A Time-Delayed and Drug-Controlled Within-Host Model

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Abstract In this paper, we present an within-host model incorporating time delay and drug control mechanisms to study the dynamics of infectious diseases. We begin by defining the basic reproduction number, R_0, and subsequently prove that when $R_0 < 1$, the disease-free equilibrium is globally attractive, while for $R_0 > 1$, the disease persists uniformly.

Keywords within-host model, time delay, drug intervention, basic reproduction number, global attractivity, disease persistence.

1 Introduction

Infectious diseases continue to pose a significant threat to global public health, with pathogens evolving and adapting to host immune responses and therapeutic interventions. Understanding the dynamics of these host-pathogen interactions is crucial for the development of effective treatment strategies. Within-host models have emerged as valuable tools for unraveling the intricacies of infection dynamics, allowing for the exploration of various factors that influence disease progression (see [2,4,7,10–12,14–16]). One critical aspect that has garnered increasing attention in recent years is the inclusion of time delays in within-host models, coupled with the integration of drug control strategies.

Time delays in within-host models are essential for capturing the realistic temporal aspects of infection dynamics (see [1,3]). These delays represent the lag between pathogen introduction, host immune response activation, and the effects of therapeutic interventions. In many cases, pathogens exploit these delays to evade the host's defenses and develop resistance to drugs. Consequently, the incorporation of time delays into within-host models enables a more accurate depiction of infection dynamics and offers valuable insights into the challenges associated with disease management.

Moreover, the integration of drug control strategies into within-host models is a pivotal step toward optimizing treatment regimens. With the increasing prevalence of drug-resistant pathogens, the development of effective drug therapies has become an urgent priority. Within-host models that incorporate drug dynamics and their interactions with the host immune response provide a platform for evaluating the efficacy of various treatment protocols. These models can assist in the design of therapeutic strategies that minimize the emergence of drug resistance, reduce treatment duration, and enhance overall patient outcomes.

In this paper, we delve into the complex realm of within-host models with time delays and drug control strategies. Our aim is to provide a comprehensive overview of the current state of research in this field, highlighting the significance of time delays in infection dynamics and the role of drug interventions in mitigating the spread of infectious diseases. We will explore key mathematical concepts underpinning these models, review recent advancements in modeling techniques, and discuss their implications for clinical practice.

This paper is organized as follows: In section 2, we will provide a detailed explanation of within-host models with time delays, emphasizing their mathematical foundations and relevance to infection dynamics. In section 3, we will study the global dynamics for the model. A brief discussion is presented in the last section.

2 Model formulation

In the study of within-host pathogen dynamics, it is crucial to identify the type of control mechanisms that affect progression and persistence of diseases. Effects of drug therapy have been incorporated since the early stages of diseases. Initially, the infectious virus (V_I) can successfully attach to and deliver its DNA/RNA into the target cells (T) for replication and recombination processes, leading to the release of new viruses. However, the uninfectious virus (V_U) loses its ability to locate and interact with the target cells due to the reduced infectivity caused by the presence of reverse transcriptase inhibitors. Another control mechanism involves limiting the production of new infectious virions in the presence of protease inhibitors in the infected target cells (I).

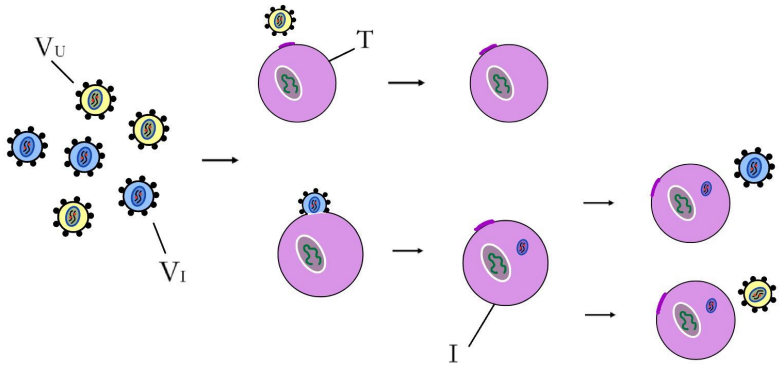

Figure 1: Schematic diagram of the effectiveness of the drug against viral transmission.

Following the models in [7, 15], we formulate the with-in host model as follows:

$$\begin{cases} \dfrac{dT}{dt} = n(T) - (1-\eta)\beta_1 T V_I - \beta_2 T I, \\ \dfrac{dI}{dt} = e^{-\mu_1\tau_1}(1-\eta)\beta_1 T(t-\tau_1)V_I(t-\tau_1) + e^{-\mu_1\tau_2}\beta_2 T(t-\tau_2)I(t-\tau_2) - \mu_1 I, \\ \dfrac{dV_I}{dt} = be^{-\mu_2\tau_3}(1-\epsilon)I(t-\tau_3) - \mu_3 V_I, \\ \dfrac{dV_U}{dt} = be^{-\mu_2\tau_3}\epsilon I(t-\tau_3) - \mu_3 V_U. \end{cases} \tag{2.1}$$

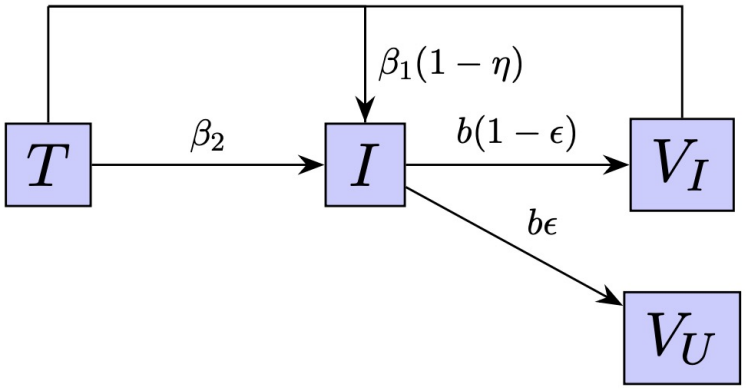

Figure 2: The schematic diagram of the with-in host model.

By the expressions in system (2.1) and the comparison principle, we can obtain the well-posedness clearly.

3 Threshold Dynamics

In this section, we first introduce the basic reproduction ratio R_0 and then study the global dynamics of 2.1. It is easy to see that the scalar linear equation has a unique positive equilibrium $T^* = \frac{s}{\mu}$ and it is globally attractive in $\mathbb{R}$. Linearizing system 2.1 at the virus-free solution $(T^*, 0, 0, 0)$, we obtain the following linear system:

$$\begin{cases} \dfrac{dI}{dt} = e^{-\mu_1\tau_1}(1-\eta)\beta_1 T^* e^{-\mu_1\tau_2} V_I(t-\tau_1) + \beta_2 T^* I(t-\tau_2) - \mu_1 I(t), \\ \dfrac{dV_I}{dt} = be^{-\mu_2\tau_3}(1-\epsilon)I(t-\tau_3) - \mu_3 V_I. \end{cases} \tag{3.1}$$

Let $\tau = \max\{\tau_1, \tau_2, \tau_3\}$, $C = C([-\tau, 0], \mathbb{R}^2)$, and $C^+ = ([-\tau, 0], \mathbb{R}^2_+)$. Then (C, C^+) is an ordered Banach space equipped with the maximum norm and the positive cone C^+. For any continuous function $H : [-\tau, \sigma) \to \mathbb{R}^2$ with $\sigma > 0$, we define $H_t \in C$ by $H_t(\theta) = H(t+\theta)$, $\forall \theta \in [-\tau, 0]$, and any $t \in [0, \sigma)$. Let F, V be two 2×2 matrix defined as follows:

$$F = \begin{bmatrix} \beta_2 T^* e^{-\mu_1\tau_1} - \mu_1 & (1-\eta)\beta_1 T^* e^{-\mu_1\tau_2} \\ 0 & 0 \end{bmatrix}, V = \begin{bmatrix} \mu_1 & 0 \\ -be^{-\mu_2\tau_3}(1-\epsilon) & \mu_3 \end{bmatrix}, \tag{3.2}$$

Then the linear system 3.1 can be written as

$$\frac{dH(t)}{dt} = FH_t - VH(t). \tag{3.3}$$

It follows from a straightforward computation in [8, 17, 19] that

$$R_0 = r(FV^{-1}) = \frac{1}{\mu_1} e^{-\mu_1\tau_2}\beta_2 n^{-1}(0) + \frac{1}{\mu_1\mu_3} be^{-\mu_2\tau_3}(1-\epsilon)e^{-\mu_1\tau_1}(1-\eta)\beta_1 n^{-1}(0).$$

Let $X = C([-\tau, 0], \mathbb{R}^4_+)$. Then we have the following results for system 2.1.

Theorem 3.1. *Assume that $\tau_1 = \tau_2$. Let $T^0 = n^{-1}(0)$. If $\mathcal{R}_0 < 1$, then the disease-free equilibrium is globally attractive for system* 2.1 *in X.*

Proof. **Case I: $\tau_3 > \tau_1$.** Define Lyapunov functional as

$$V(t) = \frac{1}{\mu_1} I(t) + \frac{c_1}{\mu_3} V_I(t) + \int_{t-\tau_1}^{t} R_0 I(s)ds + \int_{t-\tau_1}^{t} c_1 V_I(s)ds + \int_{t-\tau_3}^{t-\tau_1} c_2 I(s)ds, \tag{3.4}$$

where

$$\begin{aligned} c_1 &= \frac{1}{\mu_1}(1-\eta)e^{-\mu_1\tau_1}\beta_1 T^0, \\ c_2 &= \frac{1}{\mu_1\mu_3} b e^{-\mu_2\tau_3}(1-\epsilon)e^{-\mu_1\tau_1}(1-\eta)\beta_1 T^0. \end{aligned}$$

By calculation, we have

$$\begin{aligned} V_t &= \frac{1}{\mu_1}[e^{-\mu_1\tau_1}\beta_1(1-\eta)V_I(t-\tau_1) + e^{-\mu_1\tau_1}\beta_2 I(t-\tau_1)][T(t-\tau_1) - T^0] + (R_0-1)I(t) \\ &\le (R_0-1)I(t) \le 0, \end{aligned} \tag{3.5}$$

when $R_0 \le 1$.

Case II: $\tau_3 \le \tau_1$. Define Lyapunov functional as

$$V(t) = \frac{1}{\mu_1} I(t) + \frac{c_1}{\mu_3} V_I(t) + \int_{t-\tau_3}^{t} R_0 I(s)ds + \int_{t-\tau_1}^{t} c_1 V_I(s)ds + \int_{t-\tau_1}^{t-\tau_3} c_2 I(s)ds, \tag{3.6}$$

where

$$\begin{aligned} c_1 &= \frac{1}{\mu_1}(1-\eta)e^{-\mu_1\tau_1}\beta_1 T^0, \\ c_2 &= \frac{1}{\mu_1} e^{-\mu_1\tau_1}\beta_2 T^0. \end{aligned}$$

By calculation, we have

$$\begin{aligned} V_t &= \frac{1}{\mu_1}[e^{-\mu_1\tau_1}\beta_1(1-\eta)V_I(t-\tau_1) + e^{-\mu_1\tau_1}\beta_2 I(t-\tau_1)][T(t-\tau_1) - T^0] + (R_0-1)I(t) \\ &\le (R_0-1)I(t) \le 0, \end{aligned} \tag{3.7}$$

when $R_0 \le 1$. □

Furthermore, we have the following main result.

Theorem 3.2. *We have the following theorem,*

(i) If $\mathcal{R}_0 < 1$, then the disease-free equilibrium is globally attractive for system 2.1 *in X.*

(ii) If $\mathcal{R}_0 > 1$, then there is an $m > 0$ such that any solution

$$u(t,\phi) = (T(t,\phi), I(t,\phi), V_I(t,\phi), V_U(t,\phi))$$

of system 2.1 *with $\phi \in X$ with $\phi_2(0) > 0$, $\phi_3(0) > 0$ satisfies $\liminf_{t\to\infty}(I(t,\phi), V_I(t,\phi)) > (m,m)$.*

Proof. Take the solution map of (3.1) be $Q_t(\phi) = u(t,\phi)$ with $\phi \in C$. Let $Q = Q_1$. By [5, Theorem 6.1, Chapter 3], we have $Q(t)$ is compact for any $t \geqslant \tau$. In the case where $\mathcal{R}_0 < 1$, let $Q_\gamma(t)$ be the solution map of the following perturbed linear equation on C:

$$\begin{cases} \dfrac{dI}{dt} = e^{-\mu_1\tau_1}(1-\eta)\beta_1(T^*+\gamma)e^{-\mu_1\tau_2}V_I(t-\tau_1) + \beta_2(T^*+\gamma)I(t-\tau_2) - \mu_1 I(t), \\ \dfrac{dV_I}{dt} = be^{-\mu_2\tau_3}(1-\epsilon)I(t-\tau_3) - \mu_3 V_I. \end{cases} \tag{3.8}$$

and $\mathcal{R}_0^\gamma$ is the basic reproduction number for system (3.8). Since $\lim\limits_{\epsilon\to 0}\mathcal{R}_0^\gamma < 1$, we can fix a sufficiently small number $\gamma > 0$ such that $\mathcal{R}_0^\gamma < 1$. It is easy to verify that $Q_\gamma(t)$ is also compact and strongly monotone on C for each $t > \tau$. We can see that there is a positive function $v_\gamma(t)$ such that $u_\gamma(t) = e^{\mathcal{R}_0^\gamma t}v_\gamma(t)$ is a positive solution of system (3.8). Clearly, $\lim\limits_{t\to\infty} u_\gamma(t) = 0$. By the global stability of T^*, there exists a sufficiently large integer $N_1 > 0$ such that $N_1 \geqslant \tau$ and $T(t) < T^* + \gamma$, $\forall t \geqslant N_1 - \tau$. The solution $I(t)$ satisfies this following inequality:

$$\frac{dI}{dt} \leqslant e^{-\mu_1\tau_1}(1-\eta)\beta_1(T^*+\gamma)e^{-\mu_1\tau_2}V_I(t-\tau_1) + \beta_2(T^*I+\gamma)(t-\tau_2) - \mu_1 I(t),$$

for $t \geqslant N_1$. Choose a sufficiently large number $k > 0$ such that $I(t) \leqslant ku_\gamma(t)$, $\forall t \in [N_1, N_1+\tau]$. Thus, the comparison theorem for differential equations implies that $I(t) \leqslant ku_\gamma(t)$, $\forall t \geqslant N_1+\tau$. Thus $\lim\limits_{t\to\infty} I(t) = 0$. Taking this result back to the third equation and forth equation of (2.1), we have $\lim\limits_{t\to\infty} V_I(t) = 0$, and $\lim\limits_{t\to\infty} V_U(t) = 0$. Let $w(t) := T(t) - T^*$. In view of (2.1), we have

$$w'(t) = -\mu w - (1-\eta)\beta_1(w+T^*)V_I - \beta_2(w+T^*)I.$$

Since $\lim\limits_{t\to\infty} V_I(t) = 0$ and $\lim\limits_{t\to\infty} I(t) = 0$, it follows that $\lim\limits_{t\to\infty} w(t) = 0$. Thus, $\lim\limits_{t\to\infty} T(t) - T^* = 0$. This proves statement (i). In the case where $\mathcal{R}_0 > 1$, we will apply the persistence theory for this semiflows. Take

$$X_0 = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X : \phi_2(0) > 0,\ \phi_3(0) > 0\}$$

and

$$\partial X_0 = X \setminus X_0 = \{\phi \in X : \phi_2(0) = 0,\ \text{or } \phi_3(0) = 0\}.$$

It is easy to see that X_0 is an open set relative to X. Let $\Phi(t) : X \to X (\forall t \geqslant 0)$ be the solution semi-flow generated from system 3.1. Taking any $\phi \in X$, we conclude from the firsts equation of system 2.1 that $\dfrac{dT}{dt} = s - \mu T - (1-\eta)\beta_1 TV_I - \beta_2 TI$. It follows that $T(t,\phi) = \phi_1(0)\exp\left(-\int_0^t \mu + (1-\eta)\beta_1 V_I - \beta_2 I \mathrm{d}\xi\right) + \int_0^t s\exp\left(-\int_m^t \mu + (1-\eta)\beta_1 V_I - \beta_2 I \mathrm{d}\xi\right)\mathrm{d}m > 0$ for all $t > 0$. Similarly, we can get $V_U(t,\phi) = \phi_4(0)e^{-\mu_3 t} + \int_0^t b\epsilon e^{-\mu_3(t-s)-mu_2\tau_3}I(s-\tau_3)\mathrm{d}s \geqslant 0$, for all $t \geqslant 0$. Since $I'(t) > -\mu_1 I$ and $V_I'(t) > -\mu_3 V_I$ and $\phi_2(0) > 0$, $\phi_3(0) > 0$, it follows that $I(t,\phi) > 0$, $V_I(t,\phi) > 0$ for all $t \geqslant 0$. Thus we have the solution semiflow $\Phi(t) : X_0 \to X_0$. By the uniform and ultimate boundedness of the solution $u(t,\phi)$, it follows that $\Phi(t)$ is point dissipative. By Hale and Verduyn Lunel([5, Theorem 3.6.1]), for each $t > \tau$, $\Phi(t)$ is compact. We prove that $\Phi(t)$ is uniformly persistence with respect to $(X_0, \partial X_0)$. Let $\mathcal{R}_0^m$ be the basic

reproduction number of the following perturbed linear equation:

$$\begin{cases} \dfrac{dI}{dt} = e^{-\mu_1\tau_1}(1-\eta)\beta_1(T^*-m)e^{-\mu_1\tau_2}V_I(t-\tau_1) + \beta_2(T^*-m)I(t-\tau_2) - \mu_1 I(t), \\ \dfrac{dV_I}{dt} = be^{-\mu_2\tau_3}(1-\epsilon)I(t-\tau_3) - \mu_3 V_I. \end{cases} \tag{3.9}$$

Since $\lim\limits_{m\to 0} \mathcal{R}_0^m > 1$, we can fix a sufficiently small $m > 0$ such that $\mathcal{R}_0^m > 1$. Let $M_1 = (T^*, 0, 0, 0)$.

Claim $\limsup\limits_{n\to\infty} \|\Phi_t(\phi) - M_1\| \geqslant m$, where $\|\cdot\|$ denotes the Euclidean norm. Suppose by contradiction, that $\limsup\limits_{n\to\infty} \|\Phi_t(\phi) - M_1\| < m$ for some $\phi \in X_0$. Then there exists an $N_2 > 0$ such that $\|\Phi_t(\phi) - M_1\| < m$ for all $t \geqslant N_2$. Hence,

$$\|\Phi_t(\phi) - \Phi_t(M_1)\| = \|\Phi_t - M_1\| < m,\ t > N_2.$$

It follows that $T(t-\tau) > T^* - m$ for all $t \geqslant N_2 + \tau$. Thus,

$$u(t,\phi) = (T(t,\phi), I(t,\phi), V_I(t,\phi), V_U(t,\phi))$$

satisfies

$$\begin{aligned} \frac{dI}{dt} =& e^{-\mu_1\tau_1}(1-\eta)\beta_1 T(t-\tau_1)V_I(t-\tau_1) + e^{-\mu_1\tau_2}\beta_2 T(t-\tau_2)I(t-\tau_2) - \mu_1 I, \\ \geqslant& e^{-\mu_1\tau_1}(1-\eta)\beta_1(T^*-m)V_I(t-\tau_1) + e^{-\mu_1\tau_2}\beta_2(T^*-m)I(t-\tau_2) - \mu_1 I, \end{aligned}$$

for all $t \geqslant \tau$. Note that $\mathcal{R}_0^m > 1$. As discussed earlier, there is a positive function $v_m > 0$ such that $u_m(t) = e^{\mathcal{R}_0^m t}v_m(t)$ is a positive solution of system (3.9). Sine $\Phi(t)X_0 \subset X_0$, $I(t) > 0$ for all $t \geqslant 0$. We can choose a sufficiently small $k > 0$ such that $I(t) > ku_m(t)$, $\forall t \in [N_2+\tau, N_2+2\tau]$. By the comparison theorem for delay differential equations, it follows that $I(t) \geqslant ku_m(t)$, $\forall t \geqslant N_2 + \tau$. Clearly, $\lim\limits_{t\to\infty} u_m(t) = \infty$. Thus, $\lim\limits_{t\to\infty} I(t) = \infty$, which is a contradiction. This completes the statement (ii). □

4 Discussion

In this paper, we introduce an intricate within-host model that integrates time delay and drug control mechanisms. Our primary objective is to investigate the dynamics of infectious diseases. To commence, we establish the basic reproduction number, denoted as R_0. Subsequently, we demonstrate that when $R_0 < 1$, the disease-free equilibrium is globally attractive. Conversely, when $R_0 > 1$, the disease is uniformly persistent.

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