Landscape Epidemiology of Emerging Infectious Diseases in Natural and Human-Altered Ecosystems

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Abstract

A central challenge to studying emerging infectious diseases (EIDs) is a landscape dilemma: Our best empirical understanding of disease dynamics occurs at local scales, whereas pathogen invasions and management occur over broad spatial extents. The burgeoning field of landscape epidemiology integrates concepts and approaches from disease ecology with the macroscale lens of landscape ecology, enabling examination of disease across spatiotemporal scales in complex environmental settings. We review the state of the field and describe analytical frontiers that show promise for advancement, focusing on natural and human-altered ecosystems. Concepts fundamental to practicing landscape epidemiology are discussed, including spatial scale, static versus dynamic modeling, spatially implicit versus explicit approaches, selection of ecologically meaningful variables, and inference versus prediction. We highlight studies that have advanced the field by incorporating multiscale analyses, landscape connectivity, and dynamic modeling. Future research directions include understanding disease as a component of interacting ecological disturbances, scaling up the ecological impacts of disease, and examining disease dynamics as a coupled human-natural system.

INTRODUCTION

Emerging infectious disease (EID): a disease undergoing range expansion or increased incidence following introduction of an exotic pathogen or reemergence of one once in decline

Natural ecosystem: an ecological system consisting of wild populations of plants, animals, and microbes that is not artificially created (i.e., planted, farmed, or intensively managed) by humans

Emerging infectious diseases (EIDs) of plants and animals are impacting natural ecosystems at unprecedented rates in response to increases in human mobility, climate change, and the creation of new habitat conditions (4, 18, 51, 65). The dynamic and inherently spatial nature of epidemiological processes presents unique challenges to studying and managing the spread of EIDs in natural communities. First, natural ecosystems often exhibit nonlinear dynamics and feedbacks across a wide range of interacting (and sometimes unknown) ecological variables (93, 94). Second, the heterogeneous nature of the biotic and abiotic variables driving disease dynamics in natural ecosystems is notoriously difficult to measure, and there is almost never a single right scale of observation (32, 62) (**Figure 1**). In human-altered ecosystems (e.g., fragmented suburban forests), additional uncertainties associated with human behavior and decision-making processes can further complicate our understanding of disease systems (84). The field of disease ecology has made critical strides toward understanding how pathogens interact locally with plant and animal populations in natural systems. However, our knowledge of larger-scale interactions between the spatiotemporal heterogeneity of host and environmental conditions and the rates at which pathogens disperse through and among fragmented host populations remains limited (39, 42, 83). Consequently, the challenge of explicitly integrating landscape heterogeneity of the biophysical environment into epidemiological analyses must be overcome for us to better understand the multiple scales at which epidemiological processes operate in ecological systems.

The burgeoning field of landscape epidemiology examines interactions between landscape

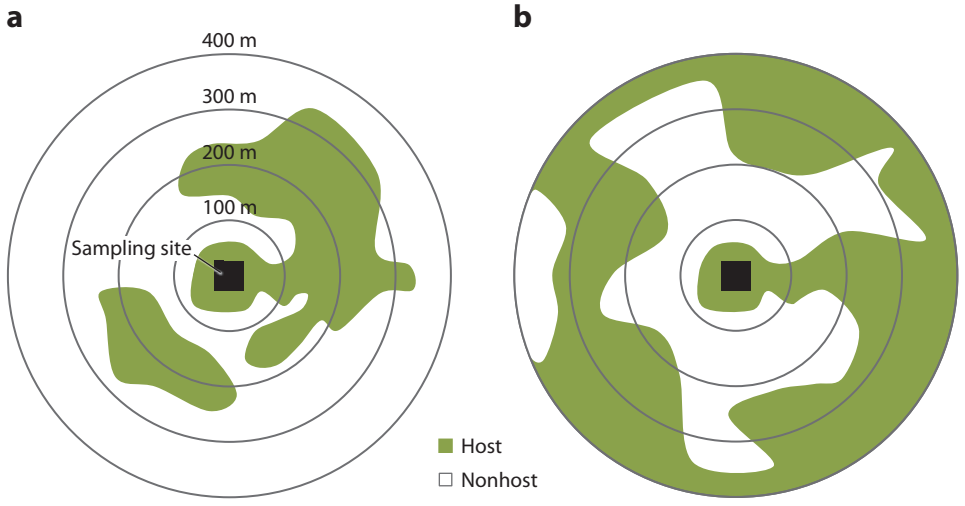

Figure 1

Diagram of two landscape scenarios illustrating scale-dependent effects of host (*shown in green*) and nonhost (*shown in white*) habitat abundance and configuration across nested scales of increasing radii (100-m increments) around a sampling site (*black square*). The amount of host habitat surrounding each site in conjunction with the structural connectivity of habitat may influence the global infection pressure on a site. If a single-scale analysis were conducted at 100 m, scenarios *a* and *b* would be identical in the amount and configuration of habitat conditions. At 200 m, however, scenario *a* would appear to be connected to a greater amount of contiguous host habitat. A multiscale examination, or an analysis that was conducted at a larger spatial extent (e.g., 400 m), would further reveal that scenario *b* is surrounded by a larger area of contiguous host habitat and thus may exhibit higher infection pressure from the surrounding landscape.

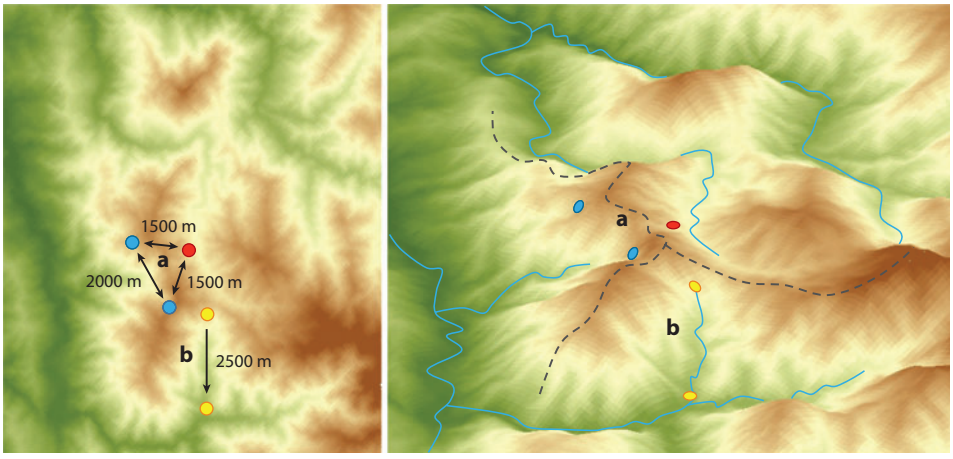

Figure 2

The spread and persistence of diseases across heterogeneous landscapes depend on spatial heterogeneity and functional connectivity of landscape conditions. (*a*) Connectivity is greater between the blue sites than it is between the blue and yellow sites and the red site, despite their greater Euclidean distance separation, because the red site is located on the other side of a mountain range, which may function as a geographic barrier to inoculum, host, and/or vector dispersal. (*b*) In a waterborne pathosystem in which inoculum is dispersed in streams, the two yellow sites (separated by the greatest Euclidean distance) could actually be the most connected because the lower yellow site is located downstream from the upper yellow site.

heterogeneity and the underlying ecological processes that drive the spread and persistence of disease (42, 58, 83, 88). By definition, landscape epidemiology integrates concepts and approaches from disease ecology with the macroscale lens of landscape ecology. The intersection of these perspectives enables us to understand how the spatial configuration and composition of landscape features influence epidemiological processes across broad geographical areas that extend beyond processes operating locally within a single community. Thus, landscape epidemiology is more than simply establishing plots in the field and examining differences in local biotic and abiotic conditions among sites; the key is to gain insight into the geographical distribution of disease and to understand how landscape connectivity influences spatial interactions between susceptible and infected individuals (**Figure 2**). The environmental conditions that determine landscape connectivity for dispersal may vary by region and depend on whether a pathogen disperses biotically (e.g., vector-borne insect movement) or abiotically (e.g., flows of wind and water). For example, rivers and streams may act as dispersal corridors that foster the spread of infection across a heterogeneous landscape for waterborne plant pathogens (53), yet in other systems, such as zoonotic diseases of terrestrial mammals, these same water bodies might function as geographic barriers by impeding host or vector movement (97).

Implementing a landscape approach is typically not a trivial task. Landscape approaches that incorporate spatiotemporal complexity in epidemiological systems require careful spatial linking of molecular and microbial observations of disease distribution with measurements of corresponding (and surrounding) biotic and abiotic conditions (7). Most landscape epidemiological studies utilize geographic information systems (GIS) and other geospatial technologies (e.g., remote sensing) to assimilate the large, spatial data sets that enable analysis of relationships between the distribution of disease and landscape heterogeneity. However, despite the many ways GIS has helped advance landscape epidemiology, GIS software is notoriously limited to providing static snapshots

Human-altered ecosystem: a natural ecosystem harboring wild populations of plants, animals, and microbes that is heavily influenced by human activities, such as urbanization or selective harvesting; does not include agroecosystems with intensive farming

Landscape heterogeneity: spatial variability of biotic and abiotic conditions over a specified geographic area

Landscape ecology: the science of studying the reciprocal interactions between spatial patterns of landscape heterogeneity and ecological processes

LEVERAGING GEOSPATIAL ANALYSIS AND COMPUTATIONAL MODELING

Understanding drivers of infectious disease dynamics across heterogeneous landscapes ultimately requires a computationally intensive integration of spatial and temporal dimensions of the environment. When implementing a landscape epidemiological approach, the first step is choosing the spatial scales (extent and grain) thought to approximate the phenomenon scale of the system. Analyses conducted at landscape to regional scales require large amounts of spatial data, which may integrate local-scale observations from fieldwork with larger-scale data derived from geospatial mapping technologies (e.g., geographic information systems, remote sensing). Integration of field data with geospatial modeling requires careful consideration to matching the sampling, analytical, and phenomenon scales (see section below, What Is the Spatial Scale?). After data collection, the voluminous data sets are typically imported into a relational geo-database (e.g., ESRI ArcSDE, MySQL) for storage, manipulation, and visualization, and may then be exported to an analytical platform capable of modeling spatial and temporal complexity (e.g., R, WinBUGS, C++). Unfortunately, the computationally demanding nature of these analytical procedures often hinders implementation in many cases, especially where there is a need for dynamic models of spatial spread. However, we expect to see a surge in the number of sophisticated landscape epidemiological analyses as advancements in high-performance computing and appreciation of interdisciplinary collaborations continue.

of spatial variables in a disease system, with relatively little ability to incorporate the types of dynamic temporal complexities (e.g., dispersal and infection) needed for process-based understanding of epidemic behavior over time. To continue moving the discipline forward, we must embrace recent advancements in spatial analysis and computational modeling, which are now more than ever offering ways to integrate both spatial and temporal dimensions in landscape epidemiological analyses (75; see sidebar, Leveraging Geospatial Analysis and Computational Modeling).

As with most emerging fields, landscape epidemiology has not yet developed a clear identity or direction for future research. We conducted a literature search of the diverse perspectives on landscape approaches in epidemiological studies in order to describe the current state of the field. We classified papers based on six categories: (*a*) research design, (*b*) static versus dynamic approach, (*c*) taxonomic focus, (*d*) spatial extent of the study area, (*e*) inferential versus predictive nature, and (*f*) whether the study used a multiscale approach (**Figure 3**). Observation-based empirical studies were much more common than simulation modeling, and only three experimental studies were returned (50, 80, 99). The overwhelming majority (74%) of these analyses were static in nature. To date, animal and zoonotic diseases have been studied in more cases using landscape epidemiological approaches as compared with plant systems (see **Table 1** for a list of plant pathogens analyzed using landscape epidemiological approaches). Across all studies, the range of spatial extents spanned <1 km^2 (one of the experimental studies) to over one million km^2, with most encompassing landscape- to regional-scale extents of 1–10,000 km^2. Only 13% used a multiscale approach. Lastly, we found that approximately two-thirds of the studies used analytical approaches that were inferential as opposed to predictive in nature (**Figure 3**).

In this paper, we review the state of the emerging field of landscape epidemiology and highlight the analytical frontiers that hold promise to advance the discipline. We focus on EIDs in natural and human-altered ecosystems because of their growing threat to ecological communities and the complexity of invasion dynamics in heterogeneous landscapes (**Table 1**). We begin by discussing fundamental considerations involved in conducting a landscape epidemiological study, including choosing an appropriate spatial scale, deciding whether the analysis is static or dynamic, distinguishing between spatially implicit and explicit approaches, selecting ecologically meaningful variables, and deciding if the research objective is statistical inference or prediction. We then turn our attention to several studies that have advanced the field in the catalyzing areas of using a multiscale lens, incorporating

Landscape connectivity: the degree to which the spatial composition and configuration of environmental conditions facilitate dispersal

Extent: the size of a study area or temporal duration; sometimes referred to as the domain

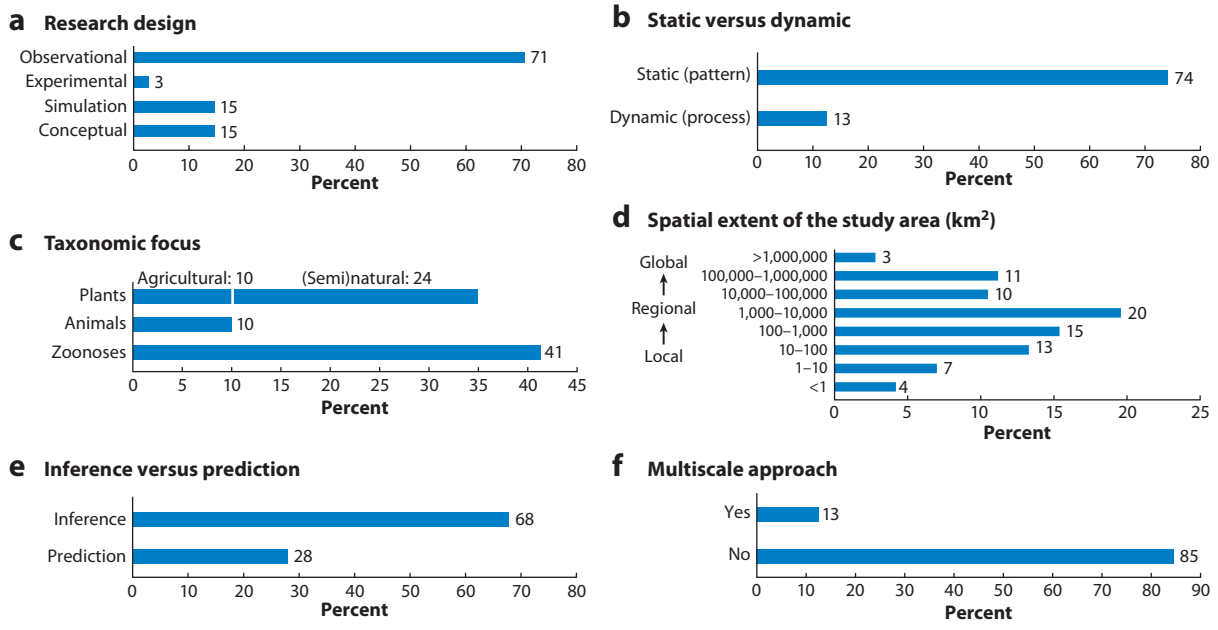

Figure 3

Literature search using the ISI Web of Science database. Search results were delimited based on the following Boolean query executed within a single search (conducted in December 2011): 1) Topic = (epidem* OR disease OR pathogen); 2) Topic = (*spatial OR geograph* OR GIS OR "remote sens*" OR spread OR "landscape heterogen*" OR "landscape structure" OR risk); and 3) Topic = (landscape*). We further refined the search by selecting only subject areas that were pertinent to our field of study. From the total of 631 returned papers, we considered 143 as true landscape epidemiological studies after assessing each paper's research objectives and methodology. We then classified papers based on the six criteria above. For taxonomic focus, we did not include diseases that affect humans only, but did include zoonoses, nonhuman animal diseases, and plant diseases. Silviculture studies were considered agriculture. Note that the sum for each histogram can be less than or greater than 100% because not all studies can be classified into a subcategory (e.g., a conceptual paper not being static or dynamic) and some studies can belong to more than one subcategory (e.g., a study is based both on observation and simulation).

landscape connectivity, and optimizing disease control with dynamic landscape modeling. We conclude with our perspectives on future directions for further development of the field.

ANALYTICAL ISSUES TO CONSIDER

What Is the Spatial Scale?

A central challenge to studying EIDs in natural and human-altered ecosystems is a landscape dilemma: Our best empirical understanding of disease dynamics mostly arises from analyses of host-pathogen-environment interactions at fine spatial scales, yet pathogen invasions and their management often occur over much broader spatial extents (e.g., white pine blister rust in the Greater Yellowstone Ecoregion; 40). Epidemiological processes are embedded within communities, ecosystems, and landscapes, and we should therefore expect that processes occurring at these larger spatial scales play a key role in disease dynamics at the local scale (83, 86) (**Figure 4**). Moreover, there is no single natural scale at which ecological phenomena, including pathogen invasions, should be studied (62; e.g., see **Figure 1**) because each species experiences its environment uniquely, depending on its life history characteristics (e.g., mode of dispersal; **Table 1**), the diversity and distribution of its

Table 1 List of plant diseases that have been analyzed using landscape epidemiology approaches. Diseases are categorized by whether or not they are an emerging infectious disease (EID), by their predominant modes of dispersal (in ranked order of importance), and by the type of ecosystem(s) studied in the analysis. Out of the 51 plant studies returned in our literature search on landscape epidemiology (see Figure 1), we highlight those that were analyzed empirically (i.e., conceptual and theoretical studies not included)

Disease	Pathogen (taxonomic class)	EID (yes/no)	Predominant dispersal mode (biotic, abiotic, human)	Ecosystem studied (natural, human-altered, agricultural)	References
Cedar root disease	*Phytophthora lateralis* (Oomycetes)	Yes	Abiotic (water), human	Natural	(52, 53)
Eastern spruce dwarf mistletoe	*Arceuthobium pusillum* (macroparasite)	No	Abiotic (seed dispersal)	Natural	(37)
Foot rot/head blight	*Fusarium culmorum/Fusarium graminearum* (Sordariomycetes)	Yes	Abiotic (rain and wind)	Agricultural	(79)
Jarrah dieback	*Phytophthora cinnamomi* (Oomycetes)	Yes	Human, abiotic (water)	Natural	(112)
Mal del ciprés	*Phytophthora austrocedrae* (Oomycetes)	Yes	Abiotic (air and water)	Natural	(59)
(No name at this time)	*Phytophthora kernoviae* (Oomycetes)	Yes	Abiotic (rain and wind)	Human-altered	(39)
Oak wilt	*Ceratocystis fagacearum* (Sordariomycetes)	Yes	Biotic (root grafting and insects)	Human-altered	(36)
Powdery mildew	*Podosphaera plantaginis* (Leotiomycetes)	No	Abiotic (wind)	Agricultural	(60)
Southern corn leaf blight	*Cochliobolus heterostrophus* (Dothiodeomycetes)	No	Abiotic (wind)	Human-altered	(50)
Sudden oak death[a]	*Phytophthora ramorum* (Oomycetes)	Yes	Abiotic (rain and wind), human	Natural, human-altered	(3, 13, 14, 17, 23, 27, 35, 39, 55, 70–73, 105)
White pine blister rust	*Cronartium ribicola* (Pucciniomycetes)	Yes	Abiotic (wind)	Natural	(98, 110)

[a]Also referred to as sudden larch death in Western Europe (9).

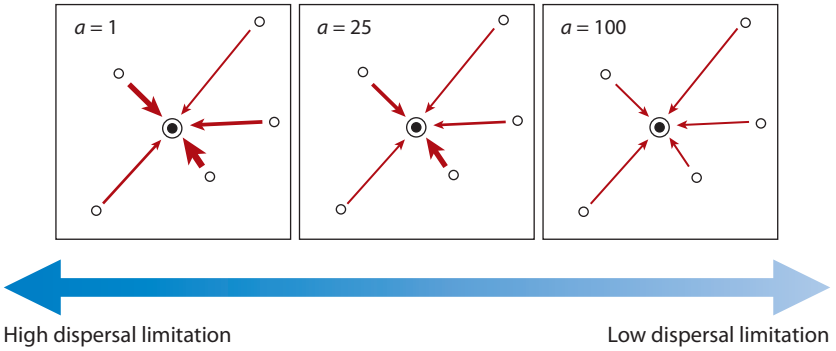

Figure 4

Schematic of the force of infection on a local site in response to sources of inoculum from variable distances across a surrounding landscape. The potential load of inoculum from each source is represented by the width of the arrows. The cumulative load experienced by the target is given by $\Sigma\exp(2d/a)$, where d = distance, represented as arrow length in the schema. Nearby sources of inoculum have more influence than far sources at low values of *a*. Reprinted with permission from Reference 70.

hosts, and the abiotic factors it encounters. For instance, Sullivan et al. (99) conducted a landscape-scale experiment to examine whether or not habitat corridors increased the incidence of plant parasites and found that outcomes varied with parasite dispersal mode. Connectivity provided by corridors increased incidence of vector-borne parasites (galls on *Solidago odora*), but wind-borne parasites (foliar fungi on *S. odora* and three *Lespedeza* spp.) were less influenced by corridors because wind dispersal occurred over larger scales with less sensitivity to landscape pattern.

When studying emerging diseases across landscape to regional scales, pathogen distributions may exhibit heightened spatial and temporal dependencies because of localized dispersal from the point of introduction (66). Thus, the amount of geographic disequilibrium that an emerging disease undergoes in space and time should be carefully contextualized when specifying the scale and heterogeneity of observations. For instance, many native pathogens (e.g., *Armillaria* or *Heterobasidion* spp. in North America) may not be considered emerging in the context of their geographic range as a whole but might be emerging at particular locations responding to changes in environment or host community structure. Similar considerations apply for temporal scale. For example, white pine blister rust has been established in North America for more than100 years, yet continues to expand its range into new areas (e.g., southwestern United States) while becoming endemic in other regions (British Columbia) (57).

The choice of spatial scale—defined by extent and grain—should be grounded in epidemiological theory (e.g., the dispersal curves of air- and splash-dispersed pathogens often display a concave shape; 10) and driven by research objectives. For example, a spatial extent with a regional to continental scope might be used to study potential impacts of emerging pathogens as large-scale agents of ecosystem disturbance (24, 31, 40, 64), whereas smaller landscape extents might be used to explore how spatial heterogeneity of host availability influences disease spread (53). Spatial grain pertains to the resolution of explanatory variables (e.g., cell size of raster data) and the response variable for the measurement of disease. For example, how might inference change if infection is measured at the level of the leaf, the tree, or the forest stand? Because nature is fine grained over large extents, researchers often face the dilemma of choosing between smaller extents that enable them to capture more detail of the system property being studied and large extent

Geographic disequilibrium: a transient state describing the spatial distribution of an organism that is changing through time

studies that may sacrifice grain for logistical reasons (62, 111). In practice, researchers are inevitably constrained by time and resource limitations, which often dictate scales of data and model structures that may not adequately capture underlying epidemiological processes (22).

Grain: the smallest resolvable measurement unit within a data set, such as the cell size of raster data

Species distribution model: numerical tool used to quantify relationships between species occurrences and environmental factors that contribute to survival and propagation

Following Dungan et al. (20), we suggest three categories for conceptualizing spatial scale in landscape epidemiology: (*a*) the phenomenon scale, e.g., the spatial spread of an infectious disease; (*b*) the sampling scale used to measure the phenomenon, such as the detail and area of measurement in the field or in grid cells of geospatial data; and (*c*) the analytical scale, which determines the manner in which data are aggregated or generalized. If the choice of sampling and analytical scales do not correspond to the phenomena scale, resulting inference and conclusions drawn from a study may be weak or unreliable (20). Scale mismatches may also suffer from the modifiable areal unit problem (MAUP) (48), which occurs when data collected at a fine grain are spatially aggregated to variably coarser resolutions, resulting in potential bias in statistical inference. The ease in which scale mismatches can occur in landscape epidemiological studies emphasizes the importance of carefully specifying all three scales when studying the spread and persistence of EIDs. These considerations are especially relevant to designing multiscale analyses of disease dynamics, although relatively few plant disease studies have embraced multiscale approaches in natural ecosystems (**Figure 3**; see section below, Using a Multiscale Lens).

Is the Model Static or Dynamic?

To date, the majority of landscape epidemiological studies have used static rather than dynamic approaches for analyzing EIDs (**Figure 3**). Careful attention to spatial data collection in static approaches has yielded novel insights into how real-world landscape heterogeneity affects disease risk but typically at the expense of ignoring epidemic behavior over time (e.g., dispersal, rate of infectious spread) (13, 30, 98). Static approaches often use correlative species distribution models that link spatially referenced data on disease occurrence with environmental variables through the use of parametric (e.g., a generalized linear model) and nonparametric (e.g., maximum-entropy) methods. Logistic regression, for example, is a standard parametric method commonly used to model disease occurrence (i.e., presence/absence) at a site (i) as a function of any number (k) of explanatory variables:

$$\begin{aligned}\mathbf{logit}(p_i) &= \ln\left(\frac{p_i}{\mathbf{1}-p_i}\right)\\ &= \beta_\mathbf{0} + \beta_\mathbf{1}x_{\mathbf{1},i} + \cdots + \beta_k x_{k,i}.\end{aligned}$$

For instance, using Bayesian statistical analyses of a static snapshot of disease distribution, Haas et al. (35) demonstrated links between forest species diversity and disease risk in a generalist plant-pathogen invasion (i.e., a dilution effect in which sites with greater biodiversity had lower infection risk; 54) after accounting for landscape heterogeneity and spatial dependence in infection. However, these results cannot suggest how diversity-disease relationships will change through future stages of disease progression. When static approaches are used to analyze EIDs, the presence of geographical disequilibrium inherent in the distribution of disease at different stages of invasion may require additional analytical considerations (**Figure 5**). For example, Václavík & Meentemeyer (107) showed that distribution models of an emerging forest pathogen calibrated from data representative of early stages of invasion were less accurate than models calibrated under scenarios closer to equilibrium because data from early stages did not capture all combinations of climate and local habitat conditions potentially harboring the pathogen.

Dynamic approaches, in contrast, allow a phenomenon to change through time to accommodate the fluctuating behavior of an epidemic during successive stages of invasion that an EID undergoes. The most widely studied class of dynamic epidemiological models take the form of SIR (susceptible-infectious-removed)

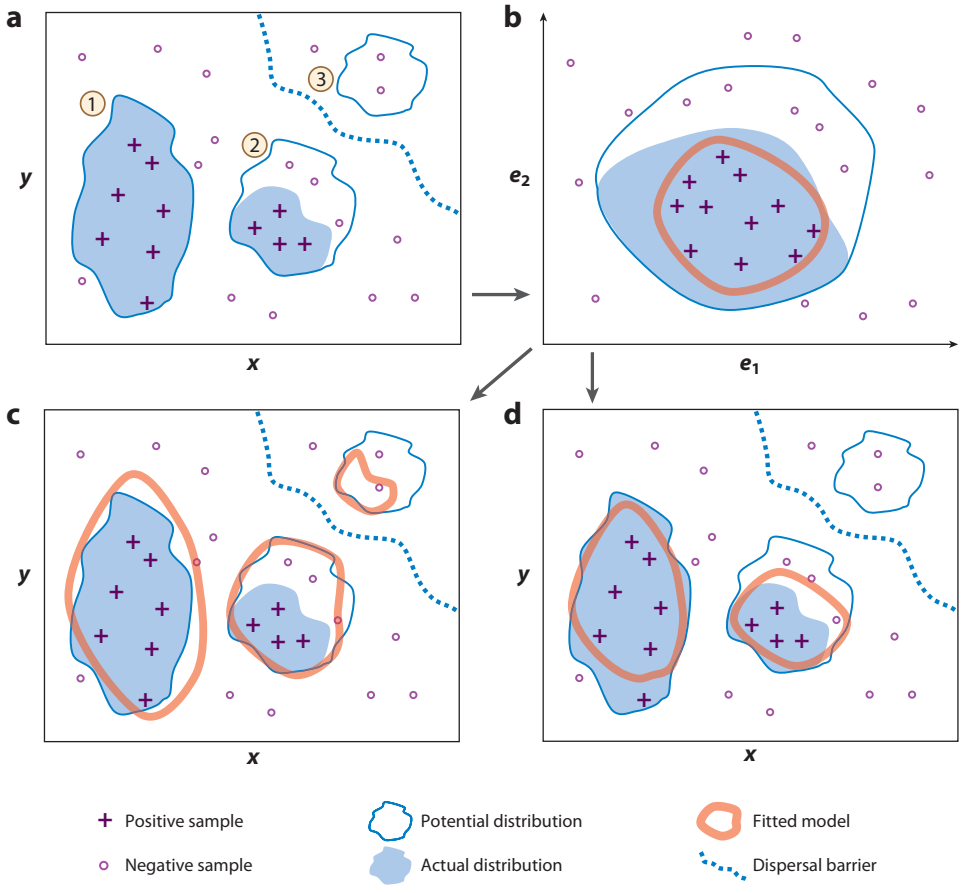

Figure 5

Methodological considerations of modeling the potential versus actual distribution of emerging infectious diseases in natural ecosystems. (*a*) A sampled geographical space with three host habitat patches: patch 1 is fully infected, patch 2 is partially infected owing to the early stage of invasion, and patch 3 is not infected because of the presence of a dispersal barrier impeding spatial spread. (*b*) A statistical model fit in environmental space to identify the pathogen's niche by relating observational data to underlying environmental conditions. (*c*) If the goal is to predict the potential distribution of a pathogen, the model should ignore dispersal constraints and utilize only positive samples (pathogen presence) to avoid underestimation of suitable habitat at risk for disease. (*d*) If the goal is to predict the actual distribution of a pathogen, the model should incorporate dispersal barriers with both positive and negative samples (pathogen presence and absence) used in model calibration to avoid overestimation of disease distribution. Figure modified from Pearson (85).

compartment models (5) that consist of a set of linked differential equations as shown below in their most basic form (β is the contact rate, r is the recovery rate):

$$\frac{dS}{dt} = -\beta SI,$$

$$\frac{dI}{dt} = \beta SI - rI,$$

$$\text{and} \quad \frac{dR}{dt} = rI.$$

With the addition of considerable complexity, dynamic epidemiological models can incorporate environmental heterogeneity and demographic processes of birth and death across spatiotemporal scales (e.g., seasonality, interactions with biocontrol agents,

metapopulation dynamics), resulting in a deeper understanding of ecological feedbacks (95). However, application of simulation models to realistic landscapes is relatively rare because of the challenge of integrating models with detailed, real-world geographical data across broad spatial extents (71). As a compromise, dynamic epidemiological models often resort to using simulated or artificial landscape data (92), which may involve questionable assumptions regarding the spatial scale and heterogeneity of a system. Yet, even when data are available or could be collected, modelers must still confront the challenge of balancing epidemiological and landscape parameters needed to capture disease dynamics without (*a*) exceeding computational and data collection costs or (*b*) overfitting models that contain large numbers of free parameters that are difficult to interpret (see section below, Optimizing Disease Control with Dynamic Landscape Modeling).

Is the Model Spatially Implicit or Explicit?

The manner in which space is considered in landscape epidemiological models naturally affects the inferences, predictions, and ultimately the conclusions drawn from a study. Although spatial information is not always required for studying ecological problems, the spread and persistence of pathogens likely depend on two basic types of spatial effects: (*a*) exogenous effects associated with broad-scale spatial trends in underlying environmental conditions (e.g., climate) and (*b*) endogenous effects caused by fine-scale processes, such as dispersal limitation, interspecific competition, and disturbance history (19, 106). Described by Peters et al. (87), models can be classified as nonspatial, spatially implicit, or spatially explicit, all of which can be conceptualized from the following geostatistical equation:

$$z_i = f(x_i) + s_i + \varepsilon,$$

where a response variable z measuring disease at a specific location, z_i, is a function of broad-scale trends from a set of explanatory variables, $f(x_i)$, measured at location i, plus a local spatial component, s_i (where s is a function of relationships measured in the neighborhood of location i), and ε are standard residual errors. In this framework, nonspatial models describe z only as a function of a set of explanatory variables with disregard to spatial location, $f(x)$. A spatially implicit approach, in contrast, models z_i with reference to the spatial location of the explanatory variables $f(x_i)$, measured but does not account for spatial dependency among neighboring sites. Finally, the spatially explicit model goes the next step by estimating z_i as a function of both spatially referenced explanatory variables $f(x_i)$, measured and a user-specified neighborhood of spatial interactions among sampling sites, s_i (**Figure 4**).

In essence, spatially implicit models are nonspatial constructs driven by spatially structured explanatory variables. For example, Smith et al. (98) examined patterns of white pine blister rust infection in the Rocky Mountains by correlating geographically referenced field observations of disease prevalence with GIS-derived environmental variables in a Poisson regression model. Here, the explanatory variables were spatially structured and a random effect was included to minimize spatial dependence among observations within sampling sites, but the analyses were spatially implicit in that they did not quantify neighborhood interactions among observations. Spatially explicit models, in contrast, directly model spatial interactions between each study location i in the surrounding landscape through gradients of inoculum pressure (35, 53; **Figure 4**), connectivity and movement of hosts (39), and biophysical flows of energy and matter (52) (**Figures 2** and **4**). Despite the potential for spatially explicit interactions s_i to increase sophistication of landscape epidemiological analyses, explicit incorporation of space requires large data sets for model calibration and testing (87).

How Ecologically Meaningful Are the Variables?

Increases in the availability of geospatial data and rich ecological databases [e.g., the National

Ecological Observatory Network (NEON)] are providing new sources of valuable information for landscape-scale research. However, studies of disease in natural systems often still focus on indirect variables at the site level. Franklin (29) defined indirect variables as environmental gradients (e.g., elevation or slope steepness) that have no direct physiological effect on an organism's survival and reproduction, but rather serve as surrogates for more functionally direct factors, such as temperature, moisture availability, and solar radiation. Indirect variables may cause two analytical problems. First, simple indirect gradients are actually complicated because they simultaneously influence multiple environmental processes. For example, elevation affects temperature, rainfall, and wind patterns as well as other underlying environmental conditions. Second, species' responses to indirect variables like elevation are likely to change depending upon the sampling location and are therefore not suitable for comparison over broad extents. For instance, a given plant pathogen will respond to environmental conditions at 1,000-m altitude in temperate zones very differently than at 1,000 m in the tropics. We suggest that measurements of direct variables in heterogeneous landscapes will lead to better mechanistic understanding of the functional responses of pathogens to their environment and help tie together findings from disparate studies. For instance, direct measurements of seasonally varying precipitation and temperature conditions—shown to affect the production of inoculum in the field (15, 16)—were used to drive the spread of an emerging forest epidemic in a dynamic landscape model (72). Altizer et al. (2) review the vital role that seasonality plays in the spread and persistence of pathogens in plant and animal populations. Seasonal variations in temperature, precipitation, and resource availability influence host behavior and susceptibility (44), spatial and temporal variations in inoculum build-up and transmission (71, 89), and pulses of host regeneration and mortality (25).

The way we measure the spatial heterogeneity and connectivity of landscapes also influences inference and prediction (**Figures 1** and **2**). For example, structural connectivity is relatively straightforward to measure—referring only to the physical attributes of the landscape (e.g., patch cohesion, nearest-neighbor distance among patches)—but it does not explicitly consider dispersal ability or behavioral responses of organisms to landscape features (11). In contrast, functional connectivity incorporates information about dispersal ability and how specific environmental conditions function as barriers or conduits to dispersal (56). For instance, movement of vectors or hosts may lead to spread that is confined to specific habitat corridors (61), impeded by geographic barriers (8, 90), or facilitated by landscape features (46) (see section below, Incorporating Landscape Connectivity). The amount of data needed to model landscape connectivity in natural ecosystems is a question that warrants careful attention in every study, as the cost of acquiring and processing these data can be high.

Is the Goal Inference or Prediction?

Landscape epidemiology combines data and models with the goal of enhancing our ability to understand and predict spatial processes in disease systems. All models involve inference to some degree, although some analyses also take the form of predictive geographical distributions (12), depending upon research objectives, e.g., obtaining a mechanistic understanding of disease transmission or forecasting epidemic outcomes across space and time. In landscape epidemiology, a central challenge stems from the fact that natural and human-altered ecosystems are high dimensional, meaning that many interacting forces are at work (e.g., see 12). When ecological inference is the primary goal, the concept of parsimony should be invoked to communicate the generality of results across disease systems and to identify functional relationships between predictor and response variables (87). However, perspectives are

Static model: describes ecological patterns at a specific moment (e.g., when data are collected) and does not account for changes over time. Process is often inferred from pattern

changing as spatial prediction of epidemic risk is becoming an increasingly common goal in response to new spatial modeling techniques, more accurate and complete geospatial data, and demand for landscape-scale strategies of disease control (28, 83). When prediction is the goal, complex models may be preferred over simple ones so long as they predict disease patterns in an accurate manner. Efforts to obtain inference versus prediction often lead to analytical trade-offs in landscape epidemiology, in part because spatial prediction requires that explanatory variables can be accurately mapped in geographic space. For example, those fine-scale variables collected in the field (e.g., host density or microclimate)—so important to inference—often prevent spatial prediction when they cannot be reliably mapped or computationally analyzed across a heterogeneous landscape (108). As a compromise, predictive models often turn to using larger-scale explanatory variables, such as land cover type or average climate conditions, that are readily mapped at coarse grains (e.g., 30 m to 1 km).

When static models are used to analyze snapshots of disease distribution at a single point in time, parametric methods (e.g., logistic regression) are well known for balancing model parsimony and prediction robustness while providing interpretation of straightforward ecological relationships. Species distribution modelers, though, are increasingly using more complex nonparametric methods (e.g., maximum entropy and support vector machines) because of their high predictive performance, ability to fit complex data, and absence of limitations posed by assumptions concerning underlying data distributions (21). However, the biogeographical modeling literature is increasingly indicating that errors in model predictions and inference stem more from faulty model structures, poor quality of data, and inappropriate selection of environmental variables than from a lack of complexity in model fitting procedures (6, 49, 100). Although complex methods are essential in certain cases, we caution that too much focus on capturing every nuance of spatial heterogeneity in a disease system may at times narrow our view to a point where analytical complexity interferes with understanding. Therefore, we expect to see complex black-box approaches of nonparametric algorithms applied when spatial prediction is the sole aim, whereas simpler approaches—based on sound ecological theory—continue to prevail for hypothesis-driven analyses.

The impacts of ignoring ecological theory in predictive models are often revealed when the actual and potential distributions of pathogen invasions are not distinguished in the goals of a study (105; see **Figure 5**). The actual distribution represents an organism's geographical range at a specific point in time restricted by the availability of suitable environmental conditions and by colonization time lags governed by dispersal constraints. In contrast, the potential distribution represents all areas in which biotic and abiotic conditions are suitable for colonization regardless of dispersal barriers. In practice, the goal of modeling the actual versus potential distribution of an EID should be clearly distinguished because methods, data, and conclusions vary when the stage of invasion is not defined (105). The contagious processes of disease spread can also lead to an excess of absence observations that can bias statistical inference or associated measures of uncertainty and thus require specific methods to account for zero-inflated data (e.g., 35).

ANALYTICAL FRONTIERS

Using a Multiscale Lens

Ecosystems are structured hierarchically by a range of ecological and anthropogenic processes across multiple scales of space and time (26, 62). To date though, only a few landscape epidemiological studies have examined EIDs from a multiscale lens (**Figures 1** and **3**). Embracing multiscale approaches—described here as data collection and analytical methods structured by two or more scales of interest—strengthens landscape epidemiological analyses for two critical reasons: (*a*) Epidemiological

processes observed at one scale may operate differently at another scale and (*b*) scaling up is feasible when relationships between disease patterns and processes are consistent across scales (i.e., the use of phenomenological relationships at one scale being used to provide information at a different scale; 104). Mundt & Sackett (81) examined scaling relationships for the spread of wheat stripe rust caused by the wind-dispersed fungus *Puccinia striiformis* f. sp. *tritici* in experimental field plots and found that the disease spread at a velocity directly proportional to the size of the initial disease focus. Their results suggest that power law dispersal of long-distance dispersing pathogens may produce scale-invariant relationships that are useful for extrapolating results from small-scale experiments to invasions spreading over larger scales. In another pathosystem, however, analyzing more than one spatial scale illustrated reversed effects of topography on the incidence of scleroderris canker caused by fungus *Gremmeniella abietina* in pine forests of southern Finland (82). These results showed that disease impacts increased with elevation at coarse scales but decreased with elevation at local scales, suggesting scale-variant effects of elevation on disease dynamics.

By revealing scale-dependent processes, multiscale approaches may help reduce the risk of making incorrect anthropogenic assumptions regarding the spatial scale of a species' response to environmental conditions (e.g., availability and connectivity of host vegetation; **Figure 1**) (43, 109). Nonetheless, all three concepts of scales—phenomenon, sampling, and analytical scales—are inevitably biased to some degree by analyst perceptions and logistical constraints no matter how many precautions are taken (62). As aptly noted by Matthews & Haydon (68), epidemiologists often seem to glance upward in scale worrying they have omitted effects of landscape features that are critical to formulating effective management strategies, whereas those conducting research at larger scales peer downward and worry that inclusion of heterogeneity at the level of the individual or gene locus is needed.

Condeso & Meentemeyer (13) conducted an observational study using a multiscale nested approach to analyze scale-dependent effects of landscape heterogeneity on the spread of the invasive forest pathogen *Phytophthora ramorum*. The study focused on the composition and configuration of host habitat surrounding 86 field plots across a spatially heterogeneous landscape. To examine the spatial scale at which *P. ramorum* responds to landscape pattern, landscape metrics such as the shape and connectivity of host habitat were calculated for nested areas of increasing radii in 50-m increments from 50 to 500 m (e.g., **Figure 1**). To isolate the scale-dependent effects, the authors accounted for local biotic and abiotic conditions by measuring host density, canopy cover, proximity to forest edges, and microclimate variation. The results showed that (*a*) incorporating larger-scale data on host availability substantially increased their ability to predict disease severity, (*b*) disease severity was greater at plots with higher connectivity of surrounding host vegetation (e.g., **Figure 4**), and (*c*) the effect of landscape pattern on disease severity is scale dependent.

In another study of the *P. ramorum* pathosystem, Václavík et al. (106) showed how the consideration of multiple scales of spatial dependence, measured as spatial autocorrelation (SAC) in patterns of disease spread, improves spatial prediction. Spatial dependence is common in biogeographical observations because of broad-scale spatial trends in underlying environmental conditions (19). In pathogen invasions, SAC also arises from contagious processes of dispersal and colonization that lead to clustered distributions and mismatches between a pathogen's potential and actual distribution (**Figure 5**). Here, the authors compared the performance of spatially implicit models to spatially explicit models that incorporated multiscale patterns of SAC using trend surface analysis, autocovariates, and spatial eigenvector mapping. The results from this observational study revealed that accounting for SAC across scales significantly enhanced spatial prediction of disease incidence,

Spatial autocorrelation (SAC): a phenomenon encountered in ecological data describing the propensity for nearby locations to influence each other more than locations that are farther apart

Force of infection: the potential contribution of cumulative inoculum input to a focal site from surrounding invaded sites

especially when finer-scale patterns of SAC were considered.

Observational approaches are receiving a resurgence of appreciation for their ability to confront ecological complexity across multiple spatial scales that typically extend beyond those feasible for experimentation (86, 94, 96). However, experimental studies of plant disease spread are beginning to be conducted at broader spatial scales. For example, Mundt et al. (80) designed large-scale field experiments to examine the effects of spatial heterogeneity—specifically host frequency, host patch size, and size of initial disease focus—on disease spread of wheat stripe rust (caused by *Puccinia striiformis* f. sp. *tritici*). This study provided unique insights into spatial spread of plant epidemics by creating controlled conditions in a closed system. In addition, we need studies that manipulate open systems across heterogeneous landscapes. For example, Johnson & Haddad (50) conducted a large-scale habitat corridor experiment—accounting for the shape, size, and connectivity of habitat patches embedded within a pine plantation matrix—to examine the movement of a wind-dispersed fungal pathogen (*Cochliobolus heterostrophus*) through a fragmented landscape. The authors showed that corridors did not facilitate pathogen movement and disease development but instead found that edge effects were the key drivers of plant disease dynamics.

Incorporating Landscape Connectivity

The establishment of emerging plant diseases in natural systems depends on many factors, although dispersal of inoculum is the first precondition for spatial spread (69). Landscape connectivity is increasingly recognized as a major factor, but rarely considered in studies of plant epidemics. However, as natural environments become increasingly fragmented (and connected in some instances) by human activities, understanding the role of landscape connectivity in plant pathogen invasions may be more important than ever (**Figure 1** and **2**).

Ellis et al. (23) studied the relative importance of functional connectivity versus local environmental conditions on the distribution of *P. ramorum* across a heterogeneous landscape in northern California. Given that passive dispersal of microscopic inoculum through wind-blown rain splash could not be traced directly (16), the researchers used least-cost path analyses to model potential transmission pathways within and between fragmented patches of host and nonhost habitat. They applied various scenarios of friction (i.e., transmission cost) assigned to each habitat type because there was little knowledge regarding the ease in which the pathogen disperses through fragmented host populations. For any given movement from a source location i to a target location i+1, the cumulative friction N_{i+1} was calculated as the cost to reach location i plus the average cost to move through location i and i+1:

$$N_{i+1} = N_i + \frac{r_i + r_{i+1}}{2},$$

where r represents the friction value in the corresponding location (1). The least-cost distances were then incorporated into a connectivity term (λ_i), modeled as force of infection (**Figure 4**) in the form of a negative exponential dispersal kernel:

$$\lambda_i = \sum_{k=1}^{n} \left[SL_k \times \exp\left(\frac{-d_{ik}}{\alpha}\right)\right],$$

where SL_k was the severity of disease in plot k, d_{ik} was the least-cost distance between plot i and plot k, and the parameter α modified the form of the kernel that indicated high or low dispersal limitation. Their results showed that functional connectivity was a significant determinant of disease severity, although not as significant as local environmental conditions. In addition, connectivity was only predictive when measured using least-cost path analysis as opposed to measuring Euclidean distances that do not consider landscape heterogeneity (e.g., **Figure 2**).

Human-altered corridors (e.g., narrow strips of restored habitat to connect isolated habitat patches; 101) often inadvertently facilitate disease spread by increasing landscape connectivity (41). For example, Jules et al.

(52) studied the spread of an exotic root rot pathogen, *Phytophthora lateralis*, across a region with riparian habitat for the host Port Orford cedar (*Chamaecyparis lawsonia*) in the western United States. Using tree-ring dating techniques, the authors assessed the roles that vehicles played in long-distance spread of infested substrate compared to shorter-range dispersal of spores by animals and human foot traffic. Their results revealed that host populations following streams connected by roadways suffered significantly greater risk of infection and that the greater connectivity of roads facilitated longer range dispersal than foot traffic. Kauffman & Jules (53) also showed that *P. lateralis* spreads along stream corridors. Their survival analysis along a 1,350-m stretch of stream further revealed evidence contrary to theoretical predictions that disease intensification is primarily dependent upon the distance of a host downstream. Instead, the more significant connectivity factor was the lateral proximity of hosts to the stream channel corridor.

The growing literature on graph theory is illustrating how networks can be used to model the connectivity of movement across large geographic regions (77, 78, 103). In a network of a pathosystem, nodes of susceptible/infected entities can be linked by infection events whose connectedness varies as a function of transmission factors driven by more than distance alone (47). For example, Harwood et al. (39) demonstrated how a nursery plant trade network can be superimposed on a landscape to allow areas of high human activity to function as dispersal shortcuts for disease transmission. The authors constructed a stochastic epidemiological model of *P. ramorum* and *Phytophthora kernoviae* using geographically explicit grids of host plants in conjunction with nursery trade networks in Great Britain to assess the consequences of different types of intervention. The simulations suggest that nursery inspections can be used to control epidemics when efforts target superconnected nodes (i.e., nodes with a high number of links). Although these types of models can be limited by the availability of appropriate data, they hold promise for providing a useful framework for integrating natural and anthropogenic features of landscapes in epidemiological models.

Optimizing Disease Control with Dynamic Landscape Modeling

Invasive plant diseases often spread rapidly in natural and human-altered ecosystems, especially when pathogens are capable of long-range dispersal and asymptomatic infection. Yet, management recommendations typically arise from small-scale experiments that by design cannot consider broader epidemic outcomes of intervention or how external sources of inoculum may affect finer-scale management efforts. Consequently, successful control depends on our ability to develop management strategies that match the spatial and temporal scale of epidemic spread in the most cost-effective manner possible. Mathematical models that incorporate space-time complexity of population dynamics can help us design management strategies across the range of scales needed to control invasions (33, 34). However, the interdisciplinary challenge of infusing geography into dynamic epidemiological models causes most modelers to use simulated or artificial data with assumptions on the spatial scale and heterogeneity in a system that may not be well justified or realistic for predicting epidemic outcomes in particular geographical regions of concern. Below, we highlight recent articles that integrate dynamic epidemiological and geographical modeling to optimize strategies for detection and control across large heterogeneous landscapes.

Meentemeyer et al. (71) developed a stochastic epidemiological model to predict the spread of *P. ramorum* through spatially heterogeneous host populations in forest ecosystems of the western United States, subject to fluctuating weather conditions. Three challenges were addressed in their research: (*a*) development of a dynamic model for predicting geographical spread of a widespread epidemic in natural ecosystems; (*b*) parameterization of a model from snapshots of data on the distribution of host, pathogen, and

Dynamic model: describes how ecological processes change over time; typically represented with difference equations or differential equations

environmental conditions that take into account the principal scales of spread without overfitting a large number of free parameters that are difficult to interpret; and (*c*) spatially explicit prediction of probable epidemic outcomes through the year 2030 to prioritize high-risk locations for detection and control. Their SI (susceptible-infected) simulation model was initiated in 1990 by infecting susceptible vegetation at three known introduction locations. Infection was modeled as a Poisson process,

$$\phi_{jt} = \sum_i \psi_{ijt},$$

where ψ_{ijt} is the rate of spread from an infected site i to site j during week t. The infection pressure from site i to site j was modeled as:

$$\psi_{ijt} = \beta(x_t(f_i)m_{it}c_{it}I_{it})\left(\frac{x_t(f_j)m_{jt}c_{jt}S_{jt}}{N^{\max}}\right) \times \frac{K(d_{ij};\alpha_1,\alpha_2,\gamma)}{d_{ij}},$$

where β controls the overall rate at which spores are produced by infected hosts within a given site per unit time. I_{it} and S_{jt} are the numbers of infected and susceptible hosts at time t in cells i and j, respectively. Host availability in each 250-m cell was derived from detailed GIS maps of Californian plant communities weighted by abundance and competency to produce inoculum (74). $N^{\max}$ is the carry capacity of host vegetation in any site. Parameters m_{jt} and c_{jt} are time- and space-dependent variations in precipitation and temperature, parameterized based on experimental studies and mapped from spatially interpolated estimates of daily weather conditions (16, 45). $K(d_{ij};\alpha_1,\alpha_2,\gamma)$ is a dispersal kernel for movement of inoculum over distance d_{ij} parameterized by Bayesian Monte Carlo Markov Chain estimation of scale parameters: α_1, controlling short-range abiotic dispersal associated with wind-driven rain and mist; α_2, controlling long-range dispersal associated with human activities, such as planting infected ornamentals and transporting infected organic material by hikers, vehicles, and animals (91); and γ, controlling the proportion of spore units that are locally (e.g., <1 km) dispersed. Finally, $x_t(f_j)$ is a phenological indicator variable, equal to 1 if susceptible hosts of type f_j are able to infect and be infected at time t, and 0 otherwise (16). The model showed that most disease spread occurs through abiotic dispersal (<250 m) but occasional long-distance dispersal events significantly increase rates of epidemic spread. Between 2010 and 2030, the model forecasts a tenfold increase in disease spread with most infection impacting northern coastal forests between San Francisco and Oregon.

In a follow-up study, Filipe et al. (27) adapted the model described in Meentemeyer et al. (71) to optimize landscape-scale strategies for managing invasive plant pathogens in natural ecosystems. Their study focused on controlling the spread of an isolated outbreak of sudden oak death in northern California. A long-range dispersal event occurred in the late 1990s that led to a rapidly expanding epidemic focus with considerable tree mortality (67, 91). The epidemiology of *P. ramorum* posed several challenges to designing effective strategies of control that required the use of dynamic landscape modeling. First, the pathogen's ability to disperse long distances with asymptomatic infection introduced substantial complexity into knowing how to best match the spatial and temporal dimensions of epidemic spread with effective control. Delayed detection in conjunction with long-range dispersal may allow a pathogen to continue spreading following treatment of symptomatic hosts (38). Second, methods for controlling the spread of *P. ramorum* have been limited to small-scale yet expensive reduction of inoculum (culling and burning infected hosts) and preemptive removal of susceptibles (no curative chemical or biological control exists) with little understanding of the type and amount of upscaling needed to be effective across landscape to regional extents. These issues are further complicated by the long infectious period and generalist nature of the pathogen, which greatly amplify the risk and uncertainty of spread.

Filipe et al. (27) used their model to explore several landscape-scale scenarios of control being considered by policy makers. The scenarios

included a combination of culling infected and susceptible hosts within and beyond the spreading focus, protective aerial spraying, and construction of a controversial host-free barrier to the north of the focus. Their modeling revealed that the proposed barrier by itself would not prevent wind-blown dispersal northward, but strategic combinations of removing inoculum and susceptible hosts beyond the focus could contain epidemic spread. This discovery was made possible by analyzing multiple scenarios of control that considered the principal scales of epidemic spread and real-world landscape heterogeneity of the pathosystem—practical results that have given policy makers critical guidance on when and where to apply costly control measures across heterogeneous landscapes.

WHAT'S NEXT?

Landscape epidemiology holds great promise for developing new interdisciplinary approaches that advance our understanding of the ecology of infectious diseases in both natural and human-altered ecosystems. In her recent MacArthur award lecture to the Ecological Society of America, Monica Turner identified "interacting disturbances" as a priority for future research efforts at larger spatial and ecosystem scales (102). Attention to interacting disturbances in disease systems is critical because the combinatorial effects of EIDs with other ecological disturbances can produce nonlinear dynamics with thresholds, feedback loops, time lags, and unexpected outcomes. For example, Metz et al. (76) discovered a complicated interaction between the forest disease sudden oak death and wildfire severity in California forests, where increased fuel load from disease-induced host mortality contributed to burn severity only in areas where the pathogen had recently invaded, reflecting the changing nature of disease impacts over time. Opportunities exist across a range of pathosystems to explore feedbacks between disease dynamics and other natural disturbances, such as wildfire, weather anomalies, floods, or an additional biological invasion. For instance, how do the joint impacts of emerging disease and other disturbances influence community trajectory, ecosystem resilience, and long-term epidemic outcomes? Can our understanding of interacting disturbances be scaled up to anticipate impacts at broad geographic extents and guide management resources?

The explicit consideration of reciprocal feedbacks between human activities and disease dynamics is a further understudied area of research likely to produce transformative discoveries. Societies depend on ecosystem services provided by natural systems, yet human activities—through direct and indirect effects—change the flows and efficiency of ecosystem provisioning, making up what socioecological researchers conceptualize as a coupled human-natural system (CHANS) (61; see **Figure 6**). Needed are CHANS-based

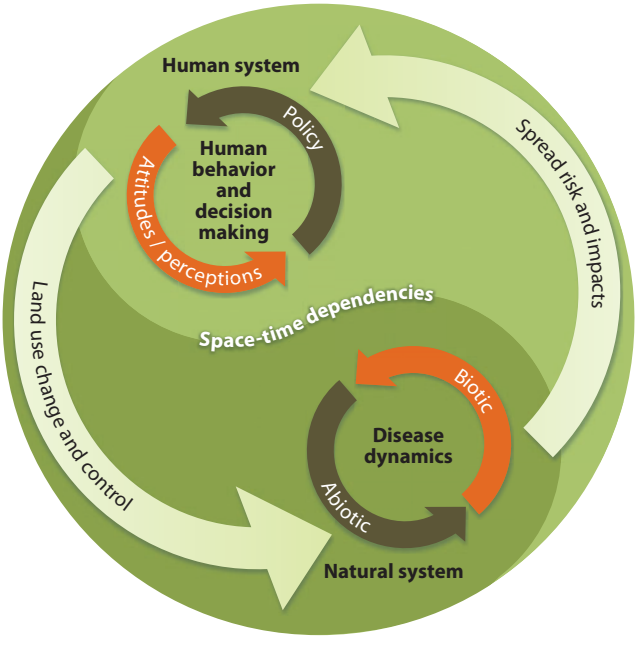

Figure 6

Schematic of a transdisciplinary framework for analyzing emerging infectious diseases of wild plant and animal populations as a coupled human-natural system (CHANS). Integrated approaches that explicitly analyze reciprocal feedbacks between human activities and disease dynamics are needed to understand which management policies and incentives influence willingness of stakeholders to participate in control and in turn how the spatial and temporal implementation of management actions influence the spread and persistence of disease.

approaches that holistically contextualize disease systems in transdisciplinary frameworks, with natural and social scientists collaborating on common questions where not only ecological processes (e.g., biodiversity and ecosystem function) and human dimensions (e.g., socioeconomics, social networks, governance) are analyzed but also feedbacks that link epidemiological processes with human behavior and decision making (**Figure 6**). However, disconnects between academic cultures and the scales required for integrated analyses make CHANS research challenging to conduct (63).

We believe the techniques and approaches fostered by landscape epidemiology can help bridge the gaps between disciplinary perspectives on disease systems. Consider the complexity of controlling an emerging forest disease across a heterogeneous landscape with a mixture of public and private land ownership and diverse stakeholder attitudes toward management action. Key questions arise that require landscape perspectives, such as should a control be applied to the center of the epidemic or to isolated outbreaks and how would delays in deploying control efforts affect epidemic outcomes and social perceptions? From the social science side, we want to learn how stakeholders perceive epidemic risk and ecological impacts, how this influences their participation in control, and which management policies and incentives change their willingness to participate. From the ecological side, we need to understand how the spatial and temporal implementation of management actions influences the spread and persistence of disease. Only when we integrate these multilevel processes within a CHANS analytical framework can we begin to explore the reciprocal feedbacks between human behavior and disease dynamics that govern the tipping point between successful collective action and out-of-control invasion.

SUMMARY POINTS

1. Landscape epidemiology is more than simply establishing plots in the field and examining differences in local environmental conditions among sites; the key is to gain insight into the geographical distribution of disease and to understand how landscape connectivity influences spatial interactions between susceptible and infected individuals.
2. The nascent field of landscape epidemiology is still striving to develop a clear identity. Few studies have applied dynamic modeling and multiscale approaches to natural and human-altered ecosystems. To date, animal and zoonotic diseases have been studied in more cases using landscape epidemiological approaches than have plant systems.
3. There is no single natural scale at which ecological phenomena, including pathogen invasions, should be studied because each species uniquely experiences its environment, depending on its life history characteristics, the diversity and distribution of its hosts, and the abiotic factors it encounters. We recommend careful consideration—based on theoretical and empirical evidence—be given to three classes of scale: the phenomenon scale, the sampling scale, and the analytical scale.
4. Dynamic epidemiological models allow phenomena to change through the successive stages of invasion that an EID undergoes, yet their application to realistic landscapes is relatively rare because of the challenge of integrating models with detailed, real-world geographical data across broad spatial extents.
5. Incorporating spatially explicit interactions among neighboring observation units is too often ignored when developing static models.

6. The challenge of measuring drivers of disease spread across heterogeneous landscapes often compromises their ecological meaningfulness. We need to measure variables that capture direct environmental gradients (e.g., temperature or moisture availability) and avoid using indirect variables (e.g., elevation) that have no direct physiological effect on a pathogen's survival and reproduction.
7. Efforts to obtain sound ecological inference versus prediction of epidemic risk often lead to analytical trade-offs between model parsimony and complexity. We caution that too much focus on capturing every nuance of spatial heterogeneity may at times narrow our view to a point where analytical complexity interferes with understanding.

FUTURE POINTS

1. As multiscale approaches to landscape epidemiology are increasingly embraced, can we begin to learn which landscape contexts allow epidemiological processes to be scaled up to large geographic extents and which do not?
2. New approaches to modeling functional connectivity in natural ecosystems are needed to better understand how landscape conditions influence the spread and persistence of disease across heterogeneous landscapes.
3. Development of dynamic landscape epidemiological models will allow us to predict impacts and optimize large-scale strategies for managing EIDs in natural ecosystems.
4. How do the joint impacts of emerging disease and other disturbances influence community trajectory, ecosystem resilience, and long-term epidemic outcomes? Can our understanding of interacting disturbances be scaled up to anticipate impacts at broad geographic extents and guide management resources?
5. The explicit consideration of reciprocal feedbacks between human activities and disease dynamics will likely produce transformative discoveries. Can a CHANS framework be used to predict the reciprocal feedbacks between human behavior and disease dynamics that govern the tipping point between successful collective action and out-of-control invasion?

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Errata

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