MINISYMPOSIUM

ASSUMING COMPARTMENTAL MODELS IN INFECTIOUS DISEASE DYNAMICS. DOES IT HURT?

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The role of mathematical models in understanding infectious disease dynamics is well established. Models have successfully guided us in designing public health prevention or control strategies as exemplified by the concept of a threshold parameter R_0 in malaria by Ross in 1911. More recently, increasing layers of complexity are added to infectious disease models, e.g. by trying to model the social structure of a population through a network.

However, a key assumption that is rarely challenged in infectious disease dynamics is the infectivity profile $A(\tau) = \beta e^{-\gamma\tau}$ (but see the seminal 1927 paper by Kermack and McKendrick for an early exception), the probability of transmission given a contact between a susceptible and an individual that was infected τ time units ago. By far the most used models are (deterministic) compartmental models for the infectious disease. In such models, individuals are classified in a finite number of stages; e.g. in the well-established Markovian SIR, individuals are susceptible, infectious or recovered. Implicitly, this assumes that an infectious individual has a constant transmission rate that becomes zero after an *exponentially* distributed time. From a biological perspective, there are few, if any, infectious diseases for which we expect this to be realistic. The main motivation is really mathematical convenience. In a deterministic setting, compartmental models lead to a description in terms of ordinary differential equations. In a stochastic setting, we can make use of the convenient Markov property. Therefore, we only need to keep track of the compartment an individual is in, rather than keeping track of how long ago it got infected.

The Markov assumption is so dominant in the infectious disease community that it is easy to forget that it is an assumption and, as a consequence, this assumption is rarely challenged. Certainly there are contexts in which the assumption will only play a small role, despite its limitations. At the same time, it has long been known that it can have a big influence on the robustness of the conclusions that we draw from our models and when doing inference, e.g. in the context of the real time growth rate r.

In this minisymposium, we consider the use of non-Markovian epidemic models, both in the stochastic and the deterministic setting. The first speaker (Odo Diekmann) will argue for a description of epidemic models in terms of renewal equations. The next three speakers consider the use of non-Markovian models in different epidemic contexts, namely network models (Gergely Röst), asymptomatically and symptomatically infected hosts (Tom Britton), and within- and between-host models (Venetia Karamitsou). Finally, the last speaker (Lorenzo Pellis) discusses assumptions concerning the individual-level transmission process, and gives an overview on the topic. The aim of the minisymposium is not to provide definite answers. Rather, by challenging the Markov assumption in different epidemic contexts, it aims to open room for thoughts and discussions.

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RENEWAL EQUATIONS SHOULD BE UBIQUITOUS IN THE WORLD OF EPIDEMIC MODELS

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Keywords: Kermack-McKendrick, Renewal equations, Age structure, Numerical bifurcation tools.

The spirit of Kermack-McKendrick's 1927 classic has, unfortunately, perished. First I try to restore this spirit, by extending the model to incorporate age-structured demography with general survival probability. Next I try to reinforce it. The latter involves delineating a dynamical systems perspective of renewal equations with a bit of attention for numerical bifurcation tools.

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PAIRWISE APPROXIMATIONS OF NON-MARKOVIAN NETWORK EPIDEMICS

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Joint work with Zsolt Vizi (Bolyai Institute, University of Szeged, Hungary), Istvan Kiss (Department of Mathematics, University of Sussex, United Kingdom)

Keywords: Pairwise models, Networks, Distribution of recovery time, Time evolution.

Pairwise models have been proven to be a flexible framework for analytical approximations of stochastic epidemic processes on networks that are in many situations much more accurate than mean field compartmental models. The non-Markovian aspects of disease transmission are undoubtedly important, but very challenging to incorporate them into both numerical stochastic simulations and analytical investigations. Here we present a generalization of pairwise models to non-Markovian epidemics on networks. For the case of infectious periods of fixed length, the resulting pairwise model is a system of delay differential equations, which shows excellent agreement with results based on the explicit stochastic simulations. For more general distribution classes (uniform, gamma, lognormal etc.) the resulting models are PDEs that can be transformed into systems of integro-differential equations. We derive pairwise reproduction numbers and relations for the final epidemic size, and initiate a systematic study of the impact of the shape of the particular distributions of recovery times on how the time evolution of the disease dynamics play out.

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EPIDEMIC MODELS WITH SYMPTOMATIC AND ASYMPTOMATIC CASES: WHO CAUSES MOST INFECTIONS?

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Joint work with Ka Yin Leung (Department of Mathematics, Stockholm University, Sweden) and Pieter Trapman (Department of Mathematics, Stockholm University, Sweden)

Keywords: SEIR, Symptomatic vs asymptomatic, Final size, Markovian models, Continuous-time Reed-Frost models.

Can you become infected when no one in your surroundings show any symptoms? There are many diseases, such as with influenza and norovirus, where some infected hosts show symptoms of the disease while others are asymptomatically infected, i.e. don't show any symptoms. What role do such asymptomatically infected individuals play in the transmission dynamics? The current paper considers a class of epidemic models following an SEIR (Susceptible $\rightarrow$ Exposed $\rightarrow$ Infectious $\rightarrow$ Recovered) structure that allows for both symptomatic and asymptomatic cases. The following question is addressed: what fraction ρ of those getting infected are infected by symptomatic (asymptomatic) cases? This is a more complicated question than the related question: what fraction of newly generated cases at the beginning of the epidemic are symptomatic (asymptomatic)? The latter question only depends on the type-specific reproduction numbers while the former question also depends on the mean latent and infectious periods of the two types as well as their probabilistic distributions. Bounds on ρ are derived for the situation where these distributions (or even their means) are unknown. The second aim of this paper is to illustrate the huge effects the choice of distribution functions for the latent and infectious periods can have. Special attention is given to the class of Markovian models and the class of continuous-time Reed-Frost models as two classes of distribution functions.

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THE IMPORTANCE OF WITHIN-HOST DYNAMICS FOR THE POPULATION LEVEL EVOLUTION OF INFLUENZA IN A NON-MARKOVIAN MODEL

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Joint work with Laurence S. Tiley (Department of Veterinary Medicine, University of Cambridge, United Kingdom) and Julia R. Gog (Department of Applied Mathematics and Theoretical Physics, University of Cambridge, United Kingdom)

Keywords: Cross-scale model, Age since infection model, Immune escape, Vaccination, Influenza evolution.

Influenza remains difficult to control due the virus' ability to generate antigenic variants that can evade the host immune response and spread through the population. Important factors that affect this process include immunity, achieved either through prior infection or vaccination, and the within-host time of emergence of such immune escape variants. But the exact way in which they affect the transmission rate of each strain and therefore its survival at the population level is not yet fully understood.

To address these questions, we developed an immuno-epidemiological model that includes the full dynamics of influenza both at the within- and the between-host levels. This is accomplished by nesting a within-host model of viral evolution into a non-Markovian, age-since-infection SIR epidemiological model. Within the host, multiple new immune escape variants can appear stochastically through mutation. These mutant strains then compete with the parent strain for resources within the host and for selection between hosts in a population that consists of both naïve and vaccinated individuals. The transmission rate is a function of the time since infection and depends on the within-host viral load and composition. Comparison of the model to a Markovian model of influenza evolution highlights the key similarities and differences that arise from the rejection of the Markov assumption.

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MODELLING THE INDIVIDUAL-LEVEL TRANSMISSION PROCESS: DO THE DETAILS MATTER?

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Keywords: Transmission process, Population structure, Model analysis, Impact of assumptions, Local VS global.

All models of infectious disease spread need to make assumptions about how they describe mathematically the transmission process between individuals. Even when presented explicitly, which is not always the case, it is rarely modified within the same analysis, and the consequences of this choice on the conclusions rarely assessed.

Rather than presenting the results of a single study, I will provide here an overview of different forms of transmission processes that appeared in the literature, and what their impact on the properties of epidemic models and their mathematical analysis is.

I will start from single-type and multi-type large population models, and show how many model properties may depend on some, but not necessarily all, elements of the transmission process. I will then move to models where the number of potential contacts is finite and show how the temporal details of the transmission process start mattering. In particular I will discuss network and households models, focusing also on exact and approximate methods for calculating the Malthusian parameter.

Finally I will share some opinions about why people might want to use a time-since-infection modelling approach. I will spend some words on nested models and the limitations of compartmental models in dealing with co-infection of multiple strains/pathogens, but other opinions will be much less developed and mostly aimed at provoking thoughts and discussions.