A biogeographical and landscape perspective on within-host infection dynamics

Robert D. Holt

Natural History Museum and Center for Biodiversity Research
Department of Ecology and Evolutionary Biology
University of Kansas, Lawrence, Kansas 66045 USA

ABSTRACT

There is a growing appreciation in general population and community ecology of the critical importance of space and spatial phenomena for understanding a wide range of ecological phenomena. At the scale of an invading pathogenic organism, a host organism in some important respects is like a large, complex landscape, on which the infection may play out in space as well as time. Many of the topics of contemporary spatial ecology — invasion dynamics, pattern generation, persistence mechanisms, source-sink dynamics, and spatial subsidies — have analogues in within-host infection processes.

Introduction: The emerging discipline of spatial ecology

From the perspective of an invading microbe, a vertebrate host individual is in effect a landscape or even continent with considerable internal heterogeneity in resource availability and mortality risks [14]. A valuable and largely unexplored apparatus for looking at within-host infection dynamics is the conceptual lens of modern spatial ecology. Because this paper is meant to be a thought piece, rather than a thorough review, references to the empirical microbial literature are drawn from a small set of authoritative medical microbiology textbooks.

An increasingly central theme in ecological research is the need to consider dynamical processes in a spatial context [16]. This realization has sparked several active areas of inquiry, including: (**1**) Metapopulation biology, which focuses on species which occupy habitats that are patchy and discontinuously distributed [3], e.g., butterflies occupying discrete meadows separated by forest [2]); (**2**) Landscape ecology, which examines the consequences and causes of spatial heterogeneity among habitat patches, and in particular is concerned with how the explicit spatial configuration of habitats influences ecological processes [16]; (3) Analytical biogeography, which takes a strongly quantitative approach to issues such as spatial patterns in species richness at very large scales [5,10], patterns in species' distributions [1] and invasion dynamics [13].

Many processes studied by spatial ecologists have clear analogues in within-host infections. There are of course major differences which may limit the utility of such analogies. For instance, patterns of connectivity among sites in a host are considerably more complex (including diffusion (e.g., on the skin), advective flows on fluid-covered surfaces, and rapid flows in the lymphatic system or bloodstream) and potentially more rapid than in terrestrial biomes,. Moreover, unlike a geographical landscape, the host body

Microbial Biosystems: New Frontiers
Proceedings of the 8th International Symposium on Microbial Ecology
Bell CR, Brylinsky M, Johnson-Green P (ed)
Atlantic Canada Society for Microbial Ecology, Halifax, Canada, 1999.

has been sculpted by selection over aeons of evolutionary history to prevent or keep in check infection (defined here as successful pathogenic invasion). Vertebrate hosts mount an astonishing array of constitutive and induced defenses against invasion [7].

Nonetheless, these complications merely ornament spatial processes, essentially the same as describing the dynamics of any species in a landscape. I propose here that recent advances in spatial ecology can provide fresh perspectives on familiar facts in infectious disease systems.

The biogeography of individual hosts

A biogeographer grapples with two principal issues regarding the biota of, say, Canada. One is at the level of single species and the other at the community level: (**1**) Some species have widespread ranges, and others are spatially restricted. The factors that explain such differences among species include differing degrees of ecological specialization, limitations on dispersal, and antagonistic species interactions. (**2**) Geographical patterns exist in species richness, as well as differences in richness among habitats. Determinants of richness patterns include both intrinsic or local factors (e.g., productivity, severity and frequency of disturbances) and extrinsic factors (e.g., coupling to external source pools) [10]. Typically, habitat area and distance to sources of colonization explain much variation in species richness. There are clear analogues for these broad biogeographical themes in microbial communities within individual hosts.

Habitat range and specialization

Microbes must contend with considerable within-host spatial and temporal heterogeneity in resource availability, abiotic conditions, mortality factors, permeability, and forces of advection [7,p. 293, 15]. Many microbes exhibit moderate to precise specialization to particular tissues and organ systems and along gradients in resources and abiotic conditions such as temperature. Just to cite an illustrative example, the agent of whooping cough, *Bordetella pertusis*, infects epithelial cells of bronchioles; this species is said to be "nutritionally fastidious" and very sensitive to fluctuations in physical/chemical factors [11, p. 291]. A large tome remains to be written, taking existing information on tissues and condition specialization by microbes and interpreting this information in terms of habitat specialization, as measured against the templet of available internal heterogeneities and gradients in the host body in resources, abiotic conditions, and defenses.

Within-host patterns of species richness in microbial communities

There is substantial spatial variation in microbial species richness within hosts. In a healthy body, blood, body fluids and deep tissues (e.g., the lungs, [7, p. 17] are normally sterile [12, p. 140]. Most commensal microbes are found on the skin, or within the lower intestinal tract or outer respiratory tract [11, p. 17]. Likewise, most infectious microbes are either restricted to the respiratory or intestinal tracts [7, p. 9]. Along the alimentary tract, there is a "U-shaped" pattern in species richness, with many species in the oral cavity and colon, and almost none in the stomach [12, p. 142].

As in macroscopic biogeography, patterns of within-host microbial species' richness should reflect the interplay of local (within-host) properties and processes operating at larger spatial scales. In large-scale biogeography one first attempts to characterize the nature of the species pool available for potential colonization. The properties of the pool

are determined by processes such as speciation, colonization, and extinction operating at larger spatial and temporal scales than defined by just the local community at hand. What determines the 'pool' of microbial species that are potentially available for infection at particular sites in an individual host? Several authors (e.g., [8] have commented on the close parallel between metapopulation models and epidemiological models. We can draw on this parallel to examine the effects of spatial constraints on species richness.

Consider a microbe specialized to a single tissue type (=habitat) which causes an infection invoking a defensive host response, but without permanent host immunity. We assume each individual host is a 'patch', and total host numbers are fixed. Let p be the fraction of hosts infected. A general expression for disease dynamics in the host population is dp/dt = [net infection rate] - [net rate of infection die-out]. Let k be the fraction of hosts potentially available for successful infection out of the entire host population, and e the per host rate of infection die- out. The net infection die-out rate is thus ep.

The parameter c will scale the infection rate of the pathogen (a rate of successful colonizations of available, susceptible hosts by pathogens). Consider two distinct colonization scenarios, one for pathogens that are specialists on a focal host, and the other for generalist pathogens sustained by multiple host species which incidentally infect the focal host species. For specialist microbes, persistence depends upon recurrent infection within the focal host population. A simple model for the rate of infection by a specialist microbe is $cp(k - p)$. For a generalist microbe, maintained in an external reservoir with no cross-infection among individuals of the focal host species, an alternative expression for net infection is $c(k - p)$. Given a constant per host rate of loss of infection e from infected hosts (akin to local extinction), the equilibrial level of infection in the focal host is predicted to be: $p^* = k - e/c$ (specialist); $p^* = kc/(e+c)$ (generalist). For the specialist pathogen, there are threshold values of the parameters, defining when the microbe will persist: if $k < e/c$, the specialist pathogen cannot persist in the focal host population. There are no such thresholds for the generalist.

These simple metapopulation models suggest several qualitative conclusions. First, pathogens which are habitat specialists should be most common in habitats (e.g., tissue types) that are most common in the host population (high k), or most easily colonized (high c), or experience low rates of die-out due to host defenses (low e). Second, sparse or inaccessible habitats (low k) should be dominated by species that mainly utilize other, more accessible habitats. Third, specialists on rare or inaccessible habitats should have unusually low extinction rates (avoid host defenses), or utilize specialized dispersal modes, relative to the entire ensemble of microbial species on the host.

The natural history of infectious diseases and the normal microflora seems consistent with these theoretical expectations. Some tissues (=habitats) have few specialist pathogens. Two quotes provide examples: (i). "Specific infections of skeletal muscle are obscure" [11, p. 786]; (ii), "Infections of the central nervous system are relatively infrequent" [11., p. 716]. Both tissue types are likely to have low c, compared to say epithelial surfaces. Internal tissues in most hosts are unavailable for infection, but are accessible in a few hosts (e.g., due to wounds); such tissues in effect also have a low k. The model predicts that relatively few microbes will be specialized to such tissues; those microbes which do manage to infect there occasionally should also be able to utilize other tissues, or be sustained in reservoirs outside the host population.

The abstract parameters of *c* and *e* determining persistence of an infection in a host population as a whole reflect the details of within-host infection dynamics, including factors such as resource availability and within-host spatial dynamics. The typical stages of infection in a host individual are: 1. Initial entry, 2.Establishment, 3. Spread, 4. Stabilization, 5. Decline, 6. Elimination, or reduction to a persistent chronic level of infection in the host. Parallels with phenomena in spatial ecology arise in each of these stages; here I focus on establishment.

Establishment

A fundamental concept in population biology is the invasion criterion: For a species to persist in a local habitat, it must be able to increase when rare. Let N be local population size. The basic model for population growth is $dN/dt = N(b - d)$ where b is per capita birth rate (a function of resources and abiotic conditions), and d is death rate + emigration/ wash-out rate. At low N, the quantity $r = b-d$ is the intrinsic growth rate. If $r < 0$, the population declines, and the invasion fails. If, instead, $r > 0$, N increases, and invasion (deterministically) proceeds.

Studies of invasion biology often reveal a relationship between probability of establishment, and initial population size, with the relationship varying by species. For instance, introductions of alien birds into New Zealand are more successful with increases in total number of individuals released [9], with considerable variation among species. Likewise, the introduced size of doses required to cause infection seem to vary enormously among microbes. For instance, an aliquot of 10 individual bacteria in *Shigella dysenteriae* apparently suffices for an infection to take off, whereas up to 10^6 individual bacteria in salmonellosis are required [7, p. 35]. Some pathogens seem to need astronomical numbers to become established (e.g., $> 10^8$ for enterotoxicogenic E. coli, [11, p. 255]).

Two general explanations can account for propagule size effects: (i). demographic stochasticity, and (ii). Allee effects. Demographic stochasticity refers to random effects of births and deaths in small populations; extinctions of a small population (e.g., at time of invasion) may occur due to a run of bad luck, even in favorable environments [11]. The lower a species' r, the longer its period of risk due to extinction from demographic stochasticity. Theoretical studies of demographic stochasticity suggest that characterizing the initial r of an infection, and quantifying how r varies as a function of (*e.g.*) resource availability, could provide insights into the likelihood of infections successfully becoming established. Qualitatively, the aliquot needed for successful infection should be smaller in pathogens with higher initial r (which could reflect a superior ability to utilize host resources or escape host defenses).

An alternative explanation for propagule size effects in establishment is the Allee effect. For several reasons, at low density per capita growth rates can increase with N. For instance, in sexual species birth rates (b) increase with N (at low N), because mating pairs can be more readily established. Another general mechanism which leads to an Allee effect is saturation in attacks by resident mortality agents, so that death rates *decrease* with increasing N. In ecological communities, resident generalist predators have this effect [3].

One is likely to observe saturation in mortality factors in early stages of microbial infections, as well. For instance, in lymphatic system, the efficiency of filtering falls off at high particle concentrations [7, p. 98]. A direct parallel to resident predators in an ecological community is provided by phagocytes, whose action is akin to consumption by

predatory protozoa [7,p. 81]. As with any predator, phagocytes should have saturating 'functional responses' (kill rates) to available 'prey' (invasive microbes)-- hence, increasing the inoculum size may saturate this component of host defenses. Allee effects may well be pervasive in early stages of microbial infection. I am unaware of attempts to quantify the 'functional response' of phagocytes to their 'prey'. One can predict that any factor which increases the 'handling time' of each ingested microbe by a phagocyte, tends to lower the threshold density needed for successful establishment.

Establishment and persistence in the heterogeneous host environment

Consider a microbe specialized to a particular tissue-habitat, surrounded by inhospitable tissue. Spatial coupling of this local habitat to the remainder of the host body can influence microbial dynamics in several ways, via controls on the supply rate of required resources, the immigration rate of macrophages, and forced emigration of the microbe. There is considerable anecdotal evidence for the direct effect of forced emigration (higher e) on microbial persistence and abundance. As a representative example "in the respiratory tract...interference with the action of cilia can permit colonization and infection" [11, p. 150]. Impediments to spatial aggregation by macrophages (lowering P above) likewise foster infections. For instance, foreign bodies (too large to be phagocytosed) facilitate infection, "presumably by giving microbes physical protection in nooks and crannies from phagocytes, etc." [7, p 293].

As a final parallel between landscape and infectious disease processes, consider an invasion which occurs in two habitats or compartments, each experiencing exponential growth (or decline) and linked by dispersal. Assume that habitat 1 is a "source" (births > deaths) and habitat 2 a "sink" (births < deaths). An invasion succeeds if a species inhabits a refuge ("source") within which its growth rate exceeds the rate at which individuals leave, no matter how bad conditions outside that refuge (in the "sink") might be. It is intriguing that *identical* mathematical models of this situation arose recently in two papers, one in landscape ecology and the other in infectious disease biology. Maurer and Holt [6] used the model to examine the influence of localized pesticide application on wildlife populations. Lipsitch and Levin [4] used the model to explore the evolution of resistance in antibacterial chemotherapy, given localized refuge sites where a pathogen is at low risk.

Conclusion

My general conclusion is that essentially all the phenomena and processes central to modern spatial ecology are also present and important in within-host infection dynamics. The examples touched upon include habitat specialization; within-host spatial gradients in species richness; effects of dispersal modes; colonization-persistence dynamics; Allee effects; spatial aggregation and saturating functional responses by natural enemies (e.g., phagocytes); the influence of spatial fluxes on local dynamics; and source-sink dynamics. Recognizing structural similarities between within-host infection dynamics and the processes of metapopulation biology, landscape ecology, and analytical biogeography may provide potential avenues for fruitful cross-fertilization between these disciplines and microbial ecology in future research endeavors.

Acknowledgements

I thank Val Smith for his invitation, the symposium participants for their insightful talks and helpful comments, and James Grover for a thorough review of the manuscript. I gratefully acknowledge financial support by the National Science Foundation and the University of Kansas.

References

1. Brown JH, Stevens GC, Kaufman DM (1996) The geographic range: size, shape, boundaries, and internal structure. Ann Rev Ecol and Syst 27:597-623.
2. Hanski I (1994) A practical model of metapopulation dynamics. J Anim Ecol 63:151-162.
3. Hanski I, and Gilpin ME (eds) (1997) Metapopulation Biology: Ecology, Genetics and Evolution. Academic Press, San Diego.
4. Lipsitch M, Levin B (1997) The within-host population dynamics of antibacterial chemotherapy: conditions for the evolution of resistance. Ciba Found Symp 207:112-130.
5. MacArthur RH, Wilson EO (1967). The Theory of Island Biogeography. Princeton University Press, Princeton, New Jersey.
6. Maurer B, Holt RD (1996) Effects of chronic pesticide stress on wildlife populations in complex landscapes. Environ Toxic and Chem 15:420-426.
7. Mims CA (1987) The Pathogenesis of Infectious Diseases. Academic Press, New York.
8. Nee S (1994) How populations persist. Nature (London) 367:123-124.
9. Pimm SL (1991) The Balance of Nature? The University of Chicago Press, Chicago.
10. Rosenzweig ML (1995) Species Diversity in Space and Time. Cambridge University Press, Cambridge, UK.
11. Schaechter M, Medoff G, and Eisenstein, BI (eds) (1993) Mechanisms of Microbial Disease. Williams and Wilkins, Baltimore, Maryland.
12. Sherris JC,(ed.) (1990) Medical Microbiology: An Introduction to Infectious Diseases. 2nd ed. Elsevier, New York.
13. Smith, VH and RD Holt (1996) Resource competition and within-host disease dynamics. Trends in Ecol and Evol 11:386-389.
14. Shigesada N and Kawasaki K (1997) Biological Invasions: Theory and Practice. Oxford, UK: Oxford University Press, Oxford, UK.
15. Turner MG (1989) Landscape ecology: the effect of pattern on process. Annual Rev Ecol and Syst 20:171-197.