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Sensitivity Analysis of the HIV-1 Infection Model with SaturatedCTL Immune Response

R. Ramya[1], R. Rohini[2], and K. Krishnan[*2]

[1]Research Scholar, PG and Research Department of Mathematics, Cardamom Planters' Association College, MADURAI KAMARAJ UNIVERSITY, Madurai-625 021

[2]Assistant Professor, PG & Research Department of Mathematics, Cardamom Planters' Association College, Bodinayakanur- 625 513

[*]drkkmaths@gmail.com (Corresponding author

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Abstract

Recently, a large number of mathematical models that are described by delay differentialequations (DDEs) have appeared in the life sciences. This is an article to show that delay differential models have a richer mathematical framework (compared with models withoutmemory or after-effects) and a better consistency with biological phenomena such as dynamical diseases and cell growth dynamics. In this paper, we present a delay differential model to describe the HIV-1 dynamics model with a CTL immune response with two time delays. We performed a sensitivity analysis of the HIV-1 dynamics model that reveals the parameter values have a major impact on the model dynamics. Our goal is to determine which parameter has the greatest influence on model dynamics and can be verified using graphs.

Keywords: HIV-1 Model, Delays, Sensitivity analysis.
Mathematical Subject Classification (2020): 90C31, 49K40, 93D20.

1 Introduction

In many applications in the life sciences a delay is introduced when there are some hidden variables and processes, which are not well understood but are known to cause a time-lag [1]. Delay differential equations (DDEs) are increasingly used in numerous application areas that include population dynamics (taking into account the gestation and the maturation time), infectious diseases(accounting for the incubation periods), physiological and pharmaceutical kinetics (modelling, for example, hematopoiesis and respiration, where the delays are due, respectively,to cell maturation and blood transport between the lung and brain, etc.), chemical and enzyme kinetics (such as mixing reactants), biological immune response (in which the antibody pro- duction by the T-cell population depends on the antigenic stimulation at an earlier time), the navigational control of ships and aircraft (with, respectively, large and short lags), and more general control problems. We refer to [2–9] for more examples in biomathematics. The objectof a sensitivity analysis is to determine systematically the effect of uncertain parameters on system solutions and the effect of the noisy data on the

certainty to which parameters may be determined; see also [10, 11].

Sensitivity analysis is concerned with the study of the relationship between infinitesimal changes in model parameters and changes in model outputs. Sensitivity information can be used to estimate which parameters are most influential in affecting the behavior of the sim- ulation. Such information is crucial for experimental design, data assimilation, reduction of complex nonlinear models, and evaluating optimization gradients and Jacobians in the settingof dynamic optimization and parameter estimation.

Let us consider the following saturated infection rate on a four-dimensional equations with two delays are as follows: [12]

$$\begin{aligned} \dot{x} &= \lambda - d_1 x(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}, \\ \dot{y} &= \frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - d_2 y(t) - \mu y(t)z(t), \\ \dot{v} &= k y(t) - d_3 v(t), \\ \dot{z} &= \frac{\gamma y(t-\tau_2)z(t-\tau_2)}{h+z(t-\tau_2)} - d_4 z(t). \end{aligned} \tag{1}$$

where the interaction between activated $CD4^+$ T cells, $x(t)$, infected $CD4^+$ T cells, $y(t)$, viruses, $v(t)$ and immune cells, $z(t)$. where activated $CD4^+$ T cells are produced at a rate of λ cells day^{-1}, decay at a rate d_1 day^{-1} and can become infected at a rate that is proportional to the number of infected $CD4^+$ T cells $y(t)$ with a infection rate constant β day^{-1}cell^{-1}. The infected $CD4^+$ T cells are assumed to decay at the rate of d_2 day^{-1} . The CTL responses eliminate at a rate that is proportional to the number of CTLs with a killing rate constant μ day^{-1}cell^{-1}. Free viruses produced from infected cells at the rate k, decay at a rate d_3 day^{-1}. The CTLs immune response to the infection rate γ, d_4 is a decay rate of CTLs immune response . We considered

$$\frac{\gamma y(t)z(t)}{h+z(t)}$$

saturated immune response function to replace the bilinear rate, here h is a saturation constant. Namely, we incorporate a time delay τ_1 to describe the period between healthy cells? contacting with viruses and complete production of viral RNA and protein. τ_2 represents theperiod between infected cells and contacting with CTL's immune cells.

Let $R_0 = \frac{\lambda\beta k}{d_1 d_2 d_3}$. It is well known the importance of the value R_0, which is called as the basic reproductive ration of system (1). Denote $R_1 = \frac{\gamma d_3 d_1 (R_0 - 1)}{khd_4(\alpha d_1 + \beta)}$ where R_1 is called

immunity-activated reproduction number of system (1). Besides, we can show that if $R_1 > 1$, system (1) has an immunity-activated equilibrium

$$I(x_2, y_2, v_2, z_2) = \left(\frac{(d_2 + \mu z_2)(\gamma d_3 + \alpha d_4 k(h + z_2))}{\gamma\beta k}, \frac{d_4(h + z_2)}{\gamma}, \frac{d_4 k(h + z_2)}{\gamma d_3}, \frac{-b + \sqrt{\Delta}}{2a}\right)$$

$$a = d_4\mu k(\alpha d_1 + \beta); \quad b = d_4 k(\alpha d_1 + \beta)(d_2 + h\mu) + d_1\mu\gamma d_3;$$
$$\Delta = (d_4 k(\alpha d_1 + \beta)(d_2 + h\mu) + d_1\mu\gamma d_3)^2 + 4d_2 d_4^2 k^2 h\mu(\alpha d_1 + \beta)^2(R_1 - 1).$$

Next we conclude the following theorems for proving stability analysis through the steady statepoints

Theorem 1. *If $R_0 < 1$, I_0 of model (1) is locally asymptotically stable for any time delay $\tau > 0$. If $R_0 > 1$, I_0 of model (1) is unstable for any time delay $\tau > 0$.*

The following theorem holds that When $R_0 > 1$, the system (1) has a immunity inactivated steady state $I_1 = (x_1, y_1, v_1, 0)$

Theorem 2. *If $R_1 < 1 < R_0$, then the immunity inactivated steady state I_1 of model (1) is locally asymptotically stable in the case of $\tau_2 = 0$. [14]*

When $R_1 < 1 < R_0$, the system (1) has a immunity activated steady state $I_2 = (x_2, y_2, v_2, z_2)$. Then the linearized system (1) at I_2 yields

$$\begin{aligned}
\dot{u}_1 &= -d\,u_1(t) - \frac{\beta v_2}{1 + \alpha v_2}u_1(t) - \frac{\beta x_2}{(1 + \alpha v_2)^2}u_3(t),\\
\dot{u}_2 &= \frac{\beta v_2}{1 + \alpha v_2}u_1(t - \tau_1) + \frac{\beta x_2}{(1 + \alpha v_2)^2}u_3(t - \tau_1) - d\,u_2(t) - \mu u_2(t)y_2,\\
\dot{u}_3 &= ku_2(t) - d_3u_3(t),\\
\dot{u}_4 &= \frac{\gamma v_2}{(h + z_2)^2}u_2(t - \tau_2) + \frac{\gamma z_2}{(h + z_2)^2}u_3(t - \tau_2) - d\,u_4(t).
\end{aligned} \tag{2}$$

From the above Jacobian matrix, we conclude the following theorem

Theorem 3. *Suppose*

1. $R_1 > 1$
2. *If $\tau_1 = 0$ and $\tau_2 > 0$, then the infected steady state I_2 of model (2) is locally asymptotically stable when $\tau_2 < \tau_2^*$. [12]*

2 Parameter sensitivity analysis

The sensitivity and identifiability analysis were done by estimating at each data point the derivative of the clinical score $P = [u_1, u_2, u_3, u_4]^T$ with respect to the vector parameter $q = [d_1, \mu, k, d_2, d_3, \beta, \gamma, \alpha, h]^T$. The sensitivities are dimensionless, as they are scaled with respect to the variables and parameter values. In the following the sensitivity functions with respect to an arbitrary parameter q, for the system (1) are denoted by,

$$P_{i,q} = \frac{\partial P_i(t)}{\partial q}, \quad i = 1, \ldots 4 \tag{3}$$

These sensitivities allow to determine which parameter is least important to the model output and these least sensitive parameters can be fixed and not used for calibration. There are different approaches to find the sensitivity functions of DDEs [13]. However, for simplicity we will use the so called direct approach to find sensitivity functions of system (1).

The corresponding sensitivity system (2), with respect to the parameter 'd_1' is as follows,

$$\begin{aligned}
(\dot{u}_{1,d_1})_{t,d_1} &= -u_{1,d_1}(t) - \frac{\beta v_2}{1+\alpha v_2} u_{1,d_1}(t) - \frac{\beta x_2}{(1+\alpha v_2)^2} u_{3,d_1}(t), \\
(\dot{u}_{2,d_1})_{t,d_1} &= \frac{\beta v_2}{1+\alpha v_2} u_{1,d_1}(t-\tau, d_1) + \frac{\beta x_2}{(1+\alpha v_2)^2} u_{3,d_1}(t-\tau, d_1) - d_1 u_{2,d_1}(t) \\
&\quad - \mu u_{2,d_1}(t) z_2 - \mu u_{2,d_1}(t) y_2, \\
(\dot{u}_{3,d_1})_{t,d_1} &= k u_{2,d_1}(t) - d_3 u_{3,d_1}(t), \\
(\dot{u}_{4,d_1})_{t,d_1} &= \frac{\gamma v_2}{(h+z_2)^2} u_{4,d_1}(t-\tau, d_1) + \frac{\gamma z_2}{(h+z_2)} u_{4,d_1}(t-\tau, d_1) - d_1 u_{4,d_1}(t).
\end{aligned} \tag{4}$$

The corresponding sensitivity system (2), with respect to the parameter 'd_2' is as follows,

$$(\dot{u}_1)_{t,d_2} = -d_1 u_{1,d_2}(t) - \frac{\beta v_2}{1+\alpha v_2} u_{1,d_2}(t) - \frac{\beta x_2}{(1+\alpha v_2)^2} u_{3,d_2}(t),$$

$$(\dot{u}_2)_{t,d_2} = \frac{\beta v_2}{(t-\tau, d_2) + u_{1,d_2}(t-\tau, d_2) - u_{2,d_2}(t)} + \frac{\beta x_2}{u_{1,d_2}(t-\tau, d_2) + u_{3,d_2}(t-\tau, d_2) - u_{2,d_2}(t)} - d_2 u_{2,d_2}(t) - \frac{\beta v_2}{(1+\alpha v_2)^2} u_{1,d_2}(t) + \frac{\beta x_2}{(1+\alpha v_2)^2} u_{3,d_2}(t) - \mu u_{2,d_2}(t) z_2 - \mu u_{2,d_2}(t) y_2,$$

$$(\dot{u}_3)_{t,d_2} = k u_{2,d_2}(t) - d_3 u_{3,d_2}(t),$$

$$(\dot{u}_4)_{t,d_2} = \frac{\gamma v_2}{(t-\tau, d_2) + u_{1,d_2}(t-\tau, d_2) - u_{4,d_2}(t)} + \frac{\gamma z_2}{u_{1,d_2}(t-\tau, d_2) + u_{3,d_2}(t-\tau, d_2) - u_{4,d_2}(t)} - d_4 u_{4,d_2}(t). \quad (5)$$

The corresponding sensitivity system (2), with respect to the parameter 'd_3' is as follows,

$$(\dot{u}_1)_{t,d_3} = -d_1 u_{1,d_3}(t) - \frac{\beta v_2}{1+\alpha v_2} u_{1,d_3}(t) - \frac{\beta x_2}{(1+\alpha v_2)^2} u_{3,d_3}(t),$$

$$(\dot{u}_2)_{t,d_3} = \frac{\beta v_2}{(t-\tau, d_3) + u_{1,d_3}(t-\tau, d_3) - u_{2,d_3}(t)} + \frac{\beta x_2}{u_{1,d_3}(t-\tau, d_3) + u_{3,d_3}(t-\tau, d_3) - u_{2,d_3}(t)} - d_2 u_{2,d_3}(t) - \frac{\beta v_2}{(1+\alpha v_2)^2} u_{1,d_3}(t) + \frac{\beta x_2}{(1+\alpha v_2)^2} u_{3,d_3}(t) - \mu u_{2,d_3}(t) z_2 - \mu u_{2,d_3}(t) y_2,$$

$$(\dot{u}_3)_{t,d_3} = k u_{2,d_3}(t) - u_3(t),$$

$$(\dot{u}_4)_{t,d_3} = \frac{\gamma v_2}{(t-\tau, d_3) + u_{1,d_3}(t-\tau, d_3) - u_{4,d_3}(t)} + \frac{\gamma z_2}{u_{1,d_3}(t-\tau, d_3) + u_{3,d_3}(t-\tau, d_3) - u_{4,d_3}(t)} - d_4 u_{4,d_3}(t). \quad (6)$$

4,d_3

The corresponding sensitivity system (2), with respect to the parameter 'β' is as follows,

$$(\dot{u}_1)_{t,\beta} = -d_1 u_{1,\beta}(t) - \frac{\nu_2}{1+\alpha\nu_2} u_{1,\beta}(t) - \frac{x_2}{(1+\alpha\nu_2)^2} u_{3,\beta}(t),$$

$$(\dot{u}_2)_{t,\beta} = \frac{\nu_2}{1+\alpha\nu_2} u_{1,\beta}(t-\tau_1,\beta) + \frac{x_2}{(1+\alpha\nu_2)^2} u_{3,\beta}(t-\tau_1,\beta) - d_2 u_{2,\beta}(t) - \mu u_{2,\beta}(t) z_2 - \mu u_{2,\beta}(t) y_2,$$

$$(\dot{u}_3)_{t,\beta} = k u_{2,\beta}(t) - d_3 u_{3,\beta}(t),$$

$$(\dot{u}_4)_{t,\beta} = \frac{\gamma y_2}{(h+z_2)^2} u_{4,\beta}(t) - \frac{\gamma z_2}{(h+z_2)} u_{2,\beta}(t) - d_4 u_{4,\beta}(t). \quad (7)$$

The corresponding sensitivity system (2), with respect to the parameter 'α' is as follows,

$$(\dot{u}_1)_{t,\alpha} = -d_1 u_{1,\alpha}(t) + \frac{\beta\alpha\nu_2}{1+\alpha\nu_2} u_{1,\alpha}(t) - \frac{\beta\alpha^2 x_2}{(1+\alpha\nu_2)^2} u_{3,\alpha}(t),$$

$$(\dot{u}_2)_{t,\alpha} = -\frac{\beta\alpha\nu_2}{1+\alpha\nu_2} u_{1,\alpha}(t-\tau_1,\alpha) + \frac{\beta\alpha^2 x_2}{(1+\alpha\nu_2)^2} u_{3,\alpha}(t-\tau_1,\alpha) - d_2 u_{2,\alpha}(t) - \mu u_{2,\alpha}(t) z_2 - \mu u_{2,\alpha}(t) y_2,$$

$$(\dot{u}_3)_{t,\alpha} = k u_{2,\alpha}(t) - d_3 u_{3,\alpha}(t),$$

$$(\dot{u}_4)_{t,\alpha} = \frac{\gamma y_2}{(h+z_2)^2} u_{4,\alpha}(t) - \frac{\gamma z_2}{(h+z_2)} u_{2,\alpha}(t) - d_4 u_{4,\alpha}(t). \quad (8)$$

The corresponding sensitivity system (2), with respect to the parameter 'μ' is as follows,

$$
\begin{aligned}
(\dot{u}_1)_{t,\mu} &= -u_1(t) - \frac{\beta v_2}{1+\alpha v_2} u_1(t) - \frac{\beta x_2}{(1+\alpha v_2)^2} u_3(t), \\
(\dot{u}_1)_{t,\mu} &= \frac{\beta v_2}{1+\alpha v_2} u_1(t-\tau,\mu) + \frac{\beta x_2}{(1+\alpha v_2)^2} u_3(t-\tau,\mu) - d_1 u_{1,\mu}(t) \\
&\quad - u_2(t) z_2 - u_2(t) y_2, \\
(\dot{u}_3)_{t,\mu} &= k u_{2,\mu}(t) - d_3 u_{3,\mu}(t), \\
(\dot{u}_4)_{t,\mu} &= \frac{\gamma y_2}{(h+z_2)^2} u_1(t-\tau,\mu) + \frac{\gamma z_2}{(h+z_2)} u_2(t-\tau,\mu) - d_4 u_{4,\mu}(t).
\end{aligned} \tag{9}
$$

The corresponding sensitivity system (2), with respect to the parameter 'k' is as follows,

$$
\begin{aligned}
(\dot{u}_1)_{t,k} &= -u_1(t) - \frac{\beta v_2}{1+\alpha v_2} u_1(t) - \frac{\beta x_2}{(1+\alpha v_2)^2} u_3(t), \\
(\dot{u}_1)_{t,k} &= \frac{\beta v_2}{1+\alpha v_2} u_1(t-\tau,k) + \frac{\beta x_2}{(1+\alpha v_2)^2} u_3(t-\tau,k) - d_1 u_{1,k}(t) \\
&\quad - u_2(t) z_2 - u_2(t) y_2, \\
(\dot{u}_3)_{t,k} &= u_2(t) - d_3 u_{3,k}(t), \\
(\dot{u}_4)_{t,k} &= \frac{\gamma y_2}{(h+z_2)^2} u_1(t-\tau,k) + \frac{\gamma z_2}{(h+z_2)} u_2(t-\tau,k) - d_4 u_{4,k}(t).
\end{aligned} \tag{10}
$$

The corresponding sensitivity system (2), with respect to the parameter 'γ' is as follows,

$$
\begin{aligned}
(\dot{u}_1)_{t,\gamma} &= -u_1(t) - \frac{\beta v_2}{1+\alpha v_2} u_1(t) - \frac{\beta x_2}{1+\alpha v_2} u_3(t),
\end{aligned}
$$

$$(1+\alpha v_2)^2 \qquad 3,\gamma$$

$$(u_i)_{t,\gamma} = \frac{\beta v_2}{(t-\tau,\gamma)+} \frac{\beta x_2}{u_2 t,\gamma\, 1+\alpha v_2} (t-\tau,\gamma) - d_2 u_{2,\gamma}(t) - \frac{u_1}{1,\gamma} + \frac{u_1}{1\,(1+\alpha v_2)^2\; 3,\gamma} - 1\,2\;\; 2,\gamma$$

$$-u_2(t)z_2 - u_2(t)y_2,$$

$$(u_3)_{t,\gamma} = u_2(t) - d_3 u_{3,\gamma}(t),$$

$$(u_i)_{t,\gamma} = \frac{y_2}{u\,(t-\tau,\gamma)+} \frac{z_2}{u\,4\;t,\gamma\,(h+z_2)^2} (t-\tau,\gamma) - d_4 u_{4,\gamma}(t). \qquad (11)$$

$$4 \qquad 2\,(h+z_2) \qquad 2,\gamma \qquad 2\,4 \;\; 4,\gamma$$

The corresponding sensitivity system (2), with respect to the parameter 'h' is as follows,

$$(u_i)_{t,h} = \frac{\beta v_2}{-u_1(t) - \frac{u_1}{1\;t,h\;1+\alpha v_2}} \frac{\beta x_2}{u_2(t) - \frac{u_1}{1,h\,(1+\alpha v_2)^2\; 3,h}} (t),$$

$$(u_i)_{t,h} = \frac{\beta v_2}{(t-\tau,h)+} \frac{\beta x_2}{u_2 t,h\, 1+\alpha v_2} (t-\tau,h) - d_2 u_{2,h}(t) - \frac{u_1}{1,h} + \frac{u_1}{1\,(1+\alpha v_2)^2\; 3,h} - 1\,2\;\; 2,h$$

$$-u_2(t)z_2 - u_2(t)y_2,$$

$$(u_3)_{t,h} = u_2(t) - d_3 u_{3,h}(t),$$

$$(u_4)_{t,h} = \frac{\gamma h^2 y_2}{(h+z_2)^2} u_4(t-\tau_2,h) - \frac{\gamma h z_2}{(h+z_2)} u_{2,h}(t-\tau_2,h) - d_4 u_{4,h}(t). \qquad (12)$$

$$2 \qquad\qquad 2$$

The semi-relative sensitivity solutions (depicted in Figures. 1- 32) are calculated by simply multiplying the unmodified sensitivity solutions by a chosen parameter which provides informa- tion concerning the amount the state will change when that parameter is doubled. It is best to calculate this type of sensitivity solution to obtain a more thorough understanding of the dynamics. Sensitivity results are obtained and its shown in the following Figures.

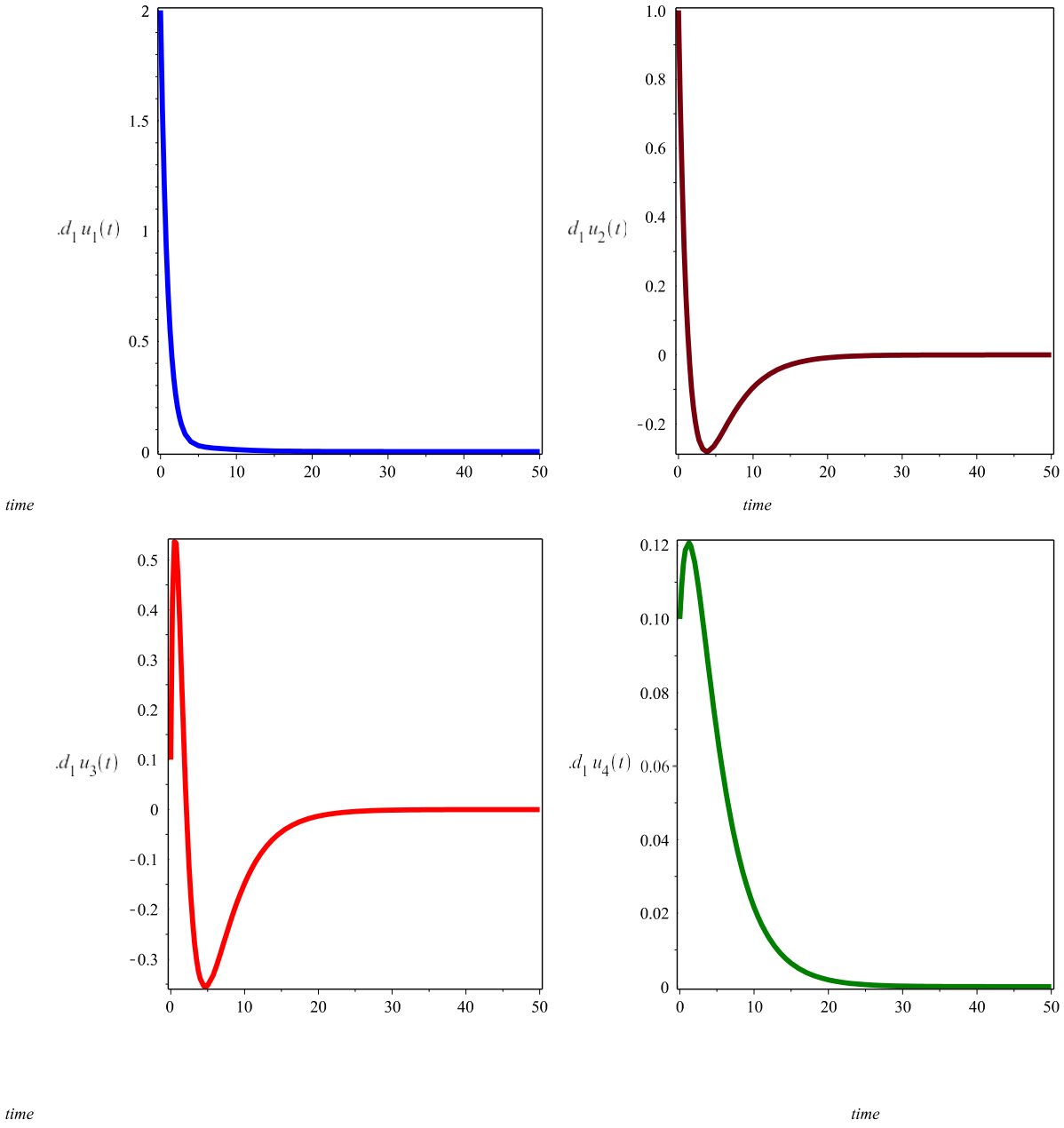

Fig. 1-4 shows the semi-relative sensitivity analysis for the system (4) for d_1 = 0.02 respectively.

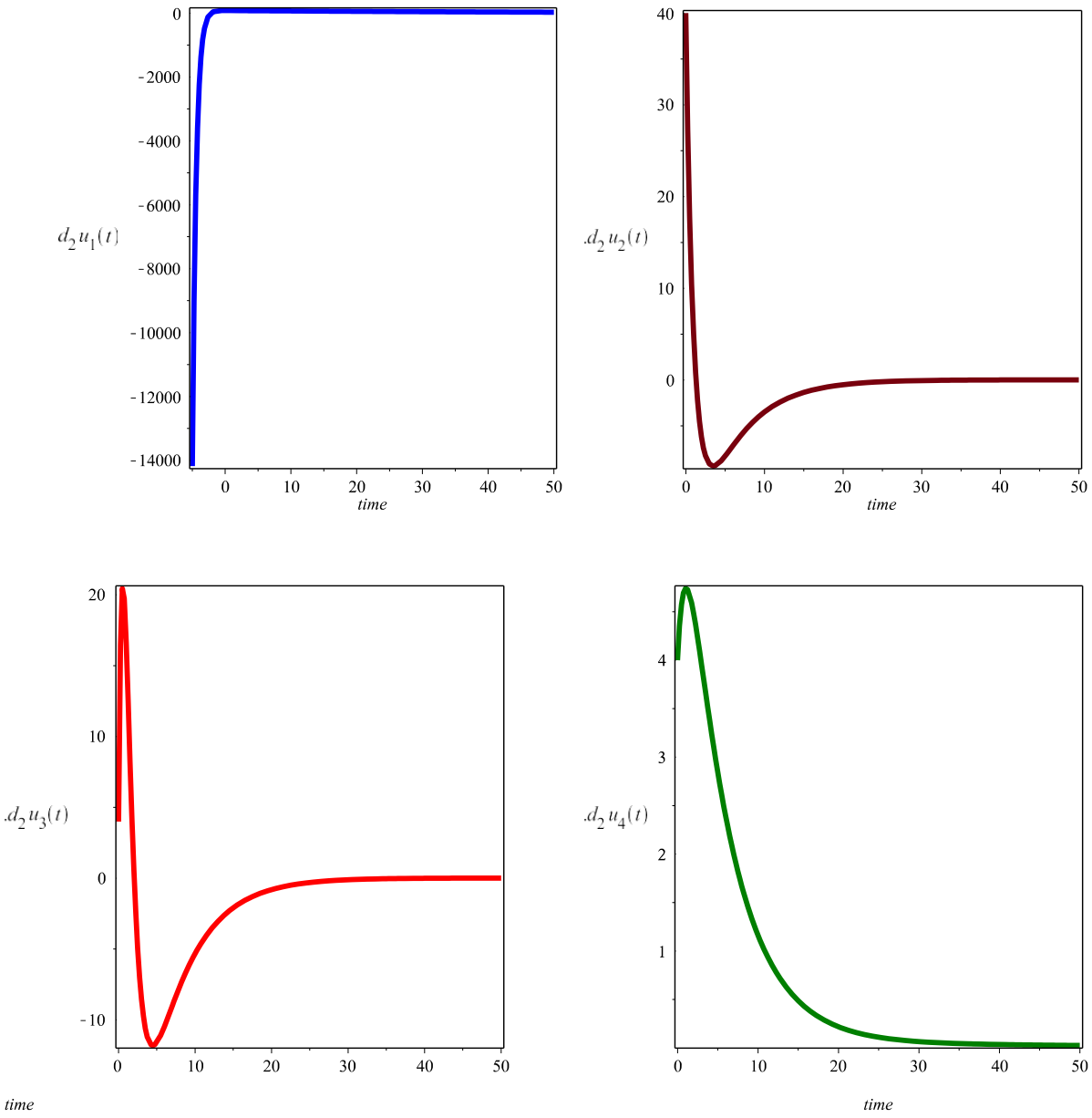

Fig. 5-8 shows the semi-relative sensitivity analysis for the system (5) for $d_2 = 0.8$ respectively.

From Fig.1-4 and 5-8 the parameters 'd_1' and d_2 are very sensitive in the free virus cells. However, those parameters are inversely proportional to increasing the initial function, and they are very sensitive in the early time intervals. In terms of the parameter, d_2 decreases with the initial function and is extremely sensitive in activated $CD4 + T$ cells.

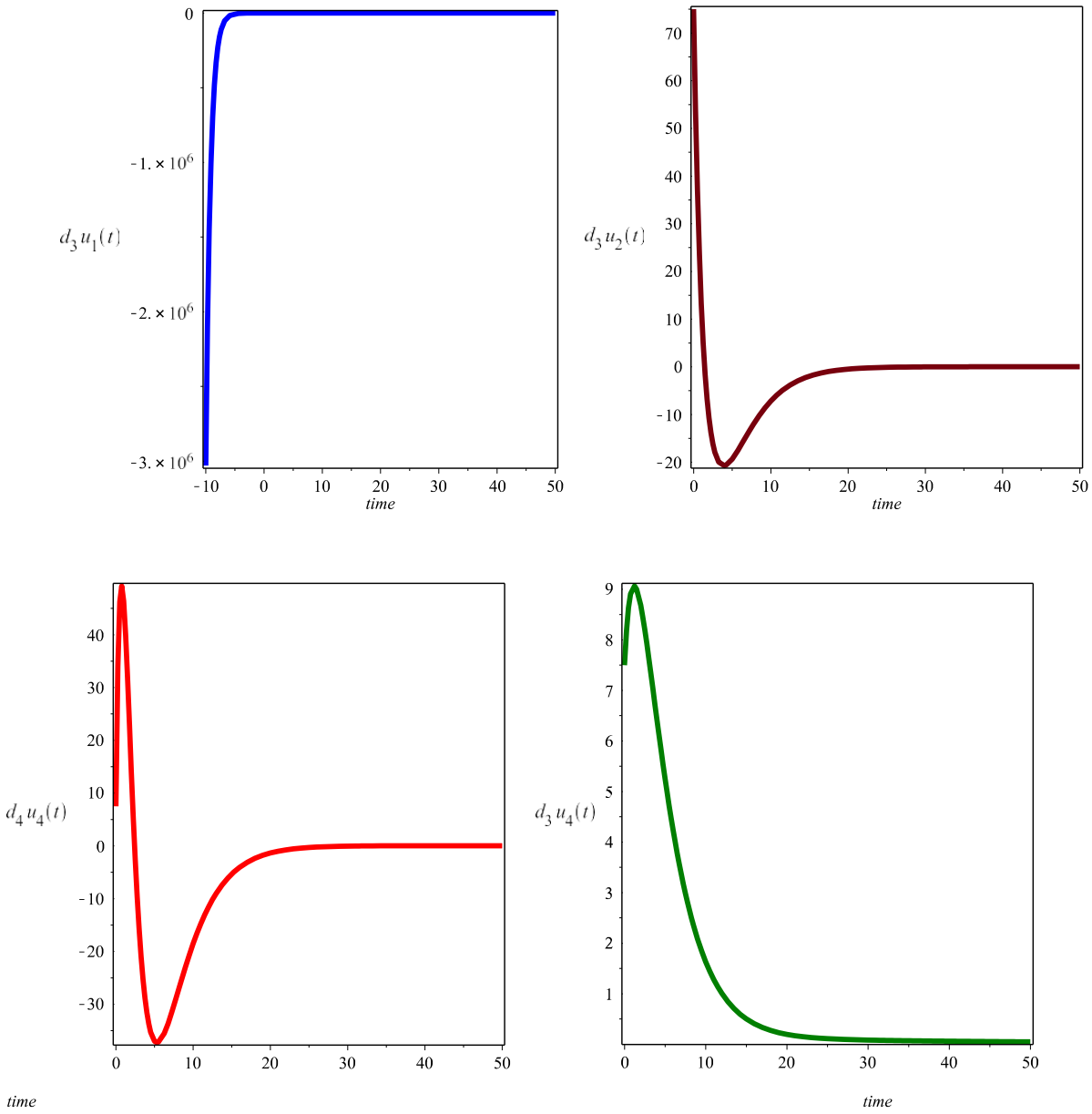

Fig. 9-12 shows the semi-relative sensitivity analysis for the system (6) for d_3 = 1.5 respectively.

According to Fig.9-12, the parameter d_3 is extremely sensitive in free virus cells. However, increasing the initial function has a negative proportional effect on this parameter, and it is very sensitive in the early time intervals. In terms of the parameter, d_3 decreases with the initial function and is extremely sensitive in activated $CD4 + T$ cells.

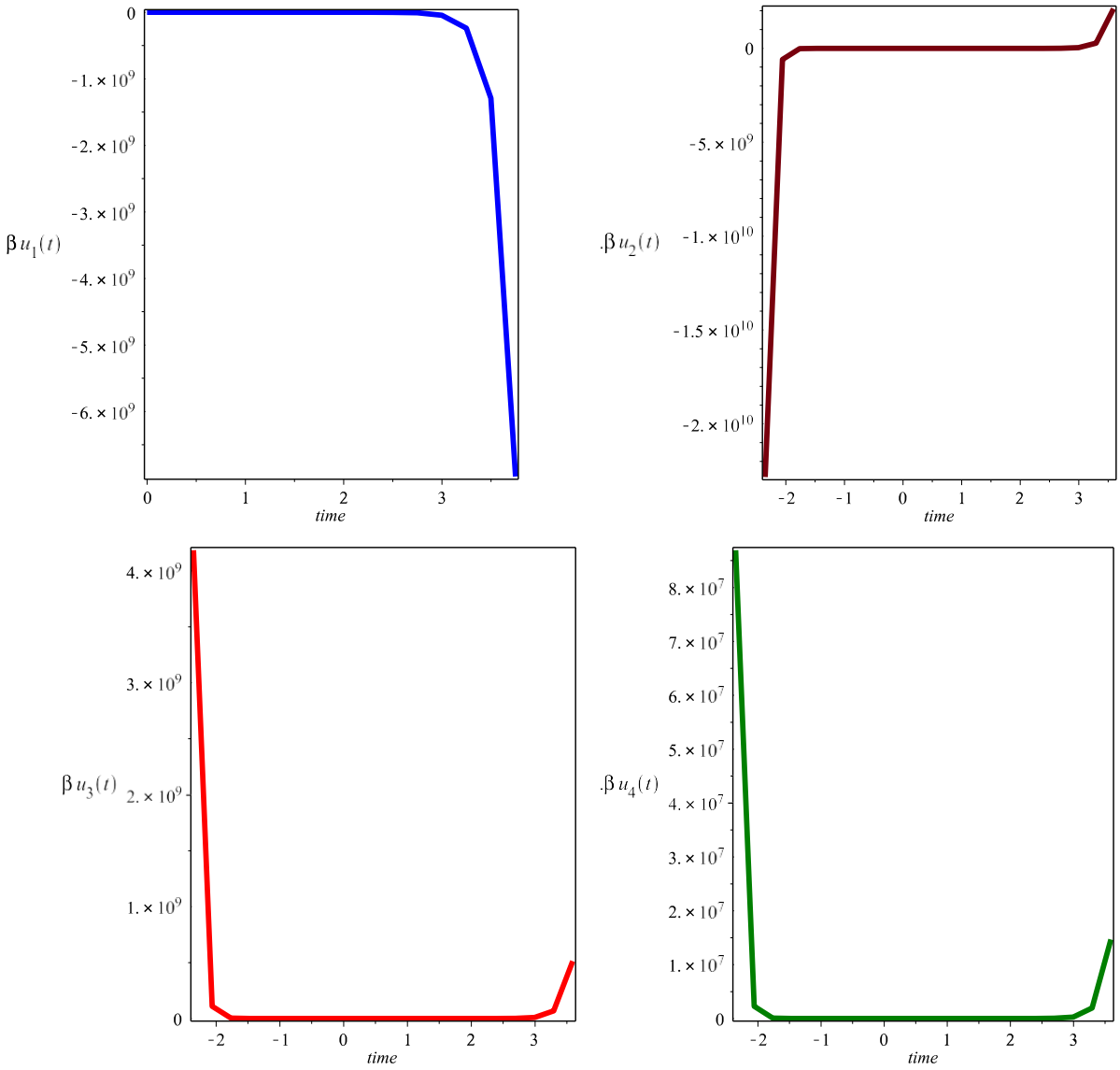

Fig. 13-16 show the semi-relative sensitivity analysis for the system (7) for β = 0.001 respectively.

From Fig. 13-16, the parameters β are sensitive in the early time intervals and their sensitivity decreases by time to be insensitive in all cells.

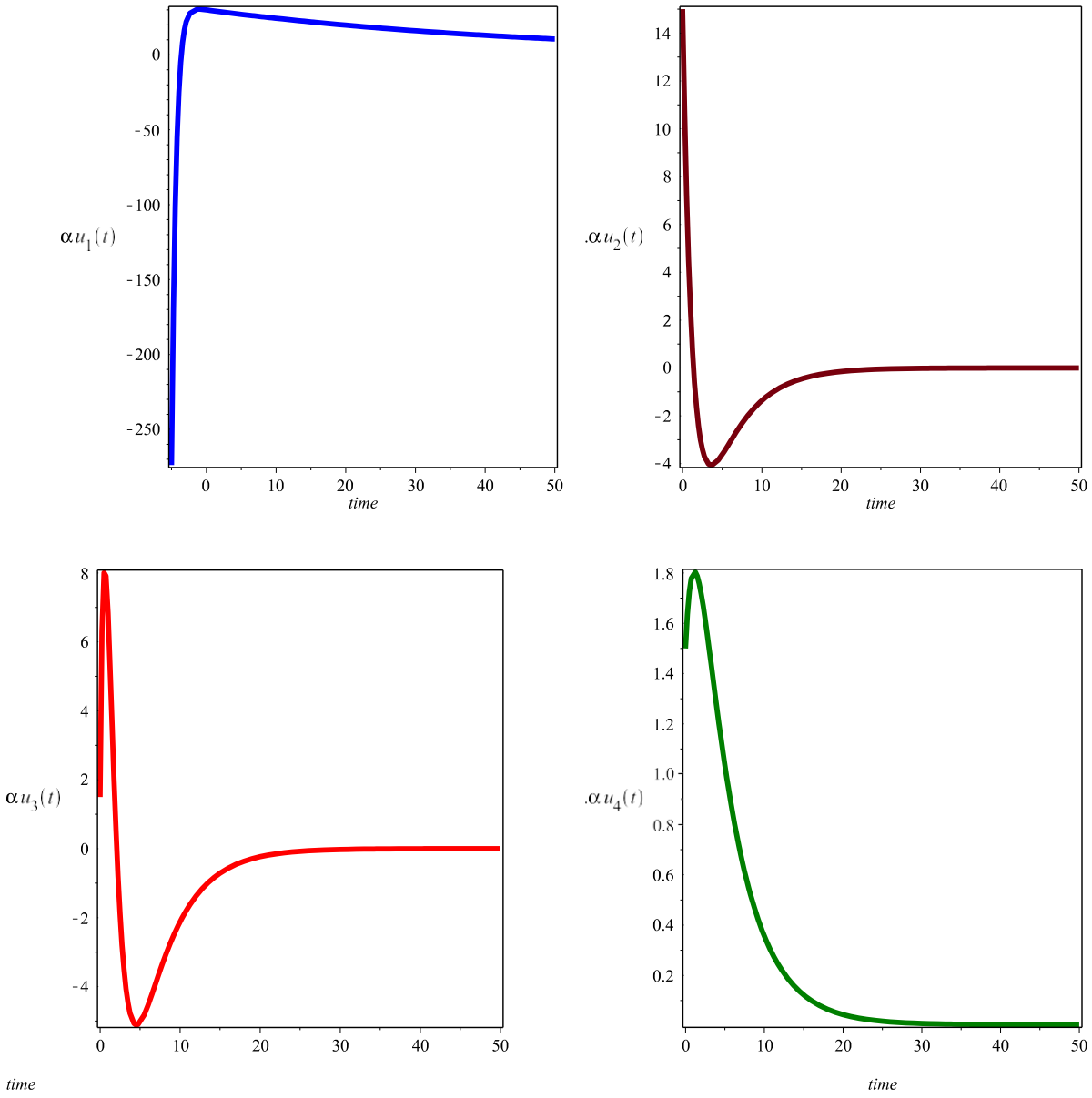

Fig. 17-20 shows that the semi-relative sensitivity analysis for the system (8) for α = 0.3 respectively.

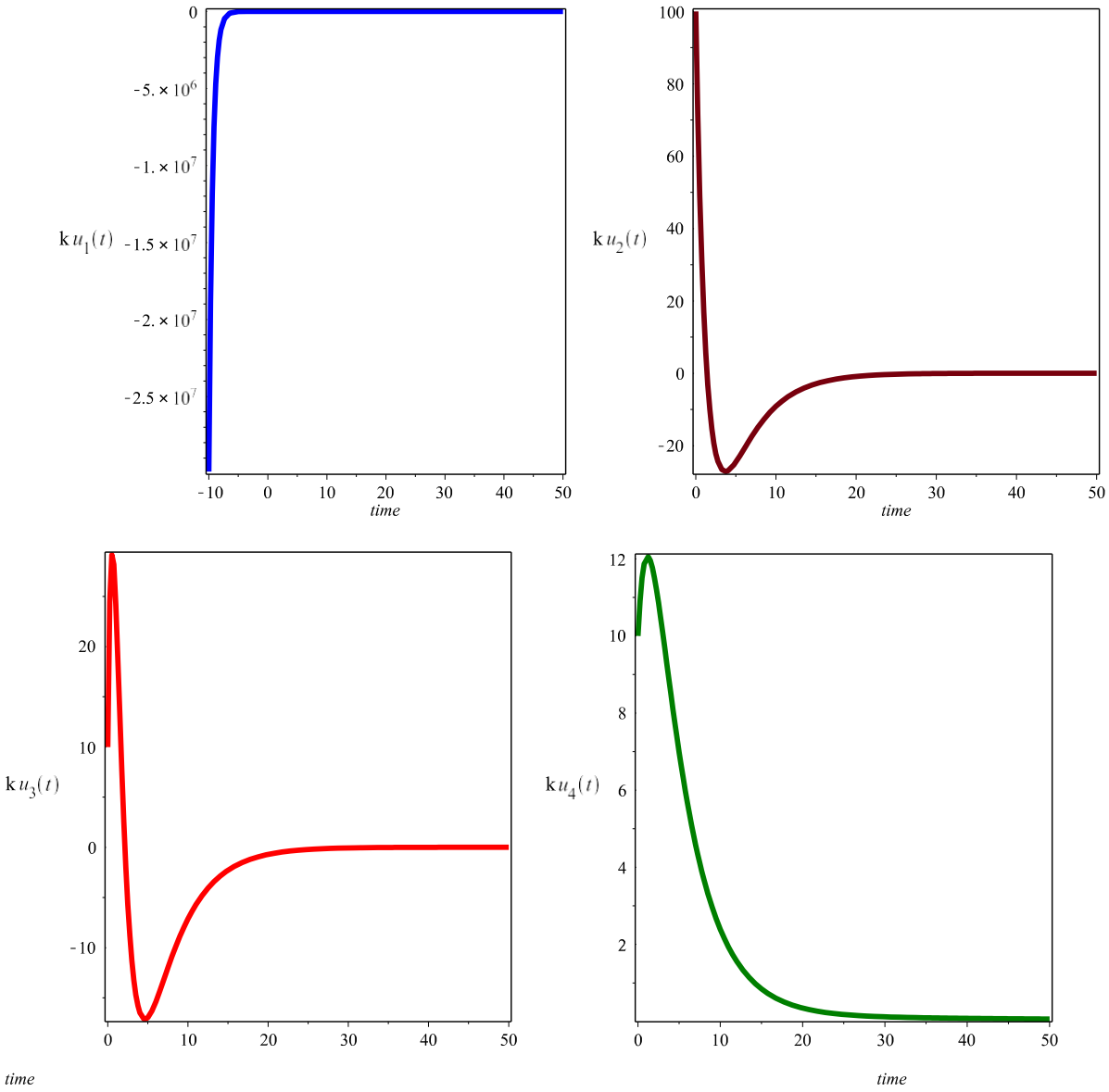

Fig. 21-24 show the semi-relative sensitivity analysis for the system (10) for *k* = 2 values respectively.

The parameters α and k are inversely proportional to increasing the initial function, as shownin Figs. 17-20 and 21-24, and they are very sensitive in the early time intervals.

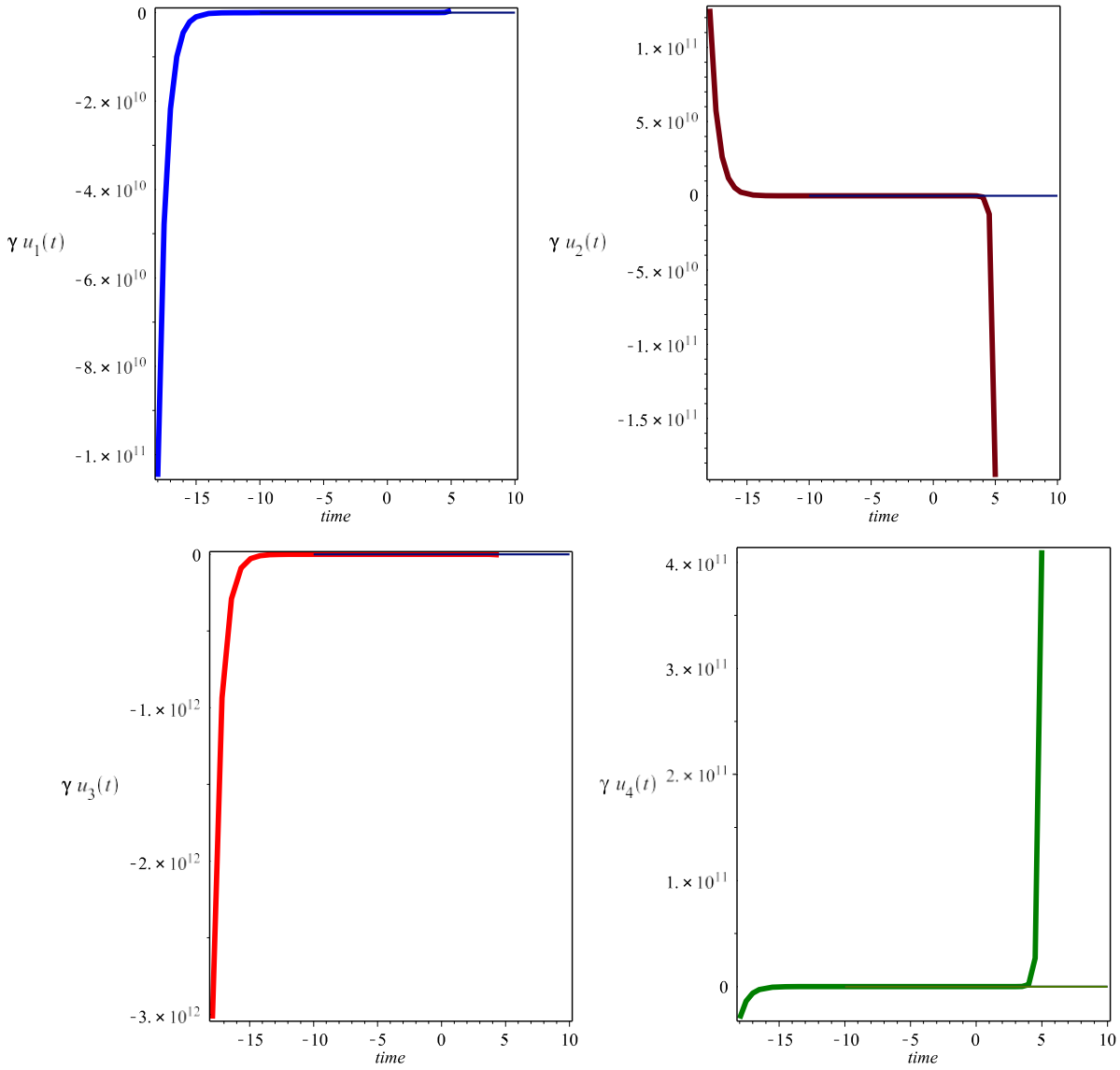

Fig. 25-28 show the semi-relative sensitivity analysis for the system (11) for γ = 0.025 respectively.

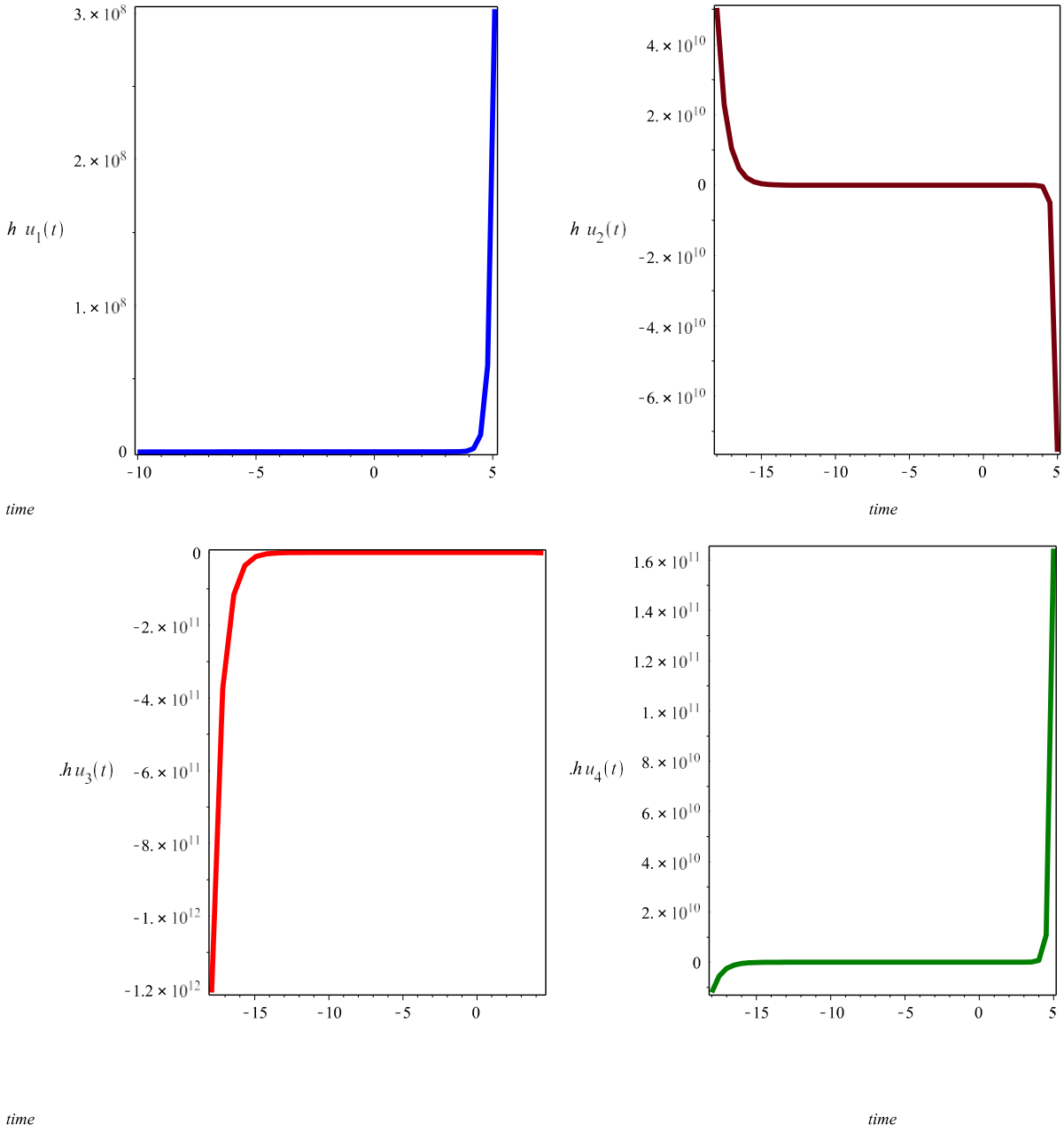

Fig. 29-32 shows that the semi-relative sensitivity analysis for the system (12) for *h* = 0.1 respectively.

From Fig. 25-28 and 29-32, the parameters γ and h are sensitive in the early time intervals and their sensitivity decreases by time to be insensitive in all cells.

Also from the above plots, we observe that a small change in any parameter can produce significant changes in the levels of the system (4-12). The parameters β, γ, and $h$play an impor- tant role in the model dynamics here. since it is very insensitive to all cells. As a result, a smallchange in the

level of infection rate β', immune response to infection rate γ, and saturation constant h has no effect on that parameter. The size of the perturbation should be selected with care when determining the effect of the parameter on the outputs.

3 Conclusion

In this paper, we have incorporated time delays into our HIV-1 dynamic model. Special em- phasis was given to investigate the sensitivity of HIV-1 model due to perturbing the parameters appearing in the model and the initial conditions of the model using the direct approach. For using these analysis, we can easily see that the infection rate parameter β, γ and h play a vital role in the model dynamics. The sensitivity functions are useful to evaluate which parameters have a significant uncertainty effect in the HIV-1 viral dynamics model.

References

[1] K. Cooke, Z. Grossman, Discrete delays, distributed delays and stability switches, *J. Math. Anal. Appl.*, 86: 592624, (1982).

[2] C.T.H. Baker, G.A. Bocharov and C.A.H. Paul, Mathematical Modelling of the Interleukin-2 T-Cell System: A Comparative Study of Approaches Based on Ordinary and Delay Differential Equations, *J. theor. Medicine* 2: 117-128, (1997).

[3] C.T.H. Baker, G.A. Bocharov, C.A.H. Paul and F.A. Rihan, Modelling and Analysis of Time-Lags in Cell Proliferation, *J. Math. Biol.* 37(4): 341-371, (1998).

[4] C.T.H. Baker, G.A. Bocharov and F.A. Rihan, A Report on the Use of Delay Differential Equations in Numerical Modelling in the Biosciences, *MCCM Tech. Rep.*, 343, Manch- ester,ISSN 1360-1725, (1999).

[5] G.A. Bocharov and A.A. Romanyukha, Mathematical Model of Antiviral Immune- Response-III - Influenza-A Virus Infection, *J. theor. Biol.*, 167: 323-360,(1994).

[6] G.I. Marchuk, A.A. Romanyukha and G.A. Bocharov, Mathematical Model of Antiviral Immune-Response. II.Parameter Identification for Acute Viral Hepatitis B, *J. theor. Biol.*,151: 41-70, (1991).

[7] P. Krishnapriya, M. Pitchaimani, Optimal control of mixed immunotherapy and chemother- apy of tumours with discrete delay, *Int. J. Dynam. Control* 5: 872-892, (2017).

[8] P. Krishnapriya, M. Pitchaimani, Tarynn M. Witten, Mathematical analysis of an influenza A epidemic model with discrete delay, *J. Comput. and Appl. Math.* , 324: 155-172, (2017).

[9] N. S. Ravindran, M. Mohamed Sheriff, P. Krishnapriya, Analysis of tumour-immune evasion with chemoimmuno therapeutic treatment with quadratic optimal control, *J. Biol. Dynam.*,11(1): 480-503, (2017).

[10] R.P. Dickinson and R.J. Gelinas, Sensitivity Analysis of Ordinary Differential Equation System- a Direct Method, *J. Comput. Phys.* 21:123-143, (1976).

[11] L. Eno, J.G. Beumee and H. Rabitz, Sensitivity Analysis of Experimental Data, *Appl. Math. Comput.*, 16:153-163, (1985).

[12] R. Ramya, M.C. Maheswari, K. Krishnan,Modified HIV-1 infection model with delay in Saturated CTL immune response *Commun. Math. Biol. Neurosci.*, doi.org/10.28919/cmbn/7581

(2022).

[13] F.A. Rihan, Sensitivity analysis of dynamical systems with time lags, *J. Comput. Appl. Math.*, 151, 445-463, (2003).

[14] Jian Ren, Rui Xu, Cand Liangchen Li Global stability of an HIV infection model with saturated CTL immune response and intracellular delay, *Mathematical Biosciences and Engineering* 18(1): 5768.