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Analysis of a within-host age-structured model with mutations between two viral strains ☆

Liman Dai *, Xingfu Zou

Department of Applied Mathematics, University of Western Ontario, London, Ontario, N6A 3K7, Canada

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ABSTRACT

In this paper, we study a within-host age-structured model with mutation and back mutation, which is in the form of partial differential equations with double-infections by two strains of viruses. For the case that the production rates of viruses are gamma distributions, the PDE model is transformed into an ODE one. To explore the effect of mutations, we analyze our model without mutations first. In this case, two strains of viruses are proved to die out when both of the individual reproductive numbers are less than one; otherwise, their evolution will comply with competitive exclusion principle meaning that the stronger one will survive finally. Then, the mutations are considered in the model. We verify that there may exist a coexistence equilibrium which is globally asymptotically stable under some specific conditions about mutation rates. Therefore, mutations can lead to coexistence of two strains.

1. Introduction

Viruses using RNA (ribonucleic acid) as their genetic material are called RNA viruses. Because of their high infection rates, RNA viruses can cause extraordinary tough human diseases, such as HIV, hepatitis C, SARS and influenza [9]. Mathematical models have been used to study the diseases caused by RNA viruses, particularly HIV, for over 25 years [8,10,11]. Results from mathematical models on virus dynamics within-host virus have been fruitful. In particular, these results conclude, if there are two strains of viruses in a single host competing for the same type of T-cells as their host cells, the competition exclusion principle generically holds in the sense that either both strains go to extinction (when the basic reproduction ratios are less than one), or one strain (the one with larger basic reproduction ratio) will win the competition. Here, the word generically means except that the two basic reproduction ratios are identical which can barely hold since these two ratios depend on a large number of model parameters (see example in [4]).

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* Corresponding author.
E-mail address: lm.dai@hotmail.com (L. Dai).

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However, mutations may alter the previous competitive balance. In general, viral RNA polymerase lacks the proof-reading ability [12], so RNA viruses have higher mutation rates than DNA viruses. Under the natural selection, their short generation times and relatively high mutation rates can help RNA viruses quickly adapt to changes in their host environment. It is difficult for scientists to develop effective vaccines to prevent diseases caused by RNA viruses [17]. For this reason, people would like to know more about mutation. There are many good research results, but most of them only study the impact of forward mutation. Generally, the backward mutations rarely survive in natural state. Recently, some researches showed that the impact of backward mutants cannot be neglected for drug resistance surveillance [13,16,20]. Therefore, two directions of mutations, forward and backward, are considered in this paper.

Ordinary differential equations models are used in [4], for which a unique coexistence equilibrium is found and its global asymptotical stability is explored when mutations are treated as small perturbations. However, adopting ordinary differential equations is a bit too idealized and simple for studying the viral evolution in hosts. This is mainly because that treating the production rate of new virus particles (virions) by an infected cell as a constant (independent of the infection age) would have neglected some important processes in virus replication. Indeed, it is known that viral proteins and unspliced viral RNA accumulate within the cytoplasm of an infected cell, and thus, they actually ramps up [2,6,18]. Therefore, infection age should be incorporated into the model. Motivated by the age-structured model

$$\begin{cases} \dfrac{\mathrm{d}T}{\mathrm{d}t} = s - dT(t) - kT(t)V(t), \\ \dfrac{\partial T^*}{\partial a} + \dfrac{\partial T^*}{\partial t} = -\delta(a)T^*(a,t), \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = \displaystyle\int_0^\infty p(a)T^*(a,t)da - cV(t), \\ T^*(0,t) = kV_1(t)T(t), \quad t \geq 0 \end{cases} \tag{1.1}$$

in [7], we extend the research by introducing a mutant strain of the virus into this age-structured model. More realistic representations about RNA virus infections will be allowed in our age-structured model. Meanwhile, the effect of forward and backward mutations between the wild strain and mutant strain on viral evolution is also considered in our work.

The rest of this paper is organized as follows. In the next section, we present the formulation of mathematical model. In Sections 3 and 4, we choose the Gamma distributions for the two kernels in the PDE model and utilize the linear chain trick to transform the partial differential equation model to an ordinary differential equations model, for which we work out the basic reproductive number. In Section 5, we study the equilibria and their respective stability in two situations, one is without mutations and the other is with mutations. Finally, we end this paper by a brief discussion about our results.

2. Model

Denote by $T(t)$ the population of the susceptible host cells, by $V_i(t)$ the population of viral strain i $(i = 1, 2)$, and let $T_i^*(a,t)$ be the population of the target cells infected by viral strain i with infection age a at time t. Uninfected cells are produced at constant rate b, and die at rate d. After infection at constant rate β_i by strain i, they progress to the productively infected class. There are two death rates in this class: one is a constant background death rate m_i; and the other is an infection dependent mortality rate $\mu_i(a)$. The infected cells can produce virus at an infection dependent rate $p_i(a)$. Free viruses are cleared at a constant rate c_i. Meanwhile, we suppose that the forward and backward mutations happen between the two