A NESTED MODEL ON HIV/AIDS, ANTIRETROVIRAL THERAPY AND DRUG RESISTANCE*

Peipei Hu[1] and Jie Lou[1,†]

Abstract A coupled within- (immunological) and between-host (epidemiological) dynamic model was developed which is about the spreading of drug-sensitive HIV strain and drug-resistant HIV strain in men who have sex with men (MSM) population. The within-host model was nested within the between-host model by linking the dynamics of the within-host model to the additional host mortality and transmission rate of the infection. The existences of equilibria and their stabilities were found, as well as the thresholds $\mathcal{R}_S$ and $\mathcal{R}_R$ for the two different strains of the nested model. Some simulations about the spreading of the two HIV strains in Beijing MSM population were given. Our results show that the drug-resistant strain will increase quite fast in this population and both strains can coexist, which will make a big pressure for China's "Four-Free-One-Care Policy".

Keywords Within-host, between-host, nested model, HIV/AIDS, drug-sensitive strain, drug-resistant strain.

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1. Introduction

Men who have sex with men (frequently shortened to MSM) have emerged as a high-risk group for HIV in China in recently years. The proportion of nationally reported HIV/AIDS cases among MSM increased from 0.7% in 2005 [1] to 21.4% in 2013 in some cities in China [2]. In China, HIV infected patients are receiving free treatments ("Four-Free-One-Care Policy") on combined antiretroviral therapy that are provided by the government. Resistance of HIV to antiretroviral drugs is a widespread problem that limits the efficacy of antiretroviral treatment.

There are two main cause for the emergence of drug-resistant HIV variants: suboptimum treatment or incomplete adherence to therapy (secondary drug resistance); and the pre-existence of drug-resistant variants within HIV quasispecies, and the transmission of HIV-resistant variants at the time of the infection (primary drug resistance) [24]. There is increasing evidence to suggest the transmission of drug-resistant strains of HIV is becoming more widespread in most countries where Highly Active Anti-Retroviral Therapy (HAART) is being used [5]. What is less well understood is the prevalence of primary drug resistance and the variation of this prevalence over time and population risk groups. Several mathematical models have
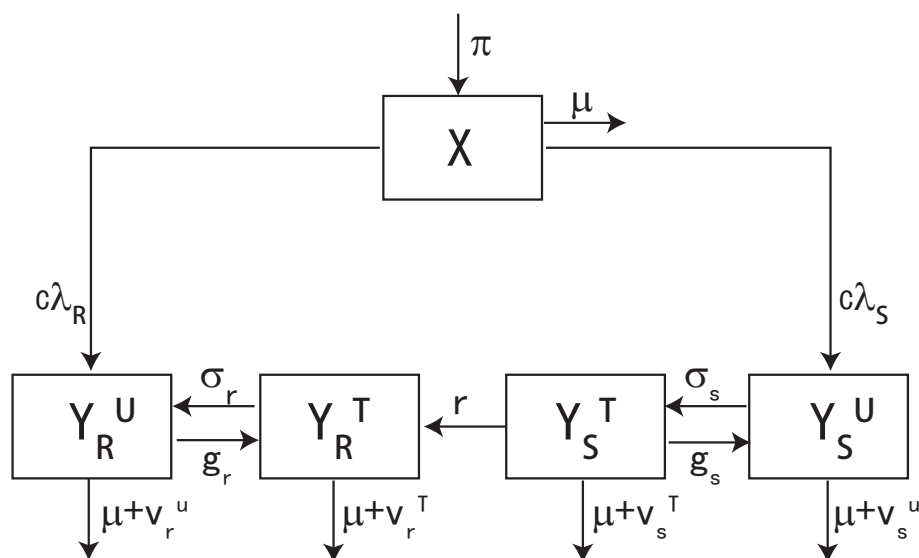

Figure 1. Flow diagram of the transmission dynamics of an HIV epidemic in the presence of combination antiretroviral therapy (ART); for model equations see system (2.4).

been developed to determine the effect of ART on HIV transmission by estimating the basic reproductive number, which represents the number of individuals that a single infectious person will infect when introduced into a completely susceptible population [4,5,9,21]. They provide a theoretical framework for tracking simultaneously the transmission of wild-type drug-sensitive and drug-resistant strains of HIV, in which, a few studies have modeled the impact of both primary and secondary drug resistance [5,12]. To predict the effectiveness of ART in the San Francisco gay community, authors in literature [5] developed and analyzed a mathematical model, which is about effects of ART on the transmission dynamics of both drug-sensitive and drug-resistant HIV strains. The model is specified by five ordinary differential equations and allowed for drug-resistant strains to emerge during treatment, i.e., secondary resistance, which is modeled by parameter r. The potential treatment effects of ART is assumed by assuming that ART reduces infectivity and increases average survival time, and that drug-resistant strains will be less responsive to therapy than drug-sensitive strains. Treatment was assumed to have three outcomes. A patient can respond to ART and remain as a nonprogressor for a specified amount of time, experience clinical failure and death without developing drug resistance, or virologically fail treatment and develop drug resistance. Individuals can go on and off ART, and drug-resistant infections can revert to drug-sensitive infections if the selective pressure of treatment is removed (Figure 1).

From another point of view, competition models have been formulated in the context of the dynamics of virus-host interactions over the last two decades [7, 10, 13, 16, 19, 20, 22]. In [13], an impulsive system of differential equations is developed to describe the within-host virus dynamics of both wild-type and drug-resistant strains when a combination of antiretroviral drugs is used to induce instantaneous

drug effects at a sequence of dosing times equally spaced while drug concentrations decay exponentially after the dosing time.

The importance of linking mathematical immunology and mathematical epidemiology was recognized in recent years [3, 6, 8, 14, 15, 17]. One important goal of the evolutionary epidemiology of infectious diseases is to understand how such nested processes affect the epidemiological and evolutionary dynamics of host-pathogen interactions. There have been several efforts directed toward nesting models of within-host dynamics into models of between-host dynamics when studying pathogen evolution. Linking within- and between-host levels of disease dynamics, literatures [6, 14, 15, 17] studied the evolution of HIV and HCV.

In this paper, a nested within- and between-host dynamic model of HIV was proposed. First an ordinary differential system of HIV dynamics within an infected host was introduced, which is the special situation of the model in literature [13]. Then an age-structured between-host HIV model was considered to describe the dynamics of host birth and death and the transmission of HIV within the host population, which will use the model of literature [5] for reference. We nest within-host model within the epidemiological model by linking the dynamics of the within-host model to the additional host mortality, treatment rate, and transmission rate of the infection. We theoretically analyze our mathematical models. Simulations further show the influence of the within-host dynamics on the between-host dynamics.

This paper is organized as follows. In section 2 we build the two models. In section 3 we show some preliminary work for theory analysis. In section 4 we discuss the existence of endemic stationary steady states and in section 5 we discuss their stability. Finally, section 6 is devoted to simulations about the spreading of drug-sensitive strain and drug-resistant strain of HIV in MSM population in Beijing, China.

2. Nested model

2.1. A micro-HIV model [13]

In this micro model, all variables are functions of time τ. Let T denote the number of the susceptible cells, I_w and I_r be numbers of the cells infected with the drug-sensitive virus and cells infected with the drug-resistant virus, V_w and V_r represent the respective concentrations of wild and drug-resistant virus. The virus dynamics is described by the following system of ordinary differential equations:

$$\begin{cases} \frac{dT(\tau)}{dt} = \lambda - dT(\tau) - \beta_w H_{rt}^w(\tau)T(\tau)V_w(\tau) - \beta_r H_{rt}^r(\tau)T(\tau)V_r(\tau), \\ \frac{dI_w(\tau)}{dt} = \delta\beta_w H_{rt}^w(\tau)T(\tau)V_w(\tau) - \alpha_w I_w(\tau), \\ \frac{dI_r(\tau)}{dt} = (1-\delta)\beta_w H_{rt}^w(\tau)T(\tau)V_w(\tau) + \beta_r H_{rt}^r(\tau)T(\tau)V_r(\tau) - \alpha_r I_r(\tau), \quad (2.1) \\ \frac{dV_w(\tau)}{dt} = pn_w H_p^w(\tau)\alpha_w I_w(\tau) - d_w V_w(\tau), \\ \frac{dV_r(\tau)}{dt} = (1-p)n_w H_p^w(\tau)\alpha_w I_w(\tau) + n_r H_p^r(\tau)\alpha_r I_r(\tau) - d_r V_r(\tau), \end{cases}$$

for $\tau \neq \tau_k$ (see impulsive conditions below).

According to literature [13], this model assumes that the susceptible cells are produced at a constant rate λ from a pool of precursor cells, and die at the constant rate d. Susceptible cells become infected at rates $\beta_w H_{rt}^w(\tau)T(t)V_w(t)$ and

$\beta_r T(t) H_{rt}^r(\tau) V_r(t)$ by sensitive and resistant virus respectively, where β_w and β_r characterize the infectivity of drug-sensitive and drug-resistant virus strains, $H_{rt}^w(\tau)$ and $H_{rt}^r(\tau)$ describe the effects of reverse transcriptase inhibitors on the wild-type and drug-resistant strains. We assume that $\beta_w > \beta_r$, so the wild-type virus is more infectious than the drug-resistant strain in the absence of the drug [22]. We assume that during the course of wild-type viral-cell infection, virus variants that are resistant to the drug arise with probability $(1 - \delta)$. In this model, α_w and α_r denote the death rates of the two different kinds of the infected cells respectively. Virions V_w and V_r are assumed to be cleared at rates d_w and d_r by the immune system, but are also assumed to be generated by the two types of the infected cells at rates $n_w \alpha_w$ and $n_r \alpha_r$, respectively, with $n_w \alpha_w \geq n_r \alpha_r$, i.e., the drug-sensitive virus is assumed to have higher replication rate [10]. We further assume that drug-resistant variants arise with probability $(1 - p)$ during the course of wild-type viral replication. The effects of protease inhibitors for wild-type and drug-resistant strains are characterized by $H_p^w(\tau)$ and $H_p^r(\tau)$, respectively.

The drug effects are described by the time-varying parameters $H_{rt}^w(\tau)$, $H_{rt}^r(\tau)$, $H_p^w(\tau)$ and $H_p^r(\tau)$. The subscript "rt" indicates reverse transcriptase inhibitors which block the translation of viral RNA into DNA for incorporation into the host genome, thus preventing the infection of new cells. In contrast, the subscript "p" denotes protease inhibitors which interfere with essential steps of protein cleavage in new virions, thus preventing infected cells from producing infectious viral particles [13]. As noted earlier, the superscripts "w" and "r" reflect the wild-type virus and drug-resistant virus, respectively. We now describe these time varying parameters. Assuming that drugs are taken at time τ_k and the effects of drugs are instantaneous. Therefore, we follow literature [20] and describe the evolution of drug concentration by impulsive differential equations. At the dosing time $\tau = \tau_k$, the drug concentration for a specific drug is

$$D(\tau_k^+) = D(\tau_k^-) + D^i, \qquad (2.2)$$

where D^i is the drug dose that is used every time. D can be either of drugs Zidovudine (AZT), Lamivudine (3TC), Nevirapine (NVP) or ritonavir (RTV). For $\tau \neq \tau_k$, the dynamic of the drug are given by (2.3).

$$\frac{dD(\tau)}{dt} = -gD(\tau), \qquad \tau \neq \tau_k, \qquad (2.3)$$

where g is the rate at which drug (3TC, AZT, NVP or RTV) is cleared.

In this paper, we suppose that infected individuals can accept optimum treatment and fully adhere to therapy, which put an end to the arising of drug resistance strain, i.e., $p = \delta = 1$. Such as, we suppose the drugs are taken every ζ period and no dose is missed, reflecting regular dosing periods. The detail description of anti-viral effect coefficients ($H_{rt}^w(\tau)$, $H_{rt}^r(\tau)$, $H_p^w(\tau)$ and $H_p^r(\tau)$) corresponding to two different treatment programs in China can be found in literature [13].

2.2. A macro-HIV model [5]

$$
\begin{cases}
\frac{dX(t)}{dt} = \pi - [c\lambda_S(t) + c\lambda_R(t) + \mu]X(t), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) Y_S^U(t,\tau) = g_S Y_S^T(t,\tau) - (\sigma_S + v_S^U(\tau) + \mu)Y_S^U(t,\tau), \\
Y_S^U(t,0) = c\lambda_S(t)X(t), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) Y_S^T(t,\tau) = \sigma_S Y_S^U(t,\tau) - (g_S + v_S^T(\tau) + \mu)Y_S^T(t,\tau), \\
Y_S^T(t,0) = 0, \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) Y_R^U(t,\tau) = g_R Y_R^T(t,\tau) - (e\sigma_R + v_R^U(\tau) + \mu)Y_R^U(t,\tau), \\
Y_R^U(t,0) = c\lambda_R(t)X(t), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) Y_R^T(t,\tau) = e\sigma_R Y_R^U(t,\tau) - (g_R + v_R^T(\tau) + \mu)Y_R^T(t,\tau), \\
Y_R^T(t,0) = 0.
\end{cases}
\tag{2.4}
$$

According to literature [5], model (2.4) keeps track of the temporal dynamics of five groups men who have sex with men (gay): susceptible individuals (X), untreated individuals infected with either drug-sensitive (Y_S^U) or drug-resistant strains (Y_R^U), and ART-treated individuals infected with either drug-sensitive (Y_S^T) or drug-resistant strains (Y_R^T). The parameter's subscript specifies whether the infection is drug-sensitive (S) or drug-resistant (R); the superscript identifies whether the individuals are treated with ART (T) or untreated (U). Parameter definitions are as follows: π: rate at which gay men join the sexually active community; $1/\mu$: average time during which a gay man acquires new sex partners; c: average number of new receptive anal sex partners per year; p: probability of a drug-resistant case (relative to a drug-sensitive case) transmitting drug-sensitive viruses; $1/q$: average time for an untreated drug-resistant infection to revert to a drug-sensitive infection; σ: per capita effective treatment rate; e: relative efficacy of ART in treating drug-resistant infections; r: rate of emergence of resistance due to acquired resistance; g: proportion of cases that give up ART per year; and v: average disease progression rate. λ: specifics the per capita force of infection for drug-sensitive (λ_S) and drug-resistant (λ_R) HIV; λ_S and λ_R are calculated from Eqs. (2.6), and are a function of the number of infected people at any particular time (Y_S^U, Y_R^U, Y_S^T, and Y_R^T) and the infectiousness (as specified by the transmissibility coefficients (β_S^U, β_S^T, β_R^U, and β_R^T) of each of the four types of infected people.

2.3. The crossover of the two HIV models

In system (2.4), define the total MSM population as

$$
N(t) = X(t) + \int_0^\infty [Y_S^U(t,\tau) + Y_S^T(t,\tau) + Y_R^U(t,\tau) + Y_R^T(t,\tau)]d\tau,
\tag{2.5}
$$

and define the infectious force functions $\lambda_S(t)$ and $\lambda_R(t)$ of system (2.4) as:

$$
\begin{aligned}
\lambda_S(t) &= \frac{1}{N(t)} \int_0^\infty [\beta_S^U(\tau)Y_S^U(t,\tau) + \beta_S^T(\tau)Y_S^T(t,\tau)]d\tau, \\
\lambda_R(t) &= \frac{1}{N(t)} \int_0^\infty [\beta_R^U(\tau)Y_R^U(t,\tau) + \beta_R^T(\tau)Y_R^T(t,\tau)]d\tau,
\end{aligned}
\tag{2.6}
$$

in which, $\beta_S^U(\tau), \beta_S^T(\tau), \beta_R^U(\tau)$ and $\beta_R^T(\tau)$ are defined as functions of variables $V_w(t), V_r(t)$ of system (2.1) which are shown as follows:

$$\beta_S^U(\tau) = \beta_S^U(V_w(\tau), V_r(\tau)) = \tilde{\beta}_S^U \cdot \left(\frac{V_w(\tau) + V_r(\tau)}{V_w(\tau) + V_r(\tau) + \Omega} \right),$$

$$\beta_S^T(\tau) = \beta_S^T(V_w(\tau), V_r(\tau)) = \tilde{\beta}_S^T \cdot \left(\frac{V_w(\tau) + V_r(\tau)}{V_w(\tau) + V_r(\tau) + \Omega} \right),$$

$$\beta_R^U(\tau) = \beta_R^U(V_w(\tau), V_r(\tau)) = \tilde{\beta}_R^U \cdot \left(\frac{V_w(\tau) + V_r(\tau)}{V_w(\tau) + V_r(\tau) + \Omega} \right), \qquad (2.7)$$

$$\beta_R^T(\tau) = \beta_R^T(V_w(\tau), V_r(\tau)) = \tilde{\beta}_R^T \cdot \left(\frac{V_w(\tau) + V_r(\tau)}{V_w(\tau) + V_r(\tau) + \Omega} \right).$$

Also, we define disease progression rate in system (2.4), $v_S^U(\tau), v_S^T(\tau), v_R^U(\tau)$ and $v_R^T(\tau)$, as functions of invariables $T_w(t), V_w(t), I_r(t), V_r(t)$ in system (2.1):

$$v_S^U(\tau) = v_S^U(T_w, V_w, I_r, V_r) = \tilde{v}_S^U \cdot \left(\frac{V_w + V_r}{V_w + V_r + \Theta_1} \right) \cdot \left(\frac{\Theta_2}{I_w + I_r + \Theta_2} \right),$$

$$v_S^T(\tau) = v_S^T(T_w, V_w, I_r, V_r) = \tilde{v}_S^T \cdot \left(\frac{V_w + V_r}{V_w + V_r + \Theta_1} \right) \cdot \left(\frac{\Theta_2}{I_w + I_r + \Theta_2} \right),$$

$$v_R^U(\tau) = v_R^U(T_w, V_w, I_r, V_r) = \tilde{v}_R^U \cdot \left(\frac{V_w + V_r}{V_w + V_r + \Theta_1} \right) \cdot \left(\frac{\Theta_2}{I_w + I_r + \Theta_2} \right), \qquad (2.8)$$

$$v_R^T(\tau) = v_R^T(T_w, V_w, I_r, V_r) = \tilde{v}_R^T \cdot \left(\frac{V_w + V_r}{V_w + V_r + \Theta_1} \right) \cdot \left(\frac{\Theta_2}{I_w + I_r + \Theta_2} \right).$$

3. Preliminary work

Consider system

$$\begin{cases} \frac{dx_1(\tau)}{d\tau} = (f_1(\tau) - \omega)x_1(\tau) + g_R x_2(\tau), \\ x_1(0) = x_1^0, \\ \frac{dx_2(\tau)}{d\tau} = e\sigma_R x_1(\tau) + (f_2(\tau) - \omega)x_2(\tau), \\ x_2(0) = 0. \end{cases} \qquad (3.1)$$

Let $\vec{x}(\tau) = (x_1(\tau), x_2(\tau))^T$. Now we investigate the solutions of the following equations:

$$\frac{d\vec{x}(\tau)}{d\tau} = \mathcal{A}(\tau)\vec{x}(\tau), \qquad (3.2)$$

where

$$\mathcal{A}(\tau, \omega) = \begin{bmatrix} f_1(\tau) - \omega & g_R \\ e\sigma_R & f_2(\tau) - \omega \end{bmatrix}.$$

Obviously, matrix $\mathcal{A}(\tau, \omega)$ have two different eigenvalues:

$$\lambda_{1,2}(\tau, \omega) = \frac{1}{2} \left[f_1(\tau) + f_2(\tau) - 2\omega \pm \sqrt{(f_1(\tau) - f_2(\tau))^2 + 4eg_R\sigma_R} \right], \qquad (3.3)$$

with $\lambda_1(\tau,\omega) > \lambda_2(\tau,\omega)$, which imply that matrix $\mathcal{A}(\tau,\omega)$ can be diagonalized. Easy to get a reversible matrix $\mathcal{P}(\tau,\omega)$ as follows:

$$\mathcal{P}(\tau,\omega) = \begin{bmatrix} \frac{\lambda_1^R(\tau)-(f_2(\tau)-\omega)}{e\sigma_R} & \frac{\lambda_2^R(\tau)-(f_2(\tau)-\omega)}{e\sigma_R} \\ 1 & 1 \end{bmatrix},$$

in which, $\left(\frac{\lambda_1(\tau)-(f_2(\tau)-\omega)}{e\sigma_R},1\right)^T$ and $\left(\frac{\lambda_2(\tau)-(f_2(\tau)-\omega)}{e\sigma_R},1\right)^T$ are eigenvectors of eigenvalues $\lambda_1(\tau,\omega)$ and $\lambda_2(\tau,\omega)$ respectively.

Through transforms $\vec{x}(\tau) = \mathcal{P}(\tau,\omega)\vec{y}(\tau), \vec{y}(\tau) = (y_1(\tau),y_2(\tau))^T$, we get that

$$\begin{bmatrix} \dot{y}_1(\tau) \\ \dot{y}_2(\tau) \end{bmatrix} = \mathcal{P}(\tau,\omega)^{-1}\mathcal{A}(\tau,\omega)\mathcal{P}(\tau,\omega) = \begin{bmatrix} \lambda_1(\tau,\omega) & 0 \\ 0 & \lambda_2(\tau,\omega) \end{bmatrix},$$

which imply that the above differential equation have general solutions:

$$\begin{bmatrix} y_1(\tau) \\ y_2(\tau) \end{bmatrix} = \begin{bmatrix} C_1 e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma} \\ C_2 e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma} \end{bmatrix}.$$

So system (3.1) have general solutions as follows:

$$\begin{bmatrix} x_1(\tau) \\ x_2(\tau) \end{bmatrix} = \mathcal{P}(\tau,\omega)\vec{y}(\tau) = C_1 \begin{bmatrix} \frac{\lambda_1(\tau,\omega)-(f_2(\tau)-\omega)}{e\sigma_R} \\ 1 \end{bmatrix} e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma}$$

$$+C_2 \begin{bmatrix} \frac{\lambda_2(\tau,\omega)-(f_2(\tau)-\omega)}{e\sigma_R} \\ 1 \end{bmatrix} e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma}.$$

Under initial conditions of $x_1(\tau)$ and $x_2(\tau)$ in system (3.1), it is easy to get that constants C_1 and C_2 should satisfy:

$$\begin{cases} C_1 + C_2 = 0, \\ x_1^0 = C_1 \frac{\lambda_1(0,\omega)-(f_2(0)-\omega)}{e\sigma_R} + C_2 \frac{\lambda_2(0,\omega)-(f_2(0)-\omega)}{e\sigma_R}. \end{cases} \tag{3.4}$$

So $C_1 = -C_2 = \dfrac{e\sigma_R x_1^0}{\lambda_1(0,\omega)-\lambda_2(0,\omega)}$. In this situation, the solution of system (3.1) is:

$$x_1(\tau) = \frac{x_1^0}{\lambda_1(0,\omega)-\lambda_2(0,\omega)}[(\lambda_1(\tau,\omega)-(f_2(\tau)-\omega))e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma}$$

$$+ (f_2(\tau)-\omega-\lambda_2(\tau,\omega))e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma}],$$

$$x_2(\tau) = \frac{e\sigma_R x_1^0}{\lambda_1(0,\omega)-\lambda_2(0,\omega)}[e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma} - e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma}].$$

Similarly, for system

$$
\begin{cases}
\frac{dx_1(\tau)}{d\tau} = (g_1(\tau) - \omega)x_1(\tau) + g_S x_2(\tau), \\
x_1(0) = x_1^0, \\
\frac{dx_2(\tau)}{d\tau} = \sigma_S x_1(\tau) + (g_2(\tau) - \omega)x_2(\tau), \\
x_2(0) = 0,
\end{cases}
\tag{3.5}
$$

the two different eigenvalues are as follows:

$$
\lambda_{1,2}^*(\tau,\omega) = \frac{1}{2}\left[g_1(\tau) + g_2(\tau) - 2\omega \pm \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_S\sigma_S}\right],
$$

$(\lambda_1^*(\tau,\omega) > \lambda_2^*(\tau,\omega))$. Then the solution of system (3.5) should be:

$$
\begin{aligned}
x_1(\tau) =& \frac{x_1^0}{\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega)}[(\lambda_1^*(\tau,\omega) - (g_2(\tau) - \omega))e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} \\
&+ (g_2(\tau) - \omega - \lambda_2^*(\tau,\omega))e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma}], \\
x_2(\tau) =& \frac{\sigma_S x_1^0}{\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega)}[e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} - e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma}].
\end{aligned}
\tag{3.6}
$$

4. The existences of equilibria

For simplify, we suppose parameter $r = 0$. It is easy to calculate that system (2.4) has one disease-free equilibrium $\varepsilon_0 = (X^0, 0, 0, 0, 0)$, where $X^0 = \frac{\pi}{\mu}$. In the following, we study the existence of the boundary endemic equilibria and the endemic equilibrium.

4.1. The existence of boundary endemic equilibria

The system can have two boundary endemic equilibria. One is $\varepsilon_S^b = (X_S^b, Y_S^{Ub}(\tau), Y_S^{Tb}(\tau), 0, 0)$ and the other is $\varepsilon_R^b = (X_R^b, 0, 0, Y_R^{Ub}(\tau), Y_R^{Tb}(\tau))$. In this subsection, we give details of the existence for the boundary equilibrium ε_R^b. For boundary equilibrium ε_S^b we can get its existence by similar method.

4.1.1. The existence of boundary equilibrium ε_R^b

For simplicity, denote

$$
-(e\sigma_R + v_R^U(\tau) + \mu) = f_1(\tau), \quad -(g_R + v_R^T(\tau) + \mu) = f_2(\tau).
\tag{4.1}
$$

Then the boundary equilibrium ε_R^b, if it exists, should satisfy

$$
\begin{cases}
\pi - \mu X_R^b - Y_R^{Ub}(0) = 0, \\
\frac{dY_R^{Ub}(\tau)}{d\tau} = f_1(\tau)Y_R^{Ub}(\tau) + g_R Y_R^{Tb}(\tau), \\
Y_R^{Ub}(0) = \frac{X_R^b}{N_R^b}\int_0^\infty c[\beta_R^U(\tau)Y_R^{Ub}(\tau) + \beta_R^T(\tau)Y_R^{Tb}(\tau)]d\tau, \\
\frac{dY_R^{Tb}(\tau)}{d\tau} = e\sigma_R Y_R^{Ub}(\tau) + f_2(\tau)Y_R^{Tb}(\tau), \\
Y_R^{Tb}(0) = 0,
\end{cases}
\tag{4.2}
$$

where $N_R^b = X_R^b + \int_0^\infty \left(Y_R^{Ub}(\tau) + Y_R^{Tb}(\tau) \right) d\tau$.

Obviously, the last four equations (the second to the fifth equations) of system (4.2) are similar to system (3.1) in section 3. Hence the solution of the initial problem of the last four equations of system (4.2) should be:

$$
\begin{aligned}
Y_R^{Ub}(\tau) = {}& \frac{Y_R^{Ub}(0)}{\lambda_1(0,0) - \lambda_2(0,0)} [(\lambda_1(\tau,0) - f_2(\tau))e^{\int_0^\tau \lambda_1(\sigma,0)d\sigma} \\
& + (f_2(\tau) - \lambda_2(\tau,0))e^{\int_0^\tau \lambda_2(\tau,0)d\sigma}], \\
Y_R^{Tb}(\tau) = {}& \frac{e\sigma_R Y_R^{Ub}(0)}{\lambda_1(0,0) - \lambda_2(0,0)} [e^{\int_0^\tau \lambda_1(\sigma,0)d\sigma} - e^{\int_0^\tau \lambda_2(\sigma,0)d\sigma}].
\end{aligned} \tag{4.3}
$$

Notice that

$$
\lambda_1(0,0) - \lambda_2(0,0) = \sqrt{(f_1(0) - f_2(0))^2 + 4eg_R\sigma_R} > 0
$$

and $\lambda_1(\tau,0) > \lambda_2(\tau,0))$, so $\lambda_1(\tau,0) > f_2(\tau)$. Since parameters' relations $e\sigma_R > g_R$ and $v_R^U(\tau) > v_R^T(\tau)$ always hold, which imply that $f_1(\tau) < f_2(\tau)$ holds, then we have $\lambda_2(\tau,0) < \frac{f_1(\tau)+f_2(\tau)}{2} < f_2(\tau)$. Then from equations (4.3) we get that $Y_R^{Ub}(\tau)$ and $Y_R^{Tb}(\tau)$ are both positive if and only if $Y_R^{Ub}(0)$ has meaning. In the following we prove this point.

Substituting N_R^b by $X_R^b + \int_0^\infty \left(Y_R^{Ub}(\tau) + Y_R^{Tb}(\tau) \right) d\tau$ in the third equation in (4.2), we get:

$$
Y_R^{Ub}(0) = \frac{X_R^b}{X_R^b + \int_0^\infty (Y_R^{Ub}(\tau) + Y_R^{Tb}(\tau))d\tau} \int_0^\infty c[\beta_R^U(\tau)Y_R^{Ub}(\tau) + \beta_R^T(\tau)Y_R^{Tb}(\tau)]d\tau,
$$

which can be rewritten as:

$$
\frac{\frac{X_R^b}{Y_R^{Ub}(0)}}{\frac{X_R^b}{Y_R^{Ub}(0)} + \int_0^\infty \frac{Y_R^{Ub}(\tau)}{Y_R^{Ub}(0)}d\tau + \int_0^\infty \frac{Y_R^{Tb}(\tau)}{Y_R^{Ub}(0)}d\tau} \int_0^\infty c\left[\beta_R^U(\tau)\frac{Y_R^{Ub}(\tau)}{Y_R^{Ub}(0)} + \beta_R^T(\tau)\frac{Y_R^{Tb}(\tau)}{Y_R^{Ub}(0)}\right]d\tau = 1. \tag{4.4}
$$

From equations (4.3) we have:

$$
\frac{Y_R^{Ub}(\tau)}{Y_R^{Ub}(0)} = \frac{[\lambda_1(\tau,0) - f_2(\tau)]\,e^{\int_0^\tau \lambda_1(\sigma,0)d\sigma} + [f_2(\tau) - \lambda_2(\tau,0)]\,e^{\int_0^\tau \lambda_2(\sigma,0)d\sigma}}{\lambda_1(0,0) - \lambda_2(0,0)}
$$

and

$$
\frac{Y_R^{Tb}(\tau)}{Y_R^{Ub}(0)} = \frac{e\sigma_R \left(e^{\int_0^\tau \lambda_1(\sigma,0)d\sigma} - e^{\int_0^\tau \lambda_2(\sigma,0)d\sigma}\right)}{\lambda_1(0,0) - \lambda_2(0,0)}.
$$

Then in the following we simply define

$$
\int_0^\infty \frac{Y_R^{Ub}(\tau)}{Y_R^{Ub}(0)}d\tau = \rho_R^1, \qquad \int_0^\infty \frac{Y_R^{Tb}(\tau)}{Y_R^{Ub}(0)}d\tau = \rho_R^2,
$$

and denote

$$
\int_0^\infty c\left[\beta_R^U(\tau)\frac{Y_R^{Ub}(\tau)}{Y_R^{Ub}(0)} + \beta_R^T(\tau)\frac{Y_R^{Tb}(\tau)}{Y_R^{Ub}(0)}\right]d\tau = \mathcal{R}_R^b.
$$

Substituting above relations in equation 4.4, we can rewrite the equation 4.4 in the following form:

$$
\frac{X_R^b \mathcal{R}_R^b}{X_R^b + (\rho_R^1 + \rho_R^2)Y_R^{Ub}(0)} = \frac{X_R^b \mathcal{R}_R^b}{N_R^b} = 1. \tag{4.5}
$$

Since

$$\pi - \mu X_R^b - Y_R^{Ub}(0) = 0 \tag{4.6}$$

and considering both (4.5) and (4.6), we get

$$X_R^b = \frac{\pi(\rho_R^1 + \rho_R^2)}{\mathcal{R}_R^b - 1 + \mu(\rho_R^1 + \rho_R^2)}, \quad Y_R^{Ub}(0) = \frac{\pi(\mathcal{R}_R^b - 1)}{\mathcal{R}_R^b - 1 + \mu(\rho_R^1 + \rho_R^2))}, \tag{4.7}$$

which are both positive when $\mathcal{R}_R^b > 1$ holds.

In brief, there is a boundary endemic equilibrium given by $\varepsilon_R^b = (X_R^b, 0, 0, Y_R^{Ub}(\tau),$ $Y_R^{Tb}(\tau)))$ when the basic reproduction number $\mathcal{R}_R^b > 1$ holds.

4.1.2. The existence of boundary equilibrium ε_S^b

For the existence of boundary equilibrium $\varepsilon_S^b = \left(X_S^b, Y_S^{Ub}(\tau), Y_S^{Tb}(\tau), 0, 0\right)$, define

$$g_1(\tau) = -(\sigma_S + v_S^U(\tau) + \mu), \quad g_2(\tau) = -(g_S + v_S^T(\tau) + \mu).$$

Then the boundary equilibrium ε_S^b, if it exists, should satisfy

$$\begin{cases} \pi - \mu X_S^b - Y_S^{Ub}(0) = 0, \\ \frac{dY_S^{Ub}(\tau)}{d\tau} = g_1(\tau)Y_S^{Ub}(\tau) + g_S Y_S^{Tb}(\tau), \\ Y_S^{Ub}(0) = \frac{X_S^b}{N_S^b} \int_0^\infty c[\beta_S^U(\tau)Y_S^{Ub}(\tau) + \beta_S^T(\tau)Y_S^{Tb}(\tau)]d\tau, \\ \frac{dY_S^{Tb}(\tau)}{d\tau} = \sigma_R Y_S^{Ub}(\tau) + g_2(\tau)Y_S^{Tb}(\tau), \\ Y_S^{Tb}(0) = 0, \end{cases} \tag{4.8}$$

where $N_S^b = X_S^b + \int_0^\infty \left(Y_S^{Ub}(\tau) + Y_S^{Tb}(\tau)\right) d\tau$.

The last four equations (the second to the fifth equations) of system (4.8) are similar to system (3.5) in section 3. Hence the solution of the initial problem of the last four equations of system (4.8), if it exists, should be:

$$Y_S^{Ub}(\tau) = \frac{Y_S^{Ub}(0)}{\lambda_1^*(0,0) - \lambda_2^*(0,0)}[(\lambda_1^*(\tau,0) - g_2(\tau))e^{\int_0^\tau \lambda_1^*(\sigma,0)d\sigma}$$
$$+ (g_2(\tau) - \lambda_2^*(\tau,0))e^{\int_0^\tau \lambda_2^*(\sigma,0)d\sigma}], \tag{4.9}$$
$$Y_S^{Tb}(\tau) = \frac{\sigma_S Y_S^{Ub}(0)}{\lambda_1^*(0,0) - \lambda_2^*(0,0)}[e^{\int_0^\tau \lambda_1^*(\sigma,0)d\sigma} - e^{\int_0^\tau \lambda_2^*(\sigma,0)d\sigma}].$$

Then from the relations of $Y_S^{Ub}(\tau), Y_S^{Tb}(\tau)$ and $Y_S^{Ub}(0)$ respectively in (4.9), we can simply define the following symbols:

$$\int_0^\infty \frac{Y_S^{Ub}(\tau)}{Y_S^{Ub}(0)}d\tau = \rho_S^1, \quad \int_0^\infty \frac{Y_S^{Tb}(\tau)}{Y_S^{Ub}(0)}d\tau = \rho_S^2,$$
$$\int_0^\infty c\left[\beta_S^U(\tau)\frac{Y_S^{Ub}(\tau)}{Y_S^{Ub}(0)} + \beta_S^T(\tau)\frac{Y_S^{Tb}(\tau)}{Y_S^{Ub}(0)}\right] d\tau = \mathcal{R}_S^b.$$

Following the methods in the subsection 4.1.1, we get

$$X_S^b = \frac{\pi(\rho_S^1 + \rho_S^2)}{\mathcal{R}_S^b - 1 + \mu(\rho_S^1 + \rho_S^2)}, \quad Y_S^{Ub}(0) = \frac{\pi(\mathcal{R}_S^b - 1)}{\mathcal{R}_S^b - 1 + \mu(\rho_S^1 + \rho_S^2))}, \tag{4.10}$$

which both positive when $\mathcal{R}_S^b > 1$ holds. Hence from (4.9) we get $Y_S^{Ub}(\tau) > 0$ and $Y_S^{Tb}(\tau) > 0$ under $\mathcal{R}_S^b > 1$. So there is a boundary endemic equilibrium given by $\varepsilon_S^b = \left(X_S^b, Y_S^{Ub}(\tau), Y_S^{Tb}(\tau), 0, 0\right)$ when the basic reproduction number $\mathcal{R}_S^b > 1$.

5. The stabilities of the equilibria

5.1. The stability of disease-free equilibrium

The system has one disease-free equilibrium $\varepsilon_0 = (X^0, 0, 0, 0, 0)$, where $X^0 = N^0 = \frac{\pi}{\mu}$. We consider the local stability of ε_0. First, we derive the linearized equations of the disease-free equilibrium. For this purpose, we introduce the following notation for the perturbations $X(t) = X^0 + x(t), Y_S^{U0}(t,\tau) = y_S^U(t,\tau), Y_S^{T0}(t,\tau) = y_S^T(t,\tau), Y_R^{U0}(t,\tau) = y_R^U(t,\tau), Y_R^{T0}(t,\tau) = y_R^T(t,\tau), N(t) = N^0 + n(t)$. Then the linearized system at the disease-free equilibrium ε_0 becomes:

$$
\begin{cases}
\frac{dx(t)}{dt} = -\mu x(t) - y_S^U(t,0) - y_R^U(t,0), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) y_S^U(t,\tau) = g_1(\tau) y_S^U(t,\tau) + g_S y_S^T(t,\tau), \\
y_S^U(t,0) = \int_0^\infty c[\beta_S^U(\tau) y_S^U(t,\tau) + \beta_S^T(\tau) y_S^T(t,\tau)]d\tau, \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) y_S^T(t,\tau) = \sigma_S y_S^U(t,\tau) + g_2(\tau) y_S^T(t,\tau), \\
y_S^T(t,0) = 0, \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) y_R^U(t,\tau) = f_1(\tau) y_R^U(t,\tau) + g_R y_R^T(t,\tau), \\
y_R^U(t,0) = \int_0^\infty c[\beta_R^U(\tau) y_R^U(t,\tau) + \beta_R^T(\tau) y_R^T(t,\tau)]d\tau, \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) y_R^T(t,\tau) = e\sigma_R y_R^U(t,\tau) + f_2(\tau) y_R^T(t,\tau), \\
y_R^T(t,0) = 0.
\end{cases}
\tag{5.1}
$$

Looking for solutions of the form

$$
x(t) = xe^{\omega t}, \quad y_S^U(t,\tau) = y_S^U(\tau)e^{\omega t}, \quad y_S^T(t,\tau) = y_S^T(\tau)e^{\omega t},
$$
$$
y_R^U(t,\tau) = y_R^U(\tau)e^{\omega t}, \quad y_R^T(t,\tau) = y_R^T(\tau)e^{\omega t},
$$

then we can obtain the following eigenvalue problem:

$$
\begin{cases}
\omega x = -\mu x - y_S^U(0) - y_R^U(0), \\
\frac{dy_S^U(\tau)}{d\tau} = (g_1(\tau) - \omega) y_S^U(\tau) + g_S y_S^T(\tau), \\
y_S^U(0) = \int_0^\infty c[\beta_S^U(\tau) y_S^U(\tau) + \beta_S^T(\tau) y_S^T(\tau)]d\tau, \\
\frac{dy_S^T(\tau)}{d\tau} = \sigma_S y_S^U(\tau) + (g_2(\tau) - \omega) y_S^T(\tau), \\
y_S^T(0) = 0, \\
\frac{dy_R^U(\tau)}{d\tau} = (f_1(\tau) - \omega) y_R^U(\tau) + g_R y_R^T(\tau), \\
y_R^U(0) = \int_0^\infty c[\beta_R^U(\tau) y_R^U(\tau) + \beta_R^T(\tau) y_R^T(\tau)]d\tau, \\
\frac{dy_R^T(\tau)}{d\tau} = e\sigma_R y_R^U(\tau) + (f_2(\tau) - \omega) y_R^T(\tau), \\
y_R^T(0) = 0.
\end{cases}
\tag{5.2}
$$

First, we discuss the solution of the second and the fourth equations in the above system (5.2), which have the same form as system (3.5). Then from the results in

section 3 we get the unique solution of the second and the forth equations of system (5.2) under initial values $y_S^U(0)$ and $y_S^T(0)$ as:

$$\begin{bmatrix} y_S^U(\tau) \\ y_S^T(\tau) \end{bmatrix} = \frac{\sigma_S y_S^U(0)}{\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega)}$$

$$\times \left(\begin{bmatrix} \frac{\lambda_1^*(\tau,\omega)-(g_2(\tau)-\omega)}{\sigma_S} \\ 1 \end{bmatrix} e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} - \begin{bmatrix} \frac{\lambda_2^{S*}(\tau,\omega)-(g_2(\tau)-\omega)}{\sigma_S} \\ 1 \end{bmatrix} e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma} \right).$$

Substituting $y_S^U(\tau)$ and $y_S^T(\tau)$ in the third equation of system (5.2) by the above equation respectively, we have

$$y_S^U(0) = \int_0^\infty c[\beta_S^U(\tau)y_S^U(\tau) + \beta_S^T(\tau)y_S^T(\tau)]d\tau$$

$$= y_S^U(0)\frac{c\sigma_S}{\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega)}$$

$$\times \int_0^\infty \left[\beta_S^U(\tau)\left(\frac{\lambda_1^*(\tau,\omega)-g_2(\tau)+\omega}{\sigma_S}e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} - \frac{\lambda_2^{S*}(\tau,\omega)-g_2(\tau)+\omega}{\sigma_S}e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma} \right) \right.$$

$$\left. +\beta_S^T(\tau)\left(e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} - e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma} \right) \right] d\tau.$$

Cancel the same $y_S^U(0)$ in the above equation, we obtain the following characteristic equation:

$$\mathcal{G}_S(\omega) = 1,$$

where

$$\mathcal{G}_S(\omega) = \frac{c\sigma_S}{\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega)} \int_0^\infty \left[\beta_S^U(\tau)\left(\frac{\lambda_1^*(\tau,\omega) - g_2(\tau) + \omega}{\sigma_S}e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} \right. \right.$$

$$\left. - \frac{\lambda_2^*(\tau,\omega) - g_2(\tau) + \omega}{\sigma_S}e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma} \right) \qquad (5.3)$$

$$\left. + \beta_S^T(\tau)\left(e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} - e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma} \right) \right] d\tau.$$

Now we prove that $\mathcal{G}_S(\omega)$ is a decreasing function. Easy to get that

$$\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega) = \sqrt{(g_1(0) - g_2(0))^2 + 4g_s\sigma_s},$$

$$\frac{\lambda_1^*(\tau,\omega) - g_2(\tau) + \omega}{\sigma_S} = \frac{g_1(\tau) - g_2(\tau) + \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_s\sigma_s}}{2\sigma_s},$$

$$\frac{\lambda_2^*(\tau,\omega) - g_2(\tau) + \omega}{\sigma_S} = \frac{g_1(\tau) - g_2(\tau) - \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_s\sigma_s}}{2\sigma_s},$$

$$e^{\int_0^\tau \lambda_{1,2}^*(\sigma,\omega)d\sigma} = e^{\frac{1}{2}\int_0^\tau g_1(\sigma)+g_2(\sigma)\pm\sqrt{(g_1(\tau)-g_2(\tau))^2+4g_s\sigma_s}d\sigma}e^{-\omega\tau}.$$

Define

$$\Lambda = \lambda_1^*(0,\omega) - \lambda_2^*(0,\omega),$$

$$A(\tau) = \frac{(g_1(\tau) - g_2(\tau)) + \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_s\sigma_s}}{2\sigma_S}$$

$$\times e^{\frac{1}{2} \int_0^\tau g_1(\sigma) + g_2(\sigma) + \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_s\sigma_s} d\sigma}$$

$$- \frac{(g_1(\tau) - g_2(\tau)) + \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_s\sigma_s}}{2\sigma_S}$$

$$\times e^{\frac{1}{2} \int_0^\tau g_1(\sigma) + g_2(\sigma) - \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_s\sigma_s} d\sigma},$$

$$B(\tau) = e^{\frac{1}{2} \int_0^\tau g_1(\sigma) + g_2(\sigma) + \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_s\sigma_s} d\sigma}$$

$$- e^{\frac{1}{2} \int_0^\tau g_1(\sigma) + g_2(\sigma) - \sqrt{(g_1(\tau) - g_2(\tau))^2 + 4g_s\sigma_s} d\sigma}.$$

Then

$$\mathcal{G}_S(\omega) = \frac{c\sigma_s}{\Lambda} \int_0^\infty e^{-\omega\tau} \left[\beta_S^U(\tau) A(\tau) + \beta_S^T(\tau) B(\tau) \right] d\tau.$$

Obviously, $\mathcal{G}_S(\omega)$ is a decreasing function. Also, it is easy to verify that

$$\mathcal{G}_S(0) = \mathcal{R}_S.$$

Similarly, we have the following characteristic equation: $\mathcal{G}_R(\omega) = 1$ for the sixth to the ninth equations of system (5.2) where

$$\mathcal{G}_R(\omega) = \frac{ce\sigma_R}{\lambda_1(0,\omega) - \lambda_2(0,\omega)} \int_0^\infty \left[\beta_R^U(\tau) \left(\frac{\lambda_1(\tau,\omega) - f_2(\tau) + \omega}{e\sigma_R} e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma} \right. \right.$$

$$\left. - \frac{\lambda_2(\tau,\omega) - f_2(\tau) + \omega}{e\sigma_R} e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma} \right) \tag{5.4}$$

$$\left. + \beta_R^T(\tau) \left(e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma} - e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma} \right) \right] d\tau.$$

Similarly we have $\mathcal{G}_R(\omega)$ is a decreasing function and

$$\mathcal{G}_R(0) = \mathcal{R}_R.$$

In the following, we discuss the stability of the disease-free equilibrium.

1. When $\max\{\mathcal{R}_S, \mathcal{R}_R\} < 1$ holds.
   Assume that $\omega = a + bi$ is a complex solution of $\mathcal{G}_j(\omega) = 1$ $(j = S, R)$ with $a \geq 0$. Then for such ω and each j and considering that $\mathcal{G}_j(\omega)$ is a decreasing function, we have

   $$\|\mathcal{G}_j(\omega)\| \leq \mathcal{G}_j(a) \leq \mathcal{G}_j(0) = \mathcal{R}_j < 1,$$

   which build contradiction. Hence, the equation $\mathcal{G}_j(\omega) = 1$ has solutions with only negative real part and the disease-free equilibrium ε_0 is locally asymptotically stable under $\max\{\mathcal{R}_S, \mathcal{R}_R\} < 1$ holds.

2. When $\max\{\mathcal{R}_S, \mathcal{R}_R\} > 1$ holds.
   Suppose $\max\{\mathcal{R}_S, \mathcal{R}_R\} = \mathcal{R}_k > 1$, for $k = S$ or R. Then for the fixed k, we have $\mathcal{R}_k = \mathcal{G}_k(0) > 1$. Furthermore, $\lim_{\omega\to\infty} \mathcal{G}_k(\omega) = 0$. Hence, according to the intermediate value theorem, the equation $\mathcal{G}_k(\omega) = 1$ has a real positive root. Therefore, the disease-free equilibrium ε_0 is unstable.

5.2. The stability of boundary endemic equilibria

From Theorem 1 we know that the boundary equilibrium $\varepsilon_R^b = \left(X_R^b, 0, 0, Y_R^{Ub}(\tau),\right.$ $\left.Y_R^{Tb}(\tau)\right)$ exists if and only if $\mathcal{R}_R > 1$ hold. Now we consider the local stability of the boundary equilibrium ε_R^b. For this purpose, we derive the linearized equations of ε_R^b and introduce the following notation for the perturbations:

$$X(t) = X_R^b + x^b(t),$$
$$Y_S^{Ub}(t, \tau) = y_S^{Ub}(t, \tau), \ Y_S^{Tb}(t, \tau) = y_S^{Tb}(t, \tau),$$
$$Y_R^{Ub}(t, \tau) = Y_R^{Ub}(\tau) + y_R^{Ub}(t, \tau), \ Y_R^{Tb}(t, \tau) = Y_R^{Tb}(\tau) + y_R^{Tb}(t, \tau),$$
$$N(t) = N_R^b + n^b(t).$$

During this process, we use the Taylor Approximation:

$$\frac{1}{N_R^b + n^b(t)} = \frac{1}{N_R^b \left(1 + \frac{n^b(t)}{N_R^b}\right)} = \frac{1}{N_R^b} \left(1 - \frac{n^b(t)}{N_R^b} + \cdots\right) \approx \frac{1}{N_R^b} \left(1 - \frac{n^b(t)}{N_R^b}\right)$$

and define

$$Q = \int_0^\infty c[\beta_R^U(\tau) Y_R^{Ub}(\tau) + \beta_R^T(\tau) Y_R^{Tb}(\tau)] d\tau,$$

then the linearized system of (2.4) at ε_R^b becomes:

$$
\begin{cases}
\frac{dx^b(t)}{dt} = -\mu x^b(t) - y_S^{Ub}(t, 0) - y_R^{Ub}(t, 0), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) y_S^{Ub}(t, \tau) = g_1(\tau) y_S^{Ub}(t, \tau) + g_S y_S^{Tb}(t, \tau), \\
y_S^{Ub}(t, 0) = \frac{X_R^b}{N_R^b} \int_0^\infty c[\beta_S^U(\tau) y_S^{Ub}(t, \tau) + \beta_S^T(\tau) y_S^{Tb}(t, \tau)] d\tau, \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) y_S^{Tb}(t, \tau) = \sigma_S y_S^{Ub}(t, \tau) + g_2(\tau) y_S^{Tb}(t, \tau), \\
y_S^{Tb}(t, 0) = 0, \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) y_R^{Ub}(t, \tau) = f_1(\tau) y_R^{Ub}(t, \tau) + g_R y_R^{Tb}(t, \tau), \\
y_R^{Ub}(t, 0) = \frac{X_R^b}{N_R^b} \int_0^\infty c[\beta_R^U(\tau) y_R^{Ub}(t, \tau) + \beta_R^T(\tau) y_R^{Tb}(t, \tau)] d\tau - \frac{Q}{N_R^b} \left(\frac{X_R^b}{N_R^b} n^b(t) - x^b(t)\right), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) y_R^{Tb}(t, \tau) = e\sigma_R y_R^{Ub}(t, \tau) + f_2(\tau) y_R^{Tb}(t, \tau), \\
y_R^T(t, 0) = 0.
\end{cases}
\tag{5.5}
$$

We look for solutions of the form

$$x^b(t) = x^b e^{\omega t},$$
$$y_S^{Ub}(t, \tau) = y_S^{Ub}(\tau) e^{\omega t}, \ y_S^{Tb}(t, \tau) = y_S^{Tb}(\tau) e^{\omega t},$$
$$y_R^{Ub}(t, \tau) = y_R^{Ub}(\tau) e^{\omega t}, \ y_R^{Tb}(t, \tau) = y_R^{Tb}(\tau) e^{\omega t},$$
$$n^b(t) = n^b e^{\omega t},$$

then we obtain the following eigenvalue problem:

$$
\begin{cases}
\omega x^b = -\mu x^b - y_S^{Ub}(0) - y_R^{Ub}(0), \\
\frac{dy_S^{Ub}(\tau)}{d\tau} = (g_1(\tau) - \omega)y_S^{Ub}(\tau) + g_S y_S^{Tb}(\tau), \\
y_S^{Ub}(0) = \frac{X_R^b}{N_R^b} \int_0^\infty c[\beta_S^U(\tau)y_S^{Ub}(\tau) + \beta_S^T(\tau)y_S^{Tb}(\tau)]d\tau, \\
\frac{dy_S^{Tb}(\tau)}{d\tau} = \sigma_S y_S^{Ub}(\tau) + (g_2(\tau) - \omega)y_S^{Tb}(\tau), \\
y_S^{Tb}(0) = 0, \\
\frac{dy_R^{Ub}(\tau)}{d\tau} = (f_1(\tau) - \omega)y_R^{Ub}(\tau) + g_R y_R^{Tb}(\tau), \\
y_R^{Ub}(0) = \frac{X_R^b}{N_R^b} \int_0^\infty c[\beta_R^U(\tau)y_R^{Ub}(\tau) + \beta_R^T(\tau)y_R^{Tb}(\tau)]d\tau - \frac{Q}{N_R^b}\left(\frac{X_R^b}{N_R^b}n^b - x^b\right), \\
\frac{dy_R^{Tb}(\tau)}{d\tau} = e\sigma_R y_R^{Ub}(\tau) + (f_2(\tau) - \omega)y_R^{Tb}(\tau), \\
y_R^{Tb}(0) = 0.
\end{cases}
\tag{5.6}
$$

In the following, we discuss the stability of ε_R^b by two steps:

1. First, we discuss the solution of the second and the fourth equations in system (5.6), which have the same form as system (3.5). Hence we get the unique solution of the second and the forth equations of system (5.6) under initial values $y_S^{Ub}(0)$ and $y_S^{Tb}(0)$ as follows:

$$
\begin{bmatrix} y_S^{Ub}(\tau) \\ y_S^{Tb}(\tau) \end{bmatrix} = \frac{\sigma_S y_S^{Ub}(0)}{\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega)} \cdot
$$

$$
\left(\begin{bmatrix} \frac{\lambda_1^*(\tau,\omega) - (g_2(\tau) - \omega)}{\sigma_S} \\ 1 \end{bmatrix} e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} - \begin{bmatrix} \frac{\lambda_2^*(\tau,\omega) - (g_2(\tau) - \omega)}{\sigma_S} \\ 1 \end{bmatrix} e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma} \right).
$$

Substituting $y_S^{Ub}(\tau)$ and $y_S^{Tb}(\tau)$ in the third equation of system (5.6) by the above equation respectively and let

$$
\begin{aligned}
\Omega_S(\omega) = &\int_0^\infty \beta_S^U(\tau)\left(\frac{\lambda_1^*(\tau,\omega) - g_2(\tau) + \omega}{\sigma_S}e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma}\right)d\tau \\
&- \int_0^\infty \beta_S^U(\tau)\left(\frac{\lambda_2^*(\tau,\omega) - g_2(\tau) + \omega}{\sigma_S}e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma}\right)d\tau \\
&+ \int_0^\infty \beta_S^T(\tau)\left(e^{\int_0^\tau \lambda_1^*(\sigma,\omega)d\sigma} - e^{\int_0^\tau \lambda_2^*(\sigma,\omega)d\sigma}\right)d\tau,
\end{aligned}
\tag{5.7}
$$

then we have

$$
\begin{aligned}
y_S^{Ub}(0) =& \frac{X_R^b}{N_R^b} \cdot \int_0^\infty c[\beta_S^U(\tau)y_S^{Ub}(\tau) + \beta_S^T(\tau)y_S^{Tb}(\tau)]d\tau \\
=& y_S^{Ub}(0)\frac{c\sigma_S}{\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega)} \cdot \frac{X_R^b}{N_R^b} \cdot \Omega_S(\omega).
\end{aligned}
\tag{5.8}
$$

Cancel the same $y_S^{Ub}(0)$ in the above equation, we obtain the following characteristic equation:

$$
\mathcal{G}_S^b(\omega) = 1,
$$

where

$$\mathcal{G}_S^b(\omega) = \frac{c\sigma_S}{\lambda_1^*(0,\omega) - \lambda_2^*(0,\omega)} \cdot \frac{X_R^b}{N_R^b} \cdot \Omega_S(\omega) = \frac{X_R^b}{N_R^b} \cdot \mathcal{G}_S(\omega), \qquad (5.9)$$

which implies that $\mathcal{G}_S^b(\omega)$ is also a decreasing function with $\lim_{\omega \to \infty} \mathcal{G}_S^b(\omega) = 0$. Note that $\dfrac{X_R^b}{N_R^b} = \dfrac{1}{\mathcal{R}_R}$, then

$$\mathcal{G}_S^b(0) = \frac{X_R^b}{N_R^b} \cdot \mathcal{G}_S(0) = \frac{X_R^b}{N_R^b} \cdot \mathcal{R}_S = \frac{\mathcal{R}_S}{\mathcal{R}_R}.$$

(a) Suppose $\mathcal{R}_S > \mathcal{R}_R > 1$ holds, i.e., $\mathcal{G}_S^b(0) > 1$, then equation $\mathcal{G}_S^b(\omega) = 1$ has at least one positive root according to the intermediate value theorem, and therefore ε_R^b is unstable.

(b) Suppose $\mathcal{R}_S < 1 < \mathcal{R}_R$. Under this situation, for ω with $\Re(\omega) > 0$, we have

$$\|\mathcal{G}_S^b(\omega)\| < \|\mathcal{G}_S(\omega)\| < \mathcal{G}_S(0) = \mathcal{R}_S < 1.$$

Hence, the equation $\mathcal{G}_S^b(\omega) = 1$ has no solution with positive real part and all the eigenvalues of this equation have negative real part.

So in the following, we consider the situation $\mathcal{R}_S < 1 < \mathcal{R}_R$ holds, under which, the boundary equilibrium ε_S^b does not exist.

2. Therefore, the stability of the boundary equilibrium ε_R^b depends on the eigenvalues of the following system when $\mathcal{R}_S < 1 < \mathcal{R}_R$ holds:

$$\begin{cases} \omega x^b = -\mu x^b - y_R^{Ub}(0), \\ \frac{dy_R^{Ub}(\tau)}{d\tau} = (f_1(\tau) - \omega)y_R^{Ub}(\tau) + g_R y_R^{Tb}(\tau), \\ y_R^{Ub}(0) = \frac{X_R^b}{N_R^b} \int_0^\infty c[\beta_R^U(\tau)y_R^{Ub}(\tau) + \beta_R^T(\tau)y_R^{Tb}(\tau)]d\tau - \frac{Q}{N_R^b}\left(\frac{X_R^b}{N_R^b}n^b - x^b\right), \\ \frac{dy_R^{Tb}(\tau)}{d\tau} = e\sigma_R y_R^{Ub}(\tau) + (f_2(\tau) - \omega)y_R^{Tb}(\tau), \\ y_R^T(0) = 0. \end{cases}$$

$$(5.10)$$

Similar to the discussion of system (3.1) in section 3, we get the unique solution of the second and the fourth equations of system (5.10) under initial values $y_R^{Ub}(0)$ and $y_R^{Tb}(0)$:

$$\begin{bmatrix} y_R^{Ub}(\tau) \\ y_R^{Tb}(\tau) \end{bmatrix} = \frac{e\sigma_R y_R^{Ub}(0)}{\lambda_1(0,\omega) - \lambda_2(0,\omega)} \cdot$$

$$\left(\begin{bmatrix} \frac{\lambda_1(\tau,\omega) - (f_2(\tau) - \omega)}{e\sigma_R} \\ 1 \end{bmatrix} e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma} - \begin{bmatrix} \frac{\lambda_2(\tau,\omega) - (f_2(\tau) - \omega)}{e\sigma_R} \\ 1 \end{bmatrix} e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma} \right).$$

From the first equation in (5.10) we obtain

$$x^b = -\frac{y_R^{Ub}(0)}{\omega + \mu}. \qquad (5.11)$$

Linearizing the equation for the total population size

$$N(t) = X(t) + \int_0^\infty [Y_S^U(t,\tau) + Y_S^T(t,\tau) + Y_R^U(t,\tau) + Y_R^T(t,\tau)]d\tau,$$

we obtain

$$n^b = x^b + \int_0^\infty [y_R^{Ub}(\tau) + y_R^{Tb}(\tau)]d\tau. \tag{5.12}$$

Also define

$$\Omega_R(\omega) = \frac{ce\sigma_R}{\lambda_1(0,\omega) - \lambda_2(0,\omega)} \cdot \int_0^\infty \left(c\beta_R^U(\tau) - \frac{Q}{N_R^b} \right)$$

$$\times \left(\frac{\lambda_1(\tau,\omega) - f_2(\tau) + \omega}{e\sigma_R} e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma} - \frac{\lambda_2(\tau,\omega) - f_2(\tau) + \omega}{e\sigma_R} e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma} \right) d\tau$$

$$+ \int_0^\infty \left(c\beta_R^T(\tau) - \frac{Q}{N_R^b} \right) \left(e^{\int_0^\tau \lambda_1(\sigma,\omega)d\sigma} - e^{\int_0^\tau \lambda_2(\sigma,\omega)d\sigma} \right) d\tau$$

$$< \mathcal{G}_R(\omega),$$

which is a decreasing function.

Substituting the expressions of $y_R^{Ub}(\tau)$, $y_R^{Tb}(\tau)$ and equation (5.12) respectively into the third equation of system (5.10), we get

$$y_R^{Ub}(0) = \frac{X_R^b}{N_R^b} \int_0^\infty c[\beta_R^U(\tau)y_R^{Ub}(\tau) + \beta_R^T(\tau)y_R^{Tb}(\tau)]d\tau - \frac{Q}{N_R^b} \left(\frac{X_R^b}{N_R^b} n^b - x^b \right)$$

$$= \frac{X_R^b}{N_R^b} \int_0^\infty c[\beta_R^U(\tau)y_R^{Ub}(\tau) + \beta_R^T(\tau)y_R^{Tb}(\tau)]d\tau + \frac{Qx^b}{N_R^b} \left(1 - \frac{X_R^b}{N_R^b} \right)$$

$$- \frac{QX_R^b}{(N_R^b)^2} \int_0^\infty [y_R^{Ub}(\tau) + y_R^{Tb}(\tau)]d\tau$$

$$= \frac{X_R^b}{N_R^b} \left[\int_0^\infty \left(c\beta_R^U(\tau) - \frac{Q}{N_R^b} \right) y_R^{Ub}(\tau) + \left(c\beta_R^T(\tau) - \frac{Q}{N_R^b} \right) y_R^{Tb}(\tau) \right] d\tau$$

$$+ \frac{Qx^b}{N_R^b} \left(1 - \frac{X_R^b}{N_R^b} \right)$$

$$= y_R^{Ub}(0) \cdot \frac{X_R^b}{N_R^b} \cdot \Omega_R(\omega) - \frac{y_R^{Ub}(0)}{\omega + \mu} \cdot \frac{Q}{N_R^b} \left(1 - \frac{X_R^b}{N_R^b} \right).$$

Cancelling $y_R^{Ub}(0)$ from both sides of the resulting equation, we obtain the following characteristic equation for ω: $\mathcal{G}_R^b(\omega) = 1$, where

$$\mathcal{G}_R^b(\omega) = \frac{X_R^b}{N_R^b} \cdot \Omega_R(\omega) - \frac{1}{\omega + \mu} \cdot \frac{Q}{N_R^b} \left(1 - \frac{X_R^b}{N_R^b} \right). \tag{5.13}$$

Substituting $\dfrac{X_R^b}{N_R^b} = \dfrac{1}{\mathcal{R}_R}$ in equation (5.13), we can rewrite the characteristic equation $\mathcal{G}_R^b(\omega) = 1$ in the following form:

$$\frac{\Omega_R(\omega)}{\mathcal{R}_R} = 1 + \frac{1}{\omega + \mu} \cdot \frac{Q}{N_R^b} \left(1 - \frac{1}{\mathcal{R}_R} \right).$$

Considering $\mathcal{G}_R^b(\omega) < \Omega_R(\omega) < \mathcal{G}_R(\omega)$, which are all decreasing functions, and $\mathcal{G}_R(0) = \mathcal{R}_R$. So for ω with $\Re\omega \geq 0$ we have

$$\left| \frac{\Omega_R(\omega)}{\mathcal{R}_R} \right| \leq 1.$$

On the other hand, the following inequality holds since $\mathcal{R}_R > 1$:

$$\left| 1 + \frac{1}{\omega + \mu} \cdot \frac{Q}{N_R^b} \left(1 - \frac{1}{\mathcal{R}_R} \right) \right| > 1.$$

Hence, the characteristic equation $\mathcal{G}_R^b(\omega) = 1$ has only solutions with negative real parts. Thus, the equilibrium ε_R^b is locally asymptotically stable when $\mathcal{R}_R > 1$ and $\mathcal{R}_S < \mathcal{R}_R$ both hold.

Similarly, we can get that the equilibrium ε_S^b is locally asymptotically stable when $\mathcal{R}_S > 1$ and $\mathcal{R}_R < 1$ both hold.

5.3. Conclusion

In short, we can summarize the discussions of stabilities of equilibria in the following Theorem 5.1:

Theorem 5.1. *Define the basic reproduction numbers*

$$\mathcal{R}_S = \mathcal{R}_S^b, \qquad \mathcal{R}_R = \mathcal{R}_R^b.$$

1. *When $\mathcal{R}_S < 1$ and $\mathcal{R}_R < 1$ both hold, the disease-free equilibrium ε_0 is locally asymptotically stable. No boundary equilibrium and endemic equilibrium exist under this situation. Otherwise, ε_0 is unstable.*

2. *When $\mathcal{R}_S > 1$ holds, the boundary equilibrium ε_S^b exists, and*

    (a) *when $\mathcal{R}_R < 1$ holds, the boundary equilibrium ε_R^b does not exist and the boundary equilibrium ε_S^b is locally asymptotically stable.*
    (b) *when $\mathcal{R}_R > \mathcal{R}_S$, ε_S^b is unstable.*

3. *When $\mathcal{R}_R > 1$ holds, the boundary equilibrium ε_R^b exists, and*

    (a) *when $\mathcal{R}_S < 1$ holds, the boundary equilibrium ε_S^b does not exist and the boundary equilibrium ε_R^b is locally asymptotically stable.*
    (b) *when $\mathcal{R}_S > \mathcal{R}_R$, ε_R^b is unstable.*

6. Simulations

We predicted the effectiveness of a high usage of ART in Beijing MSM community by analyzing our model with time-dependent uncertainty analyses. Some values of the parameters necessary for prediction are known, however, the values of other parameters are less certain. For each uncertainty analysis we used Latin hypercube sampling [5], a type of stratified Monte Carlo sampling. To make predictions, we assigned each uncertain parameter a probability density function (pdf). By perturbing individual parameters, we investigated their influence on estimates of $\mathcal{R}_S$ and $\mathcal{R}_R$. Suppose that an individual is invaded by HIV virus and the initial

value is $(300, 1, 0.001, 1000, 0.001)$. Then the immune system (such as CD4+ T cells) and HIV virus will evolve according to system (2.1). The individual has two possibilities: be infected by HIV, or not. If the individual is infected, then he (or she) will transfer HIV virus to his (or her) sexual partners during sexual behavior. The force of infection depends on HIV virus' concentration during the sexual behavior, which are denoted by expressions (2.7) and (2.8).

Suppose our target population is MSM in Beijing. The current HIV prevalence among MSM in Beijing was 12.7%, which was estimated from cross-sectional survey among 3588 participants from March 2013 to March 2014. In order to set the initial conditions, we had to estimate the target population of MSM living in Beijing in 2013. According the national census in 2013, there were about 15.4 million of people living in Beijing and 50.63% of them were male, in which 3% of males were MSM and 79% of them lived in the city. For parameter π, the rate at which MSM joined the sexually active community, we used the data of Beijing in 2013 [18] and supposed that recruitment rate into target population per year ranged from 2% to 6.4% [11]. We assume 10% HIV infected individuals carry drug-resistant strains and the other 90% carry drug-sensitive strains. Also, we assume 30% HIV positive individuals who carry drug-sensitive strain are going on ART treatment and the others no. Considering that

$$\int_0^\infty Y_S^U(0, \tau)d\tau = Y_S^{U0}$$

and the life curve that surveyed from blood donor of Anhui Province [23]

$$y = e^{-0.023 \times (\tau/365)^{2.39}},$$

we can get the initial values of HIV positive individuals who have been infected for τ long time.

The meaning of function $\beta_S^U(\tau)$ (in equations 2.7) is similar to that of parameter β_S^U in literature [5]. In [5], $\beta_S^U = 0.1$. To keep the same level, we suppose that coefficient σ_S in function $\beta_S^U(\tau)$ ranges from 0.3 to 0.5. At that in literature [5], here suppose coefficients $\widetilde{\beta}_S^T = \alpha_1 \widetilde{\beta}_S^U, \widetilde{\beta}_R^U = \alpha_2 \widetilde{\beta}_S^U$ and $\widetilde{\beta}_R^T = \alpha_3 \widetilde{\beta}_R^U$. Coefficients α_1, α_2 and α_3 are the same as that in literature [5]. In literature [5], the average survival time of untreated drug-sensitive individuals was 12 years $(1/v_S^U)$. They modeled uncertainty in the treatment effect of ART on the average survival time of drug-sensitive patients $(1/v_S^T)$ by using LHS to sample 1000 values of $1/v_S^T$ from a pdf that ranged from 18 to 36 years. They also assumed that the average survival times could range from 12 to 36 years for both treated $(1/v_R^T)$ and untreated $(1/v_R^U)$ drug-resistant patients. So for coefficients $\widetilde{v}_S^U, \widetilde{v}_S^T, \widetilde{v}_R^U$ and $\widetilde{v}_R^T$ in functions (2.8) in our model, we suppose they choose the same level distributions as their corresponding coefficients (Table 1). For parameters g_s (or g_r), proportion of cases of drug-sensitive (or drug-resistant) MSM+ that give up ART are estimated from the data base of HIV treatment of Henan province. For parameters σ_S and σ_R, the ART rate of drug-sensitive and drug-resistant MSM+, we suppose they have the same distribution. In general, meaning and value range of all parameters in the micro model are the same as that in literature [13] and parameters in the macro model are shown in Table 1.

First, we show the effect of the course of disease (age-since-infection) τ to HIV spreading in MSM in Beijing. The kernels of the two thresholds $\mathcal{R}_S$ and $\mathcal{R}_R$ are

Table 1. Parameter of Macro model

Para	Meaning	Range	Distribution	Reference
π	Rate at which MSM join the sexually active community	$(2000, 5000, 6600)$	Triangular	[11]
c	average number of new receptive anal sex partners per year	$(1, 3, 5)$	Triangular	[5]
μ_1	Rate of quit from this community	$1/(65\text{-}18)$	Constant	
g_S	Proportion of cases of drug-sensitive MSM+ that give up ART	$(0.1, 0.15, 0.3)$	Triangular	Estimated
g_R	Proportion of cases of drug-resistant MSM+ that give up ART	$(0.2, 0.3, 0.4)$	Triangular	Estimated
σ_S	ART rate of drug-sensitive MSM+	$(0.3, 0.4, 0.5)$	Triangular	Estimated
σ_R	ART rate of drug-resistant MSM+	$(0.3, 0.4, 0.5)$	Triangular	Estimated
$\widetilde{v}_S^U$	Proportionality coefficient	$1/12$		[5]
$\widetilde{v}_S^T$	Proportionality coefficient	$(1/36, 1/18)$	Uniform	[5]
$\widetilde{v}_R^U$	Proportionality coefficient	$(1/36, 1/12)$	Uniform	[5]
$\widetilde{v}_R^T$	Proportionality coefficient	$(1/36, 1/12)$	Uniform	[5]
$\widetilde{\beta}_S^U$	Proportionality coefficient	$(0.3, 0.4, 0.5)$	Triangular	Estimated
α_1	Proportionality coefficient	$(0.01, 0.5)$	Uniform	[5]
α_2	Proportionality coefficient	$(0, 1)$	Uniform	[5]
α_3	Proportionality coefficient	$(0, 1)$	Uniform	[5]

functions of the course of disease τ. It embodies the force of infection of HIV positive with course of disease τ. Figure 2 show the influence of course of disease, τ, to the kernels of $\mathcal{R}_S$ and $\mathcal{R}_R$. Both of the two kernels show a high force of infection at the beginning of infection and then tend to stable. In long time, the force of infection of the drug resistant strain is higher than that of the sensitive strain.

Second, we show the prevalence of HIV/AIDS in MSM in Beijing (Figure 3). Figure 3 (A) shows the total prevalence of HIV in MSM in Beijing in the next 10 years from 2013 and Figure 3 (B) shows the prevalence of HIV drug resistant strain in Beijing. Both of the two prevalence show fast increase tends in the next 10 years. At the end of 10 years later, the total prevalence could arrive at 38.8% in MSM in Beijing, among which, HIV drug resistant strain occupies about 20%.

Finally, we see that the effects of parameters $\sigma_r, \sigma_s, g_r, g_s, c$ and π change with respect to the whole HIV prevalence over time (Figure 4). As the average number of new receptive anal sex partners per year (c) change, it has positive correlated with strong PRCCs during the prediction (Figure 4 (E)). On the other hand, as the rate of gay men that join the susceptible community (π) change, it is negatively correlated with small PRCCs (Figure 4 (F)). Similarly, treatment rate of drug-
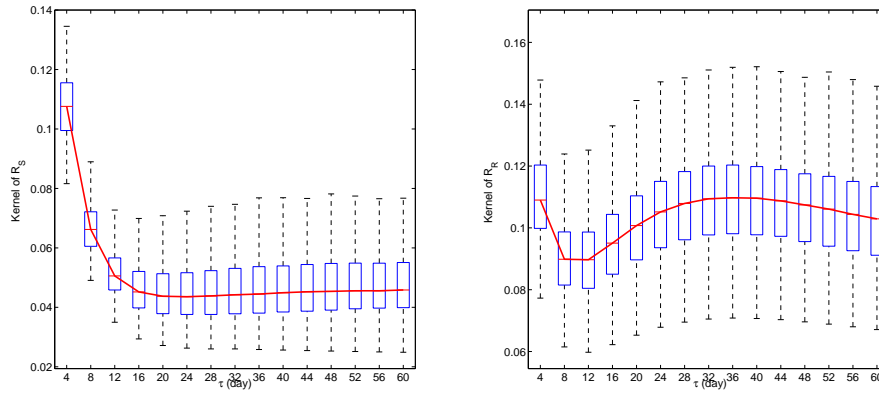
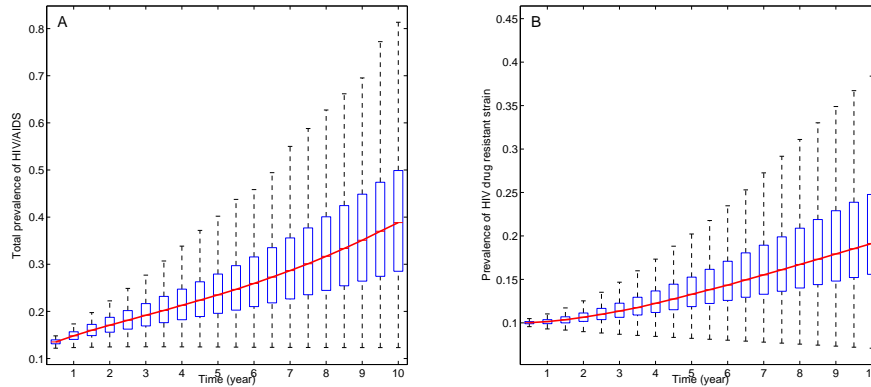**Figure 2.** The kernel of R_S and R_R range along with course of disease τ.

Figure 3. Total prevalence and rate of drug resistant strain.

resistant strain MSM+ (σ_r), proportions of give up ART in infected MSM (g_s and g_r) have positive correlated with small PRCCs (Figure 4 (A, C and D)) but treatment rate of drug-sensitive strain MSM+ (σ_s) is negatively correlated with small PRCCs (Figure 4 (B)) during the prediction. However, the effects of these parameters on the prevalence of the drug-resistant strain are slightly different (Fig. 5). Such as, treatment rate of drug-resistant strain MSM+ (σ_r, Figure 5 (A)) is negatively correlated with small PRCCs (Figure 5 (B)) but treatment rate of drug-sensitive strain MSM+ (σ_s) is positively correlated with large PRCCs (Figure 5 (B)) during the prediction of drug-resistant strain spreading. Also, the effect of the average number of new receptive anal sex partners per year (c) increases at the beginning but then decrease (Figure 5 (E)), but has smaller correlated to the drug-resistant strain spreading comparing to the whole HIV prevalence.
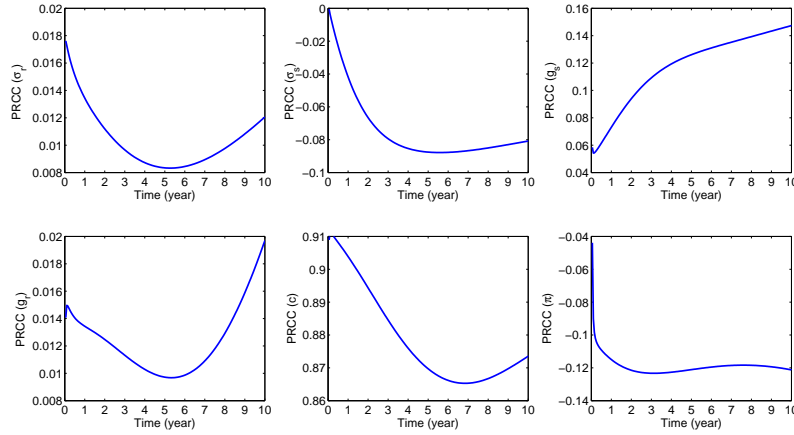
Figure 4. PRCCs of total prevalence for parameters $\sigma_r, \sigma_s, g_s, g_r, c$ and π.
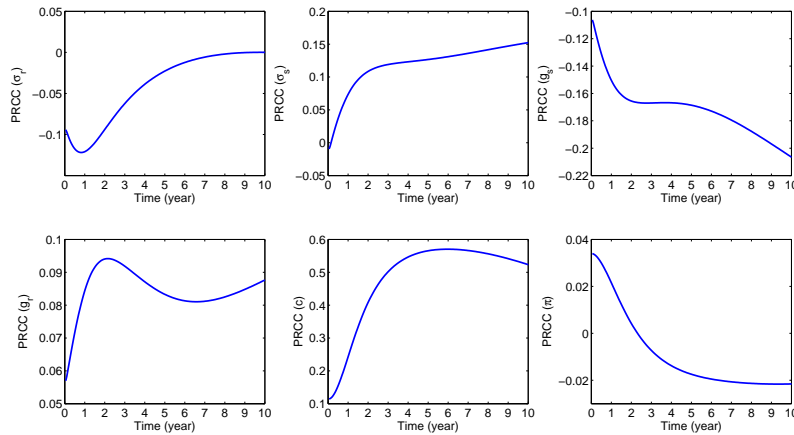

Figure 5. PRCCs of prevalence of drug-resistant strain for parameters $\sigma_r, \sigma_s, g_s, g_r, c$ and π.

7. Discussions

In this paper, a coupled within- (immunological) and between-host (epidemiological) dynamic model of HIV was proposed. first an ordinary differential system of HIV dynamics within an infected host [13] was introduced. Then an age-structured between-host HIV model was considered to describe the dynamics of host birth and death and the transmission of HIV within the host population [5]. We nest the within-host model within the epidemiological model by linking the dynamics of the within-host model to the additional host mortality, treatment rate, and transmission rate of the infection. The developed multi-scale model of HIV describes the joint affections of the immunological process and the epidemiological process,

which linked through age-since-infection and through the epidemiological parameters which depend on the within-host viral load and number of CD4+ T cells. Thresholds $\mathcal{R}_S$ and $\mathcal{R}_R$ for the between-host model were found.

Some simulations were given about the spreading of drug-sensitive strain and drug-resistant strain of HIV in Beijing MSM population. Simulations further show the influence of the within-host dynamics on the between-host dynamics. Our results show that the drug-resistant strain will increase quite fast in this population or both strains coexist, which indicates the importance of implementing the second-line treatment program as soon as possible. Our result hints that it will make a big pressure for China's "Four-Free-One-Care Policy".

References

[1] Chinese Center for Disease Control and Prevention: Analysis of HIV/STD epidemic in 2005, Beijing, China.

[2] Chinese Center for Disease Control and Prevention: Analysis of HIV/STD epidemic in 2013, Beijing, China.

[3] R. M. Anderson, *Mathematical studies of parasitic infection and immunity*, Science, 264(1994)(5167), 1884–1886.

[4] S. M. Blower, A. N. Aschenbach, H. B. Gershengorn and J. O. Kahn, *Predicting the unpredictable: transmission of drug-resistant HIV*, Nat Med, 7(2001), 1016–1020.

[5] S. M. Blower, H. B. Gershengorn and R. M. Grant, *A tale of two futures: HIV and antiretroviral therapy in San Francisco*, Science, 287(2000), 650–654.

[6] D. Coombs, M. A. Gilchrist and C. L. Ball, *Evaluating the importance of within- and between-host selection pressures on the evolution of chronic pathogens*, Theoretical population biology, 72(2007)(4), 576–591.

[7] S. D. Frost and A. R. McLean, *Quasispecies dynamics and the emergence of drug resistance during zidovudine therapy of HIV infection*, AIDS, 8(1994), 323–332.

[8] M. A. Gilchrist and A. Sasaki, *Modeling host–parasite coevolution: a nested approach based on mechanistic models*, Journal of Theoretical Biology, 218(2002)(3), 289–308.

[9] R. H. Gray, X. Li and M. J. Wawer, et al, *Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission: Rakai, Uganda*, AIDS, 17(2003)(13), 1941–51.

[10] H. Korthal Altes and V. Jansen, *Intra-host competition between nef-defective escape mutants and wild-type human immunodeficiency virus type 1*, Proc. R. Soc. Lond. B., 267(2000), 183–189.

[11] V. D. Lima, K. Johnston, R. S. Hogg, A. R. Levy and P. R. Harrigan, et al, *Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic.* J Infect Dis, 198(2008), 59–67.

[12] J. Lou, L. Bu, Y. Ruan, H. Xing and Y. Shao, *Modeling primary and secondary drug resistances under China's "Four -Free-One-Care Policy"*, International Journal of Biomathematics, 5(2012)(5), 1250032.

[13] J. Lou, Y. J. Lou and J. H. Wu, *Threshold virus dynamics with impulsive antiretroviral drug effects*, J. Math. Biol, 65(2012), 623–652.

[14] J. Lou, H. N. Zhou, D. Liang, Z. Jin and B. J. Song, *The coupled within- and between- host dynamics in the evolution of HIV/AIDS in China*, Journal of Applied Analysis and Computation, 5(2015)(4), 731–750.

[15] M. Martcheva and X. Z. Li, *Linking immunological and epidemiological dynamics of hiv: the case of super-infection*, Journal of biological dynamics, 7(2013)(1), 161–182.

[16] A. R. McLean and M. A. Nowak, *Competition between zidovudine-sensitive and zidovudine-resistant strains of HIV*. AIDS, 6(1992), 71–79.

[17] N. Mideo, S. Alizon and T. Day, *Linking within-and between-host dynamics in the evolutionary epidemiology of infectious diseases*, Trends in ecology evolution, 23(2008)(9), 511–517.

[18] http://www.askci.com/news/201402/17/171624523817.shtml.

[19] R. J. Smith and L. M. Wahl, *Distinct effects of protease and reverse transcriptase inhibition in an immunological model of HIV-1 infection with impulsive drug effects*, Bull. Math. Biol., 66(2004)(5), 1259–1283.

[20] R. J. Smith and L. M. Wahl, *Drug resistance in an immunological model of HIV-1 infection with impulsive drug effects* , Bulletin of Mathematical Biology, 67(2005), 783–813.

[21] J. X. Velasco-Hernandez, H. B. Gershengorn and S. M. Blower, *Could widespread use of combination antiretroviral therapy eradicate HIV epidemics* Lancet Infect Dis, 2(2002), 374–376.

[22] L. M. Wahl and M. A. Nowak, *Adherence and drug resistance: predictions for therapy outcome*, Proc. R. Soc. Lond. B., 267(2000), 835–843.

[23] X. Wang, X. P. Ding, B. Su, C. Xu, Y. Liu, Y. M. Zhang, J. L. Zhu, L. T. Han, Y. H. Ruan and Y. M. Shao, *The median survival and the effect of antiretroviral therapy among HIV-positive former blood donors in AnhuI province* , Zhonghua Liu Xing Bing Xue Za Zhi, 30(2009)(11), 1135–1138.

[24] S. Yerly, L. Kaiser and E. Race, et al, *Transmission of antiretrovirus drug-resistant HIV-1 variants*, Lancet, 354(1999), 729–33.