A VIRAL LOAD TIME RESPONSE ANALYSIS TO ANTI-RETROVIRAL THERAPY*

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Abstract: HIV Therapy is considered to be effective if it can reduce the viral load by 90% in less than 8 weeks and continue to suppress it to below 50 copies per mL of plasma in less than 6 months [1]. This response time to therapy as well as the time to suppress the viral load can be estimated towards the development of an interruptible control strategy for the chemotherapy of HIV. The time estimates are parameter dependent, and as such, will vary from one individual to the other. These time estimates therefore, will be useful and can be used to aid clinicians with therapy and measurement scheduling. The model used in this paper has a total of ten parameters, but in order to determine these time estimates, one only needs to know estimates for the death rate constants for the virus and actively infected $CD4^+$ T cells, the combined drug efficacy, as well as the reproductive ratio.

Key words: Effective therapy, response time, suppression time, therapy scheduling, treatment interruption.

1. INTRODUCTION

Treatment interruption can be due to a variety of reasons. The reasons could be salvage therapy, autoimmunization or to reduce the total time that the patient is on therapy. Salvage therapy is for patients whose virus has developed resistance or have virological failure on their current regimen [3]. The intention is to allow the re-emergence of the virus strain that responds to therapy. Autoimmunization is meant to allow short bursts of viral replication to augment HIV specific immune responses. Clinical studies have been carried out using this approach on patients who had initiated therapy during the acute or chronic infection stage [4,5] and had a record of sustained viral suppression to below detectable levels.

Treatment interruption for the purpose of reducing total time on Highly Active Anti-Retroviral Therapy - HAART has been tried out primarily on patients with previous viral suppression [6]. The reasoning behind reducing the total time on HAART is to reduce the toxicity associated with anti-retroviral drugs.

One approach to treatment interruption strategies is to monitor either the viral load or T cell count. Therapy is interrupted or resumed when the monitored variable rises above or below predetermined upper and lower bounds. In essence, it entails keeping the variable between an upper and lower bound by on/off control. This approach is referred to as Strategic/Supervised/Structured Therapy Interruption - STI. Another approach to treatment interruption is to have predetermined time periods for when therapy is on and when it is interrupted. This approach is referred to as Structured Intermittent Therapy - SIT [7]. SIT is easier to implement when compared to STI which requires more frequent measurements in order to check if the viral load is above or below the cut off points.

The approved USPHS Guidelines [1] for the use of anti-retroviral agents does not recommend therapy interruption because there is not enough clinical data to support it. Furthermore, therapy interruption has a similar effect on the virus as does not adhering to therapy in that they cause the virus to become resistant. The associated viral rebounds can also increase the transmission of the virus. Treatment interruption for the purpose of reducing the total time on HAART is however, getting a lot of attention because of the growing concern over the adverse side effects of HAART. Even though HAART has drastically reduced incidences of death due to AIDS related illnesses, there is an increasing rate of deaths that are related to complications caused by HAART. To this end, studies are being conducted to find ways of alleviating the toxicity of HAART. One such study on Strategies for the Management of Antiretroviral Therapies (SMART) [8] aims to "strike a balance between adequately aggressive treatment

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and minimal side effects". This is a long term study that will cover a period of up to nine years with some patients on either STI or continuous HAART.

This paper deals specifically with estimating the response time to therapy, which is the time taken to reduce the viral load by 90% and the viral load suppression time, which is the time to suppress the viral load to below 50 copies per milliliter of plasma. These time estimates will be determined for when antiretroviral therapy is initiated at the asymptomatic stage. The paper also shows how the number of model parameters required for determining the suppression and response time estimates can be reduced. The estimation of these suppression and response times to therapy is the first step towards the development of an interruptible control strategy for the chemotherapy of HIV. These time estimates can also be used to assist clinicians in therapy and measurement scheduling.

An analytic solution for the response and suppression times to therapy was obtained by using linearization and model reduction techniques. The time estimates were found to be parameter dependent, and as such, will vary from one individual to the other. The percentage error in estimation increased with decreasing drug efficacy. The approach used allows for the estimation of the minimum drug efficacy required for suppressive therapy.

The layout of the paper is as follows:
Section 2 presents the working model. Section 3 introduces the model reduction technique, while Section 4 shows how time estimates can be obtained from the reduced model. Section 5 presents some simulation results and Section 6 has the conclusions that are drawn from this study.

2. THE WORKING MODEL

The mathematical model as presented by [9] was adopted for this paper and the following is a summary of that model.

$$\dot{x}_1 = rx_2 - cx_1 \tag{1}$$

$$\dot{x}_2 = q_2\beta x_1 x_4 + kx_3 - \mu_2 x_2 \tag{2}$$

$$\dot{x}_3 = q_1\beta x_1 x_4 - kx_3 - \mu_1 x_3 \tag{3}$$

$$\dot{x}_4 = s - dx_4 - \beta x_1 x_4 \tag{4}$$

The state variables x_1, x_2, x_3 and x_4 are the plasma concentrations of the free virus particles, actively infected CD4$^+$ T cells, the latently infected CD4$^+$ T cells and the uninfected CD4$^+$ T cells and the respectively. Equation (4) describes the population dynamics of the uninfected CD4$^+$ T cells. It shows that they are produced from a source at a constant rate s, die with a rate constant d and are infected by the virus at a rate that is proportional to the product of their abundance and the amount of free virus particles. The proportionality constant β is an indication of the effectiveness of the infection process. Equation (3) describes the population dynamics of the latently infected CD4$^+$ T cells and shows that they convert to actively produce virus with a rate constant k and μ_1 is their death rate constant. Equation (2) describes the population dynamics of the actively infected CD4$^+$ T cells and shows that they die with a rate constant μ_2. Constants q_1 and q_2 are the probabilities that upon infection, the infected CD4$^+$ T cell will either become latent or actively produce virus particles. Equation (1) similarly describes the population dynamics of the free virus particles and it can be seen that an actively infected CD4$^+$ T cell produces infectious virus particles with a rate constant r and c is the death rate constant for these virus particles.

Model parameter estimates are as presented in Table 1 and are sourced from [9–13].

Table 1 : Parameter Estimates.

Parameter	Value
s	10 mm^{-3}day^{-1}
d	0.01day^{-1}
β	7.5×10^{-6}mL^{-3}day^{-1}
q_1	0.05
q_2	0.8
μ_1	0.01 day^{-1}
μ_2	0.5 day^{-1}
k	0.075 day^{-1}
r	4000 virions cell^{-1}
c	5 day^{-1}

3. MODEL REDUCTION

Equations (1) to (4) are a minimal realization of the system. The Jacobians for these equations [9] at some operating point $\bar{\mathbf{x}}$ are given by

$$A = \begin{bmatrix} -c & r & 0 & 0 \\ q_2\beta\bar{x_4} & -\mu_2 & k & q_2\beta\bar{x_1} \\ q_1\beta\bar{x_4} & 0 & -(k+\mu_1) & q_1\beta\bar{x_1} \\ -\beta\bar{x_4} & 0 & 0 & -(d+\beta\bar{x_1}) \end{bmatrix}$$

The eigenvalues are the solutions to

$$(\lambda + c)(\lambda + \mu_2)(\lambda + k + \mu_1)(\lambda + d + \beta\bar{x_1}) - r\beta\bar{x_4}(\lambda + d)(q_1 k - q_2(\lambda + k + \mu_1)) = 0$$

When suppressive therapy is initiated at the asymptomatic stage, then for the parameter estimates given in Table 1,

$$0 < r\beta\bar{x_4}q_1 k < 0.005$$

The eigenvalues can therefore be approximated very well by

$$\bar{\lambda_1} = -c;\ \bar{\lambda_2} = -\mu_2;\ \bar{\lambda_3} = -k - \mu_1;\ \bar{\lambda_4} = -d$$

From all the available parameter estimates,

$$\bar{\lambda}_1 < \bar{\lambda}_2 < \bar{\lambda}_3 < \bar{\lambda}_4$$

The dynamics of x_3 and x_4 are much slower than those of x_1 and x_2, hence x_3 and x_4 can be residualized. Note that residualizing the slower transients x_3 and x_4 is equivalent to assuming that their values remain constant for some time after therapy is initiated, as has been observed in practice. A residualization [14] can be obtained by setting $\dot{x}_3$ and $\dot{x}_4$ to zero to obtain

$$x_4 = \frac{s}{d + \beta x_1} \tag{5}$$

$$x_3 = \frac{q_1 \beta s x_1}{(d + \beta x_1)(k + \mu_1)} \tag{6}$$

A second order approximation of the full order system is therefore given by

$$\dot{x}_1 = r x_2 - c x_1 \tag{7}$$

$$\dot{x}_2 = \frac{\beta s}{(d + \beta x_1)}(q_1 \frac{k}{k + \mu_1} + q_2) x_1 - \mu_2 x_2 \tag{8}$$

and has non trivial steady states given by

$$x_{1ss} = \frac{sr}{c\mu_2}(q_1 \frac{k}{k + \mu_1} + q_2) - \frac{d}{\beta} \tag{9}$$

$$x_{2ss} = \frac{c}{r} x_{1ss} \tag{10}$$

The nonlinear term in Equation (8) can be expanded to give

$$\dot{x}_2 = \frac{\beta s}{d}(q_1 \frac{k}{k + \mu_1} + q_2) x_1 (1 - \frac{\beta}{d} x_1 + \cdots) - \mu_2 x_2$$

and when the higher order terms are ignored, the reduced order system can be linearized as

$$\dot{x}_1 = r x_2 - c x_1 \tag{11}$$

$$\dot{x}_2 = \frac{\beta s}{d}(q_1 \frac{k}{k + \mu_1} + q_2) x_1 - \mu_2 x_2 \tag{12}$$

This linearized system's characteristic equation is given by

$$\lambda^2 + (c + \mu_2)\lambda + c\mu_2(1 - R_0) = 0 \tag{13}$$

where

$$R_0 = \frac{\beta s r}{c\mu_2 d}(q_1 \frac{k}{k + \mu_1} + q_2) \tag{14}$$

is the basic reproductive number [9] and defined as the number of secondary infections resulting from one infected T cell.

4. CONTROL AND TIME ESTIMATION

4.1 *Control*

The variable under control in this paper is the viral load. Controlling the viral load entails the use of antiretroviral drugs that inhibit the replication rate of the virus. The currently used cocktail drugs (combined therapy) are a combination of reverse transcriptase and protease inhibitors. Reverse transcriptase inhibitors inhibit virus replication by reducing the infectivity rate constant β, while protease inhibitors reduce the number N of infectious virus particles produced [15].

Medically, the viral load is considered to be controllable if the control law in use can reduce the viral load by 90% or by 1 $\log_{10}$ scale, in 8 weeks from the time treatment is initiated and continue to suppress it to below 50 copies per milliliter of plasma in 6 months [1]. The time taken from when therapy is initiated to reduce the viral load by 90% is here referred to as the response time, t_{res} and the time taken to suppress the viral load to below 50 copies is the suppression time, t_{sup}. Similarly, the time from when suppressive therapy is terminated to when the viral load rebounds to more than 50 copies is referred to as the rebound time, t_{reb}. This paper only estimates the response and suppression times t_{res} and t_{sup} when therapy is initiated at the asymptomatic stage of the infection. The estimation of the rebound time and the associated duration of viral load suppression is presented elsewhere [16].

Equations (11) and (12) under antiretroviral therapy are expressed as

$$\dot{x}_1 = (1 - \eta_{pi}) r x_2 - c x_1 \tag{15}$$

$$\dot{x}_2 = \frac{(1 - \eta_{rt})\beta s}{d}(q_1 \frac{k}{k + \mu_1} + q_2) x_1 - \mu_2 x_2 \tag{16}$$

where $0 \leq u_{PI} \leq 1$ is the control variable for the protease inhibitors used, while $0 \leq u_{RT} \leq 1$ is for the reverse transcriptase. The control variable has the general expression

$$\eta_{rt,pi}(t) = \begin{cases} 0, & t < t_i, t > t_f \\ \alpha, & t_i \leq t \leq t_f \end{cases} \tag{17}$$

where t_i is the time when therapy is initiated and t_f is when therapy is ended. The variable α is the average effectiveness of the drugs and is assumed to be constant when therapy is on.

4.2 *First Approximation Using Reduced Order Model*

For a reduction in viral load therefore, as is the case with effective therapy, the clearance rate of the virus must exceed its replication rate [9]. This means that

$$c > \frac{u\beta sN}{d}(q_1\frac{k}{k+\mu_1} + q_2)$$

where $u = u_{RT}u_{PI}$ is the combined control effect of the drug combination used and $0 \leq u \leq 1$. The system is therefore stable and its eigenvalues are

$$\lambda_{1,2} = \frac{-c-\mu_2 \pm \sqrt{(c+\mu_2)^2 - 4c\mu_2(1-R_{0(u)})}}{2}$$

where

$$R_{0(u)} = uR_{0(ss)} = u$$

is the number of secondary infections resulting from an infected $CD4^+$ T cell under therapy.

The solution for the viral load $x_1(t)$ for Equations (15) and (16) has the form

$$x_1(t) = A_1e^{\lambda_1 t} + A_2e^{\lambda_2 t} \tag{18}$$

where

$$A_1 = \frac{\lambda_2}{\lambda_2 - \lambda_1}\bar{x_1} \tag{19}$$

$$A_2 = \frac{\lambda_1}{\lambda_1 - \lambda_2}\bar{x_1} \tag{20}$$

and $\bar{x_1} = x_{1ss}$ is the steady state or viral load measured before therapy.

A first estimate for the response time to therapy as well as the time to suppress the viral load can be obtained by solving equation (18). In order to do that, one only needs to know the death rate of the actively infected $CD4^+$ T cells μ_2, the clearance rate of the virus c, as well as the reproductive number $R_{0(u)}$. It is interesting to note that these three parameter estimates are attainable. For how to estimate μ_2, c and $R_{0(u)}$ from viral load measurements under therapy, refer to [9,11,13]. A method for obtaining parameter estimates by using control theory techniques is presented in [17].

4.3 *Incorporating Residualization Error*

The estimation error due to residualization is bounded [14]. If one assumes that the absolute error in time estimation is constant for high enough drug efficacies, including $u = 0$, (even though perfect inhibition of virus replication is not practically attainable) then, this could be utilized to derive an expression for the difference in time estimates due to residualization. For $u = 0$, the equations for the residualization difference model are given by

$$\dot{x}_{1r} = N\mu_2x_{2r} - cx_{1r} \tag{21}$$

$$\dot{x}_{2r} = -\mu_2x_{2r} + kx_{3r} \tag{22}$$

$$\dot{x}_{3r} = -kx_{3r} - \mu_1x_{3r} \tag{23}$$

These equations are linear and the solution for the residualization difference in viral load $x_{1r}(t)$ has the form

$$x_{1r}(t) = B_1e^{\gamma_1 t} + B_2e^{\gamma_2 t} + B_3e^{\gamma_3 t} \tag{24}$$

where

$$\gamma_1 = -\mu_2; \quad \gamma_2 = -(k+\mu_1); \quad \gamma_3 = -c$$

and

$$B_1 = \frac{\gamma_1}{\gamma_2 - \gamma_1}\frac{\gamma_3}{\gamma_3 - \gamma_1}\bar{x_1} \tag{25}$$

$$B_2 = \frac{\gamma_1}{\gamma_1 - \gamma_2}\frac{\gamma_3}{\gamma_3 - \gamma_2}\bar{x_1} \tag{26}$$

$$B_3 = \frac{\gamma_1}{\gamma_1 - \gamma_3}\frac{\gamma_3}{\gamma_2 - \gamma_3}\bar{x_1} \tag{27}$$

and $\bar{x_1} = x_{1ss}$ is the steady state or viral load measured before therapy.

Time estimates can be obtained by adding Equations (18) and (24) and solving for t_{res} and t_{sup}. This however, would increase the number of required parameters to include a not readily attainable estimate for the combined rate $k+\mu_1$, at which latently infected $CD4^+$ T cells are cleared from plasma. Figure 1 shows the viral load time response for when perfect inhibition is assumed for the full, reduced and difference models.

An alternate approach is to consider that simulations show that the differences in response and suppression time estimates due to residualization can be approximated as

$$dif_{res} = t_{res}/R_0 \tag{28}$$

$$dif_{sup} = t_{sup}(1 + 1/R_0) \tag{29}$$

where R_0 can be obtained. This means that residualization differences in time estimates can be obtained if the basic reproductive number is known, by adding the respective difference to the appropriate solution of equation (18).

5. SIMULATION

Figure 2 shows the response time graphs for the full and the reduced order systems when therapy

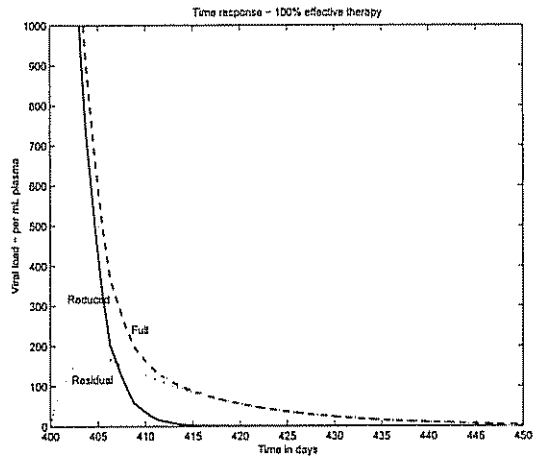

Fig. 1. Viral load time response for $u = 0$. Full (4D nonlinear), reduced (2D nonlinear) and difference(residual) models. Viral load at start of therapy is 5000 copies per mL plasma.

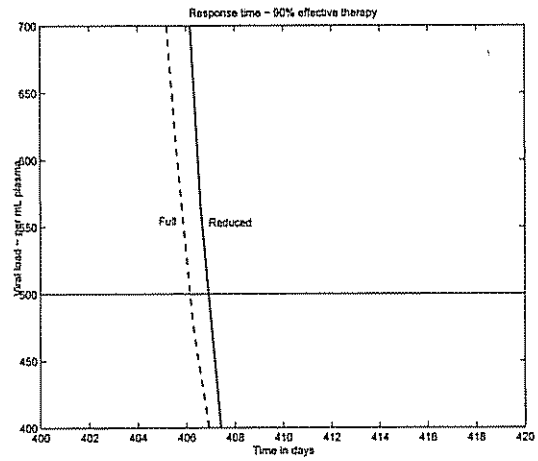

Fig. 2. Response time for full(4D nonlinear) and reduced (2D linear)order systems: chemotherapy effectiveness: 90% ($u = 0.1$). Viral load at start of therapy is 5000 copies per mL plasma.

is on and varying drug efficacies are used. Table 2 summarizes the results with the associated absolute errors in brackets. Similarly, Figure 3 shows the times to suppress the virus to below 50 copies. The results and the associated errors are summarized in Table 3.

Table 2 : Response Times.

Control u(%effect)	Full system days	Reduced days(error)
0.05 (95%)	6	7 (1)
0.10 (90%)	6	7 (1)
0.15 (85%)	7	8 (1)
0.20 (80%)	7	8 (1)
0.25 (75%)	8	9 (1)
0.30 (70%)	9	9 (0)

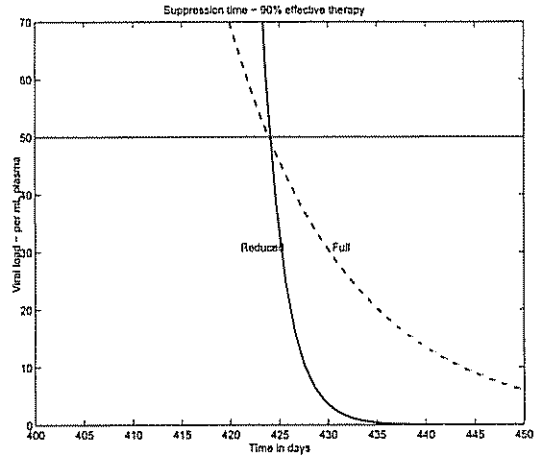

Fig 3. Suppression time for full (4D nonlinear) and reduced (2D linear) order systems: chemotherapy effectiveness: 90% ($u = 0.1$). Viral load at start of therapy is 5000 copies per mL plasma.

Table 3 : Suppression Times.

Control u(%effect)	Full system days	Reduced days(error)
0.05 (95%)	23	23 (0)
0.10 (90%)	24	24 (0)
0.15 (85%)	26	25 (-1)
0.20 (80%)	28	26 (-2)
0.25 (75%)	30	28 (-2)
0.30 (70%)	33	29 (-4)

6. CONCLUSIONS

The following conclusions can be drawn from this study.

(1) Estimates for the response time to therapy and the time to suppress the viral load, can be determined from values for the death rate of the actively infected $CD4^+$ T cells μ_2, the clearance rate of the virus c, the drug efficacy u and either, the basic reproductive number R_0, or the combined rate $k + \mu_1$ at which latently infected $CD4^+$ T cells are cleared from plasma.

(2) The time estimates are parameter dependent and will therefore vary from one individual to the other.

(3) The estimated response times do not exhibit any significant variation with drug efficacy. The initial response is heavily influenced by the virus clearance rate constant c, which is much larger than the actively infected $CD4^+$ T cell clearance rate constant μ_2.

(4) The estimated suppression times are shorter than the actual suppression times. When designing a therapy based on the estimates, the drug dosage is always conservative.

(5) The error in suppression time estimation increases with decreasing drug efficacy. This is because the perfect inhibition assumption used to determine the difference in estimation due to residualization, does not hold for low drug efficacies.

(6) This approach enables the determination of the drug efficacy in order to obtain predetermined response and suppression times.

(7) This approach can be incorporated into an interruptible control strategy for the viral load.

(8) Viral response and suppression time estimates can aid clinicians in scheduling therapy and viral load measurements.

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