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On an Infection-age Structured Epidemic Model with Multiscale*

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Abstract Considering the individual difference, this paper deals with an infection-age structured epidemic model coupling within-host and between-host for environmentally-driven infectious disease. The full system with two time scales, the cellular level and population level, is first separated into the isolated fast and slow systems. For the isolated fast and slow systems, combined with the within-host and between-host reproduction numbers, R_{w0} and R_{b0}, we give the complete global dynamics by using Lyapunov function respectively. Our results indicate that when there is no virus in environment the disease can be not only controlled, but also eliminated. However, when there is always virus in environment the disease is only controlled but not eliminated. Furthermore, the coupled slow system has complex dynamics with multiple positive equilibria and backward bifurcation. The virus contaminated environment plays a critical role on backward bifurcation. When the initial environmental virus is below some threshold the disease will be eliminated, when it is above the threshold the disease will develop an endemic disease. Some numerical simulations are performed to illustrate these results. The age structured model is more general, and this work includes some previous results.

Keywords Age structure, Coupled system, Basic reproduction number, Stability, Backward bifurcation.

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1. Introduction

There are many viral infectious diseases among human beings. The common viral infectious diseases include 2019-nCoV, influenza, AIDS, rubella, respiratory virus infection, viral hepatitis, etc. These diseases not only cause huge social and economic losses, but also cause great harm to human health. Based on the dynamical mechanisms of the disease transmission, mathematical model can be established to study the properties of the model solution, That is, the threshold conditions which have been widely used to control and predict the current and future epidemic prevalence.

Infection age, which is the time passed since a host was infected, measures the amount of viruses accumulated in an infected host. Some works on HIV/AIDS and 2019-nCoV, have found that different infection age leads to significant differences in infection rates and mortality caused by diseases. Age structured infection

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model can be used to describe the individual difference. For instance, the exposed individuals and infected individual have different transmission rates. Recently, infection age has been introduced into epidemic models to study this phenomenon, for example [1, 4, 12, 16, 24, 25]. Nevertheless, the introduction of the infection age brings about changes to the model from ordinary differential equation to first-order partial differential equation (the well-known age structured model), increasing the difficulty of the study.

However, infectious disease dynamics are dominated by many interconnected scales, from complex within-host infection processes to between hosts and environments. Therefore, the other individual difference we take account in this context is that the disease driven by environment has two time scales: the cellular level and the population level. At the cellular level, the virus infection process within the hosts is called the fast system, which usually takes the form of cell-virus interactions, while at the population level, disease transmission between hosts is a slow process, which refers to the transmission of disease among individuals. Therefore, both questions will be raised, and how does the coupling of virus and individual affect the process of disease transmission? What is the impact of infection-age structure on disease dynamics?

The dynamic behavior of the within- and between-host is often considered separately, but it is found that the establishment of the coupled model will have new insights. For Toxoplasma gondii, authors in [3,21] proposed a coupled cell virus model and SI epidemic model, where the virus in polluted environment plays a major and determinant role in transmission of Toxoplasma infectious disease. Backward bifurcation may occur in [3, 21] when the basic reproduction number is less than 1, in which stable disease-free equilibrium and endemic equilibrium can coexist. In such case, the disease can persist and be hard to control. This means the basic reproduction number will not be sufficient to described whether the disease is endemic or not, and the initial values should be paid attention to. Based on the coupling models of [3, 21], authors in [7] considered the disease-induced mortality, obtained the similar dynamic behavior and studied the evolution of virulence. The other works described virus replication and their respective immune responses while disease transmission is represented by the SI model [2], the dynamics of cholera within and between hosts [25] as well as the effects of within-host and population-level dynamics on malaria transmission dynamics [1]. Furthermore, infectious disease models with time-varying parameters and general nonlinear incidence rates have been analyzed in [12]. Authors in [13, 26] considered the impacts of *Wolbachia* on the mosquito-borne diseases in a heterogeneous environment.

The assumptions in the above articles are made on the basis of homogeneity without considering individual differences. That is, the infection age is not taken into account, especially for the coupled within- and between-host model. Authors in [20] derived a stage-structured epidemic model from an age structured model, while did not discuss the age structured model. Recently, the model of [7] has been extended in [14], where the mortality was considered as the function of the infection age. However, it did not consider the infection age of cells in the host. As stated in the pieces of literature [5, 6, 10, 11, 17–19, 27], the infection age of viral diseases is of great important. Therefore, we will introduce the infection age into the coupled within- and between-host models, which is more in line with the biological background, and increases the difficulty in mathematical research.

In this paper, our approach of establishing model is based on the idea of sep-

arating biological time scales, a fast time scale associated with the within-host dynamics and a slow time scale associated with the epidemiological process and the environment. The article is arranged as follows: In Section 2, we propose the model framework by using a hybrid system of ordinary differential equations and partial differential equations. The separate method in [8] is extended to the age structured model in terms of the singular perturbation theory. In Section 3, we obtain the main results by defining the basic reproduction numbers, establishing the positivity and boundedness of solutions, global dynamics, multiple positive equilibria, backward bifurcation, numerical simulations and biological meanings. In Section 4, a discussion is carried out to show that the age structured model is more general. Finally, the main proofs of theorems are given in Appendix.

2. Model formulation

This paper considers a general coupled within- and between-host epidemic model with infection-age structure. This model can be used to describe the environmentally-driven infectious diseases such as Toxoplasmosis. As an obligate intracellular protozoon, Toxoplasma gondii can cause the zoonotic toxoplasmosis. Humans are able to be infected via accidental ingestion of water or food contaminated with the oocysts of Toxoplasma gondii. Toxoplasmosis can result in severe clinical symptoms and even death to immunocompromised individuals such as infants and pregnant women. So far, we cannot prevent and control cat toxoplasmosis due to the lack of information on the formation of oocysts. In this paper, we try to investigate the mechanism of within- and between-host transmission of the environmentally-driven infectious diseases.

In order to consider the individual difference, we introduce age structure in the following coupled model

$$\begin{cases} \dot{T}(t) = \Lambda_c - kV(t)T(t) - mT(t), \\ \frac{\partial T^*(t,a)}{\partial t} + \frac{\partial T^*(t,a)}{\partial a} = -(m+\delta(a))T^*(t,a), \\ \dot{V}(t) = g(E) + \int_0^{+\infty} \delta(a)p(a)T^*(t,a)da - cV(t), \\ T^*(t,0) = kV(t)T(t), \\ \dot{S}(t) = \Lambda_h - \beta E(t)S(t) - \mu S(t), \\ \frac{\partial I(t,a)}{\partial t} + \frac{\partial I(t,a)}{\partial a} = -(\mu+\varphi(a))I(t,a), \\ \dot{E}(t) = (1-E(t))\int_0^{+\infty} V(t)\theta(a)I(t,a)da - \gamma E(t), \\ I(t,0) = \beta E(t)S(t), \end{cases} \tag{2.1}$$

where $T(t)$, $T^*(t,a)$ and $V(t)$ are the densities of healthy cells, infected cells with infection age a and the virus load at time t; $S(t)$ denotes the numbers of susceptible individuals; $I(t,a)$ represents the density of infectious individuals with infection age a at time t; $E(t)$ represents the level of environment contaminated by the virus at time t, or the concentration of virus per unit area or volume of a region being considered ($0 \le E \le 1$). The framework of the environmentally-driven infectious disease model (see Figure 1).

Within a host, the healthy cells are infected by the virus with the law $kV(t)T(t)$, which will flow into the infected cells. Thus, the new infected cells are given

by $T^*(t,0) = kV(t)T(t)$ (boundary condition). The recruitment of viruses within a host has two ways. One is when the cells die, the viruses are released and infect other cells. In this process, a mass of viruses are released with the level $\int_0^{+\infty} \delta(a)p(a)T^*(t,a)da$, where $\delta(a)$ and $p(a)$ are per-capita infection-induced mortality rate of cells and virus production rate with infection age a respectively. The other is the input of the virus contaminated environment given by $g(E)$. This denotes an added rate in the change of virus load due to the continuous ingestion of virus by the host from contaminated environment. In this work, we assume that environmental contamination is measured by the concentration of virus living in the environment, and that hosts acquire infection by ingesting contaminated food. The function g expresses that the environmental contamination is an increasing function of the number of viruses in the host. These biological considerations suggest that the function g should have the following properties.

(H1) $g(0) = 0$, $g(E) \geq 0$, $g'(E) > 0$, $g''(E) \leq 0$.

One of the simplest forms for $g(E)$ considered in [3,8] is the linear function $g(E) = wE$, where w is a positive constant.

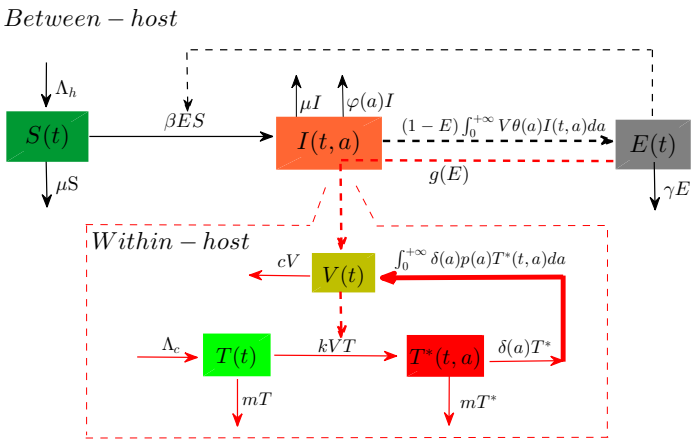

Figure 1. This framework can be used to model the environmentally-driven infectious diseases. Our multiscale model involves two scales: between-host (top) and within-host (bottom) by focusing on the transmission between susceptible and infected hosts in contaminated environment and the virus-cell interactions within an infected host.

Between hosts, the susceptible individuals are infected via ingesting the contaminated water or food described by $\beta E(t)S(t)$. Similarly, the new infected hosts are given as $I(t,0) = \beta E(t)S(t)$ (boundary condition). After a host becomes an infected individual, it releases viruses which can contaminate the environment. Let $\theta(a)$ be the virus releasing rate per host with infection age a, which is proportional to the number of infected hosts and the within-host virus concentrations. Thus, the rate of environmental contamination is $\int_0^{+\infty} V(t)\theta(a)I(t,a)da$.

We give three important assumptions as follows.

(H2) The functions $p(a)$, $\delta(a)$, $\theta(a)$, $\varphi(a) \in L_1^+(0,+\infty)$ are bounded;

(H3) The parameters Λ_c, k, m, Λ_h, β, μ and γ are all nonnegative constants, and their definitions are listed in Table 1;

Table 1 Description of parameters and frequently used symbols.

Symbol	Description
Λ_c	Recruitment of cells
k	Per-capita infection rate of cells
m	Per-capita natural mortality of cells
$\delta(a)$	Per-capita infection-induced mortality rate of cells with infection age a
$p(a)$	Per-capita virus production rate with infection age a
c	Per-capita clearance rate of virus in the host
$g(E)$	The rate of additional increase in virus concentration in the host
Λ_h	Recruitment of susceptibles
β	Per-capita infection rate of hosts in the contaminated environment
μ	Per-capita natural death rate of hosts
$\varphi(a)$	Per-capita disease-induced death rate of hosts with infection age a
$\theta(a)$	Per-capita virus releasing rate with infection age a
γ	Per-capita clearance rate of virus in the environment

(H4) The initial conditions: $T(0) \geqslant 0$, $V(0) \geqslant 0$ and $T^*(0,a) = \eta(a) \in L_1^+(0,+\infty)$; $S(0) \geqslant 0$, $E(0) \geqslant 0$ and $I(0,a) = \xi(a) \in L_1^+(0,+\infty)$.

By applying the method of characteristics, the solutions $T^*(t,a)$ and $I(t,a)$ are given by

$$T^*(t,a) = \begin{cases} kV(t-a)T(t-a)e^{-\int_0^a (m+\delta(r))dr}, & t > a, \\ \eta(a-t)e^{-\int_0^t (m+\delta(r+a-t))dr}, & t \leq a, \end{cases} \tag{2.2}$$

and

$$I(t,a) = \begin{cases} \beta E(t-a)S(t-a)e^{-\int_0^a (\mu+\varphi(r))dr}, & t > a, \\ \xi(a-t)e^{-\int_0^t (\mu+\varphi(r+a-t))dr}, & t \leq a. \end{cases} \tag{2.3}$$

Base on the above assumptions, in view of [15, Theorem 3.1], the existence and uniqueness of the solutions can be obtained by rewriting the differential equations (2.1) with boundary and initial conditions to the integral equations.

2.1. Separation of the fast and slow systems

Since the within-host dynamics and the between-host dynamics have different time sales, we next separate the two time scales by applying the perturbation theory. For this, we introduce the slow time variables $s = \epsilon t$ and $\tau = \epsilon a$, where $0 < \epsilon \ll 1$. Along almost every characteristic line, it follows that $\frac{da}{dt} = 1$. Thus, $\frac{d\tau}{ds} = 1$. Note

that the time scale of between hosts dynamics is slower than that of within hosts dynamics, and the parameters related to population level dynamics are smaller. We introduce new variables

$$\widetilde{\Lambda}_h = \frac{1}{\epsilon}\Lambda_h,\ \ \widetilde{\beta} = \frac{1}{\epsilon}\beta,\ \ \widetilde{\mu} = \frac{1}{\epsilon}\mu,\ \ \widetilde{\gamma} = \frac{1}{\epsilon}\gamma,\ \ \widetilde{\varphi}(a) = \frac{1}{\epsilon}\varphi(a),\ \ \widetilde{\theta}(a) = \frac{1}{\epsilon}\theta(a).$$

Denote '$\cdot$'=$\frac{d}{ds}$ and '$\prime$'=$\frac{d}{dt}$. Then, the full system can be written as

$$\begin{cases} T'(t) = \Lambda_c - kV(t)T(t) - mT(t), \\ \frac{\partial T^*(t,a)}{\partial t} + \frac{\partial T^*(t,a)}{\partial a} = -(m+\delta(a))T^*(t,a), \\ V'(t) = g(E(t)) + \int_0^{+\infty} \delta(a)p(a)T^*(t,a)da - cV(t), \\ S'(t) = \epsilon(\widetilde{\Lambda}_h - \widetilde{\beta}E(t)S(t) - \widetilde{\mu}S(t)), \\ \frac{\partial I(t,a)}{\partial t} + \frac{\partial I(t,a)}{\partial a} = -\epsilon\left(\widetilde{\mu} + \widetilde{\varphi}(a)\right) I(t,a), \\ E'(t) = \epsilon\left(\big(1-E(t)\big)V(t)\int_0^{+\infty}\widetilde{\theta}(a)I(t,a)da - \widetilde{\gamma}E(t)\right). \end{cases} \tag{2.4}$$

Let

$$\begin{aligned} &T_1(s) = T(t),\ T_1^*(s,\tau) = T^*(t,a),\ V_1(s) = V(t), \\ &S_1(s) = S(t),\ \ I_1(s,\tau) = I(t,a),\ \ E_1(s) = E(t). \end{aligned}$$

Therefore, with respect to the slower time s, we have

$$\begin{cases} \epsilon\dot{T}_1(s) = \Lambda_c - kV_1(s)T_1(s) - mT_1(s), \\ \epsilon\left(\frac{\partial T_1^*(s,\tau)}{\partial s} + \frac{\partial T_1^*(s,\tau)}{\partial \tau}\right) = -(m+\delta_1(\tau))T_1^*(s,\tau), \\ \epsilon\dot{V}_1(s) = g(E_1) + \int_0^{+\infty}\delta_1(\tau)p_1(\tau)T_1^*(s,\tau)d\tau - cV_1(s), \\ \dot{S}_1(s) = \widetilde{\Lambda}_h - \widetilde{\beta}E_1(s)S_1(s) - \widetilde{\mu}S_1(s), \\ \frac{\partial I_1(s,\tau)}{\partial s} + \frac{\partial I_1(s,\tau)}{\partial \tau} = -(\widetilde{\mu} + \varphi_1(\tau))I_1(s,\tau), \\ \dot{E}_1(s) = \big(1-E_1(s)\big)\int_0^{+\infty}V_1(s)\theta_1(\tau)I_1(s,\tau)d\tau - \widetilde{\gamma}E_1(s), \end{cases} \tag{2.5}$$

where $\delta_1(\tau) = \delta(a)$, $p_1(\tau) = p(a)$ and $\varphi_1(\tau) = \widetilde{\varphi}(a)$, $\theta_1(\tau) = \widetilde{\theta}(a)$.

Next, we analyze the whole system by analyzing the fast and slow dynamics of the system respectively. The fast dynamics can be analyzed by the system (2.4), when $\epsilon = 0$

$$\begin{cases} T'(t) = \Lambda_c - kV(t)T(t) - mT(t), \\ \frac{\partial T^*(t,a)}{\partial t} + \frac{\partial T^*(t,a)}{\partial a} = -(m+\delta(a))T^*(t,a), \\ V'(t) = g(E) + \int_0^{+\infty}\delta(a)p(a)T^*(t,a)da - cV(t), \end{cases} \tag{2.6}$$

in which E is considered as a constant parameter. The slow dynamics can be analyzed by the system (2.5) when $\epsilon = 0$. For unify notation, we still use the original notations and obtain

$$\begin{cases} S'(t) = \Lambda_h - \beta E(t)S(t) - \mu S(t), \\ \frac{\partial I(t,a)}{\partial t} + \frac{\partial I(t,a)}{\partial a} = -(\mu + \varphi(a))I(t,a), \\ E'(t) = \big(1-E(t)\big)\int_0^{+\infty}V\theta(a)I(t,a)da - \gamma E(t), \end{cases} \tag{2.7}$$

where the fast variable V will be replaced by its value at a steady state of the fast system (2.6).

3. Main results

In this section, we will discuss the isolated fast system, isolated slow system and the coupled slow system respectively. Combined with the reproduction numbers, we obtain the main results including the positivity and boundedness of solutions, global dynamics, multiple positive equilibria, backward bifurcation, numerical simulations and biological meanings. The corresponding proofs are given in Appendix.

3.1. Analysis of isolated fast system

Compared to the dynamics at the population level, the within-host dynamics is fast. In such case, the between-host (slow) variables can be viewed as constants. The linking variable $E(t)$ in the within-host (fast) system is a constant and $0 \leq E \leq 1$, where $E = 0$ means there is no virus in the environment, $E > 0$ represents there are viruses in the environment and $E = 1$ indicates that the virus in the environment reaches its maximum. Thus, the fast time system (2.6) is an isolated within-host virus infection system.

First, with regard to the positivity and boundedness of the solutions for system (2.6), we have the following results.

Theorem 3.1. *The solutions $(T(t), T^*(a), V(t))$ of (2.6) remain positive and ultimately bounded for nonnegative initial dates and boundary conditions.*

As we know, the basic reproduction number plays an important role on the study of epidemiology and within-host pathogen dynamics. There is an infection-free equilibrium $U_0 = (T_0, 0, 0)$ with $T_0 = \frac{\Lambda_c}{m}$, if $E = 0$. Based on the method of [9], we define the within-host reproduction number by

$$R_{w0} = \frac{1}{c} \cdot \int_0^{+\infty} \delta(a)p(a)\sigma(a)kT_0 da,$$

where $\sigma(a) = e^{-\int_0^a m+\delta(r)dr}$ is the probability that an infected cell can survive to infection age a. Note that T_0 is the number of healthy cells at the beginning of the infection, k is the infection rate of cells. Then, $\sigma(a)kT_0$ is the average number of secondary cases by one virus which can survive to infection age a. Besides, $\frac{1}{c}\int_0^{+\infty} \delta(a)p(a)da$ represents the amount of viruses released by one virus during its survival period, where $\frac{1}{c}$ is the survival time of the virus. Therefore, R_{w0} represents the average number of virus released by all secondary infected cells by one virus during the survival period of the virus at the early stage of infection.

With help of the basic reproduction number, we now discuss the existence and stability of equilibria in (2.6). For the global stability of equilibria, we will take the Lyapunov function technique combined with the LaSalle invariance principle. Since the phase space is the infinite dimensional Banach space, according to Theorem 4.2 in [22, Chapter IV], the relative compactness of the orbit should be given first. Applying the method of Theorem 3.1 in [23] for the isolated system, we can obtain the relative compactness of the orbit and omit the proof. Based on this, we next construct suitable Lyapunov functions and prove the global stability.

For the case of $E = 0$, the system (2.6) has infection-free equilibrium $U_0 = (T_0, 0, 0)$ and infectious equilibrium $U_1 = (\overline{T}, \overline{T}^*(a), \overline{V})$, if $R_{w0} > 1$, where

$$\overline{T} = \frac{T_0}{R_{w0}}, \quad \overline{T}^*(a) = \sigma(a)\Lambda_c \left(1 - \frac{1}{R_{w0}}\right), \quad \overline{V} = \frac{m(R_{w0}-1)}{k}. \tag{3.1}$$

Theorem 3.2. *Assume $E = 0$ in the system (2.6). The infection-free equilibrium U_0 is globally asymptotically stable (GAS), if $R_{w0} < 1$, and whereas the infectious equilibrium U_1 is GAS, if $R_{w0} > 1$.*

Remark 3.1. Theorem 3.2 indicates that when there is no virus in the environment, i.e., $E = 0$, the cell infection depends on the basic reproduction number R_{w0}. When $R_{w0} < 1$, the virus and the infected cells will eventually be cleared. When $R_{w0} > 1$, the virus will eventually stabilize at a positive balance $\overline{V}$. Meanwhile, the healthy and infected cells eventually stabilize at the positive equilibrium levels $\overline{T}$ and $\overline{T}^*(a)$. The case of $E = 0$ can be viewed as that infected hosts are kept in quarantine or treatment. In order to clear the virus in the host, we can decrease the basic reproductive number R_{w0}, so that $R_{w0} < 1$ by enhancing the immunity and undergoing some sort of therapy (increasing$c$), or decreasing the infection rate of cells (k), or decreasing the amount of viruses released by an infected cell during its survival period ($N = \int_0^{+\infty} \delta(a)p(a)\sigma(a)da$). These can be shown in Figure 2 in the case of $E = 0$.

For the case of $E > 0$, if the system (2.6) has an equilibrium $U_2 = (\widetilde{T}(E), \widetilde{T}^*_E(a), \widetilde{V}(E))$, then it satisfies

$$\begin{cases} \Lambda_c - k\widetilde{V}(E)\widetilde{T}(E) - m\widetilde{T}(E) = 0, \\ \frac{\partial \widetilde{T}^*_E(a)}{\partial a} = -(m + \delta(a))\widetilde{T}^*_E(a), \\ g(E) + \int_0^{+\infty} \delta(a)p(a)\widetilde{T}^*_E(a)da - c\widetilde{V}(E) = 0, \\ \widetilde{T}^*_E(0) = k\widetilde{V}(E)\widetilde{T}(E). \end{cases} \tag{3.2}$$

Simplifying the above formula yields the equation

$$\widetilde{T}^2(E) - a_1\widetilde{T}(E) + a_2 = 0, \quad \text{where } a_1 = \frac{g(E)}{mN} + T_0\left(1 + \frac{1}{R_{w0}}\right),\ a_2 = \frac{T_0^2}{R_{w0}}.$$

The discriminant of the above equation satisfies

$$\Delta = a_1^2 - 4a_2 > 0.$$

Putting the forth equation into the first formula of (3.2), we obtain $\widetilde{T}^*_E(0) = m(T_0 - \widetilde{T}(E)) > 0$ if $\widetilde{T}(E) < T_0$. It follows that the larger root does not satisfy the positivity of $\widetilde{T}^*_E(0)$, and U_2 is a unique infectious equilibrium of the system (2.6), where

$$\begin{aligned} &\widetilde{T}(E) = \tfrac{1}{2}\left(a_1 - \sqrt{a_1^2 - 4a_2}\right), \quad \widetilde{T}^*_E(a) = m\sigma(a)(T_0 - \widetilde{T}(E)), \\ &\widetilde{V}(E) = \tfrac{1}{c}\left(g(E) + m(T_0 - \widetilde{T}(E))N\right). \end{aligned} \tag{3.3}$$

We have the following results.

Theorem 3.3. *For $E > 0$ is a constant. The unique infectious equilibrium $U_2 = (\widetilde{T}(E), \widetilde{T}^*_E(a), \widetilde{V}(E))$ is GAS. Furthermore,*

$$\lim_{E\to 0} U_2 = \begin{cases} U_0 = (T_0, 0, 0), & \text{for } R_{w0} \le 1, \\ U_1 = (\overline{T}, \overline{T}^*(a), \overline{V}), & \text{for } R_{w0} > 1. \end{cases}$$

Remark 3.2. The case of $E > 0$ shows that the infected hosts are exposed. In such case, the virus in the host cannot be extinct unless there is no viral environment. Meanwhile, healthy cell, infected cell and the virus eventually stabilize at the infectious equilibrium $U_2 = (\widetilde{T}(E), \widetilde{T}^*_E(a), \widetilde{V}(E))$, which are related to the level of environment contaminated E. Furthermore, the viral equilibrium level is an increases function of E, i.e.,

$$\frac{d}{dE}\widetilde{V}(E) = \frac{1}{c}\frac{d}{dE}g(E)\left(1 + \frac{\widetilde{T}(E)}{\sqrt{a_1^2 - 4a_2}}\right) > 0.$$

Moreover, the viral equilibrium level is a decreasing function of the clearance rate of virus c, an increasing function of the infection rate of cells k and the amount of virus released by a within-host infected cell during its survival period N respectively. This is can be shown in Figure 2.

Remark 3.3. Theorems 3.2 and 3.3 show that as the virus in the environment is gradually cleared. That is, $E \to 0$, the virus in the host will be gradually removed, when $R_{w0} < 1$; even if the virus in the environment is gradually removed, the virus in the host will eventually still stabilize at a positive balance $\overline{V}$, when $R_{w0} > 1$.

As time goes on, the virus in the host will be excreted and contaminate the environment after a period of time, and conversely increases the amount of viruses in the environment. When the amount of viruses in the environment reaches a certain level, more healthy hosts will be infected, so that the virus begins to spread among the hosts. Then, the disease will be prevail among hosts and the epidemic regular pattern expressed by the age structured SIE model (2.7).

3.2. Analysis of isolated slow system

We assume V is a constant in the slow system (2.7), which becomes into an isolated between-host system.

Note that the fast system (2.6) is similar to the slow system (2.7), some results of (2.7) are the same as that of (2.6), and we omit their proof. First, we give the positivity and boundedness of the solutions.

Theorem 3.4. *For the slow system* (2.7)*, the solutions remain positive and ultimately bounded for nonnegative initial dates and boundary conditions.*

We define the between-host reproduction number as

$$R_{b0} = \frac{1}{\gamma}\beta S_0 V \int_0^{+\infty} \theta(a)\pi(a)da,$$

where $\pi(a) = e^{-\int_0^a (\mu+\varphi(r))dr}$ is the probability that an infected individual can survive to infection age a. From our assumptions, we know that $S_0 = \frac{\Lambda_h}{\mu}$ is the

number of healthy individuals at the beginning of the epidemic; β represents the infection rate of hosts; $\frac{1}{\gamma}$ is the survival time of the virus; $V\int_0^{+\infty}\theta(a)\pi(a)da$ is the amount of an infected individual discharging virus into the environment. Therefore, R_{b0} indicates the number of secondary infected cases in which an infected individual can infect susceptible in their survival time at the early stage of infection.

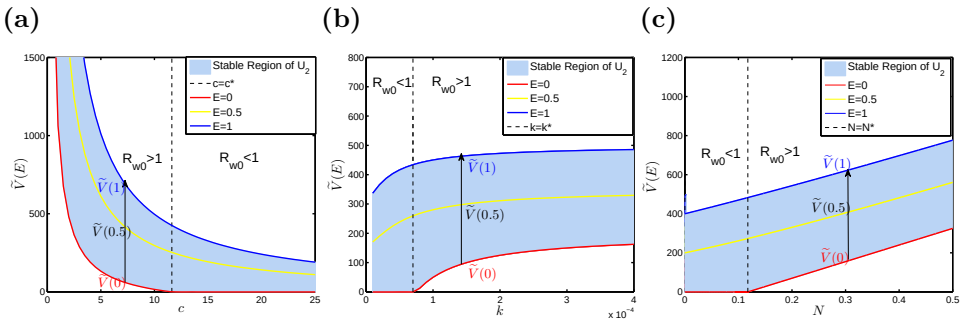

Figure 2. The monotonicity of the virus equilibria level $\widetilde{V}(E)$ as functions of the clearance rate of virus c in **(a)**, the infection rate of cells k in **(b)** and the amount of virus released by an infected cell during its survival period N in **(c)** respectively. It is easy to verify that $c = c^*$, $k = k^*$ and $N = N^*$ are equivalent to $R_{w0} = 1$ in **(a)**, **(b)** and **(c)**. The blue region is the stable region of U_2 for the case of $E \in (0, 1]$. When $E = 0$, the left red solid line, i.e., $c < c^*$ (corresponding $R_{w0} > 1$), is the stable region of U_1 and the right solid line, i.e., $c > c^*$ (corresponding $R_{w0} < 1$), is the stable region of U_0 in **(a)**. The illustrations of the red solid line in **(b)** and **(c)** are similar to **(a)**. For each figure, all other parameters are fixed, given by **(a)**: $m = 1.5 \times 10^{-2}$, $\Lambda_c = 8.5 \times 10^3$, $k = 1.5 \times 10^{-4}$, $w = 4 \times 10^3$, $N = 0.1368$; **(b)**: $m = 1.5 \times 10^{-2}$, $\Lambda_c = 5 \times 10^3$, $c = 10$, $w = 3 \times 10^3$, $N = 4$; **(c)**: $m = 1.5 \times 10^{-2}$, $\Lambda_c = 8.5 \times 10^3$, $c = 10$, $w = 4 \times 10^3$, $k = 1.5 \times 10^{-4}$.

Let $(S, I(a), E)$ denote an equilibrium of (2.7), which satisfies the following equations

$$\begin{cases} \Lambda_h - \beta ES - \mu S = 0, \\ \frac{\partial I(a)}{\partial a} = -(\mu + \varphi(a))I(a), \\ V\int_0^{+\infty}\theta(a)I(a)da(1-E) - \gamma E = 0, \\ I(0) = \beta ES. \end{cases} \tag{3.4}$$

After calculation, the disease-free equilibrium $W_0 = (S_0, 0, 0)$ always exists, and the unique endemic equilibrium $W_1 = (S_1, I_1(a), E_1)$ exists, if and only if $R_{b0} > 1$, where

$$S_1 = \frac{\Lambda_h}{\mu+\beta}\left(1 + \frac{\beta}{\mu R_{b0}}\right), \quad I_1(a) = \pi(a)\beta S_1 E_1, \quad E_1 = \frac{R_{b0}-1}{R_{b0} + \frac{\beta}{\mu}}. \tag{3.5}$$

Next, we consider the global stability of equilibria of (2.7).

Theorem 3.5. *The disease-free equilibrium W_0 is GAS, if $R_{b0} \leq 1$, and the endemic equilibrium W_1 is GAS, if $R_{b0} > 1$.*

Remark 3.4. In the within-host system, the case of $g(E) = 0$ means that the virus in the environment does not infect the cells in the host. In such case, the virus in the infected host will eventually be eradicated, and the disease caused by the virus will

eventually be eliminated, when $R_{w0} < 1$. In fact, R_{w0} measures the invasiveness of the virus to the healthy hosts. The virus can invade the hosts, if $R_{w0} > 1$.

Combining with Theorems 3.2 and 3.5, we can conclude that the disease-free equilibrium W_0 of (2.7) and the infectious equilibrium U_1 of (2.6) are GAS, if $R_{b0} < 1$ and $R_{w0} > 1$. This shows that even if the disease can be eliminated the virus still can survive in host. That is, the number of viruses in host is so low that the infected host does not infect the susceptible hosts. It happens because that although the transmitting capacity of the disease induced by virus is low, the invasive ability of the virus is so strong that it can survive in the infected host. It is even possible that the virus is gradually adapting to its hosts and becoming less dangerous. We summarize the stability of equilibria of isolated fast and slow systems in Table 2.

Table 2 Stability of equilibria.

$R_{b0} < 1$	W_0 GAS	U_0 GAS $R_{w0} < 1$	The diseases and virus will be eliminated.
		U_1 GAS $R_{w0} > 1$	The virus can survive, but the disease will be eliminated.
$R_{b0} > 1$	W_1 GAS	U_2 GAS	There is an endemic disease and the virus survival.

Remark 3.5. The between-host reproduction number R_{b0} is dependent on the virus equilibrium level V in the host. If $R_{b0} > 1$, then the virus in the infected host remains a positive equilibrium level $V > 0$, and the endemic equilibrium W_1 is GAS. This means that the virus in the environment has an increasing effect on the virus in the host, i.e.,

$$\frac{dE_1}{dV} = \frac{\mu(\mu+\beta)\beta S_0 \int_0^{+\infty} \theta(a)\pi(a)da}{\gamma(\mu R_{b0}+\beta)^2} > 0.$$

Theorem 3.3 shows that the virus always survives in the host no matter how strong the invasive ability of the virus R_{w0} is, and the equilibrium level is increased with respect of E. Thus, the endemic disease is dependent on the transmitting capacity of the disease R_{b0}.

In this subsection, we always assume that the amount of viruses in host is a constant. In fact, the equilibrium level of V is an increasing function of E, and the between-host reproduction number is also an increasing function of V. Therefore, it is necessary to investigate the coupled system.

3.3. Disease dynamics of the coupled system

In the above subsections, we assume E and V are independent constants and investigate the isolated fast and slow systems respectively. Note that $\widetilde{V}$ in (3.3) is an increasing function of E, and the solution $(T(t), T^*(t,a), V(t))$ of isolated fast system (2.6) has

$$\lim_{t\to\infty}(T(t), T^*(t,\tau), V(t)) = \begin{cases} U_0 = (T_0, 0, 0), & \text{for } E = 0, R_{w0} \le 1; \\ U_1 = (\overline{T}, \overline{T}^*(a), \overline{V}), & \text{for } E = 0, R_{w0} > 1; \\ U_2 = (\widetilde{T}(E), \widetilde{T}^*_E(a), \widetilde{V}(E)), & \text{for } E > 0. \end{cases}$$

Thus, since $E=0$ is the limit of $E>0$ ($E\to 0$), it only needs to consider the case of $E>0$. In this way, $U_2=(\widetilde{T}(E),\widetilde{T}^*_E(a),\widetilde{V}(E))$ is the unique infectious equilibrium of the fast system. When $E>0$, since the within-host dynamics is faster than the between-host dynamics, we can assume that the state of the within-host system has reached its equilibrium. Let $V(t)=\widetilde{V}(E(t))$. The system (2.7) can be rewritten as the following coupled slow system

$$\begin{cases} \dot{S}(t)=\Lambda_h-\beta E(t)S(t)-\mu S(t),\\ \frac{\partial I(t,a)}{\partial t}+\frac{\partial I(t,a)}{\partial a}=-(\mu+\varphi(a))I(t,a),\\ \dot{E}(t)=(1-E(t))\,\widetilde{V}(E(t))\int_0^{+\infty}\theta(a)I(t,a)da-\gamma E(t),\\ I(t,0)=\beta E(t)S(t),\\ S(0)=s_0,\quad I(0,a)=\xi(a),\quad E(0)=e_0. \end{cases} \tag{3.6}$$

Note that the between-host reproduction number R_{b0} is a linear increasing function of $\widetilde{V}(E)$, and the virus equilibrium level $\widetilde{V}(E)$ is an increasing function of E. Furthermore, we have the following limiting behavior of the $\widetilde{V}(E)$, as $E\to 0$:

$$\widetilde{V}(0)=\lim_{E\to 0}\widetilde{V}(E)=\begin{cases} 0, & \text{for } R_{w0}\le 1,\\ \frac{m(R_{w0}-1)}{k}, & \text{for } R_{w0}>1. \end{cases}$$

Thus, $R_{b0}\ge\hat{R}_{b0}$, where $\hat{R}_{b0}$ is defined as

$$\hat{R}_{b0}:=\frac{\beta S_0\widetilde{V}(0)}{\gamma}\int_0^{+\infty}\theta(a)\pi(a)da=\begin{cases} 0, & R_{w0}\le 1,\\ \frac{\beta S_0 m(R_{w0}-1)}{k\gamma}\int_0^{+\infty}\theta(a)\pi(a)da, & R_{w0}>1. \end{cases}$$

For the trivial case of $R_{w0}\le 1$ and $E(t)=0$, the virus in the infected host will eventually be cleared and the disease caused by the virus will eventually be eliminated. Therefore, in the following discussion, we always assume the basic reproduction number $R_{w0}>1$ or $E(t)>0$. In this case, the quantity $\widetilde{V}(0)=\frac{m(R_{w0}-1)}{k}$ represents the number of viruses within a host at the initial stage of environmental contamination. The term $\widetilde{V}(0)\int_0^{+\infty}\theta(a)\pi(a)da$ denotes the amount of viruses that an infected host discharges into the environment at the beginning of the infectious disease. S_0 is the number of healthy host at the beginning of the infectious disease. Therefore, $\hat{R}_{b0}$ indicates the number of secondary infected cases in which an infected host can infect susceptible in their survival time at the early stage of infection.

Remark 3.6. Note that the basic reproduction number R_{w0} is independent on E. If $R_{w0}<1$, both equilibria U_0 (for $E=0$) and U_2 (for $E>0$) may be GAS for the isolated fast system. Bistability may occur. We show this in Figure 6.

First, we consider the existence of equilibria of (3.6). Obviously, the coupled system (3.6) has a disease-free equilibrium $W_0(S_0,0,0)$ with $S_0=\frac{\Lambda_h}{\mu}$. Let $\widehat{W}=(\widehat{S},\widehat{I}(a),\widehat{E})$ denote the positive equilibrium of (3.6), which satisfies the following

equations

$$\begin{cases} \Lambda_h - \beta\widehat{E}\widehat{S} - \mu\widehat{S} = 0, \\ \frac{\partial \widehat{I}(a)}{\partial a} = -(\mu + \varphi(a))\widehat{I}(a), \\ (1-\widehat{E})\widetilde{V}(\widehat{E})\int_0^{+\infty}\theta(a)\widehat{I}(a)da - \gamma\widehat{E} = 0, \\ \widehat{I}(0) = \beta\widehat{E}\widehat{S}. \end{cases} \tag{3.7}$$

As discussed in the above subsection, we have

$$\widehat{S} = \frac{\mu S_0}{\beta\widehat{E}+\mu}, \quad \widehat{I}(a) = \beta\widehat{E}\widehat{S}\pi(a), \quad \widehat{E} = \frac{\widetilde{V}(\widehat{E})\int_0^{+\infty}\theta(a)\widehat{I}(a)da}{\widetilde{V}(\widehat{E})\int_0^{+\infty}\theta(a)\widehat{I}(a)da+\gamma}. \tag{3.8}$$

Obviously, $0 < \widehat{E} < 1$. Substituting $\widehat{S}$ and $\widehat{I}(a)$ into the third equation of (3.7), it follows that $\widehat{E}$ satisfies $H(\widehat{E}) = 0$, where

$$H(\widehat{E}) = F(\widehat{E}) - G(\widehat{E}), F(\widehat{E}) = (1-\widehat{E})\widetilde{V}(\widehat{E}), G(\widehat{E}) = \frac{\gamma(\beta\widehat{E}+\mu)}{\mu\beta S_0\int_0^{+\infty}\theta(a)\pi(a)da}. \tag{3.9}$$

It can be shown that H has the following properties

$$\begin{aligned} &H(0) = \widetilde{V}(0) - \frac{\gamma}{\beta S_0\int_0^{+\infty}\theta(a)\pi(a)da} = \widetilde{V}(0)\left(1 - \frac{1}{\hat{R}_{b0}}\right), \\ &H(1) = -\frac{\gamma(\beta+\mu)}{\mu\beta S_0\int_0^{+\infty}\theta(a)\pi(a)da} < 0, \\ &H'(E) = \frac{1-E}{c}\left(g'(E) - mN\widetilde{T}'(E)\right) - \widetilde{V}(\widehat{E}) - \frac{\gamma}{\mu S_0\int_0^{+\infty}\theta(a)\pi(a)da}. \end{aligned}$$

If $R_{w0} < 1$, then $\widetilde{V}(0) = 0$ and $H(0) < 0$. It is difficult to judge the sign of $H'(E)$, we continue to compute

$$H''(E) = \frac{1-E}{c}\left(g''(E) - mN\widetilde{T}''(E)\right) - \frac{2}{c}\left(g'(E) - mN\widetilde{T}'(E))\right).$$

Note that $\widetilde{T}'(E) < 0$ and $\widetilde{T}''(E) > 0$, it follows that $H''(E) < 0$, for all $0 < E \leq 1$. This shows that $H(E)$ is an upper convex function. Let $H_M = \max_{0\leq E\leq 1} H(E)$. Based on the reproduction number $\hat{R}_{b0}$, we have obtained the following results.

Theorem 3.6. *The existence of system* (3.6) *equilibria are as follows:*

(i) The system (3.6) *has a disease-free equilibrium* W_0.

(ii) If $R_{w0} < 1$, *then* $H(0) < 0$ *and* (3.6) *has two endemic equilibria* $\widehat{W}_1 = (\widehat{S}_1, \widehat{I}_1(a), \widehat{E}_1)$ *and* $\widehat{W}_2 = (\widehat{S}_2, \widehat{I}_2(a), \widehat{E}_2)$ *with* $\widehat{E}_1 < \widehat{E}_2$, *if* $H_M > 0$; (3.6) *has one endemic equilibrium, if* $H_M = 0$, *i.e.,* $\widehat{W}_1 = \widehat{W}_2$; (3.6) *has no endemic equilibrium, if* $H_M < 0$.

(iii) If $R_{w0} > 1$, *then* $\widetilde{V}(0) > 0$ *and the following results hold.*

(a)Assume $\hat{R}_{b0} < 1$. *The system* (3.6) *has two endemic equilibria* $\widehat{W}_1$ *and* $\widehat{W}_2$ *with* $\widehat{E}_1 < \widehat{E}_2$, *if* $H_M > 0$; (3.6) *has one endemic equilibrium, if* $H_M = 0$, *i.e.,* $\widehat{W}_1 = \widehat{W}_2$; (3.6) *has no endemic equilibrium, if* $H_M < 0$.

(b)Assume $\hat{R}_{b0} > 1$. *The system* (3.6) *has a unique equilibrium* $\widehat{W} = (\widehat{S}, \widehat{I}(a), \widehat{E})$.

Theorem 3.7. *The stability of system* (3.6) *equilibria are as follows:*

(i) The disease-free equilibrium W_0 *is locally asymptotically stable (LAS), if* $\hat{R}_{b0} < 1$*, and unstable, if* $\hat{R}_{b0} > 1$.

(ii) If (3.6) *has a unique endemic equilibrium* $\widehat{W}$*, then* $\widehat{W}$ *is LAS, when* $\frac{\gamma}{\mu+\beta\widehat{E}} \leq 1$.

(iii) If (3.6) *has two endemic equilibria* $\widehat{W}_1 = (\widehat{S}_1, \widehat{I}_1(a), \widehat{E}_1)$ *and* $\widehat{W}_2 = (\widehat{S}_2, \widehat{I}_2(a), \widehat{E}_2)$ *with* $\widehat{E}_1 < \widehat{E}_2$*, then* $\widehat{W}_1$ *is unstable, and* $\widehat{W}_2$ *is LAS, when* $\frac{\gamma}{\mu+\beta\widehat{E}} \leq 1$.

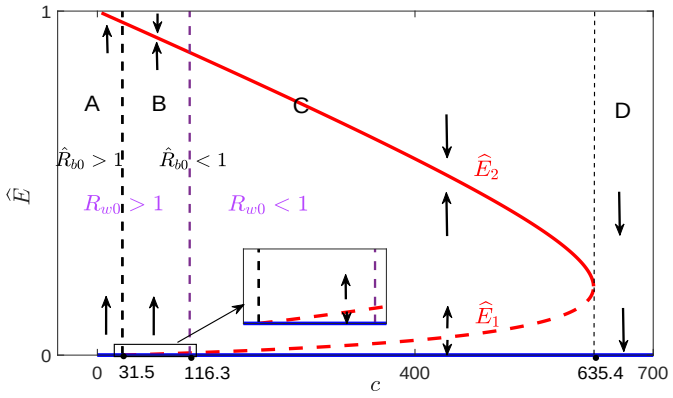

Figure 3. The backward bifurcation and stability of the multiple endemic equilibria. It plots equilibrium $\widehat{E}$ as a function of the clearance rate of virus c. The black and purple dotted lines, i.e., $c = 31.5$ and $c = 116.3$, represent $\hat{R}_{b0} = 1$ and $R_{w0} = 1$ respectively. These dotted lines divide the plane into four regions A, B, C and D. There is one stable endemic equilibrium in region A, two endemic equilibria, where one is stable the other is unstable in regions B and C, but there is no endemic equilibrium in region D. For $\hat{R}_{b0} < 1$, there may be two branches with the solid and dashed branches representing the stable and unstable interior equilibria respectively. The vertical arrows indicate the directions of solutions as time tends to infinity. Depending on the initial conditions, $E(t)$ will converge to either 0 or $\widehat{E}$ on the solid curve.

Remark 3.7. If $\hat{R}_{b0} < 1$, $\frac{\gamma}{\mu+\beta\widehat{E}} \leq 1$ and $H_M > 0$, then both equilibria W_0 and W_2 are LAS. In such case, bistability occurs. We show this in Figures 5 and 6.

Theorems 3.6 and 3.7 show that there is a backward bifurcation. For $\hat{R}_{b0} < 1$ and $\frac{\gamma}{\mu+\beta\widehat{E}} \leq 1$, the system has two endemic equilibria for $H_M > 0$, where one is stable and the other is unstable, and a unique stable endemic equilibrium for $H_M = 0$. Similarly, for $R_{w0} < 1$ and $\frac{\gamma}{\mu+\beta\widehat{E}} \leq 1$, the above conclusions are obtained. This can be shown in Figure 3. Besides, in this figure, there are four different stability cases, which will be simulated respectively. Compared with results in [7, 14], the backward bifurcation can occur not only at the case of $R_{w0} > 1$ and $\hat{R}_{b0} < 1$, but also $R_{w0} < 1$ and $\hat{R}_{b0} = 0$.

For some infection diseases with multiscale, it is difficult to obtain the experiment data characterized the biological relationship between the transmissibility and viral kinetics. This leads to many obstacles to translate the theory result of multiscale models into practical policies. In order to get relevant data by tailored experiment, it is better to provide a preliminary understanding for the infectious disease mechanism. This can be realized by rigorous analytical and numerical analysis

for the established models with multiscale. Then, we give a numerical simulations for our model to provide some help design testable functional hypotheses.

Except c, other parameters are taken as $g(E) = 4 \times 10^5 E$, $m = 1.5 \times 10^{-2}$, $k = 1.5 \times 10^{-3}$, $\Lambda_c = 8.5 \times 10^3$, $N = 0.1368$, $\Lambda_h = 70$, $\beta = 0.1$, $\mu = 7 \times 10^{-3}$, $\gamma = 1.5 \times 10^{-2}$, $\theta(a) = 1.5 \times 10^{-8}$ and $\varphi(a) = \frac{0.045}{1+5e^{-0.05a}}$. After calculation, we have $R_{w0} = 1$ and $\hat{R}_{b0} = 1$ that are equivalent to $c = 31.5$ and $c = 116.3$, and thresholds R_{w0} and $\hat{R}_{b0}$ are a decreasing function of c. As shown in Figure 3, increasing the clearance rate of c from 0 to 635.4 yields that the coupled system has at least one positive equilibrium. Once the value of c is above 635.4 the positive equilibria will disappear, leaving only the disease-free equilibrium. Next, we show the dynamics, which is dependent on the clearance rate c in the four regions of Figure 3.

In region A, i.e., $0 < c < 31.5$, take $c = 20$ as an example. The calculation yields that $R_{w0} = 5.814 > 1$, $\hat{R}_{b0} = 1.7889 > 1$, $\widehat{E} = 0.95$. Therefore, we know $\frac{\gamma}{\mu+\beta\widehat{E}} = 0.1406 < 1$. Figure 4 shows that the endemic equilibrium $\widehat{W}$ is LAS, and the disease-free equilibrium W_0 is unstable for system (3.6). In such case, the solution behavior is not dependent on the initial conditions.

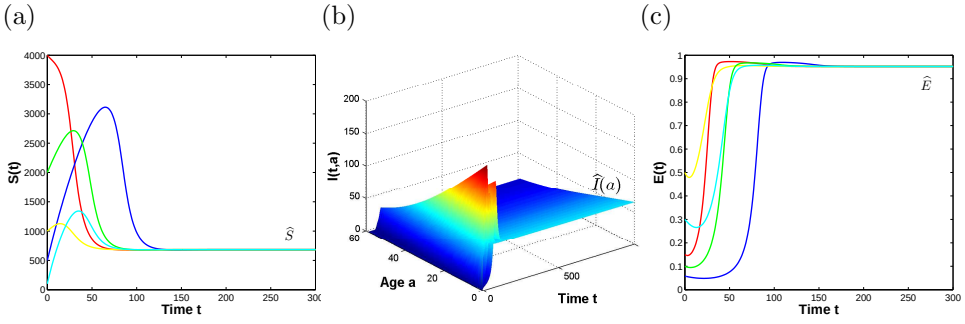

Figure 4. (a) Time series of $S(t)$; (b) The age distribution of $I(t, a)$; (c) Time series of $E(t)$. It shows that solutions will converge to an endemic equilibrium $\widehat{W}$.

In region B, i.e., $31.5 < c < 116.3$, take $c = 100$ as an example. By calculation, we obtain $R_{w0} = 1.163 > 1$ and $\hat{R}_{b0} = 0.0605 < 1$. The numerical simulations given in Figure 5 show that the disease-free equilibrium $W_0 = (10000, 0, 0)$ and an endemic equilibrium $\widehat{W}_2$ are LAS for system (3.6). In such case, the solution behavior is dependent on the initial conditions. For example in Figure 5 (c), in order to eliminate the disease we can control the initial level of $E(t)$ below a threshold 0.059 ($E_0 < 0.059$). However, if the initial level of $E(t)$ is above the threshold 0.059 ($E_0 > 0.059$), the disease can develop an endemic disease.

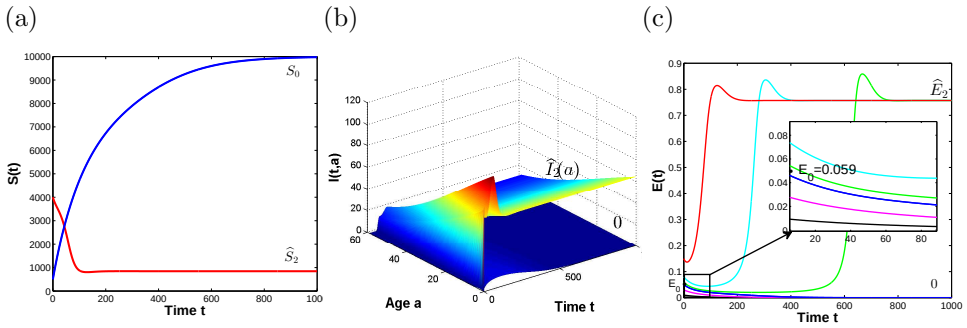

Figure 5. (a) Time series of $S(t)$; (b) The age distribution of $I(t,a)$; (c) Time series of $E(t)$. It shows that solutions will converge to either the infection-free equilibrium W_0 or the positive equilibrium $\widehat{W}_2$, depending on initial conditions.

In region C, i.e., $116.3 < c < 635.4$, take $c = 200$ as an example. By calculation, we obtain $R_{w0} = 0.5814 < 1$ and $\hat{R}_{b0} = 0$. Meanwhile, bistability occurs and the solution behavior is dependent on the initial conditions. Combined with different initial conditions, some biological meanings can be similarly given as in the above case.

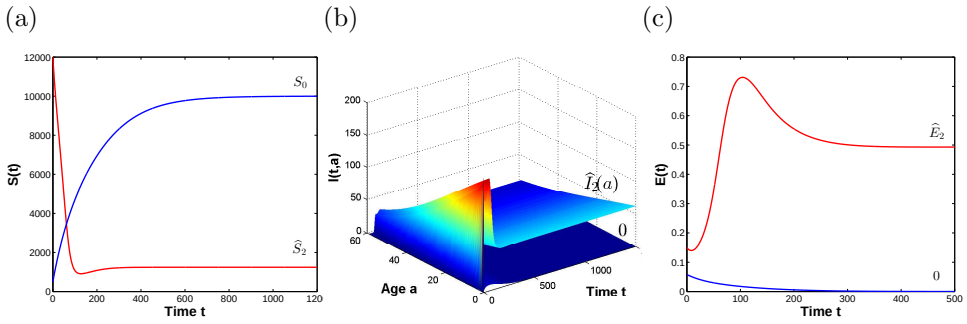

Figure 6. (a) Time series of $S(t)$; (b) The age distribution of $I(t,a)$; (c) Time series of $E(t)$. It shows that solutions will converge to either the infection-free equilibrium W_0 or the endemic equilibrium $\widehat{W}_2$, depending on initial conditions.

In region D, i.e., $635.4 < c$, take $c = 650$ as an example. By calculation, we obtain $R_{w0} = 0.1789 < 1$ and $\hat{R}_{b0} = 0$ in Figure 7. In such case, there is no endemic equilibrium, and the unique infection-free equilibrium W_0 is stable.

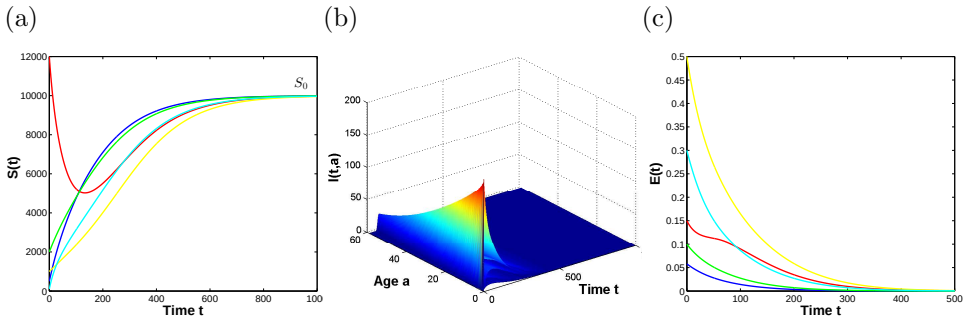

Figure 7. (a) Time series of $S(t)$; (b) The age distribution of $I(t,a)$; (c) Time series of $E(t)$. It shows that solutions will converge to the infection-free equilibrium W_0.

4. Discussion

In order to consider the individual difference, we propose an infection-age structured epidemic model for coupling within- and between-host dynamics in environmentally-driven infectious diseases. The model is described by a mixed system of ordinary and partial differential equations, which is divided into a fast time and a slow time systems with age structure by using the idea of perturbation theory. The separate method in [8] is extended to the age structured model.

For the isolated fast and slow systems, combined with the basic reproduction numbers R_{w0} and R_{b0}, we give the complete global dynamics by using the linearization method and Lyapunov function respectively. However, for the coupled system, it is difficult to obtain the global results. The analysis shows that the existence of the positive equilibria has many cases. When the system has two positive equilibria, a backward bifurcation can occur. This happens because that the disease is driven by the virus contaminated environment which links the within-host system to the between-host variable. Besides, the positive equilibrium U_2 of the fast system is always GAS whether the within-host reproduction number is greater or less than 1. In the coupled system, the existence of equilibria is dependent on the limit equilibrium $\widetilde{V}(E)$, which may be a nonlinear function of E. Thus, there may be multiple positive equilibria and backward bifurcation. A question we want to know whether the unique positive equilibrium of the coupled system is GAS. This remains a question in the future.

The coupled system we analysised in subsection 3.3 is not the full system. It does not tell us the role of the important linked function $g(E)$ on the dynamics of the full system. Besides, we consider only a linear representation of $g(E)$. In fact, there are different forms of $g(E)$ to describe the linked relation between the within- and between-host disease driven by contaminated environment. For example, authors in [2] proposed three functional forms to express transmission rates based on viral load, including linear, logical and Michaelis-Menten functions, and showed that there are significant differences between the three forms. Therefore, it is an interesting but challenging problem to consider the different forms in mathematical analysis and numerical simulation for the full system, and we leave it for future investigation.

Our results presented in this paper extend those in [7, 14]. If the parameters related to infection age are constants, that is, $\delta(a) = \delta$, $p(a) = p$ and $\varphi(a) = \varphi$,

$\theta(a)=\theta$, the system (2.1) is simplified to the system of [7]

$$\begin{cases} \dot{T}(t)=\Lambda_c-kV(t)T(t)-mT(t), \\ \dot{T^*}(t)=kV(t)T(t)-(m+\delta)T^*(t), \\ \dot{V}(t)=g(E)+\delta pT^*(t)-cV(t), \\ S'(t)=\Lambda_h-\beta E(t)S(t)-\mu S(t), \\ I'(t)=\beta E(t)S(t)-(\mu+\varphi)I(t), \\ E'(t)=\big(1-E(t)\big)V(t)\theta I(t)-\gamma E(t). \end{cases} \tag{4.1}$$

The results and some important thresholds of [7] can be directly obtain from this work. However, the existence and stability of positive equilibria for the case of $R_{w0}<1$ in [7] are not studied. This work provides complementary results as follows.

Theorem 4.1. *If $R_{w0}<1$, then $H(0)<0$ and (4.1) has two equilibria $\widehat{W}_1$ and $\widehat{W}_2$, if $H_M>0$; (4.1) has one positive equilibrium, if $H_M=0$, i.e., $\widehat{W}_1=\widehat{W}_2$; (4.1) has no positive equilibrium, if $H_M<0$.*

Theorem 4.2. *The disease-free equilibrium W_0 is LAS, if $\hat{R}_{b0}\le 1$, and unstable, if $\hat{R}_{b0}>1$. If (4.1) has two positive equilibria $\widehat{W}_1$ and $\widehat{W}_2$, then $\widehat{W}_1$ is unstable and $\widehat{W}_2$ is LAS, when $\frac{\gamma}{\mu+\beta\widehat{E}}\le 1$.*

If the difference of the cell is not taken into account, i.e., $\delta(a)=\delta$, $p(a)=p$, the system (2.1) is simplified to

$$\begin{cases} \dot{T}(t)=\Lambda_c-kV(t)T(t)-mT(t), \\ \dot{T^*}(t)=kV(t)T(t)-(m+\delta)T^*(t), \\ \dot{V}(t)=g(E)+\delta pT^*(t)-cV(t), \\ \dot{S}(t)=\Lambda_h-\beta E(t)S(t)-\mu S(t), \\ \frac{\partial I(t,a)}{\partial t}+\frac{\partial I(t,a)}{\partial a}=-(\mu+\varphi(a))I(t,a), \\ \dot{E}(t)=(1-E(t))\,V(t)\int_0^{+\infty}\theta(a)I(t,a)da-\gamma E(t). \end{cases}$$

In this case, it has been studied in [14]. However, our conclusions also can generalize conclusions of [14].

Furthermore, the model can be reduced to a stage-structured model by introducing the insidious periods of between-host and within-host, τ_1 and τ_2 respectively. That is, the total exposed and infected cells are $T_1^*(t)=\int_0^{\tau_1}T^*(t,a)da$ and $T_2^*(t)=\int_{\tau_1}^{+\infty}T^*(t,a)da$. The exposed and infected hosts are $I_1(t)=\int_0^{\tau_2}I(t,a)da$ and $I_2(t)=\int_{\tau_2}^{+\infty}I(t,a)da$, which can be defined by assuming these functions as

$$\delta(a)=\begin{cases} 0, & 0<a<\tau_1, \\ \delta, & a>\tau_1, \end{cases} \qquad p(a)=\begin{cases} 0, & 0<a<\tau_1, \\ p, & a>\tau_1, \end{cases}$$

and

$$\varphi(a)=\begin{cases}0, & 0<a<\tau_2,\\ \varphi, & a>\tau_2,\end{cases}\qquad \theta(a)=\begin{cases}0, & 0<a<\tau_2,\\ \theta, & a>\tau_2.\end{cases}$$

Combined with (2.6) and (2.7), the full system is simplified to the following system

$$\begin{cases}\dot{T}(t)=\Lambda_c-kV(t)T(t)-mT(t),\\ \dot{T}_1^*(t)=-mT_1^*(t)+kV(t)T(t)-kV(t-\tau_1)T(t-\tau_1)e^{-m\tau_1},\\ \dot{T}_2^*(t)=-(m+\delta)T_2^*(t)+kV(t-\tau_1)T(t-\tau_1)e^{-m\tau_1},\\ \dot{V}(t)=g(E)+\delta pT_2^*(t)-cV(t),\\ \dot{S}(t)=\Lambda_h-\beta E(t)S(t)-\mu S(t),\\ \dot{I}_1(t)=-\mu I_1(t)+\beta E(t)S(t)-\beta E(t-\tau_2)S(t-\tau_2)e^{-\mu\tau_2},\\ \dot{I}_2(t)=-(\mu+\varphi)I_2(t)+\beta E(t-\tau_2)S(t-\tau_2)e^{-\mu\tau_2},\\ \dot{E}(t)=(1-E(t))V(t)\theta I_2(t)-\gamma E(t).\end{cases}\tag{4.2}$$

We claim that the stage-structured model is not a special case of the age structured model, which are not equivalent. In fact, Theorem 3.3 shows that the fast system has a unique positive equilibrium, which is GAS, when $E>0$. However, a numerical simulation implies that the equilibrium of the fast stage-structured model is unstable (see Figure 8). Note that the $T_1^*(t)$ equation is decoupled from the equations of $T(t)$, $T_2^*(t)$ and $V(t)$. For the fast system, we only need to consider the three equations for $T(t)$, $T_2^*(t)$ and $V(t)$. The parameters can be taken as $g(E)=1.5$, $m=0.3$, $k=2.4\times10^{-5}$, $\Lambda_c=9\times10^3$, $c=2.1$, $\delta=0.03$ and $p=400$. The numerical simulation given in Figure 8 shows that the solutions with initial values $(751, 8520, 487000)$ are periodic oscillatory. As we know, the dynamics of (4.2) remains a challenging problem.

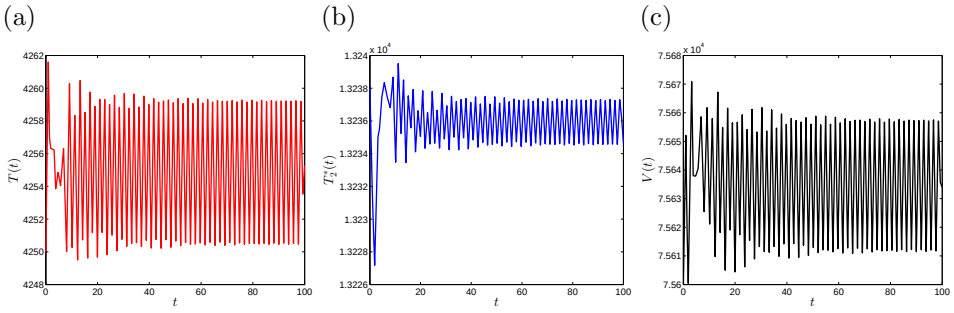

Figure 8. The periodic oscillatory of the solutions of fast stage-structured model with $\tau_1=1.9$. The other parameters has been taken as above: (a) Time series of $T(t)$; (b) Time series of $T_2^*(t)$; (c) Time series of $V(t)$.

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Appendix

Proof of Theorem 3.1. Suppose it is not true, then there will be a minimum time t_1, so that $T(t_1) = 0$, $\dot{T}(t_1) \leq 0$ and $T(t) > 0$, when $0 \leq t \leq t_1$. It is in contradiction with $\dot{T}(t_1) = \Lambda_c > 0$. Hence, $T(t) > 0$ for all $t \geq 0$.

From (2.2), $T^*(t, a)$ remains positive for nonnegative initial dates and boundary conditions. Putting $T^*(t, a)$ in (2.2) into $\dot{V}(t)$, we have

$$\dot{V}(t) = g(E) + \int_0^t kV(a)T(a)e^{-\int_0^{t-a}[m+\delta(r)]dr}\delta(t-a)p(t-a)da$$
$$+ \int_t^\infty \eta(a-t)e^{-\int_0^t[m+\delta(r+a-t)]dr}\delta(a)p(a)da - cV(t).$$

If there exists minimum time t_1, so that $V(t) > 0$ on $t \in [0, t_1)$ and $V(t_1) = 0$. Then, $\dot{V}(t_1) \leq 0$. However, according to the above equation, we derive

$$\dot{V}(t_1) = g(E) + \int_0^{t_1} kV(a)T(a)e^{-\int_0^{t_1-a}[m+\delta(r)]dr}\delta(t_1-a)p(t_1-a)da$$
$$+ \int_{t_1}^\infty \eta(a-t_1)e^{-\int_0^{t_1}[m+\delta(r+a-t_1)]dr}\delta(a)p(a)da > 0.$$

This gives a contradiction. Hence, $V(t) > 0$, for all $t \geq 0$.

Next, we prove that the solution of (2.6) is bounded. Let $W(t) = T(t) + \int_0^{+\infty} T^*(t, a)da$. It follows that

$$\dot{W}(t) = \Lambda_c - mT(t) - \int_0^{+\infty}(m + \delta(a))T^*(t, a)da \leq \Lambda_c - mW(t).$$

Therefore, $\limsup_{t\to\infty} W(t) \leq \frac{\Lambda_c}{m}$ and $T^*(t, a) < \frac{\Lambda_c}{m}$. Additionally,

$$\dot{V}(t) < g(E) + \tfrac{\Lambda_c}{m}\int_0^{+\infty}\delta(a)p(a)da - cV(t) = -cV(t) + A,$$

where $A = g(E) + \frac{\Lambda_c}{m}\int_0^{+\infty}\delta(a)p(a)da$. The assumption of $g(E)$ shows that it is bounded, if E is bounded. Therefore, $\limsup_{t\to\infty} V(t) \leq \frac{A}{c}$. This completes the proof. □

Proof of Theorem 3.2. First, we consider the LAS of the infection-free equilibrium U_0. Transmitting U_0 to the original point and linearizing (2.6) at (0, 0, 0) yields

$$\begin{cases} \dot{T(t)} = -kT_0V(t) - mT(t), \\ \frac{\partial T^*(t,a)}{\partial a} + \frac{\partial T^*(t,a)}{\partial t} = -(m + \delta(a))T^*(t, a), \\ \dot{V(t)} = \int_0^{+\infty}\delta(a)p(a)T^*(t, a)da - cV(t), \\ T^*(t, 0) = kT_0V(t). \end{cases} \tag{A.1}$$

Suppose $T(t) = c_1e^{\lambda t}, V(t) = c_2e^{\lambda t}, T^*(t, a) = c_3(a)e^{\lambda t}$ are solutions of (A.1). We obtain

$$\begin{pmatrix} \lambda + m & 0 & 1 \\ 0 & \lambda + c - \int_0^{+\infty}\delta(a)p(a)\sigma(a)e^{-\lambda a}da \\ 0 & -kT_0 & 1 \end{pmatrix}\begin{pmatrix} c_1 \\ c_2 \\ c_3(0) \end{pmatrix} = 0.$$

Therefore, we get the characteristic equation at U_0

$$(\lambda+m)\left(\lambda+c-kT_0\int_0^{+\infty}\delta(a)p(a)\sigma(a)e^{-\lambda a}da\right)=0. \tag{A.2}$$

One root of (A.2) is $\lambda=-m$, and the other satisfies $\lambda+c-kT_0\int_0^{+\infty}\delta(a)p(a)\sigma(a)e^{-\lambda a}da=0$. Furthermore, we have

$$\frac{kT_0\int_0^{+\infty}\delta(a)p(a)\sigma(a)e^{-\lambda a}da}{\lambda+c}=1. \tag{A.3}$$

To continue, (A.3) can be transformed into the following form

$$\lambda=\frac{kT_0}{R_{w0}}\int_0^{+\infty}\delta(a)p(a)\sigma(a)(R_{w0}e^{-\lambda a}-1)da.$$

Suppose $\lambda=u+iv$ is a root of the above equation. Therefore, the real part of λ is

$$u\le\tfrac{kT_0}{R_{w0}}\int_0^{+\infty}\delta(a)p(a)\sigma(a)(R_{w0}e^{-ua}-1)da.$$

If $R_{w0}<1$, then $R_{w0}e^{-ua}-1<0$ and all roots of characteristic equation have negative real parts. Accordingly, the equilibrium U_0 is LAS, if $R_{w0}<1$.

To prove that $U_0=(T_0,0,0)$ is GAS, we introduce a Lyapunov function

$$L_1(t)=T(t)-T_0-T_0\ln\frac{T(t)}{T_0}+\int_0^{+\infty}K_1(a)T^*(t,a)da+\frac{kT_0}{c}V(t), \tag{A.4}$$

where $K_1(a)=\frac{kT_0}{c}\int_a^{+\infty}\delta(\theta)p(\theta)e^{-\int_a^\theta(m+\delta(r))dr}d\theta$. A direct calculation shows that $K_1'(a)=-\frac{kT_0}{c}\delta(a)p(a)+(m+\delta(a))K_1(a)$ and $K_1(0)=R_{w0}$. Taking the derivative of $L_1(t)$ along (A.4), we obtain

$$\begin{aligned}\dot L_1(t)=&-\tfrac{m(T(t)-T_0)^2}{T(t)}-kT(t)V(t)+kT_0V(t)\\&-\int_0^{+\infty}K_1(a)\left(\big(m+\delta(a)\big)T^*(t,a)+\tfrac{\partial T^*(t,a)}{\partial a}\right)da\\&+\tfrac{kT_0}{c}\int_0^{+\infty}\delta(a)p(a)T^*(t,a)da-kT_0V(t)\\=&-\tfrac{m(T(t)-T_0)^2}{T(t)}-kT(t)V(t)-K_1(a)T^*(t,a)\Big|_{a=0}^{a=\infty}+\int_0^{+\infty}K_1'(a)T^*(t,a)da\\&+\int_0^{+\infty}\big(\tfrac{kT_0}{c}\delta(a)p(a)-K_1(a)\big(m+\delta(a)\big)\big)\,T^*(t,a)da\\=&-\tfrac{m(T(t)-T_0)^2}{T(t)}+kV(t)T(t)(R_{w0}-1).\end{aligned} \tag{A.5}$$

When $R_{w0}<1$, we have $\frac{dL_1(t)}{dt}\le 0$. Furthermore, the equality $\frac{dL_1(t)}{dt}=0$ holds, if and only if $T(t)=T_0,\ T^*(t,a)=0,\ V(t)=0$. Hence, U_0 is GAS, if $R_{w0}<1$.

Next, we consider the LAS of the infectious equilibrium $U_1=(\overline{T},\overline{T}^*(a),\overline{V})$. First, transmitting U_1 to the original point and linearizing (2.6) at (0, 0, 0). Second, we get the characteristic equation at U_1

$$(\lambda+m+k\overline{V})\left(\frac{\lambda}{c}+1\right)=(\lambda+m)\frac{\int_0^{+\infty}\delta(a)p(a)\sigma(a)e^{-\lambda a}da}{\int_0^{+\infty}\delta(a)p(a)\sigma(a)da}. \tag{A.6}$$

It is easy to see that the modulus of $\lambda + m + k\overline{V}$ is larger than the modulus of $\lambda + m$, the modulus of $\frac{\int_0^{+\infty} \delta(a)p(a)\sigma(a)e^{-\lambda a}da}{\int_0^{+\infty} \delta(a)p(a)\sigma(a)da}$ is smaller than 1 and the modulus of $\frac{\lambda}{c} + 1$ is greater than 1. Therefore, the modulus of left hand side is greater than the modulus of the right hand side, when $R_{w0} > 1$, this is a contradiction. In a word, the equilibrium $U_1 = (\overline{T}, \overline{T}^*(a), \overline{V})$ is LAS, if $R_{w0} > 1$.

To prove the GAS of the equilibrium U_1, we introduce the other Lyapunov function

$$\begin{aligned} L_2(t) = T(t) - \overline{T} - \overline{T}\ln\tfrac{T(t)}{\overline{T}} + \tfrac{1}{N}\int_0^{\infty} K_2(a)\overline{T}^*(a)\left(\tfrac{T^*(t,a)}{\overline{T}^*(a)} - 1 - \ln\tfrac{T^*(t,a)}{\overline{T}^*(a)}\right)da \\ + \tfrac{1}{N}\left(V(t) - \overline{V} - \overline{V}\ln\tfrac{V(t)}{\overline{V}}\right), \end{aligned} \tag{A.7}$$

where $K_2(a) = \int_a^{+\infty} \delta(\theta)p(\theta)e^{-\int_a^{\theta}(m+\delta(r))dr}d\theta$. Clearly $K_2(0) = \int_0^{+\infty} \delta(a)p(a)\sigma(a)da = N$. By using $\Lambda_c = k\overline{VT} + m\overline{T}$ and $\overline{T} = \frac{c}{kN}$, computing the derivative of $L_2(t)$ yields that

$$\begin{aligned} \dot{L}_2(t) = &-\tfrac{m}{T(t)}\big(T(t) - \overline{T}\big)^2 + k\overline{VT} - kV(t)T(t) - k\overline{VT}\,\tfrac{\overline{T}}{T(t)} \\ &- \tfrac{1}{N}\int_0^{\infty} K_2(a)\left(1 - \tfrac{\overline{T}^*(a)}{T^*(t,a)}\right)\tfrac{\partial T^*(t,a)}{\partial a}da \\ &- \tfrac{1}{N}\int_0^{\infty} K_2(a)\big(m + \delta(a)\big)T^*(t,a)\left(1 - \tfrac{\overline{T}^*(a)}{T^*(t,a)}\right)da \\ &+ \tfrac{1}{N}\int_0^{\infty} \delta(a)p(a)T^*(t,a)da - \tfrac{\overline{V}}{NV(t)}\int_0^{\infty} \delta(a)p(a)T^*(t,a)da + \tfrac{c\overline{V}}{N}. \end{aligned} \tag{A.8}$$

It is easy to compute that

$$\begin{aligned} \tfrac{d}{da}\left(\tfrac{T^*(t,a)}{\overline{T}^*(a)} - 1 - \ln\tfrac{T^*(t,a)}{\overline{T}^*(a)}\right) = \tfrac{1}{\overline{T}^*(a)}\left(1 - \tfrac{\overline{T}^*(a)}{T^*(t,a)}\right)\tfrac{\partial}{\partial a}T^*(t,a) \\ + \left(1 - \tfrac{\overline{T}^*(a)}{T^*(t,a)}\right)\tfrac{(m+\delta(a))T^*(t,a)}{\overline{T}^*(a)}. \end{aligned}$$

Hence,

$$\begin{aligned} \left(1 - \tfrac{\overline{T}^*(a)}{T^*(t,a)}\right)\tfrac{\partial T^*(t,a)}{\partial a} = \overline{T}^*(a)\tfrac{d}{da}\left(\tfrac{T^*(t,a)}{\overline{T}^*(a)} - 1 - \ln\tfrac{T^*(t,a)}{\overline{T}^*(a)}\right) \\ + (m + \delta(a))\left(\overline{T}^*(a) - T^*(t,a)\right). \end{aligned}$$

Then, using integration by parts, it follows that

$$\begin{aligned} &\int_0^{\infty} K_2(a)\left(1 - \tfrac{\overline{T}^*(a)}{T^*(t,a)}\right)\tfrac{\partial T^*(t,a)}{\partial a}da \\ &= K_2(a)\overline{T}^*(a)\left(\tfrac{T^*(t,a)}{\overline{T}^*(a)} - 1 - \ln\tfrac{T^*(t,a)}{\overline{T}^*(a)}\right)\Big|_{a=0}^{a=\infty} \\ &\quad - \int_0^{\infty}\left(\tfrac{T^*(t,a)}{\overline{T}^*(a)} - 1 - \ln\tfrac{T^*(t,a)}{\overline{T}^*(a)}\right)\left(K_2'(a)\overline{T}^*(a) + K_2(a)\tfrac{d}{da}\overline{T}^*(a)\right)da \\ &\quad + \int_0^{\infty} K_2(a)\left((m + \delta(a))\overline{T}^*(a) - (m + \delta(a))T^*(t,a)\right)da. \end{aligned} \tag{A.9}$$

Note that

$$K_2(0)\overline{T}^*(0)\left(\tfrac{T^*(t,0)}{\overline{T}^*(0)} - 1 - \ln\tfrac{T^*(t,0)}{\overline{T}^*(0)}\right) = Nk\overline{VT}\left(\tfrac{T(t)V(t)}{\overline{TV}} - 1 - \ln\tfrac{T(t)V(t)}{\overline{TV}}\right). \tag{A.10}$$

Putting it into $(A.9)$, it follows from $(A.3)$ that

$$\begin{aligned}
&\int_0^\infty K_2(a)\left(1-\frac{\overline{T}^*(a)}{T^*(t,a)}\right)\frac{\partial T^*(t,a)}{\partial a}da\\
&=K_2(a)\overline{T}^*(a)\left(\frac{T^*(t,a)}{\overline{T}^*(a)}-1-\ln\frac{T^*(t,a)}{\overline{T}^*(a)}\right)\Big|_{a=\infty}-Nk\overline{VT}\left(\frac{T(t)V(t)}{\overline{TV}}-1-\ln\frac{T(t)V(t)}{\overline{TV}}\right)\\
&\quad+\int_0^\infty\delta(a)p(a)\overline{T}^*(a)\left(\frac{T^*(t,a)}{\overline{T}^*(a)}-1-\ln\frac{T^*(t,a)}{\overline{T}^*(a)}\right)da\\
&\quad+\int_0^\infty K(a)\left(m+\delta(a)\right)\left(\overline{T}^*(a)-T^*(t,a)\right)da.
\end{aligned}$$

Hence,

$$\begin{aligned}
&\int_0^\infty K_2(a)\left(1-\frac{\overline{T}^*(a)}{T^*(t,a)}\right)\frac{\partial T^*(t,a)}{\partial a}da+\int_0^\infty K_2(a)(m+\delta(a))T^*(t,a)\left(1-\frac{\overline{T}^*(a)}{T^*(t,a)}\right)da\\
&=K_2(a)\overline{T}^*(a)\left(\frac{T^*(t,a)}{\overline{T}^*(a)}-1-\ln\frac{T^*(t,a)}{\overline{T}^*(a)}\right)\Big|_{a=\infty}\\
&\quad-NkV(t)T(t)+Nk\overline{TV}+Nk\overline{TV}\ln\frac{T(t)V(t)}{\overline{TV}}\\
&\quad+\int_0^\infty\delta(a)p(a)\overline{T}^*(a)\left(\frac{T^*(t,a)}{\overline{T}^*(a)}-1-\ln\frac{T^*(t,a)}{\overline{T}^*(a)}\right)da.
\end{aligned}$$

Since $\frac{c\overline{V}}{N}=\frac{1}{N}\int_0^\infty\delta(a)p(a)\overline{T}^*(a)da$, we have

$$\begin{aligned}
\frac{dL_2(t)}{dt}&=-\frac{m}{T(t)}(T(t)-\overline{T})^2-\frac{1}{N}K_2(a)\overline{T}^*(a)\left(\frac{T^*(t,a)}{\overline{T}^*(a)}-1-\ln\frac{T^*(t,a)}{\overline{T}^*(a)}\right)\Big|_{a=\infty}\\
&\quad+\frac{1}{N}\int_0^\infty\delta(a)p(a)\overline{T}^*(a)\left(1-\frac{\overline{T}}{T(t)}+\ln\frac{\overline{VT}}{V(t)T(t)}\right)da\\
&\quad+\frac{1}{N}\int_0^\infty\delta(a)p(a)\overline{T}^*(a)\left(1-\frac{\overline{V}}{V(t)}\frac{T^*(t,a)}{\overline{T}^*(a)}+\ln\frac{T^*(t,a)}{\overline{T}^*(a)}\right)da.
\end{aligned}\tag{A.11}$$

Note that $\ln\frac{\overline{VT}}{V(t)T(t)}+\ln\frac{T^*(t,a)}{\overline{T}^*(a)}=\ln\frac{\overline{T}}{T(t)}+\ln\frac{\overline{V}T^*(t,a)}{V(t)\overline{T}^*(a)}$, and putting it into (A.11), we have

$$\begin{aligned}
\frac{dL_2(t)}{dt}&=-\frac{m}{T(t)}(T(t)-\overline{T})^2-\frac{1}{N}K_2(a)\overline{T}^*(a)\left(\frac{T^*(t,a)}{\overline{T}^*(a)}-1-\ln\frac{T^*(t,a)}{\overline{T}^*(a)}\right)\Big|_{a=\infty}\\
&\quad+\frac{1}{N}\int_0^\infty\delta(a)p(a)\overline{T}^*(a)\left(1-\frac{\overline{T}}{T(t)}+\ln\frac{\overline{T}}{T(t)}\right)da\\
&\quad+\frac{1}{N}\int_0^\infty\delta(a)p(a)\overline{T}^*(a)\left(1-\frac{\overline{V}}{V(t)}\frac{T^*(t,a)}{\overline{T}^*(a)}+\ln\frac{\overline{V}T^*(t,a)}{V(t)\overline{T}^*(a)}\right)da.
\end{aligned}\tag{A.12}$$

We find that all of the terms have the properties of function $h(x)=x-1-\ln x$. This means that positive-definite function $L_2(t)$ has negative derivative. Therefore, the equality $\frac{d}{dt}L_2(t)=0$, if and only if $T(t)=\overline{T}$, $T^*(t,a)=\overline{T}^*(a)$ and $V(t)=\overline{V}$. Hence, if $R_{w0}>1$, then the equilibrium $U_1=(\overline{T},\ \overline{T}^*(a),\ \overline{V})$ is GAS. This completes the proof. □

Proof of Theorem 3.3. The proof of Theorem 3.3 is same as the case of U_1 in Theorem 3.2. In fact, the infection equilibrium U_1 exists, only when $R_{w0}>1$ and $E=0$. However, if $E>0$, the positive equilibrium is unique existent without any condition. Thus, it is easy to verify the result of Theorem 3.3 from the proof of the

GAS of U_1. □

The proofs of Theorems 3.4 and 3.5 are similar as Theorems 3.1 and 3.2.

Proof of Theorem 3.7. Let $\widehat{W} = (\widehat{S}, \widehat{I}(a), \widehat{E})$ be any equilibrium of system (3.6). Linearizing the system (3.6) at $\widehat{W}$, we have

$$\begin{cases} \frac{dS(t)}{dt} = -(\mu + \beta\widehat{E})S(t) - \beta\widehat{S}E(t), \\ \frac{\partial I(t,a)}{\partial a} + \frac{\partial I(t,a)}{\partial t} = -(\mu + \delta(a))I(t,a), \\ \frac{dE(t)}{dt} = (1-\widehat{E})\widetilde{V}(\widehat{E})\int_0^{+\infty}\theta(a)I(t,a)da \\ \qquad\quad + \left[\int_0^{+\infty}\theta(a)\widehat{I}(a)da \cdot \left(\widetilde{V}'(\widehat{E})(1-\widehat{E}) - \widetilde{V}(\widehat{E})\right)\right]E(t) - \gamma E(t), \\ I(t,0) = \beta\widehat{E}S(t) + \beta\widehat{S}E(t). \end{cases} \tag{A.13}$$

(**i**) For the disease-free equilibrium W_0, there are two cases to discuss. If $R_{w0} \leq 1$, then $\widetilde{V}(0) = 0$. The three variables $S(t)$, $E(t)$ and $I(t,\, a)$ are decreasing and W_0 is LAS. If $R_{w0} > 1$, then $\widetilde{V}(0) > 0$. We have the following characteristic equation

$$(\lambda + \mu)\left(\lambda + \gamma - \beta S_0\widetilde{V}(0)\int_0^{+\infty}\theta(a)\pi(a)e^{-\lambda a}da\right) = 0.$$

We claim W_0 is LAS, if $\hat{R}_{b0} < 1$. Otherwise, there is a root $\lambda = \sigma_1 + i\sigma_2$ with $\sigma_1 > 0$. Substituting it into the second term, the real part satisfies

$$\sigma_1 = \gamma\left(\frac{\beta S_0\widetilde{V}(0)}{\gamma}\int_0^{+\infty}\theta(a)\pi(a)e^{-\sigma_1 a}\cos(\sigma_2 a)da - 1\right) \leq \gamma\left(\hat{R}_{b0} - 1\right) < 0.$$

This is a contradiction.

Set

$$f_1(\lambda) = \gamma\left(\frac{\lambda}{\gamma} + 1 - \frac{\beta S_0\widetilde{V}(0)}{\gamma}\int_0^{+\infty}\theta(a)\pi(a)e^{-\lambda a}da\right).$$

Note that $f_1(0) = \gamma\left(1 - \hat{R}_{b0}\right)$ and $\lim_{\lambda\to\infty} f_1(\lambda) = 0$. If $\hat{R}_{b0} > 1$, the continuity and differentiability of the function $f_1(\lambda)$ tell us that there is at least one positive root. Accordingly, equilibrium W_0 is unstable, when $\hat{R}_{b0} > 1$, and is LAS, if $\hat{R}_{b0} < 1$.

(**ii**) For the unique positive equilibrium $\widehat{W} = (\widehat{S}, \widehat{I}(a), \widehat{E})$, the characteristic equation of system (3.6) at $\widehat{W}$ can be established as follows

$$\beta\widehat{S}(1-\widehat{E})\widetilde{V}(\widehat{E})\int_0^{+\infty}\theta(a)\pi(a)e^{-\lambda a}da = \frac{\lambda+\mu+\beta\widehat{E}}{\lambda+\mu}\left(\lambda + \frac{\gamma Q(\widehat{E})}{F(\widehat{E})}\right), \tag{A.14}$$

where $Q(E) = F(E) - EF'(E)$ and $F(E)$ is mentioned in (3.9). Clearly, $F'(E) = \widetilde{V}'(E)(1-E) - \widetilde{V}(E)$ and $Q'(E) = -EF''(E) > 0$. For the sake of convenience, set

$$LH(\lambda) = \beta\widehat{S}(1-\widehat{E})\widetilde{V}(\widehat{E})\int_0^{+\infty}\theta(a)\pi(a)e^{-\lambda a}da, \quad RH(\lambda) = \frac{\lambda+\mu+\beta\widehat{E}}{\lambda+\mu}\left(\lambda + \frac{\gamma Q(\widehat{E})}{F(\widehat{E})}\right).$$

By contradiction, we assume that the equilibrium $\widehat{W}$ is unstable, when $\frac{\gamma}{\mu+\beta\widehat{E}} \leq 1$. That is, the characteristic equation has at least one root $\lambda = u + iv$ with $u \geq 0$. In this case, we can get following results

$$\begin{aligned} LH &= \beta\widehat{S}(1-\widehat{E})\widetilde{V}(\widehat{E})\int_0^{+\infty}\theta(a)\pi(a)e^{-ua}\left(\cos(av) - i\sin(av)\right)da, \\ RH &= \frac{1}{(u+\mu)^2+v^2}\left((u+\mu+\beta\widehat{E})(u+\mu) + v^2 - iv\beta\widehat{E}\right)\left(u + \frac{\gamma Q(\widehat{E})}{F(\widehat{E})} + iv\right). \end{aligned}$$

Thus, $Re(LH) \leq \beta\widehat{S}(1-\widehat{E})\widetilde{V}(\widehat{E})\int_0^{+\infty}\theta(a)\pi(a)da = \gamma$. Taking the real part yields

$$Re(RH) = \frac{1}{(u+\mu)^2+v^2}\left((u+\mu+\beta\widehat{E})(u+\mu)+v^2\right)\left(u+\frac{\gamma Q(\widehat{E})}{F(\widehat{E})}\right)+\beta\widehat{E}_2v^2.$$

Based on the definition and properties of $F(E), G(E)$ and $Q(E)$, it follows that $H(\widehat{E}) - \widehat{E}H'(\widehat{E}) > 0$ (since $H(\widehat{E}) = 0$ and $H'(\widehat{E}) < 0$). That is, $Q(\widehat{E}) > \gamma\cdot\left(\beta S_0\int_0^{+\infty}\theta(a)\pi(a)da\right)^{-1}$. Thus, we have $\frac{Q(\widehat{E})}{F(\widehat{E})} > \frac{\mu}{\mu+\beta\widehat{E}}$. Furthermore, we know

$$Re(RH) > u+\frac{\gamma\mu}{\mu+\beta\widehat{E}}+f(u,\,v), \quad \text{where } f(u,\,v) = \frac{\beta\widehat{E}(u+\mu)\left(u+\frac{\gamma\mu}{\mu+\beta\widehat{E}}\right)+\beta\widehat{E}v^2}{(u+\mu)^2+v^2},$$

for $(u,\,v)\in R_+^2$. For obtaining the minimum $f_{\min}$ of f in R_+^2, we derive the partial derivative of $f(u,\,v)$ with respect to u and v

$$\frac{\partial f(u,v)}{\partial u} = \frac{v^2-(u+\mu)^2}{[(u+\mu)^2+v^2]^2}\beta\widehat{E}\mu\left(\frac{\gamma}{\mu+\beta\widehat{E}}-1\right), \quad \frac{\partial f(u,v)}{\partial v} = \frac{2(u+\mu)v}{[(u+\mu)^2+v^2]^2}\beta\widehat{E}\mu\left(1-\frac{\gamma}{\mu+\beta\widehat{E}}\right).$$

Note that $\frac{\partial f(u,v)}{\partial u} = 0 \Leftrightarrow v^2-(u+\mu)^2 = 0$ and $\frac{\partial f(u,v)}{\partial v} = 0 \Leftrightarrow (u+\mu)n = 0$. This shows that $f(u,\,v)$ has only a stationary point $(-\mu, 0)$ in R^2, and this stationary point is not in the first quadrant. Thus, the minimum of $f(u,\,v)$ in R_+^2 is reached at the boundary ∂R_+^2.

If $\frac{\gamma}{\mu+\beta\widehat{E}} < 1$, it is easy to obtain that $\frac{\partial f(u,v)}{\partial u} > 0$, when $v = 0$ and $\frac{\partial f(u,v)}{\partial v} > 0$, when $u = 0$. Hence, we have $f_{\min} = f(0,0) = \frac{\gamma\beta\widehat{E}}{\mu+\beta\widehat{E}}$. Furthermore,

$$Re(RH) > u+\mu+\frac{\beta\widehat{E}(u+\mu)}{(u+\mu)^2+v^2}\left(u+\frac{\gamma\beta\widehat{E}}{\mu+\beta\widehat{E}}\right)+\beta\widehat{E}v^2 \geq \frac{\gamma\mu}{\mu+\beta\widehat{E}}+\frac{\gamma\beta\widehat{E}}{\mu+\beta\widehat{E}} = \gamma,$$

which is a contradiction.

If $\frac{\gamma}{\mu+\beta\widehat{E}} = 1$, we directly have

$$Re(RH) > u+\mu+\frac{\beta\widehat{E}(u+\mu)(u+\mu)+\beta\widehat{E}v^2}{(u+\mu)^2+v^2} \geq \mu+\beta\widehat{E} = \gamma,$$

which leads to a contradiction. Therefore, $\widehat{W}$ is LAS, if $\frac{\gamma}{\mu+\beta\widehat{E}} \leq 1$.

(**iii**) In such case, we have $H'(\widehat{E}_1) > 0$ and $H'(\widehat{E}_2) < 0$.

For the equilibrium $\widehat{W}_1 = (\widehat{S}_1, \widehat{I}_1(a), \widehat{E}_1)$, we can rewrite the equation (A.14) in the following form $f_2(\lambda) = 1$, where

$$f_2(\lambda) = \frac{(\lambda+\mu)\beta\widehat{S}_1(1-\widehat{E}_1)\widetilde{V}(\widehat{E}_1)\int_0^{+\infty}\theta(a)\pi(a)e^{-\lambda a}da}{(\lambda+\mu+\beta\widehat{E}_1)\left(\lambda+\frac{\gamma Q(\widehat{E}_1)}{F(\widehat{E}_1)}\right)}.$$

Based on the definition and properties of $F(E), G(E)$ and $Q(E)$, we have the result $H(\widehat{E}_1) - \widehat{E}_1H'(\widehat{E}_1) < 0$. That is, $Q(\widehat{E}_1) < \gamma\left(\beta S_0\int_0^{+\infty}\theta(a)\pi(a)da\right)^{-1}$. Hence, when $\lambda = 0$, we drive

$$f_2(0) = \frac{\beta\widehat{S}_1\mu(1-\widehat{E}_1)\widetilde{V}(\widehat{E}_1)\int_0^{+\infty}\theta(a)\pi(a)da}{(\mu+\beta\widehat{E}_1)\frac{\gamma Q(\widehat{E}_1)}{F(\widehat{E}_1)}} > \frac{\beta\widehat{S}_1(1-\widehat{E}_1)\widetilde{V}(\widehat{E}_1)\int_0^{+\infty}\theta(a)\pi(a)da}{\gamma} = 1.$$

At present, we obtain $f_2(0) > 1$ and $\lim_{\lambda\to\infty} f_2(\lambda) = 0$. Consequently, the characteristic equation at $\widehat{W}_1$ at least has a unique positive part thanks to the continuity of $f_1(\lambda)$. In other words, $\widehat{W}_1$ is unstable.

If $\frac{\gamma}{\mu+\beta\widehat{E}} \leq 1$, the positive equilibrium $\widehat{W}_2$ is LAS similar to the discussion of case **ii**. □

References

[1] F. Agusto, M. Leite and M. Orive, *The transmission dynamics of a within-and between-hosts malaria model*, Ecological Complexity, 2019, 38, 31–55.

[2] A. Almocera, V. Nguyen and E. H. Vargas, *Multiscale model within-host and between-host for viral infectious diseases*, Journal of Mathematical Biology, 2018, 77(4), 1035–1057.

[3] X. Cen, Z. Feng and Y. Zhao, *Emerging disease dynamics in a model coupling within-host and between-host systems*, Journal of Theoretical Biology, 2014, 361, 141–151.

[4] Y. Chen, J. Yang and F. Zhang, *The global stability of an SIRS model with infection age*, Mathematical Biosciences and Engineering, 2014, 11(3), 449–469.

[5] Y. Chen, S. Zou and J. Yang, *Global analysis of an sir epidemic model with infection age and saturated incidence*, Nonlinear Analysis: Real World Applications, 2016, 30, 16–31.

[6] P. van den Driessche, Z. Shuai and F. Brauer, *Dynamics of an age-of-infection cholera model*, Mathematical Biosciences, 2013, 10(5–6), 1335–1349.

[7] Z. Feng, X. Cen, Y. Zhao and J. V. Hernandez, *Coupled within-host and between-host dynamics and evolution of virulence*, Mathematical Biosciences, 2015, 270(B), 204–212.

[8] Z. Feng, J. V. Hernandez and B. T. Santos, *A mathematical model for coupling within-host and between-host dynamics in an environmentally-driven infectious disease*, Mathematical Biosciences, 2013, 241(1), 49–55.

[9] H. Inaba, *Age-Structured Population Dynamics in Demography and Epidemiology*, Springer, Singapore, 2017.

[10] H. Leszczyski and P. Zwierkowski, *The rothe method for the mckendrick-von foerster equation*, Czechoslovak Mathematical Journal, 2013, 63(3), 589–602.

[11] J. Liu and Y. Zhou, *Global stability of an SIRS epidemic model with transport-related infection*, Chaos, Soliton & Fractals, 2009, 40(1), 145–158.

[12] X. Liu and P. Stechlinski, *Infectious disease models with time-varying parameters and general nonlinear incidence rate*, Applied Mathematical Modelling, 2012, 36(5), 1974–1994.

[13] M. Liu, M. Zhu and X. Song, *Modeling the Transmission of West Nile Virus with Wolbachia in a Heterogeneous Environment*, Journal of Nonlinear Modeling and Analysis, 2021, 3(2), 301–319.

[14] J. Lu, Z. Teng and Y. Li, *An age-structured model for coupling within-host and between-host dynamics in environmentally-driven infectious diseases*, Chaos, Soliton & Fractals, 2020, 139, Article ID 110024, 13 pages.

[15] Y. Lv, Y. Pei and R. Yuan, *On a non-linear size-structured population model*, Discrete and Continuous Dynamical Systems. Series B., 2020, 25(8), 3111–3133.

[16] P. Magal and C. McCluskey, *Two-Group Infection Age Model Including an Application to Nosocomial Infection*, SIAM Journal on Applied Mathematics, 2013, 73(2), 1058–1095.

[17] P. Magal, C. C. Mccluskey and G. Webb, *Lyapunov functional and global asymptotic stability for an infection-age model*, Applicable Analysis, 2010, 89(7), 1109–1140.

[18] C. C. McCluskey, *Global stability for an sir epidemic model with delay and nonlinear incidence*, Nonlinear Analysis: Real World Applications, 2010, 11(4), 3106–3109.

[19] J. A. Murillo, Z. Feng and J. Glasser, *Analysis of an epidemiological model structured by time-since-last-infection*, Journal of Differential Equations, 2019, 267(10), 5631–5661.

[20] M. Shen, Y. Xiao and L. Rong, *Global stability of an infection-age structured HIV-1 model linking within-host and between-host dynamics*, Mathematical Biosciences, 2015, 263, 37–50.

[21] A. Sullivan, F. Agusto, S. Bewick, C. Su, S. Lenhart and P. Zhao, *A mathematical model for within-host invasion dynamics*, Mathematical Biosciences and Engineering, 2012, 9(3), 647–662.

[22] J. Walker, *Dynamical Systems and Evolution Equations*, Plenum Press, New York, 1980.

[23] J. Wang, J. Lang and X. Zou, *Analysis of an age structured HIV infection model with virus-to-cell infection and cell-to-cell transmission*, Nonlinear Analysis: Real World Applications, 2017, 34, 75–96.

[24] X. Wang, Y. Bai, J. Yang and F. Zhang, *Global stability of an epidemic model for HIV-TB co-infection with infection-age*, International Journal of Biomathematics, 2014, 7(4), Article ID 1450043, 33 pages.

[25] X. Wang and J. Wang, *Disease dynamics in a coupled cholera model linking within-host and between-host interactions*, Journal of Biological Dynamics, 2017, 11(1), 238–261.

[26] Y. Xue, L. Hu and L. Nie, *Modelling the Wolbachia Strains for Dengue Fever Virus Control in the Presence of Seasonal Fluctuation*, Journal of Nonlinear Modeling and Analysis, 2021, 3(2), 209–224.

[27] Z. Zhang and J. Peng, *A SIRS epidemic model with infection-age dependence*, Journal of Mathematical Analysis and Applications, 2007, 331(2), 1396–1414.