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Robust control of HIV infection by antiretroviral therapy: a super-twisting sliding mode control approach

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Manas Kumar Bera[1] ✉, Pintu Kumar[2], Raj Kumar Biswas[2]

[1]*Department of Electronics and Instrumentation Engineering, National Institute of Technology Silchar, Silchar 788010, Assam, India*
[2]*Department of Electrical Engineering, National Institute of Technology Silchar, Silchar 788010, Assam, India*
✉ *E-mail: manas.bera@gmail.com*

Abstract: Acquired immune deficiency syndrome is an epidemic infectious disease which is caused by the human immunodeficiency virus (HIV) and that has proliferated across worldwide. It has been a matter of concern for the scientific community to develop an antiretroviral therapy, which will prompt a rapid decline in viral abundance. With this motivation, this study proposes the design of a robust super twisting sliding mode controller based on output information for an uncertain HIV infection model. The control objective is to decrease the concentration of infected CD4+ T cells to a specified level by drug administration using only the output information of the uncertain HIV infection model which is total CD4+ T cell concentration. The robust output-feedback controller has been developed in combination with a robust exact differentiator, functioning as an observer. The reported analysis demonstrates that the approach proposed here is capable of ensuring robust performance under several operating conditions, measurement and modelling error, parametric uncertainties and external disturbances and the simulation results prove the proficiency of the controller proposed.

1 Introduction

Human immunodeficiency virus (HIV), which causes acquired immune deficiency syndrome (AIDS), has become a globalised health problem for mankind. As indicated by the Global Health Observatory data reported by World Health Organisation, the number of HIV infected individuals has crossed more than 70 million and about 35 million individuals have died of AIDS-related illnesses. All inclusive, 36.7 million individuals were living with it towards the end of 2016 [1]. According to the latest release, India HIV Estimation 2015 report, national adult (15–49 years) HIV pervasiveness in India is evaluated at 0.26% in 2015 [2]. In spite of noteworthy advances in our scientific comprehension of HIV, its prevention and treatment techniques and additionally, years of continuous effort by the global health community, civil society organisations and leading government, excessively numerous individuals living with HIV or at the risk of it. At the same time, a significant portion of affected individuals do not have the opportunity to access care, treatment, and awareness of prevention, and there is still no cure. It remains a major challenge to the scientific community to develop the efficacious treatment with antiretroviral drugs which can annihilate the virus so that individuals with HIV can experience healthy life and reduce the probability of transmitting the infection to others.

HIV is a steady infection which specially targets activated CD4+ T cells, which are indispensable components of the human immune system, causing AIDS. A tainted CD4+ T-cell cannot satisfy its capacity in the immune system, turns into an infection manufacturing plant, making numerous HIV duplicates. The immune system of a patient cannot work satisfactorily with a low level of CD4+ T-cells. In current clinical immunology, an HIV patient is confirmed to have AIDS when the patient has fewer than 200 CD4+ T-cells per mm^3 of blood [3, 4].

HIV treatment can be considered effectual as per recommendation of U.S. HIV/AIDS treatment guidelines on the use of antiretroviral agents in HIV infected grown-ups and young people if it can decrease the viral load by 90% in <2 months and keep on suppressing it to below 50 copies/ml of plasma in less than half year [5]. A significant amount of growth has been noticed in the development of treatment procedure through medications of HIV infected patients, resulting in the reduction of HIV prevalence rates.

Antiretroviral therapy (ART) is medication that treats HIV. ART attempts to disturb the pathogenesis of the virus such that HIV-related symptoms are arrested and a certain level of immunity is recovered which leads to the normal life of infected individuals [1]. Thus, ART can be viewed as a control strategy applied to ensure recovery. As a result, ART makes an effort to reduce HIV load and it usually leads to quick recuperation to a reasonable level of CD4+ T cell count (>200 cells/mm^3) in the peripheral blood [6]. The available antiretroviral drugs are categorised namely, reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) which slow down the replication of the virus and prompt a quick decrease in viral plenitude. The mechanism of RTIs to prevent new HIV infection is by interrupting the conversion of viral RNA into DNA inside of T cells. The number of virus particles created by actively-infected T cells is reduced by PIs [7]. From a system theoretic point of view, these families of drugs can be thought as independent control inputs. Highly active ART, the most predominant treatment methodology, which comprises of the utilisation of multiple anti-HIV drugs, is effective to suppress the virus count of infected individuals to a predefined level. The infected person is recovered slowly and their life is prolonged because this treatment methodology can maintain the CD4+ T cell count at an acceptable level [7]. Thus, the biomedical and control engineering field has gradually enhanced its interest in the development of suitable control strategies to combat the disease such as AIDS and many works in this direction have been reported in the literature.

In the recent past, there have been a significant amount of works focused on proposing dynamic models of the HIV infection so that a model-based control strategy can be developed [6–13]. Mathematical modelling has a notable contribution to understanding HIV pathogenesis along with the design of the treatment scheme. The HIV infection process has been modelled mathematically in [6–13] which reflects the complex interactions among the HIV, aetiological agent for AIDS, CD4+ T cells, and antiretroviral drugs. The comprehension of how diseases spread and contaminate individuals plays a pivotal role to reinforce the mathematical models and to develop new methodologies for controlling the HIV proliferation and infection [7, 9, 10]. In the

literature, a wide variation in the models of HIV dynamics with different levels of complexity/details can be found but a basic element based on which all the models are built is prey/predator model. In [7, 9, 10], a third-order non-linear state space model is found, which characterise the biological phenomenon during the acute phase of HIV infection. This model consists of three state variables as the variation of the population of healthy CD4+ T cells, the infected population of CD4+ T cells, which produce new virion and the concentration of the HIV particles over time and the efficacy of the drugs, are considered as two inputs. In this work, we have considered the third-order non-linear model of HIV dynamics that captures the time rate of healthy cells, infected CD4+ T cells and the number of HIV viruses.

The inherent non-linearity involved with the HIV model, the uncertainty in the parameters and external disturbances present in the model made it not only a difficult feedback control problem but also it becomes an interesting and challenging research problem.

In [9], a state feedback control is proposed based on the linearised model of HIV/AIDS to decrease the viral load. The paper [14] has addressed the problem of controlling the predator–prey-like model of HIV based on backstepping technique. To reduce the viral load to an undetectable level, continuous time feedback control strategies are used in [10, 15, 16]. In [17], a fuzzy mathematical model of HIV dynamic is proposed and they studied a fuzzy optimal control problem minimising both the viral load and drug costs. The controller based on feedback linearisation is designed to control the viral load in [10, 18]. However, the classical feedback linearisation strategies are not robust. The exact cancellation of non-linearities is not possible to achieve in the presence of model uncertainties. Hence the above-mentioned results may not produce desired results when parametric uncertainties are present in the HIV/AIDS model. In [18], a two-loop robust controller is proposed to deal with uncertainties in the parameter of the HIV infection model but they failed to achieve the robustness with all the parameters of the model. An output feedback method is designed in [19] for antiretroviral drug therapy to control the immune response. The non-linear optimal control framework is utilised to determine the optimal methodology for administering anti-viral medication therapies to fight HIV infection in [20, 21]. In [22], model predictive control tools are applied to the model of HIV/AIDS to determine when a full dose or no medication is allowed. In [23], they investigated a control systems analysis on HIV infection dynamics and the intake of drug which is considered as an impulsive control input to enhance the immune response. The paper [24] assesses the control of HIV by the immune response and a dynamical condition for immunity is formulated from the reachability paradigm of variable structure control theory. A non-linear PI-type control strategy is designed in order to minimise the HIV concentration in blood plasma, via medical drug injection, under the framework of bounded uncertain input disturbances in [25].

The parametric uncertainties in the HIV/AIDS model are inevitable because the parameters of the HIV/AIDS model are highly affected by the patient's infection condition. The uncertainties affecting the HIV/AIDS model are crucial for the analysis and control in order to find successful drug administration therapy. These uncertainties arise from unknown external disturbances, process parameters, and parasitic/modelled dynamics. As a result, some of the reported control strategies may not achieve robust performance in the presence of uncertainties and for a wide range of operating conditions.

In this proposed work, the control objective is to reduce the concentration of infected CD4+ T cells to the predefined level in the presence of parametric uncertainties and external disturbances. Since the model is highly non-linear and uncertainties are present, it is difficult to control the viral load to an undetectable level by using the conventional control strategies. To address this problem, sliding mode control (SMC), a robust control strategy can be applied. It has been proven to be an effective control strategy to reject matched nonlinearities, disturbances, and perturbations [26]. The main technical characterisation of an SMC is to force the system state trajectories onto some predefined sliding manifolds (linear sliding surface, integral sliding surface, and terminal sliding surface) by applying a discontinuous control, such that the desired performance can be achieved such as stability, tracking ability, and disturbance rejection capability. From a practical perspective, discontinuous control could introduce unwanted oscillations, known as the chattering, that could lead to unwanted effects [27]. Various solutions exist in the literature to alleviate the problem of unintended oscillations and chattering in SMC but higher order sliding mode (HOSM) control has been widely used to mitigate the chattering phenomenon [28]. In order to reduce the detrimental effect of chattering and to retain advantages of the classical sliding mode approach such as robustness, simplicity, and finite time convergence, a class of SMC algorithms, called the second-order SMC algorithm, has been proposed in recent times [28]. The super twisting controller (STC), a popular control strategy in the family of second-order SMC is used to control systems of relative degree one. The relative degree would be defined with the number of successive differentiation of output until the control appears in the output equation. Relative degree r means that the control input first appears explicitly in the rth total derivative of output. In order to implement the STC for the relative degree r, we need to know the $(r-1)$th derivative of the sliding variable. To estimate the $(r-1)$th derivative of the sliding variable, the robust exact differentiator is proposed in [29].

There are several reported works related to human diseases being controlled by sliding mode techniques. A non-linear robust adaptive SMC strategy is presented for the influenza epidemics in the presence of model uncertainties in [30]. A non-linear robust adaptive Lyapunov-based control strategy was designed in [31] for the antiviral drug therapy of the hepatitis B virus infection with different cases of uncertainties. SMC based on the super-twisting algorithm (STA) stabilises the blood glucose concentration of a diabetic patient at the desired level [32, 33]. Motivated by the recent developments, the very first time STA controller and differentiator is proposed for an HIV infection model with parametric uncertainties and external disturbances. Thus, the treatment goal of this study is to reduce the concentration of infected CD4+ T cells to the desired value in the presence of parameter uncertainties and external disturbances.

The contributions are summarised as follows:

- An uncertain third-order non-linear model of HIV infection has been considered here and the uncertainties are considered in all the model parameters along with the external disturbances.
- The robust control strategy based on STA along with a robust exact differentiator has been designed for the HIV infection model based on output information only. The available output of this model is the total number of CD4+ T cells in blood samples. From a practical point of view, this proposed control technique based on output-feedback is effective because other states of the model are not available for measurement.

This paper is organised as follows: Section 2 describes the details of the mathematical model of HIV infected individuals being treated with ART. The control objective and the analytic background of the proposed control algorithm are described in Section 3. The design steps and analysis of the STC and differentiator are formulated in Section 4. Section 5 shows all supporting simulation results and discussion for proposed work and some concluding remarks are presented in Section 6.

2 Dynamic model of HIV infection

The non-linear dynamical equation of HIV infected individuals being treated with ART can be represented as [7]

$$\begin{aligned}\frac{\mathrm{d}x_1}{\mathrm{d}t} &= s - dx_1 - (1-u)\beta x_1 x_3 + \gamma_1(t),\\ \frac{\mathrm{d}x_2}{\mathrm{d}t} &= (1-u)\beta x_1 x_3 - \mu_2 x_2 + \gamma_2(t),\\ \frac{\mathrm{d}x_3}{\mathrm{d}t} &= (1-u_2)\kappa x_2 - \mu_1 x_3\,.\end{aligned} \tag{1}$$

Table 1 Nominal values of parameters of HIV model

Parameter	Description	Typical value and units
t	Time	days
s	source term for healthy CD4+ T cells	$295\,\text{cells}/(\text{mm}^3 \times \text{day})$
d	death rate of healthy CD4+ T cells	0.182/day
β	infectivity rate of free virus particles	$3.89 \times 10^{-6}\,\text{ml}/(\text{copy} \times \text{day})$
μ_2	death rate of infected CD4+ T cells	1.02/day
κ	rate of virus produced per infected CD4+ T cells	$5890\,\text{copies} \times \text{mm}^3/\text{cell} \times \text{ml} \times /\text{day})$
μ_1	death rate of virus	24/day

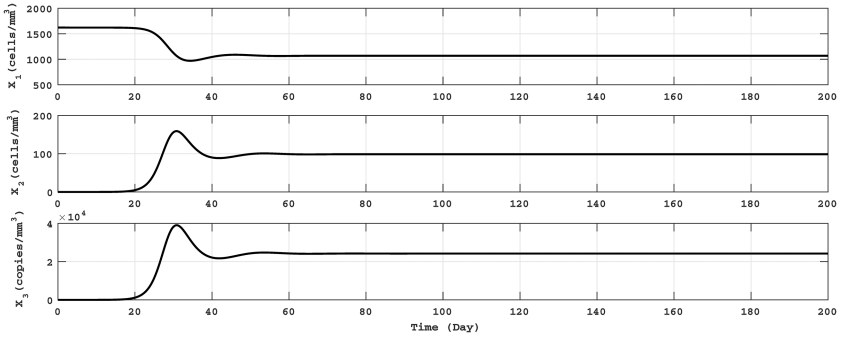

Fig. 1 *Open loop simulation of the progression of the HIV disease*

The state variables are the number of healthy CD4+ T cells in cells/mm^3 (x_1), the number of HIV-infected CD4+ T cells producing new virion in cells/mm^3 (x_2) and the concentration of HIV free virion in copies/mL (x_3). The healthy CD4+ T cells are produced by the thymus at a rate s and die at a rate d. The healthy CD4+ T cells are infected at a rate of β. The infected CD4+ cells result from the infection of healthy CD4+ cells and die at a rate of μ_2. HIV-infected CD4+ T cells produce new virion at a rate of κ and are cleared at a rate of μ_1. As in [8], for a particular HIV infected patient, these six biological rates are positive and assumed to be constant. The nominal values and their corresponding unit of these parameters are listed in Table 1. The functions $u(t)$ and $u_2(t)$ represent the two major categories of antiretroviral drugs to combat HIV namely RTIs, and PIs, respectively. They represent the effectiveness of two types of drugs, i.e. they are unit-less real numbers between 0 and 1. From the point of view of control engineering, the action of antiretroviral treatment will be considered as a control action, which helps to regulate HIV infection. Antiretroviral treatment is said to be effective when it reduces and retain the HIV virus count below the threshold of 50 HIV RNA copies/ml. The $\gamma_1(t)$ represents the immune system fluctuation of the immunal effect of a co-infection [7] and $\gamma_2(t)$ can be thought as the contribution of the reservoir to actively infected CD4+ T cells [34]. These additional terms which are added can be thought as external disturbances to the system. The output available for measurement of system (1) is assumed to be

$$y(t) = x_1 + x_2, \tag{2}$$

where $y(t)$ is the total number of CD4+ T cells in blood samples collected from patients, which can be measured by flow cytometry [24].

Assumption 1: The single application of an RTI is considered as the control input which helps to reduce the HIV infection and this leads to $u_2 = 0$.

With Assumption 1, (1) and (2) can be rewritten in the following form:

$$\begin{aligned}\begin{pmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\end{pmatrix} &= \begin{pmatrix}s - dx_1 - \beta x_1 x_3\\ \beta x_1 x_3 - \mu_2 x_2\\ \kappa x_2 - \mu_1 x_3\end{pmatrix} + \begin{pmatrix}\beta x_1 x_3\\ -\beta x_1 x_3\\ 0\end{pmatrix} u\\ &\quad + \begin{pmatrix}1 & 0\\ 0 & 1\\ 0 & 0\end{pmatrix}\begin{pmatrix}\gamma_1(t)\\ \gamma_2(t)\end{pmatrix},\end{aligned} \tag{3}$$

$$y = x_1 + x_2\,. \tag{4}$$

The equilibrium points of the nominal model (with nominal parameters of the system and external disturbances $\gamma_1(t) = \gamma_2(t) = 0$) are essential in the design of the proposed controller. With $u = 0$, means without drug treatment, the nominal model (3) has the following two equilibrium points with their numerical values:

$$\left(\frac{s}{d}, 0, 0\right) =: X_{\text{h}} = (1621, 0, 0) \tag{5}$$

and

$$\begin{aligned}\left(\frac{\mu_1\mu_2}{\beta\kappa}, \frac{s}{\mu_2} - \frac{d\mu_1}{\beta\kappa}, \frac{\kappa s}{\mu_1\mu_2} - \frac{d}{\beta}\right) &=: X_{\text{inf}}\\ &= (1068, 98.57, 24192)\,.\end{aligned} \tag{6}$$

Obviously, X_{h} and X_{inf} represent the healthy and infected persons, respectively. For the nominal system with the parameter values in Table 1 and without control $u = 0$ (open loop response) in (3), a typical disease progression can be simulated with the initial condition $[1621, 0, 1]^{\text{T}}$, as shown in Fig. 1. The numerical values of X_{inf} will be considered as the initial condition in the simulation of closed loop system response with controllers.

To calculate the desired equilibrium point $x^d = \begin{pmatrix}x_1^d & x_2^d & x_3^d\end{pmatrix}^{\text{T}}$ for the nominal system, under control input $u = u_{ss}$ with $x_2^d = r_0$ for a given $r_0 \in \mathbb{R}_+$, $\dot{x}_1^d = \dot{x}_2^d = \dot{x}_3^d = 0$ and (3) result in

$$0 = s - dx_1^d - \beta x_1^d x_3^d + \beta x_1^d x_3^d u_{ss}, \tag{7}$$

$$0 = \beta x_1^d x_3^d - \mu_2 r_0 - \beta x_1^d x_3^d u_{ss}, \tag{8}$$

$$0 = \kappa r_0 - \mu_1 x_3^d. \tag{9}$$

Using (7)–(9), the following relation can be derived:

$$x_1^d = \frac{s - \mu_2 r_0}{d}, \tag{10}$$

$$x_3^d = \frac{\kappa}{\mu_1} r_0, \tag{11}$$

$$u_{ss} = 1 - \frac{\mu_1 \mu_2 d}{\beta \kappa (s - \mu_2 r_0)}. \tag{12}$$

The control objective is to achieve $x_1 = x_1^d$, $x_2 = x_2^d = r_0$, and $x_3 = x_3^d$ in the presence of external disturbances and parametric uncertainties, which is discussed in the following section.

3 Control objective

This study intends to design a robust controller based on the STA to reduce the viral load by 90% in 2 months after treatment begins, and to maintain it below 50 copies/Ml after a half year, as per recommendation by the U.S. HIV/AIDS treatment guidelines [2]. From (11) and Table 1, $x_2^d = (\mu_1/\kappa)x_3^d = 0.204$. The treatment objective of this work is to suppress the concentration of infected CD4+ T cells to $r_0 (0 < r_0 \leq 0.2)$ cells/mm^3, which is a more stringent condition compared to the guidelines, using only the output information, the measurement of total CD4+ T cell concentrations, in the presence of parameter uncertainties and external disturbances. The control objective is to maintain $x_1 = x_1^d$ and $x_2 = x_2^d = r_0$ in the presence of external disturbances and parametric uncertainties. So the output variable can be defined as

$$\sigma = (x_1 - x_1^d) + (x_2 - x_2^d). \tag{13}$$

Now the task is to design a robust finite-time output-feedback tracking controller $u = \Psi(\sigma, \dot{\sigma})$, which can make $\sigma = \dot{\sigma} = 0$ in the presence of uncertainties. The analytical background related to the design of such a controller is as follows:

Consider a single-input single-output nonlinear system of the form as

$$\begin{aligned} \dot{x} &= f(x) + g(x)u, \\ \sigma &= \sigma(x), \end{aligned} \tag{14}$$

where $x \in \mathbb{R}^n$ are the state variables; $u \in \mathbb{R}$ are the manipulated input variables; $\sigma \in \mathbb{R}$ is a smooth scalar output. The output σ is measured in real-time. Let the vector fields $\boldsymbol{f}(x)$, $\boldsymbol{g}(x)$ be smooth but uncertain, and $\sigma(x)$ be unknown smooth functions, defined on an open set in $\mathbb{R}^n$. The uncertainties in system parameters restrict immediate transformation of (14) to any normal form with the help of standard approaches based on the information of f, g and σ.

Definition 1: The number r represents the relative degree of the output σ of the system (14) with respect to the input u at the point x_0 if the conditions [35, 36]

$$\begin{aligned} &\mathscr{L}_g \mathscr{L}_f \sigma(x) = \mathscr{L}_g \mathscr{L}_f^2 \sigma(x) = \cdots = \mathscr{L}_g \mathscr{L}_f^{r-2} \sigma(x) = 0, \\ &\mathscr{L}_g \mathscr{L}_f^{r-1} \sigma(x) \neq 0 \end{aligned} \tag{15}$$

hold in the neighbourhood of the point x_0. Here $\mathscr{L}_g, \mathscr{L}_f$ denote the Lie derivatives.

If system (14) possesses a relative degree r, the input–output dynamics can be represented as

$$\sigma^{(r)} = \mathscr{L}_f^r \sigma(x) + \mathscr{L}_g \mathscr{L}_f^{r-1} \sigma(x) u. \tag{16}$$

Let $\xi = [\sigma, \dot{\sigma}, \ldots, \sigma^{(r-1)}]^{\mathrm{T}}$, then it is always possible [35] to define a vector $\eta \in \mathbb{R}^{n-r}$ such that the map

$$x = \Phi(\xi, \eta) \tag{17}$$

is a diffeomorphism on $\mathbb{R}^n$ and the η dynamics, which are referred to as the 'internal dynamics'/ 'zero dynamics' [36], can be expressed as follows:

$$\dot{\eta} = q(\xi, \eta). \tag{18}$$

The system is said to be fully linearisable if $r = n$, which indicates there are no internal dynamics. The design of a robust output-feedback tracking controller be achieved under the following assumption:

Assumption 2: The reduced (zero) dynamics of the system (18) is asymptotically stable.

Assumption 3: The term $\mathscr{L}_f^r \sigma(x)$ and the gain of the controller, $\mathscr{L}_g \mathscr{L}_f^{r-1} \sigma(x)$, of the input–output dynamics (16) are globally bounded and Lipschitz.

According to Assumption 2, to design the finite-time output-feedback tracking controller, the internal dynamics of the HIV infection system must be stable, which is analysed in the following section.

3.1 Asymptotic stability of reduced (zero) dynamics of HIV system

The zero dynamics stability is analysed for the nominal model of the HIV dynamics. Assuming $\gamma_1(t) = \gamma_2(t) = 0$ in (3) and comparing (14) and (3), the following can be written

$$f(x) = \begin{pmatrix} s - dx_1 - \beta x_1 x_3 \\ \beta x_1 x_3 - \mu_2 x_2 \\ \kappa x_2 - \mu_1 x_3 \end{pmatrix} \text{ and } g(x) = \begin{pmatrix} \beta x_1 x_3 \\ -\beta x_1 x_3 \\ 0 \end{pmatrix}.$$

Differentiating output (13) with respect to t once, the following can be written:

$$\dot{\sigma} = \mathscr{L}_f \sigma(x) + \mathscr{L}_g \sigma(x) u, \tag{19}$$

where $\mathscr{L}_f \sigma(x) = s - dx_1 - \mu_2 x_2$ and $\mathscr{L}_g \sigma(x) = 0$. The control coefficient is identically zero for the first derivative of the output. So differentiating (19) once again we get

$$\ddot{\sigma} = \mathscr{L}_f^2 \sigma(x) + \mathscr{L}_g \mathscr{L}_f \sigma(x) u, \tag{20}$$

where $\mathscr{L}_f^2 \sigma(x) = -d(s - dx_1 - \beta x_1 x_3) - \mu_2(\beta x_1 x_3 - \mu_2 x_2)$ and $\mathscr{L}_g \mathscr{L}_f \sigma(x) = \beta(\mu_2 - d) x_1 x_3 \neq 0$ for $\{x \in \mathbb{R}^3 | x_1 x_3 \neq 0\}$. According to definition 1, the relative degree of the system with respect to output $\sigma(x)$ is 2 in $\{x \in \mathbb{R}^3 | x_1 x_3 \neq 0\}$. Using the relation (20), the state feedback control law

$$u = -\frac{\mathscr{L}_f^2 \sigma(x)}{\mathscr{L}_g \mathscr{L}_f \sigma(x)} + v \tag{21}$$

yields a system

$$\ddot{\sigma} = v. \tag{22}$$

The system order $n = 3$ and the relative degree of the system is 2, which is strictly less than the system order. This results in the existence of internal dynamics and to analyse its evolution, the system must be represented in the normal form.

In order to find the normal form, we set

$$\xi_1 = \phi_1 = \sigma(x), \tag{23}$$

$$\xi_2 = \phi_2 = \mathscr{L}_f \sigma(x). \tag{24}$$

Then ϕ_3 is selected such that the condition $\mathscr{L}_g \phi_3 = 0$. The one such choice is $\eta = \phi_3 = x_3 - x_3^d$. Now we can define a transformation

$$z = \Phi(x) = \begin{pmatrix} \xi_1 \\ \xi_2 \\ \eta \end{pmatrix} = \begin{pmatrix} x_1 + x_2 - x_1^d - x_2^d \\ s - dx_1 - \mu_2 x_2 \\ x_3 - x_3^d \end{pmatrix} \tag{25}$$

whose Jacobian matrix

$$\frac{\partial \Phi}{\partial x} = \begin{pmatrix} 1 & 1 & 0 \\ -d & -\mu_2 & 0 \\ 0 & 0 & 1 \end{pmatrix} \tag{26}$$

is non-singular for all $x \in \mathbb{R}^3$. Using (23)–(25) and (20), system (14) can be represented in the normal form:

$$\begin{aligned} \dot{\xi}_1 &= \xi_2, \\ \dot{\xi}_2 &= \mathscr{L}_f^2 \sigma(x) + \mathscr{L}_g \mathscr{L}_f \sigma(x) u, \\ \dot{\eta} &= -\mu_1 \eta + \frac{\kappa(\xi_2 + d\xi_1)}{d - \mu_2}, \end{aligned} \tag{27}$$

The detailed derivation of (27) is given in Appendix.

In order to ensure $\sigma = \dot{\sigma} = 0$ for all times, the system must be confined to the subset

$$\Omega^* = \{x \in \mathbb{R}^3 : \sigma(x) = \mathscr{L}_f \sigma(x) = 0\}. \tag{28}$$

In another way, it can be written as

$$\Omega^* = \{x \in \mathbb{R}^3 : \xi_1 = \xi_2 = 0\} \tag{29}$$

and this can be achieved by zeroing the input. For the HIV system, the zero dynamic is one-dimensional and can be easily obtained by replacing the constraints $\xi_1 = \xi_2 = 0$ (which define the manifold $\Omega^\star$) in the system equations (27). Imposing these constraints one can obtain

$$\dot{\eta}(t) = -\mu_1 \eta(t). \tag{30}$$

The solution to (30) is $\eta(t) = \exp(-\mu_1 t)\eta(0)$, which indicates that the internal dynamics is exponentially stable for any initial condition $\eta(0)$.

Remark 1: As $\lim_{t \to \infty} \eta(t) = 0$ which ensures $x_3 = x_3^d$.

4 Design and analysis of STC and differentiator

The controller based on STA is one of the popular controllers in the family of higher order sliding mode controller (HOSMC) presented in [28]. The advantage of this control strategy is that only with the knowledge of the relative degree of the system and appropriate bounds for a few expressions, the controller can be designed. So it can be thought as a black-box oriented control. Thus STA presents an alternative attractive approach to control the HIV dynamics to reduce the viral load by 90% in 2 months after treatment starts and to suppress it to below 50 copies/ml after half year. The system dynamics is inherently non-linear and with this non-linear control, the stability and performance can be ensured in the whole operating range of the system. Its design does not depend on the model's parameters and external disturbances, which guarantees the improved robustness with respect to parameter uncertainties and external disturbances.

So more precisely our control objective is to make $\sigma = 0$. This guarantees $x_1 = x_1^d$ and $x_2 = x_2^d = r_0$ in the presence of parameter uncertainties and external disturbances. The dynamics of σ is given in (20) which indicates that the relative degree of the output variable is 2. The STA is a continuous control algorithm for the system with a relative degree, $r = 1$ in the presence of bounded uncertainties. To deal with this situation, the methodology of designing the controller for this problem involves three steps.

4.1 Step 1: sliding manifold design

To ensure the relative degree 1, the sliding variable is designed as

$$S = \dot{\sigma} + c_0 \sigma, \tag{31}$$

where the coefficient $c_0 \in \mathbb{R}_+$ is chosen such that (31) has the desired behaviour. With the control based on STA enforces $S = 0$ in finite time, which ensures that σ will converge to zero asymptotically This guarantees the desired objective $x_1 = x_1^d$ and $x_2 = x_2^d$.

4.2 Step 2: design of robust exact differentiator to estimate the sliding variable

The first derivative of σ is required to implement the control and which is not available and must be evaluated by means robust exact differentiator which is robust against the measurement noise and having the property of finite time convergence. Recently, in [29], it is proposed that the arbitrary order differentiator based on higher-order sliding modes is an effective, yet robust, solution. Here the input/output relative degree is $r = 2$, only the first derivative of σ needs to be estimated under the assumption that the first derivative of σ having a known global Lipschitz constant $C_2 > 0$, and the first-order differentiator is as follows:

Consider the auxiliary system $\dot{q}_0(t) = \upsilon$, where υ is a control input. Let $\varepsilon(t) = q_0(t) - \sigma(t)$ and let the task be to keep $\varepsilon(t) = 0$ in a second-order sliding mode. In that case $\varepsilon(t) = \dot{\varepsilon}(t) = 0$, which means that $q_0(t) = \sigma(t)$ and $\dot{\sigma}(t) = \upsilon$. The system can be rewritten as

$$\dot{\varepsilon}(t) = -\dot{\sigma}(t) + \upsilon; \ |\ddot{\sigma}(t)| < C_2. \tag{32}$$

The function $\dot{\sigma}(t)$ cannot be smooth, but its derivative $\ddot{\sigma}(t)$ exists almost everywhere due to the Lipschitz property of $\dot{\sigma}(t)$. The resulting form of the differentiator is

$$\begin{aligned} \dot{q}_0(t) = \upsilon &= -\rho_0 |\varepsilon(t)|^{1/2} \operatorname{sign}(\varepsilon(t)) + q_1(t), \\ \dot{q}_1(t) &= -\rho_1 \operatorname{sign}(\varepsilon(t)), \end{aligned} \tag{33}$$

where both υ and q_1 can be taken as the differentiator outputs and the tuning conditions are $\rho_1 > C_2$, $\rho_0 > 4C_2((\rho_1 + C_2)/(\rho_1 - C_2))$, where C_2 is a Lipschitz constant of $\dot{\sigma}(t)$.

4.3 Step 3: controller design

Taking the time derivative of (31) and using (19) and (20) the sliding dynamics can be written as

$$\begin{aligned} \dot{S} &= \ddot{\sigma} + c_0 \dot{\sigma} \\ &= \mathscr{L}_f^2 \sigma(x) + \mathscr{L}_g \mathscr{L}_f \sigma(x) u + c_0 \mathscr{L}_f \sigma(x) \\ &= \mathscr{F}(\sigma, t) + \mathscr{G}(\sigma, t) u, \end{aligned} \tag{34}$$

where $\mathscr{F}(\sigma, t) = \mathscr{L}_f^2 \sigma(x) + c_0 \mathscr{L}_f \sigma(x)$ and $\mathscr{G}(\sigma, t) = \mathscr{L}_g \mathscr{L}_f \sigma(x)$. Due to the heavy uncertainties in system parameters, measurement and modelling errors and external disturbances, the exact values of the functions $\mathscr{F}(\sigma, t)$ and $\mathscr{G}(\sigma, t)$ are unknown. With these uncertainties and $u = \mathscr{G}^{-1}(\sigma, t) u_T$ (to express the sliding dynamics in regular form), where u_T is the controller input based on STA, (34) can be rewritten as

$$\dot{S} = u_T + \mathscr{F}(\sigma, t) + \tilde{\mathscr{F}}(\sigma, t), \tag{35}$$

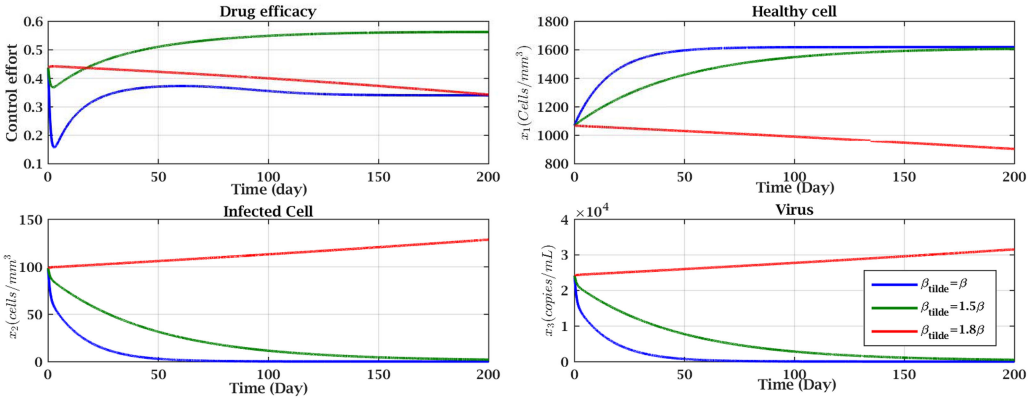

Fig. 2 *Effectiveness of the controller based on feedback linearisation with uncertainty in the parameter β*

where function $\mathcal{F}$ represents the nominal or undisturbed design model, and function $\tilde{\mathcal{F}}$ takes into account measurement, modelling error, uncertainties in the parameters, and external disturbances.

Now, a two-component control action based on STA is proposed as $u_T = u_{eq} + u_{st}$, where u_{eq} is the equivalent control for system (34) and u_{st} is designed using STA.

The expression of u_{eq} is computed from the undisturbed system (35) (i.e. $\tilde{\mathcal{F}}(\sigma, t) = 0$). It is obtained by solving u_T in the algebraic equation $\dot{S} = 0$, on the sliding surface (i.e. with $\sigma = 0$). The expression for u_{eq} is

$$\begin{aligned} u_{eq} = & -\mathcal{F}(0,t) \\ = & -d(s - dx_1^d - \beta x_1^d x_3^d) \\ & -\mu_2(\beta x_1^d x_3^d) - \mu_2 x_2^d) + c_0(s - dx_1^d - \mu_2 x_2^d)\,. \end{aligned}$$

Using this formula, (35) can be written as

$$\dot{S} = u_{eq} + u_{st} + \mathcal{F}(\sigma,t) + \tilde{\mathcal{F}}(\sigma,t) = u_{st} + \tilde{\mathcal{G}}(\sigma,t), \tag{36}$$

where $\tilde{\mathcal{G}}(\sigma,t) = \mathcal{F}(\sigma,t) - \mathcal{F}(0,t) + \tilde{\mathcal{F}}(\sigma,t)$.

Assumption 4: The uncertain term $\tilde{\mathcal{G}}(\sigma,t)$ and its time derivative $\dot{\tilde{\mathcal{G}}}(\sigma,t) \in \mathbb{R}$ are upper bounded by known constants, $\rho, \bar{\rho} \in \mathbb{R}_+$ as $\left|\tilde{\mathcal{G}}(\sigma,t)\right| \le \rho$, $\left|\dot{\tilde{\mathcal{G}}}(\sigma,t)\right| \le \bar{\rho}$.

Now, the control action expression for the term u_{st} is

$$u_{st} = -k_1 \lceil S \rfloor^{1/2} + \varphi, \tag{37}$$

$$\dot{\varphi}_2 = -k_2 \mathrm{sign}(S), \tag{38}$$

where $k_1, k_2 \in \mathbb{R}^+$ are constants, and $\lceil S \rfloor^{1/2} = |S|^{1/2}\mathrm{sign}(S)$.

Substituting this control law in an open loop system (36), the closed loop system can be obtained by

$$\begin{aligned} \dot{S} &= -k_1 \lceil S \rfloor^{1/2} + \varphi + \tilde{\mathcal{G}}(\sigma,t), \\ \dot{\varphi} &= -k_2 \mathrm{sign}(S)\,. \end{aligned} \tag{39}$$

By means of the transformation

$$z = \tilde{\mathcal{G}}(\sigma,t) - k_2 \int_0^t \mathrm{sign}(S)\,\mathrm{d}\tau \tag{40}$$

system (39) may be rewritten as

$$\dot{S} = -k_1 \lceil S \rfloor^{1/2} + z, \tag{41}$$

$$\dot{z} = -k_2 \mathrm{sign}(S) + \dot{\tilde{\mathcal{G}}}(\sigma,t)\,. \tag{42}$$

With Assumption 4, the perturbation term is bounded, i.e. $\left|\dot{\tilde{\mathcal{G}}}(\sigma,t)\right| \le \bar{\rho}$. A necessary condition of convergence is $k_2 > \bar{\rho}$, if, in addition, we select k_1 sufficiently large, the controller (37) guarantees the existence of a second-order sliding mode $S = \dot{S} = 0$ in system (39). In [28, 37], a Lyapunov function is proposed that permits the design of k_1 and k_2, which also provides the estimation of convergence time of sliding variable.

Theorem 1: Consider the closed loop systems (41) and (42). Then the closed loop dynamics is finite time stable if the gains are selected such that $k_1 > 0$ and $k_2 > \bar{\rho}$ [37].

Proof: Choosing the Lyapunov function as $V(\Theta) = \Theta^T P \Theta$, the trajectories of the closed loop systems (41) and (42) will converge to the origin in finite time smaller than t [28, 37]

$$t = \frac{2}{\xi} V^{1/2}(\Theta(0)), \tag{43}$$

where $\Theta^T = \left[|S|^{1/2}\mathrm{sign}(S)\ z\right]$ and $\xi = \lambda_{min}^{1/2}(P)\lambda_{min}(Q)/\lambda_{max}(P)$ for any positive and symmetric definite matrices $\boldsymbol{P}$ and $\boldsymbol{Q}$. The gains k_1 and k_2 are enough to bring $S \equiv 0$ in finite time. This ends the proof. □

5 Simulation results

In order to validate the proposed controller, through simulation it has been shown that the controller based on STA provides excellent treatment performance in the presence of parametric uncertainties and external disturbances. Moreover, a comparative analysis of the controller based on the STA and controller based on feedback linearisation is provided.

To investigate the effect of treatment with a controller based on feedback linearisation is designed as in [18] and simulated with the initial condition $X = [1068\ 98.57\ 24192]^T$. It has been assumed that a patient is not receiving treatment for 60 days after infection. If there is no parametric uncertainty in β, it is observed from Fig. 2 that the controller based on feedback linearisation is efficient to reduce the viral load from 50 days and can maintain a steady state value up to 200 days. The performance of this controller deteriorates significantly if there is variation in the only one parameter like β. From this, it can be concluded that the controller based on feedback linearisation is not robust against measurement and modelling error, uncertainties in the parameters, and external disturbances.

In contrast, to ensure the robust performance of the proposed controller, simulation is carried out on ten patients with a wide range of variations in the six systems parameters $s, d, \beta, \mu_1, \mu_2, \kappa$. The ranges of these parameters are chosen as per clinical observations [34]. The ranges of model parameters considered in this work are indicated in Table 2. For simulation purpose, each parameter is varied randomly about its nominal value within the specified range. The controller gains are chosen as $k_1 = 0.25, k_2 = 0.2$. The differentiator gains are selected as $\rho_0 = 12$

Table 2 Range of parameters

Parameter	Range
s	$34.67 \leq s \leq 758.57$
d	$0.045 \leq d \leq 2.1877$
β	$2 \times 10^{-6} \leq \beta \leq 6 \times 10^{-6}$
μ_2	$1 \leq \mu_2 \leq 5.57$
μ_1	$3 \leq \mu_1 \leq 18.8$
κ	$2.4 \times 10^3 \leq \kappa \leq 9.8 \times 10^3$

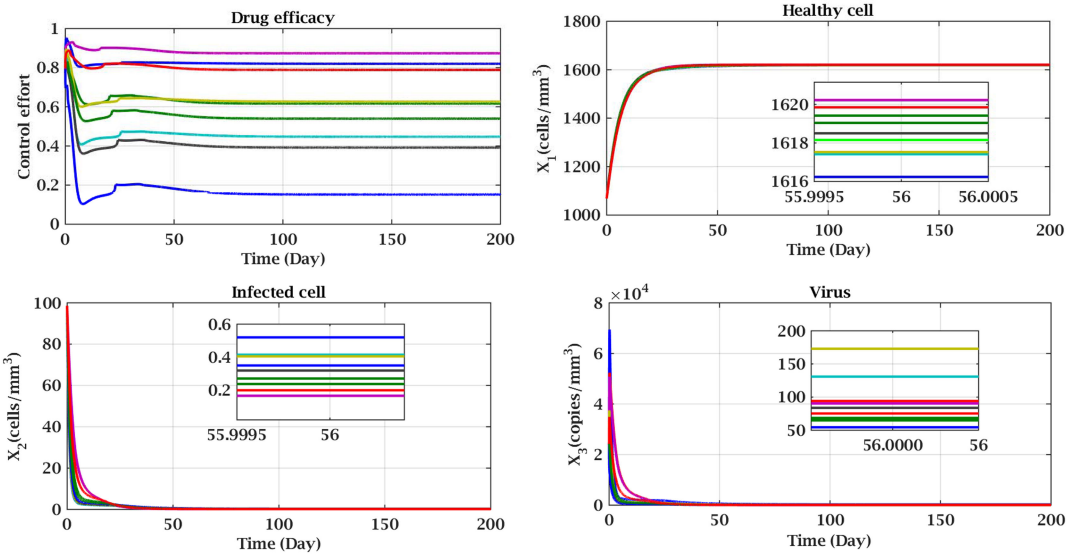

Fig. 3 *Performance of the controller based on STA with uncertainty in all the six parameters*

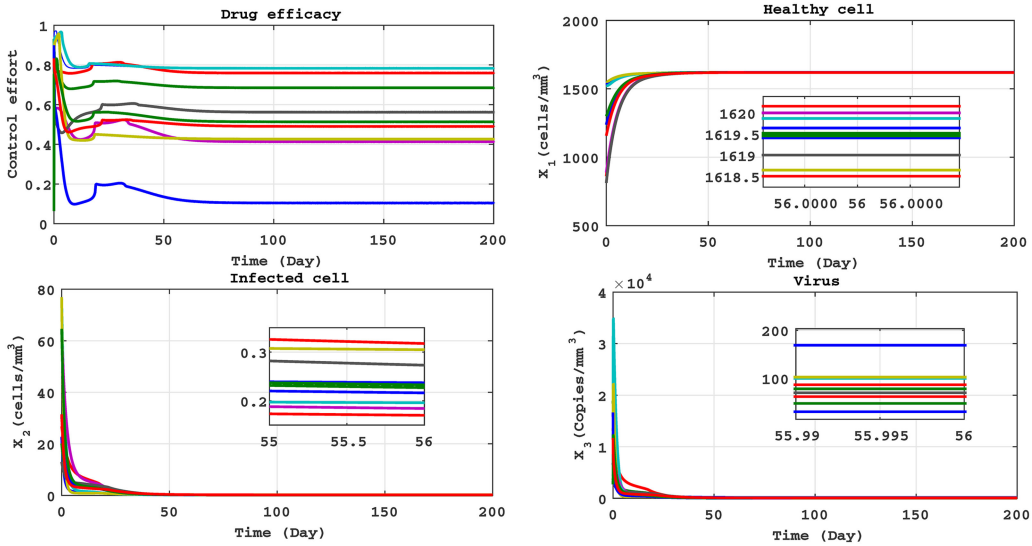

Fig. 4 *Performance of the controller based on STA with different initial conditions and with uncertainty in all the six parameters*

and $\rho_1 = 16$. It can be noticed from the simulation results in Fig. 3 for all ten patients viral load is reduced by 90% in 2 months after treatment starts and it is able to keep below 50 copies/ml after half year. This is achieved in the presence of model parameter uncertainties only. To prove the efficacy of the controller based on STA with respect to various initial conditions, it is shown in Fig. 4 that the treatment goal can be achieved even if there is a random variation in the initial condition. In this work, the initial conditions for the three states $x = [x_{10}, x_{20}, x_{30}]$ are generated randomly in the ranges of $800 \leq x_{10} \leq 1600$, $10 \leq x_{20} \leq 80$ and $1000 \leq x_{30} \leq 22$ as in [18] and simulated for ten patients. Fig. 5 shows the robust performance of STA when all six model parameters are varied randomly and the system model is affected by external disturbances. The external disturbances are considered in the form of $\gamma_i(t) = a_i + b_i \sin t$ for $i = 1, 2$, where a_i and b_i are also varied randomly between 0 and 0.5.

6 Conclusion

HIV treatment, one of the challenging control problems has been discussed. An attempt has been made for the treatment of the disease. To serve this purpose a robust feedback controller based on output information has been designed to control the drug delivery. The continuous HOSM controller based on STA is designed as a feedback controller for the non-linear uncertain HIV system. This controller stabilises the concentration of free virus to an undetectable level. The stabilisation and robustness of the entire system have been achieved in the presence of the external perturbation such as immune system fluctuation, an additional

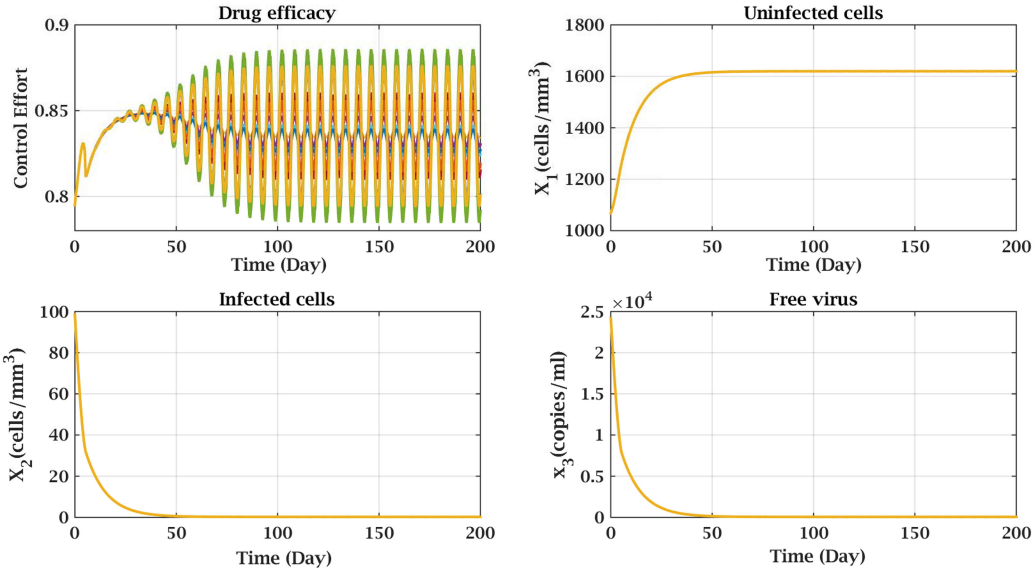

Fig. 5 *Performance of the controller based on STA with uncertainty in all the six parameters and external disturbances*

contribution of infected cells from all viral reservoir processes and model parametric uncertainties. Numerical examples are presented to show the robust high-accuracy performance of the STC. The control effort will be helpful to design drug dosages in AIDS treatment. Also, for future studies, the applicability of the controller in a practical scenario is to be assessed. The drug dosages cannot be administered in a continuous fashion for 200 days as in the example considered. So probably a hybrid model with intermittent continuous drug levels with a period of no drug action is a better model to study in the future. The results obtained are to be verified for the in-vitro environment. Finally, testing the proposed algorithm in-vivo and getting successful results, will be a milestone.

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8 Appendix

8.1 Derivation of normal form

Following is the derivation of (27). Using (25) and (3) with $\gamma_1(t) = \gamma_2(t) = 0$, the derivative of ξ_1 can be written as

$$\dot{\xi}_1 \quad = \dot{x}_1 + \dot{x}_2 = s - dx_1 - \mu_2 x_2 = \xi_2 .$$

Using (24) and (20), the derivative of ξ_2 can be written as

$$\dot{\xi}_2 = \ddot{\sigma}(x) = \mathscr{L}_{\mathrm{f}}^2\sigma(x) + \mathscr{L}_{\mathrm{g}}\mathscr{L}_{\mathrm{f}}\sigma(x)u\,.$$

Using (25), the derivative of η can be written as

$$\begin{aligned}\dot{\eta} = \dot{x}_3 &= \kappa x_2 - \mu_1 x_3\\ &= \kappa x_2 - \mu_1 x_3 + \mu_1 x_3^d - \mu_1 x_3^d\\ &= -\mu_1(x_3 - x_3^d) + \kappa x_2 - \mu_1 x_3^d\\ &= -\mu_1\eta + \kappa x_2 - \mu_1 x_3^d\,.\end{aligned}$$

Using the relation (11), the above relation can be rewritten as

$$\begin{aligned}\dot{\eta} &= -\mu_1\eta + \kappa(x_2 - x_2^d)\\ &= -\mu_1\eta + \frac{\kappa x_2(d-\mu_2) - \kappa x_2^d(d-\mu_2)}{d-\mu_2}\\ &= -\mu_1\eta + \frac{\kappa s + \kappa x_2(d-\mu_2) - \kappa s + \kappa\mu_2 x_2^d - \kappa d x_2^d}{d-\mu_2}\\ &= -\mu_1\eta + \frac{\kappa s + \kappa x_2(d-\mu_2) - \kappa d\dfrac{s-\mu_2 x_2^d}{d} - \kappa d x_2^d}{d-\mu_2}\\ &= -\mu_1\eta + \frac{\kappa s + \kappa x_2(d-\mu_2) - \kappa d x_1^d - \kappa d x_2^d}{d-\mu_2}\\ &= -\mu_1\eta + \frac{\kappa(s - dx_1 - \mu_2 x_2) + \kappa d(x_1 - x_1^d) + \kappa d(x_2 - x_2^d)}{d-\mu_2}\\ &= -\mu_1\eta + \frac{\kappa(\xi_2 + d\xi_1)}{d-\mu_2}\,.\end{aligned}$$