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Eight challenges in modelling disease ecology in multi-host, multi-agent systems

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Abstract

Many disease systems exhibit complexities not captured by current theoretical and empirical work. In particular, systems with multiple host species and multiple infectious agents (i.e., multi-host, multi-agent systems) require novel methods to extend the wealth of knowledge acquired studying primarily single-host, single-agent systems. We outline eight challenges in multi-host, multi-agent systems that could substantively increase our knowledge of the drivers and broader ecosystem effects of infectious disease dynamics.

Keywords

multiple hosts; multiple pathogens; community ecology; maintenance; food webs

Introduction

Over the past 20 years, a combination of theoretical, observational, and experimental approaches has advanced our understanding of the ecology of infectious diseases. This work has often focused on dynamics in single-host, single-agent systems with acute and symptomatic infections, which are the most theoretically and empirically tractable. As a consequence, patterns have been explored using foundational theoretical concepts, such as

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the basic reproduction number, R_0. Yet the predominance of R_0 in disease ecology has sometimes overshadowed complexities that can influence dynamics, such as feedbacks between diseases and ecosystem structure and function. Inclusion of these complexities will require re-interpretation and extension of these foundational concepts, as well as novel modelling tools, data, and thinking. This problem is exemplified by disease systems involving interactions among multiple host species and/or multiple infectious agents. In these systems, we can hope to borrow principles from community ecology and build on the strong link between disease dynamics and population ecology. Here, we outline eight challenges that will be important to understanding disease dynamics in multi-host, multi-agent systems, at scales from within-host dynamics to ecosystem-level processes.

1. What defines a maintenance population?

Classically, conditions required for maintenance of infections in populations of single host species have been defined through host population thresholds. In particular, population size or density thresholds are often used to specify the host abundance that is sufficient to maintain uninterrupted transmission of the infectious agent without subsequent imports. However, maintenance of infectious agents depends as much on demographic rates as on population size especially when epidemic intensity fluctuates far from equilibrium. This raises particular challenges in systems where density-dependent or strongly seasonal recruitment causes host abundance and relevant demographic rates to fluctuate (Lloyd-Smith et al. 2005). Reliance on population abundance thresholds is further complicated when disease risk is influenced by factors like age- or sex-structure, territoriality, or herding behavior, making the definition and quantification of host abundance as it relates to disease maintenance difficult.

Consequently, analyses of single population maintenance must be refined to recognize mechanisms beyond simple population thresholds. Spatial effects such as percolation (Davis et al. 2008) or metapopulation structure (George et al. 2013) may be important drivers of agent persistence. In addition, modelling and empirical studies are needed to understand how maintenance is influenced by diverse host/agent interactions, including phenomena such as chronic infections, intermittent shedding, or waning immunity. Data requirements to study infectious agent maintenance are always demanding, and appropriate measures of local extinction can be difficult to define (Conlan et al. 2010). This problem is exacerbated due to frequent difficulties in surveillance of both the disease process and host population size and distribution, highlighting the importance of long-term, high-resolution, time series.

2. What defines a maintenance community?

In many systems multiple host species can be infected, suggesting that an infectious agent may be maintained by several host species in a maintenance community (Haydon et al. 2002). Here, it is crucial to assess whether each infected species is infected via a dead-end process (i.e., spillover and subcritical transmission) or is contributing to maintenance by on-going transmission. Strong inferences can be made using manipulations or disturbances, such as culls or fencing, that clarify the contributions of individual species to maintenance in the broader host community. Without such perturbations, models will play a key role

integrating available evidence and identifying the manipulations that could confirm species' contribution to maintenance (Viana et al. 2014).

Of the current models, type reproduction number methods (Roberts and Heesterbeek 2003) have been used to explore multi-host maintenance at human-animal interfaces (Funk et al. 2013) and to identify species-specific contributions to transmission (Nishiura et al. 2009). These approaches typically assume a system at endemic equilibrium, although new methods have relaxed this assumption (Streicker et al. 2013). As outlined in Challenge 1, these non-equilibrium dynamics can be crucial to persistence, especially in systems with seasonality or temporally varying outbreaks. Cross-sectional data in these cases are often not at a resolution to address such variation. This problem is particularly pronounced when infection can only be determined post-mortem, highlighting the importance of assessing disease status longitudinally through nondestructive sampling. Models analyzing these data must address transient dynamics in host abundances and infection patterns, potentially building on methods for transient analysis used in conservation biology (e.g., Buhnerkempe et al. 2011).

3. What mechanisms underlie the dilution effect, and when do they apply?

Some observational data from vector-borne diseases support a 'dilution effect' whereby increasing host diversity decreases infection risk in a focal species, such that (in contrast to challenge 2) greater host diversity can diminish maintenance of the infection (Keesing et al. 2010). To test this properly, experimental perturbations of the host community are needed to reveal the mechanisms driving such a relationship and to test the underlying assumption that host competence is generally associated with species resilience. Experimental work has begun to explore such mechanisms (Johnson et al. 2013; Venesky et al. 2013), but further work is needed, especially in systems that are not conducive to laboratory manipulations. At the same time, better theory is needed to identify key experiments in these systems and to integrate resulting mechanistic insights, thus strengthening inferences about existing data.

A broader understanding of how non-host species might contribute to the dilution effect is also needed. Competitive and trophic interactions between host and non-host species can influence host abundance and community structure and hence, indirectly, the dilution effect. Network approaches may prove useful in exploring these types of interactions (see Challenge 7). Because species assemblages vary in space and time, models should also address feedbacks between larger-scale species richness and community assembly and succession processes in addition to local community composition.

4. How to estimate cross-species transmission in field settings?

Empirical estimates of cross-species transmission are crucial to understanding multi-host systems, but obtaining such estimates is a long-standing and unsolved problem. New data types are bringing new opportunities from both bottom-up and top-down perspectives, but these also raise new challenges. Once again focused experiments to quantify cross-species transmission would be helpful. In bottom-up approaches, contact is measured directly (e.g., by shared space use or spatial proximity loggers), but defining an epidemiologically relevant contact remains difficult. Even for well-defined contacts, estimating the probability of transmission per contact is a struggle. Alternatively, when transmission experiments

measure the probability of infection given a contact (e.g., Bouwknegt et al. 2008), it is difficult to relate forced contact in the lab to natural systems. These problems typically limit inference from bottom-up approaches to relative transmission hazards among regions or groups of animals. In top-down approaches, data from multiple host species can be integrated with mechanistic or time-series models to infer cross-species transmission rates (e.g. Begon 1999). However, these approaches are data-hungry, and their sensitivity and accuracy are basically unknown; similarly the relation between sampling resolution and infectious agent life history (e.g., acute vs. chronic, transmission mode) will determine the power of this approach.

Genetic studies offer increasingly powerful tools to study cross-species transmission (e.g., Streicker 2010). However, unresolved issues remain regarding the translation of genetic patterns into estimates of transmission rates, particularly given incomplete sampling of hosts. Also, current genetic methods for inferring cross-species transmission assume all cases in a 'recipient' species come directly from cross-species spillover. This assumption ignores the potential for onward, subcritical transmission in the recipient species, which will boost the number of cases biasing estimates. If transmissibility in the recipient species is known, this effect could be accounted for, but transmission data in these species are often lacking. At a minimum, future genetic models will need to characterize this potential bias or relax the spillover assumption to infer within- and between-species transmission jointly.

5. How do complex multi-host life cycles affect maintenance?

Parasites with heteroxenous life-cycles, where there is a sequence of hosts necessary to complete the parasite's life-cycle (e.g., *Ribeiroia ondatrae* (Johnson et al. 2013), schistosomiasis (Woolhouse 1996)), provide additional challenges for studying multi-host dynamics in what, by definition, is a maintenance community with distinct temporal structure. For example, the evolution of complex life-cycles in nematodes and trematodes has been explored (Parker et al. 2003), but the ultimate effect of coevolutionary processes on the maximization of short term R_0 vs. long-term maintenance of infection is poorly understood. Additionally, more proximate questions about the drivers of maintenance in many of these systems remain largely unexplored. In particular, identifying the life-stages most critical to maintenance, including those in humans, is vital for effective control of diseases like schistosomiasis (Woolhouse 1996) and echinococcosis (Atkinson et al. 2013) and would benefit from type reproduction number approaches (see Challenge 2). However, transient dynamics such as seasonal activity of intermediate hosts are likely to play a significant role here (Woolhouse 1996; Atkinson et al. 2013) and may change the importance of specific life-stages in maintenance. Stage-specific fluctuations may be related to the degree to which individual life-stages are specialized to specific host species. More specifically, generalist life-stages may potentially mediate fluctuations in a particular host species' abundance, thus reducing extinction risk. The effects of stage-specific fluctuations on parasite population persistence may also depend on the parasite's generation time, with long life-cycles potentially increasing the parasite population's tolerance to stage-specific crashes. These challenges remain relatively unexplored and could benefit from a variety of modelling approaches including an examination of dynamical trophic interactions and a food web approach (see Challenge 7).

6. How do community dynamics of parasites and pathogens within individual hosts scale up to host population processes?

As data on within-host community dynamics of parasites are beginning to emerge (Murphy et al. 2013; Telfer et al. 2010), models are needed to explore both the within-host assembly process and how this process affects host population dynamics. Earlier work on population dynamics of parasite communities (e.g., Dobson and Roberts 1994) emphasized the importance of aggregated distributions of parasite species within different host individuals in determining population-level parasite coexistence. Extensions to consider mixed parasite-pathogen communities have also shown that the combined regulation of host abundances stabilizes dynamics in general, resulting in parasite-pathogen maintenance (e.g., Fenton 2008). However, these studies largely ignore the dynamic nature of within-host infection processes. Here, immune responses may target a specific parasite or may act on an entire functional group, and these and other interactions may be localized to specific tissue compartments (Griffiths et al. 2014). Thus, the site and type of immune response may modulate within-host community assembly and sorting rules. Advances in this area are likely to come first from parasite systems where within-host infection intensity is often easier to assess. Indeed, observational studies have begun to explore these questions (e.g., Telfer et al. 2010), but these data can be unreliable at identifying key interactions again necessitating experimental perturbations (Fenton et al. 2014), which are fortunately beginning to emerge (e.g., Knowles et al. 2013). Additionally, there are many open questions about within-host interactions in mixed parasite-pathogen communities (Graham 2008). Similar immune targeting processes are likely to be as, if not more, important in mixed parasite-pathogen infections as the chances of stimulating multiple types of immune response will likely be increased. Additionally, the immune response to any new infection is shaped by the history of past infections making host demography important such that short-lived animals may respond differently than long-lived animals.

The next generation of models also needs to connect within-host community assembly to between-host dynamics, which is addressed further by Gog and others in this issue. For multi-host, multi-agent systems, it is important to note that such cross-scale models are difficult especially when the link between infection intensity and transmission may be unclear and not readily simplified (Cattadori et al. 2014). This link will be especially problematic when considering multiple infectious agents with different transmission mechanisms, particularly as work moves to understanding mixed parasite-pathogen communities where transmission is likely to be vastly different. Consequently, continued experiments and observation on the effect of parasite and pathogen community structure on transmission are needed, which may point to appropriate modelling approaches as generalities emerge.

7. How do infectious agents affect food web structure and stability?

Recent decades have seen strong growth in empirical work on the effects of infectious agents in community interactions, yielding unexpected phenomena and increasing data resources (Selakovic et al. 2014). These data have revealed that parasites may comprise as many as half of the species in some food webs (e.g., Lafferty et al. 2006). Understanding the role that infectious agents play in determining the structure and stability of food webs, both

through direct impacts on host species and indirect effects on non-host species, requires development of new theory including aspects of the above challenges. For instance, recent experimental work points to interactions between fungal pathogen communities and their tree hosts that result in negative density dependence hence increasing tree biodiversity (Bagchi et al. 2014). The ability of different pathogens to control locally abundant hosts serves to diversify the niche space available to species at the same trophic level (Bagchi et al. 2014). Across trophic levels, relatively strong links between species, such as consumer-resource interactions, can also increase community stability, even in large communities where stability is predicted to be low (Allesina and Tang 2012). However, this finding has not yet been extended to include infectious agents that may influence food web links through numerous impacts on flows of energy and biomass such as immune system investment, altered feeding behaviors, lower fecundity, or serving as a resource themselves (Selakovic et al. 2014). Additionally, weak interactions between species have been observed to increase food web stability (Neutel et al. 2002). Consequently, there is a need to explore whether the relative abundance of specialist vs. generalist infectious agents (i.e., few strong links vs. multiple weak links) serves to maintain food web structure. The potential impact of weak interactions also necessitates the exploration of non-acute infectious agents, which may form numerous weak links within host/agent food webs.

Answers to these questions will be arrived at in two ways - explicitly, where infectious agents are included as species in the overall community, or implicitly, where infectious agents modify the interactions between host and non-host species. The preferred approach may depend on whether ecological or epidemiological questions are of interest, with potential complementarity between approaches (Selakovic et al. 2014). In either case, models that explore these questions should merge dynamical systems common in infectious disease dynamics with network approaches common in food web studies. This may ultimately allow for characterization of the impact of infectious agents on ecosystem-scale processes such as nutrient cycling and storage, ecosystem productivity, and physical structure.

8. How to deal with currently unobserved ‘dark matter’ in multi-host, multi- agent systems?

For multi-host, multi-agent systems, there is no guarantee that every host and infectious agent species has been discovered. Such unobserved components, dubbed ‘epidemiological dark matter’ (Orton et al. 2013), can have qualitative impacts on disease dynamics, and hence, on the inferences about the known host and infectious agent species. In many communities, good data about disease dynamics exist only for some focal species with hazy or anecdotal information about infections in other species. How can models help to assess whether these poorly characterized species play important roles in the community dynamics of multi-host, multi-agent systems? Similarly, can modelling help to address potential uncharacterized aspects of infectious agent life history, such as subclinical infections? There is little chance of detecting such life history strategies directly if they do not trigger conspicuous signs, yet they may still influence dynamics.

New modelling approaches will play an important role in addressing these questions. In particular, genetic data and phylodynamic approaches may prove useful for inferring the

presence of unsampled populations. Additionally, models of currently available data may reveal signatures of extrinsic inputs, but this may only be possible with good information on parameter values in the focal host (e.g., Webb et al. 2006; Craft et al. 2008). There is an open question on how generalizable these approaches are to less well-characterized systems. Here, techniques that formally account for missing data, such as imputation in Bayesian models and/or Bayesian state-space models (e.g., Strelioff et al. 2013) may prove more useful.

Discussion

These challenges summarize some important future directions in modelling multi-host, multi-agent systems. Developing and validating new models to tackle these challenges will require high-quality data sets describing tractable case study systems, at appropriate spatial and temporal resolutions. One challenge for all empirical studies is to quantify the occurrence of infection, as opposed to disease, since neglecting subclinical infections can lead to misleading conclusions regarding maintenance or transmission routes in a community. On-going work has shown promise in developing such case studies and continued efforts will frame perhaps the biggest challenge for the next generation of disease ecologists: when should these types of complexities be included, and when are simplifications appropriate? Finding the correct balance will allow intuition and insights arising from the last twenty years of work (primarily on single-host, single- agent systems) to be harnessed to understand multi-host, multi-agent systems.

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