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Disease elimination and re-emergence in differential-equation models ☆

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HIGHLIGHTS

- We developed a novel framework to analyze disease elimination and re-emergence.
- We provide a simulation free method to determine if disease elimination is possible.
- We model measles eliminations and re-emergences in Iceland from 1924 to 1938.
- Iceland was likely to experience a measles re-emergence shortly after October 1927.
- Undocumented measles re-emergences in Iceland were unlikely from 1930 to 1936.

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ABSTRACT

Traditional differential equation models of disease transmission are often used to predict disease trajectories and evaluate the effectiveness of alternative intervention strategies. However, such models cannot account explicitly for probabilistic events, such as those that dominate dynamics when disease prevalence is low during the elimination and re-emergence phases of an outbreak. To account for the dynamics at low prevalence, i.e. the elimination and risk of disease re-emergence, without the added analytical and computational complexity of a stochastic model, we develop a novel application of control theory. We apply our approach to analyze historical data of measles elimination and re-emergence in Iceland from 1923 to 1938, predicting the temporal trajectory of local measles elimination and re-emerge as a result of disease migration from Copenhagen, Denmark.

1. Introduction

The ultimate goal of public health is the eradication of disease. A major challenge to this goal is that even when disease elimination can be achieved in a local population, there often remains a risk of re-emergence from other locations. Differential equation models have been employed to predict the trajectories of outbreaks and to evaluate the effectiveness of public health policies targeting disease elimination (Anderson et al., 1992; Hethcote and Van den Driessche, 2000; Keeling and Rohani, 2007). However, differential equation models do not accurately capture the dynamics of disease elimination and risk of re-emergence when disease prevalence is low. Instead, arbitrary thresholds of incidence have been used as a proxy for disease elimination in differential equation models (Andrews et al., 2012; Dowdy, 2009; Duintjer Tebbens et al., 2014; Maude et al., 2012; Silal et al., 2014; White et al., 2009). Alternatively, stochastic models have been adopted to accurately incorporate disease dynamics at low prevalence (Keeling and Rohani, 2007). However, stochastic models are significantly more computationally, analytically, and conceptually challenging (Dimitrov and Meyers, 2010).

Here we propose applying control theory (Brogliato et al., 2007; Doyle et al., 2009; Kailath, 1980; Luenberger, 1979) to model the elimination and re-emergence of an infectious disease. Typically, a control theory model combines differential equations that represent the state of the system with external factors that impact the system. Following this approach, we modeled the transmission of infection in a community at risk for re-emergence from surrounding communities. From our model, we determined parameter conditions for the elimination of an outbreak, and forecast the times until elimination and re-emergence. We used time series

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data of measles elimination and re-emergence events in Iceland to illustrate the application of our model.

2. The control theory model

To model the elimination and re-emergence of infection in a community, we developed a control system of the form

$$\frac{d\boldsymbol{x}}{dt} = f(\boldsymbol{x}, \sigma),$$

where the output variables $\boldsymbol{x}(t) \in \mathbb{R}^{\boldsymbol{n}}$ capture the state and evolution of the system, and the input variables $\sigma(t) \in \mathbb{R}^{\boldsymbol{m}}$ influence the evolution of the output variables, but are not themselves impacted by the state variables. In our model, the output variables $\boldsymbol{x}$ correspond to the state of an outbreak within a community, and the input variables σ are the external factors that impact re-emergence from other communities.

2.1. The local transmission of infection

We considered a population divided into the proportion of people susceptible (s), infected (i) and recovered (r), with $s+i+r=1$, which follow a standard SIR-type model:

$$\frac{ds}{dt} = b - \lambda s - bs,$$

$$\frac{di}{dt} = \lambda s - \gamma i - bi,$$

$$r = 1 - s - i, \tag{1}$$

where λ is the force of infection, γ is the recovery rate, and b is the rate of demographic turnover (i.e. b is both the per capita birth rate and the per capita death rate).

In SIR-type models there are many possible reasons for choosing a nonstandard force of infection: for instance, modeling such effects as the crowding of infected individuals, positive measures taken by susceptible individuals to avoid infection, the effects of behavioral changes, or disease elimination (Alexander and Moghadas, 2005; Liu et al., 1987, 1986; Ruan and Wang, 2003; Van den Driessche and Watmough, 2000). We consider a nonstandard force of infection (Guldberg and Waage, 1864; Hethcote and Van den Driessche, 1991; Liu et al., 1987, 1986),

$$\lambda = \beta i^{\alpha}, \text{where } \alpha \geq 0.$$

Here, λ includes an interaction coefficient α, and as a special case, reduces to the standard mass action when the interaction coefficient $\alpha = 1$ (Hethcote and Van den Driessche, 2000). The inclusion of interaction coefficient $\alpha \neq 1$ allows for nonlinearities in contact rates that may arise due to spatial substructuring (Bjørnstad et al., 2002). Spatial substructuring, from a region-wide perspective could account for hot spots of measles transmissions, such as within and between schools. In particular, if measles transmission within a school is greater on average than other schools, the result is spatial substructuring, and consequently motivates the selection of $\alpha \neq 1$ (Bjørnstad et al., 2002). In addition, taking $\beta i^{\alpha} s$ with an interaction coefficient $\alpha \neq 1$ direclty parallels multi-order reaction kinetics from chemical reaction theory (Savageau, 1969a, 1969b). Thereby, α can be interpreted as the order of interaction, and controls how the rate of newly infected ($\beta i^{\alpha} s$) scales with the proportion of infected i. In addition, our formulation of λ also satisfies the basic physical principles underlying transmission dynamics (Korobeinikov and Maini, 2005), such that transmission cannot occur in the absence of infection ($\lambda(0) = 0$) and transmission increases as the proportion of the infectious population increases ($\frac{d\lambda}{di} \geq 0$).

The recovery rate γi can also be more generally assumed to be proportional to i^{ξ}, with interaction coefficient ξ. The standard choice $\xi = 1$ implies that the per capita rate at which people leave the infected compartment (γ) is constant throughout the entire population, in contrast to the different durations of infection that naturally occur. Consequently, the recovery rate is taken to be:

$$\gamma = \eta i^{\xi - 1}, \text{with } \xi \geq 0.$$

The inclusion of interaction coefficient $\xi \neq 1$, in a similar fashion to α in the force of infection, allows for nonlinearities in the duration of infection that may arise due to the different rates at which people recover from infection. Once again, a way to conceptualize ξ is to think of schools as hot spots for measles transmission. Schools that exhibit higher transmission levels, are more likely to have a higher magnitude of exposure, which often leads to longer recovery times. In addition, one could also conceptualize ξ through measles transmission amongst and between similar age groups and the potential impact of age-related effects on recovery.

2.2. The reproduction numbers

The basic reproduction number, R_0, is the number of new infections caused by a single infectious person in an otherwise wholly susceptible population (Diekmann et al., 1990). The next-generation method (Diekmann et al., 1990; Heffernan et al., 2005; Liu et al., 1987; Van den Driessche and Watmough, 2002, 2000) is a standard technique to determine the R_0 for differential equation models of disease transmission. For example, under the assumption that $\alpha = \xi = 1$ in system (1), the next-generation method linearizes the flow of newly infected people, $\mathcal{F} = \beta i s$, and the flow from the infected compartments $\mathcal{V} = \eta i + bi$, at the disease-free equilibrium $E_0 = s = 1, i = 0, r = 0$:

$$F = \frac{d}{di}\mathcal{F}|_{E_0} = \beta \text{ and } V = \frac{d}{di}\mathcal{V}|_{E_0} = \eta + b$$

The next-generation matrix is the rate of production of new infected $F = \beta$, multiplied by the duration of infection $V^{-1} = \frac{1}{\eta + b}$, giving $G = \frac{\beta}{\eta + b}$. In general, the R_0 is then the largest eigenvalue of G, but since G here is scalar, $R_0 = \frac{\beta}{\eta + b}$.

However, system (1) is not linearizable (i.e. differentiable) at $i = 0$ when $\alpha < 1$ or $\xi < 1$, so the standard next-generation method cannot be used directly. Instead, since there is only one infected compartment, we can directly compute the effective reproduction number:

$$R_e(i, s) = \frac{\mathcal{F}}{\mathcal{V}} = \frac{\beta i^{\alpha} s}{\eta i^{\xi} + bi} = \frac{\beta i^{\alpha - 1} s}{\eta i^{\xi - 1} + b}$$

and the basic reproduction number:

$$R_0 = R_e(i, s)|_{s=1} = \frac{\beta i^{\alpha - 1}}{\eta i^{\xi - 1} + b}. \tag{2}$$

Importantly, R_0 depends on i in general, unlike in the case when the system is linearizable. The behavior of R_0 can be characterized by the dependency on i through the interaction coefficients. It follows that

$$R_0 \approx \begin{cases} \frac{\beta}{\eta} i^{\alpha - \xi} & \text{if } \xi < 1, \\ \frac{\beta}{\eta + b} i^{\alpha - 1} & \text{if } \xi = 1, \\ \frac{\beta}{b} i^{\alpha - 1} & \text{if } \xi > 1. \end{cases} \tag{3}$$

If the exponent of i in (3) is negative, transmission accelerates as $i \to 0^+$, with $R_0(0) = \infty$. Conversely, if the exponent of i is positive, transmission decelerates as $i \to 0^+$, and terminates at $i = 0$, i.e. $R_0(0) = 0$. Finally, if the exponent of i is exactly 0 in (3), then $0 < R_0 < \infty$ becomes constant as $i \to 0^+$ (Table 1).