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Research Article

An Efficient Therapy Strategy under a Novel HIV Model

Chunming Zhang,[1] Xiaofan Yang,[1] Wanping Liu,[1] and Lu-Xing Yang[2]

[1] *College of Computer Science, Chongqing University, Chongqing 400044, China*
[2] *College of Mathematics and Statistics, Chongqing University, Chongqing 400044, China*

Correspondence should be addressed to Xiaofan Yang, xf_yang1964@yahoo.com

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By incorporating the chemotherapy into a previous model describing the interaction of the immune system with the human immunodeficiency virus (HIV), this paper proposes a novel HIV virus spread model with control variables. Our goal is to maximize the number of healthy cells and, meanwhile, to minimize the cost of chemotherapy. In this context, the existence of an optimal control is proved. Experimental results show that, under this model, the spread of HIV virus can be controlled effectively.

1. Introduction

Numerous studies have been devoted to the description and understanding of the spread of infectious diseases (especially, the acquired immunodeficiency syndrome (AIDS)) [1–18]. Mathematical modeling of the human immunodeficiency virus (HIV) viral dynamics has offered many insights into the pathogenesis and treatment of HIV [1, 2, 4–10, 12–16, 18]. Consequently, many mathematical models have been developed to depict the relationships among HIV, etiological agent for AIDS and $CD4^{+}$T lymphoblasts, which are the targets for the virus [13]. Some of these models investigate how to avoid an excessive use of drugs because it might be toxic to human body and, hence, cause damages [1, 4–6, 8–11, 14, 15, 17, 18].

Recently, Sedaghat et al. [13] proposed a model, which describes the law governing the transition of two populations of target cells, the T cells (the abbreviation of the $CD4^{+}$T lymphoblasts) and the M cells (say, macrophages, T cells in a lower state of activation, or another cell type), in the effect of free virus (see Figure 1). The T cells produce most of the plasma virus and are responsible for the first-phase decay, while the M cells are responsible

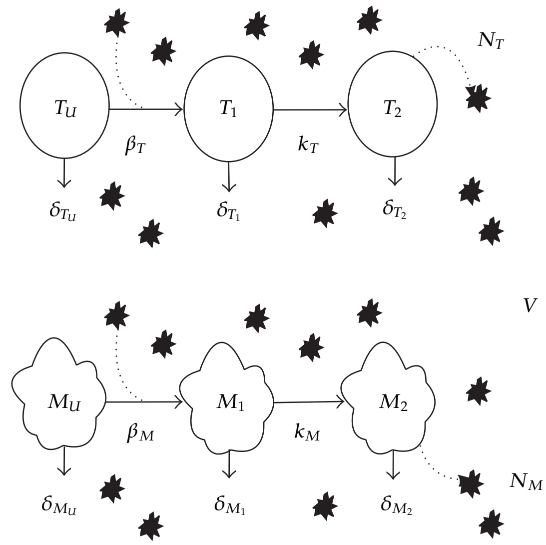

Figure 1: The HIV model.

for the second-phase decay. T cells are classified into three categories: T_U cells (uninfected T cells), T_1 cells (early-stage infected T cells), and T_2 cells (late-stage infected T cells). Let T_U, T_1 and T_2 denote the numbers of T_U cells, T_1 cells, and T_2 cells, respectively. Likewise, M cells are classified into three categories: M_u cells (uninfected M cells), M_1 cells (early-stage infected M cells), and M_2 cells (late-stage infected M cells). Let M_u, M_1, and M_2 denote the numbers of M_U cells, M_1 cells and M_2 cells, respectively. Besides, let V denote the number of free viruses. Sedaghat et al. [13] made the following reasonable assumptions.

(A_1) T_U cells are produced with constant rate θ_T. M_U cells are produced with constant rate θ_M.

(A_2) T_U cells become T_1 cells with constant rate β_T. M_U cells become M_1 cells with constant rate β_M.

(A_3) T_1 cells become T_2 cells with constant rate k_T. M_1 cells become M_2 cells with constant rate k_M.

(A_4) These cells die with constant rates δ_{T_U}, δ_{T_1}, δ_{T_2}, δ_{M_U}, δ_{M_1}, and δ_{M_2} respectively.

(A_5) Free viruses (V) are cleared at a rate c, produced by T_2 cells with a burst size of N_T, and produced by M_2 cells with a burst size of N_M, respectively.

Under these assumptions, Sedaghat et al. [13] deduced the following system of ordinary differential equations:

$$\frac{dT_U}{dt} = \theta_T - \delta_{T_U} T_U - \beta_T T_U V,$$

$$\frac{dT_1}{dt} = \beta_T T_U V - (\delta_{T_1} + k_T) T_1,$$

$$\frac{dT_2}{dt} = k_T T_1 - \delta_{T_2} T_2,$$

$$\frac{dM_U}{dt} = \theta_M - \delta_{M_U} M_U - \beta_M M_U V,$$
$$\frac{dM_1}{dt} = \beta_M M_U V - (\delta_{M_1} + k_M) M_1,$$
$$\frac{dM_2}{dt} = k_M M_1 - \delta_{M_2} M_2,$$
$$\frac{dV}{dt} = N_T T_2 + N_M M_2 - cV. \tag{1.1}$$

For a highly simplified version of this system, Sedaghat et al. [13] derived its analytic solution.

It is well known [5, 6, 8–11, 13, 15, 17] that there are mainly two categories of anti-HIV drugs: the reverse transcriptase inhibitors (RTIs), which prevent new HIV infection by disrupting the conversion of viral RNA into DNA inside of T cells, and the protease inhibitors (PIs), which reduce the number of virus particles produced by actively-infected T cells.

In consideration of this, this paper introduces a novel HIV model by incorporating the drug dosage into the above-mentioned model. Our goal is to maximize the number of healthy cells and, meanwhile, to minimize the cost of chemotherapy. In this context, the existence of an optimal control strategy is proved. Experimental results show that, under this model, the spread of HIV virus can be controlled effectively.

2. Presentation of a New Model

For our purpose, let us introduce the following notations (see Figure 2):

$u_1(t)$: the dosage of RTI at time t, which is assumed to take values in the interval $[0, 1]$;

$u_2(t)$: the dosage of PI at time t, which is assumed to take values in $[0, 1]$;

γ_1: the capability of preventing T_U cells from becoming T_1 cells with per unit dosage of RTI;

γ_2: the capability of preventing M_U cells from becoming M_1 cells with per unit dosage of RTI;

α_1: the capability of preventing T_2 cells from producing viruses with per unit dosage of PI;

α_2: the capability of preventing M_2 cells from producing viruses with per unit dosage of PI.

Next, let us consider the following assumptions.

(A_6) Due to the effect of RTIs, T_U cells become T_1 cells with rate $\beta_T(1 - u_1(t))\gamma_1$, and M_U cells become M_1 cells with rate $\beta_M(1 - u_1(t))\gamma_2$, where γ_1 and γ_2 are constants.

(A_7) Due to the effect of PIs, Free viruses (V) are produced by T_2 and M_2 cells with a burst size of $\alpha_1(1 - u_2(t))N_T$ and $\alpha_2(1 - u_2(t))N_M$, respectively, where α_1 and α_2 are constants.

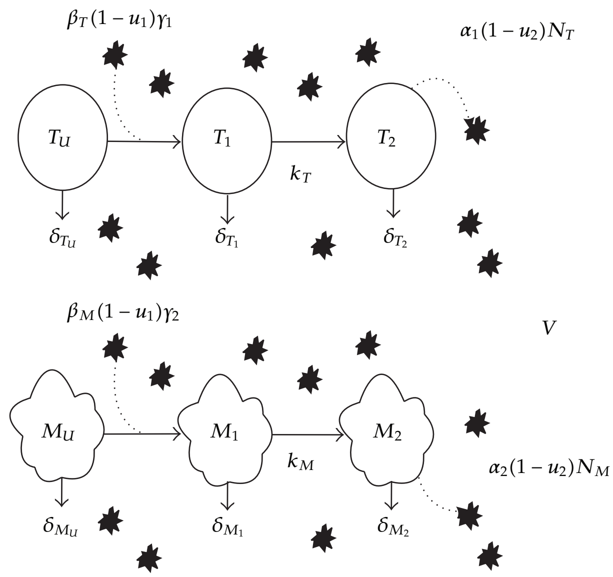

Figure 2: The HIV model with therapy strategy.

Under assumptions (A_1)–(A_7), we can derive the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dT_U}{dt} &= \theta_T - \delta_{T_U}T_U - \beta_T V T_U(1-u_1)\gamma_1,\\
\frac{dT_1}{dt} &= \beta_T V T_U(1-u_1)\gamma_1 - (\delta_{T_1} + k_T)T_1,\\
\frac{dT_2}{dt} &= k_T T_1 - \delta_{T_2}T_2,\\
\frac{dM_U}{dt} &= \theta_M - \delta_{M_U}M_U - \beta_M V M_U(1-u_1)\gamma_2,\\
\frac{dM_1}{dt} &= \beta_M V M_U(1-u_1)\gamma_2 - (\delta_{M_1} + k_M)M_1,\\
\frac{dM_2}{dt} &= k_M M_1 - \delta_{M_2}M_2,\\
\frac{dV}{dt} &= \alpha_1 N_T T_2(1-u_2) + \alpha_2 N_M M_2(1-u_2) - cV.
\end{aligned} \tag{2.1}$$

Our target is to maximize the objective functional by increasing the number of healthy T and M cells and minimizing the cost based on the percentage effect of the chemotherapy given. For that purpose, we introduce the following *objective functional*

$$\mathcal{J}(u_1(t), u_2(t)) = \int_{t_0}^{t_1} \left\{ B_1 T_U + B_2 M_U - \left[A_1 u_1^2 + A_2 u_2^2\right] \right\} dt, \tag{2.2}$$

where B_1, B_2 represent the benefit of per T_U cell and per M_U cell, respectively, and A_1, A_2 represent the cost of per unit RTI and per unit PI, respectively. Our goal is to obtain an optimal control pair (u_1^*, u_2^*) such that

$$\mathcal{J}(u_1^*, u_2^*) = \max\{\mathcal{J}(u_1, u_2) : (u_1, u_2) \in \mathcal{U}\}, \tag{2.3}$$

where $\mathcal{U}$ is the admissible control set defined by

$$\begin{gathered}\mathcal{U} = U_1 \times U_2, \\ U_1 = U_2 = \{u(t) : u \text{ measurable}, 0 \leq u(t) \leq 1, t \in [t_0, t_1]\}.\end{gathered} \tag{2.4}$$

3. Existence of an Optimal Control Pair

For our purpose, let us introduce the following four assumptions.

(A_8) The set of control and corresponding state variables is nonempty.

(A_9) The admissible control set $\mathcal{U}$ is closed and convex.

(A_{10}) All the right hand sides of equations of system (2.1) are continuous, bounded above by a sum of bounded control and state, and can be written as a linear function of u with coefficients depending on time and state.

(A_{11}) There exist positive constants c_1, c_2 and $\beta > 1$ such that the integrand (denoted by $L(y, u, t)$) of the objective functional (2.2) is concave and satisfies the condition $L(y, u, t) \leq c_1 - c_2(u_1^2 + u_2^2)^{\beta/2}$.

In what follows, it is always assumed that assumptions (A_1)–(A_7) hold.

Theorem 3.1. *Consider system* (2.1) *with initial conditions, and the objective functional* (2.2)*. There exists* $u^* = (u_1^*, u_2^*)$ *such that*

$$\mathcal{J}(u_1^*, u_2^*) = \max_{u \in U} \mathcal{J}(u_1, u_2). \tag{3.1}$$

Proof. It suffices to verify the assumptions (A_8)–(A_{11}) with respect to the seven ODEs of system (2.1).

Since the coefficients involved in the system are bounded, and each state variable of the system is bounded on the finite time interval, it follows by a result (see Appendix A) from [19] we can obtain the existence to the solution of the system (2.1).

The control set $\mathcal{U} = U_1 \times U_2$ is obviously closed and convex, because both U_1 and U_2 are closed and convex sets.

By definition, each right hand side of the ODEs of system (2.1) is continuous and can be written as a linear function of u with coefficients depending on time and states. The fact that all state variables T_U, T_1, T_2, M_U, M_1, M_2, V, and $\mathcal{U}$ are bounded on $[t_0, t_1]$, implies the rest of assumption (A_{10}).

It is easy to see that $L(y,u,t)$ is concave in $\mathcal{U}$. By setting $c_1 = \max\{B_1 T_U + B_2 M_U\}$, $c_2 = \inf(A_1, A_2)$ and $\beta = 2$, we can derive

$$\begin{aligned} L(y,u,t) &= B_1 T_U + B_2 M_U - \left[A_1 u_1^2 + A_2 u_2^2\right] \\ &\leq c_1 - c_2\left(u_1^2 + u_2^2\right). \end{aligned} \tag{3.2}$$

The proof is complete. □

4. Optimally Controlling Chemotherapy

In this section, we discuss the theorem related to the characterization of the optimal control. This result depends on the *Pontryagin's Maximum Principle*, which gives necessary conditions for the optimal control. First, we rewrite the system (2.1) in the following vector notation:

$$\begin{gathered} \frac{dy(t)}{dt} = A(y,u,t); \quad \forall t > t_0, \forall u \in U, \\ y(t_0) = y_0, \end{gathered} \tag{4.1}$$

where $y(t)$ and $A(y,u,t)$ are given by

$$\begin{gathered} y(t) = (T_U(t), T_1(t), T_2(t), M_U(t), M_1(t), M_2(t), V(t))^T, \\ A(y,u,t) = (g_1(y,u,t), g_2(y,u,t), \dots, g_6(y,u,t), g_7(y,u,t))^T. \end{gathered} \tag{4.2}$$

The *Hamiltonian* associated with our problem is

$$H(y,u,p,t) = L(y,u,t) + \lambda(t)^T A(y,u,t), \tag{4.3}$$

where the adjoint vector $\lambda(t)$ is defined by the adjoint equation

$$\begin{gathered} \frac{d\lambda(t)}{dt} = -A_y \lambda(t) - L_y, \\ \lambda(t_1) = 0. \end{gathered} \tag{4.4}$$

Here

$$A_y = \begin{pmatrix} \frac{\partial g_1}{\partial T_U} & \frac{\partial g_2}{\partial T_U} & \frac{\partial g_3}{\partial T_U} & \frac{\partial g_4}{\partial T_U} & \frac{\partial g_5}{\partial T_U} & \frac{\partial g_6}{\partial T_U} & \frac{\partial g_7}{\partial T_U} \\ \frac{\partial g_1}{\partial T_1} & \frac{\partial g_2}{\partial T_1} & \frac{\partial g_3}{\partial T_1} & \frac{\partial g_4}{\partial T_1} & \frac{\partial g_5}{\partial T_1} & \frac{\partial g_6}{\partial T_1} & \frac{\partial g_7}{\partial T_1} \\ \frac{\partial g_1}{\partial T_2} & \frac{\partial g_2}{\partial T_2} & \frac{\partial g_3}{\partial T_2} & \frac{\partial g_4}{\partial T_2} & \frac{\partial g_5}{\partial T_2} & \frac{\partial g_6}{\partial T_2} & \frac{\partial g_7}{\partial T_2} \\ \frac{\partial g_1}{\partial M_U} & \frac{\partial g_2}{\partial M_U} & \frac{\partial g_3}{\partial M_U} & \frac{\partial g_4}{\partial M_U} & \frac{\partial g_5}{\partial M_U} & \frac{\partial g_6}{\partial M_U} & \frac{\partial g_7}{\partial M_U} \\ \frac{\partial g_1}{\partial M_1} & \frac{\partial g_2}{\partial M_1} & \frac{\partial g_3}{\partial M_1} & \frac{\partial g_4}{\partial M_1} & \frac{\partial g_5}{\partial M_1} & \frac{\partial g_6}{\partial M_1} & \frac{\partial g_7}{\partial M_1} \\ \frac{\partial g_1}{\partial M_2} & \frac{\partial g_2}{\partial M_2} & \frac{\partial g_3}{\partial M_2} & \frac{\partial g_4}{\partial M_2} & \frac{\partial g_5}{\partial M_2} & \frac{\partial g_6}{\partial M_2} & \frac{\partial g_7}{\partial M_2} \\ \frac{\partial g_1}{\partial V} & \frac{\partial g_2}{\partial V} & \frac{\partial g_3}{\partial V} & \frac{\partial g_4}{\partial V} & \frac{\partial g_5}{\partial V} & \frac{\partial g_6}{\partial V} & \frac{\partial g_7}{\partial V} \end{pmatrix} = (E, F), \tag{4.5}$$

where

$$E = \begin{pmatrix} -\delta_{T_U} - \beta_T V(1-u_1)\gamma_1 & \beta_T V(1-u_1)\gamma_1 & 0 \\ 0 & -(\delta_{T_1} + k_T) & k_T \\ 0 & 0 & -\delta_{T_2} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \alpha_1 N_T(1-u_2) \\ -\delta_{M_U} - \beta_M V(1-u_1)\gamma_2 & \beta_M V(1-u_1)\gamma_2 & 0 & 0 \\ 0 & -(\delta_{M_1} + k_M) & k_M & 0 \\ 0 & 0 & -\delta_{M_2} & \alpha_2 N_M(1-u_2) \\ 0 & 0 & 0 & -c \end{pmatrix}. \tag{4.6}$$

In addition, the L_y in system (4.3) is

$$\begin{aligned} L_y &= \left(\frac{\partial L}{\partial T_U}, \frac{\partial L}{\partial T_1}, \frac{\partial L}{\partial T_2}, \frac{\partial L}{\partial M_U}, \frac{\partial L}{\partial M_1}, \frac{\partial L}{\partial M_2}, \frac{\partial L}{\partial V}\right)^T, \\ &= (B_1, 0, 0, B_2, 0, 0, 0)^T. \end{aligned} \tag{4.7}$$

Next, adding the penalty term will give us the optimality condition

$$\xi(y,u,\lambda,t) = H(y,u,\lambda,t) + \Gamma(u(t))\omega(t), \tag{4.8}$$

where Γ is an operator from $\mathbb{R}^2$ to $\mathbb{R}^4$ defined by

$$\Gamma(u(t)) = (1-u_1(t), u_1(t), 1-u_2(t), u_2(t)),$$
$$\omega(t) = \begin{pmatrix} \omega_{11}(t) \\ \omega_{12}(t) \\ \omega_{21}(t) \\ \omega_{22}(t) \end{pmatrix}, \tag{4.9}$$

where all $\omega_{ij}, i,j = 1,2$ are nonnegative penalty multipliers satisfying the following conditions:

$$\left(1-u_1^*(t)\right)\omega_{11}(t) = u_1^*(t)\omega_{12}(t) = \left(1-u_2^*(t)\right)\omega_{21}(t) = u_2^*(t)\omega_{22}(t) = 0. \tag{4.10}$$

According to the *Pontryagin's Maximum Principle*, if the control $u^*(t)$ and the corresponding state $y^*(t)$ constitute an optimal pair, there exists an adjoint vector $\lambda(t)$ defined system (4.4) such that the function $\xi(y,u,\lambda,t)$ defined by (4.8) reaches its maximum on the set $\mathcal{U}$ at the point u^*. This gives the following result.

Theorem 4.1. *Given an optimal control pair $u^*(t) = (u_1^*(t), u_2^*(t))$ and a solution $y^*(t) = (T_U^*(t), T_1^*(t), T_2^*(t), M_U^*(t), M_1^*(t), M_2^*(t), V^*(t))$ of the corresponding system, then there exist seven adjoint variables $\lambda_1(t), \lambda_2(t), \ldots, \lambda_7(t)$ satisfying*

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= \left[\delta_{T_U} + \beta_T V(1-u_1)\gamma_1\right]\lambda_1 - \beta_T V(1-u_1)\gamma_1\lambda_2 - B_1, \\
\frac{d\lambda_2}{dt} &= (\delta_{T_1} + k_T)\lambda_2 - k_T\lambda_3, \\
\frac{d\lambda_3}{dt} &= \delta_{T_2}\lambda_3 - \alpha_1 N_T(1-u_2)\lambda_7, \\
\frac{d\lambda_4}{dt} &= \left[\delta_{M_U} + \beta_M V(1-u_1)\gamma_2\right]\lambda_4 - \beta_M V(1-u_1)\gamma_2\lambda_5 - B_2, \\
\frac{d\lambda_5}{dt} &= (\delta_{M_1} + k_M)\lambda_5 - k_M\lambda_6, \\
\frac{d\lambda_6}{dt} &= \delta_{M_2}\lambda_6 - \alpha_2 N_M(1-u_2)\lambda_7, \\
\frac{d\lambda_7}{dt} &= c\lambda_7 + \beta_T T_U(1-u_1)\gamma_1\lambda_1 - \beta_T T_U(1-u_1)\gamma_1\lambda_2 \\
&\quad + \beta_M M_U(1-u_1)\gamma_2\lambda_4 - \beta_M M_U(1-u_1)\gamma_2\lambda_5,
\end{aligned} \tag{4.11}$$

with the final conditions

$$\lambda_1(t_1) = \lambda_2(t_1) = \cdots = \lambda_7(t_1) = 0. \tag{4.12}$$

Furthermore, $u_1^*(t) = \min\{\max\{0, R_1(t)\}, 1\}$, $u_2^*(t) = \min\{\max\{0, R_2(t)\}, 1\}$, *where*

$$\begin{aligned} R_1(t) &= \frac{V^*}{2A_1}\left(\beta_T T_U^* \gamma_1(\lambda_1 - \lambda_2) + \beta_M M_U^* \gamma_2(\lambda_4 - \lambda 5)\right), \\ R_2(t) &= -\frac{\lambda_7}{2A_2}(\alpha_1 N_T T_2 + \alpha_2 N_M M_2). \end{aligned} \tag{4.13}$$

Proof. According to the previous section, an optimal couple $(y^*(t), u^*(t))$ exists for maximizing the objective functional (2.2) subject to the system (2.1). Therefore, by *Pontryagin's Maximum Principle,* there exists a vector $\lambda(t) = (\lambda_1(t), \ldots, \lambda_7(t))^T$ satisfying

$$\frac{\lambda(t)}{dt} = -\frac{\partial H}{\partial y} = -L_y - A_y \lambda(t). \tag{4.14}$$

That yields

$$\begin{aligned} \frac{\lambda_1(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial T_U}, \ldots, \frac{\partial g_7(y^*, u^*, t)}{\partial T_U}\right)\lambda(t) - \frac{\partial L(y^*, u^*, t)}{\partial T_U}, \\ \frac{\lambda_2(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial T_1}, \ldots, \frac{\partial g_7(y^*, u^*, t)}{\partial T_1}\right)\lambda(t) - \frac{\partial L(y^*, u^*, t)}{\partial T_1}, \\ \frac{\lambda_3(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial T_2}, \ldots, \frac{\partial g_7(y^*, u^*, t)}{\partial T_2}\right)\lambda(t) - \frac{\partial L(y^*, u^*, t)}{\partial T_2}, \\ \frac{\lambda_4(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial M_U}, \ldots, \frac{\partial g_7(y^*, u^*, t)}{\partial M_U}\right)\lambda(t) - \frac{\partial L(y^*, u^*, t)}{\partial M_U}, \\ \frac{\lambda_5(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial M_1}, \ldots, \frac{\partial g_7(y^*, u^*, t)}{\partial M_1}\right)\lambda(t) - \frac{\partial L(y^*, u^*, t)}{\partial M_2}, \\ \frac{\lambda_6(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial M_2}, \ldots, \frac{\partial g_7(y^*, u^*, t)}{\partial M_2}\right)\lambda(t) - \frac{\partial L(y^*, u^*, t)}{\partial M_2}, \\ \frac{\lambda_7(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial V}, \ldots, \frac{\partial g_7(y^*, u^*, t)}{\partial V}\right)\lambda(t) - \frac{\partial L(y^*, u^*, t)}{\partial V}. \end{aligned} \tag{4.15}$$

Through simple calculations, we derive system (4.11). The *Pontryagin's Maximum Principle* gives the following necessary conditions to obtain the optimal pair (y^*, u^*):

$$\frac{\partial \xi(y^*, u^*, \lambda, t)}{\partial u_1} = 0, \qquad \frac{\partial \xi(y^*, u^*, \lambda, t)}{\partial u_2} = 0, \tag{4.16}$$

where $\xi(y^*, u^*, \lambda, t) = H(y^*, u^*, \lambda, t) + \Gamma(u^*(t))\omega(t)$. From (4.10) and (4.16), we have

$$\begin{aligned} &\frac{\partial \xi(y^*, u^*, \lambda, t)}{\partial u_1} = 0 \\ &\Longrightarrow \frac{\partial L(y^*, u^*, t)}{\partial u_1} + \frac{\partial\left(\lambda(t)^T A(y^*, u^*, t)\right)}{\partial u_1} + \frac{\partial(\Gamma(u^*(t))\omega(t))}{\partial u_1} = 0, \end{aligned} \tag{4.17}$$

which implies

$$u_1^*(t) = \frac{V^*}{2A_1}\left(\beta_T T_U^* \gamma_1(\lambda_1 - \lambda_2) + \beta_M M_U^* \gamma_2(\lambda_4 - \lambda 5)\right). \tag{4.18}$$

On the other hand,

$$\begin{aligned} &\frac{\partial \xi(y, u^*, \lambda, t)}{\partial u_2} = 0 \\ &\Longrightarrow \frac{\partial L(y^*, u^*, t)}{\partial u_2} + \frac{\partial\left(\lambda(t)^T A(y, u^*, t)\right)}{\partial u_2} + \frac{\partial(\Gamma(u^*(t))\omega(t))}{\partial u_2} = 0, \end{aligned} \tag{4.19}$$

which indicates

$$u_2^*(t) = -\frac{\lambda_7}{2A_2}(\alpha_1 N_T T_2 + \alpha_2 N_M M_2). \tag{4.20}$$

Now from the constraint condition, the following three cases arise.

Case 1. $t \in \{t : 0 < u_1^*(t) < 1\}$ and $\omega_{11}(t) = \omega_{12}(t) = 0$. Then $u_1^*(t) = R_1(t)$.

Case 2. $t \in \{t : u_1^*(t) = 0\}$ and $\omega_{11}(t) = 0$. Then $0 = u_1^*(t) = R_1(t) + \omega_{12}(t)$, which implies $u_1^*(t) \geq R_1(t)$ because $\omega_{12}(t) \geq 0$.

Case 3. $t \in \{t : u_1^*(t) = 1\}$ and $\omega_{12}(t) = 0$. Then $u_1^*(t) = R_1(t) - \omega_{11}(t)$, which leads to $1 = u_1^*(t) \leq R_1(t)$, owing to $\omega_{11} \geq 0$.

Hence, we have $u_1^*(t) = \min\{\max\{0, R_1(t)\}, 1\}$. Similarly, we can get that $u_2^*(t) = \min\{\max\{0, R_2(t)\}, 1\}$.

The proof is complete. □

Now, the optimality system is given by incorporating the optimal control pair in the state system coupled with the adjoint system. Thus, we have

$$\begin{aligned} \frac{dy^*(t)}{dt} &= A(y^*, u^*, t); \quad \forall t > t_0, \\ \frac{d\lambda(t)}{dt} &= -A_{y^*}\lambda(t) - L_{y^*}, \\ y^*(t_0) &= y_0^*, \\ \lambda(t_1) &= 0. \end{aligned} \tag{4.21}$$

We substitute the expressions $u^* = (u_1^*, u_2^*)$ in the above system. The uniqueness of the solution of the optimality system can be derived by a standard method (refer to [6] for more details on the proof).

5. Numerical Algorithm and Results

The resolution of the optimal system is created improving the Gauss-Seidel-like implicit finite-difference method developed by [7] and denoted by GSS1 method. It consists on discretizing the interval $[t_0, t_1]$ at the points $t_k = kl + t_0 (k = 0, 1, \ldots, n)$, where l is the time step.

In the following, we define the state and adjoint variables $T_U(t)$, $T_1(t)$, $T_2(t)$, $M_U(t)$, $M_1(t)$, $M_2(t)$, $V(t)$, $\lambda_1(t) \sim \lambda_7(t)$ and the controls $u_1(t)$ and $u_2(t)$ in terms of nodal points T_U^k, T_1^k, T_2^k, M_U^k, M_1^k, M_2^k, V^k, $\lambda_1^k \sim \lambda_7^k$, u_1^k, u_2^k as the state and adjoint variables and the controls at initial time t_0, while T_U^n, T_1^n, T_2^n, M_U^n, M_1^n, M_2^n, V^n, $\lambda_1^n \sim \lambda_7^n$, u_1^n, u_2^n as the state and adjoint variables and the controls at final time t_1. As it is well known that the approximation of the time derivative by its first-order forward-difference is given, for the first state variable T_U, by

$$\frac{dT_U(t)}{dt} = \lim_{l \to 0} \frac{T_U(t+l) - T_U(t)}{l}. \tag{5.1}$$

We use the scheme developed by Gumel et al. [7] in the following way:

$$\frac{T_U^{k+1} - T_U^k}{l} = \theta_T - \delta_{T_U} T_U^{k+1} - \beta_T \gamma_1 V^k \left(1 - u_1^k\right) T_U^{k+1}. \tag{5.2}$$

Analogously, we have

$$\begin{aligned} \frac{T_1^{k+1} - T_1^k}{l} &= \beta_T \gamma_1 V^k \left(1 - u_1^k\right) T_U^{k+1} - (\delta_{T_1} + k_T) T_1^{k+1}, \\ \frac{T_2^{k+1} - T_2^k}{l} &= k_T T_1^{k+1} - \delta_{T_2} T_2^{k+1}, \\ \frac{M_U^{k+1} - M_U^k}{l} &= \theta_M - \delta_{M_U} M_U^{k+1} - \beta_M \gamma_2 V^k \left(1 - u_1^k\right) M_U^{k+1}, \end{aligned}$$

$$\frac{M_1^{k+1}-M_1^k}{l} = \beta_M\gamma_2 V^k\left(1-u_1^k\right)M_U^{k+1} - (\delta_{M_1}+k_M)M_1^{k+1},$$
$$\frac{M_2^{k+1}-M_2^k}{l} = k_M M_1^{k+1} - \delta_{M_2}M_2^{k+1},$$
$$\frac{V^{k+1}-V^k}{l} = \alpha_1 N_T T_2^{k+1}\left(1-u_2^k\right) + \alpha_2 N_M M_2^{k+1}\left(1-u_2^k\right) - cV^{k+1}. \tag{5.3}$$

By applying an analogous technology, we approximate the time derivative of the adjoint variables by their first-order backward-difference and we use the appropriated scheme as follows:

$$\frac{\lambda_1^{n-k}-\lambda_1^{n-k-1}}{l} = \left[\delta_{T_U} + \beta_T V^{k+1}\left(1-u_1^k\right)\gamma_1\right]\lambda_1^{n-k-1} - \ \beta_T V^{k+1}\left(1-u_1^k\right)\gamma_1\lambda_2^{n-k} - B_1,$$
$$\frac{\lambda_2^{n-k}-\lambda_2^{n-k-1}}{l} = (\delta_{T_1}+k_T)\lambda_2^{n-k-1} - k_T\lambda_3^{n-k},$$
$$\frac{\lambda_3^{n-k}-\lambda_3^{n-k-1}}{l} = \delta_{T_2}\lambda_3^{n-k-1} - \alpha_1 N_T\left(1-u_2^k\right)\lambda_7^{n-k},$$
$$\frac{\lambda_4^{n-k}-\lambda_4^{n-k-1}}{l} = \left[\delta_{M_U} + \beta_M V^{k+1}\left(1-u_1^k\right)\gamma_2\right]\lambda_4^{n-k-1} - \ \beta_M V^{k+1}\left(1-u_1^k\right)\gamma_2\lambda_5^{n-k} - B_2,$$
$$\frac{\lambda_5^{n-k}-\lambda_5^{n-k-1}}{l} = (\delta_{M_1}+k_M)\lambda_5^{n-k-1} - k_M\lambda_6^{n-k},$$
$$\frac{\lambda_6^{n-k}-\lambda_6^{n-k-1}}{l} = \delta_{M_2}\lambda_6^{n-k-1} - \alpha_2 N_M\left(1-u_2^k\right)\lambda_7^{n-k},$$
$$\frac{\lambda_7^{n-k}-\lambda_7^{n-k-1}}{l} = c\lambda_7^{n-k-1} + \beta_T T_U^{k+1}\left(1-u_1^k\right)\gamma_1\left(\lambda_1^{n-k-1}-\lambda_2^{n-k-1}\right)$$
$$+ \beta_M M_U^{k+1}\left(1-u_1^k\right)\gamma_2\left(\lambda_4^{n-k-1}-\lambda_5^{n-k-1}\right). \tag{5.4}$$

Hence, we can establish an algorithm to solve the optimality system and then to compute the optimal control pair by employing the GSS1 method (5.2)–(5.4) that we denote by IGSS1 method here (see Appendix B).

5.1. Numerical Results

By making some parameter value choices, computer simulation experiments are done to verify the effectiveness of our new model by comparing the disease progression before and

Table 1

Time (days)	T_U BT	T_U AT	M_U BT	M_U AT	V BT	V AT
0	1000	1000	1000	1000	1	1
2	980.2369	980.2012	926.3417	926.1494	15.33444	19.568136
4	955.4799	953.1210	856.9665	852.1262	283.2647	334.65888
6	839.4257	889.1900	754.0975	754.1006	4710.942	315.44809
8	270.1388	833.1982	372.5725	671.2911	38782.17	297.34008
10	11.92899	784.0453	41.26735	601.1371	99155.03	280.27154
20	0.511601	628.5318	1.021524	388.0657	255003.3	208.54835
30	0.379269	597.7372	0.756860	313.0676	335762.8	155.17956
40	0.334284	574.2037	0.666976	268.0361	376288.7	115.46816
50	0.322352	555.2309	0.643089	240.5969	387774.5	85.919158

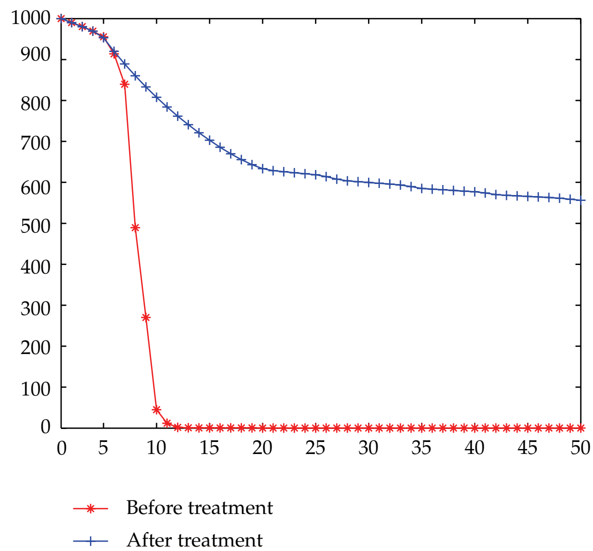

Figure 3: Uninfected T cells.

after introducing the two optimal control variables $u_1^*(t)$, $u_2^*(t)$. For the following parameters and initial values:
$\theta_T = 10$, $\theta_M = 10$, $\delta_{T_U} = 0.02$, $\delta_{T_1} = 0.5$, $\delta_{T_2} = 1$, $\delta_{M_U} = 0.0495$, $\delta_{M_1} = 0.0495$, $\delta_{M_2} = 0.0495$, $\beta_T = 0.00008$, $\beta_M = 0.00008$, $k_T = 0.1$, $k_M = 0.1$, $N_T = 100$, $N_M = 100$, $T_U^0 = 1000$, $T_1^0 = 0$, $T_2^0 = 0$, $M_U^0 = 1000$, $M_1^0 = 0$, $M_2^0 = 0$, $V^0 = 1$, $c = 0.03$.

The experimental results obtained are listed in Table 1 (in which "before treatment" and "after treatment" are denoted by BT and AT, resp.).

For more clearness, it is better to present these comparative results by the following graphs. When the viruses attack the human body, uninfected T and M cells decrease (see Figures 3 and 4).

The viruses do not stop to proliferate and so its abundance dramatically increases (see Figure 5). However, after introducing the optimal controls, the situation changes. A few days later, the effect of chemotherapy starts to appear; which explains the growth of uninfected T and M cells and the diminishing of viruses (see Figure 6).

Finally, the optimal controls $u_1^*(t)$, $u_2^*(t)$ for drug administration are presented through Figures 7 and 8.

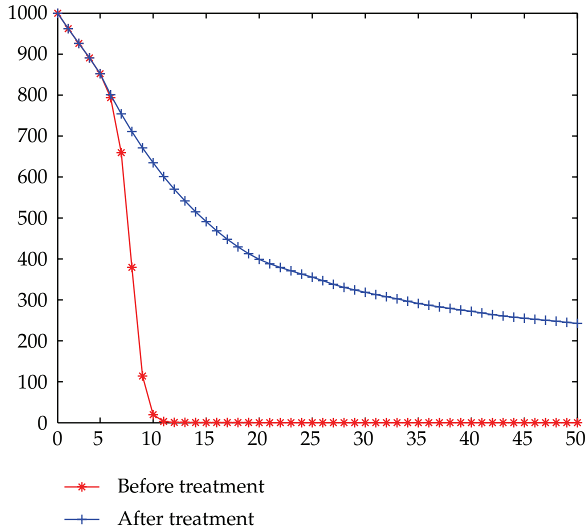

Figure 4: Uninfected M cells.

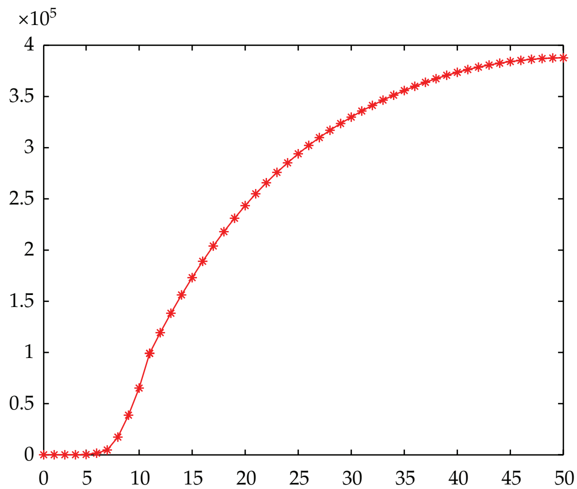

Figure 5: Virus population before optimal controls.

6. Conclusions

By incorporating the chemotherapy into a previous model describing the interaction of the immune system with the human immunodeficiency virus (HIV), this paper has proposed a novel HIV virus spread model with control variables. Our goal is to maximize the number of healthy cells and, meanwhile, to minimize the cost of chemotherapy. In this context, the existence of an optimal control has been proved. Experimental results show that, under this model, the spread of HIV virus can be controlled effectively.

Our next work is to study other kinds of models, especially those with impulsive drug effect.

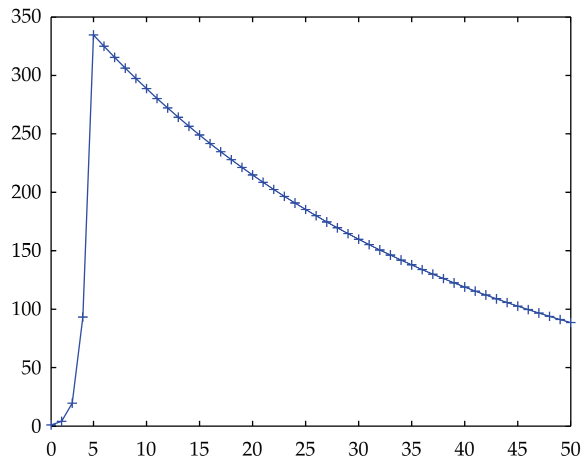

Figure 6: Virus population after optimal controls.

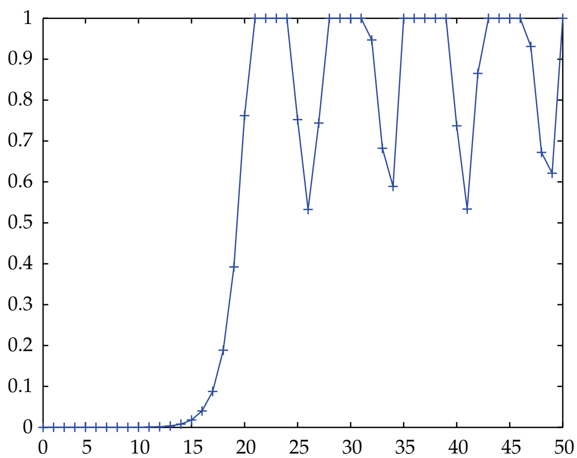

Figure 7: Optimal control variable $u_1^*(t)$.

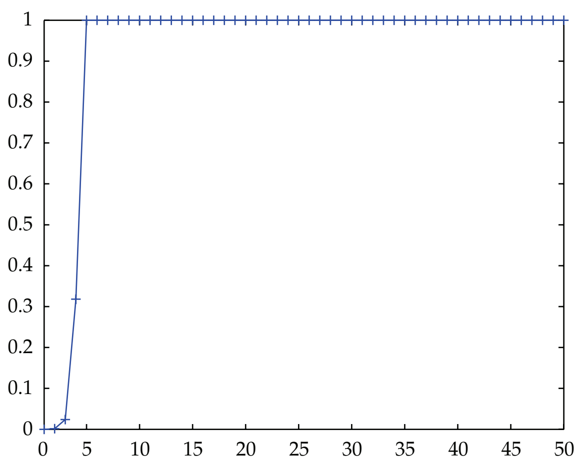

Figure 8: Optimal control variable $u_2^*(t)$.

Appendices

A. The Theorem Used in Theorem 3.1

The equations

$$\dot{x}(t) = f(t, x(t)),$$
$$x|_{t=\tau} = \xi, \tag{A.1}$$

where $(\tau, \xi) \in D$, with D a nonempty open subset of $\mathcal{R} \times \mathcal{R}^n$ and $f : D \to \mathcal{R}^n$, are called a *Cauchy problem* or *initial-value problem*.

A solution to the *Cauchy Problem* is defined to be any pair (I, ϕ) in which I is an open subinterval of $\mathcal{R}$ containing $\tau, \phi : I \to \mathcal{R}^n$ is absolutely continuous, $(t, \phi(t)) \in D$ for all $t \in I$, and ϕ satisfies the above two equations at $a.e.t \in I$.

For $x \in \mathcal{R}^n$ with coordinates x_i, define a norm on $\mathcal{R}^n$ by

$$|x| = \max_{1 \le i \le n} |x_i|. \tag{A.2}$$

The following theorem applies the Lebesgue integral and the hypothesis is stated in terms of the rectangular subset of $\mathcal{R} \times \mathcal{R}^n$ centered about (τ, ξ),

$$R_{a,b} = \{(t, x) : |t - \tau| \le a, |x - \xi| \le b\}, \quad a > 0,\ b > 0. \tag{A.3}$$

Theorem A.1 (see [19, p.182]). *The Cauchy problem has a solution if for some $R_{a,b} \subset D$ centered about (τ, ξ) the restriction of f to $R_{a,b}$ is continuous in x for fixed t, measurable in t for fixed x, and satisfies*

$$\left| f(t, x) \right| \le m(t), \quad (t, x) \in R_{a,b}, \tag{A.4}$$

for some m integrable over the interval $[\tau - a, \tau + a]$.

B. An Algorithm Using the GSS1 Method

Algorithm B.1.

Step 1.

$$\begin{gathered}
T_U(t_0) \longleftarrow T_U^0, \quad T_1(t_0) \longleftarrow T_1^0, \quad T_2(t_0) \longleftarrow T_2^0, \\
M_U(t_0) \longleftarrow M_U^0, \quad M_1(t_0) \longleftarrow M_1^0, \quad M_2(t_0) \longleftarrow M_2^0, \quad V(t_0) \longleftarrow V^0, \\
\lambda_1(t_n) \longleftarrow 0, \quad \lambda_2(t_n) \longleftarrow 0, \quad \lambda_3(t_n) \longleftarrow 0, \quad \lambda_4(t_n) \longleftarrow 0, \\
\lambda_5(t_n) \longleftarrow 0, \quad \lambda_6(t_n) \longleftarrow 0, \quad \lambda_7(t_n) \longleftarrow 0, \\
u_1(t_0) \longleftarrow 0, \quad u_2(t_0) \longleftarrow 0.
\end{gathered} \tag{B.1}$$

Step 2. for $k = 1, \ldots, n$ do

$$T_U^k \longleftarrow \frac{l\theta_T + T_U^{k-1}}{1 + l\delta_{T_U} + l\beta_T V^{k-1}\left(1 - u_1^{k-1}\right)\gamma_1},$$

$$T_1^k \longleftarrow \frac{l\beta_T\gamma_1 V^{k-1}\left(1 - u_1^{k-1}\right)T_U^k + T_1^{k-1}}{1 + (\delta_{T_1} + k_T)l},$$

$$T_2^k \longleftarrow \frac{lk_T T_1^k + T_2^{k-1}}{1 + l\delta_{T_2}},$$

$$M_U^k \longleftarrow \frac{l\theta_M + M_U^{k-1}}{1 + l\delta_{M_U} + l\beta_M\gamma_2 V^{k-1}\left(1 - u_1^{k-1}\right)},$$

$$M_1^k \longleftarrow \frac{l\beta_M\gamma_2 V^{k-1}\left(1 - u_1^{k-1}\right)M_U^k + M_1^{k-1}}{1 + (\delta_{M_1} + k_M)l},$$

$$M_2^k \longleftarrow \frac{lk_M M_1^k + M_2^{k-1}}{1 + l\delta_{M_2}},$$

$$V^k \longleftarrow \frac{l\alpha_1 N_T T_2^k\left(1 - u_2^{k-1}\right) + l\alpha_2 N_M M_2^k\left(1 - u_2^{k-1}\right) + V^{k-1}}{1 + cl},$$

$$\lambda_1^{n-k} \longleftarrow \frac{lB_1 + l\beta_T V^k\left(1 - u_1^{k-1}\right)\gamma_1\lambda_2^{n-k+1} + \lambda_1^{n-k+1}}{1 + l\delta_{T_U} + l\beta_T V^k\left(1 - u_1^{k-1}\right)\gamma_1},$$

$$\lambda_2^{n-k} \longleftarrow \frac{\lambda_2^{n-k+1} + lk_T\lambda_3^{n-k+1}}{1 + (\delta_{T_1} + k_T)l},$$

$$\lambda_3^{n-k} \longleftarrow \frac{\lambda_3^{n-k+1} + l\alpha_1 N_T\left(1 - u_2^{k-1}\right)\lambda_7^{n-k+1}}{1 + l\delta_{T_2}},$$

$$\lambda_4^{n-k} \longleftarrow \frac{lB_2 + l\beta_M V^k\left(1 - u_1^{k-1}\right)\gamma_2\lambda_5^{n-k+1} + \lambda_4^{n-k+1}}{1 + l\delta_{M_U} + l\beta_M V^k\left(1 - u_1^{k-1}\right)\gamma_2},$$

$$\lambda_5^{n-k} \longleftarrow \frac{\lambda_5^{n-k+1} + lk_M\lambda_6^{n-k+1}}{1 + (\delta_{M_1} + k_M)l},$$

$$\lambda_6^{n-k} \longleftarrow \frac{\lambda_6^{n-k+1} + l\alpha_2 N_M\left(1 - u_2^{k-1}\right)\lambda_7^{n-k+1}}{1 + l\delta_{M_2}},$$

$$\lambda_7^{n-k} \longleftarrow \frac{\lambda_7^{n-k+1} + l\left(1 - u_1^{k-1}\right)\left[\beta_T T_U^k\gamma_1\left(\lambda_2^{n-k} - \lambda_1^{n-k}\right) + \beta_M M_U^k\gamma_2\left(\lambda_5^{n-k} - \lambda_4^{n-k}\right)\right]}{1 + lc},$$

$$R_1^k \longleftarrow \frac{V^k}{2A_1}\left[\beta_T T_U^k \gamma_1\left(\lambda_1^{n-k} - \lambda_2^{n-k}\right) + \beta_M M_U^k \gamma_2\left(\lambda_4^{n-k} - \lambda_5^{n-k}\right)\right],$$
$$R_2^k \longleftarrow -\frac{\lambda_7^{n-k}}{2A_2}\left(\alpha_1 N_T T_2^k + \alpha_2 N_M M_2^k\right),$$
$$u_1^k \longleftarrow \min\left\{\max\left\{0, R_1^k\right\}, 1\right\}, u_2^k \longleftarrow \min\left\{\max\left\{0, R_2^k\right\}, 1\right\}. \tag{B.2}$$

Step 3. for $k = 1, \ldots, n$, denote

$$T_U^*(t_k) = T_U^k, M_U^*(t_k) = M_U^k, u_1^*(t_k) = u_1^k, u_2^*(t_k) = u_2^k. \tag{B.3}$$

It is easy to conclude that this algorithm takes $O(n)$ execution time.

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