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Control of HIV Infection Dynamics by the Enhancement of the Immune System

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Abstract: The human immunodeficiency virus infection, that causes acquired immune deficiency syndrome, is a dynamic process that can be modeled via differential equations. In this paper a control method to boost the response of the immune system by means of drug scheduling is introduced. The control purpose is to steer the system to an equilibrium condition, known as long-term nonprogressor, which corresponds to an infected patient that does not develop the symptoms of acquired immune deficiency syndrome. To show the feasibility of the control methodology a human immunodeficiency virus model is studied analytically and computer simulations are presented.

1. INTRODUCTION

The human immunodeficiency virus (HIV) causes acquired immune deficiency syndrome (AIDS). In the HIV positive patient the virus stays in the blood of the patient and has a chance to encounter CD4 T-cells, which are important components of the human immune system. An HIV-infected CD4 T-cell does not fulfill its function in the immune system and becomes a virus factory, making multiple HIV copies. Therefore the number of CD4 T-cells decreases in the HIV-infected patient.

Although HIV-infected patients are expected to develop AIDS, the possibility of a long-term nonprogressor (LTNP) is reported with clinical data in Lisziewicz et al. (1999); Autran and Carcelain (2000), and studied by means of mathematical models describing the progress of the HIV infection in Wodarz and Nowak (1999); Wodarz (2001); Wodarz and Nowak (2002); Adams et al. (2005). LTNP is the status of a patient who has HIV, but also a sufficient number of CD4 T-cells, so the immune system can fight off other infections. The mathematical models in the literatures, with no drug input, have at least two asymptotically stable equilibrium points, one of which corresponds to the AIDS status, while the other corresponds to the LTNP status. The state of an HIV positive patient is usually located in the region of attraction of the equilibrium corresponding to the AIDS status. Accordingly, HIV positive patients without medication generally proceed to AIDS, so it makes sense to study drug scheduling methods which drive the state of the patient into the region of attraction of the LTNP status, where drug treatment can be stopped. This problem has been studied with model predictive control methods in Zurakowski and Teel (2003, 2006); Shim et al. (2003); Chang et al. (2006). These works show that the state of a patient can be successfully driven into the region of attraction of the LTNP. Note finally that these works rely heavily on the existence of optimal control laws, thus provide little understanding on the boosting mechanism of the immune response.

The purpose of this research is to derive a new drug scheduling methodology for HIV patients on the basis of the properties of the immune system. The main idea, which stems from a simple graphical analysis and in turn leads to the design of a feedback control strategy, has been conceptually introduced in Chang and Astolfi (2007). In the present paper we justify the idea from a mathematical perspective and provide some formal properties for the resulting controlled system.

The paper is organised as follows. In Section 2 we give an introduction to the HIV dynamic model. In addition the control idea for the HIV infection model of Wodarz (2001) is briefly summarised, and a feedback control strategy is introduced and illustrated by means of computer simulations. In Section 3 we analyze the controlled HIV mathematical model to show the mechanism of action of the proposed strategy. Finally, Section 4 provides a summary and some conclusions.

2. CONCEPTUAL CONTROL IDEA

Among the available HIV models we consider the model from Wodarz (2001), described by the equations

$$\dot{x} = \lambda - dx - \eta\beta xy, \tag{1}$$
$$\dot{y} = \eta\beta xy - ay - p_1 z_1 y - p_2 z_2 y, \tag{2}$$
$$\dot{z}_1 = c_1 z_1 y - b_1 z_1, \tag{3}$$
$$\dot{w} = c_2 xyw - c_2 qyw - b_2 w, \tag{4}$$
$$\dot{z}_2 = c_2 qyw - hz_2, \tag{5}$$

where the states x, y, z_1, w, z_2 describe the populations of specific cells in a unit volume of blood and therefore are meaningful only when positive. In particular, x describes the concentration of uninfected CD4 T-cells, y the concentration of infected CD4 T-cells, z_1 the concentration of helper-independent cytotoxic T lymphocytes (CTL), w the

concentration of CTL precursors, and z_2 the concentration of helper-dependent CTLs.

The quantity η describes the effect of the drug, possibly varying between zero and one. In view of the presence of a control input, η can be rewritten as

$$\eta = 1 - \eta^* u,$$

where η^* is the maximum effect of the drug (Zurakowski and Teel (2003, 2006)). From a control perspective the input u represents the drug dose, which takes values between zero and one. If $u = 1$ a patient receives maximum dose, while $u = 0$ means no medication. Note that u is restricted to be either 0 or 1, because the use of partially suppressive therapy, that is $0 < u < 1$, is problematic (Zurakowski and Teel (2006)). The remaining parameters λ, d, β, a, p_1, p_2, c_1, c_2, q, b_1, b_2, and h are positive. For a detailed explanation of the model, see Wodarz (2001).

The model has five equilibrium points, three of which are of interest, and are given in what follows (Chang and Astolfi (2008a)).

Point A:

$$x^{(A)} = \frac{\lambda}{d},\ y^{(A)} = 0,\ {z_1}^{(A)} = 0,\ w^{(A)} = 0,\ {z_2}^{(A)} = 0.$$

Point B:

$$x^{(B)} = \frac{\lambda c_1}{dc_1 + b_1\eta\beta}, \qquad y^{(B)} = \frac{b_1}{c_1},$$

$${z_1}^{(B)} = \frac{\eta\beta x^{(B)} - a}{p_1}, \qquad w^{(B)} = 0, \qquad {z_2}^{(B)} = 0.$$

Point C:

$$y^{(C)} = \frac{[c_2(\lambda - dq) - b_2\eta\beta] - \sqrt{[c_2(\lambda - dq) - b_2\eta\beta]^2 - 4\eta\beta c_2 q d b_2}}{2\eta\beta c_2 q},$$

$$x^{(C)} = \frac{\lambda}{d + \eta\beta y^{(C)}}, \qquad {z_1}^{(C)} = 0, \qquad w^{(C)} = \frac{h {z_2}^{(C)}}{c_2 q y^{(C)}},$$

$${z_2}^{(C)} = \frac{y^{(C)}(c_2\eta\beta q - c_2 a) + b_2\eta\beta}{c_2 p_2 y^{(C)}}.$$

Under the assumption of no medication (i.e. $\eta = 1$), only two of the five equilibrium points are exponentially stable with a typical parameter set from Zurakowski and Teel (2003, 2006); Wodarz (2001). Point A models the status of a person who does not have HIV. With a typical parameters set, Point A is unstable.

The two exponentially stable equilibrium points are denoted as Point B and Point C. Point B corresponds to the status of a patient for whom HIV dominates. Point C is for a patient who does not progress to AIDS, i.e. the LTNP. With a typical set of parameters, the numbers of infected cells $y^{(C)}$ are kept low while the number of CTL precursor $w^{(C)}$ is large, which is desired. Since Point C is locally exponentially stable, with a typical set of parameters, the control goal is to drive the state near this point.

In this section we use the same system parameters as in Zurakowski and Teel (2003, 2006), namely $\lambda = 1$, $d = 0.1$, $\beta = 1$, $a = 0.2$, $p_1 = 1$, $p_2 = 1$, $c_1 = 0.03$, $c_2 = 0.06$, $q = 0.5$, $b_1 = 0.1$, $b_2 = 0.01$, $h = 0.1$, and $\eta^* = 0.9799$. The initial point is also identical to one of those used in Zurakowski and Teel (2003). This point represents a newly infected patient, that is, $x(0) = 10$, $y(0) = 0.01$, $z_1(0) = 0.01$, $w(0) = 0.01$, and $z_2(0) = 0.01$ [1].

2.1 Introduction of the control idea

The goal of the control is to enhance immunity. Particularly helper-dependent responses (i.e. w and z_2) must be enhanced to lead an HIV patient to the LTNP status (Point C) because the values of w and z_2 of Point B are zeros and those of Point C are comparatively large. In addition, z_2 depends upon w by means of equation (5). Therefore we must increase w by controlled medication scheduling.

Equation (4) can be rewritten as $\dot{w} = K(x, y)w$, where $K(x, y) = c_2xy - c_2qy - b_2$. Note that $K(x, y)$ depends upon the variables x and y of the infection dynamics, and this second order subsystem is directly affected by the drug. Accordingly, we can indirectly control $\dot{w}$ via the input u.

Fig. 1 shows same geometric properties of the function $K(x, y)$, for the given parameters, in the (x, y) positive quadrant. The dotted line describes the set $K(x, y) = 0$. Since $K(x, y) > 0$ above this line, the immune term w increases when (x, y) belongs to the set $K(x, y) > 0$. The dashed line and the solid line describe the sets $K(x, y) = 0.5$ and $K(x, y) = 1$, respectively.

The Control Procedure (Chang and Astolfi (2007))

Initialization: Select a positive number T_s. T_s denotes the sampling time for the computation of the control input. Let w denote the immune term, $K = K(x, y) = c_2xy - c_2qy - b_2$ the immune increasing factor, the set $K(x, y) \geq 0$ of the (x, y) positive orthant the immune increasing area. Finally, X_I is the initial condition of model (1)-(5).

STEP 1: Integrate model (1)-(5) with initial condition X_I for T_s time instants with full medication and with no medication. Let $X_{F,fm}$ and $X_{F,nm}$ be the values of the state of the model (1)-(5), at the end of the integration period, with full medication and with no medication, respectively. Let $\Xi_{F,fm}$ and $\Xi_{F,nm}$ be the projections of $X_{F,fm}$ and $X_{F,nm}$, respectively, on the (x, y) plane.

STEP 2: If $\Xi_{F,nm}$ is in the immune increasing area and $\Xi_{F,fm}$ is not in the immune increasing area then set $u = 0$.
If $\Xi_{F,nm}$ is not in the immune increasing area and $\Xi_{F,fm}$ is in the immune increasing area then set $u = 1$.
If both $\Xi_{F,nm}$ and $\Xi_{F,fm}$ are in the immune increasing area the control input u is selected as the one which maximizes w at the end of the integration period.
If both $\Xi_{F,nm}$ and $\Xi_{F,fm}$ are not in the immune increasing area then set $u = 0$.

STEP 3: The input determined in STEP 2 is applied to the model (1)-(5) with initial point X_I for T_s time instants. Let X_F be the value of the state at the end of the integration period.

STEP 4: Set $X_I = X_F$ and go to STEP 1.

It is possible to show that the proposed control procedure is such that all initial conditions in a sufficiently large

[1] This point is also the status of an HIV patient that has been treated with HAART for a long time (Zurakowski and Teel (2003)).

subset Ω of the positive orthant, where the system is defined, are driven to the LTNP state. The shape and size of the set Ω depend upon the system's parameters, and the value of T_s.

Fig. 2 shows the results of the application of the proposed control procedure with $T_s = 1$ (day). The control input becomes eventually zero and the patient state converges to the LTNP status, namely to Point C, which is (8.2255, 0.0216, 0, 1240, 8.0255) for the given parameters. The resulting (x, y) trajectory is displayed in Fig. 3, which shows that the (x, y) trajectory stays within the immune increasing area, $c_2xy - c_2qy - b_2 \geq 0$.

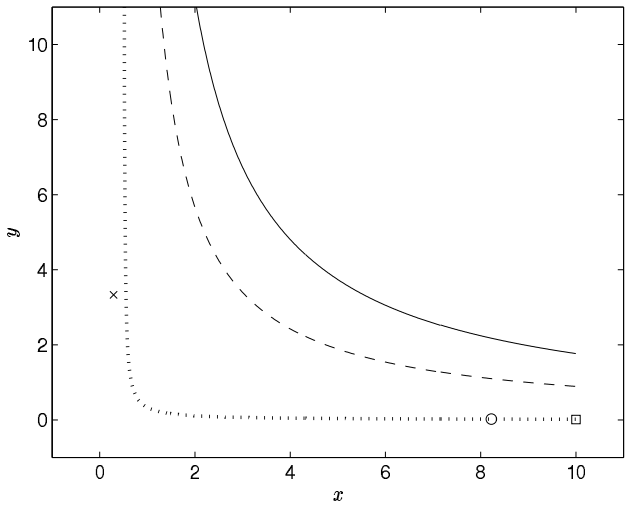

Fig. 1. Graphical properties of the immune system enhancing property in model (1)-(5). The dotted line denotes the set $K(x, y) = 0$. The dashed line and the solid line represent the sets $K(x, y) = 0.5$ and $K(x, y) = 1$, respectively. The "□"mark indicates the projection of the initial point into the (x, y) plane. The "o"and the "x"marks show the projection of points C and B in the (x, y) plane, respectively.

The set Ω To estimate the set Ω, we use computer simulations. In these simulations, it is assumed that $z_1(0) = 0.01$, $w(0) = 0.01$ and $z_2(0) = 0.01$, which means that

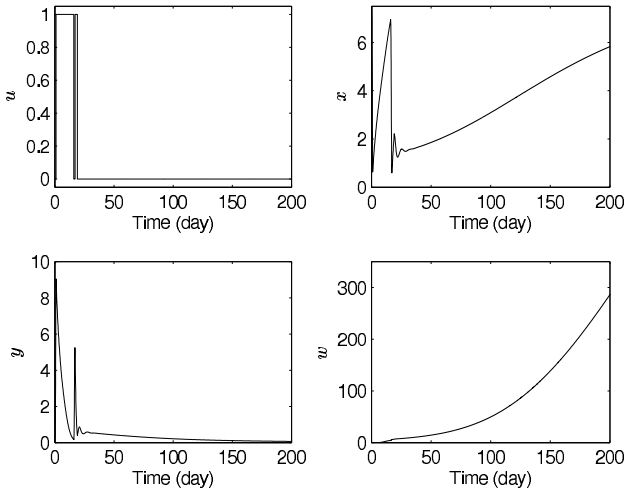

Fig. 2. Results of the application of the control procedure to model (1)-(5) with $T_s = 1$ (day).

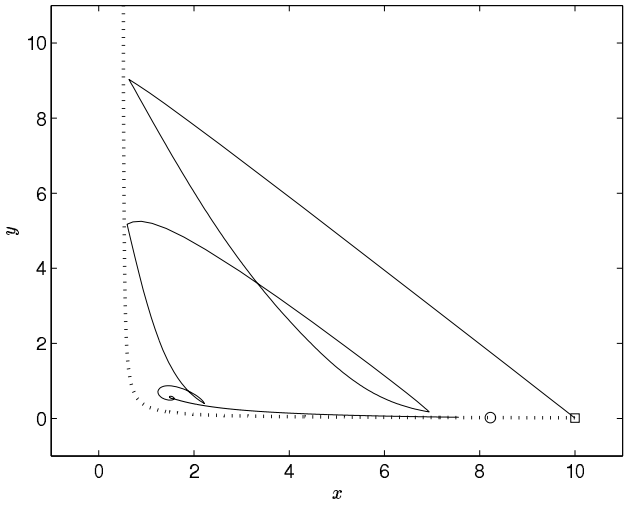

Fig. 3. The (x, y) trajectory (solid line) resulting from the proposed control strategy.

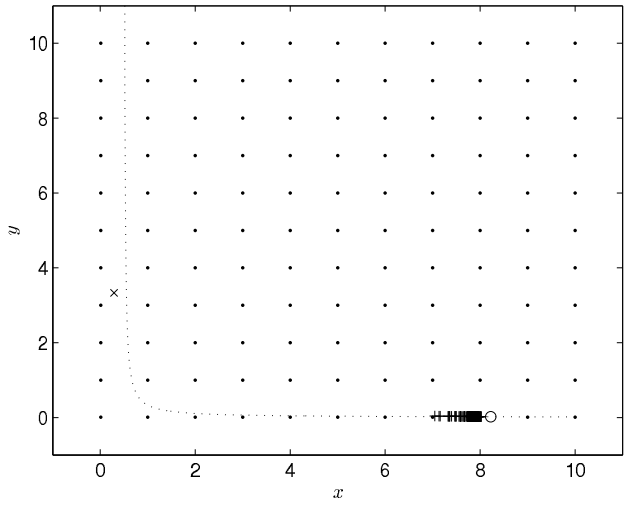

Fig. 4. Estimation of the set Ω with $z_1 = 0.01$, $w = 0.01$, and $z_2 = 0.01$. The "·"and the "+"marks denote the projections of the initial points and of the final points of the control simulations in (x, y) plane.

the immune system is hardly boosted. We simulate with pairs of initial points $(x(0), y(0))$ with $x(0)$ and $y(0)$ taking values in the set $\{0.01, 1, 2, 3, \cdots, 10\}$. All other conditions are as in the previous subsection.

In Fig. 4 the initial points are indicated with "·"marks in (x, y) plane. The "+"marks denote the (x, y) states after 400 days. Fig. 5 shows a zoomed in version of Fig. 4. All considered initial states yield trajectories which converge to the LTNP state (the "o"mark). The trajectory with $x(0) = 10$ and $y(0) = 0.01$ is displayed in Fig. 2 and Fig. 3. The suggested control idea works for all considered initial points.

2.2 Output feedback control idea for the HIV model

In this section we propose a control strategy that requires only partial state information. The states x and y are considered as output of the infection dynamics and input of the immune system. These states are also regarded as the measured output of the model (1)-(5), since they are

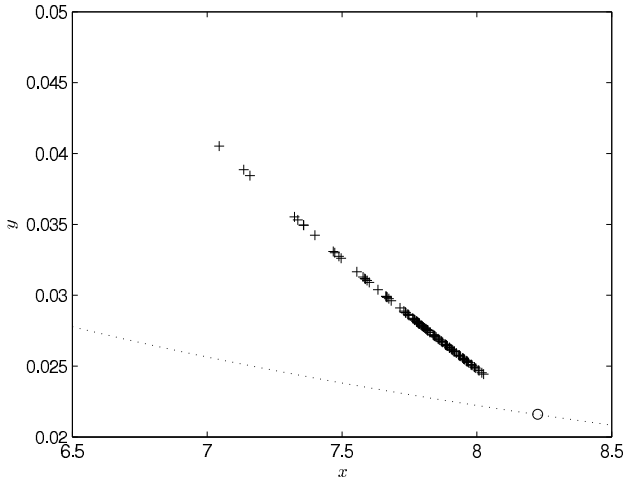

Fig. 5. Zoomed in version of Fig. 4. All "+"marks from Fig. 4 are shown in this graph. The "+"marks belong to the region of attraction of Point C, and belong to the immune increasing area.

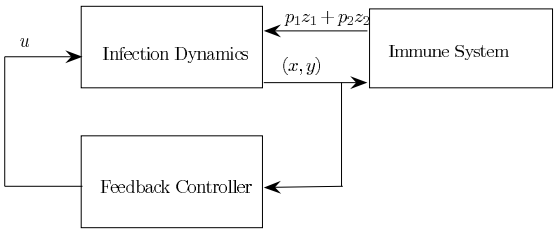

Fig. 6. Diagram describing the connections of the infection dynamics, the immune system, and the controller.

clinically measurable (Chang and Astolfi (2008a,c)). Thus the output feedback controller uses the states x and y as the controller input. The system configuration is depicted in Fig. 6 and the control law is described in the following steps.

Initialization: Select a positive number T_i. T_i denotes the period of full medication preceding the application of the proposed control scheme and driving the state to Point A. Let $L_1 = L_1(x, y) = c_1y - b_1$ and $L_2 = L_2(x, y) = y - (x - q)$. X_I is the initial condition of model (1)-(5).

STEP 1: (Preliminary Control Action)
Integrate model (1)-(5) with initial condition X_I for T_i time period with full medication.

STEP 2: (The Control Law)
If $L_1 < 0$ and $L_2 < 0$, then $u = 0$. Otherwise, $u = 1$.

Fig. 7 shows the results of the application of the feedback control procedure. The system parameters and initial condition are as in the previous simulations. In this simulation STEP 1 is skipped because the initial point $(x(0), y(0), z_1(0), w(0), z_2(0)) = (10, 0.01, 0.01, 0.01, 0.01)$ is sufficiently close to Point A. Compared with the result of the control method in Subsection 2.1, the medication period is shorter, although the immune system, i.e. w, is only slowly boosted. Note that the virus level (y) is restricted by the condition $L_1 < 0$. The control input becomes eventually zero and the patient state converges to the LTNP status, i.e. to Point C, which is denoted with

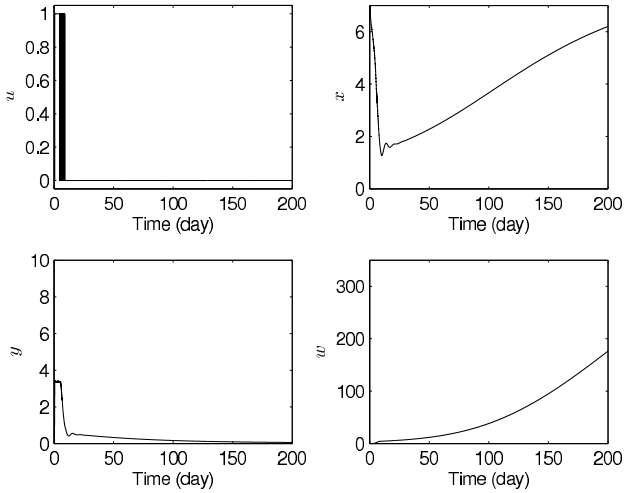

Fig. 7. Results of the application of the output feedback control scheme to model (1)-(5).

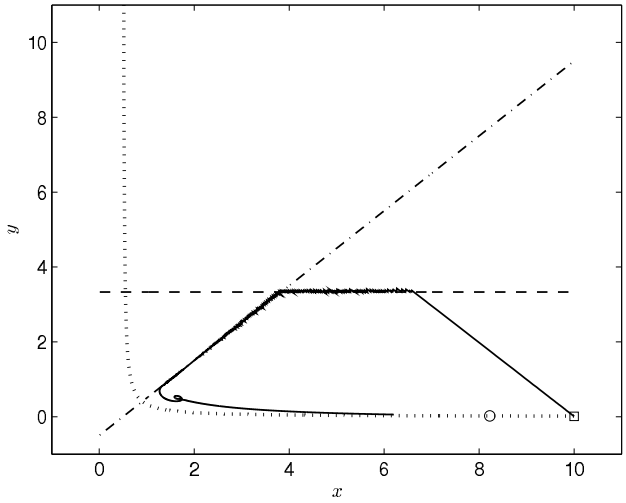

Fig. 8. The (x, y) trajectory resulting from the output feedback control strategy. The solid line indicates the (x, y) trajectory. The dashed line and the dashdot line represent the sets $L_1 = 0$ and $L_2 = 0$, respectively. The (x, y) trajectory stays within the sets $L_1 < 0$ and $L_2 < 0$, and converges to the Point C.

the "o"mark in Fig. 8. The resulting (x, y) trajectory is displayed in Fig. 8, which shows that the (x, y) trajectory stays within the sets $L_1 < 0$ and $L_2 < 0$.

3. MATHEMATICAL ANALYSIS FOR THE CONTROLLED HIV MODEL

3.1 Basic analysis for the HIV model

Let $X := [x, y, z_1, w, z_2]^T$ and let $\mathcal{U}$ denote the set of measurable functions with values in the set $[0, 1]$. Note that the input $\eta(\cdot)$ of interest belongs to $\mathcal{U}$. Finally let $\mathcal{P} = [0, \infty)^5$.

Theorem 1. (Chang and Astolfi (2008a)) For any measurable input function $\eta(\cdot) \in \mathcal{U}$, no finite time escape phenomenon exists and the set $\mathcal{P}$ is positively invariant. In other words, for any initial condition $X(0) \in \mathcal{P}$, the solution $X(t)$ of model (1)-(5) exists for all $t \geq 0$ and is contained in $\mathcal{P}$ for all $t \geq 0$.

Assumption 2. The parameters of the model (1)-(5) are such that

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

$$\beta > \frac{a}{q}, \tag{7}$$

$$\lambda > aq, \tag{8}$$

$$\frac{b_1}{c_1} > \max\left\{\frac{\lambda}{2\beta q}, \frac{1}{2}\left(\frac{\lambda}{a} - q\right)\right\}, \tag{9}$$

$$\frac{b_2}{c_2} < \min\left\{\frac{(\sqrt{\lambda} - \sqrt{dq})^2}{\beta}, \frac{1}{4}\left(\frac{\lambda}{a} - q\right)^2\right\}, \tag{10}$$

$$(1-\eta^*)\beta < \min\left\{\frac{ad}{\lambda}, \frac{(a-d)c_1}{2b_1}\right\}. \tag{11}$$

Lemma 3. Consider the model (1)-(5). Suppose Assumption 2 holds. Then $y^{(C)}$ is well-defined and positive for $u = 0$.

Lemma 4. Consider the model (1)-(5). Suppose Assumption 2 holds. Then $y^{(C)} < y^{(B)}$ for $u = 0$.

Theorem 5. Consider the model (1)-(5). Assume Assumption 2 holds and $u(t) = 1$ for all $t \geq 0$. Then all trajectories with initial condition $X(0) \in \mathcal{P}$ converge to the Point A.

3.2 Properties of the immune increasing factor K

From equation (4), $\dot{w} = K(x,y)w$, where $K(x,y) = c_2xy - c_2qy - b_2$. Then $K(x^{(A)}, y^{(A)}) = -b_2 < 0$.

Note, in addition, that

$$\begin{aligned}\dot{K} &= c_2\{\dot{x}y + x\dot{y}\} - c_2q\dot{y} \\ &= c_2y\times \\ &\quad \{\eta\beta x(x-q-y) + \lambda - dx - (x-q)(a + p_1z_1 + p_2z_2)\}.\end{aligned}$$

By Theorem 5, if $u(t) = 1$ the state of model (1)-(5) converges to the Point A. Therefore, by continuity of $K(x,y)$ with respect to x and y, there is a finite time T such that $K(x(T), y(T)) < 0$ and the state of the system is in a neighborhood of Point A [2].

Consider an initial condition close to Point A and described by $X_\delta = (\frac{\lambda}{d} - \delta_1,\ \delta_2,\ \delta_3,\ \delta_4,\ \delta_5)$. By the proof of Theorem 5 from Chang and Astolfi (2008b), δ_1, δ_2, δ_3, δ_4, and δ_5 are positive and sufficiently small. Then $\dot{K}(X_\delta)$ for $u = 0$ is given by

$$\begin{aligned}&c_2\delta_2\left\{\beta\left(\frac{\lambda}{d} - \delta_1\right)\left(\frac{\lambda}{d} - \delta_1 - q - \delta_2\right) + \lambda - d\left(\frac{\lambda}{d} - \delta_1\right)\right. \\ &\left. - \left(\frac{\lambda}{d} - \delta_1 - q\right)(a + p_1\delta_4 + p_2\delta_5)\right\} \\ >&c_2\delta_2\left\{\left(\frac{\lambda}{d} - q - \delta_1\right)\left(\beta\frac{\lambda}{d} - a - \beta\delta_1 - p_1\delta_4 - p_2\delta_5\right)\right. \\ &\left. - \beta\frac{\lambda}{d}\delta_2\right\}.\end{aligned}$$

Since, by equations (6), (7), and (8), $\left(\frac{\lambda}{d} - q\right)$ and $\left(\beta\frac{\lambda}{d} - a\right)$ are positive then $\dot{K}(X_\delta) > 0$ for $u = 0$ and δ_1, δ_2, δ_3, δ_4, and δ_5 sufficiently small.

[2] If $y(t) < \frac{b_2}{c_2(\frac{\lambda}{d} - q)}$, then $K(x(t), y(t)) < 0$ provided $x(t) < \lambda/d$ with $u = 1$.

Using the above facts, in what follows we provide some properties of the model (1)-(5).

Theorem 6. Consider the model (1)-(5) and a state $X^*(0)$ sufficiently close to Point A. Assume $u(t) = 0$ for all $t \geq 0$. Let $X^*(t)$ be the corresponding trajectory. Then there exists $T \geq 0$ such that $X^*(T)$ belongs to the immune increasing area.

Theorem 7. Consider the model (1)-(5) and a state $X^* = (x^*, y^*, z_1^*, w^*, z_2^*)$. Assume there exists $\eta \in [1-\eta^*, 1]$ such that

$$x^*\left(1 - \frac{y^*}{x^* - q}\right)\eta\beta + \frac{\lambda - dx^*}{x^* - q} - a \geq p_1z_1^* + p_2z_2^*. \tag{12}$$

Then there is a u which renders $\dot{K}(x^*, y^*)$ non-negative.

The right-hand side in equation (12) corresponds to the immune effect (see equation (2)), whereas the first term of the left-hand side includes the input u via the term η, which is multiplied by $x^*\left(1 - \frac{y^*}{x^* - q}\right)\beta$. Therefore, to maximise the left-hand side, u can be selected as

$$u = \begin{cases} 1, \text{ if } y^* > x^* - q, \\ 0, \text{ if } y^* < x^* - q. \end{cases} \tag{13}$$

Note that by equation (13), u is chosen to render $\dot{K} \geq 0$ whenever this is possible. Note that this condition does not intend to maximise $\dot{K}$.

Consider now the trapezoidal set τ defined by the inequalities $y > 0$, $y < \frac{b_1}{c_1}$, $y < x - q$, and $x + y < \frac{\lambda}{d}$, as depicted in Fig. 9.

Theorem 8. Consider the model (1)-(5) with the input u selected as in STEP 1. Then all trajectories of the model enter the set τ in finite time.

Theorem 9. Consider the model (1)-(5) with the input u selected as in STEP 2. Then the set τ is a positive invariant set, i.e. all trajectories starting in τ remain in τ for all future time t.

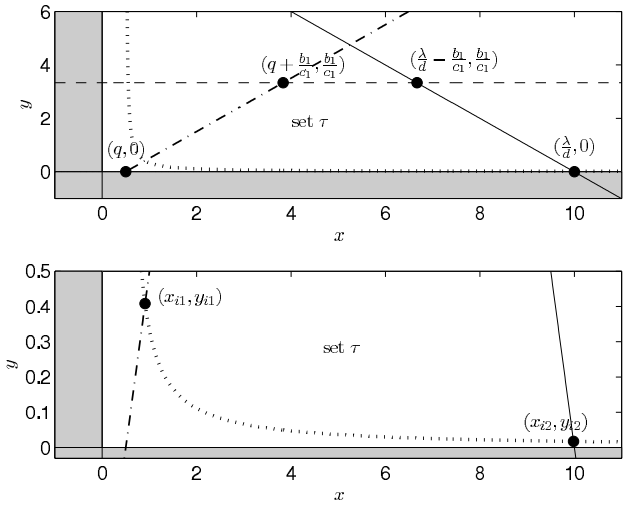

Fig. 9. The dotted line and the dashed line indicate the sets $K(x,y) = 0$ and $y = \frac{b_1}{c_1}$, respectively. The solid line and the dashdot line represent the lines $y + x = \frac{\lambda}{d}$ and $y = x - q$, respectively.

Theorems 8 and 9 imply that the feedback control guarantees that the state of the model (1)-(5), with the input as in STEPS 1 and 2, does not converge to Point B (i.e. to the AIDS status).

Note that the set τ contains points in which $K < 0$ (see the bottom graph in Fig. 9). At STEP 1 in the feedback method the states enters the set $K < 0$ in the set τ, and at STEP 2 the states enters the set $K \geq 0$ in the set τ. Then, in some cases, the states never returns to the set $K < 0$ in the set τ, as seen in Fig. 8. However, as discussed in the following statements, even if the state returns to the set $\tau \cap (K < 0)$, the feedback control method guarantees that the immune system (i.e. w and z_2) is boosted to a certain level.

Theorem 10. Consider the model (1)-(5) with the input u selected as in STEP 2. Suppose that the states $X = (x, y, z_1, w, z_2)$ is on the line $K(x, y) = 0$ at $t = T_1$ and T_2 and that $X(t)$ is in the set $K(x, y) < 0$, for $t \in [0, T_1)$, and $X(t)$ is in the set $K(x, y) > 0$ for $t \in (T_1, T_2)$. Assume that $\dot{K}$ is negative at $t = T_2$. Then $z_2^*(T_2) > z_{2m}(x^*(T_2))$ and $w^*(T_2) > \frac{hc_1}{c_2 q b_1} z_{2m}(x^*(T_2))$, where

$$z_{2m}(x^*) := \frac{1}{p_2}\left(x^*\left(1 - \frac{b_2}{c_2(x^* - q)^2}\right)\beta + \frac{\lambda - dx^*}{x^* - q} - a\right).$$

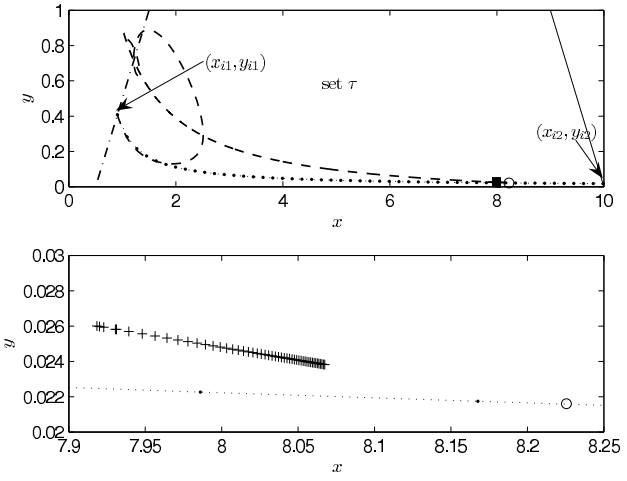

Fig. 10. Simulations for 500 days with 50 initial points on the line $K(x^*, y^*) = 0$, $(x^* \in [x_{i1}, x_{i2}])$, the levels of w^* and z_2^* in Theorem 10, and the condition $u = 0$. The "·"and the "+"marks denote the projections of the initial points and of the final points, respectively. The dashed line represents the (x, y) trajectory with initial point (x_{i1}, y_{i1}).

To show that the levels of immune system in Theorem 10 is enough for the states to be in the region of attraction of Point C for the model (1)-(5) with the given system parameters, we use computer simulations. In these simulations it is assumed that $z_1(0) = 0.01$ and $u = 0$ (note that the input is constant). We simulate with 50 pairs of initial points on the line $K(x(0), y(0)) = 0$ with $x(0)$ regularly spaced between x_{i1} and x_{i2} (see Fig. 9).

In Fig. 10, the initial points are indicated with "·"marks in (x, y) plane. The "+"marks in the same figure denote the (x, y) states after 500 days. The bottom graph shows a zoomed in version of the top graph. All considered initial states yield trajectories which converge to the LTNP state (the "o"mark). The trajectory with $x(0) = x_{i1}$ is displayed with dashed line.

4. CONCLUSION AND FURTHER DISCUSSION

We have provided a control methodology for drug scheduling and have shown its immune boosting mechanism by means of a mathematical analysis of the HIV/AIDS dynamics. The applicability of the method is demonstrated by computer simulations.

REFERENCES

B.M. Adams, H.T. Banks, M. Davidian, H. Kwon, H.T. Tran, S.N. Wynne, and E.S. Rosenberg. HIV dynamics: Modeling, data analysis, and optimal treatment protocols. *J. Comp. Appl. Math.*, 184:10–49, 2005.

B. Autran and G. Carcelain. AIDS: Boosting immunity to HIV-can the virus help? *Science*, 290(5493):946–949, 2000.

H. Chang and A. Astolfi. Control of HIV infection dynamics : Approximating high-order dynamics by adapting reduced-order model parameters. to appear *IEEE Control System Magazine*, 2008a.

H. Chang and A. Astolfi. Immune response's enhancement via controlled drug scheduling. In *Proc. of Conference on Decision and Control*, pages 3919–3924, 2007.

H. Chang and A. Astolfi. Enhancement of the immune system in HIV dynamics by output feedback. in preparation, 2008b.

H. Chang and A. Astolfi. Estimation of immune states in HIV dynamics. in preparation, 2008c.

H. Chang, N.H. Jo, and H. Shim. An applicationn of gradual reduction of drug dose to HIV infection model in consideration of drug resistance and drug dose. In *Proc. of SICE-ICASE International Joint Conference*, pages 5236–5241, 2006.

J. Lisziewicz, E. Rosenberg, J. Lieberman, H. Jessen, L. Lopalco, R. Siliciano, B. Walker, and F. Lori. Control of HIV despite the discontinuation of antiretroviral therapy. *N. Engl. J. Med.*, 340(21):1683–1684, 1999.

H. Shim, S.J. Han, I.S. Jeong, C.C. Chung, S.W. Nam, and J.H. Seo. Optimal scheduling of drug treatment for HIV infection: continuous dose control and receding horizon control. *Int. J. of Control, Automation and Systems*, 1 (3):282–288, 2003.

D. Wodarz. Helper-dependent vs. helper-independent CTL responses in HIV infection: implications for drug therapy and resistance. *J. of Theoretical Biology*, 213: 447–459, 2001.

D. Wodarz and M.A. Nowak. Mathematical models of HIV pathogenesis and treatment. *BioEssays*, 24:1178–1187, 2002.

D. Wodarz and M.A. Nowak. Specific therapy regimes could lead to long-term immunological control of HIV. *Proc. of National Academy Science*, 96(25):14464–14469, 1999.

R. Zurakowski and A.R. Teel. A model predictive control based scheduling method for HIV therapy. *J. of Theoretical Biology*, 238:368–382, 2006.

R. Zurakowski and A.R. Teel. Enhancing immune response to HIV infection using MPC-based treatment scheduling. In *Proc. of American Control Conference*, pages 1182–1187, 2003.