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## Nine challenges for deterministic epidemic models

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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.

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### 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

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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

$$\dot{S} = B - S - \frac{\beta}{\epsilon} IS$$

$$\dot{I} = \frac{\beta}{\epsilon} IS - \frac{1}{\epsilon} I - I$$

$$\dot{R} = \frac{1}{\epsilon} I - R$$

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

generality and removes the possibility of embedding more realistic infectivity profiles.

Models in which individuals are assumed to have a time-varying infectivity profile, often referred to as time-since-infection models, represent a valid alternative. This formalism provides a comprehensive theory for invasion, and useful tools for calculating the final size of *SIR* epidemics and the equilibria of *SIS* models (or *SIR* models with demography, etc.). However, a general theory of such models is still lacking, and tracking their dynamics numerically is non-trivial. Many challenges lie here. First, developing better methods for handling integral equations in infinite-dimensional spaces, both theoretically and numerically. Second, developing the framework to include waning immunity, for example by providing general tools for solving the renewal equation for the force of infection at the endemic equilibrium, which is complicated by the presence of re-infection. Third, extending such a framework to multi-strain systems, with all the attendant challenges already highlighted (Challenge 3), in particular keeping track of how individuals' past infection histories combine to shape the immunity profile in the population, which in turn regulates new infections and contributes to updating the infection histories themselves. Finally, a major challenge would be to extend the entire time-since-infection framework to structured populations of increasing complexity, for example on networks (see Challenge 6).

## 5. Modelling superinfection

*Superinfection* occurs when, following an infection that has not yet been cleared (and may or may not have triggered an immune response), the host is infected by a heterologous strain of the same pathogen (Smith et al., 2005). Most microparasite models ignore the possibility of a host being infected a second time before recovering (Diekmann et al., 2013). Such an assumption is key because it allows the infection to be treated as a process that evolves independently within the host. A modeling framework based on the concept of time-since-infection can therefore be formulated, where a clock attached to each infected host starts ticking at the time of infection, and anything that follows in that host depends only on this relative time. This approach leads to the standard definition of  $\mathcal{R}_0$  and the well-developed theory of next-generation operators (Diekmann et al., 2013). Relaxing the assumption of no superinfection is non-trivial, as the entire modeling framework collapses. However, superinfection is known to occur and might be important for infections such as HIV or TB. Some attempts at modelling superinfection have been reported, although almost always in the Markovian case of constant infection and recovery rates. These assumptions lead to exponentially distributed durations in each compartment, a condition too unrealistic for infections like HIV with a complex infectivity profile. The few exceptions (e.g., Martcheva and Thieme, 2003) assume an ad-hoc impact of superinfection, which seems difficult to generalise. The first step will be the construction of  $\mathcal{R}_0$  (or an extension of the concept), and the second the development of the next-generation operator formalism. The challenge is to develop a general theory for modelling superinfection (see also Gog et al., in this issue).

## 6. Constructing realistic spatially explicit models

Network models define contacts in a social space. Networks have a number of measurable properties, for example degree distribution, transitivity and clustering coefficient (see Pellis et al., in this issue). These properties are not sufficient to determine how good an approximation one network may be to another, and as yet no metric that fulfills this function has been defined. It should be possible to define a correspondence between large network models and

models on continuous space in such a way that some analytical results can be derived from the continuous representation. We could then have a correspondence between network properties and threshold quantities for invasion or persistence in the spatial model, and a measure that determines how close two networks appear to be with regard to the final size of an epidemic.

A spatially explicit model highlights the use of the word *typical* in the definition of  $\mathcal{R}_0$ . For example, if modelling an infectious disease previously not present in a geographic region, then the primary case is more likely to occur at a port of entry. In defining a threshold quantity for invasion, the connectivity of the primary case often influences whether an epidemic *takes off*, and for small networks the choice of primary case clearly influences the final size of the outbreak. Hence a methodology is required that assigns different thresholds for invasion to different nodes of a network, or to different locations for spatially continuous models.

An alternative spatial modelling paradigm is based on metapopulation structures, with a gravity model defining contact rates between the nodes representing communities (see Riley et al., in this issue). The contact rate between nodes  $i$  and  $j$  is proportional to (for example)  $n_i n_j / r_{ij}^2$ , where  $n_i$  is the population density at node  $i$  and  $r_{ij}$  is the distance between the nodes. More complex variations have been proposed, but whenever the contact rate is a strictly increasing function of  $n_i$  it is possible for it to attain unrealistically high values. Small values of  $r_{ij}$  have a similar effect, so saturating functional forms are required. A radiation model has been proposed for travel between cities in an attempt to address these issues (Simini et al., 2012). It is not clear how this could be used to model epidemics, and finding a tractable and realistic deterministic model with an explicit spatial structure remains a challenge.

## 7. Exploring the interaction with non-communicable diseases

Cancers are usually regarded as non-communicable diseases (NCDs), the notable exceptions being canine transmissible venereal tumour and Tasmanian devil facial tumour disease (McCallum, 2008). However, some infectious diseases are known to be risk factors for NCDs. For example, Jaagsiekte sheep retrovirus causes lung tumours in sheep and goats (Wootton et al., 2005), and the link between human papillomavirus infection and cervical cancer has been established (Walboomers et al., 1999) and investigated in a deterministic framework (Baussano et al., 2010). The interaction between a transmissible agent and an NCD may be more subtle. Antibiotic use has been associated with breast cancer (Velicer et al., 2004), and the exposure to microbes during early childhood has been associated with increased risk of conditions such as inflammatory bowel disease and asthma (Olszak et al., 2012). Increasing evidence indicates a key role for the bacterial microbiota in carcinogenesis (Schwabe and Jobin, 2013). There are complex interactions between a host and its microbiota, and an alteration to the dynamics of this interaction through infection may promote a variety of diseases, many of which may usually be regarded as non-communicable. In order to evaluate the potential role of transmissible agents in the development of these conditions, new types of mathematical model of the host-pathogen interaction will be required. These models will need to suggest testable hypotheses that connect the pathogen, the host's immune response, and the various regulatory pathways of the host that may play a part.

## 8. Defining the limitations of deterministic models

All epidemic models are inherently stochastic at the individual level. However, Kurtz (1970, 1971) proved that, for a fairly general class of Markov processes, the infinite population limit

of the stochastic system satisfies a suitably defined deterministic model. This result is not limited to homogeneously mixing models: for example household models feature local mixing in small groups, and Kurtz's result can be used to underpin the approach of House and Keeling (2008) for their analysis. Analogously, for *SIR* epidemic models on tree-like (unclustered) networks, the various deterministic models proposed in the literature (Ball and Neal, 2008; Lindquist et al., 2011; Volz, 2008), together with the standard pairwise approximation, have been shown to be exact in the infinite population limit. However, all of these models are restricted by the assumption of constant recovery rates. One important challenge is to extend Kurtz's results to other more complicated situations of practical interest, for example the time-since-infection framework described in Challenge 5.

A related problem is the widespread use of deterministic models in epidemiology without full recognition of their limitations, and with potentially misleading conclusions. For example, multi-annual predictions might involve low numbers of infected hosts in the between-epidemic troughs, and stochastic effects may not be negligible (see Britton et al, in this issue). Analogously, deterministic metapopulation models have a long successful history (Hanski and Gaggiotti, 2004), but when the coupling between subpopulations is weak they struggle to represent the system dynamics. They are unable to capture typically stochastic phenomena, like fade-out, extinction, and lack of synchrony due to random delays (Rock et al., 2014). When metapopulation models exhibit a more complex structure, deterministic analysis may describe an attractor as stable, but stochastic fluctuations may interfere with model components resulting in complex orbits. As deterministic models cannot capture these phenomena, we need to understand when they are likely to occur.

## 9. Developing robust deterministic approximations of stochastic models

The importance of stochastic effects can be quantified using deterministic moment equations. The nonlinearity in the process leads to a coupling between moment equations of different orders. For instance the nonlinear transmission term of an *SIR* model leads to equations for expectations that include second order moments:  $E(SI) = E(S)E(I) + \text{cov}(S, I)$ . The lower order approximation in which all variances and covariances are assumed to be zero, i.e. stochastic effects are ignored, leads to the simplest deterministic approximation – the so-called *mean field model*. When the population under consideration is large but finite, the solution of the mean field model may not be a good approximation to the mean behaviour of the corresponding stochastic model. To obtain a higher order approximation, an alternative assumption must be employed. The multivariate normal (MVN) closure approximation (Isham, 1991) is often used when modelling microparasites. Numerical results show that the MVN approximation often fails in situations of interest, e.g. for recurrent epidemics near the critical community size, where extinction is not uncommon (Lloyd, 2004). The MVN and multivariate negative binomial approximations have been used to model macroparasites (Herbert and Isham, 2000).

In situations where results similar to those of Kurtz's (see Challenge 8) are not available, or when intuition does not suggest a natural choice for a suitable deterministic model, other approximation schemes must be adopted. Network moment-closure approximations (see e.g. House and Keeling, 2008; Keeling, 2000; Pellis et al., in this issue) are essentially the only viable method to avoid computationally expensive fully stochastic simulations for *SIR* models on clustered networks or *SIS* models (on any network).

## Conclusion

We have discussed a selection of nine challenges in applying deterministic models to epidemiology. Clearly, our selection is not exhaustive and numerous other important challenges involving deterministic models are discussed elsewhere in this special issue. Furthermore, many challenges described here do not exclusively relate to deterministic models. In selecting our challenges, we have focussed on those where preliminary approaches have employed deterministic models, and those where it is likely that deterministic models will make a significant contribution.

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