Research article

Reaction-diffusion model of HIV infection of two target cells under optimal control strategy

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Abstract: In order to study the effects of reverse transcriptase inhibitors, protease inhibitors and flavonoids on two target cells infected by HIV in a heterogeneous environment, an HIV mathematical model at the cellular level was established. Research shows that infected cells can be categorized into immature infected cells, latent infected cells, and mature infected cells based on the infection process. The basic reproduction number R_0 was established, and it is proved that R_0 serves as a threshold parameter: When $R_0 < 1$, the disease-free steady state is globally asymptotically stable, and the disease is extinct; when $R_0 > 1$, the solution of the system is uniformly persistent, and the virus exists. Considering the huge advantages of drug intervention in controlling HIV infection, the optimal control problem was proposed under the condition that the constant diffusion coefficient is positive, so as to minimize the total number of HIV-infected cells and the cost of drug treatment. To illustrate our theoretical results, we performed numerical simulations in which the model parameters were obtained with reference to some medical studies. The results showed that: (1) as R_0 increases, the risk of HIV transmission increases; (2) pharmacological interventions are important in early treatment of HIV spread and control of viral load in the body; (3) the treatment process must consider the heterogeneity of medication, otherwise it will not be conducive to suppressing the spread of the virus and will increase costs.

Keywords: HIV model; spatial heterogeneity; stability analysis; optimal control; numerical simulations

1. Introduction

HIV (Human immunodeficiency Virus), the causative agent of AIDS (acquired immune deficiency syndrome), infects nearly 40 million people worldwide [1] and represents one of the highest overall global burdens of disease [2]. HIV is a virus that attacks the immune system. Over time, HIV can lead to a weakened immune systems, making individuals more susceptible to opportunistic infections and certain cancers [3].

HIV predominantly infects immune system cells, specifically targeting $CD4^+T$ cellls (a type of white blood cell) that play pivotal roles in orchestrating and executing the body's defense mechanisms against infections. Once the virus enters immune system cells, the viral RNA is reversely transcribed into DNA by the enzyme reverse transcriptase. When the host cell becomes activated, it begins to transcribe and translate the proviral DNA, producing new viral RNA and proteins. These viral components are assembled into new virus particles. The newly formed virus particles bud from the host cell's membrane, acquiring an outer envelope derived from the host cell membrane [4]. After HIV infects host cells, in addition to immediately starting to replicate and destroy $CD4^+T$ lymphocytes of the immune system, it can also enter the latent state of the cells. This latent state allows the virus to hide within host cells and avoid detection by the immune system, making HIV infection a chronic, sustainable disease [5]. Given the intricate nature of HIV transmission within the human body, experimental study of the entire process poses significant challenges. In contrast, the development of viral dynamics models stands as a valuable and rigorous approach for investigating the virus's transmission processes and pathogenic mechanisms within the host.

Numerous studies based on virus models have been conducted to investigate the interactions between virus and host [6–8]. With the development of modern medicine and scientific research, researchers have completed the model from adding the virus, infected cells and susceptible cells [9, 10], to gradually put more infection patterns processes into consideration [11–14], so that the model can accurately describe the dynamic process of HIV transmission in the body. The diversity of these models, as well as the corresponding theories and experiments, have made significant progress. Perelson et al. [15] proposed an ODE model of cell-free viral spread of human immunodeficiency virus in a well-mixed compartment. Using this model, they explain the characteristics of virus spread under different steady states. Müller et al. [16] also proposed a model incorporating the activation of latently infected cells. They concluded through model predictions that the residual virus after long-term suppressive treatment is likely to originate from latently infected cells. Wang et al. [17] investigated a class of HIV-1 infection models with different infection rates and latently infected cells, and obtained sufficient conditions for the global stability of both the infection-free and chronic-infection equilibria of the model.

These investigations are based on a system of ordinary differential equations and intuitively describe the trend of viral infection. However, the activities of viruses and cells within the human body are subject to changes over both time and space. Further consideration of spatial factors in modeling can provide further insight into the viral pathogenesis. Based on the spatial model, Wang et al. [18] proposed a virus infection model with multiple target cells and discussed the threshold dynamics through semigroup theory. Wang et al. [19] introduced a mathematical model to simulate hepatitis B virus infection, incorporating spatial dependence. Considering the free movement of viruses, they introduce the random mobility for viruses.

In addition, we note that the virus infection model in [19] is investigated under conditions of a well-mixed or homogeneous environment. These studies ignore the heterogeneous mobility of cells [20] and the differences in the diffusion ability of virus particle in different environments [21–23]. Under the assumption of homogeneity, there is a possibility of either underestimating or overestimating critical factors in viral pathogenesis. Wu et al. [24] argued that the use of the spatially averaged parameters may underestimate HIV infection, and explored the effect of two time delays (latency caused by latently infected cells) on the HIV infection process in a heterogeneous environment. Based on the research of [19], Wang et al. [25] further considered an virus dynamics model with spatial heterogeneity under homogeneous boundary conditions. This extension involved allowing all parameters to exhibit spatial dependence, except for the diffusion coefficient. We note that few previous models have simultaneously considered spatial heterogeneity and infection modes of both target cells. There is a lack of theoretical justification for the dynamic behavior of the model when considering susceptible and infected cell mobility.

The purpose of HIV modeling research is to inhibit the transmission and diffusion of HIV within the human body, and optimal control strategy is an effective method to explore and simulate the changes in the transmission of the virus under certain control. This method is often used to explore the optimal action time of drugs and prevent the spread of diseases. In fact, optimal control theory has been used to study HIV treatment both at the cellular level [26, 27] and at the level of individual patients [28, 29]. However, existing mathematical models have not been used to study the effects of multiple drug combination treatments and optimal control on HIV infection.

Based on the considerations mentioned above, we established an HIV model incorporating spatial heterogeneity and conducted optimization control studies. In the next section (Section 2), we will propose a spatially heterogeneous model and explain the parameters in the model. Given that the dynamical behavior of the model is crucial for investigating optimal control, we first conducted a viral dynamics analysis of the proposed model in Section 3. We discuss the threshold dynamics of the basic reproduction number R_0 and demonstrate the uniform persistence of the solution in Section 4. In Section 5, We further understand the impact of pharmacological interventions on the dynamics of HIV infection and investigate key strategies for controlling infection. In the final section (Section 6), we obtained the optimal solution of the control system through numerical simulations and presented the spatiotemporal variations of the control. Some conclusions and discussions are presented.

2. Model formulation

Mathematical models are useful to interpret the different profiles, providing quantitative information about the kinetics of virus replication. In a recent survey, Hill et al. [30] summarized the contributions that viral dynamic models have made to understand the pathophysiology of HIV infection and to design effective therapies and proposing basic viral dynamics model:

$$\begin{cases} \dfrac{dT(t)}{dt} = \lambda - \mu_T T(t) - \beta T(t)V(t), \\ \dfrac{dI(t)}{dt} = \beta T(t)V(t) - \mu_I I(t), \\ \dfrac{dV(t)}{dt} = kI(t) - cV(t), \end{cases} \tag{2.1}$$

which tracks levels of the virus V and the $CD4^+T$ cells that it infects. Uninfected target cells T are assumed to enter the system at a constant rate λ, and die with rate constant μ_T (equivalent to an average lifespan of $1/\mu_T$). Infected cells I are produced with a rate proportion to levels of both virus and target cells and the infectivity parameter β. Infected cells produce free virus at a rate k and die with rate μ_I. Free virus is cleared at rate c.

With further research on the pathogenesis of HIV, more complicated facets of infection can be inferred from looking at viral load decay curves under different types of treatments. This decay can be explained using mathematical models, and in general the multiple phases are believed to reflect distinct populations of infected cells [31, 32]. Cardozo et al. [33] modeled proviral integration in short- and long-lived infected cells, which suggests that "HIV infects two different cell subsets, one of which has a fast rate and the other a slow fusion rate". Based on the work of Hill [30] and Cardozo [33], Wang [10] considered the more general situation when the infectivity parameters of two target cells are different and then proposed the following equations to describe an HIV infection model containing two different cell subsets:

$$
\begin{cases}
\dfrac{dT_1(t)}{dt} = \lambda_1 - \mu_{T_1} T_1(t) - \beta_1 T_1(t) V(t), \\[2mm]
\dfrac{dI_1(t)}{dt} = \beta_1 T_1(t) V(t) - \mu_{I_1} I_1(t) - n_1 I_1(t), \\[2mm]
\dfrac{dT_2(t)}{dt} = \lambda_2 - \mu_{T_2} T_2(t) - \beta_2 T_2(t) V(t), \\[2mm]
\dfrac{dI_2(t)}{dt} = \beta_2 T_2(t) V(t) - \mu_{I_2} I_2(t) - n_2 I_2(t), \\[2mm]
\dfrac{dL(t)}{dt} = f n_2 I_2(t) - a L(t) - \mu_L L(t), \\[2mm]
\dfrac{dM(t)}{dt} = n_1 I_1(t) + (1-f) n_2 I_2(t) - \mu_M M(t) + a L(t), \\[2mm]
\dfrac{dV(t)}{dt} = k M(t) - c V(t),
\end{cases}
\tag{2.2}
$$

Two separate populations of target cells are hypothesized to exist, with the second type T_2, I_2 being longer lived and proceeding to integrate virus more slowly. Infected cells of either type can be divided up into those who have not yet completed the phase of the viral lifecycle where integration occurs I_i, and those mature infected cells M, which allows investigation of different dynamics in the presence and absence of integrase inhibitor drugs.

Despite our meticulous consideration in the modeling process, the speed of virus propagation within the human body varies significantly depending on its environment. Concurrently, studies have revealed that the virus spreads at different rates within the body, and the spatial movement plays a crucial role in the dissemination of the pathogenic agent. In light of these considerations, we incorporate spatial reactivity diffusion into the model to simulate the diverse spread rates of the virus among different tissues. This enhancement renders the model more practical and provides greater reference value for guiding realistic treatment plans. In addition, since what we really care about is the effect of HIV virus on the sum of two target cell concentrations, we build the model based on the following considerations:

(1) The infection process of T_1 can be regarded as a special form of the infection process of T_2. When $f = 0$, the cell subsets with a slow fusion rate will not enter the latency period, and we can regard them as the cell subsets with a fast fusion rate.

(2) From a virological perspective, when the sum of the concentrations of two types of target cells is considered, the variables and parameters of each compartment in the model can be considered together, which is beneficial to simplifying the proof of the properties of the model.

(3) If target cells are not considered together, there will be two susceptible compartments, making it challenging to analyze the global existence of a system solution.

(4) The amalgamation of two cell types has simplified the objective function for optimum control, resulting in a reduction of computational workload for numerical simulations.

Table 1. Interpretation of variables in the model.

Variables	Description
$T(x,t)$	Concentrations of susceptible $CD4^+T$ cells
$I(x,t)$	Concentrations of immature infected cells
$L(x,t)$	Concentrations of latently infected cells
$M(x,t)$	Concentrations of mature infected cells
$V(x,t)$	Concentrations of free virus particles

Table 2. Descriptions of parameters in model.

Para.	Biological significance
λ	The production rate of $CD4^+T$ cells
β	Virus infection rate
n	The proportion of immature infected cells transformed
f	The proportion of immature infected cells that transform into latently infected cells
a	The proportion of latently infected cells that transform into mature infected cells
k	Virus production rate
c	Death rate of virions
μ_T	Natural death rate of $CD4^+T$ cells
μ_I	Natural death rate of immature infected cells
μ_L	Natural death rate of latently infected cells
μ_M	Natural death rate mature infected cells
θ_0	Diffusion rate of $T(x,t)$
θ_1	Diffusion rate of $I(x,t)$
θ_2	Diffusion rate of $L(x,t)$
θ_3	Diffusion rate of $M(x,t)$
θ_4	Diffusion rate of $V(x,t)$

Finally, we establish the following spatially heterogeneous reaction-diffusion model of HIV in

human body:

$$
\begin{cases}
\dfrac{\partial T(x,t)}{\partial t} = \nabla(\theta_0(x)\nabla T(x,t)) + \lambda(x) - \mu_T(x)T(x,t) - \beta(x)T(x,t)V(x,t), \\[2mm]
\dfrac{\partial I(x,t)}{\partial t} = \nabla(\theta_1(x)\nabla I(x,t)) + \beta(x)T(x,t)V(x,t) - \mu_I(x)I(x,t) - n(x)I(x,t), \\[2mm]
\dfrac{\partial L(x,t)}{\partial t} = \nabla(\theta_2(x)\nabla L(x,t)) + f(x)n(x)I(x,t) - a(x)L(x,t) - \mu_L(x)L(x,t), \\[2mm]
\dfrac{\partial M(x,t)}{\partial t} = \nabla(\theta_3(x)\nabla M(x,t)) + (1 - f(x))n(x)I(x,t) - \mu_M(x)M(x,t) + a(x)L(x,t), \\[2mm]
\dfrac{\partial V(x,t)}{\partial t} = \nabla(\theta_4(x)\nabla V(x,t)) + k(x)M(x,t) - c(x)V(x,t)
\end{cases}
\tag{2.3}
$$

with $(x,t) \in \Omega_\Gamma = \Omega \times (0, \Gamma)$. Moreover, as a complement to the system (2.3), we introduce the no-flux condition:

$$
\frac{\partial T(x,t)}{\partial v} = \frac{\partial I(x,t)}{\partial v} = \frac{\partial L(x,t)}{\partial v} = \frac{\partial M(x,t)}{\partial v} = \frac{\partial V(x,t)}{\partial v} = 0
\tag{2.4}
$$

with the positive initial conditions:

$$
T(x,0) = T_0(x),\ I(x,0) = I_0(x),\ L(x,0) = L_0(x),\ M(x,0) = M_0(x),\ V(x,0) = V_0(x),\ x \in \Omega,
\tag{2.5}
$$

The outward normal vector to $\partial\Omega$ is denoted by ∂v. Given the complexity of describing the architecture, composition of target tissues, and the diversity of the human internal environment, the domain Ω is considered as the target tissues. The interpretation of the variables are listed in Table 1. Moreover, all parameters and their respective meanings can be found in Table 2, where $\theta_i(i = 0, 1, 2, 3, 4)$ represents the diffusion rate of each compartment, indicating that the local diffusion rate vary across different compartments. Under the condition of $x \in \Omega$, we suppose that position-dependent parameters are functions that are continuous, strictly positive, and uniformly bounded.

3. Some basic properties for system

In this section, we encompasse an exploration of the well-posedness of the solutions as well as an analysis of dynamic behavior of the model. Similar to Zhao's method [34] in the article, we consider the following scalar reaction-diffusion equation:

$$
\begin{cases}
\dfrac{\partial w}{\partial t} = \nabla(\theta_0(x)\nabla w(x,t)) + \lambda(x) - \mu_T(x)w(x,t),\ x \in \Omega,\ t > 0, \\[2mm]
\dfrac{\partial w}{\partial v} = 0, x \in \partial\Omega.
\end{cases}
\tag{3.1}
$$

According to the method of Lemma 1 in [34], similarly, we have the following lemma:

Lemma 3.1. *System (3.1) admits a unique positive steady state $w^*(x)$, which is globally asymptotically stable in the function space $C(\bar{\Omega}, \mathbb{R})$. Furthermore, $w^* = \frac{\lambda}{\mu_T}$ if λ and μ_T are positive constants.*

Let $\mathbb{D} = C(\bar{\Omega}, \mathbb{R}^5)$ equip with the uniform norm denoted by $\| \cdot \|_{\mathbb{D}}$, $\mathbb{D}^+ = C(\bar{\Omega}, \mathbb{R}^5_+)$. Then we will obtain an Banach space which is denoted as $(\mathbb{D}, \mathbb{D}^+)$. We set a mapping relation $\mathscr{T}_i(t) : C(\bar{\Omega}, \mathbb{R}) \to$

$C(\bar{\Omega}, \mathbb{R})(i = 1, 2, 3, 4, 5)$ to represent the C_0 semigroups. C_0 semigroups is associated with $\nabla(\theta_i(x)\nabla) - m_i(\cdot)$, where $m_0(\cdot) = \mu_T(\cdot), m_1(\cdot) = \mu_I(\cdot) + n(\cdot), m_2(\cdot) = \mu_L(\cdot) + a(\cdot), m_3(\cdot) = \mu_M(\cdot), m_4(\cdot) = c(\cdot)$. Thus, it comes that:

$$(\mathscr{T}_i(t)\phi)(x) = \int_\Omega \mathscr{G}_i(t, x, y)\phi(y)dy, \phi \in C(\bar{\Omega}, \mathbb{R}), \ t > 0,$$

The function $\mathscr{G}_i(t, x, y)$ denotes the Green function corresponding to the operator $\nabla(\theta_i(x)\nabla) - m_i(\cdot)$ under the Neumann boundary conditions. Building upon the theorem presented in Smith's work (1995, Corollary 7.2.3) [35], the operator $\mathscr{T}_i(t)$ ($i = 1, 2, 3, 4, 5$) is compact and strictly positive for all $t > 0$. Obviously, we can find a positive constant $M > 0$ that when $\alpha_i \leqslant 0$ and $t \geqslant 0$ satisfies $\|T_i(t)\| \leqslant Me^{\alpha_i t}$. Here, α_i represents the main eigenvalue of $\nabla(\theta_i(x)\nabla) - m_i(\cdot)$. Define operator $F = (F_1, F_2, F_3, F_4, F_5)^T : \mathbb{D}^+ \rightarrow \mathbb{D}$ by

$$F_1(\psi)(x) = \lambda(x) - \beta(x)\psi_1(x)\psi_5(x),$$
$$F_2(\psi)(x) = \beta(x)\psi_1(x)\psi_5(x),$$
$$F_3(\psi)(x) = f(x)n(x)\psi_2(x),$$
$$F_4(\psi)(x) = (1 - f(x))n(x)\psi_2(x) + a(x)\psi_3(x),$$
$$F_5(\psi)(x) = k(x)\psi_4(x),$$

where $\psi = (\psi_1, \psi_2, \psi_3, \psi_4, \psi_5)^T \in \mathbb{D}^+$. Subsequently, we rewrite the system (2.3):

$$E(t) = E^*(t)\psi + \int_0^t E^*(t - s)F(E(s))ds, \tag{3.2}$$

where $E(t) = (T(t), I(t), L(t), M(t), V(t))^T, E^*(t) = diag(T_1(t), T_2(t), T_3(t), T_4(t), T_5(t))$.

According to the conclusion of Martin and Smith (1990, Corollary 4) [36], the subtangential conditions are satisfied, and then, the following lemma is applicable:

Lemma 3.2. *For system (2.3)–(2.5) with initial condition $\psi \in \mathbb{D}^+$, when the maximum interval $[0, \tau_\infty), \tau_\infty \leqslant +\infty$ is provided, the solution $u(t, \psi) \in \mathbb{D}^+$ is mild and also unique. Furthermore, this solution to the system (2.3) is classical.*

Next we give proofs for the dynamical behavior and the existence of the global attractor.

Theorem 3.3. *There exist unique and mild solution $u(x, t, \psi) \in \mathbb{D}^+$ on $[0, \infty)$ to the system (2.3)–(2.5), when it fits the initial condition $\psi \in \mathbb{D}^+$. In addition, we can find the solution semiflow $\Psi(t) = u(t, \cdot, \psi) : \mathbb{D}^+ \rightarrow \mathbb{D}^+, t \geqslant 0$ exist a global compact attractor.*

Proof. For the sake of later discussion, we first set $\underline{g} = min_{x \in \bar{\Omega}}g(\cdot)$ and $\bar{g} = max_{x \in \bar{\Omega}}g(\cdot)$, where $g(\cdot) = \lambda(\cdot), \beta(\cdot), n(\cdot), f(\cdot)$
, $a(\cdot), k(\cdot), c(\cdot), \mu_T(\cdot), \mu_I(\cdot), \mu_L(\cdot), \mu_M(\cdot)$. According to the theory of Lemma 3.2, we can easily find the solution to the system (2.3) exists and is also unique and positive. Next, we can obtain the following conclusion: $\|u(x, t, \psi)\| \rightarrow +\infty$ for $\tau_\infty < +\infty$ refer to Martin and Smith (1990, Theorem 2) [36]. It follows from the system (2.3) that

$$\frac{\partial T(x, t)}{\partial t} \leqslant \nabla(\theta_0(x)\nabla T(x, t)) + \bar{\lambda} - \underline{\mu}_T T(x, t), \ x \in \Omega, \ t \in [0, \tau_\infty). \tag{3.3}$$

By the comparison principle and Lemma 3.1, we obtain that there admits $M_1 > 0$ such that

$$T(x, t) \leqslant M_1, \ x \in \bar{\Omega}, \ t \in [0, \tau_\infty).$$

Then, a series of equations can be established:

$$
\begin{cases}
\dfrac{\partial I(x,t)}{\partial t} \leqslant \nabla\left(\theta_1(x)\nabla I(x,t)\right) + \bar{\beta}M_1 V(x,t) - (\underline{\mu}_I + \underline{n})I(x,t), & x \in \Omega,\ t \in [0,\tau_\infty), \\[2ex]
\dfrac{\partial L(x,t)}{\partial t} \leqslant \nabla\left(\theta_2(x)\nabla L(x,t)\right) + \bar{f}\bar{n}I(x,t) - (\underline{\mu}_L + \underline{a})L(x,t), & x \in \Omega,\ t \in [0,\tau_\infty), \\[2ex]
\dfrac{\partial M(x,t)}{\partial t} \leqslant \nabla\left(\theta_3(x)\nabla M(x,t)\right) + (1 - \underline{f})\bar{n}I(x,t) - \underline{\mu}_M + \bar{a}L(x,t), & x \in \Omega,\ t \in [0,\tau_\infty), \\[2ex]
\dfrac{\partial V(x,t)}{\partial t} \leqslant \nabla\left(\theta_4(x)\nabla V(x,t)\right) + \bar{k}M(x,t) - \underline{c}V(x,t), & x \in \Omega,\ t \in [0,\tau_\infty).
\end{cases}
$$

Consider the following problem:

$$
\begin{cases}
\dfrac{\partial v_1}{\partial t} = \nabla\left(\theta_1(x)\nabla v_1\right) + \bar{\beta}M_1 V - (\underline{\mu}_I + \underline{n})I, & x \in \Omega,\ t > 0, \\[2ex]
\dfrac{\partial v_2}{\partial t} = \nabla\left(\theta_2(x)\nabla v_2\right) + \bar{f}\bar{n}I - (\underline{\mu}_L + \underline{a})L, & x \in \Omega,\ t > 0, \\[2ex]
\dfrac{\partial v_3}{\partial t} = \nabla\left(\theta_3(x)\nabla v_3\right) + (1 - \underline{f})\bar{n}I - \underline{\mu}_M + \bar{a}L, & x \in \Omega,\ t > 0, \\[2ex]
\dfrac{\partial v_4}{\partial t} = \nabla\left(\theta_4(x)\nabla v_4\right) + \bar{k}M - \underline{c}V, & x \in \Omega,\ t > 0, \\[2ex]
\dfrac{\partial v_1(x,t)}{\partial \nu} = \dfrac{\partial v_2(x,t)}{\partial \nu} = \dfrac{\partial v_3(x,t)}{\partial \nu} = \dfrac{\partial v_4(x,t)}{\partial \nu} = 0, & x \in \partial\Omega.
\end{cases} \tag{3.4}
$$

We can find that the strictly positive eigenfunction $\phi = (\phi_1, \phi_2, \phi_3, \phi_4)$ correspond to A which is principal eigenvalue to the system (3.4) based on the standard Krein-Rutman theorem. Hence, if $t \geqslant 0$, systems (3.4) has a solution $\sigma e^{At}\phi(x)$, where $\sigma\phi = (v_1(x,0), v_2(x,0), v_3(x,0), v_4(x,0) \geqslant (I(x,0), L(x,0), M(x,0), V(x,0))$ for $x \in \bar{\Omega}$. Then we will get by referring the comparison principle:

$$
(I(x,t), L(x,t), M(x,t), V(x,t)) \leqslant \sigma e^{At}\phi(x),\ x \in \bar{\Omega},\ t \in [0,\tau_\infty),
$$

Then, there exists $M_2 > 0$ that satisfies the following inequality:

$$
I(x,t) \leqslant M_2, L(x,t) \leqslant M_2, M(x,t) \leqslant M_2, V(x,t) \leqslant M_2,\ x \in \bar{\Omega},\ t \in [0,\tau_\infty),
$$

When the $\tau_\infty < +\infty$ is given, we find that it contradicts the previous conclusion ($\|u(x,t,\psi)\| \to +\infty$ when $\tau_\infty < +\infty$). Therefore, we have proved the solution is globally existed. Furthermore, we can prove that the semiflow of solution is dissipative. Refer to the comparison principle and Lemma 3.1, there exist $N_1 > 0$ and $t_1 > 0$ satisfies

$$
T(x,t) \leqslant N_1,\ x \in \bar{\Omega},\ t \in [0,\tau_\infty).
$$

Denote $S(t) = \int_\Omega (T(x,t) + I(x,t) + L(x,t) + M(x,t) + \frac{\mu_M(x)}{k(x)}V(x,t))dx$, then we have that

$$
\begin{aligned}
\frac{dS}{dt} &= \int_\Omega \left(\lambda(x) - \mu_T(x)T(x,t) - \mu_I(x)I(x,t) - \mu_L(x)L(x,t) - \frac{\mu_M(x)c(x)}{k(x)}V(x,t)\right)dx \\
&\leqslant \int_\Omega \lambda(x)dx - \min_{\bar{\Omega}}\{\mu_T(x), \mu_I(x), \mu_L(x), c(x)\}S.
\end{aligned}
$$

Thus there exist $N_2 > 0$ and $t_2 > 0$ such that $S(t) \leqslant N_2$ for all $t \geqslant t_2$.

It follows from Guenther and Lee [37] that $G_2(t, x, y) = \sum_{n \geqslant 1} e^{\tau_n t} \varphi_n(x) \varphi_n(y)$, where $\varphi_n(x)$ means the eigenfunction and the eigenvalue of $\nabla \cdot (\theta_1(x) \nabla) - \mu_I(x) - n(x)$ is τ_i. Moreover, τ_i satisfies $\tau_1 > \tau_2 \geqslant \tau_3 \geqslant \cdots \geqslant \tau_n \geqslant \cdots$. Then

$$G_2(t, x, y) \leqslant \omega_1 \sum_{n \geqslant 1} e^{\tau_n t} \quad t > 0$$

for some $\omega_1 > 0$ since φ_n is uniformly bounded. Let $\nu_n (n = 1, 2 \ldots)$ be the eigenvalue of $\nabla \cdot (\theta_1 \nabla) - \underline{\mu_I}(x) - \underline{n}(x)$ and satisfy $\nu_1 = -\underline{\mu_I} - \underline{n} > \nu_2 \geqslant \nu_3 \geqslant \cdots \geqslant \nu_n \geqslant \cdots$. According to the Theorem 2.4.7 in Wang [38], we can obtain that $\nu_i \geqslant \tau_i$ for any $i \in N_+$. Considering the trend of ν_n is similar to $-n^2$, we can obtain that

$$G_2(t, x, y) \leqslant \omega_1 \sum_{n \geqslant 1} e^{\nu_n t} \leqslant \omega e^{\nu_1 t} = \omega e^{-(\underline{\mu_I} + \underline{n})t}$$

for $t > 0$ some $\omega > 0$.

Here we set $t_3 = max\{t_1, t_2\}$. If $t \geqslant t_3$, we can also have refer to the comparison principle:

$$
\begin{aligned}
I(x, t) &= T_2(t)I(x, t_3) + \int_{t_3}^t T_2(t - s)\beta(x)T(x, s)V(x, s)ds \\
&\leqslant Me^{\alpha_2(t - t_3)}\|I(x, t_3)\| + \int_{t_3}^t \int_\Omega G_2(t - s, x, y)\beta(y)T(y, s)V(y, s)dyds \\
&\leqslant Me^{\alpha_2(t - t_3)}\|I(x, t_3)\| + \int_{t_3}^t \omega e^{-(\underline{\mu_I} + \underline{n})(t - s)} \int_\Omega \bar{\beta} N_1 V(y, s)dyds \\
&\leqslant Me^{\alpha_2(t - t_3)}\|I(x, t_3)\| + \omega N_1 N_2 \cdot \frac{\bar{\beta} \cdot \bar{k}}{\underline{\mu_M}} \int_{t_3}^t e^{-(\underline{\mu_I} + \underline{n})(t - s)}ds \\
&\leqslant Me^{\alpha_2(t - t_3)}\|I(x, t_3)\| + \frac{\omega N_1 N_2 \cdot \bar{\beta} \cdot \bar{k}}{\underline{\mu_M}(\underline{\mu_I} + \underline{n})}.
\end{aligned}
$$

Thus, $\limsup_{t \to \infty} \|I(x, t)\| \leqslant \omega N_1 N_2 \cdot \bar{\beta} \cdot \bar{k} / \underline{\mu_M}(\underline{\mu_I} + \underline{n})$. Moreover, follow the same method, there admits $N_3 > 0$ such that $\limsup_{t \to \infty} \|L(x, t)\| \leqslant N_3$. Therefore, we can show that the system is point dissipative. Furthermore, in the condition of $t > 0$, the solution semiflow $\Psi(t)$ is compact and also globally attracted based on Wu (Theorem 2.2.6) [39] and Hale (Theorem 3.4.8) [40]. $\qquad \square$

4. Threshold dynamics behavior

In this section, we delve into the fundamental concept of the reproduction number. Based on Lemma 3.1, it can be concluded that system (2.3) amdits a unique infection-free equilibrium state $E_0 = (T^0(x), 0, 0, 0, 0)$, where $T^0 = \omega^*(x)$. At the infection-free equilibrium state E_0, we can derive a

set of linearized equations:

$$
\begin{cases}
\dfrac{\partial P_2(x,t)}{\partial t} = \nabla\left(\theta_1(x)\nabla P_2\right) + \beta(x)T^0 P_5 - \mu_I(x)P_2 + n(x)P_2, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial P_3(x,t)}{\partial t} = \nabla\left(\theta_2(x)\nabla P_3\right) + f(x)n(x)P_2 - a(x)P_3 - \mu_L(x)P_3, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial P_4(x,t)}{\partial t} = \nabla\left(\theta_3(x)\nabla P_4\right) + (1 - f(x))n(x)P_2 - \mu_M(x)P_4 + a(x)P_3, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial P_5(x,t)}{\partial t} = \nabla\left(\theta_4(x)\nabla P_5\right) + k(x)P_4 - c(x)P_5, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial P_2}{\partial v} = \dfrac{\partial P_3}{\partial v} = \dfrac{\partial P_4}{\partial v} = \dfrac{\partial P_5}{\partial v} = 0, & x \in \partial\Omega, \ t > 0.
\end{cases}
$$

Letting $(P_2, P_3, P_4, P_5) = e^{At}(\psi_2(t), \psi_3(t), \psi_4(t), \psi_5(t))$, the above system can be rewritten as:

$$
\begin{cases}
A\psi_2 = \nabla\left(\theta_1(x)\nabla\psi_2\right) + \beta(x)T^0\psi_5 - \mu_I(x)\psi_2 + n(x)\psi_2, & x \in \Omega, \ t > 0, \\[2mm]
A\psi_3 = \nabla\left(\theta_2(x)\nabla\psi_3\right) + f(x)n(x)\psi_2 - a(x)\psi_3 - \mu_L(x)\psi_3, & x \in \Omega, \ t > 0, \\[2mm]
A\psi_4 = \nabla\left(\theta_3(x)\nabla\psi_4\right) + (1 - f(x))n(x)\psi_2 - \mu_M(x)\psi_4 + a(x)\psi_3, & x \in \Omega, \ t > 0, \\[2mm]
A\psi_5 = \nabla\left(\theta_4(x)\nabla\psi_5\right) + k(x)\psi_4 - c(x)\psi_5, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial\psi_2}{\partial v} = \dfrac{\partial\psi_3}{\partial v} = \dfrac{\partial\psi_4}{\partial v} = \dfrac{\partial\psi_5}{\partial v} = 0, & x \in \partial\Omega, \ t > 0.
\end{cases}
\tag{4.1}
$$

From the above equations we know the system is cooperative. According to the Krein-Rutman theorem, we find the strictly positive eigenfunction $(\varphi_2(x), \varphi_3(x), \varphi_4(x), \varphi_5(x))$ and its unique principal eigenvalue $A_0(T^0)$. Suppose the solution semigroup $\Phi(t) : C(\bar{\Omega}, \mathbb{R}^4) \to C(\bar{\Omega}, \mathbb{R}^4)$ associated with the following system:

$$
\begin{cases}
\dfrac{\partial P_2(x,t)}{\partial t} = \nabla\left(\theta_1(x)\nabla P_2\right) - \mu_I(x)P_2 + n(x)P_2, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial P_3(x,t)}{\partial t} = \nabla\left(\theta_2(x)\nabla P_3\right) + f(x)n(x)P_2 - a(x)P_3 - \mu_L(x)P_3, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial P_4(x,t)}{\partial t} = \nabla\left(\theta_3(x)\nabla P_4\right) + (1 - f(x))n(x)P_2 - \mu_M(x)P_4 + a(x)P_3, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial P_5(x,t)}{\partial t} = \nabla\left(\theta_4(x)\nabla P_5\right) + k(x)P_4 - c(x)P_5, & x \in \Omega, \ t > 0, \\[2mm]
\dfrac{\partial P_2}{\partial v} = \dfrac{\partial P_3}{\partial v} = \dfrac{\partial P_4}{\partial v} = \dfrac{\partial P_5}{\partial v} = 0, & x \in \partial\Omega, \ t > 0.
\end{cases}
$$

We set that:

$$
F(x) = \begin{pmatrix}
0 & 0 & 0 & \beta(x)T^0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}.
$$

We define the distribution of the infected with starting conditions $\psi = (\psi_2, \psi_3, \psi_4, \psi_5)$. With time goes by, the distribution of infection is denoted by $\Phi(t)\psi$. Then, the total number of cells infected and the number of viruses is:

$$
\mathscr{L}(\psi)(x) = \int_0^\infty F(x)\Phi(t)\psi \, dt.
$$

According to the method in next generation matrix theory, we get the basic reproduction number:

$$R_0 = \kappa(\mathscr{L}).$$

where we use $\kappa(\mathscr{L})$ to denote the spectral radius of $\mathscr{L}$.

According to the proof of Theorem 3.1 in Wang and Zhao [41], we use a similar method to establish the following lemma:

Lemma 4.1. $R_0 - 1$ *and* A_0 *have the same sign. When* $R_0 < 1$*, the state* E_0 *is asymptoticallyis stable, or not when* $R_0 > 1$.

The basic reproduction number serves as a critical threshold, determining whether the virus can persist or not.

Theorem 4.2. *When* $R_0 < 1$*,* E_0 *exhibits further globally asymptotic stability.*

Proof. There admits a $\delta > 0$ such that $A_0(T^0 + \delta) < 0$. Consider the first equation in the system (2.3):

$$\frac{\partial T}{\partial t} \leqslant \nabla(\theta_0(x)\nabla T) + \lambda(x) - \mu_T(x)T(x,t),\ t > 0, x \in \Omega,$$

Refer to the principle of the comparison, given t_1 is positive, we know that $T(x,t) \leqslant T^0 + \delta$ when $t \geqslant t_1$ and $x \in \Omega$. Then,

$$\begin{cases} \dfrac{\partial I}{\partial t} \leqslant \nabla(\theta_1(x)\nabla I) + \beta(x)(T^0 + \delta)V - (\mu_I(x) + n(x))I, & x \in \Omega,\ t \geqslant t_1, \\[2mm] \dfrac{\partial L}{\partial t} \leqslant \nabla(\theta_2(x)\nabla L) + f(x)n(x)I - (\mu_L(x) + a(x))L, & x \in \Omega,\ t \geqslant t_1, \\[2mm] \dfrac{\partial M}{\partial t} \leqslant \nabla(\theta_3(x)\nabla M) + (1 - f(x))n(x)I - \mu_M(x) + a(x)L, & x \in \Omega,\ t \geqslant t_1, \\[2mm] \dfrac{\partial V}{\partial t} \leqslant \nabla(\theta_4(x)\nabla V) + k(x)M - c(x)V, & x \in \Omega,\ t \geqslant t_1. \end{cases}$$

Suppose that $\alpha(\bar{\phi}_2(x), \bar{\phi}_3(x), \bar{\phi}_4(x), \bar{\phi}_5(x)) \geqslant (I(x,t), L(x,t), M(x,t), V(x,t))$. $A_0(T^0 + \delta)$ is negative and is the principal eigenvalue of the eigenfunction $(\bar{\phi}_2(x), \bar{\phi}_3(x), \bar{\phi}_4(x), \bar{\phi}_5(x))$. Thenthe comparison principle implies that:

$$(I(x,t),\ L(x,t),\ M(x,t),\ V(x,t)) \leqslant \alpha(\bar{\phi}_2(x),\ \bar{\phi}_3(x),\ \bar{\phi}_4(x),\ \bar{\phi}_5(x)),\ \ t \geqslant t_1.$$

Therefore, $\lim_{t\to\infty}(I(x,t), L(x,t), M(x,t), V(x,t)) = 0$. According to the theory in (Corollary 4.3 in Thieme [42]), we know that $\lim_{t\to\infty} T(x,t) = T^0$. These findings are all available by Lemma 4.1. □

Theorem 4.3. *When* R_0 *is greater than 1, there admits a positive number* η *such that any solution* $(T(x,t), I(x,t), L(x,t),$
$M(x,t), V(x,t))$ *with* $T(x,0) \not\equiv 0, I(x,0) \not\equiv 0, L(x,0) \not\equiv 0, M(x,0) \not\equiv 0$ *and* $V(x,0) \not\equiv 0$ *satisfies*

$$\liminf_{t\to\infty} T(x,t) \geqslant \eta,\ \liminf_{t\to\infty} I(x,t) \geqslant \eta,\ \liminf_{t\to\infty} L(x,t) \geqslant \eta,\ \liminf_{t\to\infty} M(x,t) \geqslant \eta,\ \liminf_{t\to\infty} V(x,t) \geqslant \eta$$

uniformly for all $x \in \bar{\Omega}$*. Moreover, it is obvious that there at least exists one stable state which is also positive.*

Proof. Set $D_0 = \{\psi = (T, I, L, M, V) \in \mathbb{D}^+ : I(\cdot) \not\equiv 0, L(\cdot) \not\equiv 0, M(\cdot) \not\equiv 0, V(\cdot) \not\equiv 0\}$. Obviously,

$$\partial D_0 = \{(T, I, L, M, V) \in \mathbb{D}^+ : I(\cdot) \equiv 0 \ \ or \ \ L(\cdot) \equiv 0 \ \ or \ \ M(\cdot) \equiv 0 \ \ or \ \ V(\cdot) \equiv 0\}.$$

D_0 is fixed and positive for the semiflow of solution $\Psi(t)$ based on the theory of Hopf boundary and the maximum eigenvalue. We suppose the set of forward orbit $\gamma^+(\phi) = \{\Psi(t)(\phi) : t \geqslant 0\}$ where its limit set is denoted by $\omega(\phi)$, and set $N_\partial = \{\phi \in \partial D_0 : \Psi(t) \in \partial D_0\}$.

Claim 1. $\bigcup_{\phi \in N_\partial} \omega(\phi) = E_0$.

Given that ϕ belongs to N_∂, it implies that either $I(x, t, \phi) \equiv 0$, $L(x, t, \phi) \equiv 0$, $M(x, t, \phi) \equiv 0$ or $V(x, t, \phi) \equiv 0$. Assuming $V(x, t, \phi) \equiv 0$, from the fifth equation in (2.3), we deduce that $M(x, t, \phi) \equiv 0$. Moreover, the fourth equation implies $I(x, t, \phi) \equiv 0$ and $L(x, t, \phi) \equiv 0$. Hence, as $t \to \infty$, $T(x, t, \phi)$ converges to T^0. If there exists a $t_0 \geqslant 0$ that satisfies $V(x, t_0, \phi) \not\equiv 0$, then we can prove that $V(x, t, \phi) > 0$ for all $t > t_0$ using the Hopf bifurcation theory and the maximum principle. Thus, we know that $M(x, t, \phi) \equiv 0$, $L(x, t, \phi) \equiv 0$, $I(x, t, \phi) \equiv 0$ for all $t \geqslant t_0$. From the fifth equation of (2.3), as $t \to \infty$, it can be inferred that $V(x, t_0, \phi)$ converges to 0. Consequently, Then $T(x, t, \phi)$ asymptotically approaches the solution given by Eq (3.1). Utilizing the Corollary 4.3 in [42], it follows that $T(x, t)$ converges to T^0 uniformly for $x \in \bar{\Omega}$ as $t \to \infty$. Given that $R_0 > 1$, there exists a $\varsigma > 0$ such that $A_0(T^0 - \varsigma) > 0$.

Claim 2. E_0 *is a uniform weak repeller in the sense that* $\limsup_{t \to \infty} \|\Psi(t)(\phi) - E_0\| \geqslant \varsigma$ *where* $\phi \in D_0$.

While, there comes a contradiction, there exist a $\phi_0 \in D_0$ such that $\limsup_{t \to \infty} \|\Psi(t)(\phi) - E_0\| < \varsigma$. Then, for $t_1 > 0$:

$$T(x, t, \phi_0) > T^0 - \varsigma, \forall t \geqslant t_1.$$

Therefore, we can deduce that:

$$\begin{cases} \dfrac{\partial I}{\partial t} \geqslant \nabla(\theta_1 \nabla I) + \beta(x)(T^0 - \varsigma)V - \mu_I(x)I - n(x)I, & t > t_1, x \in \Omega, \\[2mm] \dfrac{\partial L}{\partial t} \geqslant \nabla(\theta_2 \nabla L) + f(x)n(x)I - a(x)L - \mu_L(x)L, & t > t_1, x \in \Omega, \\[2mm] \dfrac{\partial M}{\partial t} \geqslant \nabla(\theta_3 \nabla M) + (1 - f(x))n(x)I - \mu_M(x)M + a(x)L, & t > t_1, x \in \Omega, \\[2mm] \dfrac{\partial V}{\partial t} \geqslant \nabla(\theta_4 \nabla V) + k(x)M - c(x)V, & t > t_1, x \in \Omega. \end{cases}$$

The eigenfunction is supposed to be $(\bar{\phi}_2(x), \bar{\phi}_3(x), \bar{\phi}_4(x), \bar{\phi}_5(x))$ and the principal eigenvalue is $A_0(T^0 - \varsigma) > 0$. Assume that $\alpha > 0$ and fulfills the condition $\alpha(\bar{\phi}_2(x), \bar{\phi}_3(x), \bar{\phi}_4(x), \bar{\phi}_5(x)) \leqslant (I(x, t), L(x, t), M(x, t), V(x, t))$. Then,

$$(I(x, t), L(x, t), M(x, t), V(x, t)) \geqslant \alpha(\bar{\phi}_2(x), \bar{\phi}_3(x), \bar{\phi}_4(x), \bar{\phi}_5(x))e^{A_0(T^0 - \varsigma)(t - t_1)}, t \geqslant t_1,$$

This is contradictory to $\lim_{t \to \infty}(I(x, t), L(x, t), M(x, t), V(x, t)) = (+\infty, +\infty, +\infty, +\infty)$.

Given a function $K : \mathbb{D}^+ \to [0, +\infty]$:

$$K(\phi) = \min\left\{ \min_{x \in \bar{\Omega}}\phi_2(x), \ \min_{x \in \bar{\Omega}}\phi_3(x), \ \min_{x \in \bar{\Omega}}\phi_4(x), \ \min_{x \in \bar{\Omega}}\phi_5(x) \right\}, \ \phi \in \mathbb{D}^+.$$

It is evident that $K^{-1}(0, \infty) \subseteq D_0$. Moreover, we obtain $K(\Psi(t)\phi) > 0$ when K satisfies the condition: $K(\phi) = 0$ and $\phi \in D_0$ or $K(\phi) > 0$. Therefore, we obtain the function K to the semiflow $\Psi(t) : \mathbb{D}^+ \to \mathbb{D}^+$ (Smith and Zhao 2001) [43]. So it comes a conclusion that any forward orbit of $\Psi(t)$ in M_∂ converges to E_0. The intersection of the stable subset $W^s(E_0)$ with D_0 is empty. Moreover, E_0 is an isolated invariant set in $\mathbb{D}^+$ and the set of ∂D_0 only contains the disease-free equilibrium E_0. According to Smith and Zhao (Theorem 3), it follows that there exist a $\varsigma_1 > 0$ satisfies: $min\{p(\psi) : \psi \in \omega(\phi)\} > \varsigma_1$ for any $\phi \in D_0$. This implies that

$$\liminf_{t\to\infty} I(x, t, \phi) \geqslant \varsigma_1, \ \liminf_{t\to\infty} L(x, t, \phi) \geqslant \varsigma_1, \ \liminf_{t\to\infty} M(x, t, \phi) \geqslant \varsigma_1, \ \liminf_{t\to\infty} V(x, t, \phi) \geqslant \varsigma_1, \forall \phi \in D_0.$$

According to the method in the Theorem 3.3, it can be established that there exist $M > 0$ and $t_2 > 0$ satisfies the following inequality:

$$I(x, t, \phi) \leqslant M, \ L(x, t, \phi) \leqslant M, \ M(x, t, \phi) \leqslant M, \ V(x, t, \phi) \leqslant M, \ t \geqslant t_2, \ for \ all \ x \in \bar{\Omega}.$$

For $T(x, t)$:
$$\frac{\partial T(x, t)}{\partial t} \geqslant \nabla \cdot (\theta_0(x)\nabla T) + \underline{A} - (\bar{\mu}_T + \bar{\beta}M)T, t \geqslant t_2, x \in \Omega.$$

Thus, we can get $\liminf_{t\to\infty} T(x, t, \phi) \geqslant \varsigma_2 := \underline{A}/(\bar{\mu}_T + \bar{\beta}M)$. Then, set $\varsigma_3 := min\{\varsigma_1, \varsigma_2\}$. we know that the uniform persistence.

According to Magal and Zhao [44], it follows that system (2.3) has at least one equilibrium in D_0. Now, we demonstrate that these equilibrium are positive. Let $(\psi_1.\psi_2, \psi_3, \psi_4, \psi_5)$ be a equilibrium in D_0. Then $\psi_2 \not\equiv 0, \psi_3 \not\equiv 0, \psi_4 \not\equiv 0, \psi_5 \not\equiv 0$, implying $\psi_2 > 0, \psi_3 > 0, \psi_4 > 0, \psi_5 > 0$. Through the maximum principle we can get $\psi_1 > 0$ or $\psi_1 \equiv 0$. Suppose $\psi_1 \equiv 0$. Then $\psi_2 \equiv 0$, contradicting the second equation of the steady state system (2.3) and the maximum principle. We final know that$(\psi_1.\psi_2, \psi_3, \psi_4, \psi_5)$ is a positive equilibrium. □

5. Optimal control of model

In addition to analyzing the global nature of the equation of HIV kinematics with spatial heterogeneity, we would like to further understand how the dynamic process of HIV transmission in the human body is affected by the action of antiviral drugs. Next, when the mathematical modeling of AIDS dynamic behavior has been completed, the role of optimal disease control can be fully exploited. Combined with optimal control theory, the help of viral infection modeling enables one to find key strategies and methods for controlling infection or enhancing prevention.

The investigation conducted by Kirschner et al. [45] delved into optimal chemotherapy strategies for a specific category of HIV models, employing methodologies rooted in optimal control theories. To reduce the number of infected people and minimize the cost of pharmacological interventions, Zhou et al. [46] considered an optimal control problem of partial differential equations based on the SIR model. Combining the above research and the purpose of this paper to establish optimal control, we want to investigate the optimal effect of drug administration while minimizing the cost and side effects of drug administration. Therefore, we introduce w_1, w_2, w_3 in the following system. The $w_1(x, t)$ represents the role of reverse transcriptase inhibitors, which are used to prevent HIV particles from transcribing RNA through susceptible cells, which means that susceptible cells will be less likely to transform into

infected cells. The $w_2(x, t)$ denotes the action of a protease inhibitor that primarily disables the process involved in the integration of proteins within the virus. This allows a portion of the free virus to be removed from the matured infected cells. The $w_3(x, t)$ represents the role of Flavonoid Compounds, which can inhibit HIV activation in latently infected cells. Then, the controlled system is as follows.

$$
\begin{cases}
\dfrac{\partial T(x,t)}{\partial t} = \theta_0 \Delta T(x,t) + \lambda - \mu_T(x)T(x,t) - \beta(x)T(x,t)V(x,t), \\[2ex]
\dfrac{\partial I(x,t)}{\partial t} = \theta_1 \Delta I(x,t) + \beta(x)T(x,t)V(x,t) - \mu_I(x)I(x,t) - n(x)(1 - w_1(x,t))I(x,t), \\[2ex]
\dfrac{\partial L(x,t)}{\partial t} = \theta_2 \Delta L(x,t) + fn(1 - w_1(x,t))I(x,t) - a(1 - w_3(x,t))L(x,t) - \mu_L(x)L(x,t), \\[2ex]
\dfrac{\partial M(x,t)}{\partial t} = \theta_3 \Delta M(x,t) + (1 - f)n(1 - w_1(x,t))I(x,t) - \mu_M(x)M(x,t) + a(1 - w_3(x,t))L(x,t), \\[2ex]
\dfrac{\partial V(x,t)}{\partial t} = \theta_4 \Delta V(x,t) + k(1 - w_2(x,t))M(x,t) - c(x)V(x,t),
\end{cases}
\tag{5.1}
$$

The system (5.1) exists only under the condition $(x,t) \in \Omega_\Gamma = \Omega \times (0, \Gamma)$. Moreover, as a complement to the system, we introduce the no-flux condition and initial conditions:

$$
\frac{\partial T(x,t)}{\partial \nu} = \frac{\partial I(x,t)}{\partial \nu} = \frac{\partial L(x,t)}{\partial \nu} = \frac{\partial M(x,t)}{\partial \nu} = \frac{\partial V(x,t)}{\partial \nu} = 0, \ (x, t) \in \Omega_\Gamma = \Omega \times (0, \Gamma),
$$

$$
T(x, 0) = T_0(x), I(x, 0) = I_0(x), L(x, 0) = L_0(x), M(x, 0) = M_0(x), V(x, 0) = V_0(x). \ x \in \Omega,
$$

The control variable can be obtained:

$$
\mathscr{W} = \left\{ w = (w_1, w_2, w_3) \in (L^2(\Omega_\Gamma))^3, 0 \leqslant w_i \leqslant 1, a.e. \ on \ \Omega_\Gamma, i = 1, 2, 3 \right\}.
\tag{5.2}
$$

The aim of the system with control is to reduce the HIV virus concentration and the cost of taking medication as much as possible. To achieve this goal, the cost function was set by us to:

$$
\begin{aligned}
\mathscr{C}(T, I, L, M, V, u) &= \int_{\Omega_\Gamma} \left[\varrho_1(x,t)T(x,t) + \cdots + \varrho_5(x,t)V(x,t) + \sum_{k=1}^{3} l_k(x,t)w_k(x,t) \right] dxdt \\
&+ \int_{\Omega} \left[\varepsilon_1(x)T(x,\Gamma) + \cdots + \varepsilon_5(x)V(x,\Gamma) + \sum_{k=1}^{3} p_k(x)w_k(x,\Gamma) \right] dx,
\end{aligned}
\tag{5.3}
$$

where the weight functions are denoted by $\varrho_i(x,t) \in L^\infty(\Omega_\Gamma)$ and $\varepsilon_i(x) \in L^\infty(\Omega_\Gamma), i = 1, 2, 3, 4, 5$; $l_k \in L^\infty(\Omega_\Gamma)$ and $p_k \in L^\infty(\Omega_\Gamma), k = 1, 2, 3$ represent the cost of pharmacological interventions. To solve the optimal control problem, we are supposed to determine an optimal control $u^* \in \mathscr{U}$ that minimizes the control cost function (5.3).

$$
\mathscr{C}(T, I, L, M, V, w^*) = \inf_{w \in \mathscr{W}} \mathscr{C}(T, I, L, M, V, w).
\tag{5.4}
$$

In this part of this article, we establish the uniqueness and existence of the solution. Additionally, we prove that the optimal control problem can be established under the system (5.1) and give the first-order necessary conditions.

5.1. Preliminaries and basic assumptions

We use the $\mathscr{H} = (L^2(\Omega))^3$ as Hilbert space and set a linear operator $\mathscr{A} : D(\mathscr{A}) \subseteq \mathscr{H} \to \mathscr{H}$ where $\mathscr{A}$ is:

$$\mathscr{A} = \begin{pmatrix} \theta_0 \Delta & 0 & 0 & 0 & 0 \\ 0 & \theta_1 \Delta & 0 & 0 & 0 \\ 0 & 0 & \theta_2 \Delta & 0 & 0 \\ 0 & 0 & 0 & \theta_3 \Delta & 0 \\ 0 & 0 & 0 & 0 & \theta_4 \Delta \end{pmatrix},$$

with

$$D(\mathscr{A}) \triangleq \left\{ (T, I, L, M, V) \in (\mathscr{H}^2(\Omega))^5, \frac{\partial T}{\partial \nu} = \frac{\partial I}{\partial \nu} = \frac{\partial L}{\partial \nu} = \frac{\partial M}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0 \right\}.$$

Denote by $Q = (T, I, L, M, V), \Theta(t, Q) = (\Theta_1(t, Q), \Theta_2(t, Q), \Theta_3(t, Q), \Theta_4(t, Q), \Theta_5(t, Q))$ with

$$\begin{cases} \Theta_1(t, Q) = \lambda - \mu_T(x)T(x, t) - \beta(x)T(x, t)V(x, t), \\ \Theta_2(t, Q) = \beta(x)T(x, t)V(x, t) - \mu_I(x)I(x, t) - n(x)(1 - w_1(x, t))I(x, t), \\ \Theta_3(t, Q) = fn(1 - w_1(x, t))I(x, t) - a(1 - w_3(x, t))L(x, t) - \mu_L(x)L(x, t), \\ \Theta_4(t, Q) = (1 - f)n(1 - w_1(x, t))I(x, t) - \mu_M(x)M(x, t) + a(1 - w_3(x, t))L(x, t), \\ \Theta_5(t, Q) = k(1 - w_2(x, t))M(x, t) - c(x)V(x, t), \end{cases} \tag{5.5}$$

where $Q = (T, I, L, M, V) \in D(Q) \triangleq \{Q \in \mathscr{H} : \Theta(t, Q) \in \mathscr{H}, \forall t \in [0, \Gamma]\}$. Then systems (5.1) with (5.2) can be reformulated as:

$$\begin{cases} \frac{\partial Q}{\partial t} = \mathscr{A}Q + \Theta(t, Q), \ t \in [0, \Gamma], \\ Q(0) = Q_0. \end{cases} \tag{5.6}$$

To give the proof of the uniqueness and the existence of the solutions to the system, we present some conclusions next.

Theorem 5.1. *We define the infinitesimal generator of C_0-semigroup as $\mathscr{A} : D(\mathscr{A}) \subseteq B \to B$, where B represent the Banach space. Consequently, it can be deduced the uniqueness of the solution $Q \in C([0, \Gamma]; B)$ when $Q_0 \in B$ of Cauchy problem (5.5):*

$$Q(t) = \tilde{T}(t)Q_0 + \int_0^t \tilde{T}(t - s)\Theta(s, Q(s))ds, t \in [0, \Gamma].$$

Furthermore, if $\mathscr{A}$ is dissipative on the Hilbert space $\mathscr{H}$ and also self-adjoint, then the mild solution meet the conditions $Q \in W^{1,2}(0, \Gamma; B) \cap L^2(0, \Gamma; D(\mathscr{A}))$.

Assumption 5.1. *Assume that the functions $T_0(x), I_0(x), L_0(x), M_0(x), V_0(x) \in \mathscr{H}^2(\Omega)$, $T_0(x) > 0, T_0(x) > 0, I_0(x) > 0, L_0(x) > 0, M_0(x) > 0, V_0(x) > 0$ and $\frac{\partial T_0(x)}{\partial \nu} = \frac{\partial I_0(x)}{\partial \nu} = \frac{\partial L_0(x)}{\partial \nu} = \frac{\partial M_0(x)}{\partial \nu} = \frac{\partial V_0(x)}{\partial \nu} = 0, x \in \partial\Omega.$*

We can deduce the uniqueness of the solution in the system (5.1) based on the similar arguments provided in Zhou et al. [46].

Theorem 5.2. *In $R^k, k \leqslant 5$, we first set a bounded domain which is denoted as Ω. Meanwhile, class $C^{2+\epsilon}, \epsilon > 0$ is the boundary of Ω. It is assumed that Assumption 5.1 holds, and for a optimal control pairs $w = (w_1, w_2, w_3) \in \mathscr{W}$, we can obtain that the solution Q of the system (5.1) is globally positive and unique with $Q = (T, I, L, M, V) \in W^{1,2}(0, T; \mathscr{H})$.*

$$T(x, t) \in L^\infty(\Omega_\Gamma) \cap L^2(0, \Gamma; \mathscr{H}^2(\Omega)) \cap L^\infty(0, T; \mathscr{H}^1(\Omega)),$$
$$I(x, t) \in L^\infty(\Omega_\Gamma) \cap L^2(0, \Gamma; \mathscr{H}^2(\Omega)) \cap L^\infty(0, T; \mathscr{H}^1(\Omega)),$$
$$L(x, t) \in L^\infty(\Omega_\Gamma) \cap L^2(0, \Gamma; \mathscr{H}^2(\Omega)) \cap L^\infty(0, T; \mathscr{H}^1(\Omega)),$$
$$M(x, t) \in L^\infty(\Omega_\Gamma) \cap L^2(0, \Gamma; \mathscr{H}^2(\Omega)) \cap L^\infty(0, T; \mathscr{H}^1(\Omega)),$$
$$V(x, t) \in L^\infty(\Omega_\Gamma) \cap L^2(0, \Gamma; \mathscr{H}^2(\Omega)) \cap L^\infty(0, T; \mathscr{H}^1(\Omega)).$$

Furthermore, there exists a $C > 0$ such that:

$$\left\|\frac{\partial T}{\partial t}\right\|_{L^2(\Omega_\Gamma)} + \|T\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \|T\|_{L^\infty(\Omega_\Gamma)} \leqslant C,$$

$$\left\|\frac{\partial I}{\partial t}\right\|_{L^2(\Omega_\Gamma)} + \|I\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \|I\|_{L^\infty(\Omega_\Gamma)} \leqslant C,$$

$$\left\|\frac{\partial T}{\partial t}\right\|_{L^2(\Omega_\Gamma)} + \|L\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \|L\|_{L^\infty(\Omega_\Gamma)} \leqslant C, \tag{5.7}$$

$$\left\|\frac{\partial T}{\partial t}\right\|_{L^2(\Omega_\Gamma)} + \|M\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \|M\|_{L^\infty(\Omega_\Gamma)} \leqslant C,$$

$$\left\|\frac{\partial T}{\partial t}\right\|_{L^2(\Omega_\Gamma)} + \|V\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \|V\|_{L^\infty(\Omega_\Gamma)} \leqslant C,$$

and

$$\|T\|_{\mathscr{H}^1(\Omega)} \leqslant C, \|I\|_{\mathscr{H}^1(\Omega)} \leqslant C, \|L\|_{\mathscr{H}^1(\Omega)} \leqslant C, \|M\|_{\mathscr{H}^1(\Omega)} \leqslant C, \|V\|_{\mathscr{H}^1(\Omega)} \leqslant C, \forall t \in [0, \Gamma]. \tag{5.8}$$

5.2. The existence of optimal solution

Theorem 5.3. *If Assumption 5.1 is valid, in that case, system (5.1) exists an optimal control $(T^*, I^*, L^*, M^*, V^*, w_1^*, w_2^*, w_3^*)$.*

Proof. Set

$$\mathscr{G}(T, I, L, M, V, w)(x, t) = \varrho_1(x, t)T(x, t) + \cdots + \varrho_5(x, t)V(x, t) + \sum_{k=1}^{3} l_k(x, t)w_k(x, t),$$

$$\mathscr{K}(T, I, L, M, V, w)(x, \Gamma) = \varepsilon_1(x)T(x, \Gamma) + \cdots + \varepsilon_5(x)V(x, \Gamma) + \sum_{k=1}^{3} p_k(x)w_k(x, \Gamma).$$

Then

$$\mathscr{C}(T, I, L, M, V, w) = \int_0^\Gamma \int_\Omega \mathscr{G}(T, I, L, M, V, w)(x, t)dxdt + \int_\Omega \mathscr{K}(T, I, L, M, V, w)(x, \Gamma)dx.$$

It can be referred from (5.7) that $\mathscr{C}(T, I, L, M, V, w)$ is proved to be bounded. Thus, there exist a minimizing sequence $\left\{w_1^m, w_2^m, w_3^m\right\}_{m \geqslant 1}$ and a positive constant $\eta = \inf\limits_{w \in \mathscr{W}} \mathscr{C}(T, I, L, M, V, w)$ such that

$$\eta = \lim_{m \to \infty} \mathscr{C}(T^m, I^m, L^m, M^m, V^m, w^m) = \inf_{w \in \mathscr{W}} \mathscr{C}(T, I, L, M, V, w),$$

Here, $(T^m, I^m, L^m, M^m, V^m, w^m)$ represents the solution of the system given by

$$\begin{cases} \dfrac{\partial T^m(x,t)}{\partial t} = \theta_0 \Delta T^m(x,t) + \lambda - \mu_T(x) T^m(x,t) - \beta(x) T^m(x,t) V^m(x,t), \\[2mm] \dfrac{\partial I^m(x,t)}{\partial t} = \theta_1 \Delta I^m(x,t) + \beta(x) T^m(x,t) V^m(x,t) - \mu_I(x) I^m(x,t) - n(x)(1 - w_1^m(x,t)) I^m(x,t), \\[2mm] \dfrac{\partial L^m(x,t)}{\partial t} = \theta_2 \Delta L^m(x,t) + fn(1 - w_1^m(x,t)) I^m(x,t) - a(1 - w_3^m(x,t)) L^m(x,t) - \mu_L(x) L^m(x,t), \\[2mm] \dfrac{\partial M^m(x,t)}{\partial t} = \theta_3 \Delta M^m(x,t) + (1-f)n(1 - u_1^m(x,t)) I^m(x,t) - \mu_M(x) M^m(x,t) + a(1 - w_3^m(x,t)) L^m(x,t), \\[2mm] \dfrac{\partial V^m(x,t)}{\partial t} = \theta_4 \Delta V^m(x,t) + k(1 - w_2^m(x,t)) M^m(x,t) - c(x) V^m(x,t), \\[2mm] \dfrac{\partial T^m(x,t)}{\partial \nu} = \dfrac{\partial I^m(x,t)}{\partial \nu} = \dfrac{\partial L^m(x,t)}{\partial \nu} = \dfrac{\partial M^m(x,t)}{\partial \nu} = \dfrac{\partial V^m(x,t)}{\partial \nu} = 0, \\[2mm] T^m(x,0) = T_0^m(x), I^m(x,0) = I_0^m(x), L^m(x,0) = L_0^m(x), M^m(x,0) = M_0^m(x), V^m(x,0) = V_0^m(x). \end{cases}$$
$$(5.9)$$

Utilizing the results of Theorem 5.2, we can verify that $T^m, I^m, L^m, M^m, V^m \in W^{1,2}(0, \Gamma; \mathscr{H})$, which implies that $T^m, I^m, L^m, M^m, V^m \in C([0, \Gamma]; L^2(\Omega))$. Furthermore, from (5.7)–(5.8), the uniformly boundedness of T^m, I^m, L^m, M^m, V^m follows; T^m, I^m, L^m, M^m, V^m are both proved to be uniformly bounded. Then given $C > 0$ and is not dependent on m satisfies that:

$$\left\|T^m\right\|_{\mathscr{H}^1(\Omega)} + \left\|T^m\right\|_{L^\infty(\Omega_\Gamma)} + \left\|T^m\right\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \left\|\frac{\partial T^m}{\partial t}\right\|_{L^2(\Omega_\Gamma)} \leqslant C, \forall t \in [0, \Gamma],$$

$$\left\|I^m\right\|_{\mathscr{H}^1(\Omega)} + \left\|I^m\right\|_{L^\infty(\Omega_\Gamma)} + \left\|I^m\right\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \left\|\frac{\partial I^m}{\partial t}\right\|_{L^2(\Omega_\Gamma)} \leqslant C, \forall t \in [0, \Gamma],$$

$$\left\|L^m\right\|_{\mathscr{H}^1(\Omega)} + \left\|L^m\right\|_{L^\infty(\Omega_\Gamma)} + \left\|L^m\right\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \left\|\frac{\partial L^m}{\partial t}\right\|_{L^2(\Omega_\Gamma)} \leqslant C, \forall t \in [0, \Gamma], \qquad (5.10)$$

$$\left\|M^m\right\|_{\mathscr{H}^1(\Omega)} + \left\|M^m\right\|_{L^\infty(\Omega_\Gamma)} + \left\|M^m\right\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \left\|\frac{\partial M^m}{\partial t}\right\|_{L^2(\Omega_\Gamma)} \leqslant C, \forall t \in [0, \Gamma],$$

$$\left\|V^m\right\|_{\mathscr{H}^1(\Omega)} + \left\|V^m\right\|_{L^\infty(\Omega_\Gamma)} + \left\|V^m\right\|_{L^2(0,\Gamma;\mathscr{H}^2(\Omega))} + \left\|\frac{\partial V^m}{\partial t}\right\|_{L^2(\Omega_\Gamma)} \leqslant C, \forall t \in [0, \Gamma].$$

From the above Eq (5.8), we know that $\{(T^m(t), I^m(t), L^m(t), M^m(t), V^m(t))\}$ is the family of equicontinuous functions. Considering $\mathscr{H}^1(\Omega)$ is compactly embedded into $L^2(\Omega)$, we get $\{(T^m(t), I^m(t), L^m(t), M^m(t), V^m(t))\}_{m \geqslant 1}$ is relatively compact in $(L^2(\Omega))^5$ and $\|T^m\|_{L^2(\Omega)} \leqslant C, \|I^m\|_{L^2(\Omega)} \leqslant C, \|L^m\|_{L^2(\Omega)} \leqslant C, \|M^m\|_{L^2(\Omega)} \leqslant C, \|V^m\|_{L^2(\Omega)} \leqslant C, \forall t \in [0, \Gamma]$. From Ascoli-Arzela Theorem [47], we obtain there exists $(T^*, I^*, L^*, M^*, V^*) \in (C([0, \Gamma] : L^2(\Omega)))^5$ and

$\{(T^m(t), I^m(t), L^m(t), M^m(t), V^m(t))\}_{m \geqslant 1}$, such that

$$
\begin{cases}
\lim\limits_{m \to \infty} \sup\limits_{t \in [0, \Gamma]} \left\| T^m(t) - T^*(t) \right\|_{L^2(\Omega)} = 0, \\
\lim\limits_{m \to \infty} \sup\limits_{t \in [0, \Gamma]} \left\| I^m(t) - I^*(t) \right\|_{L^2(\Omega)} = 0, \\
\lim\limits_{m \to \infty} \sup\limits_{t \in [0, \Gamma]} \left\| L^m(t) - L^*(t) \right\|_{L^2(\Omega)} = 0, \\
\lim\limits_{m \to \infty} \sup\limits_{t \in [0, \Gamma]} \left\| M^m(t) - M^*(t) \right\|_{L^2(\Omega)} = 0, \\
\lim\limits_{m \to \infty} \sup\limits_{t \in [0, \Gamma]} \left\| V^m(t) - V^*(t) \right\|_{L^2(\Omega)} = 0.
\end{cases}
$$

Therefore, under the condition $m \to \infty$ the optimal control problem (5.1)–(5.4) admits a optimal control variable $(T^*, I^*, L^*, M^*, V^*)$. From the estimate (5.10), there admits a $\{(T^m(t), I^m(t), L^m(t), M^m(t), V^m(t))\}$ such that

$$
\begin{cases}
\dfrac{\partial T^m}{\partial t} \rightharpoonup \dfrac{\partial T^*}{\partial t}, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
\dfrac{\partial I^m}{\partial t} \rightharpoonup \dfrac{\partial I^*}{\partial t}, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
\dfrac{\partial L^m}{\partial t} \rightharpoonup \dfrac{\partial L^*}{\partial t}, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
\dfrac{\partial M^m}{\partial t} \rightharpoonup \dfrac{\partial M^*}{\partial t}, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
\dfrac{\partial V^m}{\partial t} \rightharpoonup \dfrac{\partial V^*}{\partial t}, \ in \ L^2(0, \Gamma; L^2(\Omega)),
\end{cases}
\tag{5.11}
$$

$$
\begin{cases}
\Delta T^m \rightharpoonup \Delta T^*, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
\Delta I^m \rightharpoonup \Delta I^*, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
\Delta L^m \rightharpoonup \Delta L^*, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
\Delta M^m \rightharpoonup \Delta M^*, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
\Delta V^m \rightharpoonup \Delta V^*, \ in \ L^2(0, \Gamma; L^2(\Omega)),
\end{cases}
\tag{5.12}
$$

$$
\begin{cases}
T^m \rightharpoonup T^*, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
I^m \rightharpoonup I^*, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
L^m \rightharpoonup L^*, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
M^m \rightharpoonup M^*, \ in \ L^2(0, \Gamma; L^2(\Omega)), \\
V^m \rightharpoonup V^*, \ in \ L^2(0, \Gamma; L^2(\Omega)).
\end{cases}
\tag{5.13}
$$

Furthermore, since $w_i^m, i = 1, 2, 3$ are all bounded in $L^2(\Omega_\Gamma)$, we can get an optimal control pairs $\{w_i^m; m \geqslant 1, i = 1, 2, 3\}$ which fit:

$$
w_i^m \rightharpoonup w_i^*, \ in \ L^2(\Omega_\Gamma), i = 1, 2, 3.
\tag{5.14}
$$

At the same time, we find $\mathscr{W}$ is a weak closed set since $\mathscr{W}$ is a convex closed set in $L^2(\Omega_\Gamma)$. Hence, based on $w_i^* \in \mathscr{W}$ (5.14), we can further prove that

$$
\begin{cases}
T^m I^m \to T^* I^*, in \ L^2(0,\Gamma; L^2(\Omega)), \\
T^m L^m \to T^* L^*, in \ L^2(0,\Gamma; L^2(\Omega)), \\
T^m M^m \to T^* M^*, in \ L^2(0,\Gamma; L^2(\Omega)), \\
T^m V^m \to T^* V^*, in \ L^2(0,\Gamma; L^2(\Omega)).
\end{cases}
\tag{5.15}
$$

and

$$
T^m u_1^m \rightharpoonup T^* w_1^*, \ T^m u_2^m \rightharpoonup T^* w_2^*, \ T^m u_3^m \rightharpoonup T^* w_3^*, \ in \ L^2(0,\Gamma; L^2(\Omega)).
\tag{5.16}
$$

Then, we know that: $T^m I^m - T^* I^* = T^m(I^m - I^*) + I^*(T^m - T^*), T^m L^m - T^* L^* = T^m(L^m - L^*) + L^*(T^m - T^*)$, $T^m M^m - T^* M^* = T^m(M^m - M^*) + M^*(T^m - T^*)$, $T^m V^m - T^* V^* = T^m(V^m - V^*) + V^*(T^m - T^*)$ and $w_1^m T^m - w_1^* T^* = w_1^m(T^m - T^*) + T^*(w_1^m - w_1^*)$, $w_2^m T^m - w_2^* T^* = w_2^m(T^m - T^*) + T^*(w_2^m - w_2^*)$, $w_3^m T^m - w_3^* T^* = w_3^m(T^m - T^*) + T^*(w_3^m - w_3^*)$. We can deduce that T^m strictly converge to T^* in $L^2(\Omega_\Gamma)$ based on formula (5.11), (5.13) and the Theorem 3.1.1 in Zheng [48]. Furthermore, consider the uniformly boundedness of $T^m, I^m, L^m, M^m, V^m, w_1^m, w_2^m, w_3^m$ in $L^\infty(\Omega_\Gamma)$, we have (5.15) and (5.16). As $m \to \infty$, then we obtain an optimal control variable $(T^*, I^*, L^*, M^*, V^*)$ of the system (5.9). □

5.3. First-order necessary conditions of HIV intervention therapy with optimal control

We will introduce the adjoint equations of state variables at the beginning of this section. Let $(\hat{T}, \hat{I}, \hat{L}, \hat{M}, \hat{V})$ denote the adjoint variable:

$$
\begin{cases}
\dfrac{\partial \hat{T}}{\partial t} = -\theta_0 \Delta \hat{T} + (\mu_T + \beta V^*)\hat{T} - \beta V^* \hat{I} + \varrho_1, \\[2mm]
\dfrac{\partial \hat{I}}{\partial t} = -\theta_1 \Delta \hat{I} + (\mu_I + n(1 - w_1^*))\hat{I} - (fn(1 - w_1^*))\hat{L} - (n(1 - f)(1 - w_1^*))\hat{M} + \varrho_2, \\[2mm]
\dfrac{\partial \hat{L}}{\partial t} = -\theta_2 \Delta \hat{L} + a(1 - w_3^*)\hat{L} + \mu_L \hat{L} - a(1 - w_3^*)\hat{M} + \varrho_3, \\[2mm]
\dfrac{\partial \hat{M}}{\partial t} = -\theta_3 \Delta \hat{M} + \mu_M \hat{M} - k(1 - w_2^*)\hat{V} + \varrho_4, \\[2mm]
\dfrac{\partial \hat{V}}{\partial t} = -\theta_4 \Delta \hat{V} + c\hat{V} + \varrho_5, \\[2mm]
\dfrac{\partial \hat{T}}{\partial v} = \dfrac{\partial \hat{I}}{\partial v} = \dfrac{\partial \hat{L}}{\partial v} = \dfrac{\partial \hat{M}}{\partial v} = \dfrac{\partial \hat{V}}{\partial v} = 0, \ on \ (0,\Gamma) \times \partial\Omega, \\[2mm]
\hat{T}(x,\Gamma) = -\varepsilon_1, \hat{I}(x,\Gamma) = -\varepsilon_2, \hat{L}(x,\Gamma) = -\varepsilon_3, \hat{M}(x,\Gamma) = -\varepsilon_4, \hat{V}(x,\Gamma) = -\varepsilon_5, \ in \ \Omega,
\end{cases}
\tag{5.17}
$$

We get an optimal control pair $(T^*, I^*, L^*, M^*, V^*)$. Make a transformation: substituting the variable t with $\Gamma - t$ and letting $\zeta_1(x,t) = \hat{T}(x,\Gamma - t), \zeta_2(x,t) = \hat{I}(x,\Gamma - t), \zeta_3(x,t) = \hat{L}(x,\Gamma - t)\zeta_4(x,t) =$

$\hat{M}(x, \Gamma - t), \zeta_5(x, t) = \hat{V}(x, \Gamma - t), (x, t) \in \Omega_\Gamma$, system (5.17) then becomes

$$
\begin{cases}
\dfrac{\partial \xi_1}{\partial t} = -\theta_0 \Delta \xi_1 + (\mu_T + \beta V^*)\xi_1 - \beta V^* \xi_1 + \varrho_1, \\[2mm]
\dfrac{\partial \xi_2}{\partial t} = -\theta_1 \Delta \xi_2 + (\mu_I + n(1 - w_1^*))\xi_2 - (fn(1 - w_1^*))\xi_3 - (n(1 - f)(1 - w_1^*))\xi_4 + \varrho_2, \\[2mm]
\dfrac{\partial \xi_3}{\partial t} = -\theta_2 \Delta \xi_3 + a(1 - w_3^*)\xi_3 + \mu_L \xi_3 - a(1 - w_3^*)\xi_4 + \varrho_3, \\[2mm]
\dfrac{\partial \xi_4}{\partial t} = -\theta_3 \Delta \xi_4 + \mu_M \xi_4 - k(1 - w_2^*)\xi_5 + \varrho_4, \\[2mm]
\dfrac{\partial \xi_5}{\partial t} = -\theta_4 \Delta \xi_5 + c\xi_5 + \varrho_5, \\[2mm]
\dfrac{\partial \hat{T}}{\partial \nu} = \dfrac{\partial \hat{I}}{\partial \nu} = \dfrac{\partial \hat{L}}{\partial \nu} = \dfrac{\partial \hat{M}}{\partial \nu} = \dfrac{\partial \hat{V}}{\partial \nu} = 0, \ on\ (0, \Gamma) \times \partial\Omega, \\[2mm]
\hat{T}(x, \Gamma) = -\varepsilon_1, \hat{I}(x, \Gamma) = -\varepsilon_2, \hat{L}(x, \Gamma) = -\varepsilon_3, \hat{M}(x, \Gamma) = -\varepsilon_4, \hat{V}(x, \Gamma) = -\varepsilon_5, \ in\ \Omega.
\end{cases}
\tag{5.18}
$$

Refer to a similar process in Theorem 5.2, the solution to the system (5.18), is proved to be existed and strictly positive, and its dynamical behavior and the well-posedness of system (5.17) is also analyzed. Consequently, we will have these conclusions based on Theorem 5.2.

Lemma 5.4. *Remain all the conditions which make Theorem 5.2 valid the same, then get a control variable combination $(T^*, I^*, L^*, M^*, V^*)$. Then we can get that the solution $(\hat{T}, \hat{I}, \hat{L}, \hat{M}, \hat{V})$ to the system (5.17) such that $\hat{T}, \hat{I}, \hat{L}, \hat{M}, \hat{V} \in W^{1,2}(0, \Gamma; \mathcal{H})$. Further, $\hat{T}, \hat{I}, \hat{L}, \hat{M}, \hat{V} \in L^\infty(\Omega_\Gamma) \cap L^2(0, \Gamma; \mathcal{H}^2(\Omega) \cap L^\infty(0, \Gamma; \mathcal{H}^1(\Omega))$*

Lemma 5.5. *Remain all the conditions which make Theorem 5.2 valid the same. For $\tilde{w}_1, \tilde{w}_2, \tilde{w}_3 \in L^2(\Omega_\Gamma)$ and a positive κ, suppose that $w_1^\kappa = w_1^* + \kappa \tilde{w}_1, w_2^\kappa = w_1^* + \kappa \tilde{w}_2, w_3^\kappa = w_3^* + \kappa \tilde{w}_3 \in \mathcal{W}$. Then the problem (5.1) with $w = w^\kappa = (w_1^\kappa, w_2^\kappa, w_3^\kappa)$ has a unique solution $Q^\kappa = (T^\kappa, I^\kappa, L^\kappa, M^\kappa, V^\kappa)$. Furthermore, it can be proved that the uniformly boundedness of $\|Q^\kappa\|_{L^\infty(\Omega)}$.*

Proof. The positive strong solution's existence and uniqueness can be established using methods similar to those employed in Theorem 5.2. To demonstrate the uniform boundedness of $\|Q^\kappa\|_{L^\infty(\Omega)}$, consider the following equations.

$$
\begin{cases}
\dfrac{\partial W(x, t)}{\partial t} = \theta_0 \Delta W(x, t) + \lambda, \ in\ \Omega_\Gamma, \\[2mm]
\dfrac{\partial W(x, t)}{\partial \nu} = 0, \ on\ (0, \Gamma) \times \partial\Omega, \\[2mm]
W(x, 0) = T_0(x), \ in\ \Omega.
\end{cases}
\tag{5.19}
$$

Consider the system (5.19) and system (5.1) with $w = w^\kappa$, along with the use of the comparison principle and Gronwall's inequality, we find that

$$
0 \leqslant \|Q^\kappa(x, t)\|_{L^\infty(\Omega)} \leqslant \|W(x, t)\|_{L^\infty(\Omega)} \leqslant \varpi_1 + \lambda\Gamma, (x, t) \in \Omega_\Gamma.
$$

Here, ϖ_1 represent positive constants and is not related to κ. Therefore, we will get the uniformly boundedness of $\|T^\kappa\|_{L^\infty(\Omega)}$. Using similar methods, we know that $\|I^\kappa\|_{L^\infty(\Omega)}, \|L^\kappa\|_{L^\infty(\Omega)}, \|M^\kappa\|_{L^\infty(\Omega)}, \|V^\kappa\|_{L^\infty(\Omega)}$ are all bounded in regard to κ in Ω_Γ. □

Next, we assume that $(T^*, I^*, L^*, M^*, V^*, w_1^*, w_2^*, w_3^*)$ is an optimal pair and $Q^\kappa = (T^\kappa, I^\kappa, L^\kappa, M^\kappa, V^\kappa)$ is the solution to the problem (5.1) with $w^\kappa = (w_1^\kappa, w_2^\kappa, w_3^\kappa)$ written in Lemma 5.5. If we let $Z_T^\kappa = \frac{T^\kappa - T^*}{\kappa}, Z_I^\kappa = \frac{I^\kappa - I^*}{\kappa}, Z_L^\kappa = \frac{L^\kappa - L^*}{\kappa}, Z_M^\kappa = \frac{M^\kappa - M^*}{\kappa}, Z_V^\kappa = \frac{V^\kappa - V^*}{\kappa}$, then we have

$$
\begin{cases}
\dfrac{\partial Z_T^\kappa}{\partial t} = \theta_0 \Delta Z_T^\kappa - \beta(V^\kappa Z_T^\kappa + T^* Z_V^\kappa), \\[2mm]
\dfrac{\partial Z_I^\kappa}{\partial t} = \theta_1 \Delta Z_I^\kappa + \beta(V^\kappa Z_T^\kappa + T^* Z_V^\kappa) + n(w_1^* Z_I^\kappa + I^\kappa \tilde{w}_1) - (\mu_I + n)Z_I^\kappa, \\[2mm]
\dfrac{\partial Z_L^\kappa}{\partial t} = \theta_2 \Delta Z_L^\kappa + fn Z_I^\kappa + a(w_3^* Z_L^\kappa + L^\kappa \tilde{w}_3) - fn(w_1^* Z_I^\kappa + I^\kappa \tilde{w}_1) - a Z_L^\kappa - \mu_L Z_L^\kappa, \\[2mm]
\dfrac{\partial Z_M^\kappa}{\partial t} = \theta_3 \Delta Z_M^\kappa + n(1-f)Z_I^\kappa + a Z_L^\kappa - n(1-f)(w_1^* Z_I^\kappa + I^\kappa \tilde{w}_1) - \mu_M^* Z_M^\kappa - a(w_3^* Z_L^\kappa + L^\kappa \tilde{w}_3), \\[2mm]
\dfrac{\partial Z_V^\kappa}{\partial t} = \theta_4 \Delta Z_V^\kappa + k Z_M^\kappa - k(w_2^* Z_M^\kappa + M^\kappa \tilde{w}_2) - c Z_V^\kappa, \\[2mm]
\dfrac{\partial Z_T^\kappa}{\partial v} = \dfrac{\partial Z_I^\kappa}{\partial v} = \dfrac{\partial Z_L^\kappa}{\partial v} = \dfrac{\partial Z_M^\kappa}{\partial v} = \dfrac{\partial Z_V^\kappa}{\partial v} = 0, \ on \ (0, \Gamma) \times \partial\Omega, \\[2mm]
Z_T^\kappa(x,0) = Z_I^\kappa(x,0) = Z_L^\kappa(x,0) = Z_M^\kappa(x,0) = Z_V^\kappa(x,0) = 0, in \ \Omega.
\end{cases}
\tag{5.20}
$$

Lemma 5.6. *Remain all the conditions which make Theorem 5.2 valid the same. Then the uniqueness of strong solution Z^κ of control system problem (5.20), which satisfying $Z^\kappa = (Z_T^\kappa, Z_I^\kappa, Z_L^\kappa, Z_M^\kappa, Z_V^\kappa)^T \in W^{1,2}(0, \Gamma; \mathcal{H})$ and $Z_T^\kappa, Z_I^\kappa, Z_L^\kappa, Z_M^\kappa, Z_V^\kappa \in L^2(0, \Gamma; \mathcal{H}^2(\Omega)) \cap L^\infty(0, \Gamma; \mathcal{H}^1(\Omega))$ can be proved. Moreover, we can prove that $T^\kappa \to T^*, I^\kappa \to I^*, L^\kappa \to L^* M^\kappa \to M^*, V^\kappa \to V^*,$ in $L^2(\Omega_\Gamma)$ and $Z^\kappa \to Z$ as $\kappa \to 0$. Here, $Z = (Z_T, Z_I, Z_L, Z_M, Z_V)^T$ is the solution to this problem:*

$$
\begin{cases}
\dfrac{\partial Z_T}{\partial t} = \theta_0 \Delta Z_T - \beta(V^* Z_T + T^* Z_V), \\[2mm]
\dfrac{\partial Z_I}{\partial t} = \theta_1 \Delta Z_I + \beta(V^* Z_T + T^* Z_V) + n(w_1^* Z_I + I^* \tilde{w}_1) - (\mu_I + n)Z_I, \\[2mm]
\dfrac{\partial Z_L}{\partial t} = \theta_2 \Delta Z_L + fn Z_I + a(w_3^* Z_L + L^* \tilde{w}_3) - fn(w_1^* Z_I + I^* \tilde{w}_1) - a Z_L - \mu_L Z_L, \\[2mm]
\dfrac{\partial Z_M}{\partial t} = \theta_3 \Delta Z_M + n(1-f)Z_I + a Z_L - n(1-f)(w_1^* Z_I + I^* \tilde{w}_1) - \mu_M^* Z_M - a(w_3^* Z_L + L^* \tilde{w}_3), \\[2mm]
\dfrac{\partial Z_V}{\partial t} = \theta_4 \Delta Z_V + k Z_M - k(w_2^* Z_M + M^* \tilde{w}_2) - c Z_V, \\[2mm]
\dfrac{\partial Z_T}{\partial v} = \dfrac{\partial Z_I}{\partial v} = \dfrac{\partial Z_L}{\partial v} = \dfrac{\partial Z_M}{\partial v} = \dfrac{\partial Z_V}{\partial v} = 0, \ on \ (0, \Gamma) \times \partial\Omega, \\[2mm]
Z_T(x,0) = Z_I(x,0) = Z_L(x,0) = Z_M(x,0) = Z_V(x,0) = 0, in \ \Omega.
\end{cases}
\tag{5.21}
$$

Proof. According to the method in Theorem 5.2, we can prove that there admits a strong solution. Next, we need to prove that $Z_T^\kappa, Z_I^\kappa, Z_L^\kappa, Z_M^\kappa, Z_V^\kappa$ are all bounded in $L^2(\Omega_\Gamma)$ uniformly with regard to κ and $lim_{\kappa \to 0}\|T^\kappa - T^*\|_{L^2(\Omega_\Gamma)} = 0, lim_{\kappa \to 0}\|I^\kappa - I^*\|_{L^2(\Omega_\Gamma)} = 0, lim_{\kappa \to 0}\|L^\kappa - L^*\|_{L^2(\Omega_\Gamma)} = 0, lim_{\kappa \to 0}\|M^\kappa - M^*\|_{L^2(\Omega_\Gamma)} = 0, lim_{\kappa \to 0}\|V^\kappa - V^*\|_{L^2(\Omega_\Gamma)} = 0$. For this purpose, let

$$
W^\kappa(t) = (0, nI^\kappa \tilde{w}_1, aL^\kappa \tilde{u}_3 - fn I^\kappa \tilde{w}_1, -n(1-f)I^\kappa \tilde{w}_1 - aL^\kappa \tilde{w}_3, -kM^\kappa \tilde{w}_2)^T,
$$
$$
W^*(t) = (0, nI^* \tilde{w}_1, aL^* \tilde{w}_3 - fn I^* \tilde{w}_1, -n(1-f)I^* \tilde{w}_1 - aL^* \tilde{w}_3, -kM^* \tilde{w}_2)^T.
$$

and

$$\mathscr{T}^\kappa(t) = \begin{pmatrix} -\beta V^\kappa & 0 & 0 & 0 & -\beta T^* \\ \beta V^\kappa & n(w_1^* - 1) - \mu_I & 0 & 0 & \beta T^* \\ 0 & nf(1 - w_1^*) & a(w_3^* - 1) - \mu_L & 0 & 0 \\ 0 & n(1 - f)(1 - w_1^*) & a(1 - w_3^*) & -\mu_M & 0 \\ 0 & 0 & 0 & k(1 - w_2^*) & -c \end{pmatrix},$$

$$\mathscr{T}^*(t) = \begin{pmatrix} -\beta V^* & 0 & 0 & 0 & -\beta T^* \\ \beta V^* & n(w_1^* - 1) - \mu_I & 0 & 0 & \beta T^* \\ 0 & nf(1 - w_1^*) & a(w_3^* - 1) - \mu_L & 0 & 0 \\ 0 & n(1 - f)(1 - w_1^*) & a(1 - w_3^*) & -\mu_M & 0 \\ 0 & 0 & 0 & k(1 - w_2^*) & -c \end{pmatrix}.$$

Then system (5.20) can be rewritten as

$$\begin{cases} \dfrac{\partial Z^\kappa}{\partial t} = \mathscr{A} Z^\kappa(t) + \mathscr{T}^\kappa(t) Z^\kappa(t) + W^\kappa(t), \; in \; \Omega_\Gamma, \\ Z^\kappa(0) = 0, \; in \; \Omega. \end{cases} \tag{5.22}$$

Assuming $\mathscr{A}$ has semigroup $\{T(t) : t \geqslant 0\}$, it can be deduced from Lions [49] that the solution of (5.22) can be formulated as

$$Z^\kappa(t) = \int_0^t T(t - s)\mathscr{T}^\kappa(s) Z^\kappa(s) ds + \int_0^t T(t - s) W^\kappa(s) ds, t \in [0, \Gamma]. \tag{5.23}$$

Moreover, considering Lemma 5.4, 5.5 and Theorem 5.2, we will obtain the uniformly boundedness of $\mathscr{T}$ and U. Hence, there admits $B_1 > 0$ and $B_2 > 0$ such that

$$\|Z^\kappa(t)\|_{L^2(\Omega)} \leqslant B_1 + B_2 \int_0^t \|Z^\kappa(s)\|_{L^2(\Omega)} ds, t \in [0, \Gamma].$$

According to inequality of Gronwall that is Z^κ bounded in $L^2(\Omega_\Gamma)$. Thus we have

$$\begin{cases} \|Z^\kappa - Z\|_{L^2(\Omega_\Gamma)} = \kappa \|Z^\kappa\|_{L^2(\Omega_\Gamma)} \to 0, as \; \kappa \to 0, \\ \|I^\kappa - I\|_{L^2(\Omega_\Gamma)} = \kappa \|I^\kappa\|_{L^2(\Omega_\Gamma)} \to 0, as \; \kappa \to 0, \\ \|L^\kappa - L\|_{L^2(\Omega_\Gamma)} = \kappa \|L^\kappa\|_{L^2(\Omega_\Gamma)} \to 0, as \; \kappa \to 0, \\ \|M^\kappa - M\|_{L^2(\Omega_\Gamma)} = \kappa \|M^\kappa\|_{L^2(\Omega_\Gamma)} \to 0, as \; \kappa \to 0, \\ \|V^\kappa - V\|_{L^2(\Omega_\Gamma)} = \kappa \|V^\kappa\|_{L^2(\Omega_\Gamma)} \to 0, as \; \kappa \to 0. \end{cases}$$

We next further show $Z^\kappa \to Z$, in $L^2(\Omega_\Gamma)$. System (5.21) can be expressed as

$$\begin{cases} \dfrac{\partial Z}{\partial t} = \mathscr{A} Z(t) + \mathscr{T}^*(t) Z(t) + W^*(t), \; in \; \Omega_\Gamma, \\ Z(0) = 0, \; in \; \Omega. \end{cases} \tag{5.24}$$

Next, the solution of system (5.24):

$$Z(t) = \int_0^t T(t - s)\mathscr{T}^*(s) Z(s) ds + \int_0^t T(t - s) W^*(s) ds, t \in [0, \Gamma]. \tag{5.25}$$

Consider both the (5.23) and (5.25):

$$Z^{\kappa}(t) - Z(t) = \int_0^t T(t - s)(T^{\kappa}Z^{\kappa} - T^*Z)(s)ds, t \in [0, \Gamma].$$

In addition, The elements of matrix $T^{\kappa}(t)$ tend to the corresponding elements of matrix $T^*(t)$ in $L^2(\Omega_{\Gamma})$, and it is also bounded. We can speculate that $Z^{\kappa} \to Z$ in $L^2(\Omega_{\Gamma})$ by the inequality of Gronwall. □

Theorem 5.7. *Remain all the conditions which make Theorem 5.2 valid the same. If $(T^*, I^*, L^*, M^*, V^*, w_1^*, w_2^*, w_3^*)$ is an control combination of problem (5.1)–(5.4) and $(\hat{T}, \hat{I}, \hat{L}, \hat{M}, \hat{V})$ is the solution to the adjoint system, then we have*

$$\int_{\Omega_{\Gamma}} n(1 - f)I^*\tilde{w}_1\hat{M}dxdt + \int_{\Omega_{\Gamma}} aL^*\tilde{w}_3\hat{M}dxdt + \int_{\Omega_{\Gamma}} kM^*\tilde{w}_2\hat{V}dxdt - \int_{\Omega_{\Gamma}} nI^*\tilde{w}_1\hat{I}dxdt$$

$$- \int_{\Omega_{\Gamma}} (aL^*\tilde{w}_3 - fnI^*\tilde{w}_1)\hat{L}dxdt \geqslant - \int_{\Omega_{\Gamma}} \sum_{i=1}^3 l_i\tilde{w}_i(x, t)dxdt - \int_{\Omega} \sum_{i=1}^3 p_i\tilde{w}_i(x, \Gamma)dx. \tag{5.26}$$

Furthermore, if $p_1(x) = p_2(x) = p_3(x) \equiv 0$ in Ω, we can choose the following strategy:

$$u_1^* = \begin{cases} 1, & in \ \left\{(x, t) \in \Omega : (I^*\hat{I} + l_1)(x, t) \leqslant 0\right\}, \\ 0, & in \ \left\{(x, t) \in \Omega : (I^*\hat{I} + l_1)(x, t) > 0\right\}. \end{cases}$$

$$u_2^* = \begin{cases} 1, & in \ \left\{(x, t) \in \Omega : (V^*\hat{V} + l_2)(x, t) \leqslant 0\right\}, \\ 0, & in \ \left\{(x, t) \in \Omega : (V^*\hat{V} + l_2)(x, t) > 0\right\}. \end{cases}$$

and

$$u_3^* = \begin{cases} 1, & in \ \left\{(x, t) \in \Omega : (L^*\hat{L} + l_3)(x, t) \leqslant 0\right\}, \\ 0, & in \ \left\{(x, t) \in \Omega : (L^*\hat{L} + l_3)(x, t) > 0\right\}. \end{cases}$$

Proof. Assume that the optimal control pair $(T^*, I^*, L^*, M^*, V^*, w_1^*, w_2^*, w_3^*)$ and the control cost function $\mathscr{C}(T, I, L, M, V, w)$, which is given by (5.3). Hence,

$$\mathscr{C}(T^*, I^*, L^*, M^*, V^*, w^*) \leqslant \mathscr{C}(T^{\kappa}, I^{\kappa}, L^{\kappa}, M^{\kappa}, V^{\kappa}, w^{\kappa}), \forall \kappa > 0.$$

That is

$$\int_{\Omega_{\Gamma}} (\varrho_1(T^{\kappa} - T^*) + \varrho_2(I^{\kappa} - I^*) + \varrho_3(L^{\kappa} - L^*) + \varrho_4(M^{\kappa} - M^*) + \varrho_5(V^{\kappa} - V^*) + \sum_{i=1}^3 \kappa l_i\tilde{w}_i)(x, t)dxdt$$

$$+ \int_{\Omega} (\varepsilon_1(T^{\kappa} - T^*) + \varepsilon_2(I^{\kappa} - I^*) + \varepsilon_3(L^{\kappa} - L^*) + \varepsilon_4(M^{\kappa} - M^*) + \varepsilon_5(V^{\kappa} - V^*) + \sum_{i=1}^3 \kappa p_i\tilde{w}_i)(x, \Gamma)dx \geqslant 0.$$

Multiply both sides of the inequality by $1/\kappa$:

$$\int_{\Omega_{\Gamma}} (\varrho_1 Z_T^{\kappa} + \varrho_2 Z_I^{\kappa} + \varrho_3 Z_L^{\kappa} + \varrho_4 Z_M^{\kappa} + \varrho_5 Z_V^{\kappa} + \sum_{i=1}^3 l_i\tilde{w}_i)(x, t)dxdt$$

$$+ \int_{\Omega} (\varepsilon_1 Z_T^{\kappa} + \varepsilon_2 Z_I^{\kappa} + \varepsilon_3 Z_L^{\kappa} + \varepsilon_4 Z_M^{\kappa} + \varepsilon_5 Z_V^{\kappa} + \sum_{i=1}^3 p_i\tilde{w}_i)(x, \Gamma)dx \geqslant 0.$$

Moreover, refer to Lemma 5.6, it holds that

$$Z_T^\kappa \to Z_T, Z_I^\kappa \to Z_I, Z_L^\kappa \to Z_L, Z_M^\kappa \to Z_M, Z_V^\kappa \to Z_V \ in \ L^2(\Omega_\Gamma), as \ \kappa \to 0.$$

Hence, it holds that

$$Z_T^\kappa \to Z_T, Z_I^\kappa \to Z_I, Z_L^\kappa \to Z_L, Z_M^\kappa \to Z_M, Z_V^\kappa \to Z_V \ in \ L^1(\Omega_\Gamma), as \ \kappa \to 0.$$

Similarly,we can prove that

$$Z_T^\kappa(\Gamma) \to Z_T(\Gamma), Z_I^\kappa(\Gamma) \to Z_I(\Gamma), Z_L^\kappa(\Gamma) \to Z_L(\Gamma), Z_M^\kappa(\Gamma) \to Z_M(\Gamma), Z_V^\kappa(\Gamma) \to Z_V(\Gamma) \ in \ L^1(\Omega_\Gamma), as \ \kappa \to 0.$$

Then, sending $\kappa \to 0$:

$$
\begin{aligned}
& \int_{\Omega_\Gamma} (\varrho_1 Z_T + \varrho_2 Z_I + \varrho_3 Z_L + \varrho_4 Z_M + \varrho_5 Z_V + \sum_{i=1}^3 l_i \tilde{w}_i)(x,t) dx dt \\
& + \int_\Omega (\varepsilon_1 Z_T + \varepsilon_2 Z_I + \varepsilon_3 Z_L + \varepsilon_4 Z_M + \varepsilon_5 Z_V + \sum_{i=1}^3 p_i \tilde{w}_i)(x,\Gamma) dx \geqslant 0
\end{aligned}
\tag{5.27}
$$

From system (5.17) and (5.21), we can obtain that

$$
\begin{aligned}
& \frac{\partial \hat{T}}{\partial t} Z_T + \frac{\partial \hat{I}}{\partial t} Z_I + \frac{\partial \hat{L}}{\partial t} Z_L + \frac{\partial \hat{M}}{\partial t} Z_M + \frac{\partial \hat{V}}{\partial t} Z_V + \frac{\partial Z_T}{\partial t} \hat{T} + \frac{\partial Z_I}{\partial t} \hat{I} + \frac{\partial Z_L}{\partial t} \hat{L} + \frac{\partial Z_M}{\partial t} \hat{M} + \frac{\partial Z_V}{\partial t} \hat{V} \\
& = -\theta_0 \Delta \hat{T} Z_T - \theta_1 \Delta \hat{I} Z_I - \theta_2 \Delta \hat{L} Z_L - \theta_3 \Delta \hat{M} Z_M - \theta_4 \Delta \hat{V} Z_V + \theta_0 \Delta Z_T \hat{T} + \theta_1 \Delta Z_I \hat{I} + \theta_2 \Delta Z_L \hat{L} + \theta_3 \Delta Z_M \hat{M} \\
& \quad + \theta_4 \Delta Z_V \hat{V} + \varrho_1 Z_T + \varrho_2 Z_I + \varrho_3 Z_L + \varrho_4 Z_M + \varrho_5 Z_V + nI^* \tilde{w}_1 \hat{I} + (aL^* \tilde{w}_3 - fnI^* \tilde{w}_1) \hat{L} - n(1-f)I^* \tilde{w}_1 \hat{M} \\
& \quad - aL^* \tilde{w}_3 \hat{M} - kM^* \tilde{w}_2 \hat{V}.
\end{aligned}
\tag{5.28}
$$

Let the expression (5.28) be integrated over Ω_Γ. Then, considering the initial boundary conditions of $\hat{T}, \hat{I}, \hat{L}, \hat{M}, \hat{V}, Z_T, Z_I, Z_L, Z_M, Z_V$, we can get:

$$
\begin{aligned}
& \int_\Omega (Z_T \hat{T} + Z_I \hat{I} + Z_L \hat{L} + Z_M \hat{M} + Z_V \hat{V})(x,\Gamma) dx \\
& = \int_{\Omega_\Gamma} (\varrho_1 Z_T + \varrho_2 Z_I + \varrho_3 Z_L + \varrho_4 Z_M + \varrho_5 Z_V)(x,t) dx dt + \int_{\Omega_\Gamma} nI^* \tilde{w}_1 \hat{I} dx dt + \int_{\Omega_\Gamma} (aL^* \tilde{w}_3 - fnI^* \tilde{w}_1) \hat{L} dx dt \\
& \quad - \int_{\Omega_\Gamma} n(1-f)I^* \tilde{w}_1 \hat{M} dx dt - \int_{\Omega_\Gamma} aL^* \tilde{w}_3 \hat{M} dx dt - \int_{\Omega_\Gamma} kM^* \tilde{w}_2 \hat{V} dx dt.
\end{aligned}
$$

From the last equation of (5.17), we can get

$$
\begin{aligned}
& \int_\Omega (Z_T \varepsilon_1 + Z_I \varepsilon_2 + Z_L \varepsilon_3 + Z_M \varepsilon_4 + Z_V \varepsilon_5)(x,\Gamma) dx \\
& = \int_{\Omega_\Gamma} n(1-f)I^* \tilde{u}_1 \hat{M} dx dt + \int_{\Omega_\Gamma} aL^* \tilde{u}_3 \hat{M} dx dt + \int_{\Omega_\Gamma} kM^* \tilde{u}_2 \hat{V} dx dt - \int_{\Omega_\Gamma} (aL^* \tilde{u}_3 - fnI^* \tilde{u}_1) \hat{L} dx dt \\
& \quad - \int_{\Omega_\Gamma} (\varrho_1 Z_T + \varrho_2 Z_I + \varrho_3 Z_L + \varrho_4 Z_M + \varrho_5 Z_V)(x,t) dx dt - \int_{\Omega_\Gamma} nI^* \tilde{u}_1 \hat{I} dx dt.
\end{aligned}
$$

Then, by (5.27), one has

$$\int_{\Omega_\Gamma} n(1-f)I^*\tilde{w}_1\hat{M}dxdt + \int_{\Omega_\Gamma} aL^*\tilde{w}_3\hat{M}dxdt + \int_{\Omega_\Gamma} kM^*\tilde{w}_2\hat{V}dxdt - \int_{\Omega_\Gamma} nI^*\tilde{w}_1\hat{I}dxdt$$

$$- \int_{\Omega_\Gamma} (aL^*\tilde{w}_3 - fnI^*\tilde{w}_1)\hat{L}dxdt \geqslant - \int_{\Omega_\Gamma} \sum_{i=1}^{3} l_i\tilde{w}_i(x,t)dxdt - \int_{\Omega} \sum_{i=1}^{3} p_i\tilde{w}_i(x,\Gamma)dx.$$

Given that $\tilde{w} = (\tilde{w}_1, \tilde{w}_2, \tilde{w}_3) \in L^2(\Omega_\Gamma)$ is arbitrary, make equality transformation such as $\hat{w}_i = \tilde{w}_i - \tilde{w}_i^*$, $\forall \tilde{w}_i^* \in \mathscr{W}$, $i = 1, 2, 3$. We can get the formula (5.26) from the Theorem 5.7. $\qquad\square$

6. Numerical simulations

6.1. Model parameters and its initial values

In this section, our focus is on the concentration dynamics of each compartment under the optimal control strategy. In numerous studies and experiments, the estimated parameter values are invariant and independent of the spatial dimension, and these values can reflect the mean level of these factors. Hence, it is reasonable to use mean values to estimate parameters. The parameter values for model (2.3) are chosen from Table 3, and the mean value of $b(x)$ over $\bar{\Omega}$ is set to $\tilde{b}$, where $b = \lambda, \beta, n, f, a, k, c, \mu_T, \mu_I, \mu_L, \mu_M$. Moreover, the mean values of these parameters refer to the literature listed in Table 3. We assume that the one-dimensional bounded space area Ω_Γ can be regarded as an abstract projection of the two-dimensional space.

Considering that the basic reproduction number of HIV transmission in the human body is generally between 8 and 10, we assume that $\tilde{\beta} = 3.2 \times 10^{-10}$, which implies that $R_0 = 8.4492$. The diffusion coefficient of the uninfected cells can be set to $\tilde{\theta}_0 = 0.006$ mm^2 day^{-1}. Given that infected cells exhibit slower movement compared to uninfected cells, we hypothesized that $\tilde{\theta}_1 = 0.005$ mm^2 day^{-1}, $\tilde{\theta}_2 = 0.005$ mm^2 day^{-1}, $\tilde{\theta}_3 = 0.003$ mm^2 day^{-1}, $\tilde{\theta}_4 = 0.006$ mm^2 day^{-1}.

Table 3. Mean values of model parameters and their sources.

Parameter	Mean value	Source
$\lambda(x)$	5.0×10^5 cells/(day mL)	Nakaoka et al. [50]
$\beta(x)$	3.2×10^{-10} mL/(virions cells day)	Variable
$n(x)$	2.6 day^{-1}	Hill et al. [30]
$f(x)$	0.1 day^{-1}	Hill et al. [30]
$a(x)$	0.4 day^{-1}	Hill et al. [30]
$k(x)$	1000 virions/(cell day)	Funk et al. [51]
$c(x)$	3 day^{-1}	Nelson et al. [52]
$\mu_T(x)$	0.01 day^{-1}	Nakaoka et al. [50]
$\mu_I(x)$	0.5 day^{-1}	Nelson et al. [52]
$\mu_L(x)$	0.5 day^{-1}	Nelson et al. [52]
$\mu_M(x)$	0.5 day^{-1}	Nelson et al. [52]

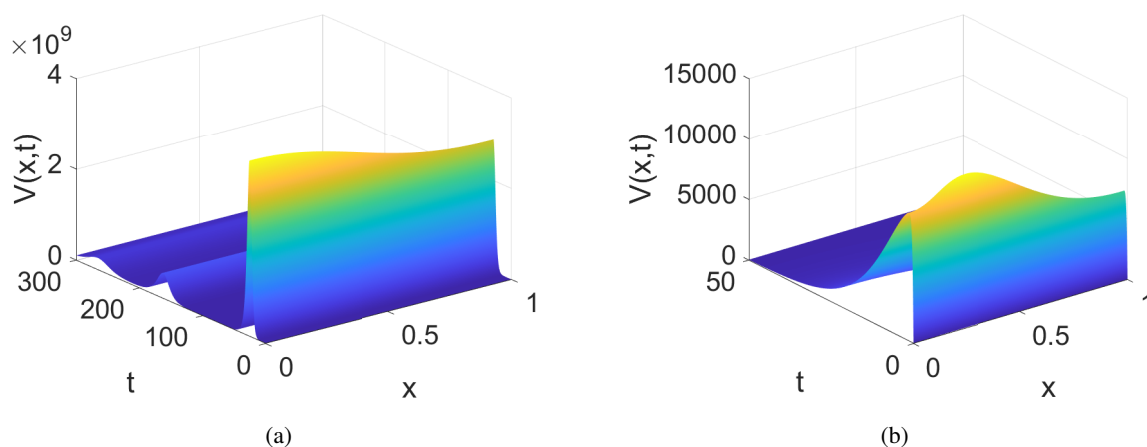## 6.2. *Numerical simulation of dynamic behavior*

Figure 1. Time variation of $V(x, t)$ for different R_0. (a) $R_0 \approx 2.1123 > 1$. (b) $R_0 \approx 0.5281 < 1$.

In Section 5, we explain that the reverse transcriptase inhibitors, protease inhibitor, and Flavonoid Compounds treatments are likely effective to prevent virus-to-cell transmission. Therefore, we assume that when these interventions are taken, the production rate of virus in infected cells and the speed of virus infection will be reduced, that is, $k(x)$ and $\beta(x)$ will be reduced. Now, set $\beta(x) = 0.25\tilde{\beta}$, the remaining parameters are set according to Table 3. Then we can calculate $R_0 \approx 2.1123$ and the virus is persistent (Figure 1(a) with $T_0(x) = 5.0 \times 10^7$, $I_0(x) = 0$, $L_0(x) = 0$, $M_0(x) = 0$, $V_0(x) = 25 \times (1 + x(1 - x)^2(2 - x)^3)$ for $x \in (0, 1]$). Set $\beta(x) = 0.125\tilde{\beta}$, $k(x) = 0.5\tilde{k}$ for $x \in (0, 1]$ and The remaining parameters remain consistent with those illustrated in Figure 1(a). Then use the same method to calculate, we calculate $R_0 \approx 0.5281$ and observe that the virions are becoming extinct (Figure 1(b)). By comparison we find that the increase in R_0 is clearly associated with an elevated risk of HIV transmission.

To study the effect of spatial heterogeneity, we assume that parameter β is spatial dependent. Under the condition that the mean value of parameter $\beta(x)$ is equal to $0.25\tilde{\beta}$ ($x \in (0, 1]$), we assume that $\beta(x) = 8 \times 10^{-11}(1 + sin(2\pi x))$. The remaining parameters are consistent with the experimental parameters in Figure1 (a). We set the following initial values: $T_0(x) = 5 \times 10^7(1 + x(1 - x)^2(2 - x)^3)$, $I_0(x) = 10 \times (1 + x(1 - x)^2(2 - x)^3)$ $L_0(x) = 10 \times (1 + x(1 - x)^2(2 - x)^3)$, $M_0(x) = 50 \times (1 + x(1 - x)^2(2 - x)^3)$, $V_0(x) = 25 \times (1 + x(1 - x)^2(2 - x)^3)$. Under the influence of heterogeneous parameters, we obtain the concentration changes in each compartment as shown in Figure 2. In addition, Figure 3 is a graph of the change in concentration of each compartment when β is a spatial homogeneous parameter ($\beta(x) = 0.25\tilde{\beta}$).

In Figures 2 and 3, the compartments representing infected cells and virions are both beyond normal levels due to infection. Susceptible compartment shows no significant changes in the short term. Comparing the cases of heterogeneous and homogeneous parameters, we find that the concentrations of the infected compartments (I, L, M, V) are significantly higher under heterogeneous parameters than under homogeneous parameters. This indicates that using spatially averaged parameters will underestimate the extent of HIV infection.
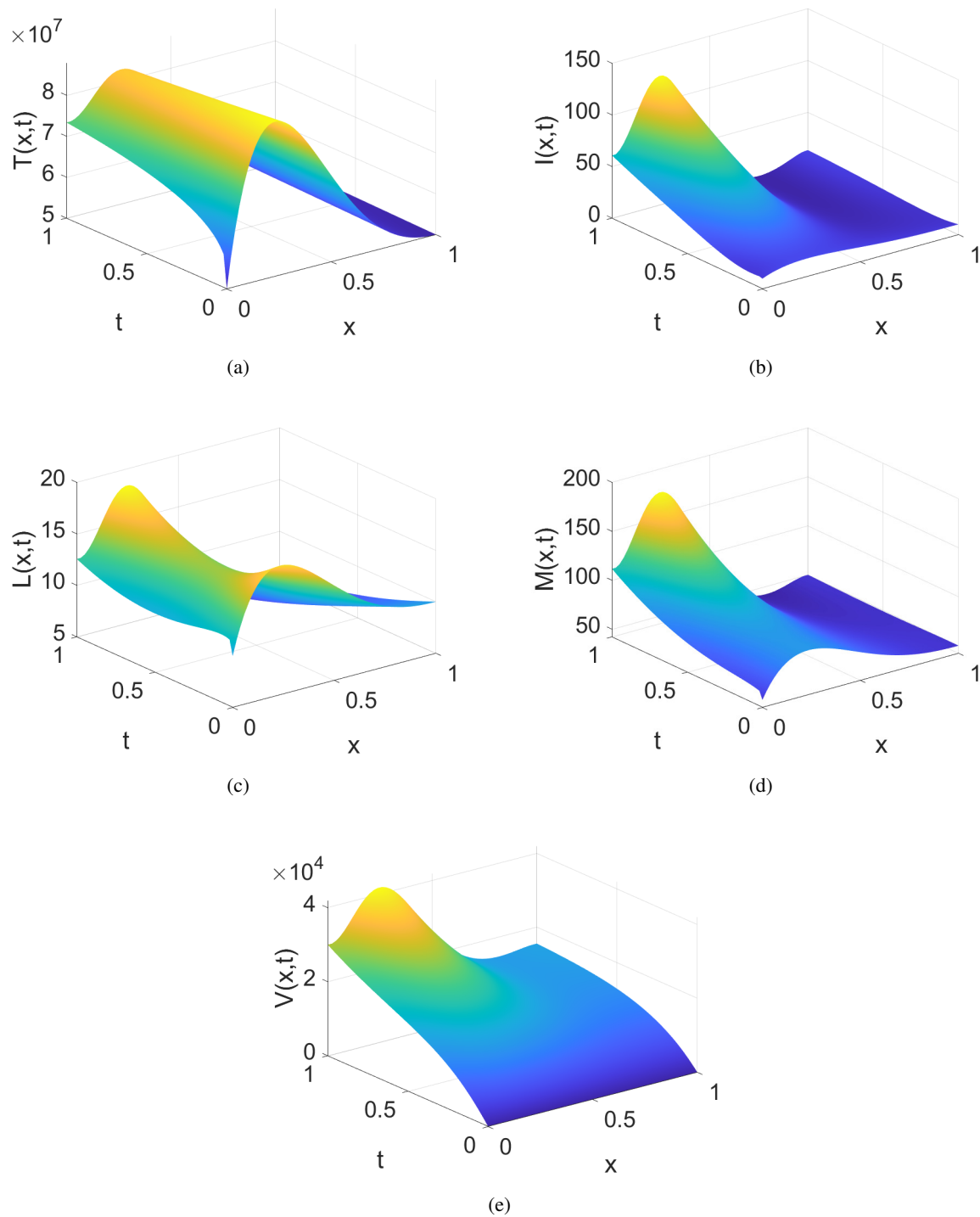
Figure 2. The solution surface to system (2.3)–(2.5) on $\Omega_\Gamma = [0, 1] \times [0, 1]$, $\beta(x) = 8 \times 10^{-11}(1 + sin(2\pi x))$.
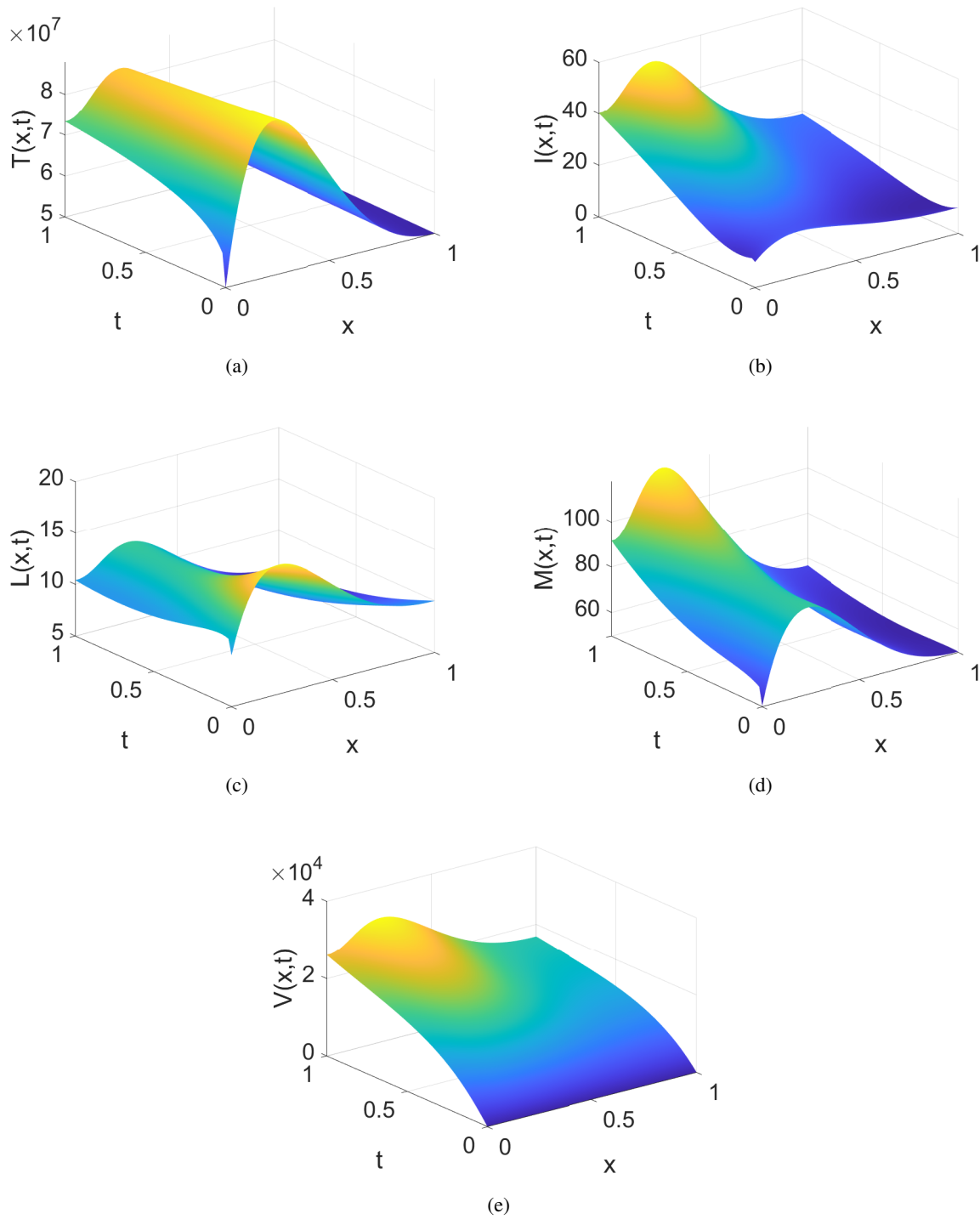
Figure 3. The solution surface to system (2.3)–(2.5) on $\Omega_\Gamma = [0, 1] \times [0, 1], \beta(x) = 8 \times 10^{-11}$.
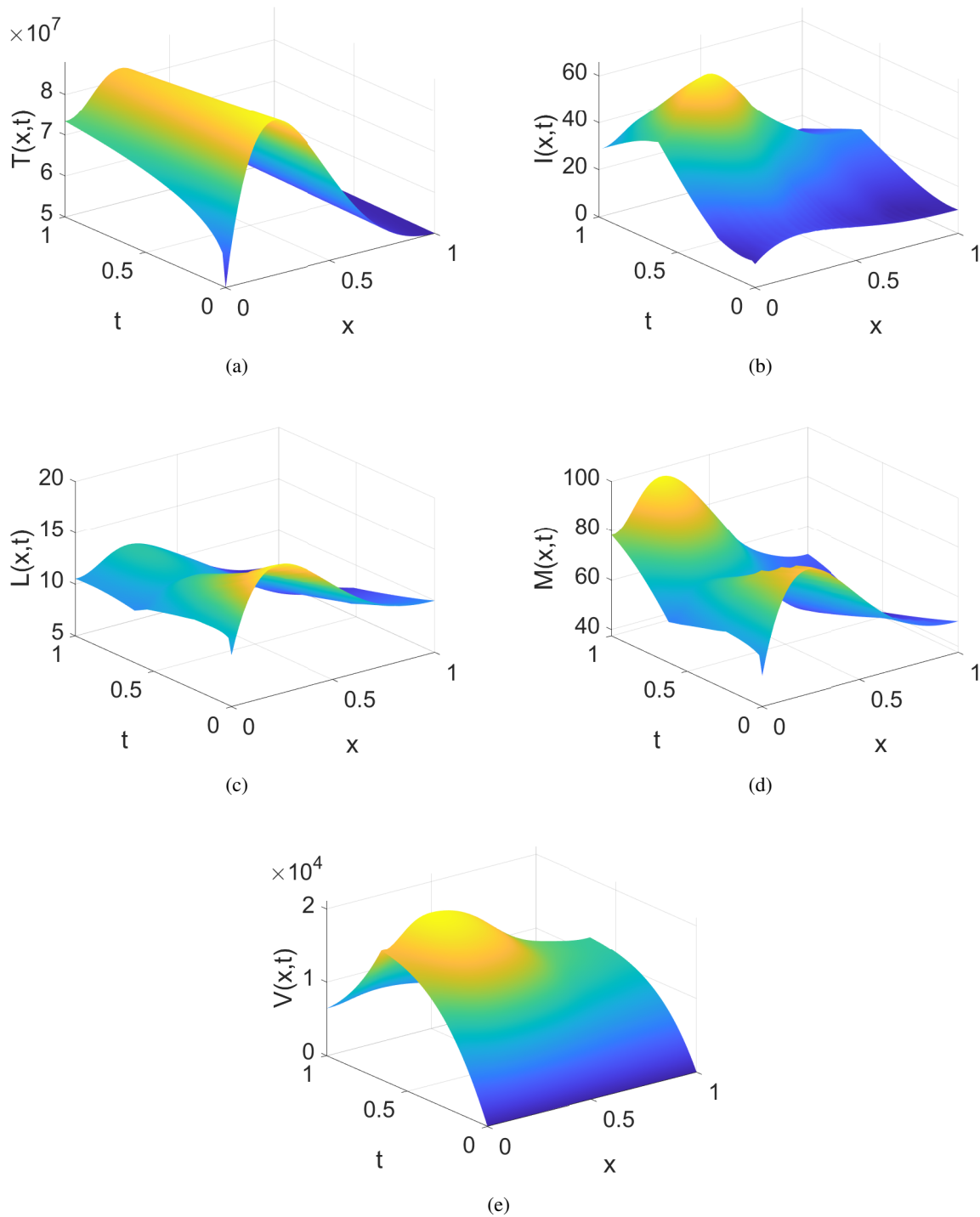
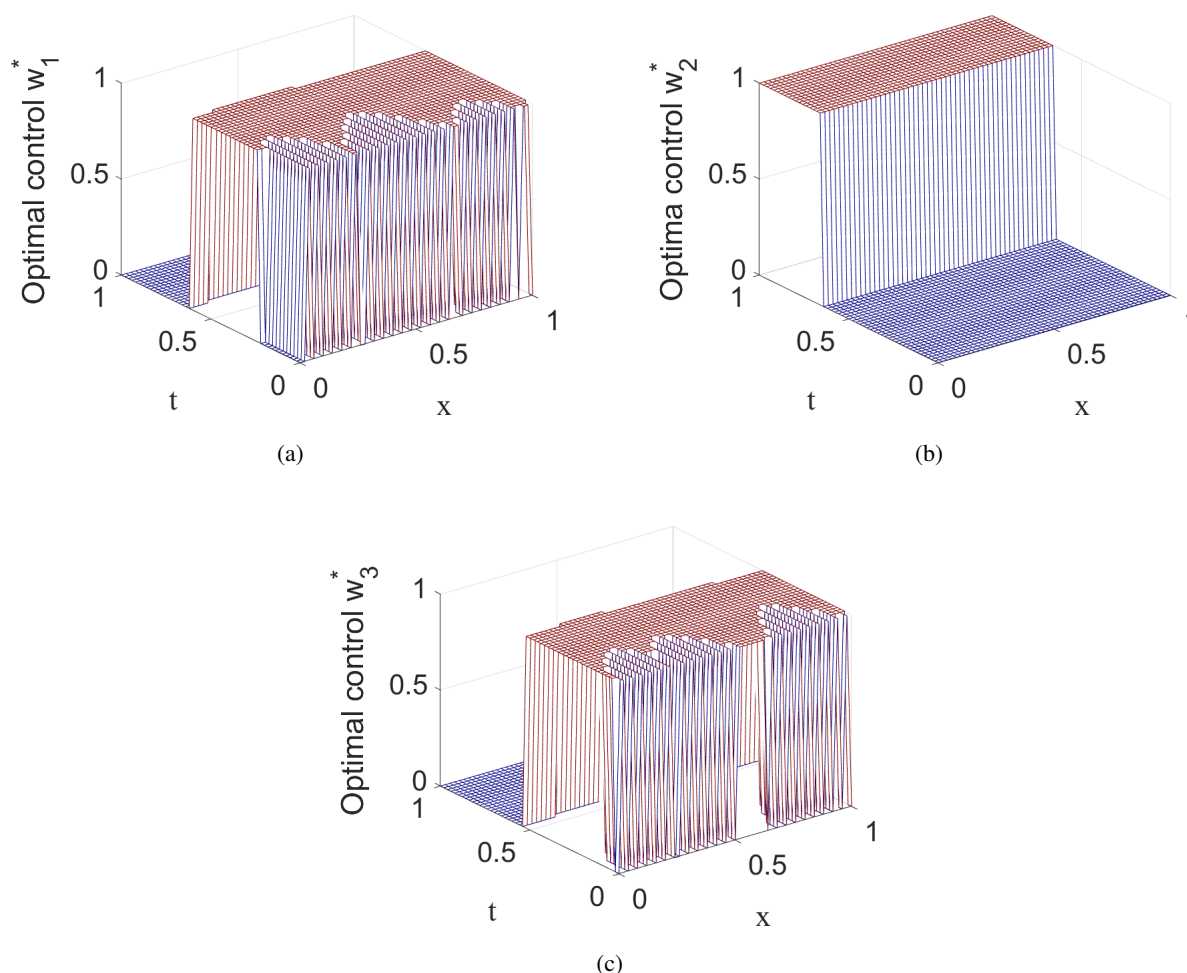**Figure 4.** The solution surface to the control system (5.1)–(5.3) on $\Omega_{\Gamma} = [0, 1] \times [0, 1]$.

Figure 5. The optimal controls on $\Omega_\Gamma = [0, 1] \times [0, 1]$.

6.3. Numerical simulation of optimal control in HIV transmission

In the context of researching optimal control problems for reaction-diffusion models, it is crucial to consider the rational selection of parameters within the objective functional $\mathscr{C}(T, I, L, M, V, w)$. The values for the parameters are as follows: $\varrho_1 = 1$, $\varrho_2 = 1$, $\varrho_3 = 1$, $\varrho_4 = 1$, $\varrho_5 = 1$, $l_1 = 0.4$, $l_2 = 0.3$, $l_3 = 0.3$, $l_4 = 0.3$, $l_5 = 0.35$, $\varepsilon_1 = 100$, $\varepsilon_2 = 100$, $\varepsilon_3 = 100$. The initial values are the same as those in Figure 3. Based on the given parameter values, we employ the finite difference method (Crank-Nicolson) to numerically simulate the optimal control problem (5.1)–(5.4). For the numerical solution of the adjoint system (5.17), we use the iterative solution of the control system (5.1) to solve backward in time by the Crank-Nicolson method.

The solution surface of the control system (5.1) is shown in Figure 4. After adding controls, we found that the load of immature infected cells, latent infected cells, mature infected cells and viral particles all decreased significantly under the optimal treatment strategy. This indicated that the optimal treatment strategy is very effective in controlling HIV infection in the host. Susceptible compartments ($CD4^+T$) did not change significantly in the short term. The base number of susceptible cells is large, and the early spread of the virus has little impact on the concentration of susceptible cells (Figure 4(a)).

The optimal control w_i^*, $i = 1, 2, 3$ is shown in Figure 5. We found that the optimal control strategies are Bang-Bang control forms. For w_1 and w_3 control, the optimal control is interrupted for a certain distance at the early time, the maximum control intensity is reached near the mid-range moment. For w_2 control, the maximum control intensity is reached near the terminal time. When the w_1 variable and w_3 variable are not controlled in the later stage, they lead to an increase in the concentration of latent infected cells and mature infected cells respectively. The free viral particle compartment converged to lower concentrations after the addition of the control term w_2, and it suggest that the ability of infected cells to produce virus was controlled at low levels. This indicates that pharmacological interventions can slow down the process of viral infection in humans and reduce the severity of the disease in the early stages of HIV transmission.

In addition, the values of optimal control are different at different spatial locations x, which means that the intensity of measures taken depends on the different spatial locations. During the clinical treatment of HIV, the differences in human body organs and tissues should be taken into consideration in the dosage. Large doses should be used in areas with a high degree of infection, and less medication should be used in areas with a mild degree of infection. In this way, on the one hand, HIV infection in the body can be accurately controlled, and on the other hand, the cost of treatment can be reduced. A treatment process that does not take heterogeneity into account is equivalent to completely equalizing medication, which is not conducive to suppressing the spread of the virus and also increases the cost.

7. Conclusions

In this paper, we develop a dynamic model of HIV transmission in human body that includes a spatially heterogeneous diffusion term to study combination effect of reverse transcriptase inhibitors, protease inhibitor and Flavonoid Compound. We study the case of bounded spaces with Neumann boundaries to obtain the persistence conditions of viruses in heterogeneous spaces. First, we discuss the case of well-posedness under Neumann boundary conditions and prove the existence of the global attractor of the system, and we derive a biologically meaningful threshold index, the basic reproduction ratio R_0. We prove that the threshold dynamics of R_0: The virus persists in body when $R_0 > 1$ and is eventually eliminated when $R_0 < 1$. The basic reproduction ratio for this model is characterized as the spectral radius of the next generation operator and can be numerically calculated when the model parameters are spatially independent.

To further investigate the optimal control strategy for pharmacological intervention in the HIV infection, we introduced control variables representing reverse transcriptase inhibitors, protease inhibitor and Flavonoid Compounds, respectively. An objective function that minimizes the number of infected cells and intervention costs while maximizing the number of susceptible cells was established. Finally, We prove the first-order necessary conditions.

In the numerical simulation section, we initially compared the changes in virus concentration under different basic reproduction number values, and that experimental and theoretical results are consistent. Next, we compared the variations in concentration over time and position in different compartments with and without control. It is shown that the implementation of the optimal treatment strategies in this paper can significantly reduce the load of infected cell and free virus, so as to effectively control HIV infection in the host.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgement

Conflict of interest

The authors declare there is no conflicts of interest.

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