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Nine challenges for deterministic epidemic models

Mick Roberts[a,*], Viggo Andreasen[b], Alun Lloyd[c,d], Lorenzo Pellis[e]

[a] Infectious Disease Research Centre, Institute of Natural and Mathematical Sciences, and New Zealand Institute for Advanced Study, Massey University, Private Bag 102 904, North Shore Mail Centre, 1311 Auckland, New Zealand
[b] Department of Science, Roskilde University, 4000 Roskilde, Denmark
[c] Department of Mathematics and Biomathematics Graduate Program, North Carolina State University, Raleigh, NC 27695, USA
[d] Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA
[e] Warwick Infectious Disease Epidemiology Research Centre (WIDER) and Warwick Mathematics Institute, University of Warwick, Coventry, CV4 7AL, UK

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ABSTRACT

Deterministic models have a long history of being applied to the study of infectious disease epidemiology. We highlight and discuss nine challenges in this area. The first two concern the endemic equilibrium and its stability. We indicate the need for models that describe multi-strain infections, infections with time-varying infectivity, and those where superinfection is possible. We then consider the need for advances in spatial epidemic models, and draw attention to the lack of models that explore the relationship between communicable and non-communicable diseases. The final two challenges concern the uses and limitations of deterministic models as approximations to stochastic systems.

Introduction

Deterministic models have a long history of being applied to the study of infectious disease epidemiology. Many earlier studies were confined to establishing criteria for the stability of the infection-free steady state and existence of an endemic steady state, perhaps in simple cases with explicit expressions for the proportion susceptible, prevalence of infection and herd immunity. Studies of the endemic state involve demographic processes that occur at a different (and longer) time scale, as well as epidemiological processes. Important concepts for structured populations such as vaccine-induced age-shift and core groups are fundamental insights that arise from this analysis, so even though disease transmission is in principle a discrete stochastic process, deterministic modelling offers a fruitful avenue to study problems of endemicity. This gives rise to our first two challenges.

The transmission dynamics of genetically varying pathogens have received considerable interest in recent years, driven by advances in molecular biology, the impact of multivalent vaccines and the emergence of drug-resistance. Important challenges remain with regard to the multi-strain models that arise. These are addressed as Challenge 3. In developing multi-scale models that link within- and between-host dynamics, for example to study the long-term evolution of pathogens, one often faces the problem of how to model superinfection. These are addressed as Challenges 4 and 5.

Spatially explicit models are usually treated in a stochastic framework, although this was not always the case (Anderson and May, 1991; Diekmann et al., 2013). Diffusion models have been proposed that give rise to travelling epidemic waves through a homogeneous population. However, in reality contacts between individuals are different due to a variety of factors, and not just spatially determined, hence a heterogeneous description is required. Taking account of this is Challenge 6.

It is well-known that non-communicable diseases (NCDs) such as asthma, some cancers and cardio-vascular diseases have risk factors in common with infectious diseases: the predominant ones are low socio-economic status, poor nutrition and poor housing. While changes in these factors could lead to changes in infectious diseases and NCDs, there has been relatively little investigation of the interaction between them. This presents Challenge 7.

Deterministic models are generally regarded as simpler to handle than stochastic models. Hence, they are often the first tool tried when a new problem presents itself (Diekmann et al., 2013). Their limitations are frequently alluded to, but often ignored. Challenge 8 is to define these limitations. Many infectious disease systems are fundamentally individual-based stochastic processes, and are more naturally described by stochastic models. Analysis of an equivalent

* Corresponding author. Tel.: +64 9 414 0800.
E-mail address: m.g.roberts@massey.ac.nz (M. Roberts).

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(in some sense) deterministic model may then yield information about the solution of the stochastic system. Our final challenge is to understand the relationship between so-called equivalent stochastic and deterministic representations of the same system.

1. Understanding the endemic equilibrium

The endemic equilibrium arises as a balance between transmission of infection and replenishment of the susceptible pool, either through loss of immunity or demographic turnover. The mathematical starting point for the characterization of the endemic equilibrium is typically a renewal equation which, under suitable assumptions about separability of the mixing function, may be expressed in terms of a scalar equation in the force of infection. Introducing the effective reproduction number $\mathcal{R}_{\text{eff}}$ as the number of new infections that a typical infectious individual produces, one may interpret the endemic equilibrium as the condition $\mathcal{R}_{\text{eff}} = 1$ (Diekmann et al., 2013). It would be interesting to determine the underlying structure of this equation, in particular for the non-separable case, which would address the implications of empirically observed mixing patterns such as those reported in Mossong et al. (2008).

For endemic infections, parameter estimation is naturally based on information about the endemic equilibrium. In simple settings one may determine $\mathcal{R}_0$, for example, from the observed average age at infection or from the fraction of the population that remains susceptible. Thus the estimation of $\mathcal{R}_0$ is indirect in the sense that it relies heavily on our understanding of the endemic equilibrium. It is striking that where $\mathcal{R}_0$ is estimated in this way (e.g. for childhood diseases, see Table 4.1 in Anderson and May, 1991), the values obtained are typically higher than those for diseases where $\mathcal{R}_0$ is determined from directly studying the onset of the epidemic (e.g. influenza, SARS or HIV).

While host renewal through demographic processes is fairly well understood, the renewal process associated with waning immunity is considerably less clear although there are applications to important diseases such as pertussis (Rohani et al., 2010) and malaria (Bailey, 1982). There is a need to study this process, both in terms of the underlying biology and in terms of its dynamic consequences (Breda et al., 2012).

It is known that regular periodic epidemics of childhood diseases depend on the seasonality of the transmission coefficient in combination with the population birth process. Oscillations around the endemic equilibrium are observed for a wide range of infectious diseases (Grassly and Fraser, 2006), but several aspects of this process are not well understood. It is clear that the variation in transmissibility (for example due to school holidays) affects the qualitative pattern of epidemics, in a way that could (at least in principle) be studied by Floquet theory. However, we do not have a comprehensive theory for the interaction, or an understanding of whether stochastic variation in the troughs between epidemics may be neglected (Billings and Schwartz, 2002, see also Challenge 9), or knowledge of how these patterns relate to so-called *skipping dynamics* (Stone et al., 2007). A challenge is to examine the renewal equation, and develop a deeper understanding of the relationship between $\mathcal{R}_{\text{eff}}$ and $\mathcal{R}_0$ that might clarify these issues.

2. Defining the stability of the endemic equilibrium

Although it is usually straightforward to determine the small amplitude linear perturbations about the equilibrium and derive the associated characteristic equation, this equation is typically too complex to provide general stability results. For example, it remains an open question under which conditions the internal equilibrium of the age-structured *SIR* model with demographic turn-over is stable, and studies have shown that stability as well as instability (through a Hopf bifurcation) may occur for specific conditions (Andreasen, 1993). Singular perturbations utilising the multiple time scales that are inherent in endemic models may offer an alternative approach. Consider an *SIR* model where time is measured in units of host life-span, and the sizes of each epidemic compartment are measured as fractions of the total population size. The underlying dynamics follow

$$\begin{aligned}\dot{S} &= B - S - \frac{\beta}{\epsilon} IS \\ \dot{I} &= \frac{\beta}{\epsilon} IS - \frac{1}{\epsilon} I - I \\ \dot{R} &= \frac{1}{\epsilon} I - R\end{aligned}$$

where $\epsilon \ll 1$ denotes the ratio of the infectious period to the host life-span, the transmission coefficient $\beta = \mathcal{R}_0(1+\epsilon) \sim 1$ and the birth rate $B \sim 1$. One would then look for a fast time scale of the epidemic, where $I \sim 1$, and a slow time scale of the demographics, where $I \sim \epsilon$. For the disease-free state this is possible (see for example Owuor et al., 2013), but it is not clear how a similar separation would work for the endemic state. In particular, the linear analysis suggests that there may in addition be an intermediate time scale of order $\sqrt{\epsilon}$. To be useful, one would then have to extend the analysis to structured populations. Finding a general paradigm for the stability of the endemic equilibrium remains a challenge for theoreticians.

3. Modelling multi-strain systems

The nature of diversity is as poorly understood in epidemiology as in many other branches of population biology. We have only two general models available: the quasi-species model of mutation-selection balance and the competitive exclusion principle. Most models of strain dynamics may be seen as special cases of these two basic models, with the complication that competition can either be directly between strains within the host (as may be the case for bacterial colonization), or indirect competition for a shared resource (as may be the case for immunizing pathogens, the resource being susceptible hosts). Super-infection and cross-immunity are special cases of these two modes of interaction that have received some attention (see Challenges 5 and 6), but we need to understand better the nature of the niches that arise due to the dynamical aspects of transmission. Examples are the pathogen strains with superior survival during troughs of low disease activity (Gog et al., 2003), and the mechanisms by which long term host immunity may interact with strain dynamics (Kucharski and Gog, 2012). As the number of co-existing species is limited by the number of shared resources, these models will in general only allow for a restricted diversity. The challenge is to extend epidemic models of strain dynamics to allow for greater diversity, as suggested by Lipsitch et al. (2009) for the case of bacterial colonization.

4. Modelling time-varying infectivity

The majority of deterministic models, and especially those used for applications in veterinary and public health, are compartmental models. These involve constant transition rates between compartments, and hence sojourn times that are exponentially distributed (or Erlang distributed in the case of multiple identical sequential compartments). The advantage of these models is that one can use ordinary differential equations and, without specialist knowledge, can benefit from the theory of dynamical systems and well-developed and readily available numerical methods. The disadvantage is that their imposed structure leads to a lack of