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Reconstruction of disease transmission rates: Applications to measles, dengue, and influenza

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HIGHLIGHTS

- Time series of transmission rates are reconstructed from disease-related data.
- Differential equations model the time evolution of infective stages and strains.
- The proposed numerical integration is fast but requires particular care.
- It is sensitive to the population size and reporting, insensitive to non-vital rates.
- Specific questions for three epidemics are answered using this methodology.

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ABSTRACT

Transmission rates are key in understanding the spread of infectious diseases. Using the framework of compartmental models, we introduce a simple method to reconstruct time series of transmission rates directly from incidence or disease-related mortality data. The reconstruction employs differential equations, which model the time evolution of infective stages and strains. Being sensitive to initial values, the method produces asymptotically correct solutions. The computations are fast, with time complexity being quadratic. We apply the reconstruction to data of measles (England and Wales, 1948–1967), dengue (Thailand, 1982–1999), and influenza (U.S., 1910–1927). The Measles example offers comparison with earlier work. Here we re-investigate reporting corrections, include and exclude demographic information. The dengue example deals with the failure of vector-control measures in reducing dengue hemorrhagic fever (DHF) in Thailand. Two competing mechanisms have been held responsible: strain interaction and demographic transitions. Our reconstruction reveals that both explanations are possible, showing that the increase in DHF cases is consistent with decreasing transmission rates resulting from reduced vector counts. The flu example focuses on the 1918/1919 pandemic, examining the transmission rate evolution for an invading strain. Our analysis indicates that the pandemic strain could have circulated in the population for many months before the pandemic was initiated by an event of highly increased transmission.

1. Introduction

Essential for modeling an infectious disease epidemic is the knowledge of the transmission rates—the rates at which susceptibles become infected by contagious individuals (Anderson and May, 1991; Grassly and Fraser, 2008). These rates are determined by the contact behavior of the involved hosts as well as the risk of transmission during contact, they are specific to the pathogen and its transmission route (Lange and Ferguson, 2009). Transmission rates fluctuate and often systematically change over time as we will examine in this paper for data of three different infections.

Combined with basic medical and demographic information, transmission rates are the most natural reference in predicting the time evolution of disease prevalence. Public health policies rely on such predictions, referring to the control of endemic infections and to the design of measures against emerging diseases, pandemics, or bio-terroristic threats (Ferguson et al., 2005; Fraser et al., 2009; Legrand et al., 2009). In practice, however, there is no straightforward way these rates are obtained from epidemiological data. The methods known are rather complicated and/or require lots of

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computing power (Finkenstadt and Grenfell, 2000; Bjornstad et al., 2002; Morton and Finkenstadt, 2005; Cauchemez and Ferguson, 2008; Hooker et al., 2011; Word et al., 2012, 2013), others have a limited range of application at this stage (Pollicott et al., 2011; Hadeler, 2011a, 2011b; Mummert, 2013; Kong et al., 2015). Addressing these issues, we will present a simple method for reconstructing transmission rates from incidence or mortality data and illustrate its wide range of application.

There are lots of computing and modeling strategies in infectious disease epidemiology, including probabilistic simulations (Morton and Finkenstadt, 2005; Cauchemez and Ferguson, 2008), networks (Read and Keeling, 2003; Keeling and Eames, 2005), and compartmental models (Kermack and McKendrick, 1927; Anderson and May, 1991), to mention a few. The conceptually simplest and mathematically most tractable ones fall into the last category. In compartmental models, transmissions between hosts are assumed to happen at random, incorporated through versions of the mass-action principle (Heesterbeek, 2005). Formulated in terms of differential equations, these models keep track of the numbers of susceptible, infective, and recovered individuals (SIR), as well as other relevant compartments of the host population. The transmission mechanism is implemented by a (time-dependent) coefficient, the transmission rate β. Normalized with respect to the removal rate of infectives λ, in simple susceptibles-infectives models, the resulting unit-free number $\mathcal{R}_0 = \beta/\lambda$ defines the basic reproductive ratio of infections (Diekmann et al., 1990)—a parameter well-known because of its importance for disease control and pathogen evolution (Anderson and May, 1991; Lange and Ferguson, 2009).

Whereas disease incidence and mortality define quantities of major interest to public health, transmission rates offer the more natural parameter in characterizing how a disease system is changing over time. Due to the internal dynamics, disease prevalence often behaves strangely, for example, shows biennial time patterns even if infection is forced by an annual period (known for measles Fine and Clarkson, 1982; Earn et al., 2000) or increases even if risk factors are decreasing (reported for dengue Thammapalo et al., 2008). Prevalence is sensitive to initial conditions and time resolution, it even shows chaotic behavior (Earn et al., 1998). The kind of information that can be captured by transmission rates will be illustrated here for three examples: measles during the pre-vaccination era, the currently re-emerging dengue epidemic, and the Spanish flu pandemic.

The measles example will be used to develop the method. It offers a test for the reconstruction results and its systematic errors. Measles data from England and Wales have been studied extensively, and much is known about the temporal pattern of transmissions (Fine and Clarkson, 1982; Bjornstad et al., 2002; Cauchemez and Ferguson, 2008).

Epidemiological data are tainted with reporting errors, including missing or false diagnoses. To correct for these errors the concept of the reporting proportion has been introduced (e.g., Fine and Clarkson, 1982; Bjornstad et al., 2002). In addition to the reporting proportion known from the literature, we introduce a second one, enabling the definition of an effectively constant population, useful when demographic information is insufficient.

Besides focusing on technical questions—regarding parameters, errors and extensibility to new compartments—we will study epidemiological questions and illustrate how the reconstruction can be applied to obtain conceptual results. Here dengue represents a generic example. Increasing cases of dengue hemorrhagic fever (DHF) in Thailand must be explained based on decreasing transmission rates (Thammapalo et al., 2008). Our method allows for re-evaluating former explanations based on strain interaction (Nagao and Koelle, 2008) and demographic transitions (Cummings et al., 2008). The third application is the influenza pandemic 1918/1919, relying on mortality data from the U.S. Here we will use the reconstruction method to investigate irregularities prior to the pandemic peak, referred to as herald waves (Taubenberger and Morens, 2006).

2. Methods

In this section we develop the procedure for reconstructing transmission rates from time series data. Measles infections are used as the main example. For other diseases the methodology (including the precise meaning of the variables, cf. Index) requires adjustments, as we illustrate for two other infections in Results.

2.1. Basic model

One of the simplest settings for an infectious disease epidemic is given by a system of three first order differential equations,

$$S' = \Gamma[S, I, R] - \beta\,\Sigma[S, I] \tag{1a}$$

$$I' = \beta\,\Sigma[S, I] - \lambda I \tag{1b}$$

$$R' = \gamma I - \rho R. \tag{1c}$$

These equations determine the time evolution of compartments, S, I, and R, which in respective order quantify the numbers of *susceptible*, *infective*, and *recovered* individuals (Kermack and McKendrick, 1927). Their sum,

$$N = S + I + R, \tag{2}$$

represents the size of the *host population*. Usually, this number differs from population data published in demographic reports (e.g., Hicks and Allen, 2006); it only includes parts of the population. Most obviously this applies to sexually transmitted infections where the host population only includes sexually active individuals.

Utilized as balance equation (i.e., replaced by $N' = \nu - \mu N$), the derivative of (2) determines the rate,

$$\Gamma = \nu - \mu S + \delta R + \Theta[I, R], \tag{3}$$

at which individuals enter, leave, and (possibly) re-enter the susceptible compartment—through birth ν, death μS, and (e.g., for flu-like infections) after loss of immunity δR. The remaining term (cf. A.1),

$$\Theta = (\lambda - \gamma - \mu)I + (\rho - \delta - \mu)R \approx 0, \tag{4}$$

obtained by adding the three Eqs. (1) and comparing the result to (3), incorporates disease-induced mortality rates specific to the compartments I and R. For many epidemics these rates can be neglected. The recovery rate and the decay of immunity are then given by $\gamma = \lambda - \mu$ and $\delta = \rho - \mu$, respectively. Though, in our third example (pandemic influenza), $\Theta > 0$.

The number of transmissions is determined by the rate at which susceptibles become infected. This rate, $\beta\Sigma$, which defines removal in (1a) and incidence in (1b), involves a functional and a coefficient. The functional, $(S, I) \mapsto \Sigma[S, I]$, represents the contacts between infected and susceptible individuals; usually it is modeled via mass-action (Heesterbeek, 2005),

$$\Sigma = SI/N. \tag{5}$$

Refined models contain fractional powers of S and I (Liu et al., 1987). The coefficient, β, defines the *transmission rate*—the parameter we intend to reconstruct from time series data.