Prediction of the Containment of HIV Infection by Antiretroviral Therapy - a Variable Structure Control Approach

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Abstract: It is demonstrated that the reachability paradigm from Variable Structure Control (VSC) theory is a suitable framework to monitor and predict the progression of the Human Immunodeficiency Virus (HIV) infection following initiation of antiretroviral therapy. A manifold is selected which characterises the desirable infection-free steady-state. A model of HIV infection together with an associated reachability analysis which considers the action of antiretroviral drugs is used to formulate a dynamical condition for the containment of HIV infection on the desirable manifold. This condition is tested using data from two different HIV clinical trials which contain measurements of the CD4+ T cell count and HIV load in the peripheral blood collected from HIV infected individuals for the six month period following initiation of antiretroviral therapy. The biological rates of the model are estimated using the multi-point identification method and data points collected in the initial period of the trial. Using the parameter estimates and the numerical solutions of the model, the predictions of the reachability analysis are shown to be consistent with the subsequent clinical diagnosis at the conclusion of the trial. The methodology captures the dynamical characteristics of eventual successful, failed and marginal outcomes. The findings evidence that the reachability analysis is an appropriate tool to monitor and develop personalized antiretroviral treatment.

1. Introduction

The Human Immunodeficiency Virus (HIV) is a persistent infection which preferentially targets activated CD4+ T cells, causing Acquired Immune Deficiency Syndrome (AIDS) [34]. Using current experimental facilities, the standard clinical data for diagnosis and monitoring HIV infection in patients are the total number of CD4+ T cells measured by flow cytometry and HIV viral load measured by Polymerase Chain Reaction (PCR) [34, 16, 19]. Experimental studies have demonstrated that the HIV-specific CD8+ T cell response is a major immunological dynamic opposing the spread of infection in the host [9, 11, 25]. This dynamical response can be regarded as a control strategy implemented by the immune system to combat HIV infection in vivo [11, 1] forming a closed-loop system that can be analysed using the tools of control theory.

Antiretroviral therapy (ART) seeks to perturb the pathogenesis of the virus to allow infected individuals to cease exhibiting HIV related symptoms and to recover a certain level of immunity so that the quality of their lives can be improved [34]. Thus, ART can be viewed as a control strategy applied to enforce recovery. In effect, ART attempts to reduce HIV load and this usually leads to recovery to a suitable level of CD4+ T cell count (> 200 cell$/mm^3$) in the peripheral blood [25, 27, 16]. However, this desirable outcome is not always achieved and the design of appropriate ART, the prediction of outcomes using clinical data and the assessment of virologic failure are the

subject of active experimental and mathematical research [37, 31].

Mathematical modelling has contributed significantly to the understanding of HIV pathogenesis along with the design of novel treatment regimes [25]. To allow mathematical models of HIV dynamics to be used as a tool for personalized clinical diagnosis and ART, it is crucial to estimate all the biological rates of the chosen model for each patients [37, 17, 27]. This can be a challenging problem using standard clinical data [37, 17]. A third order Ordinary Differential Equation (ODE) model has been shown to encompass the observed biological characteristics of the acute phase of HIV infection using the variation over time of the population of healthy CD4+ T cells, the infected population of CD4+ T cells which produce new virions along with the concentration of the HIV-1 particles [23]. Using techniques from engineering, it has been shown that the parameters of the model can be estimated from standard clinical data [38, 13]. This method is based on the computation of higher order derivatives of the output measurements to formulate a set of identification equations. Subsequently, a multiple time point (MTP) estimation algorithm using values at different time instants to reduce the need for higher order derivatives of the output measurements has been used to formulate the identification equations [37].

The outcome of a viral infection in a host is classically evaluated using the reproductive ratio R_0 which is defined as the number of new cells that a single infected cell produce at the start of infection when there is no target cell limitation [29] The reproductive ratio is an algebraic combination of biological rates and is used to determine the stability of the equilibrium points of HIV dynamic models [28, 31]. The expression for R_0 is a function of the model parameters and not the states and thus a time-invariant condition for the containment of the infection is formulated. Recent studies argue that the condition for the containment of the infection rather than being static changes during the course of the infection [26, 25, 30]; the immunological requirements may be weaker before the peak of the virus load due to the small number of viral particles at the site of the infection [26]. In addition, the parameters of the HIV model are time varying biological rates [23, 8, 17] and the condition for the containment of HIV infection provided by R_0 is fundamentally not robust to uncertainty in the model and parameters of the HIV infection dynamics. Hence, the framework of the reproductive ratio does not encompass the emerging notion that the condition for the containment of HIV infection in vivo changes during the course of the infection according to changes biological rates, cell population and viral dynamics [26, 25, 30, 31].

In this paper, the Variable Structure Control (VSC) paradigm is used to investigate a dynamical condition for the containment of HIV infection in vivo by antiretroviral therapy. The analysis is conducted on the third order model of HIV dynamics [23] to facilitate comparison of the obtained results with those in the existing literature [29, 27, 31]. The philosophy of VSC allows the control structure to change according to a predefined switching logic to achieve desired performance [32, 10]. In the domain of sliding mode control, a special type of VSC, the dynamics will typically attain a desired steady-state which is defined by a chosen sliding manifold when a so called reachability condition is met [32]. This reachability condition is basically a dynamical condition for the control input to achieve the desired dynamics. When the reachability condition fails to hold, the system will exhibit different dynamics, usually exhibiting a different equilibrium. Formulating appropriate sliding manifolds to represent immunological or therapeutical objectives enables the use of the reachability analysis to provide a dynamical condition for the containment of the infection by the HIV-specific CD8+ response as well as providing a framework to hypothesize therapeutic strategies for individual patients. Unlike the static condition provided by the reproductive ratio, the major contribution of the VSC approach resides in the fact that the reachability analysis provides a dynamical condition for antiretroviral therapy to force HIV infection dynamics in vivo to

reach and maintain the infection-free steady-state. Furthermore, this condition encompasses the nonlinearities of the model and exhibits some robustness properties with respect to parameter and modelling uncertainty. In this paper the dynamical condition for immunity provided by the VSC analysis is tested using standard clinical data collected from HIV infected individuals involved in two different HAART clinical trials [16, 27]. Collectively, the findings demonstrate the reachability analysis to be an alternative framework which provides useful insight to monitor and predict the progression of the infection in vivo along with the performance of antiretroviral therapy.

The paper is organized as follows: Firstly, the HIV model and the reproductive ratio are outlined. In Section 3 a dynamical condition for the containment of HIV infection by antiretroviral therapy is formulated using the reachability paradigm from variable structure control. The clinical data sets used for the study and the method used to estimate the parameters of the model is described and evaluated in Section 4. Section 5 presents the results of simulation experiments conducted to show that the proposed dynamical condition for immunity is a reliable tool for early diagnosis of the outcome of antiretroviral therapy on HIV infection.

2. Mathematical model of HIV infection

The dynamical equations of HIV infection for patients being treated with antiretroviral therapy can be written as:

$$\begin{aligned} \frac{dT}{dt} &= \lambda - \delta_T T - \beta_0 TV + u_1(t) \\ \frac{dP}{dt} &= \beta_0 TV - \mu_1 P - u_1(t) \\ \frac{dV}{dt} &= k_0 P - \mu_2 V - u_2(t) \end{aligned} \tag{1}$$

with $\delta_T < \mu_1$ [20, 23, 37]. The state variables are the number in $cell/mm^3$ of uninfected target CD4+ T cells (T), the number in $cell/mm^3$ of HIV-infected CD4+ T cells producing new virions (P) and the concentration in $RNA\ copies/ml$ of HIV-1 free virions (V). Uninfected CD4+ T cells are produced by the thymus at a rate λ (in $cell/day$) and die at a rate δ_T (in day^{-1}). HIV infects healthy CD4+ T cells at a rate β_0 (in $\mu lvirion/day\ x10^{-3}$). HIV-infected CD4+ T cells produce new virions at a rate k_0 (in $virion/day$) and die at a rate μ_1 (in day^{-1}). HIV free virions are cleared at a rate μ_2 (in day^{-1}) in the peripheral blood. As in [23, 37, 19], these six biological rates are non-negative and assumed to be constant for a given patient. The functions $u_1(t)$ and $u_2(t)$ represent the action of reverse-transcriptase (RT) and protease inhibitor (PT) drugs respectively. The effect of antiretroviral drugs on HIV infection dynamics can be modelled as follows:

$$u_1 = \eta_1 \beta_0 TV \tag{2}$$

$$u_2 = \eta_2 k_0 P \tag{3}$$

where $0 \leq \eta_1 < 1$ and $0 \leq \eta_2 < 1$ are constants related to the efficiency of the deployed RT and PT drugs, assuming that 100 percent drug efficacy cannot be achieved [23, 21]. The action of antiretroviral therapy will be considered from the perspective of control engineering and regarded as a control action which seeks to enforce the containment of the HIV infection. In practice, antiretroviral therapy is declared efficient when it reduces and maintains the HIV viral load in the

peripheral blood stream below the threshold of 50 HIV RNA copies/ml [21]. The available output measurements of (1) are assumed to be

$$y_1(t) = T(t) + P(t); \quad y_2(t) = V(t) \tag{4}$$

where $y_1(t)$ is the total number in $cell/mm^3$ of CD4+ T cells in blood samples collected from patients [16, 27, 17]. This choice is motivated by the information available in the clinical data sets used for later validation of the proposed methodology.

The clinical trial data available relates to the period following the initiation of antiretroviral therapy and thus it is not possible to estimate the values of β_0 and k_0 [17, 16, 19]. Thus $\beta_0(1-\eta_1)$ and $k_0(1-\eta_2)$ i.e the resultant effects in vivo of the uptake of RT and PT drugs respectively will be considered and in the model (1), the following substitutions are made

$$\beta = (1-\eta_1)\beta_0 \tag{5}$$
$$k = (1-\eta_2)k_0 \tag{6}$$

to yield the closed-loop representation

$$\begin{aligned} \frac{dT}{dt} &= \lambda - \delta_T T - \beta TV \\ \frac{dP}{dt} &= \beta TV - \mu_1 P \\ \frac{dV}{dt} &= kP - \mu_2 V \end{aligned} \tag{7}$$

This parametrization of the effects of antiretroviral drugs is as used in previous studies [37, 19, 21]. The model (7) has a trivial equilibrium corresponding to an infection-free steady-state at

$$T_{s0} = \frac{\lambda}{\delta_T}; \quad P_{s0} = V_{s0} = 0 \tag{8}$$

The expression for the non-trivial equilibrium is given by:

$$T_{s1} = \frac{\mu_1\mu_2}{\beta k}; \quad P_{s1} = \tfrac{\lambda}{\mu_1} - \tfrac{\delta_T\mu_2}{\beta k}; \quad V_{s1} = \frac{\lambda k}{\mu_1\mu_2} - \frac{\beta}{\delta_T} \tag{9}$$

This non-trivial equilibrium can represent either an undesirable steady-state corresponding to chronic infection or a desirable steady-state depending on the parameter values [25, 23, 29, 27].

2.1. The reproductive ratio

The reproductive ratio is a static condition used to investigate the stability of the infection-free steady-state (8). This may be computed from the Jacobian of the system (7) and is effectively a condition which must be satisfied for the coefficients of the corresponding characteristic polynomial to produce stable roots [6, 28, 26]. The expression for the reproductive ratio is given by

$$R_0 = \frac{\lambda}{\delta_T}\frac{1}{\mu_1}\frac{k}{\mu_2}\beta \tag{10}$$

The first term is the population size of uninfected CD4+ T cells T at the infection-free steady-state, see (8). The second term is the lifetime of a virus-producing cell. The third term is the number of virus particles produced per infected cell and the final term represents the infection rate for a single virus particle. The infection free steady-state is stable when $R_0 < 1$.

3. A reachability condition to monitor the containment of HIV infection

The sliding mode control paradigm [32, 10] is used to investigate dynamical requirements for the containment of HIV infection in vivo following the initiation of antiretroviral therapy. The immune system is a set of sophisticated biological mechanisms which aim to remove pathogens and to maintain a healthy state in the body [33]. Mathematical studies in immunology show that the antigen-specific immune response of CD8+ T cells can be appropriately modelled using a discontinuous [5, 14] or a sigmoidal function [1, 8]. The effects of these candidate immune response functions have been reviewed from a control engineering view-point in [2, 3]. It has been hypothesized that the immune response function is a state feedback mechanism which influences the stability, the performance, the transient dynamics and the steady-state population of the immune system in both health and disease. Further, it has been shown that the broad class of immune response functions appearing in the literature [4, 5, 15] can be conveniently modelled as a variable structure control system which provides a convenient synthesis tool to assess for example a dynamical condition to sustain the proliferation of memory CD8+ T cells to achieve proctective immunity following chronic viral infection [2]. It will be seen that the variable structure control paradigm will be particularly useful in explaining dynamic behaviour which occurs within a boundary layer of the infection free steady-state. Currently measured data and analytical analysis has produced conflicting conclusions in such cases [25].

The formulation of a reachability condition to monitor the containment of HIV infection involves defining an appropriate switching function to describe the desired clinical outcome of the treatment. A candidate switching manifold is chosen to be compliant with the objective of antiretroviral therapy to reduce and maintain the HIV viral load below the limit of detection. The hypothesis is that in the ideal case, the uptake of antiretroviral drugs, as a control mechanism, has to force the HIV infection dynamics to attain and remain on the infection-free steady-state (8). A valid candidate switching function is

$$s_E(t) \;\; = \;\; P(t) \tag{11}$$

because the manifold $s_E(t) = P(t) = 0$ in which the population dynamic of productively infected CD4+ T cells vanishes has been observed to be a naturally occurring attractive manifold in the state-space of (7) when the trajectories exhibit a stable motion towards the infection free steady-state (8). The reachability condition for exhibiting a sliding mode as defined in [32] may be expressed as

$$s_E \frac{ds_E}{dt} \;\; = s_E \left(\beta TV - \mu_1 P\right) < 0 \tag{12}$$

This inequality is fundamentally a dynamical condition for the manifold $s_E(t) = 0$ to be attractive. In the present context, enforcing a sliding motion on $s_E(t) = 0$ is synonymous with achieving the containment of HIV infection. In order to ensure (12) attains and remains at a negative value, the therapeutic control u_1 associated with the effects of antiretroviral drug therapy must have a sufficiently large magnitude to overcome the positive feedback $\beta_0 TV$ associated with the HIV pathogenesis. The reachability condition (12) thus represents a dynamical condition for antiretroviral drugs to force the dynamics to lie within a neighbourhood of the manifold $s_E(t) = 0$. The inequality (12) represents a dynamical condition for antiretroviral drug therapy to contain HIV infection. It should be noted that assessing the sign of $\frac{ds_E}{dt}$ is sufficient to determine whether the reachability condition is satisfied due to the fact that $s_E(t) = P(t) \geq 0$ because it represents the

number of infected CD4+ T cells producing new virions. The reachability condition (12) can be written as:

$$\beta TV - \mu_1 P \quad < 0 \tag{13}$$

The expression (12) can be written in terms of the output dynamics and their derivatives to allow direct monitoring of the condition for immunity using the measured state variables if desired:

$$\frac{ds_E}{dt} = \quad \beta y_1 y_2 - \left(\tfrac{\beta y_2 + \mu_1}{k}\right)\left(\dot{y_2} + \mu_2 y_2\right) < 0 \tag{14}$$

4. Parameter identification

4.1. The clinical data sets

Two clinical trials have been considered to evaluate the framework proposed in Section 3. It should be noted that a strong motivation of this work is to provide a prediction method that can be applied clinically and these data sets selected contain representative data that may be routinely available to the clinician. From the theoretical point of view, having more data points at equally spaced intervals may be desirable. However, the emphasis here is to use data available in the field to test the practicality of the paradigm.

In the EDV05 clinical trial [21, 19, 27], measurements of the total number of CD4+ T cells and HIV viral load in the peripheral blood stream were collected following the initiation of Highly Active Antiretroviral Therapy (HAART). HIV viral load was measured up to the limit of 50 $RNAcopies/ml$. As in [19, 27], the data collected in the first 21 days are used to compute estimates of the biological rates. This information is then used to predict the outcome of the full treatment regime. The data measured following the initial period of 21 days are used to validate the resulting theoretical predictions. The EDV05 trial has been considered because model parameters have been estimated by other studies for this patient data [22, 27, 19]. This is useful to assess the results of the proposed parameter estimation approach. The syntax pt_i is used to refer to the patients involved in the EDV05 trial where i denotes a specific patient number. The results of pt_{10} are discarded because there is no clinical data available from the final follow-up visit in the clinical trial. Thus, the efficiency of the treatment cannot be validated.

The longitudinal data recorded by the AIDS Clinical Trials Group (ACTG 315) [16] are also chosen to verify the performance of the proposed reachability condition for cases of success and failure of HAART. The syntax pa_i is used to refer to the patients involved in this study. For this trial, data points in the interval $[0, 30]$ days are used to compute the estimates of the biological rates. The limit of detection of HIV free virion in this trial is $100RNAcopies/ml$.

4.2. Parameter Identification Procedure

Previous mathematical analysis [38, 37, 27] has proved the algebraic and practical identifiability of the parameter set $\lambda, \delta_T, \beta, \mu_1, k, \mu_2$ of the model (7) using the output measurements (4). Here the multi-point identification method described in [37] is applied to identify the six biological parameters $\lambda, \delta_T, \beta, \mu_1, k, \mu_2$ of the model (7) using measurements taken at irregular intervals within a set period following initiation of antiretroviral treatment for patients across the two data sets.

For each patient, shape-preserving piecewise cubic interpolation is used to generate a continuous stream of data points within the range of the discrete set of measured clinical data considered for the computation of the estimates of the biological rates. Next, the least-squares polynomial that are the best fit for $y_1(t)$ and $y_2(t)$ are computed to evaluate the time derivatives of the measurements at different time points as in [17]. The degree of the least-squares polynomial for each patient is selected to improve the quality of the fit. Subsequently, the following multi-point identification process is carried out. Consider y_2 and its time derivative up to the third order

$$\begin{aligned} y_2^{(3)} &= \left(y_2^{-1}\dot{y}_2 - \delta_T - \beta y_2\right)\left(\ddot{y}_2 + (\mu_1+\mu_2)\dot{y}_2 + \mu_1\mu_2 y_2\right) \\ &\quad +\lambda k\beta y_2 - \mu_1\mu_2\dot{y}_2 - (\mu_1+\mu_2)\ddot{y}_2 \end{aligned} \tag{15}$$

The identification coefficient θ_1 is defined as:

$$\theta_1 = (\beta, \delta, \rho, \nu, \eta) \tag{16}$$

where

$$\beta = \beta; \delta = \mu_1; \rho = \delta_T; \nu = \mu_1\mu_2; \mu = \mu_1 + \mu_2; \eta = \lambda k\beta \tag{17}$$

This implies that four of the six parameters of the model (7) can be identified using measurement of y_2 and corresponding derivatives. The values of the parameters λ and k are indistinguishable and only their product λk can be estimated. Consider the right hand side of (15):

$$\begin{aligned} f(t, \theta_1, y_2, \dot{y}_2, \ddot{y}_2, y_2^{(3)}) &= \left(y_2^{-1}\dot{y}_2 - \delta_T - \beta y_2\right)\left[\ddot{y}_2 + \mu\dot{y}_2 + v y_2\right] \\ &\quad +\eta y_2 - \nu\dot{y}_2 - \mu\ddot{y}_2 \end{aligned} \tag{18}$$

Assume that the quantities $(y_2, \dot{y}_2, \ddot{y}_2, y_2^{(3)})$ are either available from direct measurement or can be constructed from measurements at five different time points. Denote the values of $(y_2, \dot{y}_2, \ddot{y}_2, y_2^{(3)})$ at $t = t_i$ as $(y_2(i), \dot{y}_2(i), \ddot{y}_2(i), y_2^{(3)}(i))$ and $f_i = f(t(i), \theta_i, y_2(i), \dot{y}_2(i), \ddot{y}_2(i), y_2^{(3)}(i))$ for $i = 1, ..., 5$. Using these measurements, a system of five equations and five unknowns can be constructed:

$$\varphi_1 = \left(y_2^{(3)}(i) - f_i\right) = 0 \tag{19}$$

If

$$det\frac{\delta\varphi_1}{\delta\theta_1} \neq 0 \tag{20}$$

then by the implicit function theorem, the system of equations (19) has a unique solution for θ_1. This solution provides an estimate of the biological rates δ_T, β, μ_1 and μ_2. However, λ and k cannot be identified using measurement of y_2 alone.

To recover the remaining parameters, the first derivative of y_1 is written in terms of the output dynamics as follows:

$$\dot{y}_1 = \lambda - \delta_T y_1 - \delta_P P \tag{21}$$

where $\mu_1 = \delta_T + \delta_P$. Using the expression for $\dot{y}_2$, the state variable P can be written in terms of the output dynamics y_2 and its first derivative as

$$P = \frac{1}{k}\left(\dot{y}_2 + \mu_2 y_2\right) \tag{22}$$

Substitute (22) into (21) to obtain

$$\dot{y}_1 = \lambda - \delta_T y_1 - \frac{\delta_P}{k}(\dot{y}_2 + \mu_2 y_2) \tag{23}$$

Define the identification coefficient θ_2 as:

$$\theta_2 = (\lambda, \delta_T, \xi, \sigma)$$

where $\xi = \frac{\delta_P}{k}$ and $\sigma = \frac{\mu_2 \delta_P}{k}$. Let the identification function be

$$g(t, y_1, \dot{y}_2, y_2) = \lambda - \delta_T y_1 - \xi \dot{y}_2 - \sigma y_2 \tag{24}$$

The multi-point identification process [37] is performed to estimate θ_2. Here, the values of $(\dot{y}_1, y_1, \dot{y}_2, y_2))$ are needed at four time points to construct a system of four equations and four unknowns to estimate θ_2. Consequently, the identification equation is given by

$$\varphi_2 = (\dot{y}_1(j) - g_j) = 0 \tag{25}$$

where $\dot{y}_1(j)$ and g_j denote the values of $\dot{y}_1$ and $g(t, y_1, \dot{y}_2, y_2)$ at four time points for $j = 1, ..., 4$. Proceeding as before, estimates of the biological rates λ,δ_T and μ_2 can be computed. Nevertheless, μ_1 and k cannot be identified using (25) only.

Combining θ_1 and θ_2 from (19) and (19) respectively, it is possible to construct estimates of the six biological rates in the model (7). In the presented results, λ, δ_T and μ_2 are taken from θ_2, β and $\mu_1 = -\frac{-\nu - \nu^2 + 4\mu^{\frac{1}{2}}}{2}$ are taken from θ_1 and $k = \frac{\eta}{\lambda\beta}$.

The estimation process is conducted for each patient and resulting numerical solutions of the model (7) are obtained using the Runge-Kutta method [17]. To estimate the quality of the fits, error vectors are constructed where the error at each data point is given by

$$e_{y1}(t_i) = y_1(t_i) - \hat{y}_1(t_i) \tag{26}$$
$$e_{y2}(t_i) = y_2(t_i) - \hat{y}_2(t_i) \tag{27}$$

for $i = 1, ..., n$ where i is the time point of the corresponding measurement and n is the number of measurements collected within a set period. $\hat{y}_1(t_i)$ and $\hat{y}_2(t_i)$ are the estimated values of the total number of CD4+ T cells and HIV viral load produced from the numerical model which uses the estimated parameters. The relative accuracy of the output dynamics produced using the estimated biological rates is evaluated from

$$a_{y1} = 100 \sum_{i=1}^{n} \frac{e_{y1}^2(t_i)}{y_1(t)^2(t_i)} \tag{28}$$

$$a_{y2} = 100 \sum_{i=1}^{n} \frac{e_{y2}^2(t_i)}{y_2(t_i)^2} \tag{29}$$

for $i = 1, ..., n$.

4.3. Parameter Estimation Results

In the results presented, a set of patients from each clinical trial has been randomly picked. Note that the values of the estimated biological rates presented in the following tables are rounded and the tabulated biological rates may not identically reproduce the results presented for the reproductive ratio as the values of the estimates produced by the identification algorithm are used to compute R_0, a_{y1}, a_{y2}. As will be seen in the results presented, the dynamics exhibit good robustness to such changes in the parameter values.

Previous work in the literature has estimated parameter values for the dynamics of HIV infection in the course of antiretroviral drug treatment. Here biological rates estimated using the Monte Carlo approach from [19, 27] are used to benchmark the results presented in this paper. For both estimation approaches, the initial conditions are selected such that $T(0) + P(0) = y_1(0)$ and $V(0) = y_2(0)$ where the values of $y_1(0)$ and $y_2(0)$, see (4), are taken from the clinical data set relating to the EDV05 trial as published in [27]. It is important to note that for both approaches all the parameter estimates are generated only using data obtained during the initial 30 days of the period of the trial. Motivation for this study is to be able to obtain patient specific data that can be used to predict the likely outcome of the current drug treatment. If the eventual outcome is likely to be unsuccessful, modification of the anti-retroviral drug treatment can take place based on the patient specific parameter estimates. In this work, the measured data obtained across the remainder of the trial will be used to validate the parameter estimates as will the known clinical outcome.

Table 1 reports the results of the Monte Carlo approach from [19, 27]. Table 2 shows the results obtained for the procedure described in this manuscript. A major difference between the two estimation methods is that the algorithm chosen in [19, 27] uses the same values of the decay parameter δ_T, μ_1 and μ_2 for all patients. Nevertheless, as argued in [17], it is preferable to estimate all parameters to improve personalized treatment and clinical decisions. For example, when comparing the values of the reproductive ratio R_0 presented in Table 1 with the corresponding values in Table 2 it is clear that the parameter values generated from the methodology presented in this paper generate more realistic values.

Biological rates estimated using the procedure presented in this paper and patient data from the ACTG 315 trial are shown in Table 3.

Table 1 Estimates of the biological rates taken from [19, 27]. Common parameters:$\delta_T = 0.01day^{-1}$, $\mu_1 = 0.05day^{-1}$ and $\mu_2 = 0.28day^{-1}$

Results	$T(0)+P(0)$	$V(0)$	λ	β	k	R_0	a_{y1}	a_{y2}
pt_1	200+176	10^6	8.13	1.94e-07	0.04	4.50e-04	4.28	9.25
pt_2	138+92	$10^{5.4}$	9.53	3.27e-07	0.21	0.0047	14.76	8.81
pt_3	110+75	$10^{4.54}$	1.77	8.24e-07	0.41	0.0043	13.36	2.44
pt_4	120+85	$10^{5.3}$	5.45	7.10e-08	293.00	0.809	7.06	22.90
pt_5	200+183	$10^{4.82}$	6.76	3.94e-07	0.004	7.6098e-05	2.75	5.51
pt_6	205+200	$10^{4.972}$	6.94	1.21e-07	46.80	0.2807	7.40	21.76
pt_7	5+4	$10^{5.07}$	3.01	2.43e-06	0.008	4.17e-04	147.01	85.19
pt_8	80+42	$10^{5.3}$	6.41	8.15e-07	0.002	7.46e-05	5.31	5.92
pt_9	68+50	$10^{5.21}$	5.36	7.23e-07	0.003	8.30e-05	11.13	3.95
pt_{11}	10+13	$10^{6.02}$	2.08	1.79e-07	0.012	3.19e-05	11.90	12.31
pt_{12}	200+105	$10^{5.7}$	7.66	2.56e-07	0.002	2.80e-05	4.71	12.56

Table 2 Estimates of the biological rates produced by the identification method presented in this paper. Initial conditions are identical to those in Table 1

Results	λ	δ_T	β	μ_1	k	μ_2	R_0	a_{y1}	a_{y2}
pt_1	427.15	0.98	4.09e-04	1.002	1.65	0.39	0.73	3.10	13.74
pt_2	525.63	1.13	1.14e-05	3.07	530.50	0.94	0.95	6.44	25.51
pt_3	137.97	0.70	0.0028	0.90	0.75	0.49	0.92	20.56	7.56
pt_4	91.34	0.21	8.44e-05	0.37	3.50	0.46	0.72	7.97	38.6
pt_5	511.21	1.16	0.0014	1.23	0.106	0.48	0.107	0.78	6.25
pt_6	447.26	0.87	3.83e-04	1.08	0.98	0.20	0.87	3.25	22.72
pt_7	48.54	0.88	1.05e-04	1.09	237.41	1.98	0.63	21.23	84.15
pt_8	77.45	0.30	2.39e0-5	0.67	72.35	0.66	1.002	0.91	0.10
pt_9	255.40	0.83	2.45e-04	1.48	4.66	0.50	0.46	9.50	0.08
pt_{11}	20.23	0.24	2.11e-05	1.59	717.20	0.76	1.008	5.67	0.1
pt_{12}	216.15	0.47	5.53e-04	0.53	0.57	0.87	0.30	0.54	0.01

Table 3 Estimates of the biological rates produced by the identification method presented in this paper.

Results	λ	δ_T	β	μ_1	k	μ_2	R_0	a_{y1}	a_{y2}
pa_3	19.44	0.05	1.83e-04	0.39	24.61	0.33	11.50	1.50	1.16
pa_8	72.46	0.18	7.39e-04	1.05	2.49	0.38	4.95	2.10	0.07
pa_{10}	117.28	0.15	4.15e-05	0.53	16.93	0.35	2.85	21.24	0.21
pa_{13}	46.06	0.19	3.82e-04	0.65	0.03	0.27	0.01	1.92	2.17
pa_{24}	118.39	0.34	4.84e-05	0.45	9.10	0.37	0.89	0.75	0.38
pa_{34}	169.72	0.44	1.30e-04	0.46	4.67	0.49	1.01	3.90	3.44
pa_{38}	137.66	0.49	1.76e-04	0.58	3.54	0.28	1.03	5.64	23.12
pt_{43}	234.49	0.64	2.93e-04	0.73	0.45	0.19	0.33	0.86	10.98

The estimated parameter values obtained by the proposed method and presented in Tables 2 and 3 of the six biological rates of the basic HIV model (7) using patient data from the first period of both clinical trials are reasonable and close to the ones published in other studies [22, 37, 17, 12]. Fig. 1-2 are displayed as examples to show that the output dynamics produced by the estimated biological rates are realistic. In all figures, the parameter estimates have been obtained from clinical measurements obtained in the early phase of the trial and later measurements are presented to validate the output response predicted from the model. Fig. 1 illustrates the case in which the uptake of antiretroviral drugs enforces the containment of HIV load to a small level along with the recovery to a desirable CD4+ T cell count. Fig. 2 depicts a case in which antiretroviral therapy fails. The figures reinforce that the estimation method used in this work produces responses similar to the ones generated by other studies [17, 12, 31, 19, 25] and the responses align well with subsequent measurements obtained later in the drug trial and not used within the parameter estimation procedure.

The data used to estimate the parameters can be expected to incorporate measurement error and it is important to consider the likely effect of such errors on the computed parameter estimates. A comprehensive review of the practical issues relating to the estimation of the parameters of the dynamics of HIV can be found in [35]. Results from both structural and statistical analysis

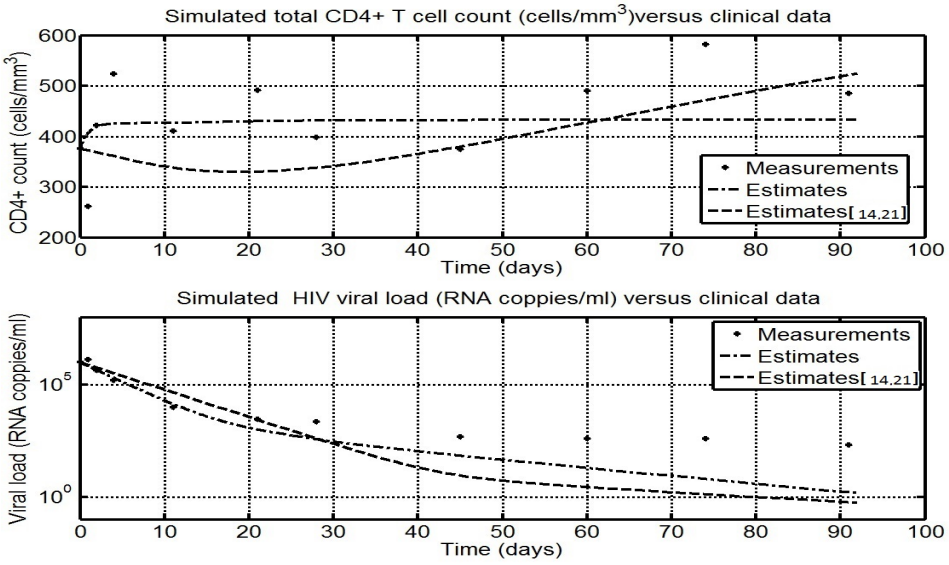

Fig. 1. *Comparison of the time evolution of measured CD4+ T cell count and HIV load versus its estimates for* pt_1

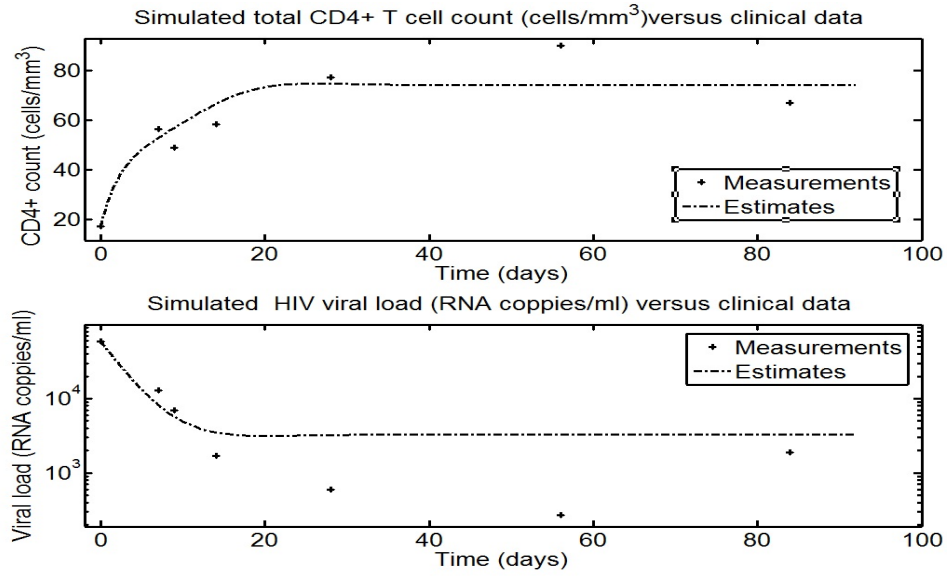

Fig. 2. *Comparison of the time evolution of measured CD4+ T cell count and HIV load versus its estimates for* pa_3

have shown that it is sensible to estimate the parameters using measurements in the early weeks following the initiation of antiretroviral therapy because the transient phase after the initiation of treatment contains more dynamic information [35, 38, 24]. This supports selecting measurements in the first month following initiation of treatment as adopted in this study. A statistical noise model for HIV standard clinical data has recently been determined in [12]. The local polynomial regression technique used in [17] was used to smooth the longitudinal data and to estimate the measurement noise. After conducting normality tests with the Chi-square and Lilliefors tests, the

authors concluded that a multiplicative zero mean Gaussian noise affects both measurements of CD4+ T cell count and HIV load. Further, similar noise parameters i.e sample mean and standard deviation have been found for two patient datasets. Interestingly, an earlier study on noise characteristics based on visual observations of the noise on the viral load data also suggested that the noise might follow a Gaussian distribution [24]. Simulation studies in a number of publications have incorporated a zero mean Gaussian noise with different levels of standard deviation to the numerical solutions of the basic HIV model to test the practical identifiability of the biological rates [17, 37, 36, 18]. Collectively, these simulation results provide evidence that reasonable parameter estimates can be obtained in the presence of noise in the measured data. Furthermore, the estimated biological rates from patient datasets has been shown to produce viral load dynamics which closely match the trajectory of observed data [24, 17, 12, 19].

To determine the robustness of the biological rates determined in this study to measurement noise, the established noise model from [12] was added to the patient data and a second set of parameter estimates was computed. The responses of the HIV model with parameter estimates generated in the presence of additional noise are compared with the results obtained with parameter estimates obtained without additional noise for pt_1 in Fig. 3. This reinforces that the output dynamics generated by the estimated biological rates are not dramatically affected by noise and the traces are visually indistinguishable. Hence, the infection dynamics following antiretroviral treatment are shown to exhibit some robustness with respect to measurement noise.

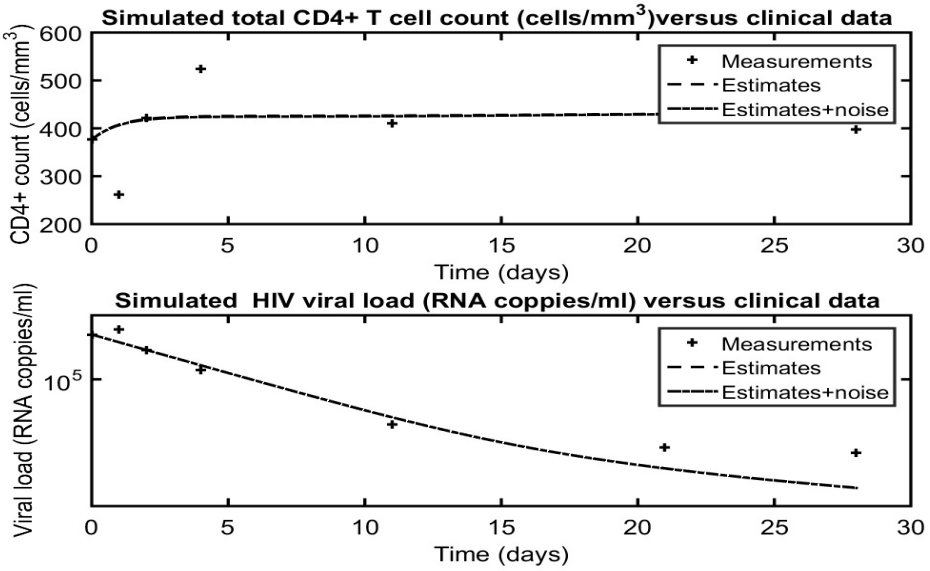

Fig. 3. *Comparison of the time evolution of measured CD4+ T cell count and HIV load for pt_1. Original data and the responses generated with parameters estimated in the presence of additional noise and without additional noise are presented.*

5. Prediction of the outcome of antiretroviral treatment

For each patient listed in Table 2 and 3, the proposed reachability analysis for the containment of HIV infection is evaluated to predict the outcome of HAART. Note that these predictions are based only on measured data obtained in the first 30 days following treatment. The predictions

are then compared with clinical outcomes determined from examining the CD4+ T cell count and HIV viral load at the conclusion of the clinical trial. The findings show that the time evolution of the reachability condition (13) and the switching function (11) exhibit a particular dynamical behaviour characterizing desirable and undesirable outcomes. This underpins the discrimination of outcomes. The predictions from the reachability analysis and indeed the reproductive ratio are congruent with clinical outcomes for all patients except pt_7 and pa_{24}. For patient pt_7 and pa_{24}, the reachability analysis suggests that HIV infection will be contained. This prediction fails for pa_{24} because, despite the fact that HIV load fell below $100(RNAcopies/ml)$ within 56 days following the initiation of treatment, a significant viral rebound i.e $y_2(175) = 670.03$ was measured at the final visit of the trial. Similarly, the data for pt_7 in [27] shows a large viral rebound i.e $y_2(29) = 2.53$ to $y_2(149) = 5.41log_{10}(RNA\ copies/ml)$ and the HIV viral load at the final clinic visit is $y_2(212) = 2.58log_{10}(RNA\ copies/ml)$. These results may correspond to cases where model predictions fail due to the appearance of drug resistance or viral rebound [31]. The results are now explored in situations corresponding to effective treatment, marginal cases and cases where treatment fails.

5.1. Effective treatment

The following results are associated with patients where antiretroviral drugs reduce and then maintain HIV load in the peripheral blood below the limit of $100(RNA\ copies/ml)$ i.e $2log_{10}(RNA\ copies/ml)$ within six months. These cases relate to patients pt_1, pt_2, pt_3, pt_4, pt_5, pt_6, pt_9, pt_{12}, pa_{13}, pa_{38}, and pa_{43}. For these patients, the reproductive ratio is below unity, see Table 2 and 3 and the existing methods successfully predict that antiretroviral treatment will be able to eradicate the infection. The time evolution of the reachability condition, see Fig. 4 for pt_1, is representative of the dynamical behaviour of the reachability condition in the other patients in this category. Antiretroviral drugs in these patients are able to render and maintain the reachability condition negative some 5 days after the initiation of treatment. As a result, the magnitude of the switching function (11) is driven to zero and the dynamics of the system (7) are forced to move and remain at the infection-free steady-state (8) such as in Fig. 1 for pt_1. Thus, the reachability analysis predicts that antiretroviral drugs are successful in eradicating the virus in these patients. Importantly, it should be noted that there is no oscillation in the magnitude of the reachability condition in the first weeks and the term βTV keeps on decreasing before and after the reachability condition is satisfied.

5.2. New insight into marginal cases

The proposed reachability analysis reveals insight into marginal cases in which the HIV viral load is not completely eradicated by HAART and remains at an undetectable level in the steady-state. From a clinical point of view, treatment of patient pt_8 is efficient because the antiretroviral drugs reduce and maintain the HIV viral load below the limit of detection of $50RNA\ copies/ml$ i.e $1.699log_{10}(RNA\ copies/ml)$ within six months. Nevertheless, the value of the reproductive ratio is above unity in this case, see Table 2. Although antiretroviral drugs are classified as efficient, the value of the reproductive ratio infers that the infection may not be eradicated. The existing prediction methodology using R_0 appears to contradict the clinical outcome. In contrast, this prediction is not supported by the reachability analysis because though the time evolution of the reachability condition in Fig. 5 shows that antiretroviral drugs are able to maintain the reachability condition negative i.e $\beta TV - \mu_1 < 0$, the switching function $s_E(t)$ does not reach the manifold of

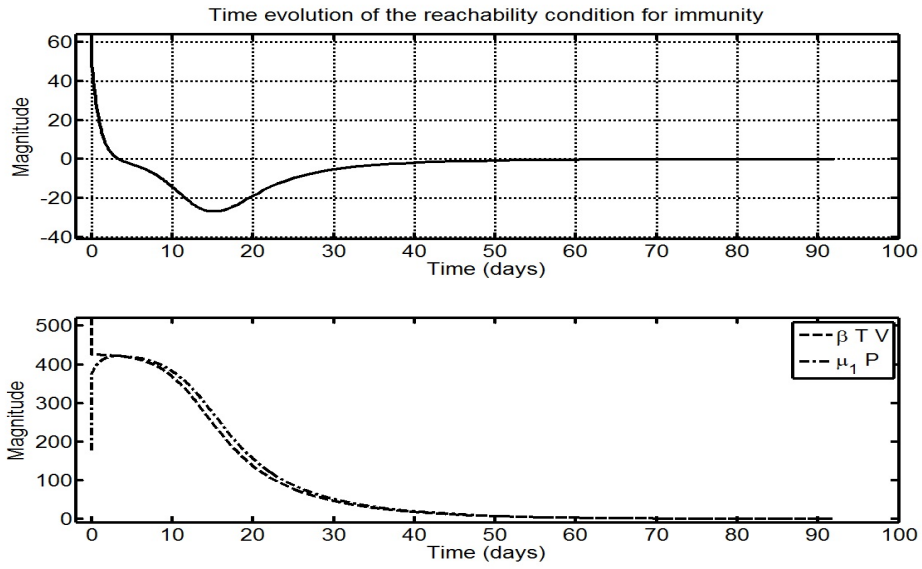

Fig. 4. *Time evolution of the dynamical condition for immunity using simulation results for* pt_1

interest. Nevertheless, it should be noted that $s_E(t)$ reaches a steady-state value which is close to the desired sliding manifold $s_E(t) = 0$. Similar results are obtained for patient pa_{34}.

Unlike the measured HIV load data of pt_8, measurements of HIV load for pt_{11} remain above the limit $2log_{10}(RNA\ copies/ml)$. However, the last measurement $2.02log_{10}(RNA\ copies/ml)$ is very close to this threshold, see data in [27]. Here again, although the $R_0 > 1$ for pt_{11}, clinicians found this patient asymptomatic because the HIV load is relatively low. The reachability analysis conducted using the biological rates estimated here indicates that $s_E(t)$ for pt_{11} attains a steady-state value close to the desired sliding manifold $s_E(t) = 0$. Further insight can be gained from the

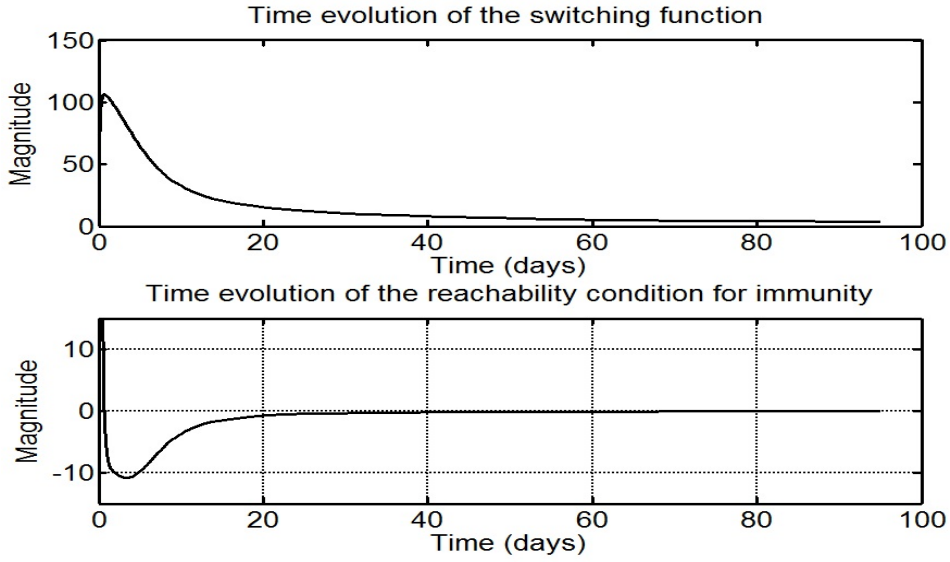

Fig. 5. *Time evolution of the switching function and dynamical condition for immunity for* pt_8

phase portrait of the sliding surface in these cases. Fig. 6 reveals that the trajectories move towards

an equilibrium point close to the origin for pt_{11}. This suggests that the infection dynamics move and remain at a clinically desirable steady-state located close to the infection free steady-state for both pt_8 and pt_{11}. It can be thus deduced that the limit of detection of the HIV viral load in the peripheral blood can be associated with a boundary layer in which the steady-state of HIV viral load is desirable. In the field of control systems, the concept of boundary layer control is well established [10, 7] and it is acceptable to have a control action which forces the sliding surface to remain within a region close to zero. It is well known that the assumed dynamics of the switching behaviour in the control strategy directly impact on the characteristics of the boundary layer. In the case of a switched control using a boundary layer implementation, ideal sliding motion, and the performance it describes, is not exhibited, yet the performance of the system may still be desirable. This finding explains the difference between the clinical observation and the outcome inferred from the reproductive ratio for these patients. The origin is not attained but the outcome is sufficiently close to the desired outcome and within the limits of accuracy of the measurement approach to be clinically satisfactory.

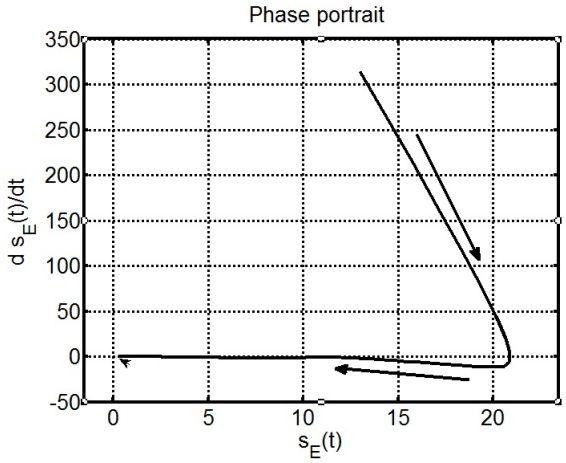

Fig. 6. *Phase portrait of the sliding surface for* pt_{11}

5.3. Failure Cases

The following results relate to patients pa_3, pa_8 and pa_{10} for whom antiretroviral drugs are unable to reduce and maintain the HIV viral load below $100 RNA\ copies/ml$ i.e $2log_{10}(RNA\ copies/ml)$ within six months. In all cases of failure of antiretroviral treatment, the estimated biological rates predict a steady-state viral load V_{s1}, see (9), which exceeds that limit significantly. Furthermore, the reproductive ratio (10) is above unity in all cases, see table 3. Therefore, the value of the reproductive ratio suggests that antiretroviral drugs are not able to render the infection-free steady-state (8) attractive and to eradicate the virus. To investigate the performance of antiretroviral drugs in these patients, the reachability analysis was performed and results from pa_3 are shown in Fig. 7 where it can be seen that the effects of antiretroviral drugs are not sufficient to zero the switching function (11). The dynamical behaviour of the reachability condition seen for pa_3 is the same for patients pa_8 and pa_{10}. The phase portrait of the sliding surface, see Fig. 8, for these failure cases demonstrates that the HIV infection dynamics do not reach the infection free steady-state located at the origin but attain a chronic HIV infection steady-state. For instance, the phase portrait of pa_3 shows dynamics moving away from the origin to reach a chronic infection steady-

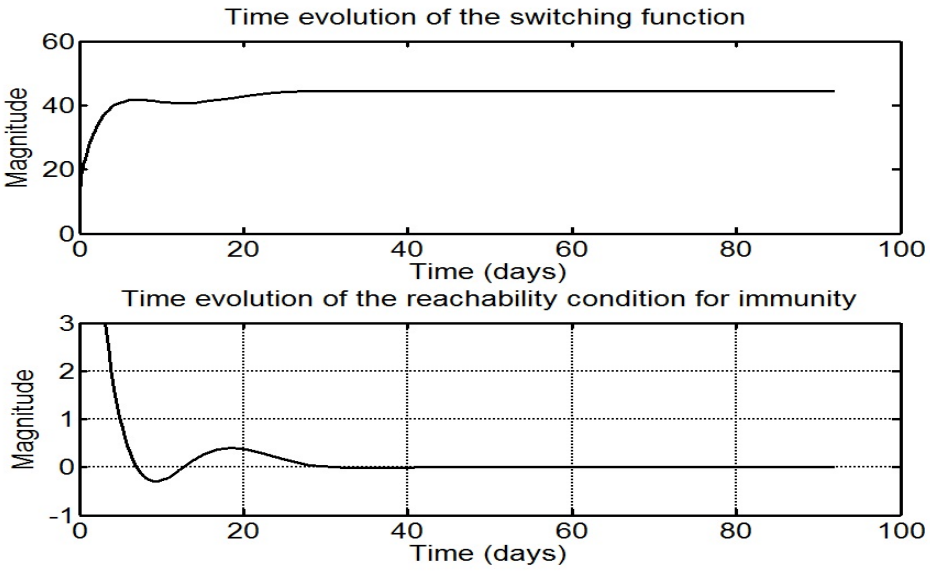

Fig. 7. *Time evolution of the switching function and dynamical condition for immunity for* pa_3

state whilst the dynamics of pa_{10} move towards the origin but stop at a chronic infection steady-state. Importantly, the comparative analysis of the phase portrait of the sliding surface for different patients reinforces the fact that the transient dynamics induced by the antiretroviral treatment are diverse in failure cases. This motivates the design of personalized antiretroviral treatment regimes to improve efficacy and demonstrates that the reachability analysis presented in this paper may be helpful in developing appropriate treatments.

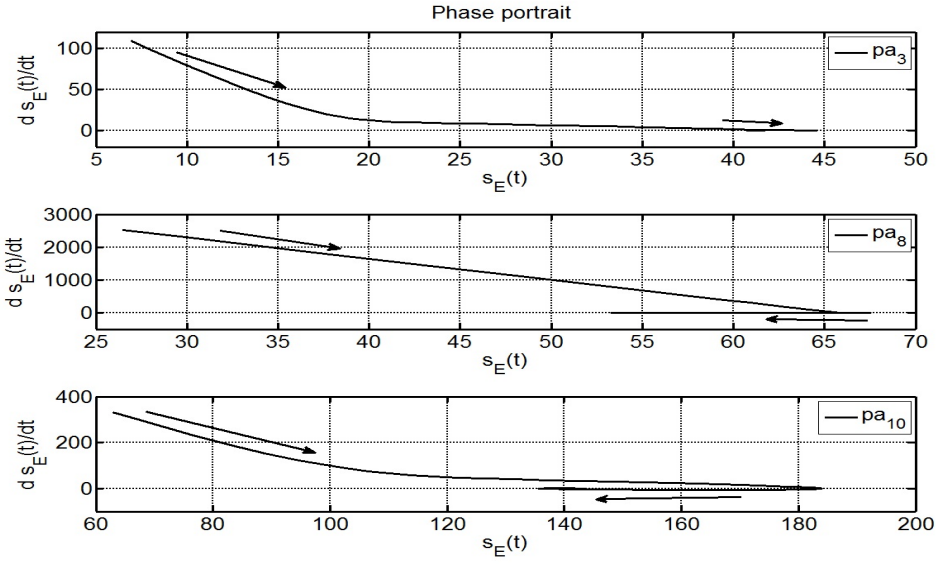

Fig. 8. *Phase portrait of the sliding surface for* pa_3*,* pa_8 *and* pa_{10}

6. Conclusion

The dynamics of HIV infection after initiation of antiretroviral therapy are analyzed from a control engineering standpoint. Using sliding mode control theory, a reachability condition has been formulated to provide a dynamical condition to assess the ability of antiretroviral therapy to enforce an infection free steady-state. Longitudinal data from two different HIV clinical trials were considered to validate the hypothesised condition. These data sets contain measurements of CD4+ T cell count and HIV load in the peripheral blood collected from HIV infected individuals after initiation of HAART during a six month period. Using the multi-point parameter identification method, the biological rates of the HIV model were estimated. These estimates have been validated by numerical simulation and by comparing the values with those published in other studies. The time evolution of the switching function and the reachability condition are shown to be good predictors of the outcome of antiretroviral treatment because the infection dynamics during HAART exhibit specific dynamical characteristics corresponding to healthy, unhealthy and marginal outcomes. The findings of this work evidence that the proposed analysis is a suitable framework to improve early diagnosis of the outcome of antiretroviral therapy for individual patients. Future work will focus on assessing the ability of the framework to inform drug treatment and support the development of personalised treatment.

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