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Five challenges for stochastic epidemic models involving global transmission

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ABSTRACT

The most basic stochastic epidemic models are those involving global transmission, meaning that infection rates depend only on the type and state of the individuals involved, and not on their location in the population. Simple as they are, there are still several open problems for such models. For example, when will such an epidemic go extinct and with what probability (questions depending on the population being fixed, changing or growing)? How can a model be defined explaining the sometimes observed scenario of frequent mid-sized epidemic outbreaks? How can evolution of the infectious agent transmission rates be modelled and fitted to data in a robust way?

1. Introduction and classification

Epidemic processes are essentially stochastic, but stochastic epidemic models have not had a straightforward history. That epidemics proceed by chance contacts with individuals was understood from the earliest days of modelling, but early modelling developments were deterministic. The development of stochastic models, from the 1950s onward (*e.g.* Bailey, 1950; Bartlett, 1956), was in parallel with developments in techniques, starting with models that dealt in total numbers of infecteds, susceptibles, etc. Individual-based models came in first to deal with spatial populations (1970s), with subsequent developments related to computer methodology (simulations, inference) and network theory.

Stochastic models can conveniently be classified according to whether their contact structure is global, network, metapopulation or spatial. Given the many other aspects of disease to be modelled, there is good reason to model contact structure as simply as possible. Models with too many parameters cannot usefully be fitted: as Euler is reputed to have said, 'Give me four parameters and I will draw you an elephant, five and I will have him wave his trunk'.

The simplest contact structure is no structure, often referred to as either global or homogeneous mixing (Mollison, 1995). Individuals' probabilities of interaction do not depend on their location in the population, such as their social group or spatial location. Global models can incorporate individual heterogeneity, for example by having different rates of infection for individuals of different age, sex, or infection history. Numerous examples of (deterministic) global models, over the range of diseases important to humans, can be found in Anderson and May (1992).

Network epidemic models (Pellis et al., in this volume) are more difficult to define. Any individual-based epidemic model can be thought of as a network or random graph: with individuals as nodes, and infection of one by another as a link. The question is rather whether network theory can be usefully applied. In recent years network models have been notably successful in analysing models where individuals vary greatly in their number of contacts (the degree distribution of the underlying graph).

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Metapopulation models (Ball et al., in this volume) deal with cases where interactions *do* depend on social group. The basic case is where the population is partitioned into non-overlapping groups, *e.g.* households; individuals have one contact rate with individuals in different groups, and another (higher) rate for individuals in the same group. More general metapopulation models allow an individual to belong to several different types of group, each with its own contact rate, or allow more levels of mixing.

Spatial models (Riley et al., in this volume) vary from simple lattices with only nearest–neighbour interactions, for which some theoretical analysis is possible, to complex models with long-distance interactions, for which only qualitative and approximate results are known. A key feature of spatial models is that they display slower than exponential growth, even in their earliest stage; this makes it difficult to approximate them adequately by deterministic models, and even to define threshold parameters.

As a simple example to illustrate these different types of model, consider a disease among two type of individual, male and female. In each case consider a simple Markov process SIR, in which infected individuals (I) have an exponentially distributed infectious period before being removed (R), during which they may infect susceptibles (S) as follows. First, suppose that the infection rates between any (I,S) pair depends only on the types of the individuals involved (perhaps individuals can only infect others of the opposite sex, and perhaps the rates from male to female and female to male are different); this is a *global* model. Second, suppose the individuals live distributed between a number of different villages, and that the rates of infection have two levels, with higher infection rates if the (I,S) pair live in the same village, lower if they live in different villages; this is a *metapopulation* model. Third, suppose instead that the individuals live in a line of houses equally spaced along a street, and that the infection rate between I and S depends on the distance between the houses they live in (normally one would take this to be a decreasing function of distance); this is a *spatial* model. Finally, in any of these populations, suppose that we think of individuals as vertices of a graph, with edges of the graph connecting pairs that have some kind of social relationship; and then take rates of infection between connected individuals that only depend on their type; this is a *network* model. Note that all the other three examples can be considered as network models, if we draw edges between all pairs of individuals (everyone knows everyone"), and add dependence of infection rates on village or distance as appropriate.

We are now ready to state our first challenge, namely: is this classification into global, network, metapopulation and spatial models sufficient for the range of contact structures of interest in understanding infectious disease dynamics?

The focus of the present paper is global stochastic epidemic models, where any (infectious) individual may infect any other (susceptible) individual at a transmission rate that may differ between different pairs of individuals, but should be of the same order $1/N$ (or 0), where N is the population size. The simplest model assumption is where all transmission rates are identical, which is called a homogeneously mixing population of homogeneous individuals, but one may also assume different mixing rates and/or that individuals are of different types with respect to susceptibility and/or infectivity. As we shall see in this section, there are several open problems also for global epidemic models (only having transmission on a global scale). In real world epidemics there is of course nearly always some local structure within which transmission is much higher. Still, results for global epidemic models have undoubtedly been most influential in affecting health policies, and for highly transmittable diseases global mixing is often a reasonable approximation.

Having specified identical transmission rates (between all pairs of individuals) does not define the model uniquely. Other aspects to consider in formulating a stochastic model include.

Type of epidemic model. An SI model is where Susceptibles may become infected and infectious, and if they do, they remain infectious forever. In an SIR model, individuals that are infectious (from now on denoted Infectives) eventually recover from the disease and become immune for the rest of their lives (measles and chicken-pox being two examples). An SIS model is where infectives, rather than recovering and becoming immune they recover and enter the susceptible state again. SEIS models admit that there is a latent (E for exposed) state where an individual has already been infected but where he or she has not yet started to shed virus or bacteria. Other examples, hopefully self-explanatory, are SEIR, SIRS, SEIRS, ...

Treatment of time. Is the time evolution of the epidemic of interest or only the end/final state of an outbreak? Is discrete or continuous time more appropriate? Do all rates/probabilities obey the practical Markov property (that future events only depend on present states and not the history, meaning that all underlying distributions are exponentials), or are durations not all exponentially distributed?

Population. Are we considering a fixed and finite population of size N, or a population having births and deaths but fluctuating randomly around N, or even a growing population? If the time-frame of interest is short, then a fixed population model might suffice, whereas if interest is on longer periods, a dynamic population is more realistic, thus allowing for influx of new individuals. If the population size fluctuates randomly around N it will eventually die out with probability 1 (and the disease will go extinct before this happens) so questions of interest then relate to population-disease properties prior to extinction (quasi-endemic) and the length of time to extinction of the disease. Alternatively, if the population grows, then it may happen that the disease will remain present in the population for ever (endemic situation).

Fluctuations over time. Do all event rates stay the same over time except for the numbers "at risk"? The simplest models answer this question with a yes, but there are situations where this is clearly not the case, for example when the infectious agent evolves on the same time scale as the epidemic outbreak, and/or because individuals start taking precautions as more and more people are struck by the disease. A (perhaps simpler) fluctuation over time is where individuals and/or transmission rates change over time for reasons other than the epidemic itself. Examples include seasonality due to school term and school closure, but also varying transmission rates due to changes in temperature.

These type of questions are dealt with in the remainder of the current paper, and several challenges for these type of models are listed.

2. Endemicity: persistence of infection

Bartlett's seminal paper (Bartlett, 1956) highlighted a severe inadequacy of deterministic models in describing the persistence of infection in an SIR (or similar) process with demography: fluctuations in the prevalence of infection about the endemic level can often be large enough for transmission to be interrupted by stochastic fade-out. Using a stochastic linearization approach, Bartlett estimated the magnitude of these fluctuations and characterizing the critical community size required for the persistence of such infections (most notably, for measles). This approach, later formalized in terms of an Ornstein–Uhlenbeck process, provides the basis of later work that derives approximations for the time to extinction when starting at the endemic (quasi-)equilibrium (*e.g.* Nåsell, 1999, and others). Improved approximations can be obtained using large deviation theory (*e.g.* Kamenev and Meerson, 2008).

The question of endemic persistence is most pointed for a newly-introduced infection given that the initial epidemic is the most severe. While it is well known how to compute the probability