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Disease clearance of tuberculosis infection: An in-host continuous-time Markov chain model

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ABSTRACT

The clearance of tuberculosis infection shows an elimination of infectious *Mycobacterium tuberculosis* (Mtb) pathogens and infected macrophage cells. The evidence shows the existence of individuals, who are still tested negative in tuberculin skin test after living with people with active tuberculosis for up to six months. Since the Mtb pathogen is spread from person to person through airborne particles, we build a continuous-time Markov chain (CTMC) model to describe the initial infection with small amount of inhaled bacteria. The CTMC model successfully simulates sample paths presenting disease clearance. We apply the theory of multitype branching processes to analytically approximate the probability of disease clearance. We also estimate the disease clearance time, which is as less than a month for $R_0 \in [1,\ 1.5]$. Our results demonstrate that the host immune factors affect both the probability and the time of the disease clearance. These relationships are linked by the basic reproduction number R_0. Our findings provide new mechanisms for disease prevention and therapy developments.

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1. Introduction

Mycobacterium tuberculosis (Mtb) is one of the most deadly infectious disease globally in 2020. Even though antibiotic treatments were invented around 80 years ago, Mtb bacteria are still not completely eradicated due to the emergence of drug-resistant and multidrug-resistant strains. Restricted by traditional antibiotic therapies, researchers currently focus on epidemiological evidences, which suggest that the host immune system is able to naturally eradicate the Mtb infection [18]. If the clearance occurs before the mount of adaptive immune responses, it is called as early clearance. If the clearance happens after the development of adaptive immune responses, it is referred to as delayed clearance [18]. In both clearance cases, the Mtb bacteria and infected macrophages (Mtb main target cells) are removed completely in a period of time after the inhalation of droplet nuclei carrying a small amount of Mtb bacteria. Moreover, the evidence demonstrates that a heavy exposure to Mtb bacteria does not guarantee the development of Mtb infection. For example, in a US naval ship, 13 sailors showed negative results in tuberculin skin test after living in the same cabin with seven others with TB disease for 6 months [12]. A better understanding of the immunological mechanisms underpinning the natural disease clearance could give new insights in both disease prevention and therapeutic development.

Mathematical modeling is a useful tool to understand the complex mechanisms of the host-Mtb interactions and predict the future of the disease. In population dynamics, the fate of an invading infectious disease is determined by the basic re-

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production number R_0, which is the " expected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a completely susceptible population" [6]. R_0 provides a good prediction in deterministic models for the case with large susceptible and infectious populations [4]. The invading disease dies out if $R_0 < 1$ and spreads if $R_0 > 1$. However, if the epidemic starts with a small number of infectious individuals, the deterministic threshold R_0 is not applicable to predict the disease destiny [4]. Whittle showed that there exists a positive probability for a minor outbreak when $R_0 > 1$ [20]. That indicates that the invading disease won't become endemic, but will eventually die out after a minor outbreak. In this situation, a continuous-time Markov chain (CTMC) model can be more realistic than the corresponding ODE model [4]. This is because the CTMC model is able to demonstrate a finite time disease extinction, while the ODE model can only predict the disease extinction as the time goes to infinity. Moreover, the disease extinction threshold from CTMC model not only depends on the basic reproduction number R_0, but also relates to the number of the initial infectious individuals. This stochastic disease extinction threshold is derived from the theory of branching processes [3,4]. Its applications range from population-level models [8,19] to cellular-level model [22].

For Mtb-host dynamics, in-host models have been used to understand the complex host-pathogen interactions, reveal the determining factors for the various TB disease outcomes, and provide potential new therapies [9,11,14–16,21]. Most of these models are in the deterministic forms. To model the initial infection with a limited amount of infectious bacteria, a CTMC model is more realistic and appropriate compared to deterministic models. A CTMC model can predict the finite disease clearance through the theory of branching processes. Specifically, CTMC models can compute the probability of early clearance when $R_0 > 1$ after an initial exposure to small amount of Mtb bacteria, while the disease extinction won't happen in deterministic model when $R_0 > 1$. Moreover, the disease extinction occurs at the infinite time in deterministic models, but at a finite time in CTMC models. Since not only environmental and pathogen factors, but also host factors affect the basic reproduction number R_0, modifying host factors can increase the probability of clearance and decrease the time to reach clearance. This helps to develop potential novel host-direct therapies [17,18]. Moreover, disease clearance, especially early clearance, is an actual example of protective immunity against Mtb and could give new insights into vaccine development. For these reasons, disease clearance should be a focus of tuberculosis research. Through branching process theory, a CTMC model is an appropriate mathematical approach to study the problem of the disease clearance after an initial exposure.

The rest of the paper is organized as follows. In Section 2, we introduce an established in-host Mtb dynamics model and its basic properties [7]. In Section 3, we carry out a unit conversion procedure, which transforms the units of the state variables from cell concentrations to numbers of cell populations. In Section 4, we build a CTMC model, which corresponds to the ODE model, that describes multitype stochastic processes with continuous time variable and discrete state variables. We further derive the corresponding forward Kolmogorov differential equation from the infinitesimal transition probabilities. Moreover, we plot simulated sample paths to show the existence of disease clearance when $R_0 > 1$. In Section 5, we derive the approximated probability of disease clearance through multitype branching processes. The clearance probability derived from analytical approach matches well with that calculated from numerical simulations. Furthermore, we investigate the probability distribution of the clearance time through numerical simulation. Finally, in Section 6 we present our conclusions and a discussion.

2. ODE Tuberculosis in-host model

The dynamics of the host immune response against Mtb infection happen in lung tissue. The major elements of the host-pathogen interactions involve the Mtb pathogen population, the Mtb ideal target cell population macrophage, and the adaptive immune cell population T lymphocytes. The 4-dimensional model (2.1) describing the dynamics is written as follows:

$$\begin{aligned}
\frac{d[M_u]}{dt} &= s_M - \mu_M[M_u] - \beta[M_u][B] \\
\frac{d[M_i]}{dt} &= \beta[M_u][B] - b[M_i] - \gamma[M_i]\frac{[T]/[M_i]}{[T]/[M_i]+c} \\
\frac{d[B]}{dt} &= \delta[B]\left(1-\frac{[B]}{[K]}\right) + [M_i]\left(N_1 b + N_2\gamma\frac{[T]/[M_i]}{[T]/[M_i]+c}\right) - [M_u][B](\eta + N_3\beta) \\
\frac{d[T]}{dt} &= s_T + \frac{c_M[M_i][T]}{e_M[T]+1} + \frac{c_B[B][T]}{e_B[T]+1} - \mu_T[T].
\end{aligned} \tag{2.1}$$

Here, $[M_u]$, $[M_i]$, $[B]$ and $[T]$ denote the cell concentrations of the uninfected and infected macrophages, Mtb bacteria and CD4+ T cells.

The initiation of Mtb infection happens when Mtb bacteria are inhaled in the respiratory tract, particularly the lung (pulmonary TB) and taken up by resident alveolar macrophages. Before engulfing the invading bacteria, the macrophages are assumed to be uninfected and have recruitment and death rates s_M and μ_M, respectively. The phagocytizing process is assumed to turn uninfected macrophages into infected with an infection rate β. The number of bacteria phagocytized by

one uninfected macrophage is N_3. Without sufficient stimuli for activation, infected macrophages fail to kill the engulfed bacteria. The phagocytized Mtb bacteria then undergo reproduction, which leads to the loss of the infected macrophages due to an excessive bacterial load or the programmed cell death. The loss rate of infected macrophages is b. The infected macrophages can also be removed out of the system by the T-cell mediated immune response. The killing is carried out by cytotoxic T cells (CD8+ T cells), which are activated by T helper cells (CD4+ T cells). The killing rate of CD8+ T cell depends on the ratio of CD4+ T cell load and infected macrophage load ($[T]/[M_i]$), with a maximum killing rate γ and a $[T]/[M_i]$ half-saturation ratio c. The bacterial influx to the system has two main sources. One is bacterial reproduction, which is modeled as a logistic term $\delta[B](1-[B]/[K])$. Here δ and K denote the maximum growth rate and the carrying capacity. The bacterial release from the death of infected macrophages is another way. The numbers of bacteria released by cell bursting and programmed cell death and by T-cell mediated immune responses are assumed as N_1 and N_2, respectively. On the other hand, if immune cells receive adequate stimulation, infected macrophages can also kill the phagocytized bacteria. The rate is assumed as η. Note that the Mtb population is comprised of extracellular and intracellular subpopulations. The growth of the extracellular subpopulation is caused by (1) extracellular bacteria division ($\delta[B](1-[B]/[K])$) and (2) intracellular bacteria release from infected macrophages programmed cell death ($b[M_i]N_1$) and infected macrophages killed by T-cell responses ($[M_i]N_2\gamma\frac{[T]/[M_i]}{[T]/[M_i]+c}$). Extracellular Mtb leave the system because of uninfected macrophages killing ($\eta[M_u][B]$) or the phagocytosis process to become intracellular ($\beta N_3[M_u][B]$). For the T-cell mediated immune responses, the role of CD8+ T cells can be modeled as a ratio of CD4+ T cells and infected macrophages. Then, instead of explicitly modeling CD8+ T cell population, we only consider the dynamics of CD4+ T cells. The recruitment and death rates of CD4+ T cells are denoted as s_T and μ_T, respectively. The maximum activation rates of CD4+ T cells by Mtb bacteria and infected macrophages are assumed as c_B and c_M. The saturating factors for these two activation processes are e_B and e_M.

A comprehensive analysis of model (2.1) was carried out in Zhang et al. [25]. The results show the existence of disease-free equilibrium $E_0 = ([M_u]_0, [M_i]_0, [B]_0, [T]_0) = (s_M/\mu_M, 0, 0, s_T/\mu_T)$. The local and global stability of E_0 are summarized as follows:

Theorem 1 ([25]). *Under the condition $b+\gamma+\frac{s_M}{\mu_M}(N_3\beta+\eta) > \delta$, the disease free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Furthermore, there exists a $M_u^{\max} = [\beta s_M(N_1 b + N_2\gamma)/(b\mu_M)+\delta]/(\eta+N_3\beta)$, such that if $[M_u] \geq M_u^{\max}$ and $R_0 < 1$, E_0 is globally stable. Here, R_0 is the basic reproduction number*

$$R_0 = \rho(FV^{-1}) = \frac{\delta\mu_M}{2s_M(N_3\beta+\eta)} + \frac{1}{2}\left[\frac{\delta^2\mu_M^2}{s_M^2(N_3\beta+\eta)^2} + \frac{4\beta(N_1 b + N_2\gamma)}{(N_3\beta+\eta)(b+\gamma)}\right]^{1/2}, \tag{2.2}$$

where

$$F = \begin{bmatrix} 0 & \frac{\beta s_M}{\mu_M} \\ N_1 b + N_2\gamma & \delta \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} b+\gamma & 0 \\ 0 & \frac{s_M}{\mu_M}(N_3\beta+\eta) \end{bmatrix}. \tag{2.3}$$

Formula (2.2) suggests that R_0 has a positive relationship with the death rate of uninfected macrophage μ_M, the Mtb proliferation rate δ, and the numbers of intracellular bacteria released from the death of an infected macrophage N_1 (bursting and programmed cell death) and N_2 (T-cell mediated immune responses). Eq. (2.2) also suggests negative relationships between R_0 and the death rate of the phagocytized Mtb bacteria η, the number of Mtb bacteria engulfed by an uninfected macrophage N_3, and the uninfected macrophage recruitment rate s_M.

3. Unit conversion

Mtb bacteria are transmitted from person to person through droplet nuclei, which each contains a limit number of bacteria. Since the numbers of inhaled Mtb bacteria and infected macrophages at the initiation of the infection are small, predictions of the ODE model are not valid. In this setting, branching process theory is more suitable to make reasonable predictions. Moreover, in the case of an exponentially distributed interevent time, the continuous-time branching process is a continuous-time Markov chain. A continuous-time branching process considers discrete random variables for the number of considered cell populations. However, the state variables in the in-host tuberculosis model (2.1) present the corresponding cell concentrations in the unit per millimeter (ml). Therefore, for the stochastic processes, the random variables must be transformed from concentrations to the numbers of cell population. We first consider the volume of lung tissue, since the tuberculosis infection dynamics take place within the lung. The mean lung tissue volume of single lungs is estimated as $V = 431$ ml by Denison et al. [5]. Then the numbers of uninfected and infected macrophages, Mtb bacteria, and CD4+ T cell population in a single lung tissue are $M_u = V[M_u]$, $M_i = V[M_i]$, $B = V[B]$, and $T = V[T]$. The in-host tuberculosis model in the

new variables are written as

$$\begin{aligned}
\frac{dM_u}{dt} &= s_M V - \mu_M M_u - \frac{\beta}{V} M_u B \\
\frac{dM_i}{dt} &= \frac{\beta}{V} M_u B - bM_i - \gamma M_i \frac{T/M_i}{T/M_i + c} \\
\frac{dB}{dt} &= \delta B\left(1 - \frac{B}{KV}\right) + M_i\left(N_1 b + N_2 \gamma \frac{T/M_i}{T/M_i + c}\right) - M_u B(\frac{\eta}{V} + N_3 \frac{\beta}{V}) \\
\frac{dT}{dt} &= s_T V + \frac{c_M}{V} \frac{M_i T}{\frac{e_M}{V} T + 1} + \frac{c_B}{V} \frac{B T}{\frac{e_B}{V} T + 1} - \mu_T T.
\end{aligned} \tag{3.1}$$

Eq. (3.1) yields new constant rates to replace the original parameters, s_M, β, K, η, s_T, c_M, c_B, e_M, and e_B in (2.1)

$$\begin{aligned}
&\tilde{s}_M = s_M V,\ \tilde{\beta} = \frac{\beta}{V},\ \tilde{K} = KV,\ \tilde{\eta} = \frac{\eta}{V},\ \tilde{s}_T = s_T V, \\
&\tilde{c}_M = \frac{c_M}{V},\ \tilde{c}_B = \frac{c_B}{V},\ \tilde{e}_M = \frac{e_M}{V},\ \tilde{e}_B = \frac{e_B}{V}.
\end{aligned} \tag{3.2}$$

4. Continuous-time Markov chain

For a better prediction, we employ a continuous-time Markov chain (CTMC) model in the case that a few Mtb bacteria are inhaled after initial infection. Let $M_u(t)$, $M_i(t)$, $B(t)$, and $T(t)$ denote discrete-valued random variables for the number of uninfected macrophages, infected macrophages, Mtb bacteria, CD4+ T cells at a time $t \in [0, \infty)$. Here, time is a continuous variable and parameters are taken as in the ODE model (3.1) from Table 1. Assuming a time-homogeneous CTMC model has only one event happening in a sufficient small-time period $\Delta t > 0$, the infinitesimal transition probability associated with the stochastic process is defined as

$$\begin{aligned}
&\text{Prob}\{(\Delta M_u(t), \Delta M_i(t), \Delta B(t), \Delta T(t)) = (\Delta u, \Delta i, \Delta j, \Delta v) | (M_u(t), M_i(t), B(t), T(t)) = (u, i, j, v)\} \\
&= p_k(u, i, j, v)\, \Delta t + o(\Delta t) := P(u, i, j, v).
\end{aligned}$$

where $p_k(u, i, j, v)$ for $k = 1, \ldots, 11$ are infinitesimal transition rates corresponding to the eleven distinct events forming this CTMC model. $p_k(u, i, j, v)$s are provided in Table 2. Here, we assume the CTMC model satisfies the Markov property. For example, the probability of the infection of an uninfected macrophage in a small period of time Δt is

$$\text{Prob}\{(-1,\ 1,\ 0,\ 0) | (M_u(t), M_i(t), B(t), T(t))\} = p_3(u, i, j, v)\Delta t + o(\Delta t) = \tilde{\beta}\, M_u(t)\, B(t)\, \Delta t + o(\Delta t).$$

Table 1
Parameter symbol, descriptions, and values by Gammack et al. [9], Marino and Kirschner [15], Wigginton and Kirschner [21].

Sym.	Description (Unites)	Value
V	lung volume	431
$\tilde{s}_M$	recruitment rate of uninfected macrophages (1/ day)	1.16 V
$\tilde{s}_T$	T-cell recruitment rate (1/ day)	0.0153 V
μ_M	death rate of uninfected macrophages (1/day)	0.01
b	loss rate of infected macrophages (1/day)	0.11
μ_T	T-cell death rate (1/day)	0.33
$\tilde{\beta}$	infection rate caused by Mtb bacteria (1/day)	8.26×10^{-5}/V
$\tilde{\eta}$	bacteria killing rate by uninfected macrophages (1/day)	1.25×10^{-8}/V
γ	T-cell killing rate (1/day)	1.5
δ	Mtb bacterial proliferation rate (1/day)	5×10^{-4}
$\tilde{c}_M$	T-cell activation rate induced by M_i (1/day)	0.4 V
$\tilde{c}_B$	T-cell activation rate induced by B (1/day)	2.0 V
$\tilde{e}_M$	saturating factor of T-cell activation related to M_i	0.04/V
$\tilde{e}_B$	saturating factor of T-cell activation related to B	0.04/V
c	half-saturation ratio for the death of M_i (T/M_i)	3
$\tilde{K}$	Mtb bacterial carrying capacity	10^5 V
N_1	max No. of Mtb released by programmed cell death (B/M_i)	50
N_2	max No. of Mtb released by T-cell killing (T/M_i)	20
N_3	$N_3 = N_1/2$ (B/M_i)	25
M_u	number of uninfected macrophages	
M_i	number of infected macrophages	
B	number of Mtb bacteria	
T	number of CD4 T-cells	

Table 2
Infinitesimal transition rates for the CTMC model (MC Rate) and for the approximating branching process for infected macrophages and Mtb bacteria (BP Rate).

Event	Transition	MC Rate $p_k(u,i,j,v)$	BP Rate $\tilde{p}_k$	Description
1	$M_u \to M_u+1$	$\tilde{s}_M$	–	M_u influx
2	$M_u \to M_u-1$	$\mu_M M_u$	–	M_u death
3	$M_u \to M_u-1\ M_i \to M_i+1$	$\tilde{\beta} M_u B$	$\tilde{\beta} M_u B$	M_u infected by Mtb
4	$M_i \to M_i-1\ B \to B+N_1$	bM_i	bM_i	programmed cell death of M_i
5	$M_i \to M_i-1\ B \to B+N_2$	$\gamma M_i \frac{T/M_i}{T/M_i+c}$	γM_i	M_i killed by T cells
6	$B \to B+1$	$\delta B(1-B/\tilde{K})$	δB	Mtb reproduction
7	$B \to B-1$	$M_u B(\tilde{\eta}+N_3\tilde{\beta})$	$M_u B(\tilde{\eta}+N_3\tilde{\beta})$	Mtb engulfed by M_u
8	$T \to T+1$	$\tilde{s}_T$	–	T-cell influx
9	$T \to T+1$	$\frac{\tilde{c}_M M_i T}{\tilde{e}_M T+1}$	–	T-cell activation by M_i
10	$T \to T+1$	$\frac{\tilde{c}_B B T}{\tilde{e}_B T+1}$	–	T-cell activation by Mtb
11	$T \to T-1$	$\mu_T T$	–	T-cell death

The forward Kolmogorov differential equation can be derived from the infinitesimal transition probabilities as follows

$$\begin{aligned}\frac{dP}{dt}(u,i,j,v) &= \tilde{s}_M P(u-1,i,j,v) + \mu_M(u+1)P(u+1,i,j,v)\\ &+ b\,i\,P(u,i+1,j-N_1,v) + \gamma\,(i+1)\frac{v/(i+1)}{v/(i+1)+c}P(u,i+1,j-N_2,v)\\ &+ \delta\,(j-1)(1-\frac{j-1}{\tilde{K}})P(u,i,j-1,v) + u\,(j+1)(\tilde{\eta}+N_3\tilde{\beta})P(u,i,j+1,v)\\ &+ \tilde{s}_T\,P(u,i,j,v-1) + \frac{\tilde{c}_M\,i\,(v-1)}{\tilde{e}_M(v-1)+1}P(u,i,j,v-1)\\ &+ \frac{\tilde{c}_B\,j\,(v-1)}{\tilde{e}_B(v-1)+1}P(u,i,j,v-1) + \tilde{\beta}\,(u+1)\,j\,P(u+1,i-1,j,v)\\ &+ \mu_T\,(v+1)\,P(u,i,j,v+1) - \textstyle\sum_{k=1}^{11} p_k(u,i,j,v)P(u,i,j,v).\end{aligned}$$

The analytical solution of the preceding forward Kolmogorov differential equation is difficult to find. Numerically simulated sample paths (stochastic realizations) are feasible to obtain for a multivariate process. We apply the Gillespie algorithm [10] for the simulation of the CTMC model. Two uniform random numbers, $u_1,\ u_2,\ \in U[0,1]$, are generated for the changes in the interevent time and one of the eleven events. The interevent time τ follows an exponential distribution, i.e., τ has a probability density function as $\lambda \exp -\lambda t$, where $\lambda = \sum_{k=1}^{11} p_k(u,i,j,v)$ and $\tau = -\ln u_1/\lambda$. For the second random variable u_2, if $u_2 \in (\sum_{k=1}^{i-1} p_k,\ \sum_{k=1}^{i} p_k]$, then the ith-event occurs.

A comparison of stochastic realizations and the solution of ODE model (2.1) is illustrated by numerical simulations in Fig. 1. We take the basic reproduction number $R_0 = 2$. The analytical results by Zhang [24] suggests that the Mtb infection will develop to an active disease, since $R_0 > 1$. This analytical prediction from the deterministic model is confirmed by the exponentially growing populations of infected macrophage and Mtb bacterium in the first 90 days after initial infection. For the simulation of the CTMC model, four sample paths closely follows the ODE solution, while one sample path (in green) hits $M_i = 0$ and $B = 0$ (the disease clearance state), which is the absorbing state. Therefore, the CTMC model indicates a positive possibility of the occurrence of disease clearance after initial infection when the basic reproduction number is greater than one.

5. Branching process approximations

In this section, we apply multitype branching process theory to study disease clearance. After an initial Mtb invasion with a small amount of inhaled bacteria, we assume that the immune system has normal levels of immune cells. That is, the uninfected macrophages and T cells are assumed to be at steady states, i.e., $M_u(t) = \bar{M}_u$ and $T(t) = \bar{T}$. Linear approximation of the CTMC near the disease-free equilibrium leads to multitype branching processes in terms of the infected macrophages and Mtb bacteria, $M_i(t)$ and $B(t)$. Here, the two nonnegative integers $M_i(t)$ and $B(t)$ take discrete random variables for $t \in [0,\ \infty)$. Assume that each infected macrophage cell and Mtb bacterium evolve independently of each other and the future states of the stochastic process do not depend on the history, the changes of $M_i(t)$ and $B(t)$ near the disease-free equilibrium are summarized as BP Rates in Table 2.

For the case with only one infected macrophage cell $M_i(t) = 1$, events 3, 4, 5, and 6 in Table 2 happen. Given $M_i(t) = 1$ and $B(t) = 0$, the offspring probability generating function (pgf) for $M_i(t)$ is

$$f_1(u_1,\ u_2) = \frac{1}{\lambda_1}\left(\tilde{p}_3\,u_1 + \tilde{p}_4\,u_2^{N_1} + \tilde{p}_5\,u_2^{N_2} + \tilde{p}_6\,u_1\,u_2\right) = \frac{b\,u_2^{N_1} + \gamma\,\bar{T}\,u_2^{N_2}}{b+\gamma\,\bar{T}}, \tag{5.1}$$

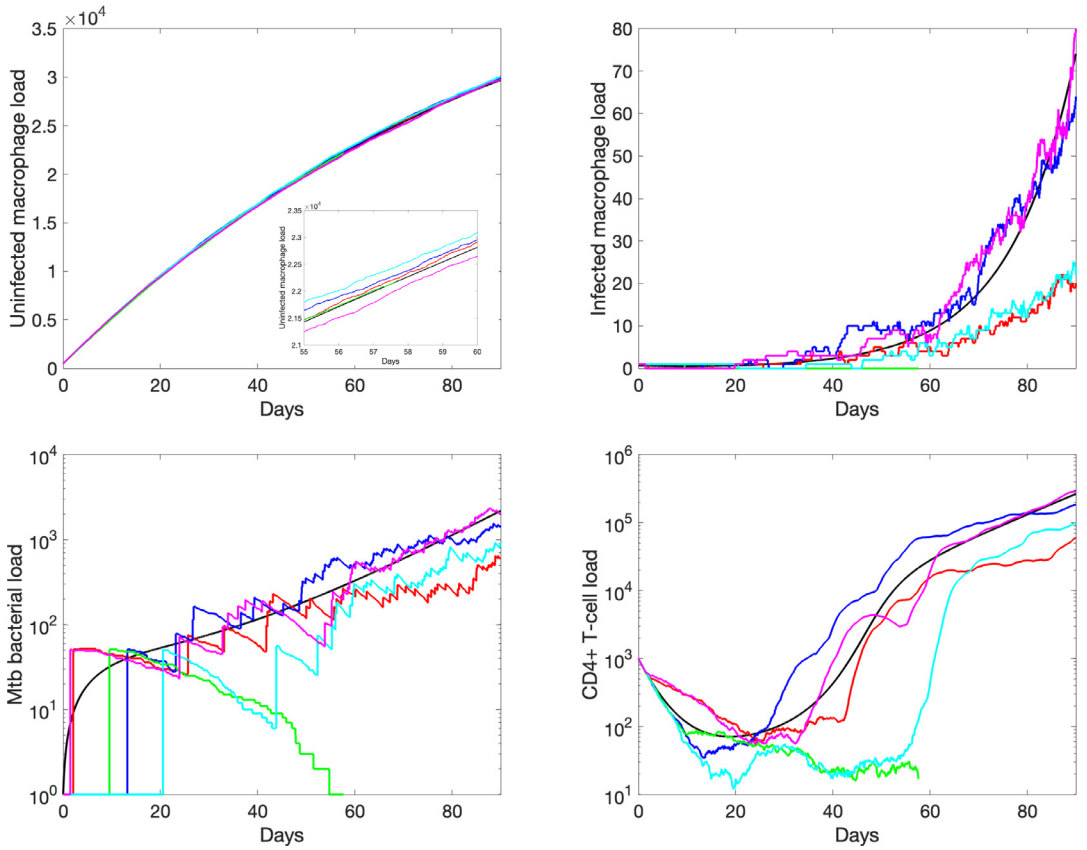

Fig. 1. Five sample paths (in color) of the CTMC model vs. the solution (in black) of the corresponding ODE model (2.1). The sample path in green color demonstrates the disease clearance (extinction). $R_0(\gamma) = 2.0$ and all the other parameter values are provided in Table 1. Initial values for five sample path and one ODE solution are taken as $M_u = 500$, $M_i = 1$, $B = 1$, and $T = 1000$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

where

$$\begin{aligned}
&\tilde{p}_3(1,0) = \tilde{\beta}\bar{M}_u B|_{\{(M_i,B)=(1,0)\}} = 0,\\
&\tilde{p}_4(1,0) = bM_i|_{\{(M_i,B)=(1,0)\}} = b,\\
&\tilde{p}_5(1,0) = \gamma\,\bar{T},\ \text{since}\ \gamma\,B\,\frac{\bar{T}}{\bar{T}+c\,B}|_{\{(M_i,B)=(1,0)\}} = \gamma\,\bar{T} + o(\bar{T}),\\
&\tilde{p}_6(1,0) = \delta\,B = 0,\ \text{since}\ \delta\,B\left(1-\frac{B}{\bar{K}}\right) = \delta\,B + o(B),\\
&\lambda_1 = \textstyle\sum_{i=3}^{6}\tilde{p}_i = b + \gamma\,\bar{T}.
\end{aligned} \tag{5.2}$$

In the case of an initial infection with only one infected macrophage, i.e. $M_i = 1$, there are only two events, this infected M_i is killed either by the overloaded intracellular bacteria with probability b/λ and releases the number of N_1 Mtb bacteria or by cell-mediated immunity with probability $\gamma\,\bar{T}/(\bar{T}+c)/\lambda_1$ and releases the number of N_2 Mtb bacteria. Note that the terms $u_2^{N_1}$ and $u_2^{N_2}$ mean one infected M_i dies and release N_1 and N_2 bacteria, which depend on the way of death. That is u_2 is raised to the power of N_1 or N_2, respectively.

For the case with only one Mtb bacterium cell, i.e. $M_i(t) = 1$, events 3, 6, and 7 in Table 2 occur. Given $M_i(t) = 0$ and $B(t) = 1$, the offspring probability generating function (pgf) for $B(t)$ is

$$f_2(u_1,\,u_2) = \frac{1}{\lambda_2}\left(\tilde{p}_3\,u_2 + \tilde{p}_6\,u_2^2 + \tilde{p}_7\right) = \frac{\tilde{\beta}\bar{M}_u\,u_1\,u_2 + \delta\,u_2^2 + \bar{M}_u(\tilde{\eta} + N_3\tilde{\beta})}{\tilde{\beta}\bar{M}_u + \delta + \bar{M}_u(\tilde{\eta} + N_3\tilde{\beta})} \tag{5.3}$$

where,

$$\begin{aligned}
&\tilde{p}_3(0,1) = \tilde{\beta}\bar{M}_u B|_{\{(M_i,B)=(0,1)\}} = \tilde{\beta}\bar{M}_u,\\
&\tilde{p}_6(0,1) = \delta,\\
&\tilde{p}_7(0,1) = \bar{M}_u(\tilde{\eta}+N_3\tilde{\beta})B|_{\{(M_i,B)=(0,1)\}} = \bar{M}_u(\tilde{\eta}+N_3\tilde{\beta})\\
&\lambda_2 = \tilde{p}_3+\tilde{p}_6+\tilde{p}_7 = \tilde{\beta}\bar{M}_u+\delta+\bar{M}_u(\tilde{\eta}+N_3\tilde{\beta}).
\end{aligned} \tag{5.4}$$

Next, we drive the differential equations for the probabilities of disease clearance. Following the derivation in Allen [3], let $p_{(i,j),(l,m)}$ be the transition probability for $M_i(t)$ and $B(t)$

$$p_{(i,j),(l,m)}(\Delta t) = Prob\{(M_i(t+\Delta t),\ B(t+\Delta t)) = (l,m)|(M_i(t),\ B(t) = (i,j)\}.$$

The generating function $G(i,j)$ for infected macrophage cells and Mtb bacteria has the following relation

$$G_{(i,j)}(u_1,u_2,t) = \sum_{l,m} p_{(i,j),(l,m)}u_1^l u_2^m = \left[G_{(1,0)}(u_1,u_2,t)\right]^i\left[G_{(0,1)}(u_1,u_2,t)\right]^j. \tag{5.5}$$

The transition probability for $M_i(t)$ and $B(t)$ have the following backward Kolmogorov differential equation

$$\begin{aligned}
\frac{dp_{(i,j),(l,m)}(t)}{dt} &= \tilde{\beta}\,\bar{M}_u\,j\,p_{(i+1,j),(l,m)}(t) + b\,i\,p_{(i-1,j+N_1),(l,m)} + \gamma\,i\,p_{(i-1,j+N_2),(l,m)}(t)\\
&\quad \delta\,j\,p_{(i,j+1),(l,m)}(t) + \bar{M}_u\,(\tilde{\eta}+N_3\,\tilde{\beta})\,j\,p_{(i,j-1),(l,m)}(t)\\
&\quad -\left[\tilde{\beta}\,\bar{M}_u\,j + b\,i + \gamma\,i + \delta\,j + \bar{M}_u\,(\tilde{\eta}+N_3\,\tilde{\beta})\,j\right]p_{(i,j),(l,m)}(t)
\end{aligned} \tag{5.6}$$

For the two cases $(i,j) = (1,0)$ and $(i,j) = (0,1)$, substituting (5.6) into (5.5) and taking the derivative in terms of time t, we obtain

$$\frac{\partial G(i,0)}{dt} = i\left[G_{(1,0)}(u_1,u_2,t)\right]^{i-1}\frac{\partial G(1,0)}{dt} \Rightarrow \frac{\partial G(1,0)}{dt} = \frac{\sum_{(l,m)}\dfrac{dp_{(i,0),(l,m)}(t)}{dt}u_1^l u_2^m}{i\,G(i-1,0)}$$

$$\frac{\partial G(0,j)}{dt} = j\left[G_{(0,1)}(u_1,u_2,t)\right]^{j-1}\frac{\partial G(0,1)}{dt} \Rightarrow \frac{\partial G(0,1)}{dt} = \frac{\sum_{(l,m)}\dfrac{dp_{(0,j),(l,m)}(t)}{dt}u_1^l u_2^m}{j\,G(0,j-1)},$$

which are originally derived in Allen [3]. Simplifying the preceding equations yields

$$\begin{aligned}
\frac{\partial G_{(1,0)}}{dt} &= \left(b+\gamma\,\bar{T}\right)[f_1(G(1,0),G(0,1)) - G(1,0)]\\
\frac{\partial G_{(0,1)}}{dt} &= \left[\tilde{\beta}\bar{M}_u+\delta+\bar{M}_u(\tilde{\eta}+N_3\tilde{\beta})\right][f_2(G(1,0),G(0,1)) - G(0,1)].
\end{aligned} \tag{5.7}$$

Substituting $G_{(1,0)}(0,0,t) = p_{(1,0),(0,0)}$ and $G_{(0,1)}(0,0,t) = p_{(0,1),(0,0)}$ to the preceding equations, the stationary solutions satisfy,

$$f_1(p_{(1,0),(0,0)}(t),\ p_{(0,1),(0,0)}(t)) = p_{(1,0),(0,0)}(t), \quad f_2(p_{(1,0),(0,0)}(t),\ p_{(0,1),(0,0)}(t)) = p_{(0,1),(0,0)}(t), \tag{5.8}$$

which are the fixed points of offspring pgfs (5.1) and (5.3).

5.1. Fixed points of offspring pgfs and their stability

According to the theory of multitype branching processes, the probability of disease clearance can be approximated by the fixed points of the offspring pgfs (5.1) and (5.3). Letting $p_{(1,0),(0,0)}(t) = u_1$, $p_{(0,1),(0,0)}(t) = u_2$, (5.8) is rewritten as

$$\frac{b\,u_2^{N_1}+\gamma\,\bar{T}\,u_2^{N_2}}{b+\gamma\,\bar{T}} = u_1, \qquad \frac{\tilde{\beta}\bar{M}_u\,u_1\,u_2+\delta\,u_2^2+\bar{M}_u(\tilde{\eta}+N_3\tilde{\beta})}{\tilde{\beta}\bar{M}_u+\delta+\bar{M}_u(\tilde{\eta}+N_3\tilde{\beta})} = u_2. \tag{5.9}$$

The first equation of (5.9) derives that

$$u_1(u_2) = \frac{(b\,u_2^{N_1}+\gamma\,u_2^{N_2})}{b+\gamma}. \tag{5.10}$$

Substituting (5.10) to the second equation of (5.9) yields

$$\begin{aligned} h(u_2) = \quad & \bar{M}_u\, b\, \tilde{\beta}\, u_2^{N_1+1} + \bar{M}_u\, \tilde{\beta}\, \gamma\, u_2^{N_2+1} + \delta\,(b+\gamma)\, u_2^2 \\ & -(b+\gamma)\,\{[(N_3+1)\,\tilde{\beta}+\tilde{\eta}]\,\bar{M}_u+\delta\}\,u_2 + \bar{M}_u\,(N_3\,\tilde{\beta}+\tilde{\eta})\,(b+\gamma) \\ = \quad & 0. \end{aligned} \tag{5.11}$$

With positive parameters for CTMC model, the total number of sign changes from one coefficient to another in the polynomial (5.11) is two. Then, according to Descartes' rule of signs, the number of positive roots of (5.11) is two if the positive root exists. Notice that $h(1) = 0$, if $h'(1) > 0$ there exist a $\tilde{u}_2 \in (1-\epsilon,\ 1)$, $0 < \epsilon \ll 1$, such that $h(\tilde{u}_2) < 0$. Because of $h(0) > 0$ we have at least another root in the interval $(0, \tilde{u}_2) \in (0,\ 1)$. $h'(1) > 0$ is verified as follows. First we have

$$\begin{aligned} \frac{dh}{du_2} = & \bar{M}_u\, u_2^{N_1}\,(N_1+1)\, b\,\tilde{\beta} + \bar{M}_u\, u_2^{N_2}\,(N_2+1)\,\tilde{\beta}\,\gamma + 2\,(b+\gamma) \\ & \left[\left(-\frac{1}{2}\,N_3\,\tilde{\beta} - \frac{1}{2}\,\tilde{\beta} - \frac{1}{2}\,\tilde{\eta}\right)\bar{M}_u + \delta\left(u_2 - \frac{1}{2}\right)\right]. \end{aligned}$$

Evaluating the preceding equation at $\bar{M}_u = \frac{s_M}{\mu_M}$ and $u_2 = 1$ yields

$$\frac{dh}{du_2}|_{u_2=1} = [(N_2 - N_3)\,\gamma + b\,(N_1 - N_3)]\,\tilde{\beta}\,\frac{s_M}{\mu_M} - \tilde{\eta}\,(b+\gamma)\,\frac{s_M}{\mu_M} + \delta\,(b+\gamma). \tag{5.12}$$

Recalling the expression of R_0 in (2.2), when $R_0 = 1$, we have

$$\begin{aligned} & \delta = \delta_0 := -\frac{s_M}{\mu_M}\left[\frac{(N_2 - N_3)\,\gamma\,\tilde{\beta} + (N_1 - N_3)\,b\,\tilde{\beta}}{b+\gamma} - \tilde{\eta}\right], \\ & \frac{dh}{du_2}|_{u_2=1,\delta=\delta_0} = 0. \end{aligned} \tag{5.13}$$

Observing (2.2) and (5.12), we find that δ has a positive relationship with R_0 and $h'(u_2)$. Thus, $h'(1) > 0 (= 0, < 0)$ if $R_0 > 1 (= 1, < 1)$. Moreover, if $u_2 \in (0, 1)$, then $u_1 \in (0, 1)$ according to expression (5.10). We summarize the results in the following theorem.

Theorem 2. *The offspring pgfs (5.1) and (5.3) always have a positive fixed point at* $(u_1,\ u_2) = (1,\ 1)$. *Moreover, if* $R_0 > 1$, *another fixed point exists and* $(u_1,\ u_2) \in (0,\ 1) \times (0,\ 1)$.

Recall that the fixed points of offspring pgfs (5.1) and (5.3) are also stationary solutions of the backward Kolmogorov differential Eq. (5.7). Their stability is determined by the eigenvalues of the Jacobian matrix $J = W(M - I)$ in Allen [1], [2], and [3]. Here, W is $diag(\lambda_1, \lambda_2)$, I is the 2×2 identity matrix, and M is the expectation matrix associated with the offspring pgfs (5.1) and (5.3) and evaluated at $(u_1,\ u_2) = (1,\ 1)$. W and M are calculated as

$$\begin{aligned} & W = \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix} = \begin{bmatrix} b+\gamma\,\bar{T} & 0 \\ 0 & \tilde{\beta}\bar{M}_u + \delta + \bar{M}_u(\tilde{\eta} + N_3\tilde{\beta}), \end{bmatrix}, \\ & M = \begin{bmatrix} 0 & \dfrac{N_1\,b + N_2\,\gamma}{b+\gamma} \\ \dfrac{\tilde{\beta}\,\bar{M}_u}{\tilde{\beta}\,\bar{M}_u + \delta + \bar{M}_u\,(N3\,\tilde{\beta} + \eta)} & \dfrac{\bar{M}_u\,\tilde{\beta} + 2\,\delta}{\tilde{\beta}\,\bar{M}_u + \delta + \bar{M}_u\,(N_3\,\tilde{\beta} + \delta)} \end{bmatrix}. \end{aligned} \tag{5.14}$$

We denote the largest real part of the eigenvalue of the Jacobian matrix $J = W(M - I)$ as $s(J)$, which determines the stability of the stationary solution of the offspring pgfs. Following [2], the branching process is subcritical, critical, or supercritical, if $s(J) < 0$, $s(J) = 0$, or $s(J) > 0$, which is equivalent to $\rho(M) < 1$, $\rho(M) = 1$, or $\rho(M) > 1$. Here $\rho(M)$ denotes the spectral radius of M. Furthermore, it is proven by [2] that $\rho(M) < 1\ (= 1, > 1)$ is equivalent to $R_0 < 1\ (= 1, > 1)$. We verify that the irreducible matrix M in (5.14) and nonsingular M-matrix V in (2.2) satisfy the following relationship

$$J = W(M - I) = \begin{bmatrix} -b-\gamma & \dfrac{\tilde{\beta} s_M}{\mu_M} \\ N_1 b + N_2\gamma & \delta - \dfrac{s_M}{\mu_M}(N_3\tilde{\beta} + \tilde{\eta}), \end{bmatrix} = F - V,$$

where we take the matrix F and V in (2.3). For the multitype branching processes approximation, we denote the smallest fixed point of the offspring pgfs as $(u_1,\ u_2) \in (0,\ 1] \times (0,\ 1]$. Given the initial infection with $(M_i(0),\ B(0)) = (k_1,\ k_2)$, an estimation of the probability of disease clearance is

$$\mathbb{P}_{clearance} = u_1^{k_1}\, u_2^{k_2}. \tag{5.15}$$

For the case $R_0 < 1$, there exists an unique fixed point $(u_1,\ u_2) = (1,\ 1)$, such that $\mathbb{P}_{clearance}|_{(1,\,1)} = 1$. For the case $R_0 > 1$, there exists another fixed point $(u_1,\ u_2) \in (0,\ 1) \times (0,\ 1)$, such that $0 < \mathbb{P}_{clearance}|_{(u_1,\,u_2)} < 1$.

5.2. Approximated probability of disease clearance

Applying the theory of the multitype branching processes, the approximated probability of disease clearance is denoted in (5.15).

To gain understanding of the disease clearance with the change of the basic reproduction number R_0, we rewrite γ in terms of R_0 based on (2.2)

$$\gamma = \gamma_0(R_0) := b\,\frac{\tilde{s}_M\,(N_3\,\tilde{\beta} - \tilde{\eta})\,R_0^2 - \delta\,\tilde{\mu}_M\,R_0 + N_1\,\tilde{\beta}\,\tilde{s}_M}{-\tilde{s}_M\,(N_3\,\tilde{\beta} + \tilde{\eta})\,R_0^2 + \delta\,\tilde{\mu}_M\,R_0 + N_2\,\tilde{\beta}\,\tilde{s}_M}. \tag{5.16}$$

Then Eq. (5.11) can be written as

$$\begin{aligned} h_2[\gamma_0(R_0)] = & \frac{b\tilde{s}_M\,\tilde{\beta}}{[(-N_3R_0^2 + N_2)\tilde{\beta} - R_0^2\tilde{\eta}]\,\tilde{s}_M\,\mu_M + \delta\mu_M R_0\mu_M} \\ & \times([(-N_3R_0^2 + N_2)\tilde{\beta}\tilde{s}_M - R_0^2\tilde{\eta}\tilde{s}_M + \delta\mu_M R_0]u_2^{N_1+1} \\ & +[(N_3R_0^2 - N_1)\,\tilde{\beta}\,\tilde{s}_M + R_0^2\,\tilde{\eta}\,\tilde{s}_M - \delta\mu_M R_0]u_2^{N_2+1} \\ & +(N_3\,u_2 + u_2 - N_3)\tilde{\beta}\tilde{s}_M(N_1 - N_2) + \tilde{\eta}(u_2 - 1)\tilde{s}_M(N_1 - N_2) \\ & -\delta u_2\mu_M(u_2 - 1)(N_1 - N_2)) = 0. \end{aligned} \tag{5.17}$$

considering the preceding equation $h_2[\gamma_0(R_0)] = 0$ and the parameter values in Table 2, the relationship between u_2 and R_0 is plotted in Fig. 2. It shows that there is a unique $u_2 = 1 \in [0,\,1]$ for $R_0 < 1$, and another $u_2 \in [0,\,1)$ exists for $R_0 > 1$.

For five different values of R_0, we solve $h_2[\gamma_0(R_0)] = 0$ in (5.17) for the fixed point u_2 of the offspring pgf (5.3). The corresponding fixed point u_1 is calculated according to (5.10). Assuming the initial infection with one infected macrophage cell and one Mtb bacterium, i.e. $(M_i(0),\,B(t)) = (1,\,1)$, the probability of disease clearance approximated by multitype branching processes is computed by the formula in (5.15) with $k_1 = k_2 = 1$. The five values set of R_0, u_1, u_2, and $\mathbb{P}_{clearance}$ by branching process are summarized in Table 3.

Next, we compare the analytical approximated probability of disease clearance by branching process with the probability estimated by numerical simulation of the CTMC model. We count the number of extinct sample paths, which are absorbed by $(M_i,\,B) = (0,\,0)$ before the end of simulation time (90×2 days/ three months). Then, the approximated probability of disease clearance from the CTMC model is obtained through dividing the number of extinct sample paths by 10,000, which is the total number of CTMC simulations. The estimation of $\mathbb{P}_{clearance}$ by CTMC simulations is stored in the second column of Table 3. It is shown that the approximated probability of disease clearance by analytical and numerical approaches are closely matched. Moreover, the probability of disease clearance after the initial infection decreases with the growth of R_0.

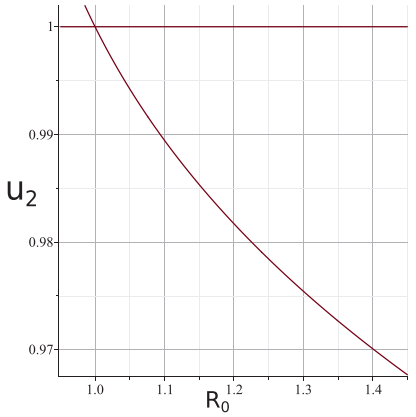

Fig. 2. The fixed point u_2 in terms of R_0, according to the equation $h_2[\gamma_0(R_0)] = 0$ in (5.17). Parameter values are taken in Table 1.

Table 3
Comparison of the probability of disease clearance estimated by CTMC model with 10,000 simulations and estimated by branching process in the formula (5.15).

R_0	$\mathbb{P}_{clearance}$ by CTMC	u_1	u_2	$\mathbb{P}_{clearance}$ by branching process
1.0	0.8914	1	1	1
1.1	0.6783	0.7339	0.9894	0.7261
1.2	0.4999	0.5350	0.9817	0.5252
1.3	0.3452	0.3716	0.9754	0.3625
1.4	0.2170	0.2307	0.9701	0.2238
1.5	0.1485	0.1050	0.9651	0.1013

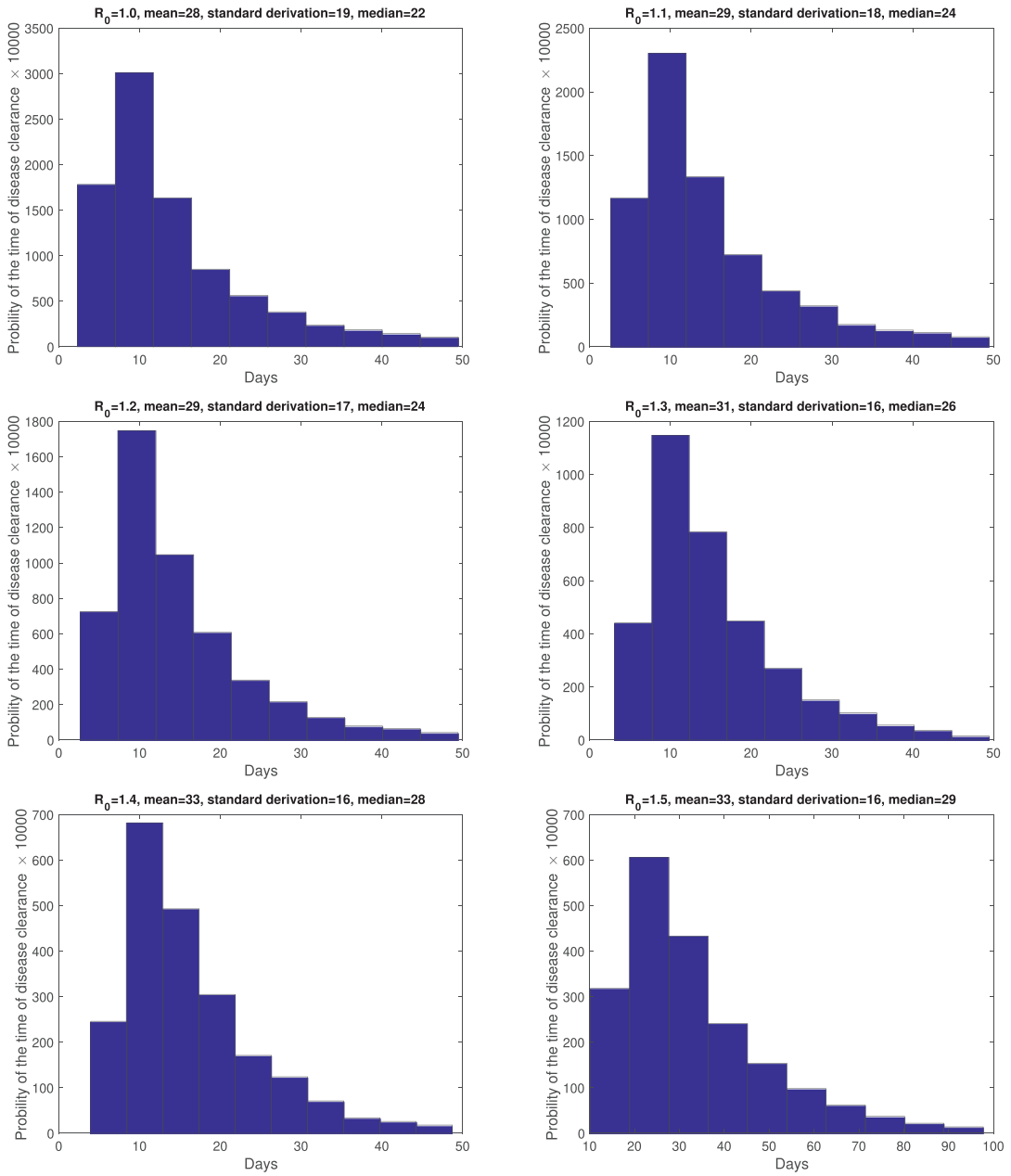

Fig. 3. Histograms to the time of disease clearance for the CTMC model after the initial Mtb infection with one infected macrophage cell and one Mtb bacterium.

5.3. Time to disease clearance

Through stochastic processes, we can estimate the finite time of disease clearance. While the ODE model can only simulate disease clearance when the time goes to infinity. To approximate the probability distribution of the disease clearance time, we simulate 10,000 sample paths by applying Gillespie algorithm on the CTMC model. The period for primary infection is usually a few weeks or up to three months [13]. We therefore set the simulation time as 90 days and assume that the infection starts by one inhaled Mtb bacterium and one Mtb infected macrophage cell. Fig. 3 demonstrates the approximated probability distribution for the time of disease clearance for the CTMC model with $R_0 = 1.0$, $R_0 = 1.1$, $R_0 = 1.2$, $R_0 = 1.3$, $R_0 = 1.4$, $R_0 = 1.5$. With the increase of R_0, the probability of disease clearance decreases and the mean day and the median day to disease clearance increase. In general, the median day to disease clearance after initial Mtb infection is less than a month. The most common day for disease clearance day is around two weeks. It is shown as peaks in Fig. 3. Most of the

disease clearance happens within the initial first two months after the initial Mtb infection. Longer disease clearance time, up-to three months, is required with a large reproduction number, such as $R_0 = 1.5$ in Fig. 3.

6. Conclusion and discussion

In this paper, we capture the occurrence of finite-time disease clearance after an initial infection with a small amount of infectious Mtb bacteria through a continuous-time Markov chain model. Evidence shows the existence of disease clearance in individuals who are heavily exposed to Mtb pathogens. Correspondingly, the CTMC model demonstrates sample paths with extinctions on infected macrophage and Mtb bacterial populations in finite time. The analytical approximation for the probability of disease clearance is calculated through the theory of multitype branching processes. This result matches well with simulated results calculated via 10,000 sample paths. For $R_0 > 1$, the approximated probability for disease clearance is positive and shows a negative relationship with the growth of the basic reproduction number R_0. Furthermore, we investigate the probability distribution of the disease clearance time, which is roughly within a month for $R_0 \in [1, 1.5]$. The clearance time increases with the growth of R_0.

Our results predict the probability of and the time to disease clearance in terms of the basic reproduction number R_0. Host immune factors affect R_0, and thusly, can be used to modulate the probability of and the time to disease clearance. For example, HIV infection can induce an increase in macrophage turnover. Due to the positive relationship between R_0 and the death rate of uninfected macrophages μ_M and the negative relationship between R_0 and the probability of disease clearance, HIV infection can thus eventually reduce the probability of disease clearance. Negative relationships occur between the probability of disease clearance and the number of intracellular bacterial released from an infected macrophage, killed by bursting N_1 and T-cell mediated immune responses N_2. Because HIV infection impairs the protective immune process of programmed cell death (apoptosis), it then leads to a high amount of Mtb bacterial release. This explains why individuals carrying HIV viruses have higher TB burden. On the other hand, effective host immune responses can inhibit the pathogen reproduction δ, which has a positive relationship with R_0. It then results in a higher probability for disease clearance. Host-direct therapy is another example to enhance host immune ability against TB infection [17]. Vitamin D is a potent adjunctive therapy with host-beneficial effects in TB. It has been shown that vitamin D intake can promote the killing of the phagocytized Mtb bacteria, which is represented as an increase in η [18]. It can increase the chance for disease clearance. Moreover, vitamin D has been proven to promote autography in cell culture [23], which in turn reduces intracellular bacterial releases N_1 and N_2 and raise the probability of disease clearance. Overall, the probability, time, and mechanisms of TB clearance revealed in this investigation could give new insights in TB prevention and the development of new therapies.

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