Chapter 9
Integrating Landscape Hierarchies in the Discovery and Modeling of Ecological Drivers of Zoonotically Transmitted Disease from Wildlife

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Abstract Changes in landscape and land use can drive the emergence of zoonoses, and hence, there has been great interest in understanding how land cover change and the cascade of ecological effect associated with it are associated with emerging infectious diseases. In this chapter, we review how a spatially hierarchical approach can be used to guide research into the links between landscape properties and zoonotic diseases. Methodological advances have played a role in the revival of landscape epidemiology and we introduce the role of methodologies such as geospatial analysis and mathematical modeling. Importantly, we discuss cross-scale analysis and how this would provide a richer perspective of the ecology of zoonotic diseases. Finally, we will provide an overview of how hierarchical research strategies and modeling might be generally used in analyses of infectious zoonoses originating in wildlife.

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9.1 Introduction

Zoonotic diseases, or zoonoses, are infectious diseases transmitted to humans from animals and may be bacterial, viral, or parasitic in origin. Approximately 58% of the pathogens associated with infectious diseases in humans have originated through spillover from wildlife—e.g., ebolaviruses, hantaviruses, coronaviruses, henipaviruses (Jones et al. 2008; Lloyd-Smith et al. 2009; Smith et al. 2014; Woolhouse and Gowtage-Sequeria 2005). Since 1980, zoonotic pathogens represent the bulk of the outbreaks in human populations in both number (87% versus 13% by vector-borne pathogens) and diversity (Smith et al. 2014). The recently reported increase in zoonoses has been attributed to a variety of reasons, although a major driver is changes in land use resulting from the increased demands of human populations on the natural environment through agriculture intensification and deforestation (Jones et al. 2013; Woolhouse and Gowtage-Sequeria 2005). Land alteration for food production, broadly defined to include both agriculture and pastoral activities, has produced profound changes in the type and structure of the earth’s vegetation cover. It has also altered the way humans interact with their environment, for example, in some geographical areas suppressing wildlife-human interaction (e.g., contact with large predators common among hunter-gathers) and instead favoring contact between humans and peridomestic species such as rodents, which are common reservoirs for many zoonotic pathogens. Numerous examples of emergent zoonoses have often accompanied land clearance, and hence, there has been great interest in understanding how land cover change and the cascade of ecological effects associated with it are ecologically associated with emerging infectious diseases (McFarlane et al. 2013; Woolhouse and Gowtage-Sequeria 2005).

A persistent question in modeling of pathogen emergence is what is the spatial scale at which these processes occur? How do we measure and integrate the impact of processes that occur at varying and nested spatial scales that result in the observed disease distribution (Watts et al. 2005)? For example, climate (which can vary in scale from local to continental) and landscape are each associated with disease patterns and have been cited as factors in zoonotic disease outbreaks. Land cover change and land-use intensification often occurs at finer scales than climate and can thus be thought of as nested within the climate system. At still finer scales, population dynamics and habitat interactions of the pathogen and its reservoir communities (and, indeed, with the human populations vulnerable to disease transmissions from these communities) occur within the climate and landscape scales and are influenced, but not necessarily determined, by them. This hierarchical nesting (Fig. 9.1) of these processes complicates the overall study and modeling of the spillover and transmission dynamics of wildlife pathogens to human populations. However, there are existing bodies of theory which can help shed light on these processes. Hence, we review some of these conceptual ideas, focusing especially on landscape epidemiology, a body of theory first developed in the 1930s and more recently updated to include modern tools and techniques for studying both disease and environmental process (Ostfeld et al. 2005), and hierarchy theory, a framework which incorporates the idea of multiple, nested spatial scales (Allen and Starr 1982).
In the following, we will review how a spatially hierarchical approach can be used to guide research into the links between landscape properties and zoonotic diseases. This will show how landscape concepts have been used to analyze the occurrence and spatial patterning of zoonotic diseases and how many of these studies are being conducted at particular spatial scales. This review will be followed by an illustration of how an integrated, cross-scale analysis might be employed to gain a deeper understanding of the ecology of zoonotic diseases, using an example from our own research. As earlier noted, methodological advances have played a role in the revival of landscape epidemiology. We will therefore discuss the role of methodologies such as geospatial analysis and mathematical modeling—again using examples drawn from our current research. We will show how cross-scale analysis might be employed to gain a deeper understanding of the ecology of zoonotic diseases. Finally, we will provide an overview of how hierarchical research strategies and modeling might be generally used in analyses of infectious zoonoses originating in wildlife.

9.2 Landscape Epidemiology and Ecology

Landscape epidemiology is the study of spatial patterns of disease and disease risk arising from underlying environmental causes. The fundamental concepts of landscape epidemiology, first proposed by Evgeniĭ Pavlovskiĭ, stem from the idea that the spatial occurrence of disease could be understood by studying landscape and environmental factors associated with the disease (Pavlovskiĭ 1966). Pavlovskiĭ’s ideas have undergone a revival, stimulated in part by widespread availability of geospatial data, analysis tools, and models. In particular, satellite remote sensing data analyzed within a geographic information systems (GIS) framework has equipped landscape epidemiologists with a powerful suite of tools for analyzing environmental patterns associated with disease occurrence. Landscape epidemiology has also benefited from the theoretical perspective of landscape ecology, another relatively new discipline that attempts to understand the relationship between spatial pattern and ecological process (Meentemeyer et al. 2012). For example, landscape
epidemiologists have made use of ecological concepts such as fragmentation to analyze disease vectors (Brownstein et al. 2005; Reisen 2010). One aspect of landscape ecology that remains relatively unexplored in infectious disease applications is the concept of spatial hierarchy.

### 9.2.1 Hierarchy Theory

Hierarchy in ecology is a multifaceted theory incorporating elements of nonlinear dynamics and complexity; for a comprehensive treatment of hierarchy theory, see Allen and Starr (1982). The fundamental concept of hierarchy theory is that processes occurring at finer scales (i.e., “lower” in the spatial hierarchy) are constrained by processes at higher levels. Hierarchical levels can also be distinguished by the rates at which ecological processes occur—faster at finer scales, slower at coarser ones.

Hierarchy theory in ecology arose as a response to the need for a rigorous method of handling middle-number systems, that is, systems whose components are too few to treat statistically but too many to address with classical Newtonian mathematics. Hierarchy provides a framework by which these middle number systems can be decomposed into a series of manageable units, whose environmental drivers can be characterized by the scale (and thus the rate) at which they occur. Such a framework is amenable to the study of landscape epidemiology, since the linkages between environmental factors and disease are often multivariate, nonlinear, and not confined to a specific spatial scale.

Spatial scale is a crucial aspect of hierarchy theory. Any discussion of the relationship between ecological process and scale therefore must first define how the term is used and to what characteristic dimensions these terms apply. These definitions are complicated by the number of ways that the term “scale” is used. Scale is frequently referred to by descriptive adjectives such as “large” or “small,” which Meentemeyer (1989) noted can have opposing meaning depending on whether one is referring to cartographic scale (where small scale refers to less spatial detail) or ecological scale, where smaller scale equates to smaller spatial area and greater detail. Ecologists generally distinguish between the grain and extent of a process, where extent refers to the area over which a process occurs, and grain denotes the smallest resolvable component of the process. Typically, grain can be described as either “fine,” indicating small resolvable elements, or “coarse,” indicating larger elements. Thus, we might characterize the scale process like tropical deforestation as occurring at relatively large extent, because a large area is affected, but at relatively fine grain, because the individual deforested units can be quite small. Csillag et al. (2000) argue that for ecological uses of scale, it is preferable to adopt specific terminology to distinguish between extent and grain. In hierarchy theory, spatial extent is probably the more commonly used sense of scale (Jenerette and Wu 2000). In describing spatial hierarchies, it is often useful to apply descriptive names to realms of scale. Terms such as “global,” “continental,” “regional,” and “local” are often used, although the precise areas referred to often vary. For our review of hierarchy in infectious disease analysis, we will operationally define continental scale as areas exceeding $10^6$ km$^2$, regional scales as ranging from $10^3$ km$^2$–$10^6$ km$^2$, etc.
local scale from $10^1$–$10^3$ km$^2$, and microscale <$10^1$ km$^2$. The lower end of the microscale represents the general size range of a small rodent’s world.

Landscape analyses across spatial scale frequently use remote sensing data (Kitron et al. 2006; Wu 1999). Currently, imagery is available from an array of orbital sensors with widely varying spatial, temporal, and spectral resolutions (Table 9.1). Grain size (or resolution, as it is more commonly termed in remote sensing) is an engineered property of these sensors, dependent on the optical characteristics of the sensor and orbital characteristics of the platform. Theoretically,

| Instrument          | Platform          | Spatial resolution (m) | Notes                                      |
|---------------------|-------------------|------------------------|--------------------------------------------|
| Pleiades 1A         | Pleiades          | 2.0 m (VNIR) 0.5 m (PAN) | Available 2011–Present                     |
| Worldview           | Worldview 1–4     | 1.41–1.84 (VNIR) 0.31m–0.46 m (PAN) | Resolution is at nadir. Finer resolution sensor on WV-3 and -4. Available 2007–present |
| GeoEye-1            | GeoEye            | 1.84 m (VNIR) 0.46 (PAN) | Available 2008–present Resolution is at nadir value |
| QuickBird           | QuickBird         | 2.63 (VNIR) 0.73 (PAN)  | Available 2001–2015                         |
| IKONOS              | IKONOS            | 3.2 (VNIR) 0.82 (PAN)   | Available 2007–2105                         |
| HRV                 | SPOT 1–3          | 20 m (VNIR) 10 m (PAN)  | Available 1986–1997                         |
| HRVIR               | SPOT 4–5          | 20m (VNIR, SWIR) 10 m (Pan) | Available 1998–2015                        |
| Vegetation          | SPOT 4–5          | 1000 m                  | Produces a vegetation index (NDVI) product |
| Azersky             | SPOT 6–7          | 6 m (VNIR, SWIR) 1.5 m (PAN) | Available 2012–present                     |
| Multispectral scanner (MSS) | Landsat 1–5 | 79 m                     | Available 1972–1999                         |
| Thematic Mapper/ Enhanced Thematic Mapper + (TM/ETM+) | Landsat 4,5,7 | 30 m (VNIR, SWIR) 120 m (TIR) 20 m (Pan) | Available 1984–2013 (ETM+ experienced partial failure in 1999) |
| OLI/TIRS            | Landsat 8         | 30 m (VNIR, SWIR) 100 m (TIR) 15 m (Pan) | Available 2013–present                     |
| LISS                | IRS 1C/1D         | 23.5 m (VNIR, SWIR) 7.5 PAN | Available 2003–present                     |
| Sentinel-2          | Sentinel-2        | 10 m (VNIR) 20 m (SWIR)  | Available 2015–present                     |
| Terra/Aqua          | MODIS             | 250 m (Red, NIR 500 m (VNIR, SWIR) 1000 m (VNIR, SWIR, TIR) | Available 1999–present                     |
| AVHRR               | NOAA polar orbiters | 1000 m (VNIR, TIR)     | Available 1979–present                     |
there are no limitations to the extent of any of these systems, although practical limitations (particularly cost of data acquisition) dictate a rough correspondence between extent and resolution. Thus, the extents listed in Table 9.1 are based on these practical limitations. The variety of remote sensor data available has certainly facilitated hierarchical landscape analysis, but in some sense, it has also imposed limitations. Each remote sensor represents a “window” through which ecological process at some combination of grain size and extent can be observed. These limitations also extend to the range of spectral wavelengths each sensor can detect and the number and width of bands in which these wavelengths are detected. Combining these discrete views into an integrated picture is a central challenge for hierarchical analysis of infectious disease processes.

9.3 Landscape and Zoonotic Disease: A Selected Review of Literature

There is a large body of work relating infectious disease to environmental factors. Most of these studies have concentrated on a single class of causative factor operating over a characteristic spatial scale. In the following, we will briefly review several examples which represent different classes of landscape factors that have been shown to impact zoonotic viral emergence. Since our intent is to show how landscape spatial hierarchies influence disease processes, we will concentrate on examples that show the influence of landscape and land cover processes at various spatial scales, using the concept and terminology of scale developed in the previous section.

For convenience, we will group the literature reviewed here into two categories. First, we will review the relationship between land cover disturbance (including anthropogenic and natural disturbance) and zoonotic disease emergence. Included in this category are causes due to landscape structure, including natural landscape barriers, land cover change and disturbance, and fragmentation. This category also includes disturbance due to agricultural practices. The second class of landscape impacts that we will review are climate-driven landscape changes, which include climate-influenced changes in vegetation phenology patterns as well as persistent or transient superficial changes such as flooding. Processes contained within these two categories are not exclusive; however we will review them based on their predominant process.

9.3.1 Disturbance-Driven Landscape Change

Landscape structure refers to the pattern and arrangement of habitats on the Earth’s surface. Like all landscape variables, structure is complex. It varies with scale and per organism. The same landscape might be structurally very different for birds, small mammals such as rodents, and larger animals, and since zoonotic disease
reservoirs vary in their body size and habitat, structural effects on disease also vary. Structure can arise naturally due to topographic, edaphic meaning related to the soil, or climatic conditions, as well as through human landscape alteration. Both types of structural changes can be relevant to disease processes. Landscape structure has been related to zoonotic disease at a variety of spatial scales. At regional scale, Russell et al. (2006) show how natural landscape barriers such as rivers and preferred habitat can limit rabies spread by raccoons and be used to manage wildlife through vaccination efforts. Smith et al. (2002) used landscape heterogeneity as a predictor of the spread of rabies. Langlois et al. (2001) showed that the distribution of hantavirus-bearing rodents in North America was influenced by landscape fragmentation. Their analysis was unusual in that the extent of the study was continental, but the grain size was local (≈1 km). Estrada-Peña and Oteo (1991) showed that landscape structure, particularly landscape connectivity, showed a strong influence on the abundance of Lyme disease vectors in Spain.

Land cover changes are known to affect zoonotic diseases through controls on the population dynamics of reservoir species (especially wild mammals) as well as disease vectors (Patz et al. 2008). Giraudoux et al. (2003) used regional-scale land cover changes in France and China to show how host mammal communities affect transmission dynamics of the endoparasite Echinococcus multilocularis. Using the ROMPA (ratio of optimal to marginal patch area) hypothesis of Lidicker and others, it has been shown that regional-scale landscape dynamics of intermediate host species can in turn affect parasite egg survival and transmission (Lidicker 1995). The Giraudoux et al. (2003) study also considered the role of landscape change on establishing minimum thresholds, which they termed “filters” or “screens” of suitability for disease transfer.

Agriculture practices led to the Nipah virus outbreak in Malaysia (Epstein et al. 2006; Pulliam et al. 2012). Using a combination of field, laboratory, and modeling approaches, these efforts have supported the hypothesis that emergences of viruses such as Nipah are due to ecological and not evolutionary drivers. These findings underscore the importance of having multidisciplinary teams work together to build predictive models for discovery of the relationships between anthropogenic environmental change and the transmission or spillover of infectious agents.

### 9.3.2 Climate-Driven Landscape Change

Climate-driven landscape change in this context refers to the effect of atmospheric processes (most notably precipitation) on the habitat of zoonotic host organisms. Variations in rainfall magnitude and frequency have notable effects on vegetation phenology, causing variations in surface greenness that can be tracked using remote-sensing instruments (De Beurs and Henebry 2004; Reed et al. 2009). The emergence of several zoonotic diseases including hantavirus pulmonary syndrome (HPS) (Yates et al. 2002), Argentine hemorrhagic fever (Simone et al. 2010), and Bolivian hemorrhagic fever (Kilgore et al. 1995) can be clearly linked to landscape.
Several studies have linked climate-driven changes to patterns of disease occurrence at different spatial scales. Two groups have evaluated the relationship between temporal patterns of Normalized Difference Vegetation Index (NDVI) and occurrence of Ebola virus in West Africa (Pinzon et al. 2004; Tucker et al. 2002). They found that NDVI trajectories showed distinctive “trigger events” prior to occurrences of the disease in humans and apes, which they hypothesized might be used to forecast conditions conducive to outbreaks of Ebola hemorrhagic fever. The remotely sensed data for this analysis came from the NOAA-AVHRR sensor, with continental spatial extent and observation grain size (pixel resolution) of 1 km$^2$. The observed NDVI trajectories were related to precipitation patterns, reinforcing the link between climate and disease occurrence. Estrada-Peña and Oteo (1991) and Estrada-Peña et al. (2006) used coarse resolution vegetation index data to model and predict the continental-scale relationship between climate-driven landscape change and Lyme disease. Again, the resolution and extent of this study were consistent with the idea that climate constrains disease processes at higher levels in the spatial hierarchy. At finer spatial scales, Glass et al. (2000) used patterns of reflectance in Landsat Thematic Mapper (TM) data to statistically model the presence of HPS in the Southwestern United States. At this spatial scale, the spectral response of the surface incorporates climatic factors (especially antecedent precipitation) but also integrates structural and compositional factors of the vegetation canopy itself. Models based on these techniques have shown some utility for predicting hantavirus cases (Glass et al. 2002).

### 9.4 Hierarchical Analysis of an Emergent Zoonosis: An Example

One of the important advantages of a hierarchical approach is that it allows a multifactorial explanation for the occurrence of the infection and disease. The environmental, landscape, and climatic processes each contribute to processes that may alter species interactions within their habitat. These extrinsic factors can alter the reservoir population dynamics, drive extinction, and affect maintenance (persistence) of the microorganism. Essentially, these factors can create constraints within their spatial scale and across scales. In this section, we explore an example of hierarchical observation that can be used in conjunction with modeling to test hypotheses regarding the effects of environment, landscape, and climate upon zoonotic pathogen distribution. For this we draw upon our work and others in the study of *Hantavirus* with a focus on South America (Jonsson et al. 2010; Palma et al. 2012).
Hierachy theory suggests that processes at coarser grain also occur over longer time frames and can often be assumed to be static with respect to finer-scale processes. The phylogeographical patterns of South American hantaviruses within the Southern Cone (“El Cono Sur,” a subcontinental region roughly defined as consisting of the country Argentina, often including Chile, plus sometimes considered to include Uruguay and Paraguay) mapped with environment at the coarsest spatial scales (Chu et al. 2006). In other words, the phylogenetic clades of hantaviruses from the Southern Cone of South America appear tied to coherent spatial patterns consistent with subcontinental-scale biogeographic features such as the major biomes (Chu et al. 2006). In Fig. 9.2, the locations of strains from three major subclades of South American hantaviruses are shown in the context of the major biomes based on the World Wildlife Fund terrestrial ecoregions data (Olson et al. 2001). For example, we find members from one subclade (i.e., Laguna Negra, Río Mamoré, and Alto Paraná viruses) carried by rodent reservoirs that span the tropical grass and shrubland and dry broadleaf forest areas along the western, central regions of South America (Chu et al. 2006; Johnson et al. 1997; Richter et al. 2010; Yahnke et al. 2001). In contrast, a second subclade of rodents that harbor Jabora, Maporal, and Necocli hantaviruses inhabit mainly the moist broadleaf forest biome stretching from Venezuela and Colombia into Paraguay (Chu et al. 2009; de Oliveira et al. 2011; Fulhorst et al. 2004; Londoño et al. 2011). Knowing the extent of prevalence of these closely related viruses over this vast region would certainly be fascinating from a phylogeographical point of view. It is interesting that these viruses are not yet associated with cases of HPS. There are numerous strains of hantaviruses that have been identified in the Atlantic Forest (extends along the eastern coast of Brazil and into eastern Paraguay) and in the temperate grass and shrubland of Argentina. The third clade of rodents, those that harbor the Juquitiba, Oran, and Lechiguanas viruses, resides in the more humid Lower Chaco (a region that encompasses the flooded savannas of Southern Paraguay and forms a transitional environment between the arid Gran Chaco) and temperate coniferous forests in Argentina, Brazil, and Uruguay (De Araujo et al. 2015; Delfraro et al. 2008). Andes, Maciel, and Pergamino viruses reside in rodents in the temperate grass and shrubland biome in Argentina (Bohlman et al. 2002; González-Ittig et al. 2014). Andes virus is also found in Chile in Mediterranean woodland and shrub biome (Torres-Perez et al. 2004). Araraquara viruses are associated with rodents that largely reside within agriculturally transformed areas of Brazil (i.e., sugarcane production fields) that were formerly areas of moist broadleaf forest biome (De Araujo et al. 2015; de Sousa et al. 2008; Suzuki et al. 2004).
9.4.2 Regional-Scale Land-Cover Association with Pathogen Prevalence

Coarse-scale analysis has shown a relationship between hantavirus genetics and broad ecological pattern. Narrowing this view to a more regional scale begins to reveal how land cover (and land cover disturbance) affects the spatial variability of hantaviruses. Like all zoonotic disease, the ecology of each species of Hantavirus is closely related to that of its host organism; thus, generalization of virus-landscape relationships cannot be made without considering the habitat characteristics of the reservoir host. We do not have abundant data on the microhabitat characteristics of many host species (Lozada and Guthmann 1998). However, general habitat types defined at grains sizes of ~1 km might be useful to study preferences among various

Fig. 9.2 Illustration of the major biomes of South America from the World Wildlife Fund terrestrial ecoregions data (Olson et al. 2001). Selected strains of closely related hantaviruses are presented from three distinct subclades as indicated by the color of the yellow or pink dot at their location. The viruses represented by the pink dot and pink with yellow represent two distinct lineages from one subclade
host species, and be relevant to the landscape epidemiology of hantaviruses, regardless of whether certain land cover types are more closely associated with the presence of the virus.

A regional-scale analysis of rodent reservoirs of hantaviruses in Paraguay (Goodin et al. 2006) showed that the host species do indeed show patterns of land cover preference, even when land cover is mapped into very general categories. The most common hantavirus host rodents in Paraguay, *Akodon montensis* and *Oligoryzomys* spp., both showed disproportionately high probabilities of occurring in areas subjected to large-scale agricultural disturbance (Goodin et al. 2006). Even more significant, however, was the fact that rodents found to be antibody positive for hantavirus (indicating exposure to the virus at some point) were more likely to be associated with the human-disturbed land cover types. This relationship held even when the underlying differences in habitat preference were controlled. This finding suggests that some aspect of land cover disturbance or change increases the likelihood that a member of a host species will be infected with the virus. While analysis at the regional scale shows that human land cover alteration is associated with hantavirus presence, discovering the specific nature and causes for this observation cannot be addressed at this scale. Questions of causation must be addressed at finer spatial scales, in large part because that is the scale to which most host populations and individuals are interacting with their environment (Lozada and Guthmann 1998; Owen et al. 2010).

### 9.4.3 Local Scale: Host and Habitat Associations

Simply presumed, because rodents species have specific requirements with respect to habitat, and because each hantavirus species seemingly persists only in certain rodent species, one might assume that a predictive map can be made for the prevalence of a particular hantavirus based on knowledge of the associated rodent species. Unfortunately, for most rodents, we know very little about their general life cycles and other important biological information that is critical for modeling (e.g., age at sexual maturity, birth rates, litter sizes). Further, we have only a minimal amount of information on their habitat preferences, although some recent studies have indicated that fine-grained evaluations are necessary to understand rodent species distributions and community composition (Goodin et al. 2009; Lozada and Guthmann 1998; Poindexter et al. 2012; Schnell et al. 2010).

### 9.4.4 Microscale: Virus and Host Interactions

At the microscale level, pathogen survival and reproduction depend on the dynamics within the reservoir host, which in turn depend on the habitat or the reservoir. A rodent may live within an approximate 1 km range for most of its life barring fire,
flooding, and other natural disasters. In the case of a viral pathogen, the virus must overcome physical barriers of the host and be compatible with cell receptors to gain entry into a target cell (Allen et al. 2012). Viral replication depends on host and viral genetics and other host factors such as prior pathogen or other immunogenic exposure, nutritional status, coinfection, age, sex, reproductive status, and the host immune response (Allen et al. 2012). These and other factors determine outcome when a pathogen enters a host, with the possibilities including severity of any associated disease and whether the pathogen either is to be cleared by the host immune system, or the pathogen will persist in the host. For example, the survival of hantaviruses in nature depends on maintenance of persistent infections within their specific rodent reservoir. Hantaviruses infect and persist only in the rodent reservoir with which the virus has coevolved, and the infection is believed to last the life of the animal (Meyer and Schmaljohn 2000). Notably, persistent infection of rodent reservoirs by hantaviruses shows continuous virus replication, without complete clearance by the immune system, and no pathological changes (Jonsson et al. 2010; Vaheri et al. 2013). Humans are not a natural reservoir for these viruses, and as such humans typically become infected only upon contact with aerosolized excreta from the rodent reservoir. In humans, hantavirus infection can result in severe disease although outcomes vary with different hantaviral species. The molecular basis for different disease outcomes in humans has been attributed to difference in receptor preferences of nonpathogenic and pathogenic hantaviruses. Models that connect data on the outcomes associated with immune response in reservoir versus human hosts are just beginning to be developed.

9.5 Role of Mathematical Modeling in Spatial Ecology of Infectious Diseases

Mathematical models are valuable tools for synthesizing information and testing hypotheses to provide insight into how and why disease outbreaks or spatial patterns of infections might arise in wildlife populations. Several books and review articles summarize some of the modeling efforts on zoonotic infectious diseases (Alexander et al. 2012; Allen et al. 2012; Grenfell and Dobson 1995; Heesterbeek et al. 2015; Hudson et al. 2002; Lloyd-Smith et al. 2009). A variety of modeling formats, deterministic and stochastic, have been applied to the study of zoonotic diseases. These models include compartmental, agent-based, individual-based, metapopulation, network, and ecological niche, but these classifications overlap. Agent-based, individual-based, and metapopulation models may be classified under network models, where the nodes are infectious agents, individuals or populations, connected via an underlying network (Riley et al. 2015). Simple compartment models (SEIR—susceptible, exposed, infectious, and recovered) are connected via a dispersal network in what is often called a patch model or metapopulation model (Allen et al. 2009; Arino et al. 2005; McCormack and Allen 2007b). Ecological
niche models contain less detail about individual dynamics, and instead they are closely related to landscape, presence/absence data, and GIS-based climatic and environmental data (Alexander et al. 2012; Peterson 2014).

Mathematical tractability and the complexity of interactions among pathogens, reservoirs, and human hosts and the environment have often restricted the model formulation to the reservoir host and to a single spatial scale—landscape, population, or within-host. Coupling temporal scales (hours to years or longer), biological complexity levels (genes to cells to ecosystems), and spatial scales (local to global) have been a continuous challenge to modelers (Heesterbeek et al. 2015). Recent theoretical investigations on coupling within-host and between-host models are advancing (Feng et al. 2013; Gilchrist and Coombs 2006; Mideo et al. 2008).

Hantaviruses and rabies are two examples where spatial patterns of infection involving multiple species have been observed (Chu et al. 2009, 2006; Haydon et al. 2002; Rhodes et al. 1998; Smith et al. 2002). Spatially explicit computer simulations that incorporate landscape heterogeneity and spatial genetic structure are being applied to study control of rabies and other zoonotic diseases (Alexander et al. 2012; Parratt et al. 2016; Real and Biek 2007; Rees et al. 2013). Models with multi-host species and multi-pathogens are being investigated. For example, mathematical models for hantavirus infection in rodents have been studied in the context of multiple host species, spatial spread, and environmental variability (Abramson and Kenkre 2002; Abramson et al. 2003; Allen et al. 2006a, b, 2009; McCormack and Allen 2007a, b). These models have shown that those random or seasonal variations which impact an ecosystems carrying capacity for a particular rodent species can trigger outbreaks when rodent densities and contacts rates are high (Allen et al. 2006b). In addition, theoretical analyses have shown that when multiple species, as opposed to a single species, are involved in the transmission process, there may be a dilution or amplification effect that impacts disease persistence (Dobson 2004; McCormack and Allen 2007a). Models for spatial spread among discrete patches have shown the importance of there being at least one patch where the disease persists (Arino et al. 2005; Allen et al. 2009; McCormack and Allen 2007b).

### 9.6 Conclusions

Wu and Loucks (1995) have suggested that the most significant contribution of hierarchy theory is as a framework for explicitly incorporating heterogeneity and scale into ecological analysis. In this chapter, we have tried to show some ways in which hierarchical consideration of spatial (and to some extent, temporal) scale can be incorporated into ecological analyses of zoonotic diseases. Our review of the literature also suggests some of the opportunities in infectious disease research resulting from the hierarchical consideration of scale but also some of the challenges. Spatial patterns of zoonotic hosts, the pathogens they harbor, and the host-zoonosis relationships may appear quite different depending on the scale at which we view
them. Although patterns derived from different size scales are often referred to as “emergent” patterns, it is unclear whether the newly recognized large-scale or the small-scale patterns might not be emergent from scale levels either above or below them. Although we could view these scales to be nested subsets of one another, it may be more useful both conceptually and in practice, to view the patterns derived from different scales as complementary information requiring integration, rather than as contradictory results requiring amelioration.

One area of opportunity for the application of hierarchical concepts in zoonotic disease ecology corresponds to scale-related questions facing the global change research community in general; how does global environmental change, especially global warming, manifest itself spatially? It has long been recognized that the spatial distribution of both individuals and communities of species is linked to climate and that these are two-way linkages; however much uncertainty remains about where, when, and how species will respond to climate change (Potter et al. 2013). Fundamentally, the issue reduces to one of scale; the potential impacts of climate change are most often conceptualized at the macroscale (i.e., regional or global) but operate across a range of scales including those more proximate to the host or reservoir organisms (Ashcroft et al. 2009; Diffenbaugh et al. 2005; Suggitt et al. 2011). Adoption of the complementary, hierarchical view of scale provides a framework to address these and similar questions in disease ecology.

Model selection among the wide array of potential formats depends on the virus-host ecological system being investigated, data availability, and the questions to be addressed. Many challenges remain in model formulation, analysis, and simulation of zoonotic disease dynamics that relate to landscape and climate and the wide range of temporal and spatial scales (Allen et al. 2012; Buhnerkempe et al. 2015; Heesterbeek et al. 2015; Lloyd-Smith et al. 2009; Pellis et al. 2015). Addressing the challenges of scale can be met through mathematical and computational approaches and methods being developed in a variety of fields including computer science, ecology, geography, immunology, genetics, mathematics, statistics, and virology. This will require the continued close collaboration across numerous disciplines to converge toward models that reflect the immense biological diversity of pathogen-host ecology.

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Compliance with Ethical Standards

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**Conflict of Interest** Douglas G. Goodin declares that he has no conflict of interest. Colleen B. Jonsson declares that she has no conflict of interest. Linda J. S. Allen declares that she has no conflict of interest. Robert D. Owen declares that he has no conflict of interest.

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

References

Abramson G, Kenkre VM (2002) Spatiotemporal patterns in the hantavirus infection. Phys Rev E Stat Nonlin Soft Matter Phys 66:011912

Abramson G, Kenkre VM, Yates TL, Parmenter RR (2003) Traveling waves of infection in the hantavirus epidemics. Bull Math Biol 65:519–534

Alexander KA, Lewis BL, Marathe M, Eubank S, Blackburn JK (2012) Modeling of wildlife-associated zoonoses: applications and caveats. Vector Borne Zoonotic Dis 12:1005–1018

Allen TFH, Starr TB (eds) (1982) Hierarchy: perspectives for ecological complexity. University of Chicago Press, Chicago

Allen LJ, McCormack RK, Jonsson CB (2006a) Mathematical models for hantavirus infection in rodents. Bull Math Biol 68:511–524

Allen LJS, Allen EJ, Jonsson CB (2006b) The impact of environmental variation on hantavirus infection in rodents. In: Gumel AB, Castillo-Chavez C, Mickens RE, Clemence DP (eds) Modeling the dynamics of human diseases: emerging paradigms and challenges. AMS, Providence, RI, pp 1–15

Allen LJS, Wesley CL, Owen RD, Goodin DG, Koch D, Jonsson CB, Chu Y-K, Hutchinson S, Paige R (2009) A habitat-based model for the spread of hantavirus between reservoir and spillover species. J Theor Biol 260:510–522

Allen LJ, Brown VL, Jonsson CB, Klein SL, Laverty SM, Magwedere K, Owen JC, van den Driessche P (2012) Mathematical modeling of viral zoonoses in wildlife. Nat Resour Model 25:5–51

Arino J, Davis JR, Hartley D, Jordan R, Miller JM, van den Driessche P (2005) A multi-species epidemic model with spatial dynamics. Math Med Biol 22:129–142

Ashcroft MB, Chisholm LA, French KO (2009) Climate change at the landscape scale: predicting fine-grained spatial heterogeneity in warming and potential refugia for vegetation. Global Change Biol 15:656–667

Bohlman MC, Morzunov SP, Meissner J, Taylor MB, Ishibashi K, Rowe J, Levis S, Enria D, St Jeor SC (2002) Analysis of hantavirus genetic diversity in Argentina: S segment-derived phylogeny. J Virol 76:3765–3773

Brownstein JS, Skelly DK, Holford TR, Fish D (2005) Forest fragmentation predicts local scale heterogeneity of Lyme disease risk. Oecologia 146:469–475
Buhnerkempe MG, Roberts MG, Dobson AP, Heesterbeek H, Hudson PJ, Lloyd-Smith JO (2015) Eight challenges in modelling disease ecology in multi-host, multi-agent systems. Epidemics 10:26–30

Chu YK, Milligan B, Owen RD, Goodin DG, Jonsson CB (2006) Phylogenetic and geographical relationships of hantavirus strains in Eastern and Western Paraguay. Am J Trop Med Hyg 75:1127–1134

Chu YK, Goodin D, Owen RD, Koch D, Jonsson CB (2009) Sympatry of two hantavirus strains, Paraguay, 2003-2007. Emerg Infect Dis 15:1977–1980

Csillag F, Fortin M-J, Dungan JL (2000) On the limits and extensions of the definition of scale. Bull Ecol Soc Am 81:230–232

De Araujo J, Duré AIL, Negrão R, Ometto T, Thomazelli LM, Durigon EL (2015) Co-circulation in a single biome of the Juquitiba and Araraquara hantavirus detected in human sera in a sub-tropical region of Brazil. J Med Virol 87:725–732

De Beurs KM, Henebry GM (2004) Land surface phenology, climatic variation, and institutional change: analyzing agricultural land cover change in Kazakhstan. Remote Sens Environ 8:497–509

de Oliveira RC, Padula PJ, Gomes R, Martinez VP, Bellomo C, Bonvicino CR, Freire E Lima DI, Bragagnolo C, Caldas ACS, D’Andrea PS, de Lemos ERS (2011) Genetic characterization of hantaviruses associated with sigmodontine rodents in an endemic area for hantavirus pulmonary syndrome in southern Brazil. Vector Borne Zoonotic Dis 11:301

de Sousa RL, Moreli ML, Borges AA, Campos GM, Livonesi MC, Figueiredo LT, Pinto AA (2008) Natural host relationships and genetic diversity of rodent-associated hantaviruses in Southeastern Brazil. Intervirology 51:299–310

Delfraro A, Tomé L, D’Elía G, Clara M, Achával F, Rossi JC, Rodonz JRA (2008) Juquitiba-like hantavirus from 2 nonrelated rodent species, Uruguay. Emerg Infect Dis 14:1447–1451

Diffenbaugh NS, Pal JS, Trapp RJ, Giorgi F (2005) Fine-scale processes regulate the response of extreme events to global climate change. Proc Natl Acad Sci U S A 102:15774–15778

Dobson A (2004) Population dynamics of pathogens with multiple host species. Emerg Infect Dis 10:1127–1134

Dobson A (2004) Population dynamics of pathogens with multiple host species. Emerg Infect Dis 10:1127–1134

Epstein JH, Field HE, Luby S, Pulliam JR, Daszak P (2006) Nipah virus: impact, origins, and causes of emergence. Curr Infect Dis Rep 8:59–65

Estrada-Peña A, Oteo JA (1991) Vectors of Lyme disease in Spain. Res Rev Parasitol 51:101–102

Estrada-Peña A, Venzal JM, Acebedo Sanchez C (2006) The tick *Ixodes ricinus*: distribution and climate preferences in the Western Palaearctic. Med Vet Entomol 20:350–359

Feng Z, Velasco-Hernandez J, Tapia-Santos B (2013) A mathematical model for coupling within-host and between-host dynamics in an environmentally-driven infectious disease. Math Biosci 241:49–55

Fulhorst CF, Cajimat MNB, Utrera A, Milazzo ML, Duno GM (2004) Maporal virus, a hantavirus associated with the fulvous pygmy rice rat (*Oligoryzomys fulvescens*) in Western Venezuela. Virus Res 104:139–144

Gilchrist MA, Coombs D (2006) Evolution of virulence: interdependence, constraints, and selection using nested models. Theor Popul Biol 69:145–153

Giraudoux P, Craig PS, Delattre P, Bartholomot B, Harraga S, Quere JP, Raoul F, Wang Y, Shi D, Vuittion DA (2003) Interactions between landscape changes and host communities can regulate *Echinococcus multilocularis* transmission. Parasitology 127:121–131

Glass GE, Cheek JE, Patz JA, Shields TM, Doyle TJ, Thoroughman DA, Hunt DK, Enscore RE, Gage KL, Irland C, Peters CJ, Bryan R (2000) Using remotely sensed data to identify areas at risk for hantavirus pulmonary syndrome. Emerg Infect Dis 6:238–247

Glass GE, Yates TL, Fine JB, Shields TM, Kendall JB, Hope AG, Parmenter CA, Peters CJ, Ksiazek TG, Li CS, Patz JA, Mills JN (2002) Satellite imagery characterizes local animal reservoir populations of Sin Nombre virus in the Southwestern United States. Proc Natl Acad Sci U S A 99:16817–16822
González-Ittig RE, Rivera PC, Levis SC, Calderón GE, Gardenal CN (2014) The molecular phylogenetics of the genus *Oligoryzomys* (Rodentia: Cricetidae) clarifies rodent host–hantavirus associations. *Zool J Linnean Soc* 171:457–474

Goodin DG, Koch DE, Owen RD, Chu Y-K, Hutchinson JMS, Jonsson CB (2006) Land cover associated with hantavirus presence in Paraguay. *Global Ecol Biogeogr* 15:519

Goodin DG, Paige R, Owen RD, Ghimire K, Koch DE, Chu YK, Jonsson CB (2009) Microhabitat characteristics of *Akodon montensis*, a reservoir for hantavirus, and hantaviral seroprevalence in an Atlantic forest site in Eastern Paraguay. *J Vector Ecol* 34:104–113

Grenfell BT, Dobson AP (1995) Ecology of disease in natural populations. *Cambridge University Press, Cambridge, UK*

Haydon DT, Cleaveland S, Taylor LH, Laurenson MK (2002) Identifying reservoirs of infection: a conceptual and practical challenge. *Emerg Infect Dis* 8:1468–1473

Heesterbeek H, Anderson RM, Andreasen V, Bansal S, De Angelis D, Dye C, Eames KT, Edmunds WJ, Frost SD, Funk S, Hollingsworth TD, House T, Isham V, Klepac P, Lessler J, Lloyd-Smith JO, Metcalf CJ, Mellison D, Pellis L, Pulliam JR, Roberts MG, Viboud C, Isaac Newton Institute, I.D.D.C. (2015) Modeling infectious disease dynamics in the complex landscape of global health. *Science* 347:4339

Hudson PJ, Rizzoli A, Grenfell BT, Heesterbeek H, Dobson AP (2002) The ecology of wildlife diseases. *Oxford University Press, Oxford*

Jenerette GD, Wu J (2000) On the definitions of scale. *Bull Ecol Soc Am* 81:104–105

Johnson AM, Bowen MD, Ksiazek TG, Williams RJ, Bryan RT, Mills JN, Peters CJ, Nichol ST (1997) Laguna Negra Virus associated with HPS in Western Paraguay and Bolivia. *Virology* 238:115–127

Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P (2008) Global trends in emerging infectious diseases. *Nature* 451:990

Jones BA, Grace D, Kock R, Alonso S, Rushton J, Said MY, McKeever D, Mutua F, Young J, McDermott J, Pfeiffer DU (2013) Zoonosis emergence linked to agricultural intensification and environmental change. *Proc Natl Acad Sci USA* 110:8399

Jonsson CB, Figueiredo LT, Vapalahti O (2010) A global perspective on hantavirus ecology, epidemiology, and disease. *Clin Microbiol Rev* 23:412–441

Kilgore PE, Peters CJ, Mills JN, Rollin PE, Armstrong L, Khan AS, Ksiazek TG (1995) Prospects for the control of Bolivian hemorrhagic fever. *Emerg Infect Dis* 1:97–100

Kitron U, Clennon JA, Cecere MC, Gürüler RE, King CH, Vazquez-Prokopec G (2006) Upscale or downscale: applications of fine scale remotely sensed data to Chagas disease in Argentina and schistosomiasis in Kenya. *Geospatial Health* 1:49–58

Langlois JP, Fahrig L, Merriam G, Artsob H (2001) Landscape structure influences continental distribution of hantavirus in deer mice. *Landscape Ecol* 16:255–266

Lidicker WZ (1995) Landscape approaches in mammalian ecology and conservation. *University of Minnesota Press, Minneapolis*

Lloyd-Smith JO, George D, Pepin KM, Pitzer VE, Pulliam JR, Dobson AP, Hudson PJ, Grenfell BT (2009) Epidemic dynamics at the human–animal interface. *Science* 326:1362–1367

Londoño AF, Díaz FJ, Agudelo-Flórez P, Levis S, Rodas JD (2011) Genetic evidence of hantavirus infections in wild rodents from northwestern Colombia. *Vector Borne Zoonotic Dis* 11:701

Lozada M, Guthmann N (1998) Microhabitat selection under experimental conditions of three sigmodontine rodents. *Ecoculture* 5:51–55

McCormack RK, Allen LJS (2007a) Disease emergence in multi-host epidemic models. *Math Med Biol* 24:17–34

McCormack RK, Allen LJS (2007b) Multi-patch deterministic and stochastic models for wildlife diseases. *J Biol Dyn* 1:63–85

McFarlane RA, Sleigh AC, McMichael AJ (2013) Land-use change and emerging infectious disease on an island continent. *Int J Environ Res Public Health* 10:2699–2719

Meentemeyer V (1989) Geographical perspectives of space, time, and scale. *Landscape Ecol* 3:163–173
Richter MH, Hanson JD, Cajimat MN, Milazzo ML, Fulhorst CF (2010) Geographical range of Rio Mamoré virus (family Bunyaviridae, genus Hantavirus) in association with the small-eared pygmy rice rat (*Oligoryzomys microtis*). Vector Borne Zoonotic Dis 10:613

Riley S, Eames K, Isham V, Mollison D, Trapman P (2015) Five challenges for spatial epidemic models. Epidemics 10:68–71

Russell CA, Real LA, Smith DL (2006) Spatial control of rabies on heterogeneous landscapes. PLoS One 1:e27

Schnell GD, De Lourdes Romero-almaraz M, Martínez-chapital ST, Sánchez-hernández C, Kennedy ML, Best TL, Wooten MC, Owen RD (2010) Habitat use and demographic characteristics of the west Mexican cotton rat (*Sigmodon mascotensis*). Mammalia 74:379–393

Simone I, Cagnacci F, Provensal C, Polop J (2010) Environmental determinants of the small mammal assemblage in an agroecosystem of central Argentina: the role of *Calomys musculinus*. Mammal Biol 75:496–509

Smith DL, Lucey B, Waller LA, Childs JE, Real LA (2002) Predicting the spatial dynamics of rabies epidemics on heterogeneous landscapes. Proc Natl Acad Sci U S A 99:3668–3672

Smith KF, Goldberg M, Rosenthal S, Carlson L, Chen J, Chen C, Ramachandran S (2014) Global rise in human infectious disease outbreaks. J Royal Soc 11:20140950

Suggitt AJ, Gillingham PK, Hill JK, Huntley B, Kunin WE, Roy DB, Thomas CD (2011) Habitat microclimates drive fine-scale variation in extreme temperatures. Oikos 120:1–8

Suzuki A, Bisordi I, Levis S, Garcia J, Pereira LE, Souza RP, Sugahara TK, Pini N, Enria D, Souza LT (2004) Identifying rodent hantavirus reservoirs, Brazil. Emerg Infect Dis 10:2127–2134

Torres-Perez F, Navarrete-Drogueut J, Aldunate R, Yates TL, Mertz GJ, Vial PA, Ferres M, Marquet PA, Palma RE (2004) Peridomestic small mammals associated with confirmed cases of human hantavirus disease in southcentral Chile. Am J Trop Med Hyg 70:305–309

Tucker CJ, Wilson JM, Mahoney R, Anyamba A, Linthicum KJ, Myers M (2002) Climatic and ecological context of the 1994–1996 ebola outbreaks. Photogr Eng Rem Sens 68:147–152

Vaheri A, Strandin T, Hepojoki J, Sironen T, Henttonen H, Makela S, Mustonen J (2013) Uncovering the mysteries of hantavirus infections (Disease/Disorder overview). Nat Rev Microbiol 11:539

Watts DJ, Muhamad R, Medina DC, Dodds PS (2005) Multiscale, resurgent epidemics in a hierarchical metapopulation model. Proc Natl Acad Sci U S A 102:11157

Woolhouse MEJ, Gowtage-Sequeria S (2005) Host range and emerging and reemerging pathogens. Emerg Infect Dis 11:1842

Wu J (1999) Hierarchy and scaling: extrapolating information along a scaling ladder. Can J Rem Sens 25:367–380

Wu J, Loucks OL (1995) From balance of nature to hierarchical patch dynamics: a paradigm shift in ecology. Q Rev Biol 70:439–466

Yahnke CJ, Meserve PL, Ksiazek TG, Mills JN (2001) Patterns of infection with Laguna Negra virus in wild populations of *Calomys laucha* in the central Paraguayan chaco. Am J Trop Med Hyg 65:768

Yates TL, Mills JN, Parmenter CA, Ksiazek TG, Parmenter RR, Vande Castle JR, Calisher CH, Nichol ST, Abbott KD, Young JC, Morrison ML, Beaty BJ, Dunnum JL, Baker RJ, Salazar-Bravo J, Peters CJ (2002) The ecology and evolutionary history of an emergent disease: hantavirus pulmonary syndrome. BioScience 52:989–998