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Global analysis of age-structured multi-stage epidemic models for infectious diseases☆

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ABSTRACT

We formulate a multi-stage SEIR model for infectious diseases with continuous age structure for each successive infectious stage during a long infective period. The model can describe disease progression through multiple infectious stages as in the case of HIV, hepatitis B and hepatitis C. Mathematical analysis shows that the global dynamics are completely determined by the basic reproductive number $\mathcal{R}_0$. If $\mathcal{R}_0 \leq 1$, the disease-free equilibrium is globally asymptotically stable and the disease dies out. If $\mathcal{R}_0 > 1$, a unique endemic equilibrium is globally asymptotically stable, and the disease persists at the endemic equilibrium. The proof of global stability of endemic equilibria utilizes a Lyapunov functional. Numerical simulations are illustrated and model generalization is also discussed.

1. Introduction

Typical compartmental epidemic models assume that all individuals within one compartment behave identical or homogeneous, regardless of how long they have spent in the compartment. In many epidemiological models, it were assumed that all infected individuals are equally infectious during the entire infectivity period, which is reasonable for some diseases such as influenza. However, for some infectious diseases with a longer infectious period, such as HIV/AIDS, hepatitis B, hepatitis C, and schistosomiasis, infecting force of the infected individuals may be different during various stages in progression, in that their infectivity usually depends on the parasite levels in vectors or viral loads in infectives.

Staged progression (SP) models have been proposed to supplement such a gap for disease progression through successive discrete stages of infection, characterized by varying degrees of transmissibility at different stage [14]. Global dynamics of staged progression models and various modifications have been studied in [1,6–8,28] and reference therein. SP models, even those with Gamma distributions further approximate the age-dependent infectivity or latency for infectious diseases [12,31].

Age is an important consideration in infectious disease modelling, due to its typical character in epidemiological data collected in practice [3]. Mathematical models with infection, latency or vaccination age have been used widely to describe the potential impact of age on the disease progression in studied populations [2–4,13,18,19,30,33,34,36]. In these models, age structure or age of infection is formulated to describe the heterogeneity in infectious, latent or vaccinated individuals, such as the waiting time in the infectious class to be a function of age.

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Age-structured models usually form a system of partial differential equations (PDEs), and their mathematical analyses are particularly challenging. Although the dynamical analysis is difficult, complete global stability for some type of age-structured models has been studied recently by constructing Lyapunov functionals [2,13,16,18–21,24,33,34,36,38] and reference therein. The pioneer work in Magal et al. [18] studied an infection-age SI model with both infectiousness and removal rate depending on the infection age. The resulting system with one age-structured variable was described by integral semigroups for its persistence, and the global stability of its positive equilibrium was proved by constructing a Lyapunov functional.

In [13], dynamical properties of an age-structured HIV model were established, to allow production rate of viral particles and death rate of infected cells depending on their infection age. McCluskey in [19] further studies an SEI model with two age structures for both exposed and infectious classes, extending his earlier work in [18] with one age variable. In [2], a cholera model incorporating both infection age of infectious individuals and biological age of pathogen in the environment was formulated and fully studied. In [20], the author generalized the SEI model in [19], by adding age-dependent immigration into susceptible, latent and infectious classes. A differential susceptibility, differential infectivity endemic model was studied in [32] to describe the differential infectivity with age of infection in each independent infectious class. Age-dependent susceptibility was firstly considered in [22] for its global properties. A hepatitis B virus model with age structure in both infectious patients and chronic carriers was considered in [36]. In [24], an multi-group SVEIR model with vaccination age and infection age was studied by graph-theoretical approach combined with Lyapunov functional techniques. In [16], A multi-group SIR epidemic model with age structure in susceptible, infectious and recovered classes was investigated using the combined method of graph-theory and Lyapunov functionals.

To our knowledge, there are few results related to global properties of epidemiological models with a group of age-structures, to describe complex infection age progression process of interconnected infection ages during a long infectious period. In [23], global analysis for a PDE model with infection age structure in three successive infectious stages for HIV-1 modeling was obtained. In this paper, one goal is to study the global dynamics of a PDE model with infection age structure in each successive infectious stage, based on a class of multi-stage progression SEIR models studied in [6–8]. To achieve this, the entire infectious period $[0, +\infty)$ is partitioned into $n+1$ stages defined by infection age intervals $(a_{m-1}, a_m]$, where $0 = a_0 < a_1 < \cdots < a_m < \cdots < a_n < a_{n+1} = \infty$, with the aim to study the possible effects of multiple infectious stages with multi-age structure, and variable infectivities in each stage on the disease dynamics. The infection age in the *mth* stage is characterised by its relation to its adjacent stages, i.e., when the time since infection exceeds a_m, then the infected individual has experienced its *mth* stage and would move to the $(m+1)th$ stage. Such a division for infection age during the infectious period in our model is different from those mentioned above. The dynamic behaviors of our model are completely determined by the basic reproductive number $\mathcal{R}_0$, which determines whether or not the disease dies out. When the basic reproduction number is not larger than one, the disease-free equilibrium is globally asymptotically stable and the disease dies out regardless of the initial condition; whereas when it is larger than one, there exists a unique endemic equilibrium that is globally asymptotically stable, and the disease persists at the endemic equilibrium. Uniform persistence is proved and the global stability of endemic equilibrium is completed by constructing suitable Lyapunov functionals.

The paper is organized as the following. The multi-stage SEIR model with infection-age structure is formulated in Section 2. In Section 3, we study the existence, stability of steady states, and calculate the basic reproduction number $\mathcal{R}_0$. Global attraction of disease-free equilibrium and local stability of endemic equilibrium are shown either. In Section 4, we analyze uniform persistence. The main result of global stability of endemic equilibrium is illustrated in Section 5. Numerical simulations are presented in Section 6, based on a simplified model with two infectious stages that is typical for hepatitis B. We conclude in Section 7 with discussions.

2. Model formulation

According to disease status, the total population can be divided into four classical groups: susceptible, exposed, infectious and recovered. Let $S(t)$, $E(t)$ and $R(t)$ be the total number of individuals in susceptible, exposed, and removed compartments at time t, respectively. Recruitment into the susceptible is a constant flux Λ, and σ is the per capita transfer rate from the exposed to the infectious. The per capita death rate for susceptible, exposed, and recovered classes are μ_S, μ_E and μ_R, respectively.

The infectious compartment is further structured by age of infection a. Let $i_m(a, t)$ denote the infection age density at time t of the individuals in the *mth* infectious stage, and $\int_{a_{m-1}}^{a_m} i_m(a,t)da$ $(m = 1, \ldots, n+1)$ be the total number of infectious individuals at time t who have been infectious for duration a between a_{m-1} and a_m in the *mth* stage. $\int_0^\infty i(a,t)da = \sum_{m=1}^{n+1} \int_{a_{m-1}}^{a_m} i_m(a,t)da$ denotes the total infectives at time t. The flow diagram is displayed in Fig. 1.

Individuals in each infectious stage have varying infectivities, and even in the same stage may have different infectivity as a function of infection age a. The incidence of new infection is modeled by classical mass action form. Let $\beta_m(a)$ be the age-dependent transmission coefficient in the *mth* infectious stage, which describes the varying probability of infectiousness in the mth stage. Thus, total new infections in the mth infectious stage is the rate $\int_{a_{m-1}}^{a_m} \beta_m(a)S(t)i_m(a,t)da$. The total force of infection at time t is the sum $\sum_{m=1}^{n+1} \int_{a_{m-1}}^{a_m} \beta_m(a)S(t)i_m(a,t)da$ during the whole infectious period.

All new infections enter the exposed class, and progression of infectious individuals in the mth stage enter the $(m+1)$th stage through the critical infection age a_m. Individuals who have stayed in the mth infectious stage for duration a recover at