Heterogeneity of mixing and spatio-temporal models: advances and open problems

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March 11, 1997

1 Introduction

Despite optimistic predictions [37], many infectious diseases of humans, other animals, and plants persist in the face of modern medicine and technology. Epidemiological theory has a vital role to play in disease control; even if medical and molecular science could provide a "magic bullet"—a cheap, 100% effective treatment with no side effects—we would still need practical advice about how to target it effectively in the population. In the absence of perfect cures and unlimited resources, theory has to provide practical advice on how to predict, control, and (eventually) eradicate various infectious diseases.

These practical challenges connect with particular issues in theoretical epidemiology. To *predict* the course of an epidemic requires us to understand the mechanisms of disease spread; to *control* disease, we need to know how much effort will reduce disease incidence to a certain level, which in turn requires us to understand what determines endemic levels of disease; and to *eradicate* disease, we must understand how disease persists in a population. These problems are not new; the classical foundations of theoretical epidemiology are based on answering these questions in a hypothetical, homogeneous population [51, 52]. Much of the subsequent development of theoretical (dynamical) epidemiology has extended these results to populations with various forms of heterogeneity, particularly *heterogeneity of mixing*: variability in the probability or rate of epidemiological contact between individuals. For example, epidemiological modellers have studied differences in contact rates among and between age groups [5, 6, 29, 92], and among and between different sexes, racial groups and sexual activity groups [28, 41, 54, 71].

Spatial structure is one of the most important forms of mixing heterogeneity. Space matters in epidemics because transmission depends on the distance between individuals. "Distance" can be defined either narrowly, as Euclidean distance between two points on the plane or geographic distance between two cities, or broadly, as the social distance between individuals in different families, neighborhoods, and so forth. In fact, we can really turn the definition around and define space in terms of epidemics, so that all distances are proportional to transmission probabilities. All we really mean by space is a particular kind of structured contact between individuals; spatial models use spatial structure to narrow the impossibly general variety of possible contact structures in populations.

Human, non-human animal, and plant epidemics differ both in their spatial dynamics and in treatment and control options.

- Plant epidemics are clearly spatial, because of the fixed spatial positions of plants; spatial transmission occurs by random movement of wind or water, or by more directed movement of vectors, usually insect herbivores or pollinators. Plant epidemics can be controlled by chemical treatments, or perhaps by producing resistant types of plants which replace or mix with susceptible varieties.

- Animal epidemics are most clearly spatial when they spread among distinct populations, or when they involve territorial animals. Epidemics of livestock can sometimes be treated, but with many agricultural and most wildlife epidemics the only choices are vaccination or destruction of infected animals and susceptible animals, the latter in hopes of reducing susceptible density below a threshold level.
- Human epidemics have the most complicated form of spatial dynamics; whether we consider countries, cities and towns, or neighborhoods, humans interact along a complicated hierarchical social network. Human epidemics can be controlled by vaccines or behavioral changes, or by quarantining or treating infectious individuals.

Spatial models suggest answers to outstanding problems in many areas of epidemiology. We can divide the effects of spatial structure on epidemics according to the different practical problems addressed above:

- *Persistence.* Many diseases persist surprisingly well in populations where non-spatial (deterministic and stochastic) models suggest they should go extinct [40]; spatial models suggest that the nonlinear interactions of weakly-coupled stochastic populations may lead to "rescue effects" [20], where disease is reintroduced from neighboring populations. (Note that as always we can also generate explanations for disease persistence at the level of individual hosts, for example if asymptomatic carriers exist. The distinction between individual- and population-level explanations must be empirical.)
- *Endemic levels.* Any time that infectives come in contact with each other or with recovered (immune) individuals more often than with susceptible individuals (relative to some rate expected from homogeneous-mixing), infective contacts are "wasted" and speeds of spread and endemic levels of disease are reduced. Wasted contacts occur in any non-homogeneous model, but can be particularly important in stochastic spatial models where infectives tend to infect nearby susceptibles, and as a result end up eventually (at equilibrium) in neighborhoods with more infectives and recovered individuals than average. Wasted contacts will lower the endemic incidence of disease—as infectiousness and contact rates go up, so will the proportion of wasted contacts. Conversely, "macroscopic" estimates of epidemic parameters based on endemic incidence levels will be biased downward, leading to overoptimistic control predictions [34].
- *Spread.* If we want to know about spread of a disease, we almost always care about space. Questions about when a spatially-spreading disease will reach a particular community are obviously spatial; less obviously, spatial structure and spatial effects of a population will affect even average rates of spread because contacts will be wasted, as described above. Although epidemiologists have studied some forms of spreading waves of disease for a long time, new studies of the patchiness of disease spread are suggesting that the wasted-contact phenomenon may be important.

These problems have all been addressed in the literature, especially in [38,67]; this review aims to discuss useful recent developments in theoretical epidemiology, and what the open problems appear to be. We start by briefly reviewing the basics of some of the main approaches to spatial models, then go on to discuss what these different approaches say about disease control and eradication and how we can calibrate and test the models against data from epidemics.

2 Modelling frameworks

We will divide spatial models into three broad categories (many other categorizations are possible), according to the ways in which they trade off different kinds of assumptions about contact structure with generality and mathematical and statistical tractability. Compartment models divide the population into locally well-mixed populations with some kind of between-population contact structure; continuum models assume that individuals are located at points in a continuous plane and that their contact rate is fairly directly related to the Euclidean distance between them; and network models assume that individuals are located the nodes of a graph (often with some hierarchical structure) which contact rates related to the presence or strength of links between different nodes.

2.1 Box models

Box models have been the standard way of dealing with spatial heterogeneity in human populations [4]; they assume that contacts *within* a compartment (city, neighborhood, social group) are homogeneously distributed (these are also called "compartmental models", but note that the social/spatial compartments are added to the division of the population by infection status [e.g. Susceptible, Infective, Removed]).

- In the most general case [41,46,47,77,91,93] we have arbitrary mixing among boxes, subject only to general structural constraints that all contacts coming from one box must find recipients in another box. The general theory gives criteria for the stability of endemic equilibria in compartmental systems; it has been applied, very usefully, to the possible interactions between "core groups" and a larger population [44, 46, 89]. However, the general theory is linear and only tells us about behavior in the neighborhood of the equilibria for models with nonlinear dynamics.

  The basic theory of box models was well established in the 1980s, but does not say much about spatial systems in particular. A subclass of analytic box models that has been more widely used for spatial systems makes stronger assumptions about connections between boxes, for example that all boxes are equally strongly connected (*pseudo-spatial* models or *metapopulation* models) [42], that they are connected strongly to a central box ("cities and villages" [4,58]), or that they are evenly spaced along a line, on a lattice, or around a ring [57,83]. The stability properties of metapopulations in particular have been very carefully analyzed, although mostly for the host-parasitoid dynamics rather than diseases *per se* [42,83]: however, many of the results from this active area of research may be applicable to epidemics in human and wildlife populations. A general lesson from theoretical studies of host-parasitoid metapopulation is that stochastic effects, which may at first appear to be irrelevant for large populations, can be amplified when the population is subdivided into many small neighborhoods [85]; this phenomenon in principle carries over to all spatial systems, and is discussed in more detail below (Section 3.2).

- Geographic models [21–24, 86, 88, 90] generally fit into the category of compartment models. They concentrate heavily on the details of geographic structure and how they can be estimated from disease patterns and from other sources of information about human movement. Geographic models are more dynamic than the most general analytic compartmental models, often asking questions about spread between cities, but they tend to consider only simple, qualitative models of dynamics.

- To get results about the dynamics of nonlinear, stochastic compartmental systems we often have to resort to numerical simulation, which actually has a respectable tradition in epidemiological theory [**?**, 11, 18, 72]. Simulation is of course getting more powerful all the time with the explosion in computational power, although the combinatorial explosion of possible structures and parameters in many-compartment models will always leave some questions out of reach. Numerical models are unrestricted in their applicability, but can be hard to understand and test against real systems; I discuss these problems further below (Section 4).

All box models share some of the same problems. They start by making strong assumptions about breaking the population up into relatively few large, homogeneous compartments; if they use smaller compartments then the number of compartments increases and the number of parameters may explode. Smaller compartments also open up the possibility of stochastic dynamics, although analytical tools for this possibility are starting to be developed [?, **?**]. On the positive side, box models fit easily into analytic and computational procedures, they match the way epidemiological data are often reported, and they fit our simple mental models of the way human society works.

2.2 Continuous-space models

Continuous-space models take a completely different approach from box models, using the spatial structure of plane geometry to simplify the mathematical description of space. If we can measure the location of individuals, and relate transmission to spatial distances, then we can use a variety of mathematical techniques for the behavior of populations in space.

- Classical mathematical results on the existence of travelling wave solutions for diffusion equations are useful for predicting the behavior of diseases spreading in space [48, 73, 74]. These methods have been extended to some stochastic systems [64–66], and to systems with non-local movement [60, 95]. These models do, however, encounter some technical difficulties with incorporating discrete individuals and with some kinds of long-range contact. Recent extensions have begun to deal with some of these problems [56].

- More recently, ecologists and mathematicians have considered the behavior of epidemics on a lattice. Lattice models are easier to simulate and are susceptible to some powerful analytic tools; the implicit assumption is that in some limit, the lattice dynamics will approximate the dynamics of the disease in a more realistic spatial setting. Computational [9,15–17,49,68] and analytic approaches [55,87] are starting to make a dent in these technically difficult problems; some of them preserve the discrete nature of individuals while retaining the features of more traditional reaction-diffusion models [19].

Continuous-space models are powerful, and they can provide at least qualitative understanding of the processes governing spatial spread and persistence of diseases in space. For plant epidemics, or for epizootics among territorial animals, they can be matched fairly precisely to the details of dispersal of disease carriers (spores, pollinator vectors, or infectious animals). For human epidemics, however, we must ask whether we can gain quantitative as well as qualitative insights from continuous-space models, or whether Euclidean space is too rough an approximation of the complexities of human social space to be useful. We must also (as always) ask whether simpler spatial or non-spatial models can achieve the same qualitative behaviors and quantitative fits to the data.

2.3 Network models

Possibly the most realistic models for spread of disease in human populations, although also the most computationally and analytically difficult, are network models With these models, we can construct approximations to the true contact structure, which consists of interlinked hierarchical networks of schools, families, neighborhoods, and cities. The general network problem combines both the most realistic aspects of compartmental and continuous-space models: individuals or small groups are dealt with in a discrete, stochastic way, without imposing artificial spatial structures. However, these realistic aspects are also the most difficult ones.

- Some work has been done with computational models of disease on networks, mostly in specific cases of STDs and AIDS in particular where at least the pairwise nature of disease contact and transmission is easy to understand. [2, 3, 50, 76]. The stumbling block for these models is finding the balance between drawing general conclusions and being able to estimate parameters for specific systems, both in the face of a combinatorial explosion of possible parameters and network structures; these problems are discussed further in Section 4.

- Analytical models for epidemics on networks are in their infancy; although graph theory is a well-developed branch of mathematics, it generally gives only very broad qualitative answers that do not answer useful questions in epidemiology. A very promising recent development is the extension of "pair approximations", developed to study dynamics on lattices, to more general network structures [**?**, 2]. If some of the appropriate parameters can be measured (Section 4) this theory could eventually lead to an extremely useful set of tools for modelling human epidemics.

3 Disease prediction, control and eradication

As mentioned in the Introduction, the ultimate purpose of epidemiological studies is to lead us to methods for disease prediction and control. How does each of the model classes described above support this effort, and how do the new phenomena that epidemiologists are exploring connect with real-world problems?

3.1 Compartment models

Box models have been very successful in suggesting eradication criteria and appropriate vaccination targets for simple cases such as vaccine-preventable diseases in "cities and villages" models [4, 58]. In the simple case where it is possible to vaccinate at a desired level, the suggestions of simple compartment models will be accurate. When in the more usual case public health agencies are able to get near, but not over, the eradication threshold, issues of *stochastic extinction* become important. Then we need to know the answers to questions like: what is the *critical community size*, below which disease go extinct through stochastic processes during epidemic troughs [11, 12]—and more fundamentally, what is the appropriate spatial scale for defining populations themselves [75]? Can we develop phenomenological or analytical rules for the effective population sizes of discrete populations with weak but non-negligible coupling? How do nonlinear dynamics, correlation between sub-populations, and population structure within and between sub-populations affect the persistence of disease [18, 23, 24]? Are recent lessons from ecological dynamics about the dynamics of strongly nonlinear, weakly coupled subpopulations [1, 43, 84] relevant to epidemiology?

For diseases that are harder to control, we would like predictions of spread from one place to another [86, 88] or of the dynamics of an epidemic over time. Here compartmental models are less well established, in part because the heterogeneity within populations—let alone among different sub-populations within a geographic region—is poorly understood.

3.2 Continuous space

Continuous-space models are more widely used for prediction and control of plant and animal than of human diseases. The most prominent case study for epizootic prediction and control is the case of fox rabies, where diffusion models have been used to predict the spread of disease and to estimate the width of "firebreaks" (areas where the hosts are exterminated or their density reduced) necessary to stop a disease [10, 26, 27, 36, 48, 74, 78]. Researchers have also used computational stochastic models for the same purposes [94,98]. However, since many of these models have focused on the (so far unrealized) potential for a fox rabies epidemic in Great Britain, their predictions have not been rigorously tested. Plant epidemiologists have made great strides toward quantitative, predictive models for the spread of focal plant epidemics [62,63,95–97,100,101], but have been mostly unable thus far to deal with the case of patchy epidemics [39, 61].

Modellers overlooked *stochastic clustering* for a long time while they concentrated on deterministic spatial dynamics, but this basic phenomenon is now emerging from a variety of lattice and point-process models. In this process, the stochastic nature of demographic events (birth, death, infection) and the spatially local nature of transmission lead to spatial clustering of infectives, which then feeds back on the dynamics of the epidemic itself. For some situations, particularly with very short-range contact, stochastic spatial clustering leads to critical behavior (long-range, highly complex spatial patterns) that can nevertheless be analyzed by rigorous probabilistic methods [25, 30, 32, 33]. (Critical behavior has been suggested by relatively realistic models of measles dynamics in small populations [80–82] as well as in simpler, more heuristic models.) In the more relaxed case where epidemic parameters are farther from an extinction threshold, or where there is some long-range dispersal or mixing in the system, various forms of *pair* or *moment approximations*—equations that assume the system can be described in terms of dyads, or conditional probabilities, or spatial covariances [19, 55, 56, 87]—can give good quantitative results, and suggest that stochastic clustering may be explain spatial patterning and some component of overall dynamics in a very broad range of epidemic systems.

Models of stochastic clustering are still young, and it remains to be seen whether they will be useful practical tools; however, it is promising that this area of mathematical interest overlaps with areas of significant practical concern, such as the patchy nature of epidemics and how it affects spread and endemic levels of disease.

3.3 Network models

Network models are relatively recent. Nevertheless, they are conceptually very close to the way we think human contact networks really work; if we can overcome their computational and statistical challenges (discussed in Section 4), network models may yet become the tool of choice for modelling the endemic levels, persistence, and rate of spread of epidemics in human populations. Whether they become useful in the broad, qualitative way that classical homogeneous and age-structured models have will depend on whether we can build a framework (such as one using pair approximation) that will begin to give us mathematical insights into the kinds of modifications of classical dynamics that we can expect from spatial epidemics.

4 Measuring mixing heterogeneity and testing models

4.1 Compartment models

The number of parameters we need to estimate to parameterize a completely general n-compartment model goes roughly as n^2. How can we hope to estimate these values for a large data set? In almost all cases we have to start with some assumptions about population structure to reduce the number of estimated parameters to a manageable number; for example, we could assume some amount of assortative mixing, or a "mixing kernel" in continuous space, or assume that contacts between compartments were inversely proportional to distance (measured as geographic distance, travel time, cost of travel, frequency of travel ...)

Once we have made these assumptions (at best we could choose several different sets of simplifying assumptions and test among them), we need to estimate the remaining parameters. One way is by brute force, building a model of the entire system and fitting the parameters, by trial and error or more sophisticated numerical optimization, directly to available incidence data [72].

A slightly more sophisticated approach could extend a framework that has been used for estimating seasonal and age-structured contact rates [5, 35]. The first step estimates the number of susceptibles ($\vec{S}(t)$), infectives ($\vec{I}(t)$), and new cases ($\vec{I}(t+1)$) in each compartment (age or spatial) in the population at a given age or season by various means from incidence or serological data [5]. Then, using a "WAIFW" (who-acquires-infection-from-whom) matrix to reduce the number of independent entries in the contact matrix $\boldsymbol{\beta}$, the estimation problem reduces to solving the linear system $\vec{I}(t+1) = \vec{S}(t)\boldsymbol{\beta}\vec{I}(t)$. It should be possible to extend this framework for childhood viral diseases, by back-estimating susceptible populations [14], but the project would clearly involve major challenges; in particular, it might be necessary to use a regression-based approach rather than the simple linear solutions used in the past.

In a few cases, we can measure incidence, or contacts among groups, directly at the "microscopic" level of individuals within neighborhoods, schools, or families. If we can get contacts directly (usually for STDs, by contact tracing), we use statistical methods like log-linear modelling to estimate the parameters [70]. If we have incidence data instead, we can fit maximum-likelihood models to the observed disease chains to estimate contact parameters [13].

The most exciting advance in parameter estimation would be the ability, for some real disease, to estimate the parameters at the microscopic and the macroscopic levels and compare them; this test would provide real information about the level of our knowledge of epidemiology.

4.2 Continuous-space models

In the right systems, continuous-space models can be the easiest type of models to calibrate with data; in air- or water-dispersed plant disease systems, for example, individual-level disease dynamics (latent periods, spore production, and so forth) and spore dispersal dynamics are straightforward to measure and match with model parameters [53, 96]. The successful calibration of deterministic models for plant disease spread which contain all of the same microscopic behaviors as (for example) stochastic point-process models is highly encouraging. Vector-borne plant diseases are more complicated, but still eminently measurable [7, 59, 79]. Less precise but reasonable calibration can be done for animal diseases, where animal movement can be tracked by radiotransmitters [rabies refs.]; the calibration can be particularly simple in the case of territorial animals. When we get to human diseases, however, the difficulty of connecting human social structure realistically to the mathematical structure of the plane means that quantitative parameter estimation becomes nearly impossible. Even for widely-spreading diseases like influenza, where we can at least visualize the spread of disease on a two-dimensional map, it is hard to imagine estimating a diffusion coefficient or dispersal kernel that makes very much sense.

Lattice models have their own set of problems. While they provide useful qualitative insights into spread and clustering, they can be extremely difficult to calibrate in a sensible way at microscopic levels [31]. how does one decide what constitutes a grid cell, a lattice node, or a nearest neighbor, in an animal or human population? If this mapping from individual behavior to model rules and parameters is impossible, then models may be limited to qualitative uses. Molofsky [69] has made some efforts along these lines for plant competition models, but it may take a great deal of effort before lattice models become *quantitatively* useful tools for epidemiological research.

4.3 Network models

The same criticism does not apply to network models, but here the measurement problems may be even more daunting. As with compartmental models, the two choices for estimation seem to be macroscopic model-fitting by brute force simulation and microscopic parameter-fitting by maximum likelihood (or other statistical techniques), using detailed incidence data.

On the macroscopic level, brute-force model fits may be even harder than for the compartmental models, because of the flexibility of network topology. Even if we specify general structural parameters of the network (distribution of the degrees of each node and covariances between nodes and their neighbors), we may end up having to average across possible network configurations and across possible epidemics spreading across the network in order to get a general estimate of epidemic behavior.

Measuring microscopic parameters may be equally difficult [13, 99]. The biggest problem is whether data can be gathered and models fit at a large enough hierarchical scale; if, for example, network connections between neighborhoods and school districts have a significant effect on the dynamics of epidemics, then we will need to gather detailed incidence data for hundreds or thousands of individuals. Sufficient data may be hard to obtain for populations that are not isolated, and such microscopic-level parameters are probably harder to generalize across different countries and cultures than parameters that are either more biological (latent period, infectiousness) or cruder (overall contact rate). A completely different strategy, although still very speculative, would be to use some kind of molecular markers to track spread of a disease through a network and estimate microscopic parameters [45].

5 Conclusions

There are many new ideas and new approaches to modelling spatial dynamics and heterogeneity of mixing. Epidemiological theory now has the potential to go well beyond deterministic models of spatially homogeneous populations to start asking questions about the interactions of spatial structure, stochastic events, and nonlinear dynamics. Two particularly important phenomena, which both interest theoreticians and may have real applications to epidemic prediction and control, are stochastic spatial clustering and the interactions between epidemics in a large number of weakly-coupled subpopulations.

As theoreticians pursue new results, they must make sure to communicate their practical value to applied infectious disease epidemiologists. The only way that these theories can gain lasting recognition is to prove their worth in the real world. The first steps in this direction are to talk with epidemiologists and biologists about the processes going in their systems; to find ways to estimate parameters and calibrate epidemiological models from measurable data; and to make careful comparisons of predicted and observed dynamics. If new models of spatial dynamics can pass these tests, they will both prove their worth and raise the standards for epidemiological theory in general.

6 Acknowledgements

I would like to thank Jonathan Dushoff, Andy Dobson, Bryan Grenfell, and David Smith for useful comments and discussion.

References

[1] J. Allen, W. Schaffer, and D. Rosko. Chaos reduces species extinction by amplifying local population noise. *Nature*, 364:229–232, 1993.

[2] M. Altmann. Susceptible-infected-removed epidemic models with dynamic partnerships. *Journal of Mathematical Biology*, 33(6):661–675, 1995.

[3] M. Altmann, B. Wee, K. Willard, D. Peterson, and L. Gatewood. Network analytic methods for epidemiologic risk assessment. *Statistics in Medicine*, 13(1):53–60, 1994.

[4] R. Anderson and R. May. Spatial, temporal, and genetic heterogeneity in host populations and the design of immunization programmes. *IMA Journal of Mathematics Applied in Medicine and Biology*, pages 233–266, 1984.

[5] R. Anderson and R. May. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. *Journal of Hygiene (Cambridge)*, 94:365–436, 1985.

[6] R. M. Anderson and R. M. May. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. *Journal of Hygiene (Cambridge)*, 94:365–436, 1985.

[7] J. Antonovics, P. Thrall, A. Jarosz, and D. Stratton. Ecological genetics of metapopulations: the *Silene-Ustilago* plant-pathogen system. In L. A. Real, editor, *Ecological Genetics*, chapter 8, pages 147–169. Princeton University Press, Princeton, NJ, 1994.

[8] P. Bacon. *Population Dynamics of Rabies in Wildlife.* Academic Press, London, 1985.

[9] N. T. J. Bailey. The simulation of stochastic epidemics in two dimensions. *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*, 4:237–257, 1967.

[10] F. Ball. Spatial models for the spread and control of rabies incorporating group size. In *Population Dynamics of Rabies in Wildlife* [8], pages 197–222.

[11] M. S. Bartlett. Measles periodicity and community size. *Journal of the Royal Statistical Society Series A*, 120:48–70, 1957.

[12] M. S. Bartlett. The critical community size for measles in the U.S. *Journal of the Royal Statistical Society Series A*, 123:37–44, 1960.

[13] N. Becker. *Analysis of Infectious Disease Data.* Chapman and Hall, 1989.

[14] G. Bobashev, S. Ellner, and B. Grenfell. Reconstructing susceptible populations from measles incidence data. in prep.

[15] N. Boccara and K. Cheong. Automata network SIR models for the spread of infectious diseases in populations of moving individuals. *Journal of Physics A*, 25(9):2447–2461, 1992.

[16] N. Boccara and K. Cheong. Critical behavior of a probabilistic automata network SIS model for the spread of an infectious disease in a population of moving individuals. *Journal of Physics A*, 26(15):3707–3717, 1993.

[17] N. Boccara, K. Cheong, and M. Oram. A probabilistic automata network epidemic model with births and deaths exhibiting cyclic behavior. *Journal of Physics A*, (5):1585–1597, 1994.

[18] B. Bolker and B. Grenfell. Impact of vaccination on the spatial correlation and persistence of measles dynamics. *Proceedings of the National Academy of Sciences*, 93(22):12648–12653, 1996.

[19] B. Bolker and S. Pacala. Using moment equations to understand stochastically driven spatial pattern formation in ecological systems. *Theoretical Population Biology*, in press.

[20] J. Brown and A. Kodric-Brown. Turnover rates in insular biogeography: effect of immigration on extinction. *Ecology*, 55:445–449, 1977.

[21] A. Cliff, P. Haggett, and M. Smallman-Raynor. *Measles: an historical geography of a major human viral disease from global expansion to local retreat, 1840-1990.* Blackwell Reference, Oxford, 1993.

[22] A. D. Cliff, P. Haggett, J. K. Ord, and G. R. Versey. *Spatial Diffusion: An Historical Geography of Epidemics in an Island Community.* Cambridge University Press, 1981.

[23] A. D. Cliff, P. Haggett, and D. F. Stroup. The geographic structure of measles epidemics in the northeastern United States. *American Journal of Epidemiology*, 136:592–602, 1992.

[24] A. D. Cliff, P. Haggett, D. F. Stroup, and E. Cheney. The changing geographical coherence of measles morbidity in the United States, 1962-88. *Statistics in Medicine*, 11:1409–1424, 1992.

[25] J. Cox and R. Durrett. Limit-theorems for the spread of epidemics and forest fires. *Stochastic Processes and Their Applications*, 30(2):171–191, 1988.

[26] J. David and L. Andral. Modelling of spatial evolution and dynamics of a population of healthy then rabies-infected foxes. *Comparative Immunology, Microbiology and Infectious Diseases*, 5:351–358, 1982.

[27] J. David, L. Andral, and M. Artois. Computer simulation model of the epi-enzootic disease of vulpine rabies. *Ecological Modelling*, 15:107–125, 1982.

[28] K. Dietz and K. Hadeler. Epidemiological models for sexually transmitted diseases. *Journal of Mathematical Biology*, 26:1–25, 1988.

[29] K. Dietz and D. Schenzle. Mathematical models for infectious disease statistics. In A. C. Atkinson and S. E. Feinberg, editors, *A Celebration of Statistics*, pages 167–204. Springer, New York, 1985.

[30] R. Durrett. Stochastic growth-models - bounds on critical-values. *Journal of Applied Probability*, 29(1):11–20, 1992.

[31] R. Durrett and S. A. Levin. Stochastic spatial models: A user's guide to ecological applications. *Phil. Trans. R. Soc. Lond. B*, 343:329–350, 1994.

[32] R. Durrett and J. Steif. Fixation results for threshold voter systems. *Annals of Probability*, 21(1):232–247, 1993.

[33] R. Durrett and G. Swindle. Coexistence results for catalysts. *Probability Theory and Related Fields*, 98(4):489–515, 1994.

[34] J. G. Dushoff. *Modeling the effects of host heterogeneity on the spread of human diseases.* PhD thesis, Princeton University, 1997.

[35] P. E. M. Fine and J. A. Clarkson. Measles in England and Wales-I: an analysis of factors underlying seasonal patterns. *International Journal of Epidemiology*, 11:5–15, 1982.

[36] G. Gardner, L. Gardner, and J. Cunningham. Simulations of a fox-rabies epidemic on an island using space-time finite elements. *Zeitschrift für Naturforschung*, 45c:1230–1240, 1990.

[37] L. Garrett. *The Coming Plague: Newly Emerging Diseases in a World Out of Balance.* Penguin, 1995.

[38] B. Grenfell and A. Dobson, editors. *Ecology of Infectious Diseases in Natural Populations.* Cambridge University Press, 1995.

[39] J. Gressel, L. Segel, and J. Ransom. Managing the delay of evolution of herbicide resistance in parasitic weeds. *International Journal of Pest Management*, 42(2):113–129, 1996.

[40] D. A. Griffiths. The effect of measles vaccination on the incidence of measles in the community. *Journal of the Royal Statistical Society Series A*, 136:441–449, 1973.

[41] K. P. Hadeler and C. Castillo-Chavez. A core group model for disease transmission. *Math. Biosci.*, 128:41–55, 1995.

[42] M. Hassell, R. May, S. Pacala, and P. Chesson. The persistence of host-parasitoid associations in patchy environments. 1: A general criterion. *American Naturalist*, 138(3):568–583, 1991.

[43] A. Hastings and K. Higgins. Persistence of transients in spatially structured ecological models. *Science*, 263(5150):1133–1136, 1994.

[44] H. W. Hethcote and J. A. Yorke. *Gonorrhea Transmission Dynamics and Control*, volume 56 of *Lecture Notes in Biomathematics.* Springer-Verlag, Berlin, 1984.

[45] E. Holmes, S. Nee, A. Rambaut, G. Garnett, and P. Harvey. Revealing the history of infectious-disease epidemics through phylogenetic trees. *Philosophical Transactions of the Royal Society of London Series B- Biological Sciences*, 349(1327):33–40, 1995.

[46] J. Jacquez, J. Koopman, T. Perry, L. Sattenspiel, and C. Simon. Modeling and analyzing HIV transmission: the effect of contact patterns. *Mathematical Biosciences*, 92:119–199, 1988.

[47] J. A. Jacquez, C. P. Simon, and J. S. Koopman. Core groups and the R_0's for subgroups in heterogeneous SIS and SI models. In D. Mollison, editor, *Epidemic Models : Their Structure and Relation to Data.* Cambridge University Press, 1995.

[48] A. Källén, P. Arcuri, and J. Murray. A simple model for the spatial spread and control of rabies. *Journal of Theoretical Biology*, 116:377–393, 1985.

[49] K. Kaneko. Spatiotemporal chaos in one-dimensional and two-dimensional coupled map lattices. *Physica D*, 37, 1-3:60–82, 1989.

[50] J. Kephart, S. White, and D. Chess. Computers and epidemiology. *IEEE Spectrum*, 30(5):20–26, 1993.

[51] W. Kermack and A. McKendrick. A contribution to the mathematical theory of epidemics. Part II. the problem of endemicity. *Proceedings of the Royal Society of London A*, 138:55–83, 1932.

[52] W. Kermack and A. McKendrick. A contribution to the mathematical theory of epidemics. Part III. further studies of the problem of endemicity. *Proceedings of the Royal Society of London A*, 141:92–122, 1933.

[53] A. Kleczkowski, D. Bailey, and C. Gilligan. Dynamically generated variability in plant-pathogen systems with biological control. *Proceedings of the Royal Society of London Series B*, 263(1371):777–783, 1996.

[54] A. Lajmanovich and J. Yorke. A deterministic model for gonorrhea in a nonhomogeneous population. *Mathematical Biosciences*, 28:221–236, 1976.

[55] S. Levin and R. Durrett. From individuals to epidemics. *Philosophical Transactions of the Royal Society of London Series B*, 351(1347):1615–1621, 1996.

[56] M. Lewis, S. Pacala, and G. Hurtt. A tale of two tails: the mathematical link between a patchy invasion and the underlying dispersal process. in prep.

[57] A. L. Lloyd and R. M. May. Spatial heterogeneity in epidemic models. *Journal of Theoretical Biology*, 179:1–11, 1996.

[58] R. May and R. Anderson. Spatial heterogeneity and the design of immunization programs. *Mathematical Biosciences*, 72:83–111, 1984.

[59] P. McElhany, L. Real, and A. Power. Vector preference and disease dynamics: a study of barley yellow dwarf virus. *Ecology*, 76(2):444–457, 1995.

[60] H. Metz and F. van den Bosch. Velocities of epidemic spread. In Mollison [67].

[61] K. Minogue. Disease gradients and the spread of disease. chapter 12, pages 285–310.

[62] K. Minogue and W. Fry. Models for the spread of disease: model description. *Phytopathology*, 73:1168–1173, 1983.

[63] K. Minogue and W. Fry. Models for the spread of plant disease: some experimental results. *Phytopathology*, 73:1173–1176, 1983.

[64] D. Mollison. The rate of spatial propagation of simple epidemics. In *Proceedings of the Sixth Berkeley Symposium on Mathematical Statistics and Probability*, volume 3, pages 579–614, 1972.

[65] D. Mollison. Spatial contact models for ecological and epidemic spread (with discussion). *Journal of the Royal Statistical Society B*, 39:283–326, 1977.

[66] D. Mollison. Dependence of epidemic and population velocities on basic parameters. *Mathematical Biosciences*, 107:255–287, 1991.

[67] D. Mollison, editor. *Epidemic Models: Their Structure and Relation to Data*. Cambridge University Press, 1994.

[68] D. Mollison and K. Kuulasmaa. Spatial epidemic models: theory and simulations. In *Population Dynamics of Rabies in Wildlife* [8], pages 291–309.

[69] J. Molofsky. Population dynamics and pattern formation in theoretical populations. *Ecology*, 75(1):30–39, 1994.

[70] M. Morris. Epidemiology and social networks: modeling structured diffusion. In S. Wasserman and J. Galaskiewicz, editors, *Advances in Social Network Analysis: Research in the Social and Behavioral Sciences*, pages 26–52. Sage, Thousand Oaks, CA, 1994.

[71] M. Morris and L. Dean. Effect of sexual behavior change on long-term human-immunodeficiency-virus prevalence among homosexual men. *American Journal of Epidemiology*, 140(3):217–232, 1994.

[72] G. D. Murray and A. D. Cliff. A stochastic model for measles epidemics in a multi-region setting. *Institute of British Geographers*, 2:158–174, 1975.

[73] J. Murray. *Mathematical Biology*, volume 19 of *Biomathematics*. Springer-Verlag, 2d edition, 1990.

[74] J. Murray, E. Stanley, and D. Brown. On the spatial spread of rabies among foxes. *Proceedings of the Royal Society (London) B*, 229:111–150, 1986.

[75] D. Onstad. Temporal and spatial scales in epidemiologic concepts. *Journal of Theoretical Biology*, 158(4):495–515, 1992.

[76] D. Peterson, K. Willard, M. Altmann, L. Gatewood, and G. Davidson. Monte Carlo simulation of HIV infection in an intravenous-drug- user community. *Journal of Acquired Immune Deficiency Syndromes*, pages 1086–1095, 1990.

[77] W. M. Post, D. L. DeAngelis, and C. C. Travis. Endemic disease in environments with spatially heterogeneous host populations. *Math. Biosci.*, 63:289–302, 1983.

[78] E. Preston. Computer simulated dynamics of a rabies-controlled fox population. *Journal of Wildlife Management*, 37:501–512, 1973.

[79] L. Real and P. McElhany. Spatial pattern and process in plant-pathogen interactions. *Ecology*, 77(4):1011–1025, 1996.

[80] C. Rhodes and R. Anderson. Persistence and dynamics in lattice models of epidemic spread. *Journal of Theoretical Biology*, 180(2):125–133, 1996.

[81] C. Rhodes and R. Anderson. Power laws governing epidemics in isolated populations. *Nature*, 381(6583):600–602, 1996.

[82] C. Rhodes and R. Anderson. A scaling analysis of measles epidemics in a small population. *Philosophical Transactions of the Royal Society of London Series B- Biological Sciences*, 351(1348):1679–1688, 1996.

[83] P. Rohani, R. M. May, and M. P. Hassell. Metapopulations and equilibrium stability: The effects of spatial structure. *Journal of Theoretical Biology*, 181:97–109, 1996.

[84] G. Ruxton. Low-levels of immigration between chaotic populations can reduce system extinctions by inducing asynchronous regular cycles. *Proceedings of the Royal Society of London Series B-Biological Sciences*, 256(1346):189–193, 1994.

[85] G. D. Ruxton and P. Rohani. The consequences of stochasticity for self-organized spatial dynamics, persistence and coexistence in spatially extended host-parasitoid communities. *Proc. Roy. Soc. B*, 263(1370):625–631, 1996.

[86] L. A. Rvachev and I. M. Longini Jr. A mathematical model for the global spread of influenza. *Mathematical Biosciences*, 75:3–22, 1985.

[87] K. Satō, H. Matsuda, and A. Sasaki. Pathogen invasion and host extinction in lattice structured populations. *Journal of Mathematical Biology*, 32:251–268, 1994.

[88] L. Sattenspiel and K. Dietz. A structured epidemic model incorporating geographic mobility among regions. *Mathematical Biosciences*, 128:71–91, 1995.

[89] L. Sattenspiel, J. Koopman, C. Simon, and J. Jacquez. The effects of population structure on the spread of the HIV infection. *American Journal of Physical Anthropology*, 82:421–429, 1990.

[90] L. Sattenspiel and C. Powell. Geographic spread of measles on the island of Dominica, West Indies. *Human Biology*, 65:107–129, 1993.

[91] L. Sattenspiel and C. P. Simon. The spread and persistence of infectious diseases in structured populations. *Math. Biosci.*, 90:341–366, 1988.

[92] D. Schenzle. An age-structured model of pre- and post-vaccination measles transmission. *IMA Journal of Mathematics Applied in Medicine and Biology*, 1:169–191, 1984.

[93] C. P. Simon and J. A. Jacquez. Reproduction numbers and the stability of equilibria of SI models for heterogeneous populations. *SIAM J. Appl. Math.*, 52:541–576, 1992.

[94] G. Smith and S. Harris. Rabies in urban foxes (*Vulpes vulpes*) in Britain: the use of a spatial stochastic simulation model to examine the pattern of spread and evaluate the efficacy of different control regimes. *Philosophical Transactions of the Royal Society of London* **B**, 334:459–479, 1991.

[95] F. van den Bosch, J. Metz, and O. Diekmann. The velocity of spatial population expansion. *Journal of Mathematical Biology*, 28(5):529–565, 1990.

[96] F. van den Bosch, J. Zadoks, and J. Metz. Focus expansion in plant-disease. I. the constant rate of focus expansion. *Phytopathology*, 78(1):54–58, 1988.

[97] F. van den Bosch, J. Zadoks, and J. Metz. Focus expansion in plant disease. II. realistic parameter-sparse models. *Phytopathology*, 78(1):59–64, 1988.

[98] D. Voight, R. Tinline, and L. Broekhoven. A spatial simulation model for rabies control. In *Population Dynamics of Rabies in Wildlife* [8], pages 311–349.

[99] S. Wasserman and K. Faust. *Social network analysis: methods and applications*. Cambridge University Press, 1994.

[100] J. Zadoks and F. van den Bosch. On the spread of plant-disease: a theory on foci. *Annual Review of Phytopathology*, 32:503–521, 1994.

[101] M. Zawolek and J. Zadoks. Studies in focus development: an optimum for the dual dispersal of plant pathogens. *Phytopathology*, 82(11):1288–1297, 1992.