Spatial epidemiology: an emerging (or re-emerging) discipline

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Spatial epidemiology is the study of spatial variation in disease risk or incidence. Several ecological processes can result in strong spatial patterns of such risk or incidence: for example, pathogen dispersal might be highly localized, vectors or reservoirs for pathogens might be spatially restricted, or susceptible hosts might be clumped. Here, we briefly describe approaches to spatial epidemiology that are spatially implicit, such as metapopulation models of disease transmission, and then focus on research in spatial epidemiology that is spatially explicit, such as the creation of risk maps for particular geographical areas. Although the spatial dynamics of infectious diseases are the subject of intensive study, the impacts of landscape structure on epidemiological processes have so far been neglected. The few studies that demonstrate how landscape composition (types of elements) and configuration (spatial positions of those elements) influence disease risk or incidence suggest that a true integration of landscape ecology with epidemiology will be fruitful.

Spatial epidemiology
Pathogens use many different modes to disperse from an infected to an uninfected host. Some modes involve direct contact (e.g. pathogens transmitted during aggressive or sexual encounters), some involve near-direct contact (e.g. pathogens excreted by one host and inhaled or consumed by another), whereas others rely on an arthropod vector. In most cases, the probability of transmission declines dramatically with distance from an infected host. As a consequence, factors affecting the spatial positions of pathogens, hosts and vectors, and their probability of close encounter, are fundamentally important to disease dynamics. Spatial epidemiology has arisen as the principal scientific discipline devoted to understanding the causes and consequences of spatial heterogeneity in infectious diseases, particularly in zoonoses (i.e. diseases that are transmitted to humans from non-human vertebrate reservoirs).

Much credit for the early development of spatial epidemiology should go to the Russian parasitologist, Pavlovsky, whose work [1] from the 1930s describing what he called ‘landscape epidemiology’ was ‘discovered’ by Western epidemiologists several decades later. Pavlovsky’s historical concept of landscape epidemiology consists of three basic observations. First, diseases tend to be limited geographically; second, this spatial variation arises from underlying variation in the physical and/or biological conditions that support the pathogen and its vectors and reservoirs; and third, if those abiotic and biotic conditions can be delimited on maps, then both contemporaneous risk and future change in risk should be predictable.

Maps or no maps?
Given that the transmission of pathogens leading to disease requires the close juxtaposition of a susceptible individual with an infected conspecific, vector, or environmental source of pathogens, transmission dynamics are inherently spatial processes. However, understanding the spatial processes that contribute to variation in disease transmission might not require maps of geographical entities. One such example is the use of the metapopulation concept, whereby hosts are assumed to exist in largely isolated subpopulations, each subject to colonization and extinction dynamics. Typically, such an approach does not involve the creation of physical maps of abiotic or biotic elements, but instead is ‘spatially implicit’ in avoiding the placement of subpopulations or individuals at explicit spatial coordinates. Because metapopulation approaches to infectious disease have been reviewed recently [2], we restrict our focus to spatially more explicit approaches.
Mapping spatiotemporal dynamics of disease

Maps have been used for two distinct purposes in epidemiology. The first involves retrospective analyses of spatiotemporally dynamic epidemics to understand what factors govern the spatial pattern and rate of spread of diseases. For example, a spatiotemporally dynamic approach was used to research foot and mouth disease (FMD) in cows and sheep in the UK. During 2001, FMD underwent explosive growth, resulting in the culling of millions of livestock [3]. The effectiveness of alternative culling strategies was predicted by using epidemiological models in which farms of different sizes (number of livestock), species composition (cattle only, sheep only, or mixed), and infection status (infected or susceptible) were mapped [4]. The spatial clustering and spread of FMD, combined with the observation that larger farms containing both cattle and sheep were most susceptible, were used to model local and long-distance transmission rates. These results were used to predict how different control strategies (prophylactic vaccination, reactive vaccination, or culling) would impact FMD epizootics [5]. The models showed that vaccination programs could be effective if they were spatially targeted and quickly followed FMD detection [5]; however, for political reasons, culling was the strategy used, in this instance, to stop the epizootic [3].

Spatiotemporally dynamic approaches have also been used to describe the characteristics of ‘traveling waves’ in epidemics of measles and dengue hemorrhagic fever. Before vaccination was common, measles epidemics in England and Wales tended to peak every other year and traveled in waves from large cities to small surrounding towns [6]. In large cities, measles occurred as endemic disease until the number of susceptible children exceeded a threshold, triggering an epidemic that traveled to surrounding smaller towns. In these towns, the epidemic was followed by the extinction of the measles virus because the population of susceptible children was below a critical threshold necessary to sustain transmission. Where cities were connected to one another by surrounding towns, measles epidemics fluctuated synchronously, but for cities at large distances from one another, biennial peaks in incidence were out of phase [6]. Vaccination caused synchronous epidemic cycles of measles to degrade into an irregular, asynchronized disease [7]. In the first demonstration of a traveling wave pattern in a vector-borne disease, Cummings et al. [8] described how epidemics of dengue hemorrhagic fever traveled from Bangkok through-out Thailand at the extraordinary speed of ~150 km month \(^{-1}\), repeating about once every three years.

Spatiotemporally dynamic analyses require that data on disease incidence be highly precise, both in space and time, and also require sophisticated spatial models to describe patterns in detail. When these requirements are met, the approach appears quite useful for targeting disease prevention or treatment in space and time.

Static risk mapping

The second major use of maps in epidemiology is to characterize spatial variation in contemporaneous (static) ecological risk of infection and potential causes of that variation. Ecological risk can be defined as the probability of exposure to an infection in the absence of active preventative measures. Efforts to create risk maps pertaining to specific diseases have increased in recent years, and these can be categorized as being based on distributions of arthropod vectors, vertebrate reservoirs, or actual cases of disease in the host, usually in humans (Table 1). Irrespective of the focal entity, the most common procedure is to: (i) construct distribution maps of the vector, reservoir, or disease; (ii) use remote-sensing data (Box 1) and geographical information systems (GIS; Box 2) to characterize the distribution of abiotic conditions and sometimes vegetation that might influence the vector or reservoir; (iii) select remote-sensing variables that are most strongly associated with the distribution of the vector, reservoir, or disease; and either (iv) project the distribution of the identified remote-sensing variables to either other areas or future times, to make predictions about disease risk beyond the current map; or (v) guide the imposition of interventions, such as pesticide application or vaccination [9,10]. Because arthropod vectors, vertebrate reservoirs and cases of disease in humans represent distinct challenges for the mapping of disease risk, each approach is discussed in turn.

Risk mapping based on vectors

Demographic rates of arthropod vectors of human pathogens tend to be sensitive to variation in temperature and moisture. Cold temperatures induce mortality or diapause, slow developmental rates, or reduce host-seeking activity [11,12]. Similarly, rainfall creates habitat for breeding (e.g. for mosquitoes and midges), and high humidity is necessary for survival of some insect and tick vectors [13]. The dependence of vectors on specific abiotic conditions, combined with advances in remotely sensing and mapping variation in abiotic conditions, has stimulated efforts to create risk maps for vector-borne diseases [9,10]. From an almost infinite number of abiotic variables that can be spatially referenced on maps, typically a subset is chosen and confronted with data on either presence versus absence or abundance of vectors. Those abiotic variables showing the greatest degree of spatial concordance with vector distribution are assumed to be causative and are often used to predict current distributions of vectors in unstudied areas or future distributions under different scenarios of climate change (Table 1).

Limitations to this approach fall into two major categories. First, disease risk or incidence is more closely correlated with the abundance of pathogen-infected vectors, rather than with simply presence of vectors, or total abundance of vectors. For instance, Lyme disease in North America is largely restricted to the northeastern and upper Midwestern USA in spite of widespread populations of the tick vector in southeastern and lower Midwestern regions [14,15]. The invasion of North America by West Nile Virus appears unrelated to changes in the distribution or abundance of mosquitoes, but rather with changes in the distribution of the virus in vectors and avian reservoirs [16]. Only in rare cases [17] is the abundance of infected vectors used to create maps of risk. Second, such studies are fundamentally
correlational, so that the direct causal relationship linking environmental conditions to vector distribution or abundance remains to be established.

**Risk mapping based on reservoirs**

Less commonly, risk maps are created from distributions of wildlife reservoirs for human pathogens (Table 1). Such efforts have been most successful in predicting the risk of directly transmitted zoonoses, such as hantavirus pulmonary syndrome. Abundance of the deer mouse *Peromyscus maniculatus* reservoir in the southwestern USA is predictable from plant community composition (pine and oak abundance, which is determined with the plant community composition and spatial values of satellite imagery), and hantavirus pulmonary syndrome cases, in turn, are predictable from mouse abundance [18] (Figure 1). By contrast, in the case of tularemia, a bacterial disease that is highly pathogenic to wildlife and humans (causative agent, *Francisella*...
In incidences treatment is risk include: (i) discrepancies filtration of drinking water, can strongly reduce incidence with statistically robust measures of spatiotemporal assumption that incidence and risk are highly correlated to new geographical areas or future times, under the extrapolate the risk of exposure from current distributions. Spatial data on disease incidence can be used to the typical situation for mapping vectors and reservoirs. For some diseases, particularly those of humans, extensive reservoir remains unknown [16].

There are numerous satellite-based remote-sensing systems that can be used to monitor environmental conditions. They vary in three key aspects: their spatial, temporal and spectral resolution [51]. The spatial resolution, as measured by the picture element (pixel) resolution provides information about the level of spatial detail that can be interpreted. Among civilian-based systems, there are three major resolution groups: high-resolution (0.5–1.8 m); mid-resolution (2.0–36 m); and low-resolution (>36 m) [52]. High-resolution systems are of increasing interest because of their usefulness in evaluating the classification accuracy (ground-truth) of environmental data that has been interpreted from mid- and low-resolution imagery. However, high-resolution imagery often covers much smaller areas on the ground in a single image so that high-resolution swaths are in the 8–28 km range whereas mid-resolution images typically cover a 70–185-km swath [52]. Platforms also vary in their temporal revisit rate, making them more or less appropriate for monitoring daily or seasonal environmental changes. Temporal resolution can be as much as 16–17 days. Particularly with passive systems, factors such as cloud cover over a region might extend this timescale to the next revisit that is cloud-free. Particularly in regions of the world with seasonal variation marked by intensive rains, this might represent several months.

Spectral resolution is an area of major development in remote sensing. Previous systems, such as Landsat and SPOT, recorded reflected energy over relatively large bands of the electromagnetic spectrum. Current interest is focusing on hyperspectral imaging, the simultaneous acquisition of images in many, narrow, contiguous, spectral bands. The resulting hyperspectral data are intended to offer a more detailed view of the spectral properties of a region and make interpretation more accurate. Radar and lidar (light detection and ranging) represent two other systems for remote sensing. Active microwave systems, in particular, represent an active area of investigation. Three civilian systems currently are available and nine are planned by 2010 [52].

Many of the challenges facing the use of remotely sensed data involve issues related to data management and access related to the collection, archiving and accessibility of data on global scales [52]. The detailed coverage provided by each individual sensor generates extremely large amounts of data whose primary value comes from researchers being able to use them to examine changes in environmental conditions over time. When this is coupled with the large numbers of planned sensors ease of data integration and seamless access will help determine the extent of the usefulness of this technology to epidemiologists, as well as to researchers in other fields. Unfortunately, this aspect of data management appears least developed and the lack of planned sources for the metadata on the materials that will be collected will make it difficult to locate needed materials.

tularensis), GIS descriptions of the habitats most suitable for the common vole Microtus arvalis, which is considered to be an important natural reservoir, did not predict the locations in which European hares Lepus europaeus undergo epizootics [19]. Recently, GIS modeling combined with statistically robust measures of spatiotemporal clustering of epidemiological events demonstrated that the locations of dead American crows Corvus brachyrhynchos around New York City during 2000 could be used to predict the locations of human victims of West Nile virus during 2001 [20]. Five of seven human cases of West Nile encephalitis occurred in areas designated high or medium risk based on crow mortality. American crows are frequently killed by West Nile virus, although their status as a wildlife reservoir remains unknown [16].

Risk mapping based on disease incidence
For some diseases, particularly those of humans, extensive data sets with good spatial accuracy exist, in contrast to the typical situation for mapping vectors and reservoirs. Spatial data on disease incidence can be used to extrapolate the risk of exposure from current distributions to new geographical areas or future times, under the assumption that incidence and risk are highly correlated (Table 1). Risk maps based on distributions of actual disease cases can be seen as incorporating spatial variation in all risk factors, such as the distribution of vectors, reservoirs and human contact with key species (Figure 2). Some major disadvantages of using disease incidence to estimate risk include: (i) discrepancies between risk and incidence. For instance, the widespread use of preventative measures, such as mosquito bednets or filtration of drinking water, can strongly reduce incidence in areas where risk of exposure is high [21]. A related complication occurs when high exposure to a parasite leads to immunity and, consequently, to low disease incidence for the subset of the population previously exposed [22]; (ii) poor or inconsistent standards of case reporting, especially across geopolitical boundaries. Under-reporting is a notorious problem, but for diseases with generalized symptoms and diagnostic difficulties, over-reporting might be quite common. Variation in types of surveillance (passive, active, clinical and laboratory) or case definitions can reduce consistency (Figure 2; [23]); and (iii) discrepancies between locations where infection was obtained and where the disease case was reported. This is particularly a problem for fine-scale analyses. For all of these disadvantages, a key unresolved issue is when the factors simply contribute to random error and when they introduce spatial or temporal biases into geographical analyses.

The following examples illustrate how spatial distributions of disease incidence have been used to either postulate specific habitat features associated with disease, or to extrapolate from current to future distributions.

Hantavirus pulmonary syndrome In a retrospective study of hantavirus pulmonary syndrome in the southwestern USA, areas of high incidence could be identified on the basis of both Landsat Thematic Mapping bands, representing soil type and moisture, and vegetation structure [24] (Figure 1). Satellite data could then be used to predict locations where outbreaks were expected [24].

Falciiparum malaria Rogers and Randolph mapped the worldwide distribution of falciparum malaria to derive the multivariate (temperature, precipitation and vapor pressure) abiotic boundary conditions within which malaria occurs [25]. They then projected the future distribution of
Box 2. Recent developments in GIS for analysis of spatial data in epidemiology

GIS are techniques to input, store, retrieve, manipulate, analyze and output data that have spatial attributes associated with them [53]. As such, they form an underlying tool for examining landscape epidemiology. They can be used to locate cases of disease, and establish the spatiotemporal relationships among the cases and selected environmental features. The need to integrate data derived from various sources accurately and efficiently manipulate and represent disparate data has driven the development of software systems over the past decade.

More recent advances have focused on methods to analyze spatially associated data, with earlier attempts driven primarily by the creation of maps to represent the results. Attempts to apply traditional statistical methods were generally unsatisfactory because underlying spatial correlation among observations violates one of the key assumptions (independence of observations) made for most analyses. This violation typically results in the assumption of greater statistical significance than is warranted [54].

Three major areas of statistical analysis of GIS data have received most attention. Much progress has been made in applying or developing methods to detect spatial and/or temporal clusters of cases [54]. However, most methods simply detect potential clusters, leaving the causes of the clustering unknown. If the purpose of the investigation is to identify places and times for further investigation or for intervention this is less problematic than if the goal is to identify environmental risk factors, themselves.

Geostatistical methods used to estimate disease exposure levels at unsampled locations have also advanced in recent years [54]. For example, several modeling approaches that account for spatial correlation have been developed to estimate human exposure to disease agents vectored by *Ixodes scapularis* ticks in unsampled regions [17,39,55,56]. Finally, modeling and estimating risk factors for disease outcomes through empirical Bayesian or generalized linear mixed modeling approaches are receiving increased attention as methods that can incorporate correlations in observation sets.

Visceral leishmaniasis Werneck et al. used spatial analysis of visceral leishmaniasis cases in northern Brazil to identify proximity to forests and pastures as the major risk factor [27]. The parasite causing visceral leishmaniasis is transmitted from vertebrate reservoirs to humans by sand fly vectors and, in some cases, domestic dogs are known to be important reservoir hosts.

those boundary conditions according to climate projections to predict the future distribution of malaria. Their projections, based on climatic conditions correlated with human malaria cases, suggested a much smaller increase in cases of malaria with global warming than did projections based on climatic conditions correlated with mosquito distributions [26].

![Figure 1. Conceptual model of the relationship between environmental factors that influence disease and observed incidence of that disease in humans. Underlying environmental factors (e.g. temperature, precipitation, land use and soil type) can influence the distribution of vectors and hosts for a particular disease. These distributions influence the risk to humans of coming into contact with the pathogen that causes the disease, and variation in this risk is one factor that determines the actual number of cases of human disease. Because of differences in surveillance and reporting and other issues discussed in the main text, the observed incidence in humans is likely to be a subset of actual cases. A similar model is detailed in [23].](https://www.sciencedirect.com)
Identification of forests and pastures, rather than peridomestic habitat, as particularly risky habitats suggests a wildlife, rather than domestic, reservoir for the Leishmania parasite [27].

LaCrosse Encephalitis Similarly, for LaCrosse encephalitis in Illinois, Kitron et al. used GIS and spatial statistics to identify physical features such as gullies and ravines, which often contain both natural and artificial breeding sites for mosquitoes, as major risk factors [28].

Onchocerciasis and schistosomiasis About 50% of the variation in onchocerciasis incidence among West African villages was explained by variation in forest cover and landcover class, with little explanatory power of rainfall, temperature, or soil [29]. Satellite-determined normalized difference vegetation index (NDVI) was a strong predictor of schistosomiasis distributions in Bahia, Brazil [30].

Tick-borne diseases Diseases borne by ticks have received considerable attention from spatial epidemiologists. In an early study of Lyme disease in Maryland, Glass et al. found that individuals living in rural residences on sandy loamy soils and embedded within forest had increased risk [31]. By contrast, both human and canine exposure to Lyme disease in the Midwestern USA is associated with residences near urban forests and on sandy soils [32]. In New York State, Lyme disease incidence is spatially aggregated at a scale of ~120 km, which appears to pertain to dispersal distances of key tick hosts rather than to environmental variables [33]. The distribution of tick-borne encephalitis in Europe can be predicted from NDVI and land-surface temperature [34]. Although NDVI appears to represent suitable abiotic conditions for the tick vector, land-surface temperature has a more subtle effect on the transmission dynamics of the pathogen from vertebrate host to tick. Transmission of tick-borne encephalitis requires infected nymphs and uninfected larvae to co-feed simultaneously on individual hosts, and the
probability of co-feeding depends on synchronous seasonal activity by larvae and nymphs, which, in turn, depends on seasonal changes in land-surface temperature [34]. Because the tick-borne encephalitis transmission cycle is an unstable consequence of conditions favoring larva–nymph synchrony, climate change scenarios are predicted to shift tick-borne encephalitis initially northward in Europe, followed by its almost complete loss from the continent [35]. These examples illustrate how remote-sensing data on biotic and abiotic features, combined with spatial data on disease incidence, can be used to explore underlying causes of disease risk. However, they also suggest that, when vectors, reservoirs, pathogens and humans respond differentially to biotic and abiotic factors, correlations between remotely sensed habitat features and disease incidence might not provide insights into underlying mechanisms.

Incorporating explicit landscape elements
If vectors, reservoirs and pathogens are influenced only by highly localized habitat features, then spatial epidemiologists need not concern themselves with the structure of the surrounding landscape. However, landscape ecologists have compiled many examples of how landscape context, in addition to localized habitat features, influence populations of animals and plants [36–38]. Only recently, and for only a few disease systems, have the types, sizes and positions of landscape elements (e.g. habitat patches, physical or biotic gradients, and type of matrix surrounding patches) and their connectivity been considered potentially important drivers of risk or incidence. For Lyme disease, tick abundance in a landscape has been correlated with patch shape and the degree of connectivity between high quality patches for ticks and other patches, suggesting that host movements contribute importantly to tick distribution [39–41]. Both the abundance and proportion of ticks infected with the Lyme disease spirochete increased with decreasing size of forest fragments in a suburban matrix in New York State [42]. Spatial modeling of raccoon rabies in the northeastern USA revealed that specific landscape features, such as large rivers and mountain ranges, can strongly influence the rate and direction of rabies invasion, interrupting the otherwise wave-like spread [43,44]. Landscape composition (percent of suitable habitat) and landscape configuration (fragmentation of habitat) were key positive determinants of Sin Nombre virus (the agent of hantavirus pulmonary syndrome) seroprevalence in deer mouse populations across Canada [45]. Similarly, degree of fragmentation of white-footed mouse habitat was positively associated with the prevalence and intensity of infection of mice by the raccoon roundworm Baylisascaris procyonis [46].

These examples illustrate that, at least in some cases, the structure and composition of the landscape surrounding focal sites must be considered together with the set of highly localized biotic and abiotic features to understand disease risk. Two major research challenges are determining how often disease risk can be predicted from local conditions alone, and how often the landscape context modifies or overrides the impact of local conditions.

Caveats and future directions
The overarching question for spatial epidemiologists is whether disease risk or incidence can be explained by (or predicted from) the distribution of vectors, reservoir hosts or human cases. But distribution is a difficult concept. Creating distribution maps based on presence or absence (i.e. boundary conditions) is relatively simple, but excludes potentially crucial information about abundance of vectors, cases, and so on, within their range. Even when the abundance of vectors, reservoirs, or disease incidence are mapped, misleading results might occur if:
(i) Vector infection varies spatially (e.g. Anopheles mosquitoes are abundant in large geographical areas with no malaria because the Plasmodium parasite has been eliminated), destroying an assumed correlation between simple vector abundance and disease risk.
(ii) The abundance of vertebrate reservoirs is highly dynamic spatially or temporally [14], which could lead to significant variation in risk that would be invisible to cross-sectional mapping exercises.
(iii) Vertebrate reservoirs are less strongly (or simply) delimited by climatic or vegetation variables that can be remotely sensed and organized with GIS.
(iv) The disease system is in disequilibrium; for example, when vector or pathogen range is expanding. In the case of an expanding range, the assumption that the vector or pathogen lives everywhere it can currently live is violated and, therefore, projecting future distributions is compromised. The importance of landscape composition (number and types of patches) and configuration (spatial relationships among patches) [47] to disease dynamics is only beginning to be explored. Landscape structure has a strong potential to influence disease dynamics through impacts on both abiotic conditions (e.g. abundance of edges or changes to environmental gradients) and species interactions that are important to disease spread and prevalence. For instance, by reducing or eliminating predators on disease reservoirs, fragmentation could increase disease risk above that expected from local habitat quality alone [48]. Pathogens, vectors, reservoirs and hosts are all embedded within ecological communities within which they interact directly or indirectly with many other species. As diseases invade new areas or change distribution with climate and land-use change, a major research challenge will be to determine the level of ecological complexity that is necessary to predict spatial dynamics accurately. At one extreme is the notion that species (including pathogens) are restricted to specific abiotically defined niches, which can be accurately mapped and tracked into the future [49]. At the other is the argument that trophic interactions among species and landscape structure contribute crucially to current patterns of abundance and distribution, such that future distributions cannot be predicted simply by tracking changes in abiotic conditions [50]. The spatial ecology of disease seems to be an excellent platform from which to explore these issues.

Finally, the use of spatial models to generate risk maps, followed by assessment of the sensitivity and specificity of these models, could lead to the formulation of specific plans to manage or control disease. Techniques of spatial
epidemiology can generate recommendations concerning where to target interventions to prevent disease spread, but the usefulness of suggested interventions will require collaborative efforts among ecologists, epidemiologists and health care professionals to evaluate feasibility and efficacy. Such collaborations, if successful, would stimulate the further development of this emerging research area.

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