Control of Dynamic HIV/AIDS Infection System with Robust H_∞ Fuzzy Output Feedback Controller

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***Abstract*—This paper considers the problem of designing robust H_∞ output feedback controllers for HIV/AIDS infection system with dual drug dosages described by a Takagi-Sugeno (TS) fuzzy model. Based on a linear matrix inequality (LMI) approach, we develop an H_∞ output feedback controller which guarantees the L_2-gain of the mapping from the exogenous input noise to the regulated output to be less than some prescribed value for the system. A sufficient condition of the controller for this system is given in term of Linear Matrix Inequalities (LMIs). The effectiveness of the proposed controller design methodology is finally demonstrated through simulation results. It has been shown that the anti-HIV vaccines are critically important in reducing the infected cells.**

***Index Terms*—Robust H_∞ fuzzy control, Takagi-Sugeno (TS) fuzzy model, linear matrix inequalities (LMIs), HIV/AIDS infection.**

I. Introduction

HIV is a retrovirus that primarily infects vital organs of the human immune system such as CD4+T cells (a subset of T cells), macrophages and dendritic cells. It directly and indirectly destroys CD4+T cells. Once HIV has killed so many CD4+T cells such that there are fewer than 200 of these cells per micro liter (μL) of blood then cellular immunity is lost. In the absence of antiretroviral therapy, the average time of progression from HIV infection to AIDS is about nine to ten years, and the average survival time after developing AIDS is only 9.2 months [1]. However, the rate of treated disease progression is varied between individuals, from two weeks up to 20 years. Fig. 1 shows the natural history of HIV infections dynamics as currently accepted [1]-[6]. When a body has been received HIV virus in primary infection, a number of HIV virus will dramatically increase in first 30 days (resulting CD4+T cells reduction). After the primary infection period, a body builds HIV antibodies for agent virus so that, the infection still stabilizes an approximate steady state. In the last period, the antibody of healthy CD4+T cells will be drastically reduced. Finally, the patient develops to be an AIDS person.

Over the past two decades, there has been rapidly growing interest in application of fuzzy logic to control problem. Recently, a great amount of effort has been devoted to describing a nonlinear system using a Takagi-Sugeno fuzzy model; see [7]–[13]. The Takagi-sugeno fuzzy model represents a nonlinear system by a family of local linear models which smoothly blended together through fuzzy membership functions. Fuzzy modelling is essentially a multi-model approach in which simple sub-models (typically linear models) are fuzzily combined to describe the global behavior of a nonlinear system. Based on this fuzzy model, a number of systematic model-based fuzzy control design methodologies have been developed.

Over the past few decades, the nonlinear H_∞-control theory has been extensively studied by many researchers; see [14]-[16]. The nonlinear H_∞-control problem can be stated as follows: given a dynamic system with the exogenous input noise and the measured output, find a controller such that the L_2-gain of the mapping from the exogenous input noise to the regulated output is less than or equal to a prescribed value. Presently, there are two commonly used approaches for providing solutions to the nonlinear H_∞-control problems. The first approach is based on the dissipativity theory and theory of differential games; see [14], [17], [18]. The second approach is based on the nonlinear version of classical Bounded Real Lemma; see [16]. Both approaches show that the solution of the nonlinear H_∞-control problem is in fact related to the solvability of Hamilton-Jacobi inequalities (HJIs).

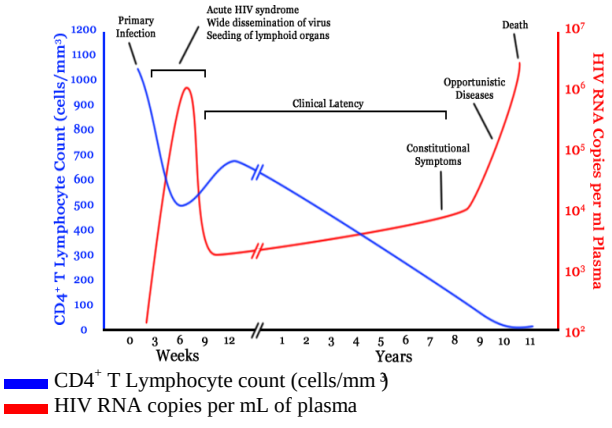

Fig. 1. A generalized graph of the relationship between HIV copies (viral load) and CD4+T cell [1-4].

In this paper, based on an LMI approach, we develop a output feedback controller for HIV/AIDS infection system with dual drug dosages such that the L_2-gain of the mapping from the exogenous input noise to the regulated output is less than a prescribed value. This paper is organized as follows. In Section II, system descriptions and definition are presented. In Section III, based on an LMI approach we

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develop a technique for designing a fuzzy H_∞ controller for HIV/AIDS infection system with dual drug dosages that guarantees the L_2-gain of the mapping from the exogenous input noise to the regulated output is less than a prescribed value. The validity of this approach is finally demonstrated through simulation results in Section IV. Finally in Section V, the conclusion is given.

II. System Description

A. HIV Dynamic Model

Fig. 2 shows HIV model which describes the interaction of three variables; the healthy cells, the free virus, and the infected cells. In most cases, HIV virus affects the level of CD4+T cells which these cells are important in helping a body fighting to infection. Free virus means the HIV virus found in blood plasma. The healthy CD4+T cells are produced from a source, such as the thymus represented by constant rate s and died at rate d. The coefficient β is the infection rate. The infected cells result from the infection of healthy CD4+T cells and die at a rate μ. A free-virus particle is known as virions, so called viral load, and cleared at a rate c (death rate of virus). The variable k is a rate of virions product per infection CD4+T cell.

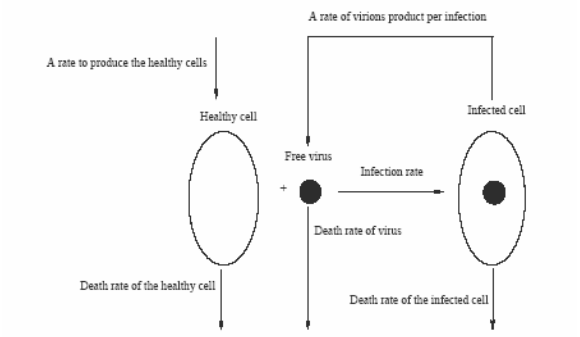

Fig. 2. Schematic illustration of the basic HIV model [1]-[4].

The infection described previously can be summarized by differential equations [1].

$$\begin{aligned} \dot{x}_1(t) &= s - dx_1(t) + \beta x_1(t)x_3(t) \\ \dot{x}_2(t) &= \beta x_1(t)x_3(t) - \mu x_2(t) \\ \dot{x}_3(t) &= kx_2(t) - cx_3(t) \end{aligned} \tag{1}$$

where $x_1(t)$ is concentration of healthy cells or T cells, $x_2(t)$ is concentration of infected cells, $x_3(t)$ is concentration of virions (free virus particles), s is the constant rate to produced the healthy CD4+T cells, d is the death rate of the healthy CD4+T cells, β is the coefficient of the infection rate, μ is death rate of the infected cells, k is a rate of virions product per infection CD4+T cell, and c is death rate of virus. Current treatment for HIV infection consists of highly active antiretroviral therapy, or HAART. The HAART treatment used drug in the group of protease inhibitor. The doctors will assess the viral load, CD4+T counts, rapidity of CD4+T decline, and patient readiness. While deciding, the doctors recommend initiating treatment to the patient [6]. The parameters and typical values are listed in Table I [5]. The information of HIV model parameters obtain from [5] which the initial conditions correspond to a healthy person infected with a virus given by Table I. In 2007, M. Barao and J.M. Lemos proposed the nonlinear dynamic model to describe HIV with treatment as follows [5]:

$$\begin{aligned} \dot{x}_1(t) &= s - dx_1(t) + (1-u_1(t))\beta x_1(t)x_3(t) \\ \dot{x}_2(t) &= (1-u_1(t))\beta x_1(t)x_3(t) - \mu x_2(t) \\ \dot{x}_3(t) &= (1-u_2(t))kx_2(t) - cx_3(t) \end{aligned} \tag{2}$$

where the controller input $u_1(t)$ and $u_2(t)$ are a number of expedient drugs in the treatment of HAART represented by Reverse Transcriptase Inhibitors-RTI (to reduce the virus performance) and Protease Inhibitors-PI (to reduce the productivity of free virions), respectively [5].The healthy CD4+T cells are produced from a source, such as the thymus represented by constant rate s and died at rate d. The coefficient β is the infection rate. The death rate of virus is described by c.

TABLE I: HIV Model Parameters [5]

Parameter	Typical Value	Unit
t	-	Days
d	0.02	Per Day
k	100	Count Cell^{-1}
s	100 mm^3	Per Day
β	2.4 x 10^{-5}	Per Day
c	2.4	Per Day
μ	0.24	Per Day

The model includes antiretroviral treatment and factors such as adhesion and medication potency. The concepts of our proposes are joined with fuzzy set theory and exogenous input noise with biological variable values such as person factor, mental state etc. Mostly, HIV virus dynamics are modeled using a nonlinear represented by cell. Each cell represents an uninfected cell, an infected cell of the type T lymphocyte of CD4+, a free virus particle, or specific antibodies such as CTL (Cytotoxic T Lymphocyte). Fuzzy systems perform an approximate reasoning using the compositional rule of inference. In fuzzy rule-based systems, the inferred output is a fuzzy set. Often, especially in biological systems model, we require a real-valued output.

B. Nonlinear Fuzzy Model

In this subsection, we generalize the TS fuzzy system to represent a TS fuzzy system with parametric uncertainties. In this paper, we examine a TS fuzzy system with parametric uncertainties as follows:

$$\begin{aligned} \dot{x}(t) &= \sum_{i=1}^{r} \mu_i\left(v(t)\right)\left[[A_i + \Delta A_i]x(t)\right. \\ &\quad \left.+[B_{1_i} + \Delta B_{1_i}]w(t) + [B_{2_i} + \Delta B_{2_i}]u(t)\right], \qquad x(0) = 0 \\ z(t) &= \sum_{i=1}^{r} \mu_i\left(v(t)\right)\left[[C_{1_i} + \Delta C_{1_i}]x(t)\right. \\ &\quad \left.+[D_{12_i} + \Delta D_{12_i}]u(t)\right] \\ y(t) &= \sum_{i=1}^{r} \mu_i\left(v(t)\right)\left[[C_{2_i} + \Delta C_{2_i}]x(t)\right. \\ &\quad \left.+[D_{21_i} + \Delta D_{21_i}]w(t)\right] \end{aligned} \tag{3}$$

where $v(t) = [v_1(t) \cdots v_g(t)]$ is the premise variable vector that may depend on states in many cases, $\mu_i(v(t))$ denotes the normalized time-varying fuzzy weighting functions for each

rule (i.e., $\mu_i(v(t)) \geq 0$ *and* $\sum_{i=1}^{r} \mu_i(v(t)) = 1$), ϑ is the number of fuzzy sets, $x(t) \in \Re^n$ is the state vector, $u(t) \in \Re^m$ is the input, $w(t) \in \Re^p$ is the disturbance which belongs to $L_2[0;\infty)$, $y(t) \in \Re^\ell$ is the measurement, $z(t) \in \Re^s$ is the controlled output, the matrices A_i, B_{1_i}, B_{2_i}, C_{1_i}, C_{2_i}, D_{12_i} and D_{21_i} are of appropriate dimensions, and *r* is the number of IF-THEN rules. The matrices ΔA_i, ΔB_{1_i}, ΔB_{2_i}, ΔC_{1_i}, ΔC_{2_i}, ΔD_{12_i} and ΔD_{21_i} represent the uncertainties in the system and satisfy the following assumption.

Assumption 1:

$$\Delta A_i, = F(x(t),t)H_{1_i}$$
$$\Delta B_{1_i}, = F(x(t),t)H_{2_i}, \ \Delta B_{2_i}, = F(x(t),t)H_{3_i}$$
$$\Delta C_{1_i}, = F(x(t),t)H_{4_i}, \ \Delta C_{2_i}, = F(x(t),t)H_{5_i}$$
$$\Delta D_{12_i}, = F(x(t),t)H_{6_i}, \ \Delta D_{21_i}, = F(x(t),t)H_{7_i}$$

where H_{j_i}, j = 1, 2, …, 7 are known matrix functions which characterize the structure of the uncertainties. Furthermore, the following inequality holds:

$$\|F(x(t),t)\| \leq \rho \tag{4}$$

for any known positive constant ρ.

Next, let us recall the following definition.

Definition 1: Suppose γ is a given positive number: A system (3) is said to have an L_2-gain less than or equal to γ if

$$\int_0^{T_f} z^T(t)z(t)dt \leq \gamma^2 \left[\int_0^{T_f} w^T(t)w(t)dt \right], \quad x(0) = 0 \tag{5}$$

for all $T_f \geq 0$ and $w(t) \in L_2[0,T_f]$,

Note that for the symmetric block matrices, we use (*) as an ellipsis for terms that are induced by symmetry. In addition, for simplicity without loss originality, we use $\mu_i(v(t)) = \mu_i$ for the rest of the paper.

III. Robust H_∞ Fuzzy Output Feedback Controller for HIV/AIDS Infection System

This section aims at designing a full order dynamic H_∞ fuzzy output feedback controller of the form

$$\begin{aligned} \dot{\hat{x}}(t) &= \sum_{i=1}^{r}\sum_{j=1}^{r} \mu_i \mu_j \left[\hat{A}_{ij}\hat{x}(t) + \hat{B}_i y(t) \right] \\ u(t) &= \sum_{j=1}^{r} \mu_i \hat{C}_i \hat{x}(t) \end{aligned} \tag{6}$$

where $\hat{x}(t) \in \Re^n$ is the controller's state vector, $\hat{A}_{ij}$, $\hat{B}_i$ and $\hat{C}_i$ are parameters of the controller which are to be determined, and μ denotes the normalized time-varying fuzzy weighting functions for each rule (i.e., $\mu_i \geq 0$ and $\sum_{i=1}^{r} \mu_i = 1$), such that the inequality (5) holds. Note that for simplicity without loss originality, we use $\mu_i(v(t)) = \mu_i$ for the rest of the paper.

Theorem 1: Consider the system (3). Given a prescribed H_∞ performance $\gamma > 0$ and a positive constant δ, if there exist a matrix $X = X^T, Y = Y^T, \mathcal{B}_i$ *and* $\mathcal{C}_i$ i = 1, 2, …, r, satisfying the following liner matrix inequalities:

$$\begin{bmatrix} X & I \\ I & Y \end{bmatrix} > 0 \tag{7}$$
$$X > 0 \tag{8}$$
$$Y > 0 \tag{9}$$
$$\Psi_{11_{ii}} < 0 \qquad i = 1, 2, ..., r \tag{10}$$
$$\Psi_{22_{ii}} < 0 \qquad i = 1, 2, ..., r \tag{11}$$
$$\Psi_{11_{ij}} + \Psi_{11_{ji}} < 0 \qquad i < j \leq r \tag{12}$$
$$\Psi_{22_{ij}} + \Psi_{22_{ji}} < 0 \qquad i < j \leq r \tag{13}$$

where

$$\Psi_{11_{ij}} = \begin{pmatrix} \begin{pmatrix} A_i Y + Y A_i^T + B_{2_i}\mathcal{C}_j + \mathcal{C}_i^T B_{2_j}^T \\ +\gamma^{-2}\tilde{B}_{1_i}\tilde{B}_{1_j}^T \end{pmatrix} & (*)^T \\ \left[Y\tilde{C}_i^T + \mathcal{C}_i^T \tilde{D}_{12_j}^T \right]^T & -I \end{pmatrix} \tag{14}$$

$$\Psi_{22_{ij}} = \begin{pmatrix} \begin{pmatrix} A_i^T X + X A_i + \mathcal{B}_i C_{2_i} + C_{2_i}^T \mathcal{B}_j^T \\ +\tilde{C}_{1_i}^T \tilde{C}_{1_j} \end{pmatrix} & (*)^T \\ \left[X\tilde{B}_{1_i} + \mathcal{B}_i \tilde{D}_{21_j} \right]^T & -\gamma^2 I \end{pmatrix} \tag{15}$$

with

$$\tilde{B}_{1_i} = \begin{bmatrix} \delta I & I & \delta I & B_{1_i} & 0 \end{bmatrix},$$

$$\tilde{C}_{1_i} = \begin{bmatrix} \frac{\gamma\rho}{\delta} H_{1_i}^T & 0 & \frac{\gamma\rho}{\delta} H_{5_i}^T & \sqrt{2}\lambda\rho H_{4_i}^T & \sqrt{2}\lambda\rho C_{1_i}^T \end{bmatrix}^T,$$

$$\tilde{D}_{12_i} = \begin{bmatrix} 0 & \frac{\gamma\rho}{\delta} H_{3_i}^T & 0 & \sqrt{2}\lambda\rho H_{6_i}^T & \sqrt{2}\lambda\rho D_{12_i}^T \end{bmatrix}^T,$$

$$\tilde{D}_{21_i} = \begin{bmatrix} 0 & 0 & 0 & \delta I & D_{21_i} & I \end{bmatrix}$$

and $\lambda = \left(1 + \rho^2 \sum_{i=1}^{r}\sum_{j=1}^{r} \left[\left\| H_{2_i}^T H_{2_j} \right\| + \left\| H_{7_i}^T H_{7_j} \right\| \right] \right)^{\frac{1}{2}}$,

then the prescribed H_∞ performance γ > 0 is guaranteed. Furthermore, a suitable controller is of the form (6) with

$$\begin{aligned} \hat{A}_{ij} &= \left[Y^{-1} - X \right]^{-1} \mathcal{M}_{ij} Y^{-1} \\ \hat{B}_i &= \left[Y^{-1} - X \right]^{-1} \mathcal{B}_i \\ \hat{C}_i &= \mathcal{C}_i Y^{-1} \end{aligned} \tag{16}$$

where

$$\begin{aligned} \mathcal{M}_{ij} = &-A_i^T - X A_i Y - X B_{2_i}\hat{C}_j Y \\ &-\left[Y^{-1} - X \right] \hat{B}_i C_{2_j} Y - \tilde{C}_{1_i}^T \left[\tilde{C}_{1_j} Y + \tilde{D}_{12_j}\hat{C}_j Y \right] \\ &-\gamma^{-2} \left\{ X\tilde{B}_{1_i} + \left[Y^{-1} - X \right] \hat{B}_i \tilde{D}_{21_i} \right\} \tilde{B}_{1_j}^T. \end{aligned} \tag{17}$$

Proof: The proof is omitted for brevity.

IV. Simulation Results

A simulation result is given in this section to illustrate the procedure of designing a fuzzy controller. Let us recall (2) included with noise term. The parameters and typical values are listed in Table 1.

$$\begin{aligned}\dot{x}_1(t) &= s - dx_1(t) + (1-u_1(t))\beta x_1(t)x_3(t) + w_1(t)\\ \dot{x}_2(t) &= (1-u_1(t))\beta x_1(t)x_3(t) - \mu x_2(t) + w_2(t)\\ \dot{x}_3(t) &= (1-u_2(t))kx_2(t) - cx_3(t) + w_3(t)\end{aligned} \quad (18)$$

where $w_1(t)$, $w_2(t)$ and $w_3(t)$ are the disturbance factor from the patients and the controlled output is

$$\begin{aligned}z(t) &= \begin{bmatrix}x_1(t) & u_1(t) & u_2(t)\end{bmatrix}^T\\ y(t) &= x_1(t).\end{aligned} \quad (19)$$

The nonlinear system plant can be approximated by TS fuzzy rules. Let us choose the membership functions of the fuzzy sets as follows.

$$M_1(x_1(t)) = \begin{cases}1 & : x_1(t) \le 200\\ 3 - 0.01x_1(t) & : 200 < x_1(t) \le 300\\ 0 & : x_1(t) > 300\end{cases}$$

$$M_2(x_1(t)) = \begin{cases}0.01x_1(t) - 2 & : 200 < x_1(t) \le 300\\ 1 & : 300 < x_1(t) \le 500\\ 6 - 0.01x_1(t) & : 500 < x_1(t) \le 600\end{cases}$$

$$M_3(x_1(t)) = \begin{cases}0 & : x_1(t) \le 500\\ 0.01x_1(t) - 5 & : 500 < x_1(t) \le 600\\ 1 & : x_1(t) > 600\end{cases}$$

$$N_1(x_2(t)) = \begin{cases}1 & : x_2(t) \le 10\\ 2 - 0.1x_2(t) & : 10 < x_2(t) \le 20\\ 0 & : x_2(t) > 20\end{cases}$$

$$N_2(x_2(t)) = \begin{cases}0.1x_2(t) - 1 & : 10 < x_2(t) \le 20\\ 1 & : 20 < x_2(t) \le 90\\ 10 - 0.1x_2(t) & : 90 < x_2(t) \le 100\end{cases}$$

$$N_3(x_1(t)) = \begin{cases}0 & : x_2(t) \le 90\\ 0.01x_2(t) - 9 & : 90 < x_2(t) \le 100\\ 1 & : x_2(t) > 600\end{cases}$$

$$q_1(x_3(t)) = \begin{cases}1 & : x_3(t) \le 1\\ 2 - x_3(t) & : 1 < x_3(t) \le 2\\ 0 & : x_3(t) > 2\end{cases}$$

$$q_2(x_3(t)) = \begin{cases}x_3(t) - 2 & : 1 < x_3(t) \le 2\\ 1 & : 2 < x_3(t) \le 3\\ 4 - x_3(t) & : 3 < x_3(t) \le 4\end{cases}$$

$$q_3(x_3(t)) = \begin{cases}0 & : x_3(t) \le 3\\ x_3(t) - 3 & : 3 < x_3(t) \le 4\\ 1 & : x_3(t) > 4\end{cases}$$

The membership functions of three variables are the healthy cell of CD4+T, the infected cells and the free cells. The TS fuzzy plant model can be obtained as:

Plant Rule i:

If $x_1(t)$ is M_i and $x_2(t)$ is N_j and $x_3(t)$ is q_k

then

$$\begin{aligned}\dot{x}(t) &= [A_i + \Delta A_i]x(t) + B_i u(t) + B_w w(t)\\ z(t) &= C_1 x(t) + D_{12} u(t)\\ y(t) &= C_2 x(t)\end{aligned}$$

where $i, j, k = 1, \ldots, 3$

$$A_i = \begin{bmatrix}-d & 0 & -\beta x_1(t)\\ 0 & -\mu & \beta x_1(t)\\ 0 & k & -c\end{bmatrix}, \quad B_w = \begin{bmatrix}1 & 0 & 0\\ 0 & 1 & 0\\ 0 & 0 & 1\end{bmatrix},$$

$$B_i = \begin{bmatrix}\beta x_1(t)x_3(t) & 0\\ -\beta x_1(t)x_3(t) & 0\\ 0 & kx_2(t)\end{bmatrix}, \quad C_1 = \begin{bmatrix}1 & 0 & 0\\ 0 & 0 & 0\\ 0 & 0 & 0\end{bmatrix},$$

$$C_2 = \begin{bmatrix}1 & 0 & 0\end{bmatrix}, \quad D_{12} = \begin{bmatrix}0 & 0\\ 1 & 0\\ 0 & 1\end{bmatrix},$$

$$\Delta A_i = F(x(t),t)H_{1_i},$$

$$x(t) = \begin{bmatrix}x_1^T(t) & x_2^T(t) & x_3^T(t)\end{bmatrix}^T,$$

and $w(t) = \begin{bmatrix}w_1^T(t) & w_2^T(t) & w_3^T(t)\end{bmatrix}^T$.

Now by assuming that in (2), $\|F(x(t),t)\| \le \rho = 1$ and since the value of μ, d, and c are uncertain but bounded within 10% of their nominal value in (18), we have

$$H_{1_i} = \begin{bmatrix}-0.1d & 0 & 0\\ 0 & -0.1\mu & 0\\ 0 & 0 & -0.1c\end{bmatrix}.$$

Using the LMI optimization algorithm and following Theorem 1 with set as $\gamma = 0.1$, we obtain the results given in Fig. 3 - 5.

Remark 1: When a body has been received HIV virus in primary infection (about 4-8 weeks), the doctors will assess the viral load, CD4+T counts, rapidity of CD4+T decline, and patient readiness before beginning treatment. Fig. 3 shows the plot of healthy cells, i.e., if CD4+T are more than 500 cells/μL the patient will develop the disease of HIV at low risk. Fig. 4 shows the plot of Reverse Transcriptase Inhibitors-RTI, which are a class of antiretroviral drug used to treat HIV infection, tumors, and cancer. RTIs inhibit activity of reverse transcriptase, a viral DNA polymerase enzyme that retroviruses need to reduce the virus performance, and Fig. 5 shows the plot of Protease Inhibitors-PI, which are molecules that inhibit the function of proteases.

V. Conclusion

This paper has presented a robust H_∞ fuzzy output feedback control design for nonlinear positive HIV infection dynamic model. This paper has developed a fuzzy controller

for applying in HIV nonlinear dynamic model to solve with antiretroviral therapy by using a fuzzy rule-based system with two inputs, the medication potency and the treatment adhesion rate. The effective of controller can prevent infection. The progression is the key to success of fighting against AIDS.

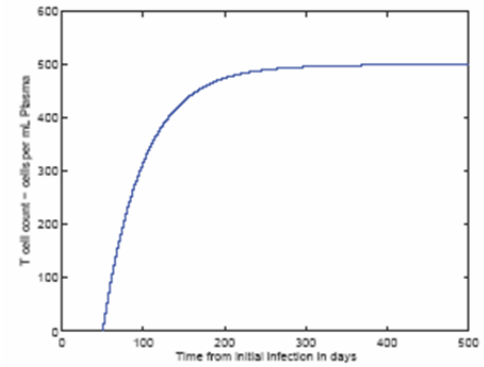

Fig. 3. The simulation result of dual drug dosages for healthy cell, $x_1(t)$.

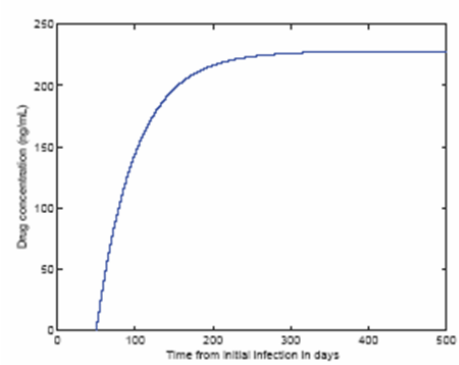

Fig. 4. The simulation result of dual drug dosages for RTI, $u_1(t)$.

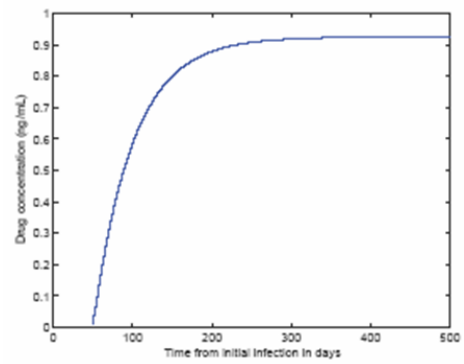

Fig. 5. The simulation result of dual drug dosages for PI, $u_2(t)$.

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