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REVIEW

Spatial dynamics and genetics of infectious diseases on heterogeneous landscapes

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Explicit spatial analysis of infectious disease processes recognizes that host–pathogen interactions occur in specific locations at specific times and that often the nature, direction, intensity and outcome of these interactions depend upon the particular location and identity of both host and pathogen. Spatial context and geographical landscape contribute to the probability of initial disease establishment, direction and velocity of disease spread, the genetic organization of resistance and susceptibility, and the design of appropriate control and management strategies. In this paper, we review the manner in which the physical organization of the landscape has been shown to influence the population dynamics and spatial genetic structure of host–pathogen interactions, and how we might incorporate landscape architecture into spatially explicit population models of the infectious disease process to increase our ability to predict patterns of disease occurrence and optimally design vaccination and control policies.

Keywords: spatial dynamics; rabies; infectious disease dynamics

1. INTRODUCTION

The dependence of infectious disease processes on their specific spatial and ecological context has been receiving considerable recent attention. Explicit spatial analysis of infectious disease processes recognizes that host–pathogen interactions occur in specific locations at specific times and that often the nature, direction, intensity and outcome of specific interactions depend upon the specific location and identity of both host and pathogen (Real & McElhany 1996; Hess *et al.* 2001). The recognition of significant forms of spatial heterogeneity over the ecological landscape that might influence disease processes has contributed to our growing recognition of the need to anchor infectious disease processes within their explicit spatial context (Ostfeld *et al.* 2005). Spatial heterogeneities can take either of two forms both of which can influence underlying dynamics but affecting populations through vastly different mechanisms.

First, individuals in the population may aggregate spatially over a uniform landscape or exhibit non-random interactions due to non-random forms of social interaction, limited dispersal or other mechanism that increases local interactions at the expense of global connectedness. In these instances, the structure of the landscape does not dictate the spatial organization of the population. Rather, that organization is an epiphenomenon of the intrinsic population process. For example, sexually transmitted diseases in human populations are often both non-random and spatially aggregated due to social processes (e.g. shooting galleries where needle exchange is common, sex worker concentration in urban centres, etc.). Under such circumstances, the environment can be ignored for increased attention to the details of host identity and social processes.

On the other hand, environments themselves can act as the principal organizers for spatial processes, sometimes acting on a rather homogeneous host or pathogen population or at least within a well-mixed population that assorts into different spatial locations due to environmental influences. A classic example would be the asymmetry of measles spread from large cities to small cities and towns due to the asymmetry in the number of susceptible hosts (Grenfell *et al.* 2001).

The distinction between spatial aggregates formed through social and behavioural interactions versus environmental heterogeneity has been well recognized in plant–pathogen systems. In the agricultural literature, these two forms of infectious disease process have been designated as either 'truly contagious' or 'apparently contagious' processes (Campbell & Madden 1990). True contagion is a focal point process where an epidemic begins by infection of a few, often randomly

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spaced, individuals. Spatial aggregates (i.e. patches) develop as foci around these initially infected individuals, because the limited dispersal capabilities of the pathogen generate regions of high disease prevalence around the sites of initial disease occurrence (Zadoks & Vandenbosch 1994). Spatial aggregates could also emerge where there are heterogeneous degrees of connectivity among individuals within a distributed network of interactions (e.g. where some individuals are 'super-spreaders' or 'super-shedders') and these heterogeneous patterns of connectedness may be quite independent of the environmental structure (e.g. they may be the properties of the individual host genotype).

Apparent contagion, on the other hand, assumes that the pathogen or host is uniformly dispersed and randomly connected to individuals across the networks. Spatial aggregates generate from the inherent heterogeneity in the environment that acts as a selective sieve on the establishment and productivity of local interactions. For example, wind-dispersed fungal pathogens of plants can be widely distributed but may establish only among patches of plants where the temperature and humidity are favourable to fungal spore development. Both true and apparent contagion will generate spatially heterogeneous populations of hosts and pathogen.

Apparent and true contagious processes do not exhaust the possible influences of environmental heterogeneity on disease process, especially patterns of spread. In plant systems (especially agricultural crops), most discussion is restricted to deciphering the relative contributions of these two types of contagious interaction in generating spatial heterogeneity in disease incidence. Most probably, this is because plants do not move, so the host population distribution is considered a fixed property of the environment and pathogens distribute themselves over the fixed population of hosts. Animal populations, obviously, are quite mobile and the movement patterns of individuals may reflect spatial heterogeneity in the environment giving rise to spatial heterogeneity in patterns of incidence. As a general rule, whenever environment influences the distribution or movement of host individuals, this has the potential to affect transmission dynamics and pathogen population structure. Physical attributes of the environment may restrict or enhance particular trajectories of movement-effecting patterns of disease spread, establishment, gene exchange and population connectivity (or its converse, isolation). In this paper, we review the evidence for a direct effect of the physical structure of the landscape on patterns of disease dynamics and genetics, and how landscape structure has been incorporated into model architectures. We focus on infectious diseases of wild animal and plant populations, for which the influence of environmental heterogeneity is often most obvious. As examples, we especially draw on studies of wildlife rabies, in part owing to our own experience with this system, but also owing to the historic role that it played in driving the development of analytical tools for modelling disease dynamics in heterogeneous landscapes.

2. DISEASE DYNAMICS INFLUENCED BY PHYSICAL HETEROGENEITIES

The system we have examined most closely for the effects of spatial heterogeneity on the dynamics of epidemic expansion has been the ongoing rabies virus epizootic within raccoon populations in the eastern USA (Lucey *et al.* 2002; Russell *et al.* 2004, 2005; Smith *et al.* 2002, 2005). We suspect that this epizootic was initiated in the Mid-Atlantic region by the inter-state translocation of raccoons incubating rabies from an established focus of raccoon rabies in the southeastern USA (Nettles *et al.* 1979; Smith *et al.* 1984). Since the mid-1970s, this raccoon-adapted variant of rabies virus has spread north to Maine and Ontario, Canada and west to Ohio, causing one of the most intensive (and extensive) outbreaks of animal rabies ever recorded. The magnitude of this epizootic was enhanced by the spread of virus through naive raccoon populations of very high density, often in states that had not experienced rabies in terrestrial carnivores for decades (Rupprecht & Smith 1994).

Since the mid-1970s, state public health offices have reported wildlife rabies incidence monthly by county (or in some cases, township) to the US Centers for Disease Control and Prevention. We have used these reports to construct a detailed account of the spatial and temporal dynamics of rabies during the course of its epizootic expansion in the US (figure 1) and to construct spatially explicit predictive models for rabies spread that incorporate heterogeneities in the epizootic landscape.

We developed a discrete-event simulator (Smith *et al.* 2002) for which the infection of each township (i.e. rabies detected) occurred at a unique point in time. An infected township, i, infects its adjacent neighbour, j, at a rate λ_{ij}. In addition, a township j may become infected owing to translocation of rabid raccoons at a rate μ_j. Heterogeneity was incorporated into the model by allowing the local rates from the neighbours $[\lambda_{ij}]$ and the rate of translocation $[\mu_j]$ to be functions of local habitat characteristics. A schematic of the spatial model and the execution algorithm is presented in figure 2.

We compared the predictive power of alternative models where each model represented a different weighted combination of effects due to spatial heterogeneities corresponding to the presence or absence of rivers, spatial variation in human population density and variation in global transport of infected animals. Our stochastic spatial simulator was able to mimic the spread of rabies only when environmental heterogeneity was incorporated explicitly into the model. The best-fit model (figure 3) suggested that slower local spread of rabies was strongly associated with river crossings; the global spread by translocation was relatively frequent; and human population density had very little effect on the local spread of rabies. In a separate study, we demonstrated how human population density influenced the magnitude of raccoon rabies epizootics but not the time to first detection (Childs *et al.* 2001).

Townships separated by rivers had a sevenfold reduction in local transmission. All of the models that incorporated slowing at rivers had a better fit than the

alternative models without rivers. Even though local transmission accounted for most transmission, long-distance translocation was important. Of the 159 townships not on the western border of Connecticut, 21 townships (13%) recorded their first case of raccoon rabies when no adjacent townships were infected. All of the outlying townships (figure 3) identified by our model became infected with rabies earlier than predicted, caused in most circumstances by probable long-distance translocation.

To assess the consequences of this spatial heterogeneity on the overall dynamics of rabies, we further simulated the epizootic with and without rivers and with and without long-distance translocation. Rivers delayed the appearance in southeastern Connecticut by approximately 16 months (figure 4) without translocation and by 11 months with translocation (Lucey *et al.* 2002; Smith *et al.* 2002). Environmental heterogeneities have played a significant role in determining the rate and direction of epizootic expansion of this important disease. Qualitative observations supporting the effect of rivers as barriers have also been made for the spread of fox rabies in Western Europe (Sayers *et al.* 1985).

Large rivers probably represent movement barriers for most non-volant animals and thus would be generally expected to temporarily reduce the velocity of infection waves in terrestrial host species. This assumes, however, that the river is situated perpendicular to the general direction of spread, as was the case in the previous example of raccoon rabies in Connecticut. In other cases, disease spread may actually be the fastest alongside rivers, essentially increasing habitat connectivity from the parasite perspective (Russell *et al.* 2004; Smith *et al.* 2005). Such an accelerating effect of rivers was seen, for example, during the initial spread of myxoma virus among feral rabbits in Australia (Ratcliffe *et al.* 1952). What accounted for this river effect is not well understood. While earlier work attributed it to a higher density of mosquito vectors in riparian areas (Ratcliffe *et al.* 1952), subsequent data indicated that the rate of myxoma spread may not be related to vector abundance (Le Brereton 1953). Faster disease spread along rivers may be anticipated if host or vector species are specifically associated with riparian habitat. However, many animal species use riparian corridors specifically for dispersal (Harrison 1992). To the extent that regular patterns of animal dispersal also affect pathogen transmission, it is therefore conceivable that rivers play a more widespread role in facilitating disease spread in natural landscapes.

The distribution of rivers or streams will also have an obvious effect on the transmission dynamics of pathogens that are water-borne. The fungal root pathogen *Phytophthora lateralis*, for example, is dispersed in flowing water, which allows it to infect its host, a riparian tree species. On a landscape scale, this leads to predictable dynamics regarding the general direction of spread, because new infections require transmission from upstream sources (Jules *et al.* 2002). Interestingly, this directional component does not explain which trees are at risk at smaller spatial scales: within a site, the speed of invasion does not depend on distance to

already infected trees upstream but on other host characteristics such as age and distance from the stream (Kauffman & Jules 2006). This illustrates the importance of scale for evaluating which sources of heterogeneity significantly affect the overall dynamics and rates of spread. Similarly, the barrier effect of rivers on rabies spread discussed above is most obvious at the local (i.e. township) level and when considering monthly intervals. However, when calculating annual spread rates across the entire Mid-Atlantic region, the effect of rivers on the rate of spatial invasion largely disappears (Biek *et al.* in press).

Roads represent another form of linear landscape element that can affect disease spread by connecting disjunct habitat patches. In the just-mentioned tree pathogen *P. lateralis*, spores can travel in the mud that sticks to vehicle tyres and this source of infection was found to account for most cases in which new drainages became invaded. In addition, trees along streams that were not crossed by a road had a significantly lower probability of being infected (Jules *et al.* 2002). Since roads are often lined by specific types of vegetation, disease vector or reservoir species associated with these habitats may be able to disperse and increase their range along motorways. The rodent species acting as the main reservoir for the zoonotic Junin virus in Argentina, for example, appears frequently to live alongside roads (Mills *et al.* 1992), which may, therefore, allow the disease to increase its geographical range.

Birds are naturally less constrained in terms of their movement, and thus their ability to spread diseases, by the physical environment. Still, Hosseini *et al.* (2006) found that elevation had a limiting effect on the spread of *Mycoplasma gallisepticum*, an emerging avian pathogen of house finches in eastern North America, apparently reflecting a preference of the birds for habitats at lower altitudes. Seasonal movements of migratory birds are another reason why avian diseases may exhibit spatially heterogeneous patterns of spread. Spring and autumn migration had a profound effect in the case of the *M. gallisepticum* house finch system (Hosseini *et al.* 2006) and considerable research effort is currently directed at understanding how flight pathways of migratory birds can help to predict the global spread of the pathogenic H5N1 strain of avian influenza (Kilpatrick *et al.* 2006).

Certain landscape features may only play a seasonal role in infection dynamics. This can apply, for example, to localized resources that are only available for certain parts of the year. During those times, however, the probability of transmission may be greatly enhanced. Recent data documenting Ebola virus outbreaks among lowland gorilla populations strongly point towards transmission among social groups (Bermejo *et al.* 2006). This has been puzzling because infection requires close contact, which rarely occurs among different gorilla groups. Primatologists therefore suspect that seasonally fruiting trees, which are visited by many groups simultaneously, could represent 'transmission islands' for the virus (Caillaud *et al.* 2006). Bird feeders are thought to play a similar role for house finches becoming infected with *M. gallisepticum*, because contact among birds that is sufficiently close to allow
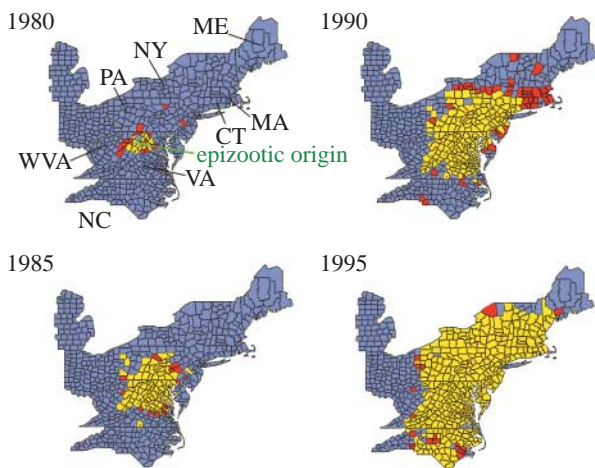
Figure 1. The spread of epizootic rabies among raccoons in the Mid-Atlantic region and northeastern United States from a focus (epizootic origin) at the Virginia (VA)/West Virginia (WVA) border illustrated at 5-year intervals from 1980 through 1995. Cells correspond to individual counties within states with violet corresponding to uninfected counties, yellow corresponding to already infected counties and red corresponding to counties that became infected during that year. State abbreviations are ME, Maine; MA, Massachusetts; NY, New York; CT, Connecticut; PA, Pennsylvania; and NC, North Carolina. Data were collected from state public health office assessments of the monthly cases of animal rabies reported annually to the Centers for Disease Control and Prevention.
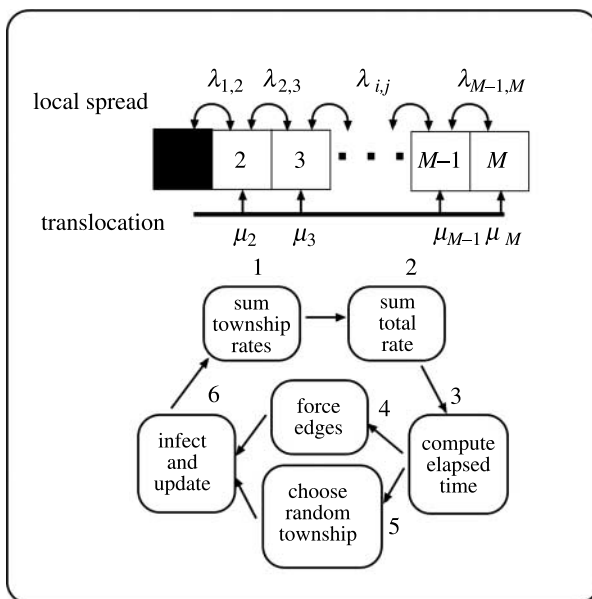

Figure 2. Schematic of the stochastic spatial simulator and the execution algorithm used to model the spatial dynamics of rabies virus spread. Each geo-political unit (e.g. township, county, city, etc.) is connected locally (λ_{ij}) and globally (μ). These transmission rates can be variables and determined by habitat and population characteristics (after Smith *et al.* 2002).

for transmission is otherwise rare (Dhondt *et al.* 2005). Given that localized resources lead to seasonal aggregation in many species (e.g. waterholes in arid systems, hibernation sites, etc.), the phenomenon may apply to a wide range of parasite–host systems.
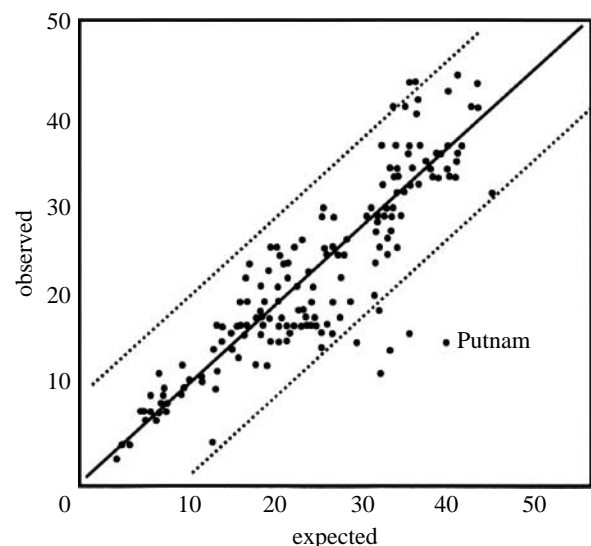

Figure 3. The data and output from the parameterized stochastic spatial simulator developed to predict the spatial spread of raccoon rabies across the state of Connecticut plotting the expected time to first appearance of rabies in raccoons based on stochastic simulation versus the observed time to first appearance of rabies across the 169 townships in Connecticut. Expected time to first appearance was established using the best-fit stochastic simulator and incorporated both heterogeneity in local transmission and long-distance translocation of rabies. Rivers induced a sevenfold reduction in rates of local transmission. Four outlier townships had observed times to first appearance of rabies significantly earlier than that predicted by the model. One township in particular, Putnam, was earlier than all others and is the site of a major trash incinerator for the east coast. Putnam may be experiencing considerable long-distance translocation of animals through the movement of trucks to the incinerator site (Smith *et al.* 2002).

3. EFFECTS OF HETEROGENEOUS LANDSCAPES ON THE POPULATION GENETIC STRUCTURE OF PARASITES

Despite a growing interest in landscape genetics, i.e. the ways in which geographical and environmental factors affect the population genetic structure of species (Manel *et al.* 2003), examples focusing on infectious organisms in this context are still limited. A number of recent studies have examined the evolutionary history of parasites at the intraspecies level but these studies are usually concerned with biogeographic patterns at larger spatial scales (Nieberding *et al.* 2004; Criscione & Blouin 2007). Even fewer studies have considered how the population genetic structure of parasites is influenced by the process of spatially heterogeneous spread. Recent advances in related areas of evolutionary research (Wegmann *et al.* 2006) point to some interesting possibilities in this regard.

Generally, any landscape feature that enhances or reduces the probability of transmission has the potential to also affect the spatial genetic structure of the pathogen. During the process of invasion, one could predict, for example, that transmission barriers act as random 'filters' on parasite genotypes, in that only a subset of them will be able to cross the barrier. Indeed,
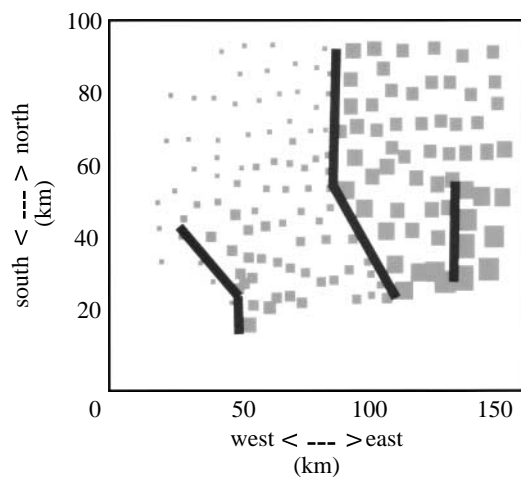
Figure 4. A schematic map of the differential between time to first appearance across townships in Connecticut when the epidemic was simulated with and without rivers. The size of each grey square corresponds to the difference between the time of first appearance at the country centroid of that location when simulations were run with and without the presence of three rivers. The three black lines correspond to the locations of the three major rivers in Connecticut (i.e. the Housatonic, Connecticut and Thames rivers). Results from the simulations suggest that a sevenfold reduction in local transmission across rivers leads to a 16-month delay in the expected appearance of rabies in the southeast corner of Connecticut. The expected delay is reduced to 11 months when long-distance translocation is added to the simulations (after Smith *et al.* 2002).

such a restriction in genetic diversity, followed by rapid expansion, was seen in raccoon rabies virus in Ohio that had breached a vaccine corridor (L. A. Real 2006, unpublished data). Until then, the vaccine corridor had halted the westward spread of the disease for several years and the data indicate that a single infected individual introducing the virus to the opposite side of the barrier probably caused the outbreak. Such events are comparable to genetic founder effects occurring during island colonization (Nieberding *et al.* 2006).

A similar phenomenon may explain the surprisingly low genetic divergence among all Ebolavirus Zaire isolates found during recent outbreaks in Gabon and the Republic of Congo (Walsh *et al.* 2005). All sequences from these outbreaks (2001–2003) could be traced back to a common ancestor that was found in 1996 near the town of Booue, just south of the Ogooue River, one of the largest waterways in the region. All previous outbreaks up to that point had been observed on the opposite side of that river (Lahm *et al.* 2007). Furthermore, timing and location of subsequent outbreaks, which took place several hundred kilometres further east, suggested that the virus had been spreading in that direction at a rate of approximately 50 km per year. The strength of the correlation between genetic and spatial distances was maximized when the putative pathway of viral spread was routed through Booue. Together, these results strongly point to a scenario in which the virus was able to cross the Ogooue River near Booue, causing a strong genetic bottleneck, followed by subsequent diversification as the virus invaded the region to the east (Walsh *et al.* 2005).

On the other end of the spectrum, habitat types associated with increased opportunities for transmission can leave their own characteristic genetic signatures, indicative of demographic expansion. Especially in RNA viruses, for which population dynamics and the accumulation of mutational changes take place at similar temporal scales, changes in population growth rates over the course of spatial invasion can be discerned from molecular sequence data using coalescent approaches (Pybus *et al.* 2000; Drummond *et al.* 2005). During the recent incursion of raccoon rabies virus into the Mid-Atlantic region, the highest velocities of viral spread were seen in the most urbanized areas that support some of the highest raccoon densities and also experienced the largest outbreaks (Childs *et al.* 2001). This demographic expansion was also detectable in viral sequence data, in that invasion of these areas coincided with the fastest rise in the number of infections, as estimated from the genealogical pattern of genetic diversification in the virus (Biek *et al.* in press). Considering these examples, it is possible that molecular data, given appropriate levels of sampling, could in fact be used to assess the relative permeability of different habitats and landscape elements to disease spread. Especially in combination with fine-grained spatial and temporal data, such approaches could make exciting contributions to our understanding of landscape epidemiology.

Landscape heterogeneities will affect the population genetic structure not only during invasion but also once a parasite has become endemic, i.e. once it has established itself within a geographical area. However, it may often remain difficult to discern how specific landscape elements influence the partitioning of genetic variation in space, given that the existence of spatial genetic structure may be strongly dependent on historical factors. In the case of rabies spread into raccoon populations in Ontario during the 1950s, rabies virus entered the southern Ontario peninsula almost simultaneously from two different directions, with each wave representing a genetically distinct lineage. The two waves met eventually and were brought to a mutual halt, presumably due to limited opportunities for spread into raccoon populations already affected by rabies and thus partly depleted of susceptibles. Even five decades later, this contact zone is still visible as a distinct boundary between the two viral clades, each representing the descendents of a different lineage of invaders (Nadin-Davis *et al.* 1999; Real *et al.* 2005; figure 5). The boundary approximately corresponds to the edge of the Canadian Shield, and thus a change in landscape physiognomy may be a significant organizer of this genetic landscape. However, some caution is called for since similar boundaries are often seen in many areas recently invaded by wildlife rabies and often appear to persist in the absence of any obvious landscape discontinuities (R. Biek & L. A. Real 2007, unpublished data).

Another example of historical processes, rather than landscape attributes, facilitating spatial genetic patterns involves a feline lentivirus that infects cougars (*Puma concolor*) as its only host (Biek *et al.* 2006). Despite cougar host populations being continuously distributed, highly mobile and without much genetic
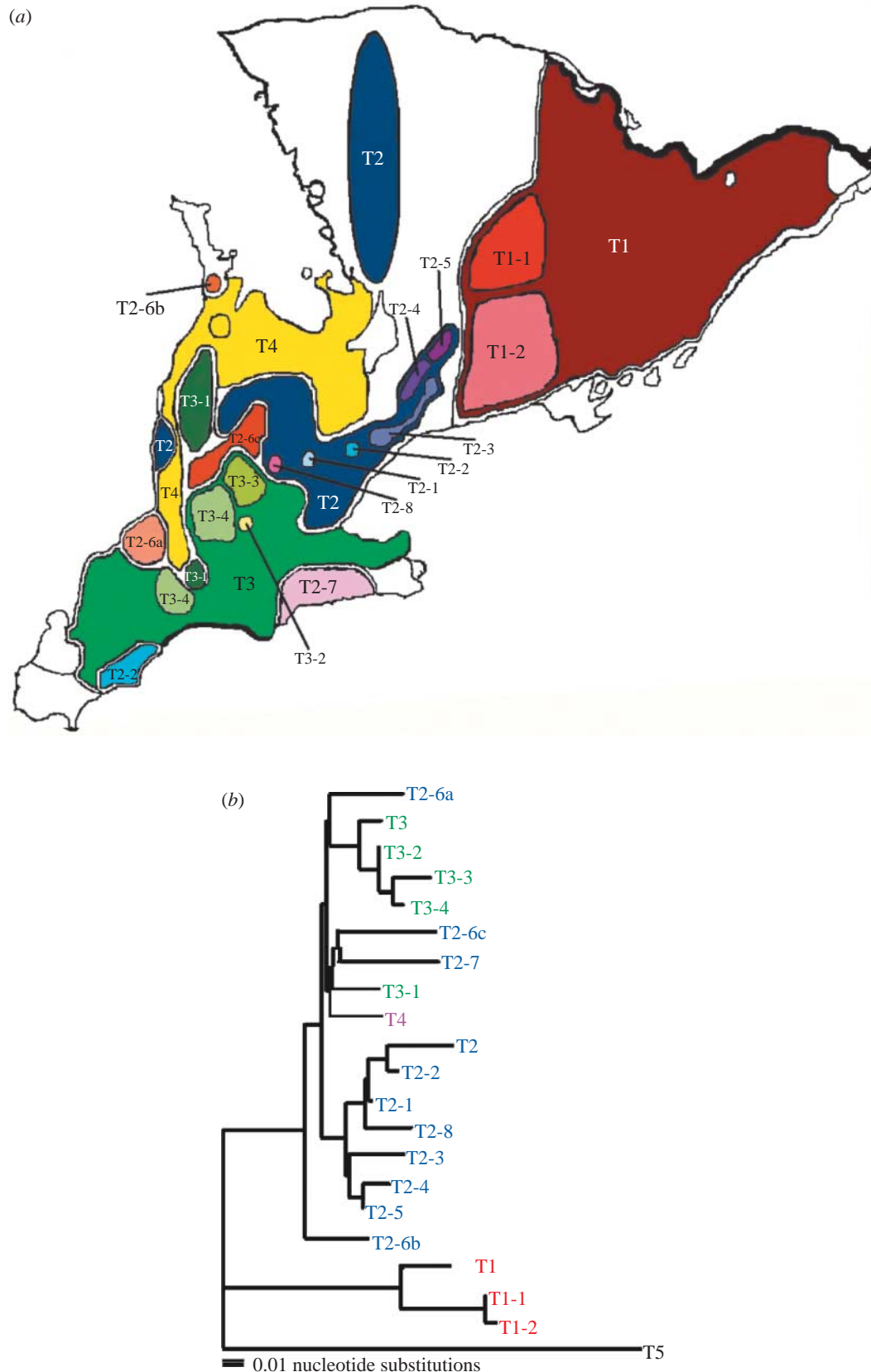
(a)

(b)

Figure 5. (a) Map of southern Ontario with a superimposed geographical cluster analysis of 20 different G-gene sequence types identified from 83 fox rabies virus variant samples with known geographical coordinates. (b) Maximum likelihood tree based on 1572 bp G-gene nucleotide sequence of fox rabies virus variant over southern Ontario (Real *et al.* 2005).

structure in a Rocky Mountain study area, viral genotypes isolated from cougars fell into distinct clades with strong spatial clustering (figure 6). Moreover, the genetic data provided evidence for a recent demographic

increase in viral populations as well as a positive relationship between the age of a clade ancestor and the size of the geographical area that clade occupies, suggesting that viral groups are currently expanding

their respective range. The idea of recent expansion was consistent with data showing that cougar populations had only recently started to rebound from a severe demographic bottleneck that presumably had also temporarily restricted the distribution of viral genotypes on the landscape (Biek *et al.* 2006).

The previous examples illustrate the challenge of separating the effect of the physical landscape from other factors, including temporal fluctuations of pathogen and host populations, when assessing how parasite populations are genetically structured in space. As a further complicating factor, spatial genetic structure can arise even in completely homogeneous landscapes as a product of spatial autocorrelation, especially if transmission occurs predominantly at the local scale. Under such circumstances, genetic and spatial distances will be positively correlated, resulting in a spatial genetic gradient generally referred to as isolation-by-distance. In fact, isolation-by-distance will often provide the appropriate null model against which any evidence for landscape genetic effects should be tested (Epperson 2003).

Genetic sequence data that permit the use of genealogical methods provide the opportunity to test for phylogeographic structure, meaning the existence of distinct genetic clades with little or no geographical overlap (Avise 2000). The assumption is that these boundaries between clade distributions do not occur at random locations but correspond to features in the landscape (e.g. rivers or mountain ranges) that significantly restrict gene flow. Unfortunately, just as the spatial clustering of genotypes mentioned before, spatial discontinuities in genealogies can emerge even without physical barriers to gene flow, making it difficult to determine to what extent phylogeographic patterns are really attributable to the landscape, especially if such interpretations are done *post hoc*. Simulation studies indicate that this problem particularly arises for populations of small size and with limited dispersal (Irwin 2002). This suggests that 'spontaneous' phylogeographic structure most probably arises in parasite systems where (i) the parasite's local effective population size is low, for example, because the fraction of infected hosts or individual parasites within a host that actually contribute to future infections is small (Criscione & Blouin 2005; Lloyd-Smith *et al.* 2005); (ii) the parasite has no life stages that remain infectious outside infected host, making it completely reliant on its host for dispersal; and (iii) host dispersal is limited to short distances (Criscione & Blouin 2005). Ironically, by increasing the effect of genetic drift acting at small spatial scales, these are the very same characteristics that also increase the chance of detecting barriers to parasite gene flow in the first place. For parasites that meet these criteria, evidence for phylogeographic structure should be examined very carefully and, as in any biogeographic study using genetics, data should ideally be derived from multiple independent loci. Since stochastic sorting events will affect the genealogy of each locus differently (Rosenberg & Nordborg 2002), congruent results for several loci provide strong support that a phylogeographic break indeed represents a zone across which gene flow is

limited. However, a fair number of parasites undergo asexual reproduction, which means that genetic data will essentially represent a single locus. In such cases, additional insights may be gained from examining molecular data from the host for genetic discontinuities in the suspected geographical areas (Nieberding *et al.* 2004; Criscione & Blouin 2007). In addition, it may be possible to find other supporting evidence that genetic structure is landscape-induced, for example, if the putative boundary also marks a significant change in disease prevalence.

Understanding the genetic structure of parasite populations on natural landscapes is important not only because it can reveal important aspects of disease ecology and epidemiology but also because it provides a prerequisite for local adaptation. Landscapes may affect the process of coevolution among parasites and hosts in two major ways. First, as outlined above, the physical environment can determine relative amounts of gene flow among populations. Theoretical work has demonstrated the profound effect of parasite and host gene flow on the process of local adaptation and the evolution of virulence (Boots & Sasaki 1999; Lively 1999; Gandon 2002). The landscape determines the levels of host gene flow both in terms of relative permeability to dispersal and in the relative number of dispersers produced as a function of local habitat quality. Second, spatial heterogeneity may come into play in the form of different environmental conditions acting as selective forces on host and parasite populations.

4. SOME APPROACHES TO MODELLING DISEASE DYNAMICS WITH PHYSICAL HETEROGENEITY

Our analysis of rabies epidemiology in eastern North America relied on the development of an explicit spatial model for disease dynamics that incorporated physical heterogeneity in the environment (e.g. Smith *et al.* 2002; Russel *et al.* 2004). While our approach used interactive networks, other theoreticians have exploited alternative model structures to examine the effects of physical heterogeneities on patterns of emergence and spread. Broadly speaking, model architectures fall into two alternatives: those models that incorporate space and heterogeneity explicitly (e.g. reaction–diffusion systems and spatially defined networks) versus those that treat space as an implicit function of population substructure but where the actual spatial coordinates are not defined (e.g. much of metapopulation theory applied to infectious diseases and almost all of the current work on networks, where nodes of the network are not spatially located).

4.1. Reaction–diffusion in heterogeneous environments

The earliest approaches to spatial modelling of infectious disease (both with and without heterogeneity) relied on extensions of the Fisher–Skellam reaction–diffusion equations (Fisher 1937; Skellam 1951). Noble (1974) used a diffusion model to explain the spread of bubonic plague through Europe during the 1347–1350

period of the Black Death using a modified form of the Kermack–McKendrick (1927) model

$$\frac{\partial S(x,t)}{\partial t} = D\frac{\partial^2 S}{\partial x^2} - \beta SI,$$

$$\frac{\partial I(x,t)}{\partial t} = D\frac{\partial^2 I}{\partial x^2} + \beta SI - \gamma I, \qquad (4.1)$$

where $S(x,t)$ and $I(x,t)$ are the densities of susceptible and infective people at spatial location x at time t, respectively; β is the transmission rate; γ is the death rate due to infection; and D is the diffusion coefficient that accounts for the migration and movement of individuals in space (Shigesada & Kawasaki 1997). In a series of elegant examples, Murray and co-workers (Murray *et al.* 1986; Murray & Seward 1992) and Shigesada & Kawasaki (1997) used reaction diffusion equations to model the spread of rabies in red fox hosts across Europe. Rabies emerged in Eastern Europe following World War II and spread westward through the 1980s. The westward expansion of rabies in foxes has largely been halted through the delivery of a highly effective oral vaccine (Jackson & Wunner 2002). The early spread of rabies and the consequences of emergence events beyond the control region have been modelled using

$$\frac{\partial S(x,t)}{\partial t} = D_S\frac{\partial^2 S}{\partial x^2} + (a-b)S - \mu SN - \beta SI,$$

$$\frac{\partial H(x,t)}{\partial t} = D_H\frac{\partial^2 H}{\partial x^2} + \beta SI - (b+\sigma+\mu N)H, \quad (4.2)$$

$$\frac{\partial I(x,t)}{\partial t} = D_I\frac{\partial^2 I}{\partial x^2} + \sigma H - (b+b_I+\mu N)I,$$

where the new term $H(x,t)$ corresponds to the density of exposed but not yet infectious foxes; $N(x,t)$ is the total population density; and the new parameters are a = birth rate of foxes, b = death rate, b_I = death rate of infectives, μ = intraspecific competition coefficient and σ = rate of onset of disease (incubation rate). What is the most interesting for our focus in this paper is the inclusion of variation in the diffusion coefficients. Each subclass of the population is indexed with a different movement pattern. Murray *et al.* (1986) and Murray & Seward (1992) treated $D_S = D_H \ll D_I$, i.e. the movement of infected animals was considered much greater than the movement of susceptible or incubating foxes. The movement of individual animals in equation (4.2) is assumed to occur across a uniform environment and what heterogeneity that exists in the system is the result of behavioural variations induced by disease. Murray *et al.* (1986) did incorporate heterogeneity into the landscape by constructing the spatial distribution of red fox population densities over the southern half of England (based on field data) and then carried out a large-scale computer simulation in which equation set (4.2) was solved in a two-dimensional space representing England's topography and geographical distribution of fox densities. As expected, their model showed differential rates of rabies expansion associated with the rapid movement of rabies across high-density areas.

Direct simulation is not the only method of incorporating spatial heterogeneity into disease dynamics on heterogeneous landscapes. Equation set (4.2) suggests an alternative general method for incorporating spatial heterogeneity into a reaction–diffusion framework. Shigesada *et al.* (1986, 1987) incorporate habitat heterogeneity within an explicit Fisher–Skellam model by assuming that the diffusion rate and population birth rate vary within different habitat patch types. They consider two patch types alternating in a one-dimensional spatial arrangement with the population undergoing dispersal and logistic growth. Their model corresponds to the population equation

$$\frac{\partial N(x,t)}{\partial t} = D(x)\frac{\partial^2 N}{\partial x^2} + \{\varepsilon(x) - \mu N\}N, \qquad (4.3)$$

and where the diffusion coefficient $D(x)$ and intrinsic growth rate $\varepsilon(x)$ are given by the periodic step functions defined by

$$D(x) = \begin{cases} d_1, \\ d_2, \end{cases} \quad \varepsilon(x) = \begin{cases} \varepsilon_1 & (\text{for } x_{2m} \leq x < x_{2m+1}), \\ \varepsilon_2 & (\text{for } x_{2m+1} \leq x < x_{2m+2}), \end{cases}$$

$$m = 0, \pm 1, \pm 2, \ldots,$$

$$(4.4)$$

where $x_0 = 0$, $x_i + l_i + 1$ $(i = 0, \pm 1, \pm 2, \ldots)$ and l_i is the width of the ith patch.

Unfortunately, it is very difficult to obtain general solutions to equation (4.3) when the patch widths, l_i, are arbitrary in value and even more difficult for multiple (more than 2) different diffusion coefficients. Shigesada & Kawasaki (1997) present some special cases where general solutions can be obtained. Nonetheless, for environments that are highly heterogeneous, other modelling structures will be more tractable.

4.2. Mixing matrices and optimal control

Many infectious diseases are not uniformly transmitted among different individuals in the population, but instead there is a significant variation in transmission rate within specific subpopulations within the larger population. For example, transmission rate variation within different subpopulations of the human population is common for many sexually transmitted diseases; for example, heterogeneous transmission of HIV often includes subpopulations representing heterosexuals, homosexuals and intravenous drug users (Heathcote 1996). The majority of these substructured models employ a 'mixing matrix' that characterizes the heterogeneity within the population and often these subgroups have (at least implicitly) a geographical component. Consider a larger population that is spatially subdivided. We can construct a mixing matrix such that the transmission rate between any two cells is a function of both the distance between the two cells and the environmental characteristics of each cell.

In Asano *et al.* (in press), we have used this approach to model the delivery of rabies vaccine to wildlife over a landscape partitioned into n geographically distributed subpopulations connected to each other through

Table 1. Parameter and state variable definitions for the spatially explicit raccoon rabies population dynamics model with vaccine control.

symbol	definition
a_{ij}	the rate of geographical movement of non-infected ones (susceptible and immune classes) from subpopulation i to subpopulation j
c_{ij}	the rate of geographical movement of infected ones from subpopulation i to subpopulation j
β_j	the rate of transmission in subpopulation i
μ_S, μ_I, μ_R	the mortality rate in each class: S, I, R
σ_i	the rate of vaccine bait distribution (control)
γ	the efficacy of vaccination distribution
S_i	the number of susceptibles in subpopulation i
I_i	the number of infected ones in subpopulation i
R_i	the number of individuals immune to the disease in subpopulation i

immigration and emigration (figure 7). Subpopulation i is divided into three classes: susceptibles, S_i; infectives, I_i; and a removed class, R_i, corresponding to those individuals that have become immune through vaccination. The spatial expansion of rabies is controlled through the delivery of an oral rabies vaccine (ORV) distributed in advance of the current wavefront of expansion (Hanlon & Rupprecht 1998), and we were particularly interested in modelling the optimal spatial distribution of ORV under the conditions of an emergency outbreak situation similar to what has recently occurred in northeast Ohio in the USA (Russell *et al.* 2005). The dynamics of the spatial ensemble are governed by

$$
\begin{aligned}
\frac{dS_i}{dt} &= -\beta_i S_i I_i - \gamma \sigma_i S_i + \sum_{j, j \neq i}^{n} a_{ji} S_j - \sum_{j, j \neq i}^{n} a_{ji} S_i - \mu_S S_i, \\
\frac{dI_i}{dt} &= \beta_i S_i I_i + \sum_{j, j \neq i}^{n} c_{ji} I_j - \sum_{j, j \neq i}^{n} c_{ij} I_i - \mu_I I_i, \\
\frac{dR_i}{dt} &= \gamma \sigma_i S_i + \sum_{j, j \neq i}^{n} a_{ji} R_j - \sum_{j, j \neq i}^{n} a_{ji} R_i - \mu_R R_i,
\end{aligned}
$$

(4.5)

where parameter values are defined as in table 1. There are two important features of this system pertinent to our discussion. The first is the structure of the set of movement parameters a_{ij} and c_{ij} and the second is the introduction of a spatially defined control set $U = \{\sigma_1, \sigma_2, \ldots, \sigma_n\}$. Depending on the habitat characteristics and geographical orientation/configuration of subpopulations, movement may not be symmetric, i.e. a_{ij} may not be the same as a_{ji}, and similarly for c_{ij} and c_{ji}. The specific values for movement are assumed to be inversely proportional to the distance between subpopulations i and j and are also defined by the particular pattern of environmental heterogeneity. For instance, figure 8 shows two examples of possible spatial configurations of four subpopulations. In figure 8a, subpopulation 1 is located equidistant from the other subpopulations 2, 3 and 4. In this case, the rates of geographical movement are the same across all subpopulations. In figure 8b, if distances vary, for example, with the distance between subpopulations 3 and 1 the largest, then the rate a_{13} is the smallest. In a similar fashion, if we have subpopulation classes defined by physical or habitat characteristics, these distinct

types can have definable effects on the movement rates that then combine with any distance effects. We used habitat differences, for instance, to define variation in local transmission rates in elucidating the effects of rivers on the spread of rabies (Smith *et al.* 2002). However, in that analysis, there was no explicit incorporation of geographical distance on rates of movement and transmission across neighbouring subpopulations. The inclusion of a control set U in the dynamics of spread opens the possibility for determining an optimal policy that guides the spatial distribution of control, in this case, the spatial distribution of the rate of vaccine delivery. An optimal policy might consist of minimizing the total number of infections produced during the course of an emergence and the total cost of the vaccination programme. Such a goal is expressed by forming the objective functional $J(\sigma)$, which is appropriately minimized, over space

$$
\text{minimize } J(\sigma) = \sum_{i=1}^{n} \int_0^T (I_i + \alpha \sigma_i^{\delta}) dt,
$$

where α and δ are weight factors in the cost of control. Asano *et al.* (in press) examine the general properties of this control problem and show how one can use Pontryagin's Maximum Principle (Pontryagin *et al.* 1962) to derive the necessary conditions for spatial optimization in a homogeneous environment where transmission among subpopulations is simply controlled by geographical distance. However, the technique should prove easily extendable to situations requiring the incorporation of physical features of the landscape.

4.3. Individual-based models and networks

Continued subdivision of the population into smaller and smaller geographical units ultimately leads to modelling the fate of individual agents rather than collections. Ecologists have long recognized that some aspects of population dynamics will require simulations at the individual level (Grimm & Railsback 2005). For example, Donalson & Nisbet (1999) used an agent-based model to examine the role of local predator–prey interactions and discrete time and birth processes on population persistence, both processes not captured by traditional Lotka–Volterra dynamics. The need for individual level analysis becomes increasingly apparent
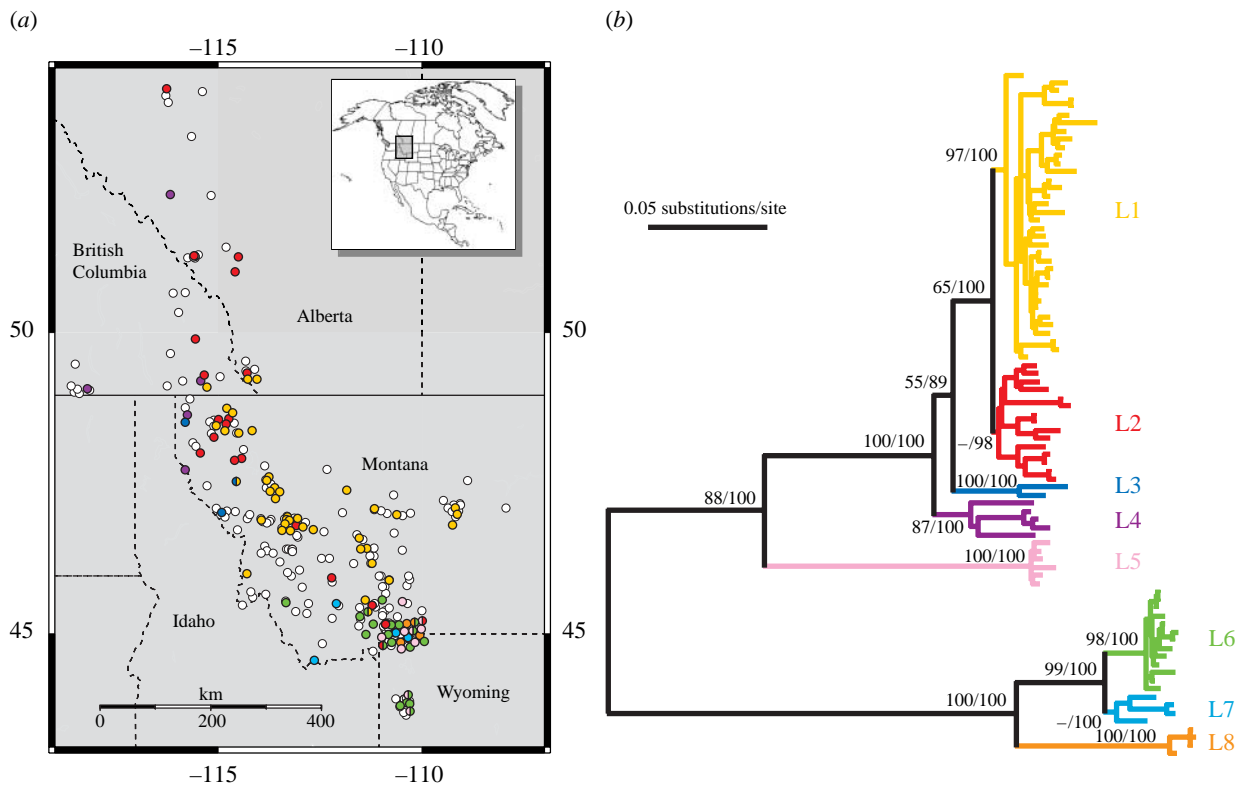
Figure 6. Genetic diversity of a feline lentivirus in its Rocky Mountain cougar host and spatial distribution of viral groups. (*a*) Origin of infected (colours as in *b*) and uninfected samples (white circles). Area covered by samples in Montana roughly reflects distribution of cougar habitat (forest). (*b*) Phylogeny of the virus based on concatenated sequence data from two genes. L1 through L8 represent distinct viral lineages with greater than 5% divergence (Biek *et al.* 2006).

as the landscape becomes increasingly heterogeneous. For highly variable landscapes, the characteristics of individuals (such as genotypic susceptibility and resistance, social memberships, fecundity and survivorship rates, etc.) may become highly idiosyncratic and this variation may best be captured through explicit attention to the individual agent. Often this variation interacts with the physical and geographical structure of the landscape, for example, when temperature and soil conditions explicitly select for specific genotypes in plant populations that may be subject to pathogenic attack. There are currently two dominant approaches to modelling at the level of individual agents within specific spatial contexts.

Individual-based models have been used to simulate spatial dynamics of some infectious diseases. For example, Haydon *et al.* (2006) followed such an approach to develop spatially explicit vaccination strategies for a population of the highly endangered Ethiopian wolf. This population had repeatedly suffered from outbreaks of rabies virus, which had spilled over from infected domestic dogs in the surrounding villages. Detailed data on outbreak size as well as on the sizes and spatial configurations of wolf packs were available from long-term field studies. These data permitted the parameterization of a demographically stochastic SEIR model, distinguishing classes of susceptible, exposed, infectious and recovered/vaccinated individuals. Simulation results yielded spatially explicit estimates of the reproductive number of rabies (R_0) at the level of individual packs and suggested that
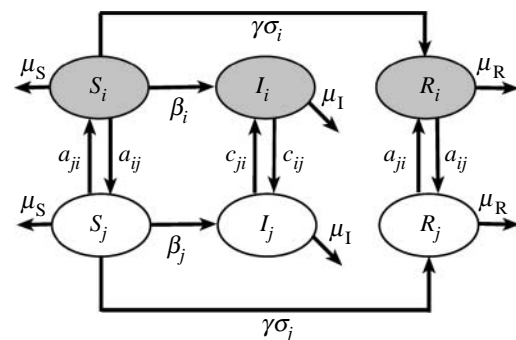

Figure 7. Schematic flow for rabies dynamics over a spatially distributed set of linked *n* subpopulations where each subpopulation *i* contains susceptibles (S_i), infectious (I_i) and removed (R_i) individuals. Removed individuals correspond to susceptibles that have become immune through the deliver of oral vaccine (Asano *et al.* in press).

appropriate temporal and spatial windows over which vaccination of wolves, even at low coverage, could keep epidemic sizes to a minimum.

The difficulty (and in no small measure the intellectual dissatisfaction) associated with individual-based approaches is their lack of generalization. The models are, more or less, an engineering approach to understanding disease phenomena—rich in detail, very realistic and predictive, but not general. An alternative to completely individual-based modelling is the new emerging interest in contact networks and graph-theoretic models of the disease process (Keeling & Eames 2005; Meyers *et al.* 2005, 2006) that capture
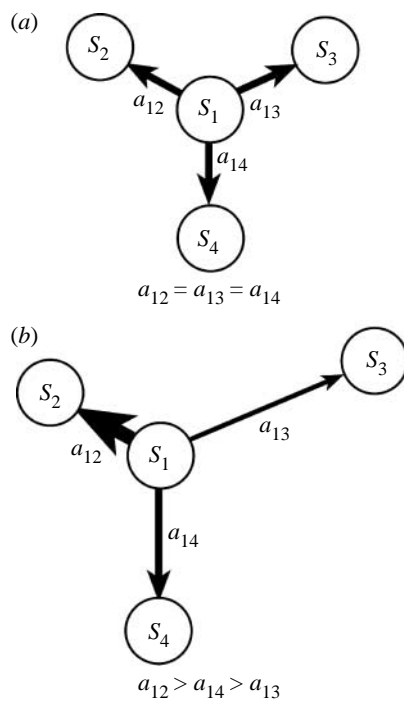
Figure 8. Schematic of the rates of geographical movement a_{ij} between subpopulations. (*a*) Set of movement relations that corresponds to equidistant subpopulations experiencing equal rates of movement. (*b*) Set of movement relations that corresponds to subpopulations which are variably distant from each other and where movement between subpopulations is inversely proportional to distance between subpopulations. (*a*) $a_{12} = a_{13} = a_{14}$; (*b*) $a_{12} > a_{14} > a_{13}$.

some features of agent-based approaches, while still producing general broad theoretical results. Networks are constructed from a defined set of individuals (nodes) that can be of different types (say, susceptible, infected and resistant individuals) but rather than assumed random mixing (as in the usual SIR model) are constrained in interactions specified by the set of connections among the nodes of the graph (figure 9). The set of connection can be specific to the properties of the individuals or to their spatial location. Networks can be both spatially explicit (where the metric distance between nodes effect contact pattern) and spatially implicit (where only the overall contact topology is of interest). The standard features of traditional SIR dynamics (e.g. basic reproductive number, herd immunity and velocity of spatial propagation) can be encapsulated within network models (Meyers *et al.* 2005, 2006). However, most of these models do not consider the landscape characteristics of the environments upon which the contact network is constructed, though it is possible to do so. For example, nodes could be characterized not only by their disease state, but also by the habitat in which they reside. Also, the strength of connections among particular pairs of nodes could be affected by the landscape within which contacts between these individuals takes place. The inclusion of landscape heterogeneity into network models is, undoubtedly, an area for future development within this emerging approach to disease modelling.
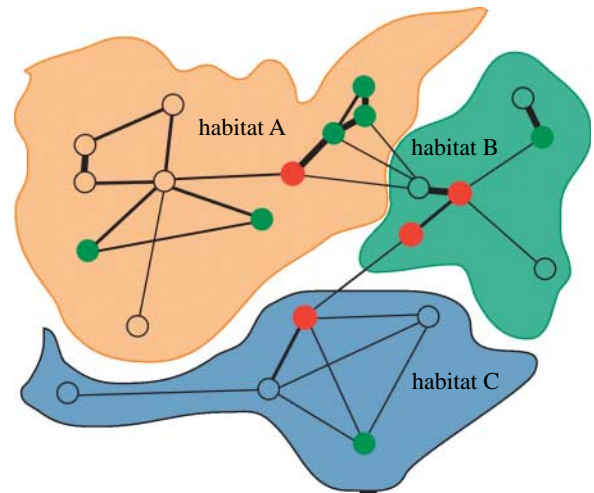

Figure 9. A schematic of a contact network among susceptible (open circles), infectious (red circles) and recovered/removed (green circles) distributed over three habitat types. Note that the contact rates/probabilities are functions of distance between individuals and habitat type. The wider connections correspond to higher contact rates. Also, contact rates may be influenced by the existence of a 'contact bridge' across landscapes, as might occur between habitat A and B.

5. CONCLUSION AND AREAS FOR FUTURE RESEARCH

The physical landscape clearly influences both the genetic structure and the spatial dynamics of host–pathogen interactions. That it does is both a benefit and a complication. Our ultimate goal in any modelling activity should be to construct predictive theories of when and where infectious diseases will occur and how their dynamics will change under the influence of both evolutionary and ecological transformations. Aspects of the physical environment, in many cases, must be included if we are to make accurate and helpful predictions. Consequently, the physical environment is a complication and we must add these complications to theory. However, from a practical perspective, the physical environment is often easily measured. Topographic databases have been constructed for many regions of the world. Major rivers, mountain ranges, valleys and vegetation types have been mapped and are easily accessed. If physical aspects of the environment are strong drivers in channelling ecological and evolutionary dynamics, then we can access these readily available databases to help generate timely and (one hopes) useful predictions. We exploited this connection between the physical environment and underlying population processes in making predictions about rabies spread in North America. Much of our early modelling activity was directed at ascertaining how much of the dynamics of spread could be encapsulated by simple physical environmental variables that act as surrogate measures for population attributes. The population biological properties of raccoons—for example, population densities, individual movements and contact rates—are extremely difficult to measure. However, topographic features already in analysable form are easily accessed from public, and often even online, sources. We are optimistic about our

ability to substitute environmental measures for population processes of other infectious diseases since much of the dynamics of the spread of rabies was accurately predicted simply using physical landscape heterogeneities as a surrogate for more complicated population dynamics approaches. At the same time, we need to understand how these physical heterogeneities actually influence population processes that support their use as surrogate variables.

The literature on spatial population dynamics abounds with examples where the endogenous, truly contagious processes (i.e. those processes dependent on individual dispersal characteristics, social interactions and contact patterns) may generate spatial aggregates across the landscape. Less attention has focused on the exogenous, apparently contagious processes that generate spatial aggregation through the intervention of physical heterogeneities in the habitat that essentially act as a filter on the spatial organization and movement of individuals across the landscape. We have highlighted the importance of the physical characteristics of the environment in this filtering process since they are often underappreciated. For example, models of HIV transmission often incorporate population heterogeneities due to social interactions such as occur at shooting galleries. At the same time, these shooting galleries often occur at spatial locations dictated by the external characteristics of the environment (e.g. neglected areas of the city versus suburbia). As another example, the environment may determine the location of individuals of particular genotypes due to selection (e.g. heat tolerance or resistance to desiccation). Those genotypes may also exhibit different forms of resistance or susceptibility to pathogens. So, clusters of resistance or susceptibility might arise due to the underlying structure of the environmental landscape. Yet once established, the pattern of transmission may simply reflect the dispersal and contact patterns among extant individuals. Thus, true and apparent (endogenous versus exogenous) forces may themselves interact and resulting spatial patterns will invariably be the consequence of the (often subtle) interactions between multiple exogenous and endogenous processes many of which we are only beginning to attend to.

In closing, we suggest a number of research questions directed at establishing the linkage between environmental heterogeneity and host–pathogen dynamics. These include the following.

— How does seasonality interact with and influence the formation of spatial heterogeneities; for example, the formation of seasonal transmission islands where hosts gather around seasonally scarce resources leading to a temporally and spatially restricted increase in the transmission rate?
— What is the interaction between host–parasite evolutionary and ecological dynamics and how should we explicitly combine ecological and genomic information into population models? What new methodologies need to be developed to better detect genetic and ecological interactions across heterogeneous landscapes? Despite the increasing ease of obtaining genetic data, relatively few attempts have

been made to incorporate this source of information into spatial disease models, particularly in a quantitative fashion.
— Most laboratory experimental systems rely on homogeneous conditions. What are the most appropriate laboratory experimental systems to explore the role of environmental heterogeneity on disease dynamics and how should such heterogeneous microcosms be constructed? How could microbial laboratory systems, in which many relevant questions in ecology and evolution have already been successfully addressed (Jessup *et al.* 2004; Kassen & Rainey 2004), be exploited in this context? Are there a specific set of issues that are particularly amenable to experimental analysis, e.g. in the same manner as the way in which the evolution of antimicrobial resistance has been experimentally examined?
— As in the case with rabies where rivers have a significant effect at the scale of townships but may disappear at a larger regional scale, how do we determine within natural environments the appropriate scale to assess the impact of physical heterogeneities?
— How are the relative contributions of physical heterogeneities that lead to increased levels of isolation among subpopulations counterbalanced by heterogeneities associated with increasing connectivity on landscapes?

We realize that this list is a partial one. Nonetheless, answers to any of these questions will require extensive reformulations of existing theory and the development of broad research collaborations that will undoubtedly lead to an increased capacity for predicting the dynamics of diseases within their real-world contexts.

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