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Modeling relapse in infectious diseases

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Abstract

An integro-differential equation is proposed to model a general relapse phenomenon in infectious diseases including herpes. The basic reproduction number $\mathscr{R}_0$ for the model is identified and the threshold property of $\mathscr{R}_0$ established. For the case of a constant relapse period (giving a delay differential equation), this is achieved by conducting a linear stability analysis of the model, and employing the Lyapunov–Razumikhin technique and monotone dynamical systems theory for global results. Numerical simulations, with parameters relevant for herpes, are presented to complement the theoretical results, and no evidence of sustained oscillatory solutions is found.

Keywords: Infectious disease; Relapse; Basic reproduction number; Integro-differential equation; Delay

1. Introduction

Herpes simplex virus type 2 (herpes) is a human disease that is transmitted by close physical or sexual contact, and the incidence of this disease has risen over the last three decades [10]. Important features of herpes are that an individual once infected remains infected for life, and the virus

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reactivates regularly with reactivation producing a relapse period of infectiousness (see, e.g., Blower et al. [5] and the references therein, and Hart [10]).

An ordinary differential equation (ODE) compartmental model for herpes was formulated by Tudor [18], who also noted that such a model is appropriate for pseudorabies in swine (see also Smith and Grenfell [15]). In this model the constant population is divided into three compartments depending on disease status. Individuals not previously exposed to the virus are *susceptible*, individuals infected and shedding virus are *infective* (infectious), and individuals previously infected with the virus but not currently shedding virus are *recovered* (latent). At time t, the numbers in each of these compartments are denoted by $S(t)$, $I(t)$, and $R(t)$, respectively, giving an SIRI model. Assuming standard incidence, a basic reproduction number $\mathscr{R}_0$ is identified, and it is shown to be a sharp threshold determining whether or not the disease dies out or approaches an endemic value.

This ODE model was extended to include more general incidence functions by Moreira and Wang [13] and a similar threshold result identified. Blower [4] summarized four different compartmental models for herpes. One model [5] contains an ODE model with six compartments to predict how much drug resistance would emerge if antiviral treatment rates of herpes were increased.

Our aim is to formulate a more general three compartmental model for a disease with relapse, and in particular to investigate the consequences of different assumptions about the relapse period. For the ODE models cited above, the infectious and relapse periods are assumed to have distributions that are negative exponentials. We allow for a more general relapse distribution, and in particular consider a case in which the relapse time is a constant. Mathematically this arises from taking a step function distribution for the relapse period, and leads to a delay differential equation. Such equations can have a Hopf bifurcation leading to sustained oscillatory solutions, but we find no evidence of this in our model.

In Section 2, we formulate our general SIRI model that can be applied to a disease with relapse. This is given in terms of $P(t)$, the fraction of recovered individuals remaining in the recovered class t units after recovery. Some basic results, including calculation of $\mathscr{R}_0$, are given in Section 3. For $P(t)$ a negative exponential, the ODE model dynamics are briefly summarized in Section 4. In Section 5, $P(t)$ is assumed to have compact support. The disease-free equilibrium is shown to be globally asymptotically stable if $\mathscr{R}_0 < 1$, and a Lyapunov–Razumikhin type theorem is used to determine a condition under which the endemic equilibrium is globally asymptotically stable if $\mathscr{R}_0 > 1$. For $P(t)$ a step function (Section 6), the endemic equilibrium is proved to be locally asymptotically stable if $\mathscr{R}_0 > 1$, and global asymptotically stable if, in addition, the relapse time is short. Finally in Section 6, numerical simulations using parameters appropriate for herpes [5] are presented that complement the theoretical results and indicate that $\mathscr{R}_0$ is a sharp threshold also for the step function case.

2. Model formulation

Let $S(t)$, $I(t)$ and $R(t)$ be the numbers of individuals in the susceptible, infective and the recovered classes, respectively, with the total population $N(t) = S(t) + I(t) + R(t)$. Assuming standard incidence for the disease transmission, the rate of change of $S(t)$ with time is

$$S'(t) = bN(t) - \lambda \frac{S(t)I(t)}{N(t)} - dS(t), \tag{2.1}$$