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Five challenges for spatial epidemic models

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ABSTRACT

Infectious disease incidence data are increasingly available at the level of the individual and include high-resolution spatial components. Therefore, we are now better able to challenge models that explicitly represent space. Here, we consider five topics within spatial disease dynamics: the construction of network models; characterising threshold behaviour; modelling long-distance interactions; the appropriate scale for interventions; and the representation of population heterogeneity.

Introduction

There have been many important ecological and public health questions related to the transmission of infectious disease that neither need, nor would benefit from, a mechanistic model in which space is represented explicitly. In many instances, the concept of the average behaviour of a large population is sufficient to provide genuinely useful insight and to extract good information from the data that are available.

However, the importance of the spatial component of many transmission systems is being increasingly recognised. When there is a need to consider spatially heterogeneous interventions, it is clearly essential to represent the location of hosts and the pattern of transmission. Sometimes the location of the hosts in space is clearly defined and easily measured – such as for plant systems and some livestock systems. However, for humans and wild animals, the single location assigned to a host represents the best average from the complex social behaviour of each individual.

If it is thought that the aggregate characteristics of epidemic incidence are being driven by spatial aspects of transmission (such as waves), it is difficult to investigate data from these systems with models that do not represent space in some way. Also, and perhaps most importantly for future modelling work, where data are provided with high spatial resolution, even when the primary hypotheses of interest for a given phenomenon does not relate directly to spatial effects, it is often necessary to account for spatial processes in order to discount plausible alternate explanations for an observed feature in the data.

Mechanistic spatial models are usually described as being; an individual-based simulation, a metapopulation model or a network model. Individual-based models explicitly represent every individual host within a simulation algorithm and usually assume a highly variable – but non-zero – probability that any infectious host can infect any susceptible host. Metapopulation models do not represent individuals. Rather, they keep track of the number of individuals at different locations who are in each state of the natural history. Often, they also assume that each location (patch) is connected to all others, but, again, with highly variable strengths of connection. Network models typically define each node to be an individual host and assume that each host is connected to only a small subset of other hosts. Also, usually, the strengths of connection along each arc in a network epidemic model are assumed to be equal.

Here we consider five broad challenges for theoretical infectious disease dynamics.

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1. How can network models best be constructed to reflect spatial population structure?

The three types of spatial model outlined above do not form disjoint sets. We can think of the network formulation as a potential unifying framework within which the other two can be nested. Individual-based simulations are very dense fully connected networks with highly variable edge weights. Similarly, metapopulation models become network models as the average number of individuals represented in each patch approaches 1. Therefore, given that it has proven difficult to obtain analytical results for metapopulation models and individual-based simulations, it may be possible to make more analytical progress in our ability to describe complex spatial phenomena by basing analysis on network formulations that mimic these other model structures.

There is a long history of using regular lattices as a basis for infection spread (Mollison and Kuulasmaa, 1985), often in the context of plant populations. Random geometric graphs (Penrose, 2003) provide another, less highly structured, way to represent a spatial process by a simple graph. They are constructed by starting from a spatial Poisson point process, which need not necessarily be homogeneous. Pairs of points (nodes) that are within some critical distance are connected by an edge to form a graph, after which the underlying spatial structure is ignored. The conditional independence properties of Poisson processes mean that the analytic properties of such graphs are well understood. When they form the underlying contact structure for epidemic processes (Isham et al., 2011), random geometric graphs provide a nice way of escaping the lack of local correlation and clustering that are implicit properties of the configuration graphs often used to explore epidemic dynamics.

The spatial construction of the random geometric graph leads naturally to the question of how transmission is affected when the hosts move in space, so that edges are continuously broken and created. This scenario has direct application to computer viruses spreading on wifi computer/phone networks (e.g. Rhodes and Nekovee, 2008). In other applications, it may be appropriate to model the creation and annihilation of nodes and edges. Network dynamics is discussed in section “How do we define a threshold parameter for spatial models?” of the chapter on Networks (this volume).

In most metapopulation and network models, the group or network structure of the host population is fixed. The actual contacts between hosts in which transmission takes place are not explicitly represented; implicitly one might imagine some local spatial movement that brings the two hosts in contact. In contrast, in an alternative modelling approach, hosts move between a set of discrete spatial locations that form the nodes of a graph, and infection is only possible between hosts in the same location. Thus, in a simple model, hosts might perform independent random walks on the graph (Draief and Ganesh, 2011; Abdullah et al., 2011).

Work is needed to develop other network models that reflect spatial structure and, when that network is not fully connected, to explore how well the properties of an epidemic running on the network approximate the full spatial dynamics.

2. How should we model contact structure in spatially heterogeneous populations?

Human populations are never distributed uniformly in space. Hence, the movement of people to achieve their daily tasks in life is driven strongly by the distribution of population density around them. In rural areas, people must travel further on average to shop compared with urban areas; while they may travel less far to socialise. The movement of hosts is clearly an important feature of spatially explicit infectious disease models (Riley, 2007). It is also an important aspect of human behaviour for the study of other social phenomena: urbanisation, disaster planning, transport planning, and many others. There has been considerable interest in developing parsimonious models of human movement in recent years in order to support these different studies (González et al., 2008; Wang et al., 2009; Simini et al., 2012).

Most quantitative descriptions of human movement are based on the concept of a gravity model: that the flux of individuals from area dA_1 to area dA_2 is proportional to the product of the populations of the two areas n_1 and n_2 and inversely proportional to the distance between them r_1, raised to some power (Viboud et al., 2006). If the analogy with Newtonian gravity is direct, movement between areas is assumed to be proportional to $n_1 n_2 / r^2$. With only minor refinements, for some systems, this formulation describes observations extremely well. For example, the number of people travelling between Germany and 28 other European cities by air can be well estimated with simple gravity-based models (Grosche et al., 2007).

However, spatial models of infectious disease are often defined for an individual (as well as for linked metapopulations). Therefore flux models must be refined so as to be consistent with simulated infections between individuals. This is usually achieved by assuming that the infectious contacts of individuals are determined by a mobility kernel: the probability that an individual at location r_1 will make contact with an individual at location r_2. The kernel itself can be defined only up to a constant of proportionality, with the number of infection events determined by a separate parameter (Riley and Ferguson, 2006). Effectively, individual mobility becomes relative to available opportunities.

The discovery of flexible and accurate movement models is a current challenge for infectious disease dynamics, with high interest in the recently proposed radiation flux model. In the radiation model, the degree of flow between two populations is driven by their population sizes, the distance between them and also by the total number of people who live the same distance away from each population (or closer) (Simini et al., 2012). Thus, the intervening population absorbs journeys in the same way that radiation is absorbed as it passes through a media. Although the radiation model as currently proposed has no free parameters and is attractive in its simplicity, it is not yet clear to what degree previously proposed gravity-like mobility kernels can achieve similar or better fits to observed patterns by estimating two or three key parameters.

One obvious way forward is for the underlying movement assumptions of spatial models of infectious disease to be compared using spatially resolved social contact data (Read et al., 2014).

3. How do we define a threshold parameter for spatial models?

The basic reproductive number R_0 is most commonly understood to be the average number of infections generated by one infectious individual in an otherwise susceptible population. Therefore, for simple non-spatial homogeneous mixing models, the critical or threshold value of a straightforward R_0 parameter is unity: that is, when $R_0 \leq 1$, the expected outbreak size is small; when $R_0 > 1$, there is a significant probability of a large outbreak.

Where the population includes individuals of different infectious types, a more sophisticated approach defines R_0 as the largest eigenvalue λ_* of the next generation operator for those types (Diekmann and Heesterbeek, 2000; Heesterbeek, 2001). This is appropriate for most non-spatial models, for which branching process approximations can be applied (Ball, 1983; Davis et al., 2008), showing that early growth is exponential, with the nth generation of infectives $\propto \lambda_*^n$, and with infectious numbers of each type in

the ratios of the corresponding right eigen-vector. Thus, it can reasonably be claimed to be the natural generalisation of the simple homogeneous case – and again the threshold value of R_0 – is unity.

For spatial models, where the numbers of infectives often grow only quadratically, rather than exponentially, this generalised definition of R_0 is not applicable (Diekmann and Heesterbeek, 2000; Mollison, 1986). For simple spatial models with just one type of individual, the original definition as the average number of infections generated by one infectious individual in an otherwise susceptible population can be used. However, because of the clumping effects inherent in spatial models, the threshold value of this R_0 will be greater than unity: for example, for nearest-neighbour lattice models it lies between 2 and 2.4 (Mollison and Kuulasmaa, 1985). Therefore, the transmissibility defined by $R_0 = 1$ in this case underestimates the true critical value of transmissibility.

For more complex spatial models that do exhibit exponential growth, ideally we should be calculating a next generation operator whose quasi-stationary state would be analogous to the leading eigenvector of the homogeneously mixing case, but in general this is not feasible. One can calculate the average number of secondary infections generated by a randomly chosen individual in an otherwise susceptible population, R_0^* say, but it is not clear that this parameter will consistently under- or over-estimate critical transmissibility. Intuitively, it seems likely that infection from a randomly chosen individual will be less transmissible than an individual chosen in accordance with a theoretical eigen-vector. Therefore, the critical threshold of transmissibility based on R_0^* will be an overestimate of the true critical threshold. However, there may be unusual distributions of mixing and transmissibility within a population that force the effect in the opposite direction. A proper generalisation of R_0 to the spatial multi-type case remains elusive.

One alternative is for models to be parameterised such that the hazard of infection for all infection events is defined to be proportional to a single parameter, β. Then β's threshold value, β_0, can be found iteratively using simulations to arbitrary levels of precision, and R_0 defined as β/β_0. One merit of this definition of R_0 is that the critical vaccination level is immediately seen to be $1 - 1/R_0$, as in simple homogeneous mixing models.

4. How should we analyse models with long distance interactions?

A basic challenge concerns the relationship between contact structure and the duration T of an epidemic in a population of size N. For global models, where growth and decline are both exponential, the duration is of order $\log(N)$, whereas for a spatial model with only local contacts growth goes only as a quadratic (in 2 dimensions), so that the duration is much longer, of order $\sqrt{N}$.

There are two well-studied types of model between the entirely local and the entirely global. The simpler, "great circle" (Ball et al., 1997) or "small world" (Watts and Strogatz, 1998) approach, just adds a proportion of global contacts. The justification for the second name is that it takes only a relatively small proportion of global links to greatly reduce the diameter of the contact network.

The second approach introduces long-distance contacts through an arbitrary dispersal distribution V. If V has exponentially bounded tails, a simple linearisation technique can be used to estimate the velocity of spread (Mollison, 1991). For lattice models, the question of when the velocity is finite, or more generally how does the graph distance of vertices within Euclidean distance r scale in r, has been answered with robust analysis (Biskup, 2004; Trapman, 2010). This model has recently been extended to inhomogeneous individuals and weights on the vertices (Deijfen et al., 2013). Detailed results on the exact scaling of the number of vertices that can be reached within k infection steps for a spatial epidemic on a square lattice are needed.

Even for SIR epidemics on a network, it is interesting to know how the number of vertices that can be reached within k infection steps scales with k. Random graphs are often constructed as if this growth can only be exponential. Furthermore, epidemiologists often assume that this growth is exponential.

Methods need to be developed to investigate the proper scaling for available empirical networks based on data. Those methods might also provide some insights into how long it takes for an epidemic to go extinct in a spatial setting.

5. On what scale is intervention most effective?

At what spatial resolution, or broken down into what spatial units, should modelling be carried out? The natural scale for transmission, for data availability, and for intervention are not necessarily the same (for administrative reasons, for example, school closure may take place at a county level). In order to give useful guidance, models need to contain the same granularity as that used for interventions. This requirement is likely to result in additional model complexity that may not match the availability of data, presenting challenges for model fitting and specification.

Where global or long-distance contacts are important, simple large-scale interventions can be effective, as for example restrictions on air travel in the case of SARS and on transport of animals in the 2001 UK foot and mouth epidemic. Such interventions can reduce a large-scale outbreak into a number of local outbreaks that can then be dealt with separately.

Examples of spatially localised interventions include ring vaccination (Tildesley et al., 2006) and ring culling (as carried out in the 2001 UK foot and mouth epidemic, (Keeling et al., 2001)), local school closure (House et al., 2011), and local top-up vaccination campaigns. Since nations typically determine their own intervention strategies, every intervention is in some sense local, and therefore spatially heterogeneous.

Interventions can be targeted in a number of different ways: they may attempt to interfere with transmission by isolating infected individuals or introducing biosecurity measures (e.g. face masks in SARS); they may attempt to trace potential cases and contacts using knowledge of the (spatial) network of transmission; they may be based on an understanding of the general nature of the transmission process to apply locally but not individually targeted interventions, e.g. ring vaccination. In many instances, several of these approaches may be followed at once (Keeling et al., 2001). The spatial heterogeneities of intervention add another layer of complexity to the system, and provide a challenge for modelling, particularly in incorporating sufficiently detailed data to offer firm conclusions.

Spatially localised mass treatment is a crude approach compared to detailed contact tracing (Riley and Ferguson, 2006), but likely to be quicker to implement in practice. However, its broad-brush nature brings problems: the number of individuals subject to the intervention will likely be larger, with the associated burden of dealing with this greater load; when the intervention is detrimental at the individual level (e.g. culling or quarantine), a large number of individuals will suffer unnecessarily. Models need to incorporate costs, timescales, and logistical constraints, and account for the full burden of the intervention, including the possibility that public opinion may make some interventions impossible to implement or to sustain. Consideration should be given to how more and less focussed interventions can be best combined.

It is important to recognise that spatially heterogeneous interventions may change transmission patterns in unintended ways. For example, restricting cattle movements in one part of a country

may boost trade and increase movements elsewhere. Where there is scope for a reorganisation of contacts, a misapplied intervention may do more harm than good: people leaving a town to avoid quarantine may seed infection elsewhere. Models need to consider the impact of interventions on spatial mixing beyond the region in which the intervention takes place.

Conclusions

Adding a spatial component to an applied infectious disease model has been viewed, to this point, as a complex technical extra only to be considered when absolutely necessary. While many practically relevant insights into infection dynamics can be gained without incorporating spatial features, nevertheless as the open source coding toolbox available for the construction of these models improves and spatial data become available at the level of the individual, the explicit representation of space will likely become the norm rather than the exception for applied disease dynamics. Here we have highlighted a number of currently open challenges that, if met, should improve the quality of insight derived from the future application of spatial models.

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