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Probability of a major infection in a stochastic within-host model with multiple stages

Fan Bai*, Linda J.S. Allen

Department of Mathematics and Statistics, Texas Tech University, Lubbock, TX 79409-1042, United States

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ABSTRACT

Establishment or spread of a viral infection within healthy individuals depends on exposure to a viral source, either through virus particles or through cells that have been infected. We assume that a potential infection has reached the site of the healthy target cells and we apply stochastic within-host models and multitype branching processes to investigate whether a major infection becomes established. The model includes multiple latent and actively infected stages. It is shown that the probability of a major infection is generally more likely after the virus has entered the target cell and the cell is actively infected. In some cases, the probability of a major infection is less likely if the burst size of actively infected cells is small.

1. Introduction

Establishment or spread of a viral infection within a susceptible host depends on many host, viral, and environmental factors. A major infection can be established after the virus has entered specific target cells of the host and the virus successfully replicates within these target cells. The target cells are unique to the particular virus. For example, the main target cells for influenza A virus are the epithelial cells of the respiratory tract, whereas the primary target cells for hantavirus, a zoonotic disease carried by wild rodents, are the microvascular endothelial cells. The model considered here represents the early phase of viral infection and does not include the specific cells of the immune response. Our goals are to extend the stochastic models in [1,2] by including more general transition, reproduction, and death rates and to apply multitype branching process theory to compare estimates for probability of a major viral infection.

An ordinary differential equation (ODE) model for a within-host viral infection serves as a framework for formulation of a continuous-time Markov chain (CTMC) model [3]. The model includes multiple stages for the eclipse period, when the target cell is infected but not actively reproducing virus particles, and multiple stages for the infectious period, during actively reproducing infected cells. The variables are uninfected target

* Corresponding author.
E-mail addresses: fan.bai@ttu.edu, baifan.ubc@gmail.com (F. Bai).

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Table 1
Discrete events of the CTMC model and the infinitesimal transition probabilities.

Event	Transition	Probability
Infection of T	$(T, L_1, V) \to (T-1, L_1+1, V-1)$	$\beta VT\Delta t + o(\Delta t)$
Death of L_k	$L_k \to L_k - 1$, $k = 1, \ldots, m$	$\mu_k L_k \Delta t + o(\Delta t)$
Death of I_k	$I_k \to I_k - 1$, $k = 1, \ldots, n$	$\mu_{m+k} I_k \Delta t + o(\Delta t)$
Transition L_k to L_{k+1}	$(L_k, L_{k+1}) \to (L_k - 1, L_{k+1} + 1)$, $k = 1, \ldots, m-1$	$\delta_k L_k \Delta t + o(\Delta t)$
Transition L_m to I_1	$(L_m, I_1) \to (L_m - 1, I_1 + 1)$	$\delta_m L_m \Delta t + o(\Delta t)$
Transition I_k to I_{k+1}	$(I_k, I_{k+1}) \to (I_k - 1, I_{k+1} + 1)$, $k = 1, \ldots, n-1$	$\sigma_k I_k \Delta t + o(\Delta t)$
Production of V	$V \to V + 1$	$\sum_{k=1}^{n} b_k I_i \Delta t + o(\Delta t)$
Death of V	$V \to V - 1$	$cV\Delta t + o(\Delta t)$

cells, T, m stages for the infected target cells that are latent, L_k, $k = 1, \ldots, m$, n stages for the actively reproducing infected target cells, I_k, $k = 1, \ldots, n$, and the free virus or virions, V. The multiple stages have a more general distribution for the duration of the eclipse and infectious periods. During the early phase of infection, cell reproduction is neglected.

The ODE model is given in Eqs. (1)–(2). Parameter μ_k is the death rate per cell in stage k, δ_k is the transition rate per kth latent stage, σ_k is the transition rate per kth infected cell, β is the rate of viral entry into a target cell (per virion or per target cell), b_k is the production rate of virions per kth infected cell and c is the clearance rate of the virus. Here we assume that it takes just one virion to infect a target cell. For the special case $m = n = 1$ and $\mu_k = 0$, $k = 1, 2$, the duration of each stage is exponentially distributed. For $m > 1$, in the special case of $\mu_k = 0$, $k = 1, \ldots, m$ and $\delta_k = m\delta$, the duration for the eclipse period has a gamma distribution (also known as an Erlang distribution) with mean $1/\delta$ and shape parameter $k = m$ [4]. In addition, if $m \to \infty$ or $n \to \infty$, the model has a fixed delay for the eclipse period or a fixed delay for the infectious period [1]. We assume all parameters are positive.

$$\text{Target Cells} \begin{cases} \dot{T} = -\beta VT, \\ \dot{L}_1 = \beta VT - \delta_1 L_1 - \mu_1 L_1, \\ \dot{L}_k = \delta_{k-1} L_{k-1} - \delta_k L_k - \mu_k L_k, \quad k = 2, 3, \ldots, m, \\ \dot{I}_1 = \delta_k L_k - \sigma_1 I_1 - \mu_{m+1} I_1, \\ \dot{I}_k = \sigma_{k-1} I_{k-1} - \sigma_k I_k - \mu_{m+k} I_k, \quad k = 2, 3, \ldots, n-1, \\ \dot{I}_n = \sigma_{n-1} I_{n-1} - \mu_{m+n} I_n, \end{cases} \tag{1}$$

$$\text{Virions} \begin{cases} \dot{V} = \sum_{i=1}^{n} b_i I_i - \beta VT - cV. \end{cases} \tag{2}$$

The infection-free equilibrium for model (1)–(2) is the initial number of healthy target cells, $\bar{T} = T(0)$. The basic reproduction number $\mathcal{R}_0$ for model (1)–(2) is

$$\frac{\beta \bar{T}}{\beta \bar{T} + c} \prod_{i=1}^{m} \frac{\delta_i}{\delta_i + \mu_i} \left[\sum_{j=1}^{n-1} \left(\prod_{k=1}^{j-1} \frac{\sigma_{k-1}}{\sigma_{k-1} + \mu_{m+k-1}} \right) \frac{b_j}{\sigma_j + \mu_{m+j}} + \left(\prod_{k=1}^{n-1} \frac{\sigma_k}{\sigma_k + \mu_{m+k}} \right) \frac{b_n}{\mu_{m+n}} \right]. \tag{3}$$

If the basic reproduction number $\mathcal{R}_0 > 1$ in the ODE model, then a major infection occurs but this is not the case in the stochastic formulation.

A time-homogeneous, CTMC model is formulated based on the ODE framework. The same notation used for the ODE model is applied to the discrete random variables in the CTMC model, $T, L_k, I_k, V \in \{0, 1, \ldots\}$. All events and the infinitesimal transition probabilities of each event are summarized in Table 1. The CTMC model includes more general transition, reproduction, and death rates not considered in other within-host models [1,2]. The parameter ω for the interevent time in the Markov process is the sum of the parameters in the right column of Table 1, i.e.,

$$\omega = \beta VT + \sum_{k=1}^{m} \mu_k L_k + \sum_{k=1}^{n} \mu_{m+k} I_k + \sum_{k=1}^{m} \delta_k L_k + \sum_{k=1}^{n-1} \sigma_k I_k + \sum_{k=1}^{n} b_k I_k + cV.$$