2002; Bjørnstad et al., 2002).

The presence and absence of spatial synchrony can play important roles in the dynamics and persistence of disease. As discussed earlier, heterogeneity can vastly increase the long-term persistence of a disease through local recolonisation and repeated rescue events. This effect is heightened if there are demographic or size differences between the populations. Heterogeneities at a smaller scale can also alter the observed aggregate dynamics. Case reports are often aggregated at the community or regional level; however, such data may be composed of multiple smaller epidemic within wards or population cliques. As these subepidemics are likely to be somewhat out of phase, the aggregate picture is of a slower, longer duration epidemic. Figure 17.5 shows a simple example of this, while each localized epidemic (gray) is of short duration, the aggregate (black) is far longer with a much diminished epidemic peak.

Throughout the examples that follow, we refer continually to the aforementioned four basic elements of spatially structured disease dynamics: isolation, stochasticity, extinction, and heterogeneity. We discuss how

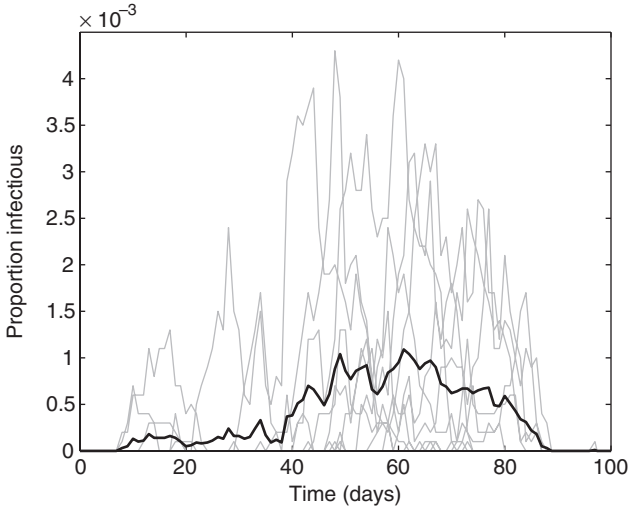

Fig. 17.5 The dynamics of 20 coupled SIR populations (gray) and the aggregate epidemic (black). (Population size is 10,000, $R_0 = 10$, infectious period is 1 day, coupling $\sigma = 0.0025$).

metapopulation models (both full stochastic metapopulations and the simpler Levins metapopulations) can be used to represent additional spatial structure and the insights that can be gained from such idealized models. We begin by studying the implications of spatial structure at the range of scales, starting with the individual and working up to the community or even country level. The general ideas are illustrated in subsequent case studies.

17.4 DISEASE METAPOPULATIONS AT DIFFERENT SCALES

Individual Level

The standard SIR equations can be explored by considering each individual host as a patch using a modified form of the metapopulation formulation. The mechanistic approach would model the interaction of the disease and the host's immune system, leading to models comparable to those used in the study of macroparasites, which classify hosts in terms of their burden of parasites (Anderson and May, 1991). However, the more classical models where hosts are described as unoccupied but suitable habitat (susceptible), occupied (infected), or unoccupied but exhausted habitat (recovered) have a much closer analogy to standard metapopulation models for successional habitats. From this perspective, birth and deaths correspond to the creation and destruction of habitat. Strictly speaking, SIR-type dynamics cannot correspond to "true" Levins metapopulation dynamics at the individual level because recovered patches cannot regain infection. However, most sexually transmitted diseases exhibit SIS dynamics; that is, once an infected individual recovers, it is once again susceptible to infection. In such cases there is a direct correspondence between the standard Levins model and the SIS equations (Ovaskainen and Grenfell, 2003).

The Levins metapopulation has an extensively developed theoretical armoury than can be applied to the description and understanding of disease dynamics (Chapter 4). Sexually transmitted diseases, which are characterized by a low transmission rate and long infectious period, can be thought of as poor colonizers, but a persistent species with low local extinction rates. In contrast, childhood diseases, which are short lived and transmitted rapidly, can be conceptualized as good colonizers that exploit the local resource rapidly, driving themselves extinct. This concept may be extended fruitfully to consider the competition between cross-resistant strains of disease (Gupta et al., 1998), in which case low transmission rates (poor colonizing ability) can be offset by good competitive ability within a patch.

The compartmental classification of "habitat" needs not necessarily operate at the level of the individual. Work on the 2001 foot-and-mouth epidemic in Great Britain considers each farm an epidemic unit ("patch") to be classified as susceptible, exposed, infectious, or removed (Keeling et al., 2001; Ferguson et al., 2001). Patch "removal" was in this case through massive culling of all potential host animals on a farm. In modeling the outbreak, the within-farm epidemic was ignored in favor of this Levins-type classification. Despite this great simplification, these models predicted the course of the epidemic with great accuracy at the regional level, justifying the approximation.

Within-Community Metapopulations

Many communities, especially large ones, can be subdivided into various weakly interacting components. This subdivision may take place along social, age, or simply spatial boundaries, but inevitably there are many factors that prevent the random mixing of the population and therefore break the assumptions underlying standard models. This necessitates the use of metapopulation-type equations to model the dynamics of these partially separated components.

Regional Metapopulations

The epidemic dynamics at regional or country level begs the use of metapopulation concepts. Here each local population represents a community, and hence there is a one-to-one correspondence between the scale at which the model operates and the available data. Using regional dynamics holds two main challenges: understanding the detailed consequences of demographic heterogeneities between the communities and analyzing the epidemic coupling between communities on real landscapes. The scientific development of the latter issue mimics the succession from the naive to more realistic models of metapopulation theory (see Chapters 4, 5, 20, and 22). The traditional models of identical local populations, with low levels of global coupling, have given way to models with distance-based coupling rates. Such models are slowly being replaced with models embracing heterogeneous patch sizes (with obvious parallels to the current generation of incidence function models and stochastic patch occupancy models as described throughout this book). However, for a complete understanding of epidemic metapopulations, it is becoming increasingly clear that a deeper knowledge of the complex geometries of the "transportation networks" for the infections is required (Cliff and Haggett,

1988). This is likely to provide an exciting area for future research with great theoretical, empirical, and statistical challenges.

17.5 CASE STUDIES

Prevaccination Measles in England and Wales

Of all infectious diseases, the dynamics of childhood microparasites, such as measles and whooping cough, are arguably among the best understood with respect to both local and regional dynamics. In particular, the rich data base and the comparatively simple natural history of measles have made this the prototypical system in the study of spatiotemporal dynamics of infectious disease (Anderson and May, 1991; Bartlett, 1957; Cliff et al., 1993; Grenfell and Harwood, 1997; Keeling and Grenfell, 1997; Grenfell et al., 2001, 2002; Keeling et al., 2001; Bjørnstad et al., 2002). Measles, along with other childhood infections, was made a notifiable disease in the United Kingdom in 1944. This resulted in the collection of weekly reports in 1400 communities in England and Wales through to the present. As such, this is likely to represent the longest and most detailed record of any epidemic metapopulation. Not surprisingly, these data have been studied extensively from epidemiological, mathematical modeling, and time-series analysis perspectives. Due to its very high basic reproductive ratio, $R_0 = 17$, most children were infected with measles (before the onset of mass vaccination campaigns in the late 1960s) with an average age of infection around 4–5 yr. Before mass vaccination was introduced in the United Kingdom, measles displayed predominantly biennial dynamics, with a major epidemic in odd years (Fig. 17.6A) (for further details see Bjørnstad et al., 2002; Grenfell et al., 2002).

Demographic stochasticity plays an important role in the dynamics of measles in small communities. This arises from the individual nature of populations (the fact that there must be whole numbers of cases) and the probabilistic nature of events, such that transmission of infection in particular occurs by chance. Stochasticity has two basic effects on the patterns of disease behavior: it can push trajectories away from the deterministic attractor such that transient dynamics play a more major role and it can lead to chance extinctions due to the random failure of chains of transmission (Figs. 17.6B and 17.6C). The role of patch size (host population size) on epidemic extinction rates is illustrated wonderfully in the public records. Extinction rates appear to decay exponentially with host population size so that above the critical community size of around 300,000 hosts, extinctions are rare (Bartlett, 1957). This pattern of size-based extinctions and recolonizations warrants interpretation from the metapopulation point of view.

Childhood diseases, such as measles or whooping cough, are spread predominantly by school children mixing within the primary school environment. In this respect, the host populations are generally subdivided into school catchment areas. Considering an average primary school has an intake of around 150 children in each year, then each school serves a population of around 10,000; this determines our basic unit of subdivision. A Levins-type metapopulation model (global dispersal, no local dynamics, etc.), which splits

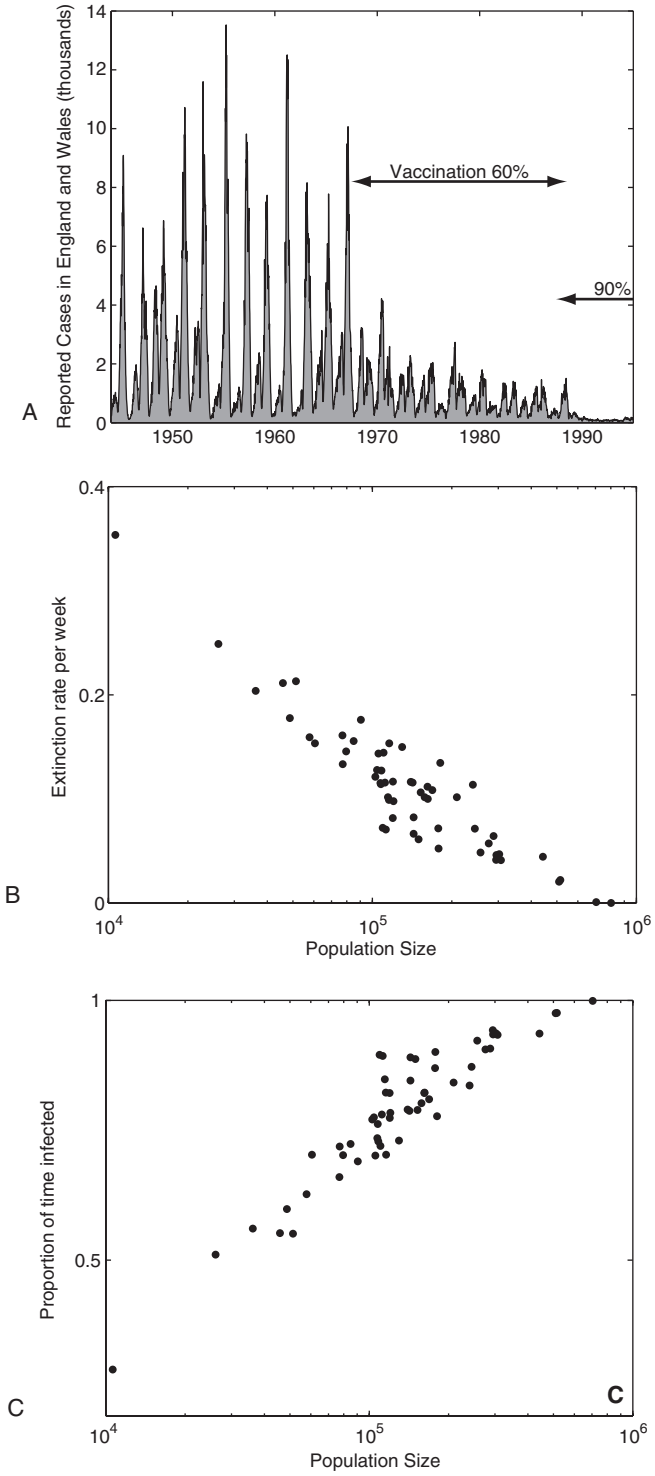

Fig. 17.6 Dynamics of measles in England and Wales. (A) Reported cases from 1944 to 1999 showing levels of vaccination. (B and C) Average rate of extinction and the proportion of time with recorded cases for measles in 60 towns and cities in England and Wales. Data taken from 1944 to 1968 before mass vaccination was begun. There are clear relationships with population size, such that large populations rarely suffer a stochastic extinction.

each community into school catchment areas of 10,000 people, motivates the following model for the proportion of "diseased" local populations (D) in the city:

$$\frac{dD}{dt} = -eD + cD(1 - D) + i(1 - D) \tag{17.7}$$

where e is the extinction rate, c is the colonization rate from other catchment areas (local populations) within the city, and i is the rate at which external imports of infection arrive in a local population. This corresponds to an ecological model with migration both from a permanent mainland population and among local populations. If a metapopulation is composed of N such local populations, then the probability P_n that n catchment areas are infected is given by

$$\begin{aligned}\frac{dP_n}{dt} = {} & enP_{n+1} + c(n-1)(N+1-n)P_{n-1} + i(N+1-n)P_{n-1} \\ & -\left[en + cn(N-n) - i(N-n)\right]P_n\end{aligned} \tag{17.8}$$

with the equilibrium solution,

$$P_{n+1} = \frac{(i + cn)(N - n)}{en}P_n \text{ such that } \sum_{n=0}^{N} P_n = 1 \tag{17.9}$$

This provides easy calculation of the long-term distribution of disease within the metapopulation, the associated extinction rates ($= eP_1$), and the proportion of time the disease should be present ($= 1 - P_0$). We may compare these theoretical predictions with data on measles incidence. Figure 17.7 shows the resultant comparison as the total population size and hence the number of local populations increase. It thus appears that Levins-type local patch dynamics can reproduce the pattern in data.

The Levins approach, which completely ignores the local epidemic dynamics, works surprisingly well for predicting the presence or absence of the disease across a range of population sizes. However, it breaks down if we wish to predict the *level* of infection within the population. This is for three reasons. First the local dynamics of different cities are highly correlated, such that the level of infection is an increasing function of the colonization rate, which in turn is proportional to number of occupied patches (Fig. 17.8). Second, in the absence of infection, the level of susceptibles increases; any ensuing epidemic is therefore critically dependent on the local number of susceptibles, which in turn is dependent on the time since the last epidemic. This induces a level of memory to the local dynamics that breaks with the underlying Markovian assumption of the Levins model. Finally, the distribution of infection (Fig. 17.8) does not conform to the Levins-type metapopulation ideal, which assumes that local prevalence should be bimodal and dominated by a zero and a nonzero equilibrium level. For a detailed understanding of the population dynamics, we need to consider a metapopulation with detailed stochastic dynamics within each patch (Swinton et al., 1998).

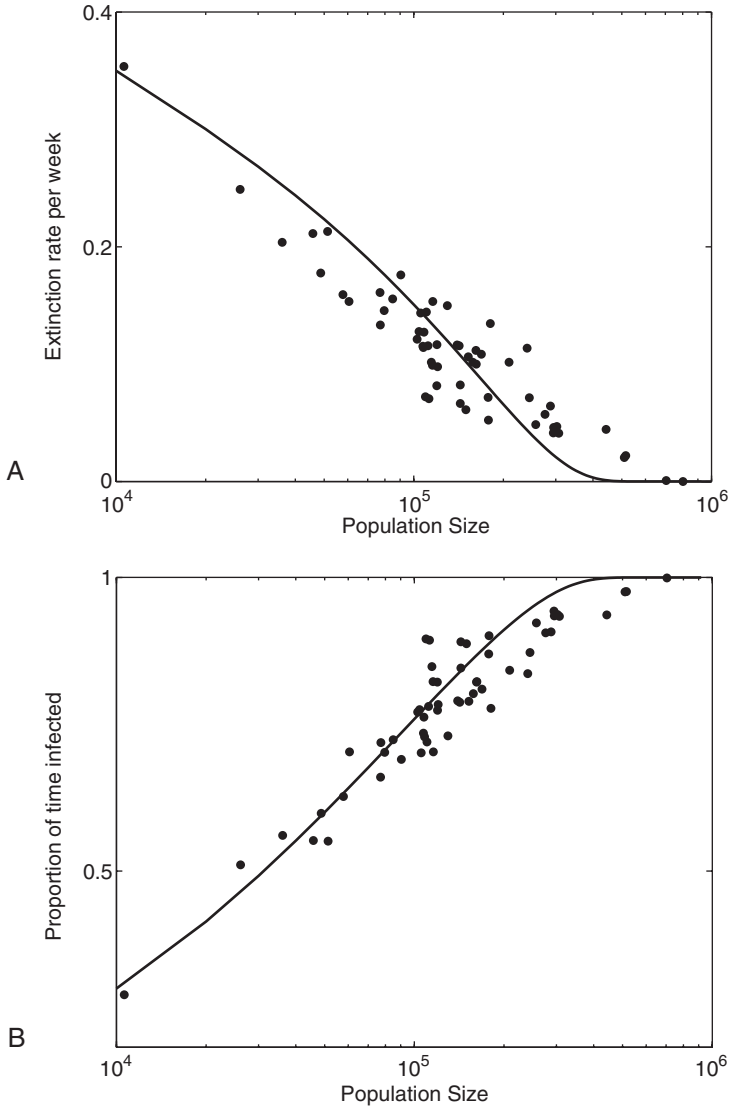

Fig. 17.7 Rate of extinction (A) and the proportion of time with infection (B) from a metapopulation model with local populations of 10,000 individuals. The extinction rate of each local population is $e = 0.35$, the colonization rate is $c = 0.01$, and the rate of external imports is taken as $i = 0.15/\sqrt{(N)}$. This local population level of imports means that the metapopulation level of imports scales with the square root of population size, as was conjectured originally by Bartlett (1957) and supported by measles report data from England and Wales. All timescales are measured in weeks to correspond to the aggregation of case reports. Theoretical results (line) compare well to measles data from England and Wales (dots).

We explore the breakdown of the Levins-type metapopulation model through a comparison with the full stochastic analogues across a variety of scenarios. A range of *single species* models, with a variety of forms of density dependence, have been explored elsewhere (Keeling, 2000b). These conform to Levins-type metapopulation behavior when (a) the distribution of population sizes falls into two distinct classes, extinct and close to carrying capacity, and

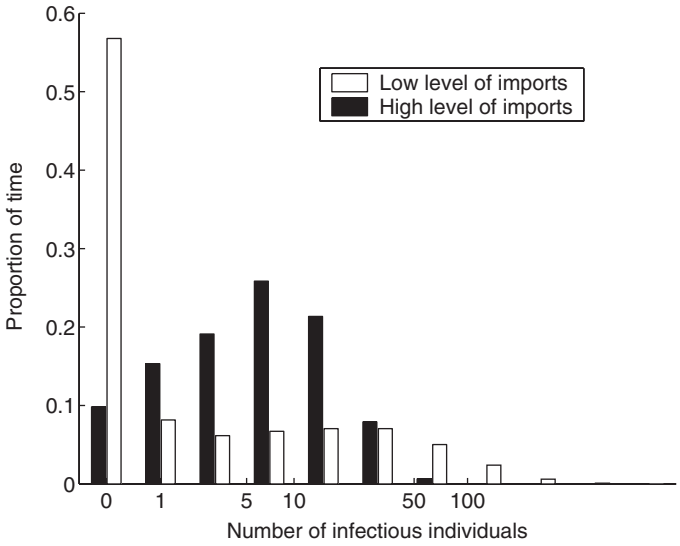

Fig. 17.8 Distribution of the number of infectious individuals in a stochastic SIR model of 10,000 with measles-like parameters (R_0 = 17, infectious period is 13 days) for two different levels of imports. The two levels of imports correspond to the effects of being part of a metapopulation where either all or few of the other patches are infected and close to the carrying capacity. Clearly the local population level dynamics are influenced strongly by the global metapopulation behavior.

(b) the carrying capacity and extinction rate are not significantly affected by the number of extinct patches. For such single-species systems the Levins framework is the ideal tool for describing the metapopulation dynamics (Figs. 17.9A and 17.9B). However, for disease models (and most likely many other enemy–host interactions), a different pattern of regional behavior arises due to the synchronization that occurs as an integral part of the space–time dynamics (Chapter 4). In particular, this synchrony of epidemics across the metapopulation will bias the extinction and colonization rates relative to the Levins assumption. Extinctions are, hence, far less common and colonizations more common than expected when the majority of patches are infected (Figs. 17.9C and 17.9D). In general, this leads to two distinct forms of global behavior: persistent endemic infections or irregular short-duration epidemics. Both of these states will be stable in the medium to long term. Which type of behavior is observed is critically dependent on the initial conditions.

Spatial coupling in epidemic metapopulations consisting of a geographic mosaic of cities and villages (May and Anderson, 1991, Grenfell and Bolker, 1998) has represented a thorny scientific question for more than half a century. No simple answer has as yet been found. As ever, Bartlett (1957), in his study of the scaling of epidemiological coupling, has been seminal in prompting detailed work in both spatial geography and epidemiology. Fifty years, hence, the challenge of understanding epidemic coupling still stands. Progress is likely to lie in combining models for the nonlinear, seasonally forced local dynamics of measles with detailed transportation data. We see two strands of recent work that offer a way forward in the face of this daunting challenge.

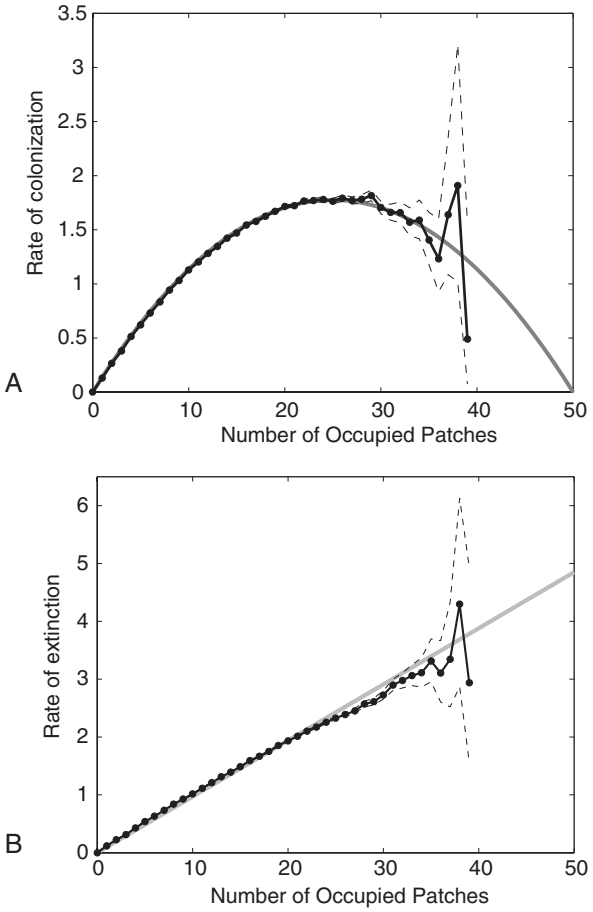

Fig. 17.9 Comparison between a full stochastic metapopulation and idealized functional forms of the Levins metapopulation. The average rates of extinction and colonization that occur whenever a simulation has a given number of occupied patches are shown. For simplicity, changes due to external imports are ignored. (A and B) Results for a single-species logistic model, which conforms well to the Levins ideal.

First, the development of discrete time versions of the SIR model (Finkenstädt and Grenfell, 2000; Bjørnstad et al., 2002; Grenfell et al., 2002) has allowed us to model the local scaling of dynamics and importation of infection over four orders of magnitude in host population size. Second, time series analysis of England and Wales data using wavelet phase analysis has testified to well-defined hierarchical traveling waves of infection, moving from large centers to the surrounding hinterland (Fig. 17.10; Grenfell et al., 2001).

These waves echo, on a larger spatiotemporal scale, the hierarchical waves detected in earlier geographical work (Cliff et al., 1981). Simplistic spatiotemporal models (Grenfell et al., 2001) show that the waves arise essentially from "forest fire"-like dynamics (Bak et al., 1990; Rand et al., 1995) in which epidemic "sparks" of infection from the large core populations ignite epidemics in smaller, locally extinct centers. These studies offers a glimpse of an ultimate understanding of the space–time dynamics of measles, but much is yet to be

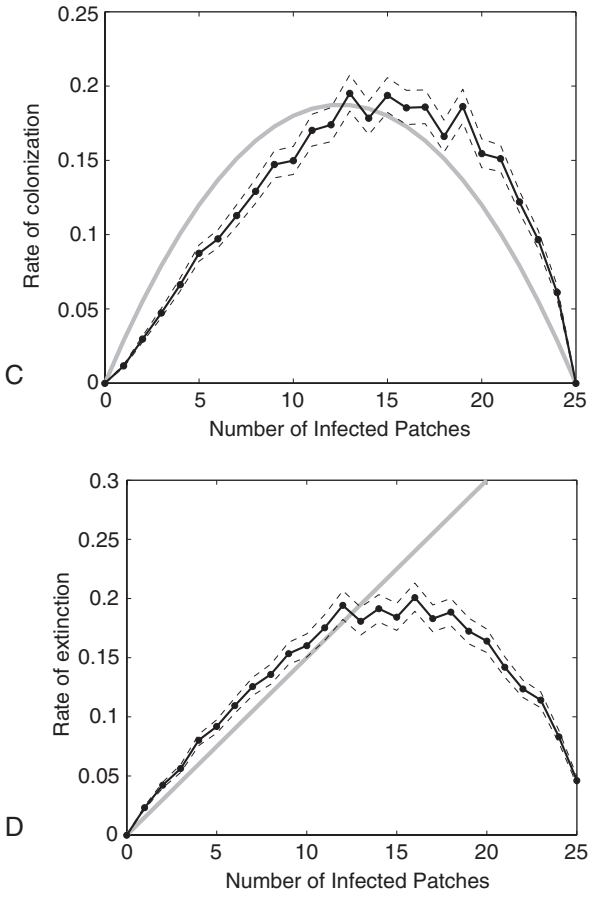

Fig. 17.9 *Continued.* (C and D) A SIR disease model with measles-like parameters and a between-patch coupling of $\mu = 0.001$. Clearly the latter contrasts with the Levins paradigm.

uncovered. In particular, developing models and theories that scale into the vaccination era appear to hold significant challenge.

Bubonic Plague in the Middle Ages

Bubonic plague invaded Europe in 1364, spreading rapidly north from the ports of southern Italy (Nobel, 1974). For the next 300 years or so the disease ravaged the towns and cities of Europe causing vast mortality (Shrewsbury, 1970). Bubonic plague is a disease of rodents that is generally transmitted by fleas, occasionally it spreads to humans, which is when cases are generally first noticed. Records show that although the disease was endemic in Europe as a whole through three centuries, each community displayed isolated epidemics in the human host population cases followed by "disease-free" periods. It has therefore long been thought that bubonic plague exhibited classic metapopulation behavior at the regional scale, with the infection continually going extinct and then recolonizing communities (Appleby, 1980). This conventional wisdom contradicts two pieces of

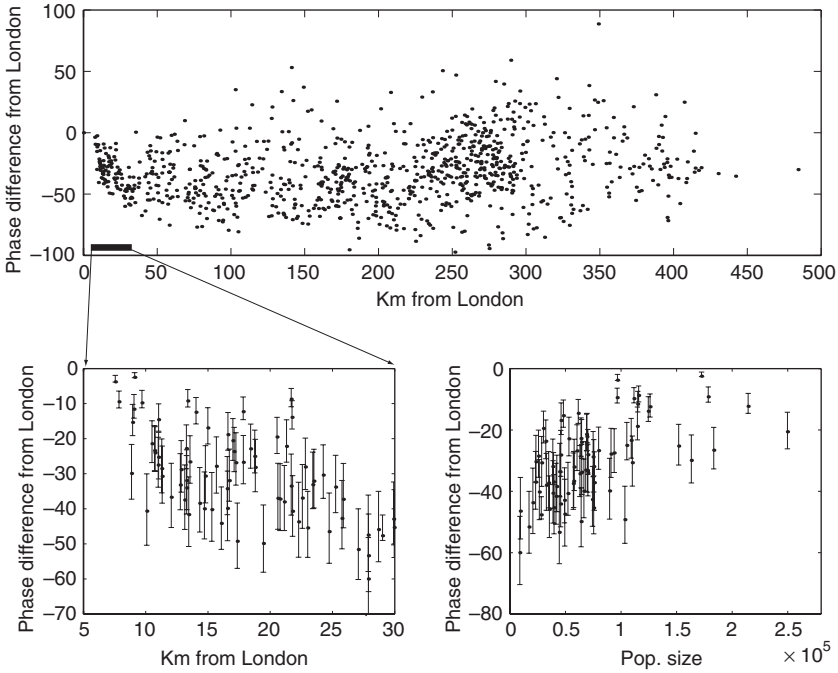

Fig. 17.10 Average phase differences for prevaccination urban and rural measles epidemic in the United Kingdom. (Top) Mean urban phase difference from London for major (biennial) epidemics during 1950–1966. Note that most places lag behind London. (Lower left) Mean urban phase difference from London for 1950–1966 in the London region (within 30 km) as a function of distance from the capital showing a significant correlation of phase difference and distance ($r = -0.59$, 99% bootstrap limits: -0.75 to -0.39); error bars are 99% bootstrapped confidence limits. (Lower right) Relationship between epidemic phase difference and local urban population size. The positive relationship between phase lag and population size is consistent with a "hierarchical forest fire" explanation for the waves (see Grenfell et al., 2001).

historical evidence. First, there is a fairly regular cyclic nature to human epidemics, which is unlikely to be caused by random imports of infection. Second, even in communities with tight quarantine controls, there is little change to the pattern of epidemics (Appleby, 1980).

Keeling and Gilligan (2000a,b) focused on the interaction among rats, fleas, and humans within a metapopulation setting. The life cycle of the plague can be partitioned into distinct stages and follows a general pattern for vector-borne diseases. Fleas that feed on an infected rat ingest the bubonic plague bacteria (*Yersinia pestis*) and become infectious. When an infected rat dies, its fleas, which are by now infectious, leave to search for a new host. Usually the fleas find other rats, infect them, and so spread the disease through the rodent community. Only when the density of rats is low are the fleas forced to feed on alternative hosts, such as humans, and spark off a human epidemic. Humans are considered a dead-end host, as transmission from humans to fleas is rare. Direct transmission between humans is possible if the pneumonic form of the disease develops, but due to the rapidity and virulence of such infection,

pneumonic epidemics are small and short lived. These epidemiological observations can be translated into a mathematical model:

$$\frac{dS_R}{dt} = r_R S_R\left(1 - \frac{T_R}{K_R}\right) + R_R(1 - p) - d_R S_R - \beta_R \frac{S_R}{T_R} F\left[1 - \exp(-aT_R)\right],$$

$$\frac{dI_R}{dt} = \beta_R \frac{S_R}{T_R} F\left[1 - \exp(-aT_R)\right] - (d_R + m_R) I_R,$$

$$\frac{dR_R}{dt} = r_R R_R\left(p - \frac{T_R}{K_R}\right) + m_R g_R I_R - d_R R_R,$$

where $T_R = S_R + I_R + R_R$ (the total rat population size).

$$\frac{dN}{dt} = r_F N\left(1 - \frac{N}{K_F}\right) + \frac{d_F}{T_R} F\left[1 - \exp(-aT_R)\right],$$

$$\frac{dF}{dt} = \left[d_R + m_R(1 - g_R)\right] I_R N - d_F F.$$

$$\frac{dS_H}{dt} = r_H(S_H + R_H) - d_H S_H - \beta_H S_H F \exp(-aT_R),$$

$$\frac{dI_H}{dt} = \beta_H S_H F \exp(-aT_R) - (d_H + m_H) I_H,$$

$$\frac{dR_H}{dt} = m_H g_H I_H - d_H R_H. \qquad (17.10)$$

where S_R, I_R, and R_R refer to the number of susceptible, infectious, and resistant rats, respectively S_H, I_H, and R_H are similar quantities for the human population, N is the average number of fleas on a rat, and F is the number of free-living infected fleas that are searching for a host. Table 17.1 lists the meaning and value of all other parameters used in the model, which have been estimated from historical data or experiments (Keeling and Gilligan, 2000b).

The behavior of the theoretical model for this system is critically dependent on stochasticity and scaling. For large host populations, a deterministic solution gives rise to a constant level of infection in the rodents (as expected from most SIR-type models) and a negligible number of human cases. However, when stochastic effects play a major role, unusually large epidemics may drive the rat population to such low levels that the fleas are forced to feed on alternative hosts and a human epidemic occurs. This results in localized extinction of the disease. The subsequent local dynamics depends on the build-up of the susceptible rat population. Fairly rapid recolonizations of infection lead to an endemic persistence in the rat population and few, if any, human cases. In contrast, if recolonization is rare and hence the susceptible rat population has time to increase to high levels, major epidemic cycles with resultant spillover in human hosts occur. Thus, the epidemic dynamics is determined by the mixture of local transmission dynamics, stochasticity, and spatial coupling.

Good evidence suggests that in any large town or city, rats are unlikely to act as a homogeneously mixing host population, and therefore a spatially segregated metapopulation approach may be more appropriate. Studies performed by the Plague Commission in India (1906) showed that the spatial

TABLES 17.1 Parameters Used in the Bubonic Plague Model

Parameter	Value	Meaning
r_R	5	Reproductive rate of rat
p	0.975	Probability of inherited resistance
K_R	2500	Carrying capacity of rat
d_R	0.2	Death rate of rats
β_R	4.7	Transmission rate
m_R	20	(Infectious period)$^{-1}$
g_R	0.02	Probability of recovery
μ_R	0.03	Movement rate of rats
a	4×10^{-3}	Flea searching efficiency
r_F	20	Reproductive rate of flea
d_F	10	Death rate of fleas
K_F	$3.29 \rightarrow 11.17$ mean 6.57	Carrying capacity of flea per rat
μ_F	0.008	Movement rate of fleas
r_H	0.045	Reproductive rate of humans
d_H	0.04	Death rate of humans
β_H	0.01	Transmission rate to humans
m_H	26	(Infectious period)$^{-1}$
g_H	0.1	Probability of recovery

spread of the epidemic through the rodent population was extremely slow due to their largely territorial nature; this corresponds well with historical evidence of slow-moving waves of infection in the large medieval cities. Figure 17.11 shows the number of bubonic plague cases in rodents in a metapopulation model consisting of 25 local populations. Persistence of the metapopulation is due to the local populations that remain close to the endemic state (e.g., central site for the latter part of the simulation), whereas human cases (and thus historical reports) are due to the stochastically driven large epidemics. Due to the time necessary for the susceptible rat population to recover, these large epidemics have a period of around 10–12 yr, which corresponds remarkably well with the historical observations.

As observed earlier, the classic Levins metapopulation does not readily capture the dynamics of spatially structured epidemics due to the strong correlations that often exist between local and global levels of infection. However, for plague, such correlations are weak, and the local populations can be classified into three basic states: endemic (low level of infection and low risk of extinction), epidemic (high level of infection and high risk of extinction), and extinct (but susceptible). The extinct class is further subdivided so as to mimic the gradually increasing susceptible rat population. Figure 17.12 shows a caricature schematic of the Levins-type model for bubonic plague.

For this type of spatiotemporal dynamics, where the behavior is classified easily into a discrete set of states, the Levins approach provides great improvements in computational efficiency and clarity. The Levins approach allows us to consider the dynamics at a far larger scale and hence observe the wave-like spread of the epidemics away from the endemic centers (Keeling and Gilligan, 2000b). From these models it is clear that the epidemic wave is often short lived and self-extinguishing, confirming the importance of endemic populations in allowing for long-term disease persistence.

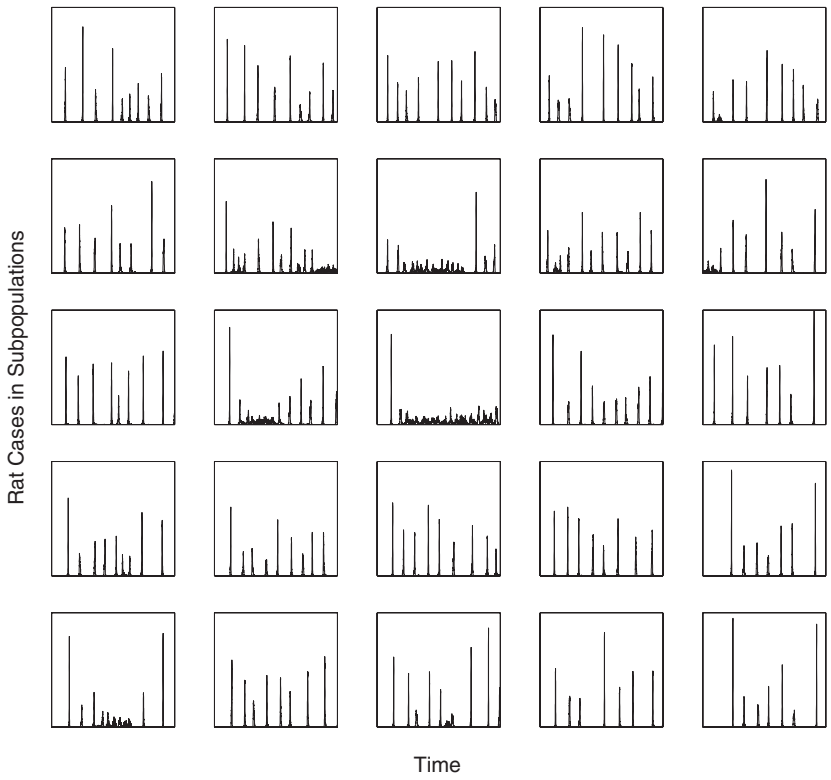

Fig. 17.11 Stochastic model dynamics of bubonic plague in a metapopulation. Each local population has a stochastic model for the behavior of rats, fleas, and humans, and the 25 local populations are coupled spatially with a low movement rate of rats and fleas between adjacent patches. For each local population, the number of cases in rodents over a 100-yr period is shown; during this time, the disease persists without the need for imports from outside the metapopulation.

Conservation or Contamination

An interesting extension to the classic metapopulation models for the population dynamics of endangered species is the inclusion of disease (Hess, 1996; Gog et al., 2002). In the absence of infection, increasing the spatial coupling between isolated habitats will increase the level of patch occupancy and decrease the risk of global extinction for one threatened species. Within the Levins metapopulation framework, x is the occupancy level and σ is the amount coupling. This is given as

$$\begin{aligned} \frac{dx}{dt} &= \sigma c x(1 - x) - ex \\ x &\longrightarrow 1 - \frac{e}{\sigma c} \end{aligned} \tag{17.11}$$

where e is the extinction rate and c is the probability that invasion of an empty patch is successful. From this simple model it is clear that movement between largely isolated habitats improves the persistence of the endangered species.

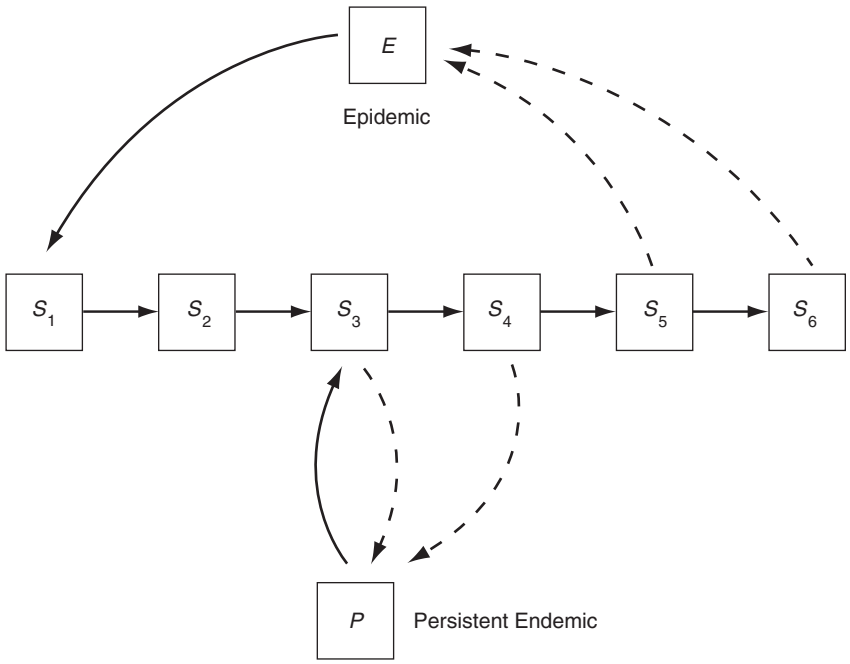

Fig. 17.12 Representation of transition states in a structured metapopulation model (Gyllenberg et al., 1997) of bubonic plague. Solid arrows represent probabilistic transitions, which occur independently of the surrounding environment. Dashed arrows show transitions that only occur due to the import of infection from a neighboring patch. Rates of transition can be measured from the full stochastic metapopulation model.

This is for two distinct reasons. Primarily, increased coupling σ leads to a higher colonization rate, which increases the likelihood of rescue events and the number of occupied local populations at equilibrium. Second, large amounts of movement between patches synchronize the dynamics, the local populations act effectively as one large habitat, and large populations suffer a relatively less extinction risk from stochasticity. The single-species model thus reveals no benefit of demographic heterogeneities between local populations as one large population (or several tightly coupled populations) shows the greatest persistence. This result is echoed by full stochastic metapopulation equations with explicit within-patch dynamics (Keeling, 2000b).

This conclusion can be altered radically in the presence of a virulent infectious disease, as coupling also facilitates the spread of infection (Hess, 1996). The resultant cost–benefit trade-off depends on the relative levels of host extinction with and without the disease, as well as the relative colonization rates. Gog and Colleagues (2002) used the following model to explore the dynamics of infected (I) and uninfected (S) habitat:

$$\begin{aligned} \frac{dS}{dt} &= \sigma S(1 - I - S) - e_S S - \sigma\delta IS - gS \\ \frac{dI}{dt} &= \sigma I(1 - I - S) - e_I I + \sigma\delta IS + gS \end{aligned} \tag{17.12}$$

where σ is the rate of movement to and colonization of empty habitat, e_S and e_I are the patch level extinction rates, δ is the chance that movement leads to the spread of infection, and g is the import rate of infection from outside the considered population. As this is a model of wildlife disease, the coupling between populations occurs as the random dispersal of organisms rather than the short-duration commuter movements associated with human disease transmission. The focus of this model is conservation of an endangered host, and therefore is the reverse of the scenarios discussed earlier where the eradication of infection was the main aim. In agreement with the earlier work of Hess (1996), this Levins-like model shows that under certain circumstances greater movement between patches (larger σ) can lead to a reduction in the number of occupied patches and an increased risk of global extinction to highlight an important conservation risk (Fig. 17.13).

It is informative to consider an extreme variation of this model. Suppose that the disease within an infected patch is severe and widespread so that animals from infected patches are unable to colonize a new habitat successfully. The model then can be rewritten as

$$\frac{dS}{dt} = \sigma S(1 - I - S) - (\sigma\delta)IS - e_S S - gS$$
$$\frac{dI}{dt} = (\sigma\delta)IS - (e_I - e_S)I - e_S I + gS \qquad (17.13)$$

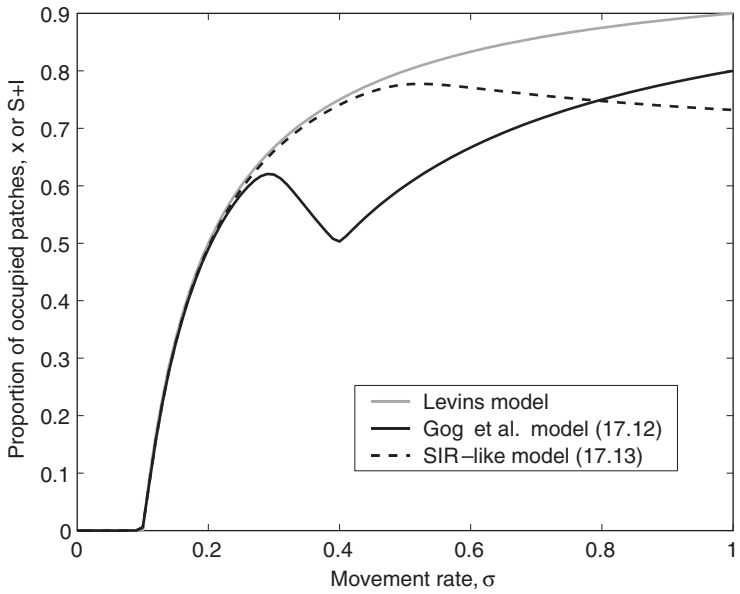

Fig. 17.13 Effects on patch occupancy of between-patch coupling σ for the three models are shown. Both the model of Gog et al. (2002) and the simplified SIR-like version show that increased levels of coupling can decrease patch occupancy in the presence of an infectious disease ($c = 1$, $e = e_S = 0.1$, $e_I = 0.2$, $\delta = 0.5$, $g = 0.001$). [AU1]

This model then shares many elements with standard SIR disease models; $\sigma\delta$ plays the role of the transmission parameter β, e_S corresponds to the natural death rate, and $e_I - e_S$ equates to the recovery rate. The emergent parallel with classical disease models allows us to intuit about the resultant dynamics. For example, changes in the movement rate σ correspond to a trade-off between an increase in the birth rate and an increase in disease transmission.

Vaccination, Pulses, and Synchrony

A key issue of metapopulation modeling for infectious diseases is to compare different vaccination strategies to optimize the likelihood of disease eradication. As discussed earlier, the global persistence of a disease is determined by two main factors: the local extinction rate and the rate of recolonization, which in turn is related to the heterogeneity of the metapopulation. Figure 17.14 shows how these two facets change as the level of vaccination increases; we first consider the solid black line, which corresponds to continuous random vaccination. Below the critical vaccination level of 90% the local extinction rate shows only a moderate increase with the level of vaccination so that the expected length of an epidemic decreases slowly. In contrast, the correlation between two coupled local populations starts to decrease from the onset of vaccination. Therefore, in the Levins formulation, moderate levels of vaccination only cause a small increase in the extinction rate, which may be counteracted by the increase in heterogeneity and therefore the increase in rescue effects when they are most needed.

The balance between vaccination increasing the stochastic extinction rate but reducing the synchrony between populations depends on the demographic and epidemiological parameters. Thus while moderate levels of vaccination will always act to reduce the total number of cases, they may surprisingly increase the global persistence of the disease if the loss of synchrony is dramatic enough. However, as the level of vaccination approaches the critical eradication threshold, the rapid rise in the rate of local extinctions will overwhelm any rescue effects and global extinction will inevitably follow.

Obviously, vaccination would be a much more effective tool if as well as reducing the number of cases it could also decrease the global persistence of the disease. In principle, this can be achieved by superimposing periodic "pulses" of vaccination on the overall background rate. Pulsed vaccination has been proposed to increase the efficiency of vaccination (Agur et al., 1993), but it could also have a spatial benefit by "lining up" epidemic troughs and therefore reducing rescue effects (Earn et al., 1998). The impact of a simple model for pulse vaccination (in the absence of background vaccination) is shown in gray in Fig. 17.14. The first observation is that pulse vaccination is associated with a slightly lower local extinction rate, and also more cases of the disease; this is because in the gaps between the vaccination pulses children that would have been immunized under continuous vaccination have a chance of catching the infection. However, this could be compensated for by only vaccinating susceptible children and therefore not wasting vaccine. In contrast, for the correlation between populations, the difference between pulsed and continuous vaccination is more dramatic. The significant perturbation caused by a periodic vaccination campaign acts to synchronize the dynamics of the two

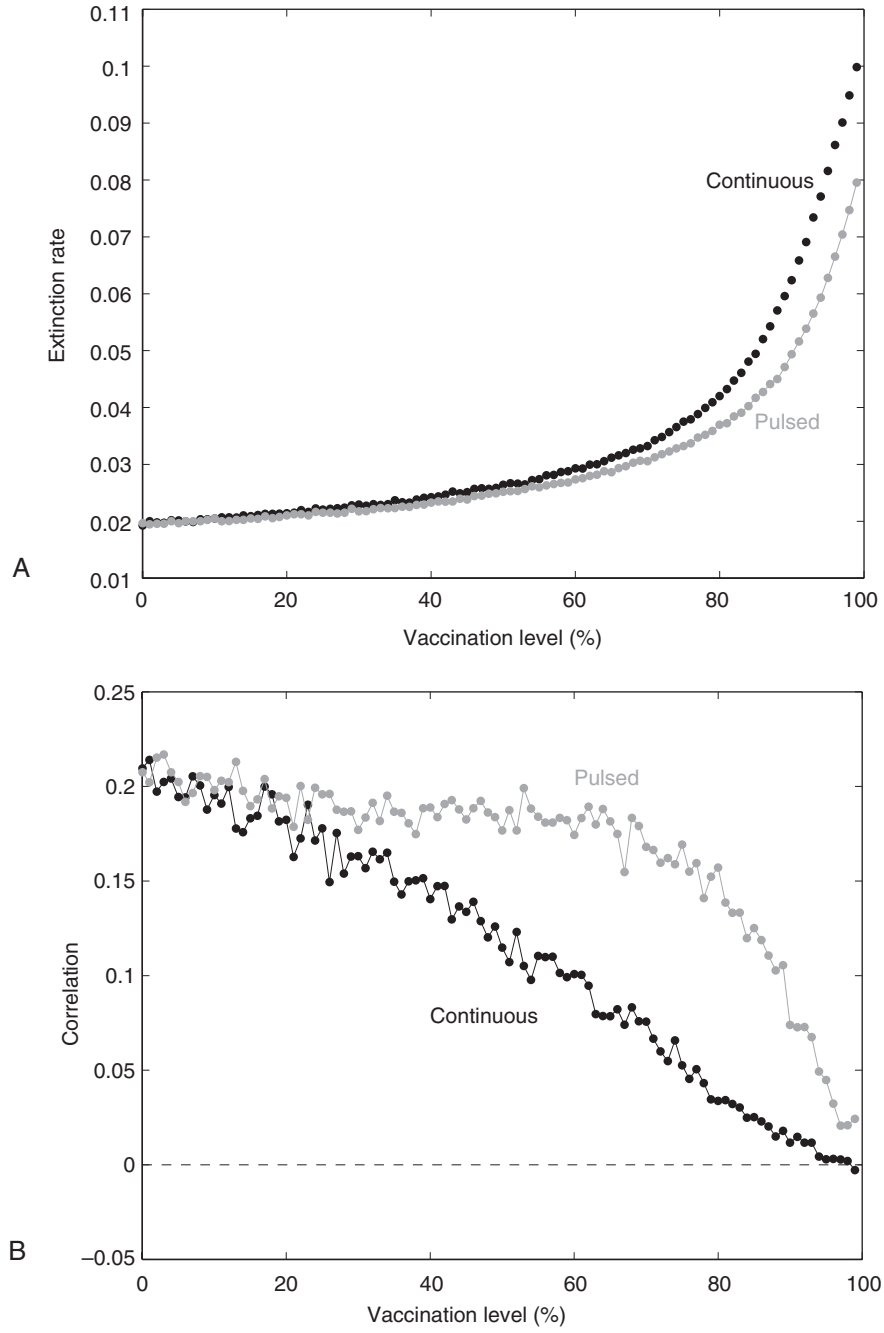

Fig. 17.14 Effects of vaccination on the characteristics of unforced SIR epidemics. Black symbols refer to constant random vaccination at birth, whereas gray symbols correspond to pulse vaccinating randomly at regular 4-yr intervals; similar results are achieved for more frequent yearly pulses. (A) Change in the local extinction rate (per day) of an isolated population. (B) Change in the correlation between two local populations coupled at a level $\sigma = 0.01$. (Population size is 10,000, $R_0 = 10$, $g = 10$ days, import rate is 5 per year.)

populations, thus for pulsed vaccination the correlation remains approximately constant for vaccination levels below 60%.

Pulsed vaccination therefore provides a potentially important tool for increasing local extinctions, without increasing the effective rescue events, and therefore increasing the likelihood of global extinctions (compare to Levins, 1969). Results shown in Fig. 17.14 have ignored seasonal forcing, which naturally leads to greater synchronization of the dynamics. When seasonal forcing is important (such as for most childhood diseases), the interaction of vaccination pulses and seasonal effects may be very complex, such that the precise timing of vaccination could increase the chance of eradication dramatically. However, this is very much an open problem for future research.

17.6 FUTURE DIRECTIONS

Metapopulation theory has a rich history in the ecological literature and has proved itself continually as both an applied tool and an insightful description of the complex world (Gilpin and Hanski, 1991; Hanski and Gilpin, 1997). The use of metapopulations has been somewhat more limited in epidemiology due to the more complex within-patch dynamics. However, in recent years this balances has begun to be redressed. Several key theoretical and practical issues still need to be dealt with successfully to allow the subject to develop further.

1. A better understanding of how the epidemiological and demographic parameters translate into the Levins-type metapopulation parameters of extinction and colonization rates. The ability to translate stochastic within-patch population dynamics into a simple set of population level states would lead to a vast increase in computational speed and provide powerful insights into the spatiotemporal dynamics of disease spread and extinction. Although moment-closure approximations and quasi-equilibrium solutions offer a likely approach, they have yet to be applied to realistic seasonally forced dynamics.
2. More detailed simulations of heterogeneous patches with complex connections (Chapter 4). So far the majority of studies have considered equally sized local populations and global coupling. While this is a natural starting point, the real world is far more complex, and developing models and intuition for such scenarios will be important if spatially targeted control measures are to be applied most effectively.
3. A range of more powerful statistical and mathematical techniques are also required to deal with coupling. First, there is the complex problem of how to estimate the coupling between communities from case reports. This estimation process is confounded by stochasticity, seasonality, and heterogeneities in demographic rates, although some progress has been made. Associated with this problem is developing mathematical rules for the coupling between populations as a function of their separation. In a metapopulation of N patches, there are $N(N-1)$ coupling terms, hence in large systems estimating or even storing all the coupling rates becomes problematic so analytical approximations become necessary. Developing

gravity (Cliff and Hagget, 1988) and other formulations of the relationship between human movement and disease spread is an important problem for both fundamental population biology and applied epidemiology.

Although these three problems present formidable challenges, metapopulations are likely to see far more use in the future as the degree of realism and resolution required from models increases.

[AU1] Is 17.12, 17.13 needed in the Figures.

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