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Estimation of Immune States in HIV Dynamics

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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 the literature of control applications, model-based control methods to boost the immune system by means of drug scheduling have been reported. 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. In this paper we investigate methods to estimate the state of the immune system based on the available outputs of the HIV model. A nonlinear observer is designed and an approximate observer is also given. Computer simulations are presented to show the feasibility of the estimation methodology.**

I. 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. In 2006, the estimated number of people infected with HIV worldwide was 39.5 million and more than three-million people died of AIDS [14].

While HIV-infected patients are expected to develop AIDS, the possibility of a long-term nonprogressor (LTNP) is supported by the clinical data in [3], [10], and studied by means of mathematical models[1] describing the progress of the HIV infection in [1], [15], [16]. 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 literature, 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 [17], [18], and a control method based on the understanding of the boosting mechanism of the immune response has been proposed in [5], [6]. These works show that the state of a patient can be successfully driven into the region of attraction of the LTNP.

The purpose of this research is to provide an observation methodology for the immune system of the HIV patient on the basis of available measurements. In this paper we justify the state estimation idea from a theoretical perspective and also show the applicability of this idea with numerical simulations. Note that experimental verification by clinical data is out of the scope of the paper.

The paper is organised as follows. In Section II we describe the HIV dynamic model of [15], and results from [6] are briefly summarised. Section III proposes a state estimation method based on a nonlinear observer. The method is illustrated by means of computer simulations. In Section IV we suggest an alternative method to monitor the immune status of the HIV infected patient taking into account implementation issues. Finally, Section V describes some future works, and discusses available measurements and their relation with the states of the HIV model.

II. HIV MODEL AND OUTPUT FEEDBACK CONTROL

A. HIV Model

In this paper we consider the model from [15] 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

$$\eta(t) = 1 - \eta^* u(t),$$

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[1]A number of HIV models are already available, but only several models describe the LTNP phenomenon.

where η^* is the maximum effect of the drug [18]. 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 [18]. 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 [15].

The model with $u = 0$ has five equilibrium points, three of which are of interest, and are given in what follows [7].

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:

$$y^{(C)} = \frac{c_2(\lambda - dq) - b_2\eta\beta - \sqrt{[c_2(\lambda - dq) - b_2\eta\beta]^2 - 4\eta\beta c_2 q d b_2}}{2\eta\beta c_2 q},$$
$$x^{(C)} = \frac{\lambda}{d + \eta\beta y^{(C)}}, \qquad z_1{}^{(C)} = 0, \qquad w^{(C)} = \frac{h z_2{}^{(C)}}{c_2 q y^{(C)}},$$
$$z_2{}^{(C)} = \frac{y^{(C)}(c_2\eta\beta q - c_2 a) + b_2\eta\beta}{c_2 p_2 y^{(C)}}.$$

In this paper we regard (1), (2) as the infection dynamics and (3)-(5) as the immune system. Also, we use the same parameters as in [18], 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 for all simulations is also identical to one of those used in [18], namely $x(0) = 10$, $y(0) = 0.1$, $z_1(0) = 0.1$, $w(0) = 0.1$, and $z_2(0) = 0.1$. Note that this point represents a newly infected patient.

B. Existing Results

Results from [6] are recalled in this subsection. Consider the following output feedback control procedure.

Initialization: Select a sufficiently large positive number[2] T_i. Let $L_1 = L_1(x, y) = y - C_y$ and $L_2 = L_2(x, y) = y - (x - q)$ where $y^{(C)} < C_y < y^{(B)}$. 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 days with full medication.

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

[2] T_i denotes the period of full medication preceding the application of the proposed control scheme and driving the state to Point A.

The purpose of the output feedback is to boost the response of the immune system in order to steer the system to Point C, the LTNP status. This control idea stems from the concepts of immune increasing factor and immune increasing area introduced in [5].

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

$$d < a,\ \frac{a}{q} < \beta,\ aq < \lambda,$$
$$\frac{b_1}{c_1} > \max\left\{\frac{\lambda}{2\beta q}, \frac{1}{2}\left(\frac{\lambda}{a} - q\right)\right\},$$
$$\frac{b_2}{c_2} < \min\left\{\frac{(\sqrt{\lambda} - \sqrt{dq})^2}{\beta}, \frac{1}{4}\left(\frac{\lambda}{a} - q\right)^2\right\},$$
$$(1 - \eta^*)\beta < \min\left\{\frac{ad}{\lambda}, \frac{(a - d)c_1}{2b_1}\right\}.$$

By Assumption 1 the components of Point C (the target state of this paper) are well-defined and positive [6]. Moreover the interpretation of Assumption 1 and the proofs of the following propositions are given in [6]. Let $X(t) = [x(t), y(t), z_1(t), w(t), z_2(t)]^T$ and $\mathcal{P} = [0, \infty)^5$.

Proposition 1: Consider the model (1)-(5). Assume Assumption 1 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.

Consider now the trapezoidal set[3] τ defined by the inequalities $y > 0$, $y < C_y$, $y < x - q$, and $x + y < \frac{\lambda}{d}$.

Proposition 2: 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.

Proposition 3: 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. In addition $\lim_{t\to\infty} z_1(t) = 0$.

Assumption 1 requires a strongly effective drug and the mathematical analysis in the paper is based on this assumption. However the value of η^* from [18] is such that Assumption 1 does not hold. Nevertheless, in simulations we use this value of η^* to highlight the robustness of the proposed methodology.

C. Simulations

Fig. 1 shows the results of the application of the output feedback control with $C_y = 0.5$ and $T_i = 20$. In STEP 1 the state moves sufficiently close to Point A and enters the set τ. The control input becomes eventually zero and the patient state converges to the LTNP status, i.e. to Point C. The top graph of Fig. 1 shows that the (x, y) trajectory stays within the set τ, which is the area enclosed by the dotted line.

Fig. 2 shows the result of the same control scheme applied using a sample-and-hold device. The sample period T_s is 0.25 (day). Note that a sufficiently small T_s guarantees that the (x, y) trajectory is such that $y(t) < \frac{b_1}{c_1}$ because $C_y < \frac{b_1}{c_1}$.

[3] The conditions in Initialization guarantee that Point C and Point B are located inside and outside of the set τ, respectively.

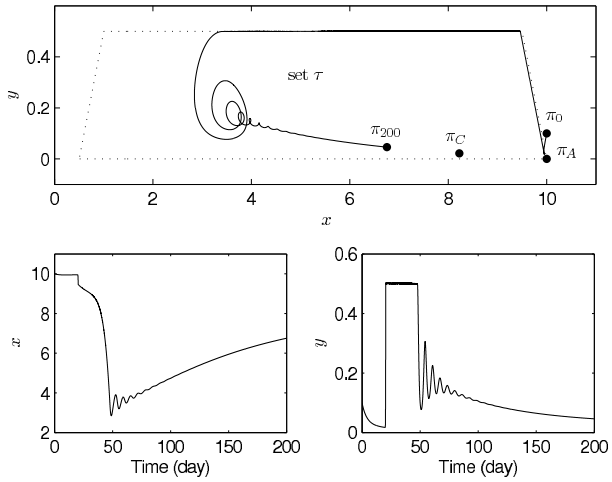

Fig. 1. Results of the application of the control procedure of Section II-B to model (1)-(5). The top graph shows the state trajectory in the (x, y)-plane. The (x, y) trajectory stays within the set τ, and converges to the Point C.

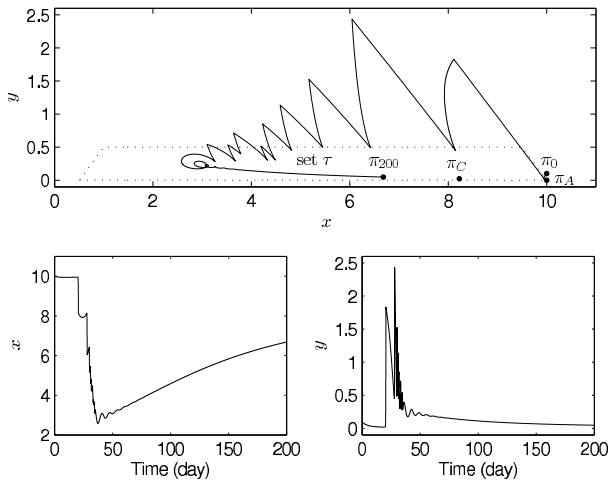

Fig. 2. Results of the application of the control procedure of Section II-B with a sample-and-hold device.

In these figures the solid line indicates the (x, y) trajectory, and the area enclosed by the dotted line corresponds to the set τ. Also, π_0 and π_{200} indicate the projection into the (x, y)-plane of the initial state and the state after 200 days, respectively. π_A and π_C correspond to the projection into the (x, y)-plane of Point A and Point C, respectively. Note that the projection of Point B (i.e. π_B) is not located in the range of these figures.

III. State Estimation of Immune System

In this section we suggest a state estimation method for the immune states in model (1)-(5). The method is aimed to be used during the control STEP 2. Note that we do not need any state estimation during STEP 1 because we know the state converges to Point A by Proposition 1. Also, in STEP 2, z_1 does not need to be estimated because it goes to 0 by Proposition 3.

A. Nonlinear Observer Design

Lemma 1: Consider model (1)-(5) and assume that Assumption 1 holds. Then $x(t) + y(t) < \frac{\lambda}{d}$ for all $t > T_f$, for some $T_f > 0$.

Lemma 1 implies that even if the initial condition of (x, y) is located outside the right-angled triangle shown in Fig. 3, the point $(x(t), y(t))$ enters the shaded triangle after a while, and then remains within this triangle.

Theorem 1: Consider the model (1)-(5). Assume that Assumption 1 holds, $z_1(t)$ is sufficiently small[4] for all t, and the states x and y are the system outputs and are twice differentiable. Then the states of the system

$$\dot{\hat{w}} = K(x, y)\hat{w} + L_w\gamma_w - L_w\hat{w}, \tag{6}$$

$$\dot{\hat{z}}_2 = c_2qy\gamma_w + L_{z_2}\gamma_{z_2} - (h + L_{z_2})\hat{z}_2, \tag{7}$$

where $K(x, y) = c_2xy - c_2qy - b_2$, $L_w > K(\frac{1}{2}\left(\frac{\lambda}{d} + q\right), \frac{1}{2}\left(\frac{\lambda}{d} - q\right))$, $L_{z_2} > -h$,

$$\gamma_{z_2} = \gamma_{z_2}(x, \dot{x}, y, \dot{y}) = \frac{\lambda - dx - ay - \dot{x} - \dot{y}}{p_2y},$$

and

$$\gamma_w = \gamma_w(x, \dot{x}, \ddot{x}, y, \dot{y}, \ddot{y}) = \frac{1}{c_2qp_2y^2}\times$$
$$\left[\left(h - \frac{\dot{y}}{y}\right)(\lambda - dx - ay - \dot{x} - \dot{y}) - (d\dot{x} + a\dot{y} + \ddot{x} + \ddot{y})\right],$$

converge to the states of the system (4), (5) exponentially.

Proof: By Lemma 1 the point (x, y) enters the shaded triangle in Fig. 3, where the function $K(x, y)$ is bounded by $K(\frac{1}{2}\left(\frac{\lambda}{d} + q\right), \frac{1}{2}\left(\frac{\lambda}{d} - q\right))$ (see Fig. 3). By (1), (2), and the assumption on $z_1(t)$, $\gamma_{z_2}(x, \dot{x}, y, \dot{y}) = z_2$. Then, by (5), the function $\gamma_w(x, \dot{x}, \ddot{x}, y, \dot{y}, \ddot{y})$ is such that

$$\frac{1}{c_2qp_2y}\left[\frac{h}{y}(\lambda - dx - ay - \dot{x} - \dot{y}) - \right.$$
$$\left.\left(\frac{\dot{y}}{y^2}(\lambda - dx - ay - \dot{x} - \dot{y}) + \frac{1}{y}(d\dot{x} + a\dot{y} + \ddot{x} + \ddot{y})\right)\right]$$
$$= \frac{1}{c_2qp_2y}\left[h\frac{1}{y}(\lambda - dx - ay - \dot{x} - \dot{y})\right.$$
$$\left.+\frac{d}{dt}\left(\frac{1}{y}(\lambda - dx - ay - \dot{x} - \dot{y})\right)\right]$$
$$= \frac{1}{c_2qy}(hz_2 + \dot{z}_2) = w.$$

Hence, from (6) and (7),

$$\dot{\hat{w}} = K(x, y)\hat{w} + L_w(w - \hat{w}),$$
$$\dot{\hat{z}}_2 = c_2qyw + L_{z_2}(z_2 - \hat{z}_2) - h\hat{z}_2.$$

Consider now the errors

$$e_w = w - \hat{w},$$
$$e_{z_2} = z_2 - \hat{z}_2,$$

[4]During the proposed drug treatment $z_1(t)$ decreases exponentially by Proposition 1 and Proposition 3. Consequently $z_1(t)$ becomes negligible as time goes by.

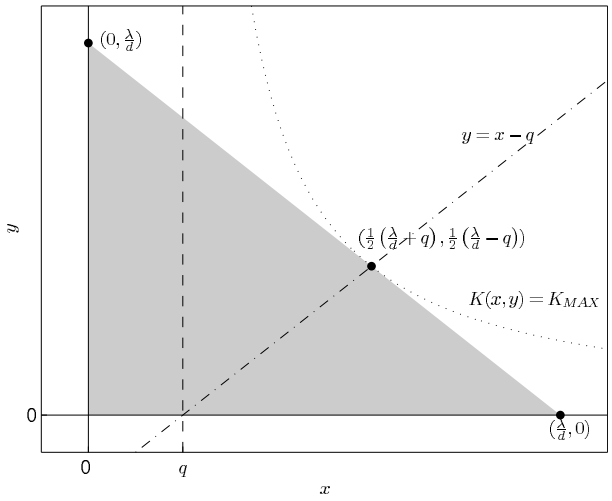

Fig. 3. Proof of Theorem 1. $K(x,y) = c_2xy - c_2qy - b_2$ and $K_{MAX} = K(\frac{1}{2}\left(\frac{\lambda}{d}+q\right), \frac{1}{2}\left(\frac{\lambda}{d}-q\right))$. The shaded right-angled triangle is an attractive region by Lemma 1.

and note that

$$\begin{aligned}\dot{e}_w &= K(x,y)(w-\hat{w}) - L_w(w-\hat{w}) \\ &= (K(x,y) - L_w)\, e_w.\end{aligned}$$

Thus e_w converges to 0 exponentially because $L_w > K(\frac{1}{2}\left(\frac{\lambda}{d}+q\right), \frac{1}{2}\left(\frac{\lambda}{d}-q\right))$. Similarly,

$$\begin{aligned}\dot{e}_{z_2} &= -hz_2 - L_{z_2}(z_2 - \hat{z}_2) + h\hat{z}_2 \\ &= -(h + L_{z_2})e_{z_2},\end{aligned}$$

with $L_{z_2} > -h$. Hence the state of system (6), (7) converges to the state of system (4), (5) exponentially. ■

In Theorem 1 we assign a sufficiently high gain L_w to the nonlinear observer (6), (7) to make the error dynamics exponentially stable. However we can have a different observer by using a function $L_w(x,y)$, instead of a constant L_w, as shown in the following corollary.

Corollary 1: Under the assumptions of Theorem 1, the state of the system

$$\begin{aligned}\dot{\hat{w}} &= K(x,y)\hat{w} + L_w(x,y)\gamma_w - L_w(x,y)\hat{w}, \\ \dot{\hat{z}}_2 &= c_2qy\gamma_w + L_{z_2}\gamma_{z_2} - (h + L_{z_2})\hat{z}_2,\end{aligned}$$

where $L_w(x,y) = c_2xy - c_2qy - L_w^*$, with $L_w^* < b_2$, converges to the state of system (4), (5) exponentially.

B. Simulations

Two simulations of the nonlinear observer have been carried out for the examples from Section II-C. We use the ODE command of MATLAB to solve the differential equations numerically and the time ranges of the graphs are selected to show the performance of the observer clearly. Note that the output of this observer is not used in the feedback control loop (see Fig. 4). The purpose of the observer is to monitor the immune system.

Fig. 5 shows the behaviour of the nonlinear observer (6), (7) in the interval $[50, 100]$ for the case in Fig. 1. The initial

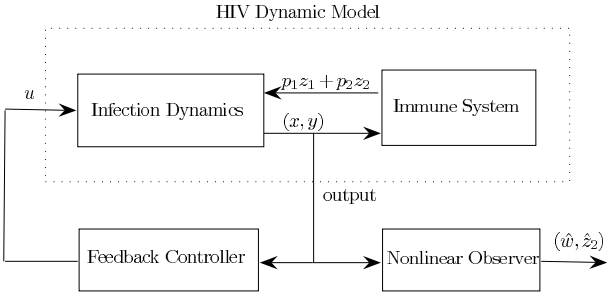

Fig. 4. Diagram describing the connections of the HIV model, the controller, and the nonlinear observer. The block inside the dotted-line indicates the HIV dynamics (1)-(5), which consist of two subsystems, the infection dynamics and the immune system.

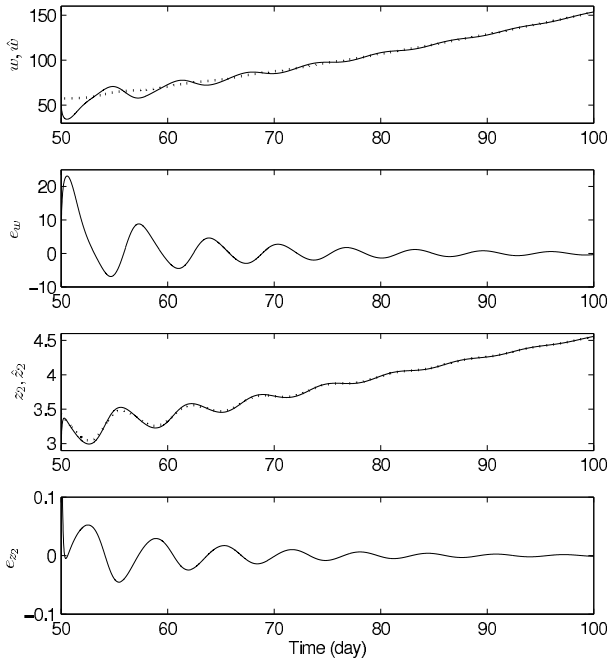

Fig. 5. State histories of the nonlinear observer (6), (7) for the example in Fig. 1 for the time interval $[50, 100]$. $w(t)$ and $z_2(t)$ of model (1)-(5) are depicted with dotted lines in the first and third graph, respectively.

condition $(\hat{w}(50),\ \hat{z}_2(50))$ is (50, 3), and the observer gains L_w and L_{z_2} are both equal to 10. Note that the value of $K(\frac{1}{2}\left(\frac{\lambda}{d}+q\right), \frac{1}{2}\left(\frac{\lambda}{d}-q\right))$ is 1.3438.

From the assumptions of Theorem 1, the observer (6), (7) cannot guarantee good performance in the interval $[20, 50]$, because this interval includes too many switches between 0 and 1 of the input function $u(t)$. The switching renders $\dot{x}$ and $\dot{y}$ discontinuous, by (1) and (2), which implies that $\ddot{x}$ and $\ddot{y}$ are not defined.

However we can apply the observer (6), (7) in the time interval $[20, 200]$ for the case in Fig. 2, because this case has only a few input switching instants and we can integrate the observer piece by piece for each period in which the input is constant. Note that constant input u implies twice differentiable system outputs, x and y, by (1) and (2). Fig. 6 shows $\hat{w}$ and e_w, particularly in the interval $[26, 38]$. $\hat{z}_2$ and e_{z_2} are not shown in the figure, and the observer gain L_w is

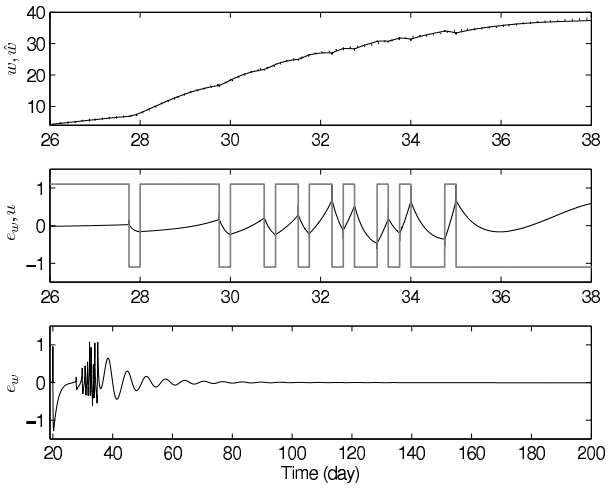

Fig. 6. State histories of the nonlinear observer (6), (7) for the example in Fig. 2 for the time interval $[26, 38]$. $w(t)$ is depicted by the dotted line in the top graph. e_w and a rescaled $u(t)$ are presented in the second graph. Note that the time range of the bottom graph is $[20, 200]$.

1.5. The third graph in the figure confirms the performance of the observer in the whole time period, $[20, 200]$.

IV. State Inference of Immune System

Although the system (6), (7) is a nonlinear observer for the immune system, we need to consider an alternative state estimation method because the continuous output injection in (6), (7) is hardly implementable in practice. In fact, the levels of x and y are measured at discrete time instants from patient's blood sample (see Section V-B for more discussion on HIV measurements). This implies that we cannot use the observer (6), (7) which requires $\dot{x}$, $\ddot{x}$, $\dot{y}$, and $\ddot{y}$. The method in this section relies on approximations hence we use the terminology, state inference.

Firstly, we infer $z_2(t)$ for the example in Fig. 2, where x and y are measured every 0.25 day. The approximation idea stems from [12]. We can approximately calculate $\dot{x}$ and $\dot{y}$ from two samples of x and y, respectively. Also approximation $\ddot{x}$ and $\ddot{y}$ can be obtained from three samples of x and y, respectively.

We assume that z_1 is sufficiently small, because $y(t)$ is such that $y(t) < \frac{b_1}{c_1}$. Then, by (1) and (2),

$$z_2 = \frac{\lambda - dx - ay - \dot{x} - \dot{y}}{p_2 y},$$

and the inference of z_2, denoted by $\tilde{z}_2$, is plotted in Fig. 7. In the first graph, the solid line corresponds to $z_2(t)$ from the model (1)-(5) and the points depict $\tilde{z}_2$, at every 0.25 (day) in the time interval $[26, 38]$. The second graph shows the error between z_2 and $\tilde{z}_2$ from the first graph. The last graph presents the overall performance of the inference method in the time interval $[20, 200]$. We see that discrete-time measurements of x and y can be used to estimate the level of z_2.

w is inferred using the same method. By equation (5)

$$w = \frac{1}{c_2 q}\left(\frac{\dot{z}_2 + h z_2}{y}\right),$$

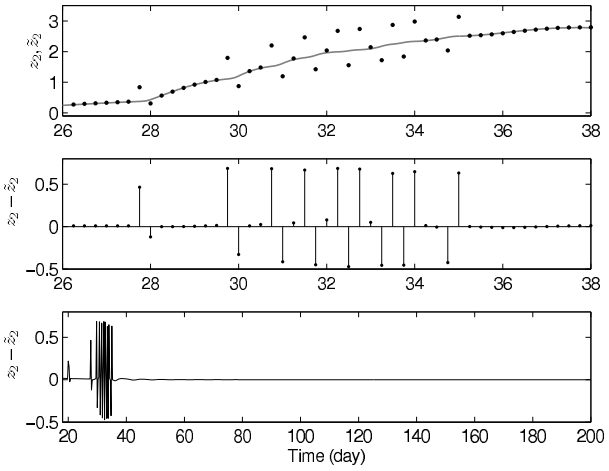

Fig. 7. State inference of z_2 for the example in Fig. 2 with 1 sample each 0.25 (day) period. In the top graph, $\tilde{z}_2$ is the inference of z_2. $\tilde{z}_2$ is given by points at each 0.25 (day), while z_2 is shown with the solid line.

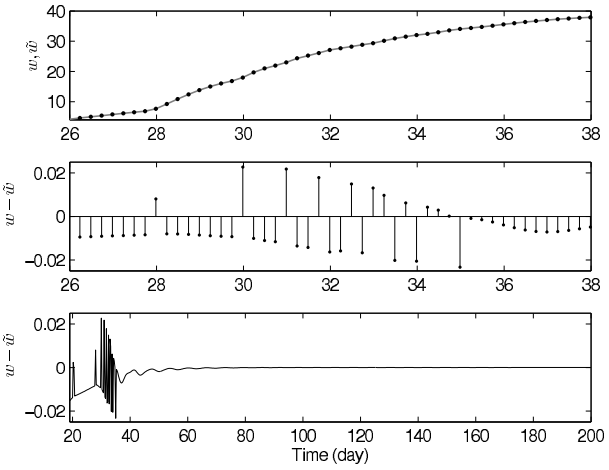

Fig. 8. State inference of w for the example in Fig. 2 with 4 samples each 0.25 (day) period. In the top graph $\tilde{w}$ is the inference of w. $\tilde{w}$ is given by points at each 0.25 (day), while w is shown with the solid line.

and an approximation of $\dot{z}_2$ is obtained from $\tilde{z}_2$. However $\tilde{z}_2$ is oscillating in the interval $[26, 36]$, which makes the inference of w unreliable in this interval. This oscillation is caused by the switching of the input u between 0 and 1. If the input u is changed from 1 to 0 (or vice versa) at a certain instant, then $\tilde{z}_2$ is not reliable by (1) and (2), because $\dot{x}$ and $\dot{y}$ are not continuous.

To overcome this problem in $\tilde{z}_2$, we apply the method used in the previous section. By multiple measurements in each period, where the input u is guaranteed to be constant, we reliably obtain not only $\tilde{z}_2$ but also $\tilde{w}$, i.e. the inference of w, as shown in Fig. 8. From the ideas in [12], three measurements of x and y are needed to approximate $\ddot{x}$ and $\ddot{y}$, respectively, although we use four measurements to infer $\tilde{w}$ in Fig. 8.

V. Conclusion

We have presented two estimation methods to monitor the immune status in a HIV dynamic model. In particular, the

second method allows us to infer the states of the immune system using only three (or four) measures of x and y if the system parameters are known. We complete the paper with further remarks as well as a discussion on current HIV measurements.

A. Further Remarks

1) The function γ_w in Theorem 1 does not depend on the w dynamics (4) except for c_2 and q which are scaling factors. Thus we do not need any information on (4) in order to know the trend of w. This implies that we can use extremum seeking methods for the boosting of the immune term w regardless of (4), which will be the subject of future research.
2) The control example in Fig. 2 requires four HIV measurements in a day, which means the patient's blood must be sampled every 6 hours. This is hard to be achieved practically. However this frequent sampling is not needed in all the time interval $[20, 200]$. In other words, we need a 0.25 (day) sampling period only for the first few days in order for the HIV patient to be driven into the region of attraction of the LTNP. For example, if we assign 0.25 (day) sampling period in the interval $[20, 28)$, 1 (day) period in the interval $[28, 35)$, and 7 (day) period in the interval $[35, 200]$, then the immune system of the patient is boosted enough to be in the region of attraction of LTNP. (This result is not presented in this paper.)
3) Although we obtain an input function $u(t)$ to enhance the immune system of the HIV patient, the implementation of $u(t)$ in the human body should be studied with care. In this paper we assume that $u(t)$ is a square wave. However, the dynamics of drug effect in the human body cannot be assumed to be a square wave. Further modeling of the drug delivery dynamics must be included in the model (1)-(5).
4) While the high gain observer (6), (7) shows exponentially stable error dynamics by Theorem 1, measurement noise and model uncertainty problems should be researched for the observer in future works. Also the cases in which Assumption 1 does not hold should be considered in future research.

B. Discussion on HIV Measurement

In [7] we have assumed that the states x and y are clinically measurable by means of polymerase chain reaction (PCR) test and flow cytometry. PCR returns the level of HIV loads while a flow cytometer counts the level of CD4 T-cells (see [8], [11] for more information on PCR). The population of HIV is not explicitly shown in the model (1)-(5)[5], and the y state corresponds to infected CD4 T-cell in model (1)-(5). The state y is approximately considered as proportional to the HIV load [4], [15], because the turnover of HIV is much faster than that of y [13].

Although we have assumed that x corresponds to the CD4 T-cells measured by a flow cytometer in [7], different assumptions are claimed in [1] because the result from flow cytometer could include the number of infected CD4 T-cells as well as uninfected CD4 T-cells. Nevertheless we can measure the number of infected CD4 T-cell y with the help of PCR.

To this end, firstly we must separate white blood cells from blood sample of the HIV patient by Ficoll-Hypaque method [9]. The PCR measures the number of HIV genome [2], and an infected CD4 T-cell has the HIV genome in its cellular DNA. Consequently, if we do PCR with the separated white blood cells, then we can count only the number of infected CD4 T-cells y and we obtain the number of healthy CD4 T-cells x by subtracting y from the CD4 count $x+y$ of flow cytometry.

[5]See [16] for a model including the population of HIV explicitly.

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References

[1] 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.
[2] K. Alcorn, A. Poppa, and M. Nicholson. *HIV and AIDS treatments directory*. National AIDS Manual, 16 edition, 1999.
[3] B. Autran and G. Carcelain. AIDS: Boosting immunity to HIV-can the virus help? *Science*, 290(5493):946–949, 2000.
[4] S. Bonhoeffer, M. Rembiszewski, G.M. Ortiz, and D.F. Nixon. Risks and benefits of structured antiretroviral drug therapy interruptions in HIV-1 infection. *AIDS*, 14:2313–2322, 2000.
[5] 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.
[6] H. Chang and A. Astolfi. Enhancement of the immune system in HIV dynamics by output feedback. submitted to *Automatica*, 2008.
[7] H. Chang and A. Astolfi. Control of HIV infection dynamics Approximating high-order dynamics by adapting reduced-order model parameters. *IEEE Control Systems Magazine*, 28:28–39, Apr. 2008.
[8] S. Hughes and A. Moody, editors. *PCR*. Scion Publishing Ltd, 1st edition, 2007.
[9] M.A. Lichtman, E. Beutler, T.J. Kipps, U. Seligsohn, K. Kaushansky, and J.T. Prchal, editors. *Williams Hematology*. McGraw-Hill, 7th edition, 2006.
[10] 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.
[11] M. McPherson and S. Møller. *PCR*. Taylor & Francis Ltd, 2nd edition, 2006.
[12] D.A. Ouattara, M.-J. Mhawej, and C.H. Moog. Clinical tests of therapeutical failures based on mathematical modeling of the HIV infection. *IEEE Trans. Automat. Contr.*, 53(1):230–241, 2008.
[13] A.S. Perelson, A.U. Neumann, M. Markowitz, J.M. Leonard, and D.D. Ho. HIV-1 dynamics *in vivo*: virion clearance rate, infected cell lifespan, and viral generation time. *Science*, 271(5255):1582–1586, 1996.
[14] UNAIDS/WHO. *AIDS epidemic update : December 2006*. UNAIDS, Geneva, 2006.
[15] 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.
[16] D. Wodarz and M.A. Nowak. Mathematical models of HIV pathogenesis and treatment. *BioEssays*, 24:1178–1187, 2002.
[17] R. Zurakowski. An output-feedback MPC-based scheduling method for enhancing immune response to HIV. In *Proc. of American Control Conference*, pages 4800–4805, 2006.
[18] R. Zurakowski and A.R. Teel. A model predictive control based scheduling method for HIV therapy. *J. of Theoretical Biology*, 238:368–382, 2006.