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STABILITY AND CONTROL ANALYSIS OF AN HIV TREATMENT MODEL

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ABSTRACT. We consider stability analysis and control of an HIV model. The stability analysis helps us to get additional insight into the model problem as well as design appropriate controls. The dynamics of the control problem is an impulsive ordinary differential equation. The objective of the control problem is to find an optimal control to guide the system to the basin of attraction of LTNP (Long term Non-Progressor) equilibrium point while the cost of treatment is minimal and the viral load is undetectable and CD4+T cell count is at an acceptable level. Simulation results are presented and discussed.

AMS (MOS) Subject Classification. 35K60, 35K57

1. INTRODUCTION

There are two immune responses in the human body: the humoral immune response and the cellular immune response [1]. The humoral immune response employs antibodies produced by B cells to attack antigens in body fluids, while the cellular immune response employs CD4+T cells to destroy body cells that have been infected with virus [2]. When an alien enters our system T-helper cells (CD4 +T) identify it and alert our body's defense system so that the body forms some kind of defense mechanism. Unlike many other common diseases HIV virus attacks CD4+T cells. By killing, and converting the T-cells to hosts of the virus, the disease weakens our immune mechanism. Eventually when the CD4+ T cell count is not high enough the patient shows symptoms of AIDS.

Even after the patient develops AIDS our body defense systems do not stop fighting the disease. As the virus enters T-cell and changes it to a host; it will be attacked by CTLes (cytotoxic T-Lymphocytes effectors) which are deployed by CTLPS (cytotic T-lymphocytes precursors) which are coded to memorize the disease and convert to CTLes cells which kill the infected CD4+T cells [2].

Controlling HIV virus needs intervention by medication. The medication kills HIV virus and helps in generation of CTLps and CTLes cells. This in turn can cause the number of healthy CD4+T cells, number of infected CD4+T cells, number of

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CTLes and number of CTLps to eventually reach a steady state. The steady state we want to reach is one with low unhealthy CD4+T cell count, high CD4+T cells and high CTLPs count [17].

We start by considering mathematical model presented in [3] and [4]. We follow the same argument given by [2]. Both models use cell counts of uninfected, infected, CTLP and CTLe cells to study "Long Term Non-Progressor" (LTNP). Although it is usual for HIV infected patients to progress to AIDS after a certain latent period, less than 1% of them still have a sufficient amount of T-helper cells and never develop AIDS. Thus, their immune system is able to fight off other diseases in spite of the HIV infection. They are called long-term non-progressors (LTNP) and may provide clues to the control of HIV without continued drugs [2].

As function of medication the model has at least two equilibrium points in the state space where both of them are asymptotically stable. One of them corresponds to AIDS and the other to LTNP. Without medication it is a common phenomenon for the system to end up in the basin of attraction of AIDS. Hence we rely on drug treatment. The drug treatment helps to guide the system to enter into the basin of attraction of LTNP and once it is there we terminate the medication [2].

In [3] and [4] such possibility has been suggested by the use of the structured treatment interruption, which is basically a switching scheme between zero and maximum medication. Since then, this problem has been dealt with by various methodologies such as model predictive control [5], [6], [7], optimal control [8], [9], and an approximation method [10]. On the other hand, a control theoretic approach has been used to determine when to initiate HIV therapy [11], and to estimate the parameters of HIV models [12], [13].

As a function of drug dose; there are four equilibrium points for the model. Three of them have biological meaning but not the fourth one. The organization of this paper is: in **section 2** we discuss stability analysis of the equilibrium point of the model. This section help us to design our control system. The main body of this paper is in **section 3**. In this section we formulate a control problem to guide our system to the basin of attraction of the LTNP equilibrium point and that is the main reason why we include **section 2** in this paper.

2. Stability Anaylysis Of An HIV-Infection Mathematical Model

In this section we present an HIV-infection mathematical model, determine the equilibrium points and present the stability analysis of the model.

2.1. HIV Infection Mathematical Model.

An HIV infection mathematical model with drug treatment is [2]

$$\dot{x} = \lambda - dx - (1 - \eta u)\beta xy$$

$$\begin{aligned}\dot{y} &= (1-\eta u)\beta xy - ay - pyz\\ \dot{w} &= cxyw - cqyw - bw\\ \dot{z} &= cqyw - hz \end{aligned} \tag{1}$$

where,
x is number of healthy CD4+T cells.
y number of unhealthy CD4+T cells.
w number of CTLP cells (memory cells).
z number of CTLe cells.
The term $(1-\eta u)$, possibly $0 \le 1-\eta u \le 1$, η gives us the maximal effect of the drug. The drug is 100% efficient if $\eta u = 1$ and completely inefficient if $\eta u = 0$. For simplicity of notation we use the notation $\eta^* = 1 - \eta u$.

2.2. **Stability Of Equilibrium Points Of The Model.** In this section we determine the equilibrium points of model (1) as a function of drug dose η^*. We set $\dot{x} = \dot{y} = \dot{w} = \dot{z} = 0$ to have the equilibrium points. We do have four equilibrium points as a function of drug dose where three of them have biological meaning but not the fourth one.

1. HIV free equilibrium point $X_A(\eta^*) = (x_A, y_A, w_A, z_A)$.

$$x_A = \frac{\lambda}{d}, \quad y_A = w_A = z_A = 0. \tag{2}$$

2. AIDS stage $X_B(\eta^*) = (x_B, y_B, w_B, z_B)$.

$$x_B = \frac{a}{\eta^*\beta}, \quad y_B = \frac{\lambda\beta - da}{a\eta^*\beta}, \quad w_B = z_B = 0. \tag{3}$$

3. Long term non-progressor $X_C(\eta^*) = (x_C, y_C, w_C, z_C)$. Let $K := [c(\lambda + dq) - b\eta^*\beta]^2 - 4c^2\lambda qd$

$$\begin{aligned} x_C &= \frac{[c(\lambda+dq) - b\eta^*\beta] + \sqrt{K}}{2cd}, \quad y_C = \frac{b}{c(x_C - q)}, \quad w_C = \frac{hz_C}{cqy_C},\\ z_C &= \frac{\eta^*\beta x_C - a}{p}. \end{aligned} \tag{4}$$

4. The fourth equilibrium point $X_D(\eta^*) = (x_D, y_D, w_D, z_D)$.

$$\begin{aligned} x_D &= \frac{[c(\lambda+dq) - b\eta^*\beta] - \sqrt{K}}{2cd}, \quad y_D = \frac{b}{c(x_D - q)}, \quad w_D = \frac{hz_D}{cqy_D},\\ z_D &= \frac{\eta^*\beta x_D - a}{p}. \end{aligned} \tag{5}$$

We consider the following two sets of assumptions for the purpose of our analysis.

1. ***Assumption 1:***

$$d < a. \tag{6}$$

$$b < h. \tag{7}$$

$$q < \frac{\lambda}{d}. \tag{8}$$

$$c > \frac{4abd}{(\lambda - dq)^2}. \tag{9}$$

$$\beta < \frac{c(\sqrt{\lambda} - \sqrt{dq})^2}{b}. \tag{10}$$

$$\beta > \frac{ac(\lambda + dq) - \sqrt{a^2c^2(\lambda + dq)^2 - 4a^2cd(ad + cq\lambda)}}{2(ab + cq\lambda)}. \tag{11}$$

2. ***Assumption 2:***

The basic reproductive ratio [18] is less than unity by the application of drug, i.e., $\eta^* \frac{\lambda\beta}{ad} < 1$.

We need the following values for stability analysis

$$\eta_1^* := \frac{ad}{\beta\lambda}. \tag{12}$$

$$\eta_2^* := \frac{ac(\lambda + dq) - \sqrt{a^2c^2(\lambda + dq)^2 - 4a^2cd(ad + cq\lambda)}}{(2(ab + cq\lambda)\beta)}. \tag{13}$$

$$\eta_3^* := \frac{ac(\lambda + dq) + \sqrt{a^2c^2(\lambda + dq)^2 - 4a^2cd(ad + cq\lambda)}}{2(ab + cq\lambda)\beta}. \tag{14}$$

Theorem 2.1. *Under* ***Assumption 1*** *we have the following.*

1. $X_A(\eta^*)$ *is locally exponentially stable if* $\eta \in [0, \eta_1^*)$ *and unstable if* $\eta \in (\eta_1^*, 1]$.
2. $X_B(\eta^*)$ *is locally exponentially stable if* $\eta \in (\eta_1^*, \eta_2^*) \cup (\eta_3^*, 1]$ *and unstable if* $\eta^* \in (0, \eta_1^*) \cup (\eta_2^*, \eta_3^*)$.
3. $X_C(\eta^*)$ *is locally exponentially stable if* $\eta^* \in (\eta_2^*, 1]$ *and unstable if* $\eta \in (0, \eta_2^*)$.

Corollary 2.2. *Transcritical bifurcation occurs at* η_1^*, η_2^* *and* η_3^*.

3. Control Analysis Of An HIV Treatment Model

Consider the HIV treatment model (1) with cost

$$\begin{aligned} J(\bar{c}_1, \bar{c}_2, \ldots, \bar{c}_n) = &\sum_{i=1}^{n} R\frac{\bar{c}_i^2}{2} + S_x\frac{(x_{f+1}(t_{f+1}) - x_f)^2}{2} + S_y\frac{(y_{f+1}(t_{f+1}) - y_f)^2}{2} \\ &+ S_w\frac{(w_{f+1}(t_{f+1}) - w_f)^2}{2} + S_z\frac{(z_{f+1}(t_{f+1}) - z_f)^2}{2} \end{aligned} \tag{15}$$

Here R is the cost associated with the intake of the drug, which includes the cost of the drug as well as the amount of damage to the health due to the drug taken, where, x_f, y_f, w_f, z_f are chosen so that if the system is left without further medication after this point, it converges to the desired equilibrium point which is high healthy cell count and low unhealthy cell count.

1. Consider the optimal control problem in the last interval $[t_{n-1}, t_n]$. Let the objective function in this interval be

$$J_n(\bar{c}_1, \bar{c}_2, \ldots, c_n) = \sum_{i=1}^{n} R\frac{c_i^2}{2} + S_x\frac{(x_{f+1}(t_{f+1}) - x_f)^2}{2} + S_y\frac{(y_{f+1}(t_{f+1}) - y_f)^2}{2} + S_w\frac{(w_{f+1}(t_{f+1}) - w_f)^2}{2} + S_z\frac{(z_{f+1}(t_{f+1}) - z_f)^2}{2} \tag{16}$$

Let $J_n = J_n(\bar{c}_1, \bar{c}_2, \ldots, c_n)$. The control problem is

$$\begin{aligned} &\min_{c_n} \quad J_n \\ &Subject\ to \\ &\dot{X}_n(t) = f_n(X_n(t)), t_{n-1} < t < t_n \\ &X_n(t_{n-1}) = \bar{X}_{n-1}(t_{n-1}) + h_n(\bar{X}_{n-1}(t_{n-1}))c_n \\ &h_n(X_n(t)) = diag(0\ 0\ 0\ 0\ 1) \end{aligned} \tag{17}$$

The variation of the dynamics with respect to variation of the optimal impulsive control $\bar{c}_n$ is

$$\begin{aligned} \frac{d}{dt}\delta X_n &= f_{n,X_n}(X_n(t))\delta X_n \\ \delta X_n(t_n^+) &= h_n(\bar{X}_{n-1}(t_n^-))\delta c_n \end{aligned}$$

Let $L_n(t, t_{n-1})$ be fundamental matrix solution of the following linear ODE

$$\begin{aligned} \frac{d}{dt}L_n(t, t_{n-1}) &= f_{n,X_n}(X_n)L_n(t, t_{n-1}) \\ L_n(t_{n-1}, t_{n-1}) &= I \end{aligned}$$

Then,

$$\delta X_n(t) = \tilde{Q}_n(t_{n-1})L_n(t, t_{n-1})\delta c_n \tag{18}$$

where,

$$\tilde{Q}_n(t_{n-1}) = h_n(t_{n-1})$$

Variation of the cost J_n with respect to variation of the optimal impulsive control $\bar{c}_n$ is

$$\delta J_n = \Theta_{X_n}(X_n(t))\delta X_n(t) \tag{19}$$

Using (20) the variation of the cost is

$$\delta J_n = \Theta_{X_n}(X_n(t_n))L_n(t_n, t_{n-1})Q_n(t_{n-1})\delta c_n \tag{20}$$

Then the derivative of the cost is

$$\delta J_n = \Theta_{x_n}(t_n)L_n(t_n, t_{n-1})Q_n(t_{n-1})\delta c_n \tag{21}$$

2. Moving one step backward to interval $[t_{n-2}, t_{n-1}]$. The cost is

$$J_{n-1}(\bar{c}_1, \bar{c}_2, \ldots, \bar{c}_{n-1}, c_{n-1}, \bar{c}_n) = \sum_{i=1}^{n} R\frac{c_i^2}{2} + S_x\frac{(x_{f+1}(t_{f+1}) - x_f)^2}{2} + S_y\frac{(y_{f+1}(t_{f+1}) - y_f)^2}{2}$$
$$+ S_w\frac{(w_{f+1}(t_{f+1}) - w_f)^2}{2} + S_z\frac{(z_{f+1}(t_{f+1}) - z_f)^2}{2} \tag{22}$$

We let $J_{n-1} = J_{n-1}(\bar{c}_1, \bar{c}_2, \ldots, \bar{c}_{n-1}, c_{n-1}, \bar{c}_n)$. In this interval the control problem is

$$\begin{aligned} \min_{c_{n-1}} \quad & J_{n-1} \\ Subject\ to & \\ \dot{X}_{n-1}(t) &= f_{n-1}(X_{n-1}(t)), t_{n-2} < t < t_{n-1} \\ X_{n-1}(t_{n-1}) &= \bar{X}_{n-2}(t_{n-2}) + h_{n-1}(\bar{X}_{n-2}(t_{n-2}))c_{n-1} \\ h_{n-1}(\bar{X}_{n-1}(t)) &= diag(0\ 0\ 0\ 0\ 1) \end{aligned}$$

The variation of the dynamics is

$$\begin{aligned} \frac{d}{dt}\delta X_{n-1} &= f_{n-1,X_{n-1}}(\bar{X}_{n-1}(t))\delta X_{n-1}(t) \\ \delta X_{n-1}(t_{n-2}^+) &= h_{n-1}(\bar{X}_{n-2}(t_{n-1}^-))\delta c_{n-1} \end{aligned}$$

Let $L_{n-1}(t, t_{n-2})$ be fundamental matrix solution of the following linear ODE

$$\begin{aligned} \frac{d}{dt}L_{n-1}(t, t_{n-2}) &= f_{n,X_n}L_{n-1}(t, t_{n-2}) \\ L_{n-1}(t_{n-1}, t_{n-2}) &= I \end{aligned}$$

We know that the dynamics in interval $[t_{n-1}, t_n]$ is affected by the perturbation of $\bar{c}_{n-1}$. Consider the following linear ODE in interval $[t_{n-1}, t_n]$

$$\begin{aligned} \frac{d}{dt}L_n(t, t_{n-1}) &= f_{n,X_n}(X_n)L_n(t, t_{n-1}) \\ L_n(t_{n-1}, t_{n-1}) &= I \end{aligned} \tag{23}$$

Let $L_n(t, t_{n-1})$ be fundamental matrix solution (25) and

$$\delta X_n(t) = I\delta X_{n-1}(t_{n-1}) \tag{24}$$

Also,

$$\delta X_{n-1}(t_{n-2}) = \tilde{Q}_{n-1}(t_{n-2})\delta c_{n-1}, \tag{25}$$

where $\tilde{Q}_{n-1}(t_{n-2}) = h_{n-1} = h$. Then the Gâteaux derivative of the cost is

$$\delta J_{n-1} = \Theta_{X_n}(t_n)L_n(t_n, t_{n-1})IL_{n-1}(t_{n-1}, t_{n-2})Q_{n-1}(t_{n-2})\delta c_{n-1} \tag{26}$$

3. Continuing the same way, at the ith interval $[t_{n-(i+1)}, t_{n-i}]$. The control problem is

$$\begin{aligned} &\min_{c_{n-i}} \quad J_{n-i} \\ &Subject\ to \\ &\dot{X}_{n-i}(t) = f_{n-i}(X_{n-i}(t)), t_{n-(i+1)} < t < t_{n-i} \\ &X_{n-i}(t_{n-(i-1)}) = h_{n-i}(\bar{X}_{n-(i-1)}(t_{n-(i-1)}))c_{n-i} + \bar{X}_{n-(i+1)}(t_{n-(i+1)}) \\ &h_{n-i}(X_{n-i}(t)) = diag(0\ 0\ 0\ 0\ 1) \end{aligned} \tag{27}$$

where,

$$J_{n-i} = J_{n-i}(\bar{c}_1, \bar{c}_2, \ldots, \bar{c}_{n-(i+1)}), c_{n-i}, \bar{c}_{n-(i-1}, \ldots, \bar{c}_n).$$

The variation of the dynamics is

$$\begin{aligned} \frac{d}{dt}\delta X_{n-i}(t) &= f_{n-i,X_{n-i}}(X_{n-i}(t))\delta X_{n-i}(t) \\ \delta X_{n-i}(t_{n-(i-1)}) &= h_{n-i}(\bar{X}_{n-(i-1)}(t_{n-(i-1)}))\delta c_{n-i} \end{aligned} \tag{28}$$

The perturbation of $\bar{c}_{n-i}$ affects the dynamics in the succeeding intervals. The variation of the dynamics in those affected intervals is

$$\begin{aligned} dL_{n-i}(t, t_{n-(i+1)}) &= f_{n-i,X_{n-i}}(X_{n-i}(t))L_{n-i}(t, t_{n-(i+1)})dt \\ i &= 0, 1, 2, \ldots, i-1 \end{aligned} \tag{29}$$

Let fundamental matrix solution of the systems in (29) be $L_{n-i}(t, t_{n-(i+1)})$, where, $i = 0, 1, 2, \ldots, i-1$. Then the variation of the cost is

$$\delta J_{n-i} = \Theta_{X_n}(t_n)L_{n-i}(t, t_{n-(i+1)})\tilde{Q}_{n-i}(t_{n-(i+1)}) \cdots L_n(t_n, t_{n-1})\delta c_{n-i}. \tag{30}$$

The Gâteaux derivative of the cost is

$$\delta J_{n-i}(\bar{c}_1, \bar{c}_2, \ldots, \bar{c}_n) = \Theta_{X_n}(t_n)\tilde{Q}_{n-i}(t_{n-(i+1)})L_{n-i}(t, t_{n-(i+1)}) \cdots L_n(t_n, t_{n-1})\delta c_{n-i}. \tag{31}$$

3.1. **Numerical Computation And Simulation.** We use four intervals $[t_0, t_1]$, $[t_1, t_2]$, $[t_2, t_3]$, $[t_3, t_4]$ where $t_3 = t_f$ for the simulation. With impulsive controls applied at t_1, t_2 and t_3. That means we do have four impulsive control problems one in each interval. The fourth interval is included to give the system enough time to come closer to the intended cell count. The dynamics in interval $[t_{i-1}, t_i]$ is given by

$$\begin{aligned} \dot{x_1} &= \lambda - dx_i - (1 - \eta u_i)\beta x_i y_i \\ \dot{y_i} &= (1 - \eta u_i)\beta x_i y_i - a y_i - p y_i z_i \\ \dot{w_i} &= c x_i y_i w_i - cq y_i w_i - b w_i \\ \dot{z_i} &= cq y_i w_i - h z_i \\ \dot{u_i} &= -u_i \end{aligned}$$

$$X_i(t_{i-1}) = X_{i-1}(t_{i-1}) + h(X_{i-1}(t_{i-1}))c_i$$
$$i = 1, 2, 3, 4.$$

Also we have

$$X_1(t_0) = (2, 0.4, 0.22, 0.1)^t$$
$$X_4(t_3) = (2, 2, 0.4, 0.25)^t$$

The cost is

$$J(\bar{c}_1, \bar{c}_2) = \frac{R}{2}((\bar{c}_1)^2 + (\bar{c}_2)^2) + S_x\frac{(x_4(4) - 2)^2}{2} + S_y\frac{(y_4(4) - 2)^2}{2} + S_w\frac{(w_4(4) - 0.4)^2}{2} + S_z\frac{(z_4(4) - 0.25)^2}{2}$$

The next step is to determine the fundamental matrix solutions, $L1$, $L2$, $L3$, and $L4$. The L_i's are determined from the following equation

$$\frac{dL_i}{dt} = f_{i,X_i}(\bar{X}_i(t))L_i(t)$$
$$L_i(t_{i-1}) = I$$
$$t_{i-1} < t < t_i$$
$$i = 1, 2, 3, 4.$$

Also,

1. in the interval $[t_3, t_4]$ $\tilde{Q}_4$ is defined by $\tilde{Q}_4 = (diag(0, 0, 0, 1))^t$
2. in the interval $[t_2, t_3], [t_1, t_2], [t_0, t_1]$ $\tilde{Q}_3, \tilde{Q}_2, \tilde{Q}_1$ are defined by $\tilde{Q}_3 = \tilde{Q}_2 = \tilde{Q}_1 = I_4$

The numerical simulation we are going to carry out is based on the state equations and the impulsive controls. We use steepest descent method for optimization purpose.

The parameters value we use are [4] $\lambda = 1$, $e = 0.1$, $d = 0.1$, $a = 0.2$, $\eta = 0.5$, $\beta = 0.42$, $p = 1$, $b = 0.1$, $h = 0.1$, $q = 0.5$, and the initial amount of medicine in the body chosen to be $u_0(0) = 0$. The numbers S_x, S_y, S_w, S_z are measures of importance attached to the difference between the final cell numbers and desired cell counts. These values are all chosen to be 2.

3.1.1. ***Conclusion***. Taking $R = 0.1$, we have the following cost and optimal impulsive values:
$Cost = 0.042833315801935$, $c1 = 0.523975314189902$, $c2 = 0.349153540962085$.
Table 1 gives us the cell counts for the first three and last three iteration of our simulation.

TABLE 1

$Healthy\ cells$	$Unhealthy\ cells$	$Memory\ cells$	$Effectors$	$Control$
3.411988	0.9208089	0.3096524	0.1031824	0.1120595
3.063783	1.203528	0.3222986	0.1078693	0.9651733
2.799905	1.417936	0.3290286	0.1113703	0.8556089
2.024841	2.038927	0.3335831	0.1216719	0.5363530
2.024838	2.038922	0.3335830	0.1216724	0.5363640
2.024835	2.038917	0.3335829	0.1216729	0.5363750

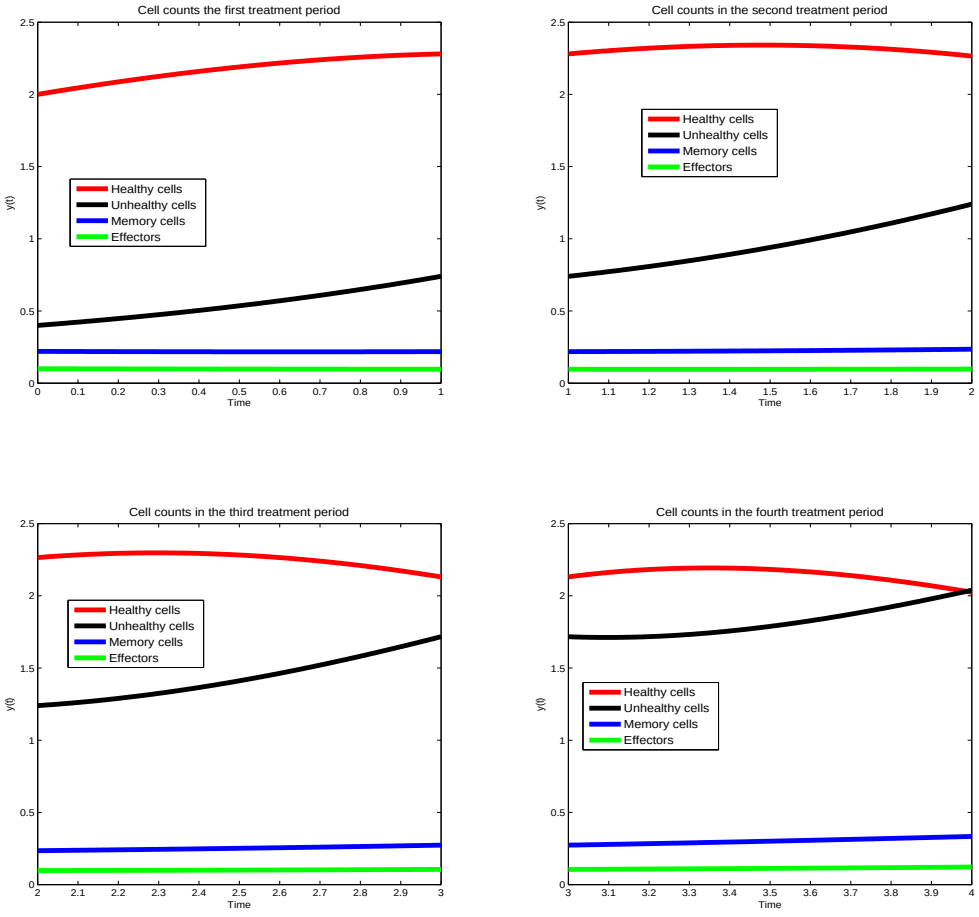

FIGURE 1. Cell count of the simulation.

What we showed here is that by applying the optimal amount of medication, we guided our system to go from the given cell count $(2, 0.4, 0.22, 0.1)$ to a cell count $(2.024835, 2.038917, 0.3335829, 0.1216729)$ which is closer to the target cell count $(2, 2, 0.4, 0.25)$. Our conclusion is that if the patient's cell count is not below thresh hold cell count, then it is possible to guide the system to basin of attraction of equilibrium point X_B which is LTNG starting from the existing cell count by giving optimal amount of medication in a finite time horizon with minimum cost and minimum side effect.

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