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Disease evolution on networks: the role of contact structure

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Owing to their rapid reproductive rate and the severe penalties for reduced fitness, diseases are under immense evolutionary pressure. Understanding the evolutionary response of diseases in new situations has clear public-health consequences, given the changes in social and movement patterns over recent decades and the increased use of antibiotics. This paper investigates how a disease may adapt in response to the routes of transmission available between infected and susceptible individuals. The potential transmission routes are defined by a computer-generated contact network, which we describe as either local (highly clustered networks where connected individuals are likely to share common contacts) or global (unclustered networks with a high proportion of long-range connections). Evolution towards stable strategies operates through the gradual random mutation of disease traits (transmission rate and infectious period) whenever new infections occur. In contrast to mean-field models, the use of contact networks greatly constrains the evolutionary dynamics. In the local networks, high transmission rates are selected for, as there is intense competition for susceptible hosts between disease progeny. By contrast, global networks select for moderate transmission rates because direct competition between progeny is minimal and a premium is placed upon persistence. All networks show a very slow but steady rise in the infectious period.

Keywords: spatial dynamics; spatial heterogeneity; small-world models; transmission; selection

1. INTRODUCTION

Evolution is one of the few universal concepts in biology, and implementation of evolutionary theory allows us to understand the observed characteristics of organisms. Generally this has been applied to the social behaviour of large creatures (Axelrod & Hamilton 1981; Ridley 1996; Clutton-Brock *et al.* 1998) although it also holds for the demographic attributes of all organisms. Owing to their relatively simple natural history and rapid life cycle, diseases provide the ideal opportunity to understand their dynamics in terms of an evolutionary adaptation to their environment. Here, we take preliminary steps towards this goal.

On a more immediate time-scale the evolution of infectious diseases poses a significant dilemma for practitioners of disease control. For example, the development of antibiotic resistance (Baquero & Blázquez 1997) within the pathogen population, and the emergence of novel strains for which no herd immunity exists (e.g. the emergence of novel influenza strains) are both serious threats to human health. Selective pressure is likely to be very high for such resistant diseases of humans, given the resources expended on control and eradication (e.g. antibiotic and vaccine use). This, coupled with the relative shortness of pathogen life cycles, means the evolutionary development of disease is also likely to be rapid. The ability to predict the probable consequences of control measures for the evolution and emergence of disease behaviour is therefore of great importance.

The vast majority of models of disease evolution make two basic assumptions. First, they assume that the populations of host and pathogen are well mixed. In well-mixed (mean-field) populations all individuals have an equal likelihood of encountering infection, and hence the resulting force of infection is equal for all (Anderson & May 1992). Second, the models assume that there are *a priori* constraints upon the range of evolutionary outcomes, often involving disease virulence (Anderson & May 1992; Frank 1992; Mosquera & Adler 1998; Boots & Sasaki 1999). Although the within-host dynamics of diseases and their interaction with the immune system will place some constraints upon the possible population-level dynamics (Read & Schrag 1991; Messenger *et al.* 1999), there are currently very few data to suggest either the range and form of these constraints or whether they are likely to have a major impact.

Spatial heterogeneity and the local nature of interactions have been demonstrated to have profound effects on the transmission and persistence of diseases (Comins *et al.* 1992; Grenfell & Harwood 1997; Wallinga *et al.* 1999; Keeling 2000*a*), and to produce qualitative changes in ecological and evolutionary dynamics in general (DeAngelis & Gross 1992; Nowak & May 1992; Tilman & Kareiva 1996). The standard mean-field models ignore three important properties of human disease-transmission networks: first, the finite number and variability of potential contacts—these lead to the build-up of spatial correlations (Keeling 1999) and heterogeneities of risk between individuals; second, the 'small-world' property, where, on average, any two individuals are connected by a small number of social or transmission steps (Milgram 1967; Watts & Strogatz 1998); and finally, the clustering of social contacts such that adjacent individuals in contact space are likely to have many shared social or sexual contacts—a simple example being 'my friends are likely to know each other' (this characteristic is referred to as 'tran-

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sitivity' in social-network literature (de Sola Pool & Kochen 1978; Wallinga *et al.* 1999)). These properties are evidenced by studies of social-contact networks (de Sola Pool & Kochen 1978; Klovdahl *et al.* 1994), networks of injecting drug users (Friedman *et al.* 2000) and sexual networks (Klovdahl 1985; Potterat *et al.* 2002). Thus, while mean-field models have proved a useful tool in understanding and developing epidemiological theory, the complex nature of potential infection transmission routes (whether in real space, or in the more abstract contact space) could have severe implications for the reliability of predictions made by such methods.

In this paper, we consider how the social structure of a population, in the form of a contact network, affects the evolutionary selection of the parameters determining infectious-disease transmission dynamics. Specifically, we consider how the routes available for the infection to spread through such networks determine the adaptation of the transmission rate and the infectious period. This is a complex process with multiple feedbacks at a variety of spatial and temporal scales. In particular, while the network has a strong influence on the evolution of the disease, the disease dynamics in turn modify the available susceptible network. The next section sets up the model framework and describes the basic disease dynamics within the contact network. Section 3 describes the various simulations that have been performed in order to tease apart the evolutionary forces. Finally, § 4 considers the long-term evolutionary behaviour of the diseases, contrasting the influences of local and global networks.

2. MODEL DESCRIPTION

The epidemic and endemic dynamics of infection within a network of susceptible individuals have been studied using lattice models (Mollison 1977; Rand *et al.* 1995; Levin & Durrett 1996; Rhodes & Anderson 1996), small-world models (Watts & Strogatz 1998; Moore & Newman 2000; Kuperman & Abramson 2001; Pastor-Satorras & Vespignani 2001; Zekri & Clerc 2001) and pairwise correlation models (Keeling 1999; Ferguson & Garnett 2000). However, these methods of approximating spatial or network structure generally suffer from a lack of heterogeneity at the individual level, and most have severe difficulty incorporating birth and death processes in a biologically realistic manner. For example, if individuals that recover from infection are simply replaced by susceptible individuals, then such births (new susceptibles) become spatially correlated with incidence of disease. Moreover, where new susceptibles are recruited in adjacent locations to susceptibles (Keeling 2000*b*), severe local density dependence is invoked and the location of births becomes negatively correlated with infection. The spatial structure that develops is unrealistic for general human or animal populations and may have a large qualitative impact on the results.

The model presented here attempts to overcome these limitations by direct simulation of the spread of infection through a computer-generated network. Individuals are distributed randomly in space with an average density of one individual per unit area (figure 1*a*,*b*). The distance between individuals determines the probability that a link (representing a potential pathogen transmission route) is formed between them. This connection probability kernel is formulated such that the expected number of links per individual (n) and the average distance between linked individuals (D) may be predetermined (see Appendix A). Thus, a range of possible network configurations may be considered, forming different 'landscapes of selection' within which a disease can spread, adapt and persist. In particular we consider two distinct forms of network, classified according to the shape of the kernel. Local networks are highly aggregated, with many social cliques (high transitivity), and hence share many properties with the social networks associated with the transmission of airborne pathogens. Global networks are dominated by random long-distance connections, and possess few cliques (low transitivity); they are therefore a more extreme version of the transmission routes involved in the spread of sexually transmitted diseases (based on analysis of the social and sexual network data presented by Klovdahl (1985)). This analogy between our static networks and the dynamic behaviour of human social and sexual networks should be used cautiously; our networks represent two structural extremes and hence are merely qualitative caricatures. A quantitative model of realistic human transmission networks would require vast amounts of detailed sociological data, and would be more difficult to analyse and understand.

Communication through a global network is much faster than through a local network, even though both have the same average number of contacts per individual (figure 1). This crucial difference has profound consequences for the spread of infection and the selection of infectious-disease behaviour. An important feature of the contact structure is the heterogeneity of contacts per individual (figure 1*c*,*d*): a few individuals have far more contacts than average. This is a generic property of human contact networks (Klovdahl 1985; Klovdahl *et al.* 1994; Brisson *et al.* 1999; Rosenburg *et al.* 1999; Liljeros *et al.* 2001) that is generally omitted from non-network models (e.g. cellular automata and small-world models).

Birth and death rates of the host (b and d, respectively) are assumed to be equal and independent of modelled population size, although the model does not specifically require this. New susceptibles (births) are introduced at random locations in contact space and connected to other individuals according to the distance between them, with a probability specified by the connection kernel (see Appendix A). The death of an individual simply removes them from the network, together with any associated contact links.

The infection statuses of individuals are divided into three discrete classes: *susceptible*, *infectious* and *recovered* (SIR) as in the traditional SIR model framework (Anderson & May 1992). All individuals begin life as susceptibles. A susceptible in contact with an infectious individual becomes infected by that particular strain of the disease at a strain-specific probabilistic rate τ (see Appendix A). Infected individuals remain in this class for a fixed period (P_{inf}), determined by the infecting strain, during which they maintain a constant level of transmission to all their contacts. Finally, the host's immune system is assumed to combat the infection, and they move directly into the recovered class, where individuals are no longer infectious and are assumed to have full immunity from further infection. For simplicity, we assume no multiple

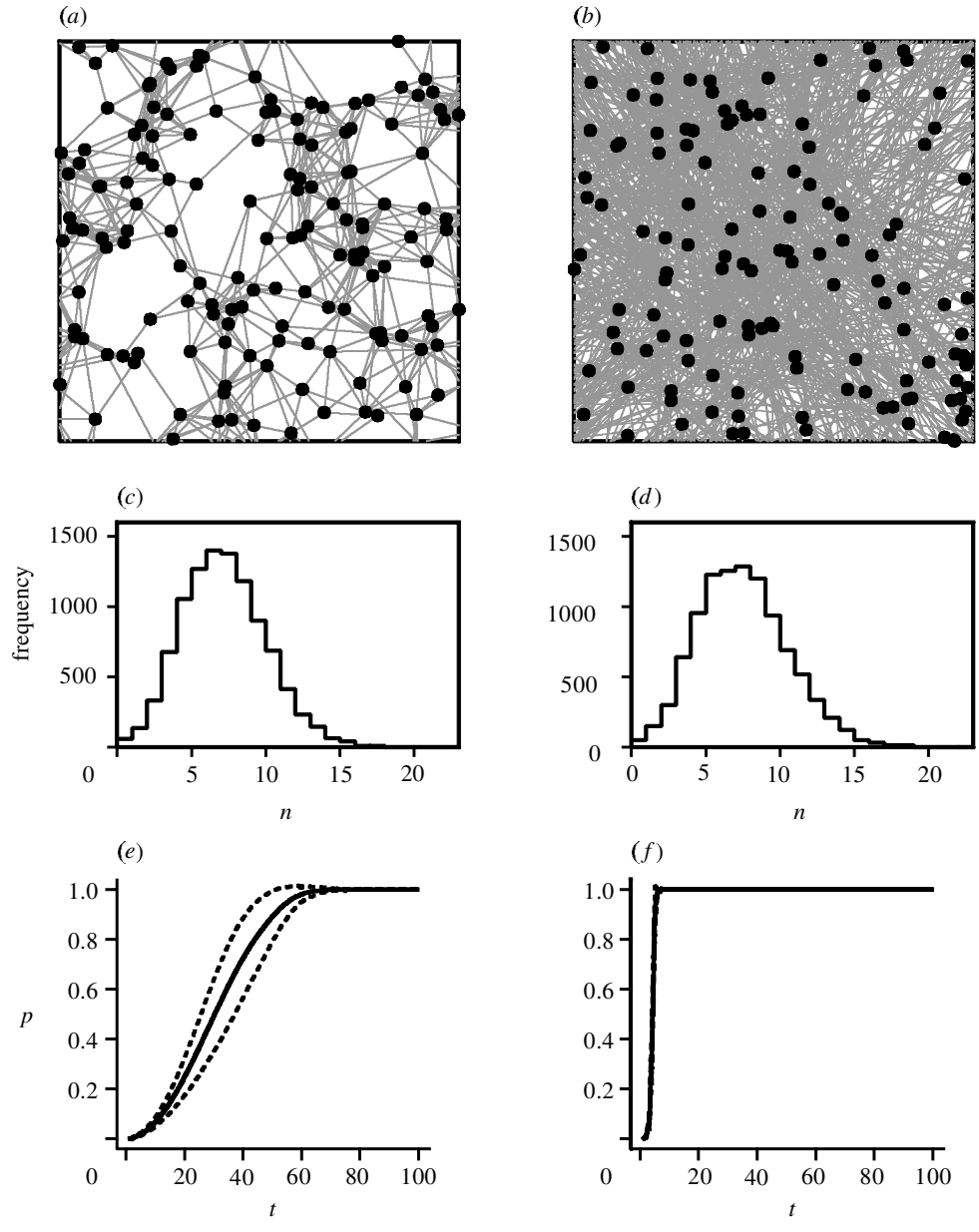

Figure 1. Example regions of (*a*) local and (*b*) global networks, showing individuals (black circles) and their contact links (grey lines). The distribution of contacts per individual, n, for (*c*) local and (*d*) global networks. Finally, to demonstrate the connectivity of the entire network, we calculate the proportion of the network reached, p, in t steps from a random individual in each network type, (*e*) local and (*f*) global; the solid line is the mean of 100 such procedures, and the dashed lines are the standard deviations of the mean.

infections and that, once recovered, an individual acquires full cross-immunity to all possible strains of the disease. This allows us to consider the evolution of one dominant infection strategy, without the complication of multiple coexisting strains of infections (Gog & Swinton 2002).

In this model, disease strains have two characteristic components that determine their local behaviour: the probabilistic transmission rate between an infected and a susceptible individual across a link (τ) and the duration of infection (P_{inf}). Both of these characteristics are inherited from ancestral infections with mutation and, for simplicity, are assumed to mutate independently (see Appendix A). Thus, as in nature, evolution proceeds via the accumulation of many random mutations.

As the transmission of infection is a stochastic process and the population size is finite, we can expect to observe extinctions of the disease. To counteract this, a low level of infection is assumed to enter the population from an external source, at a probabilistic rate m. These imported infections are positioned at random in contact space, and are connected using the appropriate kernel (in the same way as births); their characteristic parameters follow the most recent strain parameters within the network (see Appendix A). Thus, imports will not cause dramatic jumps in disease parameters, and they act as if we are observing the dynamics in a single element of a weakly coupled metapopulation (Grenfell & Harwood 1997).

3. SIMULATIONS

A typical simulation consists of the following sequential events: network generation, the introduction of disease

Table 1. Values assigned to parameters in simulations.

parameter	meaning	value
N	population size	10 000
T	time-period of simulation (iterations)	100 000
n	average contacts per individual	8
D	measure of connection distance	1 (local) or 50 (global)
b	average births per iteration	0.39
d	average deaths per iteration	b
m	infected immigrants per iteration	0.01
std(τ)	mutation distance in transmission rate	0.05
std(P_{inf})	mutation distance in infectious period	0.5
initial τ	initial transmission rate	0.025
initial P_{inf}	initial infectious period (iterations)	20

into the susceptible population, and subsequent iterations until the end of the allotted simulation time (T). During an iteration, births and deaths may occur, individuals may become infected or recovered (depending on their status and circumstance) and the import of infection may occur. A full account of assigned parameter values is given in table 1.

Networks of susceptibles were generated using the prescribed connection kernel. Two main network forms were simulated: local connections, with an average of eight contacts per individual; and global connections, also with an average of eight contact neighbours. These correspond to two extreme levels of contact structure, and allow us to ascertain the effects of cliques within host populations on the evolution of transmissible disease.

Initially, a single individual was infected by a disease strain with $\tau = 0.025$ and $P_{\mathrm{inf}} = 20$ iterations. Average daily birth and death rates were chosen to maintain a stable population size, and to set the average lifespan of the host at 25 550 iterations—if each iteration corresponds to 1 day then the average host lifespan is 70 years. In most human societies, however, removals and additions to contact networks (in our model, deaths and births) may occur much more rapidly, and therefore an iteration may correspond to a far shorter time-scale. Hence, the evolutionarily stable parameters are not only functions of the network structure, but also scale directly with the rate of turnover of connections. (One simulation therefore corresponds to about four complete regenerations of the network.)

The model population status was updated synchronously, and most simulations were performed for up to 100 000 iterations; a few longer ($T = 1$ million iterations) simulations were also performed to check the long-term validity of results. Stochasticity enters our model formulation from four distinct sources: the demographic dynamics that determine the network, occasional imported infection, the transmission of infection, and the random mutation of strain parameters. Therefore, to observe general trends, 100 replications were made of each treatment, and the disease parameters and timing of every new infection were recorded.

4. RESULTS

The standard mean-field model of SIR-type infection predicts that if two strains are competing for susceptible hosts, the strain with the greater basic reproductive ratio, $R_0 \propto \tau.P_{\mathrm{inf}}$, will always outcompete the other. Stochastic birth, death and transmission processes do not significantly alter this conclusion (figure 2*a*,*b*). Therefore, evolution will always favour infections with greater values of R_0, so that in such mean-field models we observe runaway behaviour with selection for ever higher transmission rates and ever longer infectious periods. In particular, deterministic theory supported by stochastic simulations of this process (figure 2*a*,*b*) predicts that the transmission rate experiences by far the strongest selective pressure and therefore increases most rapidly.

In contrast to the mean-field models, the results from network simulations consistently show more constrained evolutionary behaviour (figure 2; note the disparity of time-scales): the rate of evolutionary change is far slower and is not limited simply by the mutation rate. The evolutionary dynamics also show greater variability than their mean-field counterparts, being strongly influenced by recent epidemic history. In particular, there is strong selection against rapid changes in R_0. Large reductions in the value of R_0 render the infection unable to survive in the environment. However, there are also severe penalties for high transmission rates: an infection with a high transmission rate will spread rapidly through all accessible susceptibles within a connected cluster. In such a scenario, there is an increased risk of the host resource becoming exhausted before enough births are introduced to provide a link to other susceptible parts of the network (host 'burn-out'); extinction of the strain lineage is therefore more likely to occur (Rand *et al.* 1995; Keeling 2000*b*). Thus the dynamics are naturally constrained to evolve much more slowly than the mutation rate allows.

Within the global networks, average transmission rate evolves to an asymptotic optimum rate, $\tau \approx 0.16$ (figure 2*f*). Short-duration and low-transmission strains are strongly selected against, as the ability of the disease to infect would be severely reduced, while very high-transmission strains are not favoured because of the increased risk of depleting the susceptibles and the consequently greater risk of extinction. However, an increase in the birth rate (increased 'restocking' of the susceptible population) should result in a decreased extinction risk, and in correspondingly reduced penalties for high transmission rates in global networks. Indeed, in additional simulations performed, where $b = 3.9$, disease extinction ceased to occur, the infection became endemic, and very high transmission rates were selected for.

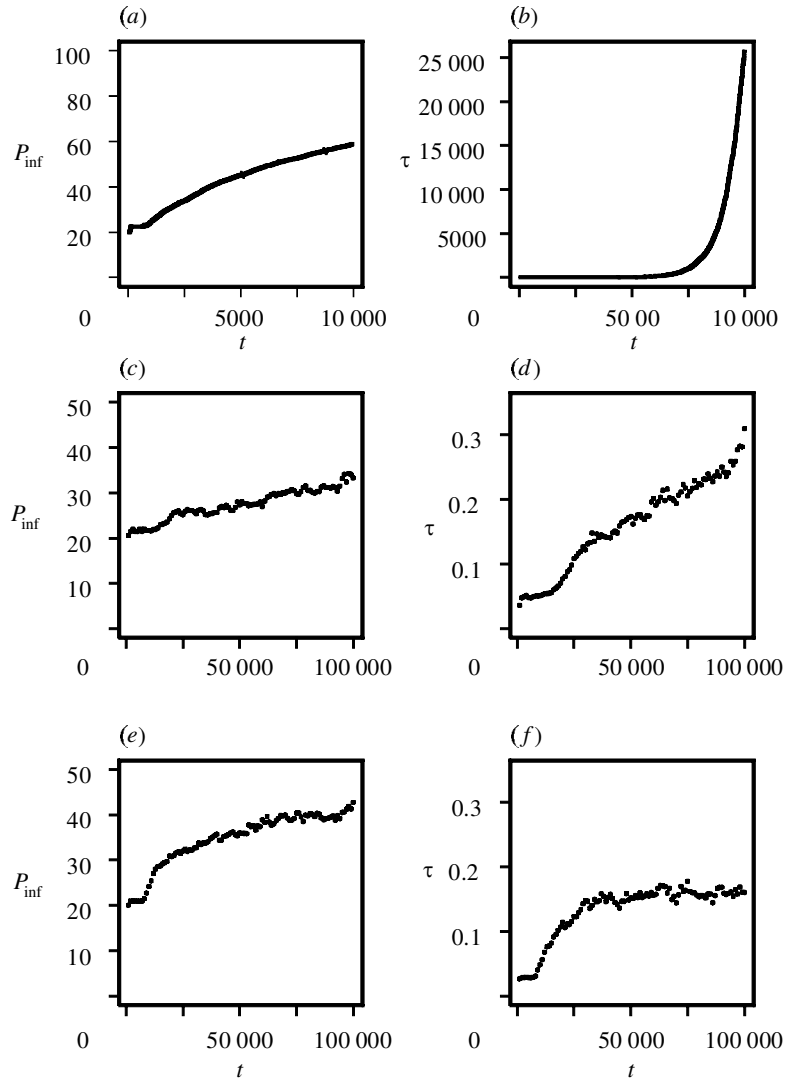

Figure 2. Evolution of average strain characteristics from a stochastic mean-field model (*a*,*b*), and within local (*c*,*d*) and global (*e*,*f*) networks. For the mean-field model (*a*) and (*b*) show the average infectious period (P_{inf}) and transmission rate (τ) respectively per iteration across 100 simulations. For the local and global networks, the parameters are averaged over 1000 iterations, and again 100 simulations are used. Although all models use the same mutation rates, the mean-field model shows far more rapid dynamics—note that the mean-field behaviour is shown over a much shorter time-scale.

By contrast, no such optimum transmission rate is reached in the local-network simulations within the standard time-frame simulated. When simulations were performed over a greater time-period ($T = 1$ million iterations) transmission rate steadily increased in local networks. Local networks are characterized by a high aggregation of contacts and the forming of small social cliques, and this attribute generates a strong selective pressure on infections. As any two connected individuals generally share some mutual contacts, direct competition between disease progeny for available susceptible hosts is likely to be commonplace, causing selection for a more rapid transmission rate. That no optimum transmission rate is attained in local-network simulations suggests that this competition is a far stronger selective force than the increased risk of extinction.

No optimum infectious period is attained in either local- or global-network simulations, and P_{inf} gradually increases throughout the simulation, though at a greater rate in global networks. We have found this to hold true even in simulations of longer duration.

The differences between the evolutionary behaviours on local and global networks are clearly the result of the governing network structure and connection kernel. To understand how, we must consider how successive infections, and birth and death processes, alter the available transmission network of susceptibles. In a typical simulation, there is an initial large epidemic that quickly depletes the number of susceptibles. During this period, evolution is rapid, owing to the fast turnover of infection and the high selective pressures upon disease strains with parameter values near the initial values. In all of our simulations, disease extinction occurs when the level of susceptibles is driven so low that only very small susceptible 'clusters', which cannot support the infection, remain. The infection at this moment has previously evolved only in an environment of abundant susceptibles. In simulations where the birth rate is dramatically increased, these isolated clusters soon become connected, and the disease can persist.

Under normal circumstances, with subsequent iterations, births gradually increase the number of suscep-

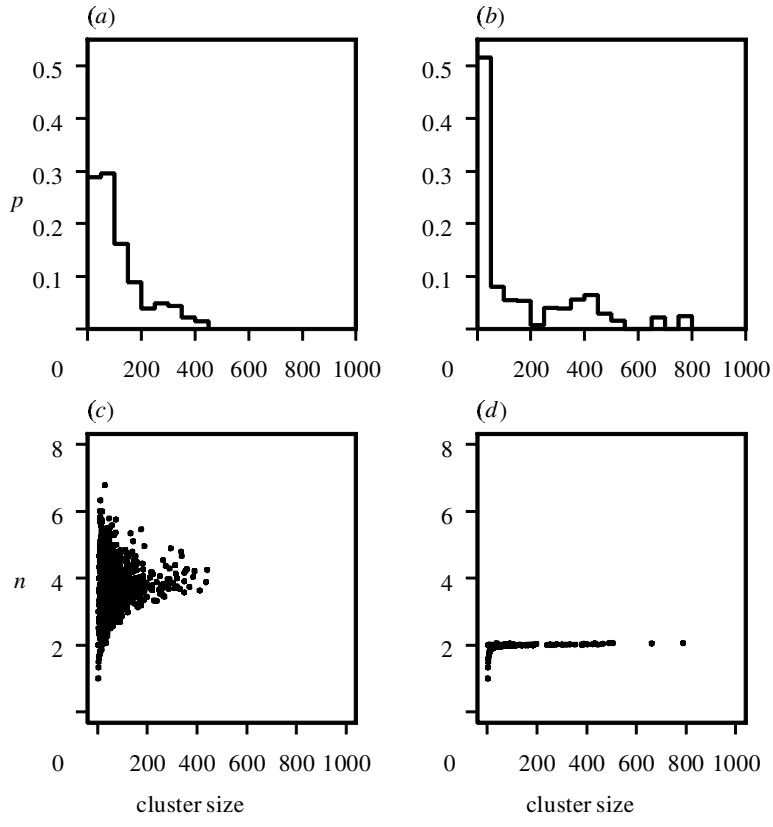

Figure 3. Characteristics of susceptible clusters at the end of the simulation, $t = 100\,000$. The probability, p, of a susceptible individual selected at random belonging to a particular cluster size in (*a*) local- and (*b*) global-network simulations, across all replicates. The average number of contacts per individual member of a cluster, n, plotted against the total size of the cluster in (*c*) local and (*d*) global networks.

tibles, and connectivity between susceptibles also increases. The subsequent reintroduction of an infectious individual (infectious import; see Appendix A) may cause a small epidemic that is localized to the cluster of connected individuals it happens to infect.

The size of the resulting epidemic (if there is one) depends on the size and the density of these susceptible clusters, which are determined by three interrelated factors: the location and magnitude of previous epidemics, the rates of infectious import and birth, and the contact kernel determining network connections. Previous epidemics form 'barriers' of recovered individuals between clusters of susceptibles that may isolate them from subsequent infection (Rand *et al.* 1995; cf. Friedman *et al.* 2000). Isolated susceptibles become more connected with time, as new susceptibles (births) are added to contact space, connecting previously isolated individuals and clusters: birth rate and infectious-import rate effectively govern the interval between epidemics. How an individual connects to the existing population will also influence subsequent epidemic dynamics, as globally connected individuals will tend to form a network that facilitates disease spread. Thus, the disease dynamics influence the available susceptible network, which, in turn, determines future epidemic behaviour and the evolutionary dynamics of the disease.

Figure 3 shows the likelihood of a reintroduced infection encountering a suitable cluster of susceptibles for both network types at the end of the simulations; this snapshot of the average network is representative of networks throughout the latter half of the simulations. In general, the local network develops small clusters of highly connected individuals (each individual has many susceptible neighbours), whereas the global network develops larger weakly connected clusters (the average number of susceptible neighbours is consistently no more than two). These differences arise primarily from the ease with which infection spreads across the entire network: in the local network, where spread is more restricted (figure 1*e*), clusters may remain isolated and uninfected for longer periods of time, allowing them to grow. The characteristics of such susceptible clusters can be used to explain the different evolutionary forces that are operating.

In the small well-connected clusters of local networks there are many short loops between individuals adjacent in contact space. Thus, a strain's progeny (secondary infections) are more likely to be in direct competition for available hosts. This leads to 'scramble' competition, where the most transmissible strains are the fittest: those progeny with the fastest transmission rates are likely to produce the most descendants in the next generation. It is therefore not surprising that high transmission is selected for, as this is the only way that a strain can outcompete other strains, even though it confers an increased chance of extinction, as the strain will infect and 'burn through' the cluster in a shorter time. Interestingly, this is contrary to some well-established views on altruistic behaviour, in which spatial clustering generally promotes self-sacrifice (May *et al.* 1995; van Baalen & Rand 1998).

By contrast, in a global network, progeny are unlikely to be in direct competition for hosts, so a moderate trans-

mission rate that balances persistence against infection is an evolutionarily stable strategy. In all situations, diseases face a trade-off between leaving a suitable environment for their progeny (the conservation of susceptible hosts) and the immediate benefit of producing a large number of secondary infections (causing rapid depletion of immediately available susceptibles)—this places a natural constraint on the evolutionary dynamics. The network structure determines where the trade-off between long-term and short-term gains lies. The dominant selective force in *global* networks is the *ability to persist*, whereas in *local* networks *ability to infect* is most important.

Longer infectious periods are selected for in both local and global networks; indeed, even when the initial starting strain has a very long infectious period ($P_{\mathrm{inf}} = 100$ iterations), selection still acts to increase it. Therefore, while it is clear that a high transmission rate destroys the local patch dynamics for future generations, a longer infectious period has no such disadvantage. The strength of selection for long infectious periods is, however, very weak and variable, relative to the strength of selection for transmission rate, although statistical tests show that the infectious period is not simply undergoing a random walk. Therefore, while an unconstrained model predicts the slow continual increase in P_{inf}, even small physiological constraints or trade-offs could easily overcome this.

Figure 4 shows the average direction and strength of evolution at each parameter value: as such it represents the evolutionary bias to the random drift caused by mutation. We stress that these are average quantities; the actual values are subject to large amounts of stochasticity and are highly dependent upon the recent epidemic and evolutionary history. Low values of transmission rate or infectious period have large evolutionary forces acting towards increasing values. Both types of network show some evidence for a stable fixed point (an evolutionarily stable strategy) but this is strongly influenced by the stochastic nature of the evolutionary dynamics. The global network clearly has a fixed point close to $\tau = 0.1$; however, in this region the selective pressure on the infectious period is weak and we expect to observe a random drift to ever higher values. For local networks, there is again a weak locally stable fixed point, but once stochasticity pushes the disease parameters away from the immediate vicinity of this point, we expect to see runaway evolution to ever higher values. Thus, these evolutionary diagrams support our earlier conclusions.

A similar pattern for transmission rate and infectious period is observed when the average number of contacts per individual is doubled ($n = 16$). Owing to the increase in the number of contacts, comparable levels of transmission translate into a doubling of the reproductive ratio R_0. As the number of neighbours increases, so the system becomes more like the mean-field models, which experience runaway evolution—so we may predict selection for higher transmission rates than when $n = 8$. This is what we find in global networks: doubling n increases the optimal transmission rate; however, in the local networks, the evolution of transmission rate is unaffected. These dynamics can again be attributed to the structure of available susceptible clusters. Increasing n reduces the number of large susceptible clusters in the global network, as it is less likely that they remain isolated, and so are more likely to be infected. However, increasing n has little effect on susceptible-cluster properties in local networks, which are determined largely by the disease dynamics. These phenomena highlight the complicated relationship between evolution of pathogen and network in our model.

5. DISCUSSION

Standard homogeneous models for disease dynamics ignore the heterogeneities and correlations that develop in the realistic spread of infection across a network of contacts. In mean-field models, those strains with the largest reproductive ratio dominate, and therefore constraints or trade-offs need to be included to achieve meaningful evolutionary behaviour (Anderson & May 1992; Frank 1992; Mosquera & Adler 1998; Boots & Sasaki 1999). By contrast, we have shown here that the dynamics of infection through a network place strong constraints on evolutionary behaviour, and, in particular, that the form of the network can determine the evolutionarily stable parameters of a disease.

The history of epidemics largely determines the course of the evolutionary behaviour of a disease: once a network pattern has emerged it is difficult for radically different strains to invade and take over. Essentially, any new strains with a lower reproductive ratio (and in particular a lower transmission rate) are immediately outcompeted; however, although those with a higher reproductive ratio do better locally, they rapidly deplete the environment of susceptibles, thereby disadvantaging their progeny. The balance between immediate reproductive gain and preservation of the local environment for one's descendants is central to the evolution of diseases, and may have parallels in the evolution of other natural enemy systems.

We have considered two distinct forms of network, local and global, as caricatures of two extreme types of human contact network structure. The host demography was parameterized according to human lifespans and assuming that network connections were made for life. Assuming a shorter lifespan or a more rapid turnover of connections should be reflected in a simple rescaling of all parameters. Obviously, the true mixing patterns of humans are far more complex than can be captured by such simple networks, but the full simulation of realistic scenarios is beyond the scope of this paper and of current computational power. However, our results suggest that differences in observed disease behaviour may be explained by the character of contact networks, without necessarily invoking other constraints such as virulence–transmission trade-offs (Bonhoeffer & Nowak 1994; Messenger *et al.* 1999).

While the transmission rate is clearly constrained by the network dynamics, the infectious period consistently shows a slow increase with a clear deterministic component. This evolutionary trend is far slower, however, than in the mean-field models, suggesting that even a very weak functional trade-off between transmission rate and infectious period would be sufficient to balance the dynamics. Evidence for such a trade-off can be observed in sexually transmitted diseases (Blanchard 2002), although whether this is the result of physiological constraints, or the result of evolutionary processes, is not clear. The most obvious candidates for creating trade-offs would be host coevolution, or the interaction of the disease with the host

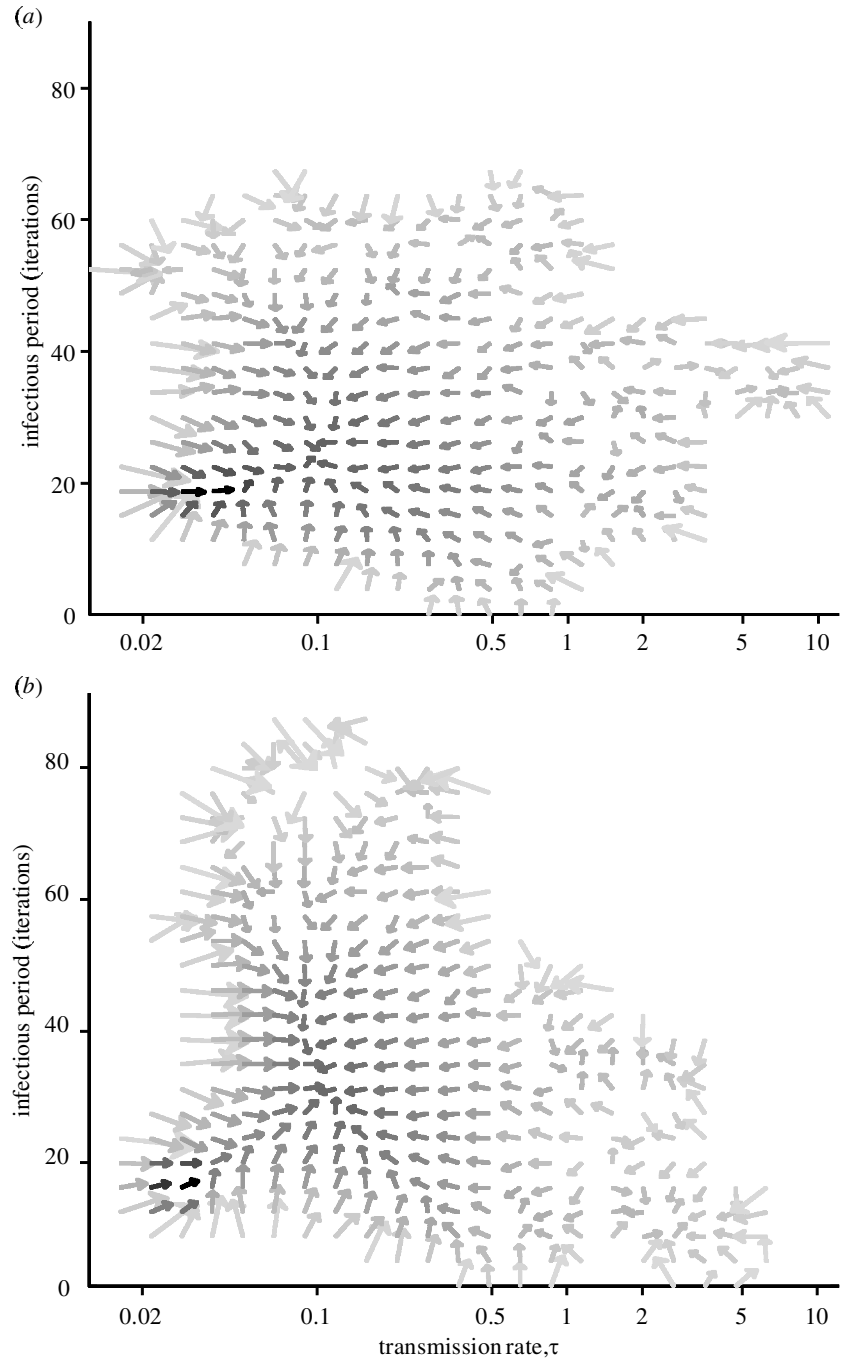

Figure 4. The direction and strength of strain evolution over parameter space for (*a*) local and (*b*) global networks. The arrows show the average evolutionary trajectory of simulations that pass through each region of parameter space. The size of the arrow indicates the speed of evolution, while the shade indicates the amount of data available and therefore the certainty of the prediction (black is for the most data).

immune system—both of these factors would add considerably to the computational costs of the model.

In essence, our model predicts that diseases that transmit via networks that consist of many long-distance random connections (non-cliquey) should have conservative transmission rates and long infectious periods. By comparison, where a disease transmission network contains many cliques, diseases should possess very high transmission rates and shorter infectious periods. Examples of human contact networks that are unambiguously local or global in character are difficult to identify: real networks tend to contain the structural characteristics of both local and global networks (see Klovdahl 1985; Klovdahl *et al.* 1994; Potterat *et al.* 2002), and links are not usually static for the lifetime of an individual. More research is required to evaluate the impact of such attributes on our predictions. In addition, we have found that both the average number of contacts per individual and the rate of contact turnover affect selection pressure; the comparison of disease characteristics found on real networks is likely to be confounded by differences in these qualities. This suggests that predicting the likely evolutionary effects of social change on human diseases may be complicated by the presence of interacting factors.

The role of spatial structure in the evolution of organisms, and in particular of infectious diseases, is far from clear-cut: several facets interact over a range of spatial and temporal scales. As with many systems, evolutionary fitness is environment-specific and the environment is in turn modified by the organism. Much more work is necessary before modelling techniques can quantitatively predict the behaviour of diseases from an evolutionary perspective, although general patterns have emerged. We have highlighted the complexities involved in understanding evolution in a spatial context, and have demonstrated that ignoring the spatial component (as in mean-field models) leads to large qualitative errors.

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APPENDIX A

(a) *Network construction*

A transmission network is comprised of N individuals (nodes) uniformly distributed across a plane of dimensions $\sqrt{N} \times \sqrt{N}$, thereby ensuring the average density of individuals remains constant regardless of network size. The connectivity kernel, K, defines the probability of connection between nodes separated by a distance d:

$$K = p.\exp\left(\frac{-d^2}{2D^2}\right),$$

where the value of p is chosen such that the expected number of connections per individual is n, and D determines the average distance between linked individuals. In this way local networks ($D = 1$) and global networks ($D = 50$) can be constructed such that they have approximately the same mean number of connections per node. For an infinitely large population,

$$p = \frac{n}{2\pi D^2}.$$

In practice, the finite size of the population together with edge effects will mean that p will have to be increased from this theoretical prediction. This discrepancy is corrected by comparing the average number of connections per node within a trial network (constructed assuming a value of p for an infinitely large population) to the desired n, and scaling p accordingly. During a simulation, new nodes (births or infectious imports) are connected to the existing network using K, in an identical manner to normal network construction.

(b) *Disease dynamics*

The model is updated synchronously and therefore compares to a discrete-time model of infection. Given a link between a susceptible individual and an infected individual, the per iteration probability, p, that infection passes across the link is

$$p = 1 - \exp(-\tau),$$

where τ is the transmission rate of the strain concerned. The time since infection is tracked so that the infectious period is modelled as a fixed length, which is an integral number of iterations. After this allotted time individuals pass into the recovered class, and are removed from the network as they play no further role in the SIR model.

(c) *Strain evolution*

Whenever a susceptible host becomes infected, the disease parameters of the 'strain' that colonizes the newly infected host deviate slightly from those possessed by the source of infection, thus mimicking the random mutation of disease parameters. This mutation occurs at each new infection event. In particular, for a given transmission rate τ, the transmission rate of secondary infections is given by

$$\tau' = \tau(1 + \varepsilon\tau),$$

where $\varepsilon\tau$ is a Gaussian distribution with mean zero and a standard deviation of std(τ), and for a given infectious period

$$P'_{\mathrm{inf}} = P_{\mathrm{inf}} + \varepsilon P_{\mathrm{inf}},$$

where $\varepsilon P_{\mathrm{inf}}$ is a Gaussian distribution with mean zero and a standard deviation of std(P_{inf}). Mutated infectious periods are rounded to the nearest integer and must be positive or zero. It is more natural to deal with transmission rate in this form, so that mutation acts multiplicatively, although this does not affect our results. Thus mutation alone should lead to an unbiased random walk.

(d) *Infected imports*

To prevent complete extinction of the disease for the whole time-period of each simulation, we introduce infected individuals at a low probabilistic rate, m, at the end of an iteration and connect them to the host contact network in a similar manner to births. We assume that these imports are representative of recent infections by using running averages of both τ and P_{inf} over the last 100 infections.

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