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Numerical solution for linear fuzzy differential equation in HIV infection

Muhammad Badrul Ramle and Normah Maan
Department of Mathematical Sciences, Faculty of Science, Universiti Teknologi Malaysia, 81310 Johor Bahru, Johor, Malaysia.
Corresponding Author: normahmaan@utm.my

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ABSTRACT

This study discusses a fuzzy mathematical model of human immunodeficiency virus (HIV) infection consist a linear fuzzy differential system. The system describes the uncertain immune cell level and the viral load for different immune system's strength of HIV-infected patients. The immune system consists of the cluster of differentiation 4 (CD4+ T) and cytotoxic T-lymphocyte (CD8+ T) cell. The dynamic behavior of the immune system and the viral load of the different group of patients which weak, moderate and strong immune strength are analyse and compared. The numerical solution of the system is obtained by Runge-Kutta fourth order method. Simulation results show that the fuzzy differential system can describe the uncertainty immune cell level and HIV viral loads which due to the existing patients with different strength of the immune system.

Keywords Numerical Solution, Fuzzy Differential Equation, Runge-Kutta Fourth-Order Method.

1. INTRODUCTION

Fuzzy differential equation is one of the ways to model the dynamical system under uncertainty. This topic has become the popular among the mathematic researchers since it can be used in many different branches such as in the physics, astronomy, biology and population. These equations are used to modelling the cell growth, the dynamical population and dynamical human immunodeficiency virus (HIV) infection problem [1].

The term fuzzy differential equation was introduced in 1978 by the Kandel and Byat [2]. Since then, the theory of fuzzy differential equations seems to have split into two independent branches, where the first one relies upon the notion of Hukuhara derivative while the other does not [3]. The solution of fuzzy differential equation interpreted by Hakuhara derivative becomes fuzzier as time goes by. Hence the fuzzy solution behaves quite differently from the crisp solution [4]. In 1985, Takagi and Sugeno [5] first proposed the use of fuzzy rules in a fuzzy dynamic model [6].

Mathematical modelling has been used to study the HIV pathogenesis behaviour and articles can be found in [4], and [7-16]. Since there are many parameters involve that are uncertain, Zarei et *al* [3] used fuzzy approach to investigate the intrinsic fuzziness of the immune system's strength in HIV-infected patients. In their paper they use the approximate explicit solution based on a fitting method in order to solve the equation.

In this paper, the linear fuzzy differential system is used in order to describe the behaviour of CD4+ T-cells and CTLs level and the viral load in different patients. The numerical solution of the system by Runge-Kutta Fourth-order method is discussed.

2. PRELIMINARIES

We give some definitions and terminologies on fuzzy theory that necessary in this work.

Definition 1 [17]
A fuzzy set A, $A = \{(x, \mu_A(x)) | \, x \in R\}$ in R is characterized by a membership function $\mu_A(x)$ which associates with each point in R a real number in the interval [0, 1], with the values of $\mu_A(x)$ at x, representing the "degree of membership" of x in A. Thus, the nearer value of $\mu_A(x)$ to 1, the higher the grade of membership of x in A.

Definition 2 [17]
We define α-cut of A, $\mu_\alpha = \{x \in R | \mu_A(x) \geq \alpha\}$ with $0 < \alpha \leq 1$.

Definition 3 [17]
A fuzzy set μ is called a fuzzy number in R if

i. μ_A is upper semicontinous on R.
ii. A is a convex fuzzy set, that is, $\mu_A(\gamma x + (1-\gamma)y) \geq \min\{\mu_A(x), \mu_A(y)\}$ for all $x, y \in R, \gamma \in [0,1]$.
iii. μ_A is normal, that is there exist a unique $\mu_A(x_0) = 1$,
iv. The support of A is compact.

Fuzzy arithmetic of fuzzy number in term α-cut are as follows:

i. $[u \oplus v]_\alpha = [\underline{u}_\alpha + \underline{v}_\alpha, \overline{u}_\alpha + \overline{v}_\alpha]$

ii. $[u \ominus v]_\alpha = [\underline{u}_\alpha - \overline{v}_\alpha, \overline{u}_\alpha - \underline{v}_\alpha]$

iii. $[u \otimes v]_\alpha = [min\{\underline{u}_\alpha \underline{v}_\alpha, \underline{u}_\alpha \overline{v}_\alpha, \overline{u}_\alpha \underline{v}_\alpha, \overline{u}_\alpha \overline{v}_\alpha\}, min\{\underline{u}_\alpha \underline{v}_\alpha, \underline{u}_\alpha \overline{v}_\alpha, \overline{u}_\alpha \underline{v}_\alpha, \overline{u}_\alpha \overline{v}_\alpha\}]$

where $\oplus$, $\ominus$, $\otimes$ denote the addition, minus and multiplication operator.

Definition 4 [17]
Fuzzy triangular membership function is formulated as below:

$$\mu_A(x) = \begin{cases} 1 - \dfrac{m-x}{b}, & m - b \le x < m \\ 1 - \dfrac{x-m}{c}, & m \le x \le m + c \\ 0 \quad, & otherwise \end{cases}$$

The membership function of the triangular fuzzy number be characterized with the canter m, left wide b ≥0, and the right wide c ≥ 0. And we use the notation $A = (m, b, c)$. A triangular fuzzy number is called the symmetric triangular fuzzy number if it left width and the right width is equal (b=c) and denote by $A = (m, b)$. Figure 1 is an example of triangular fuzzy number.

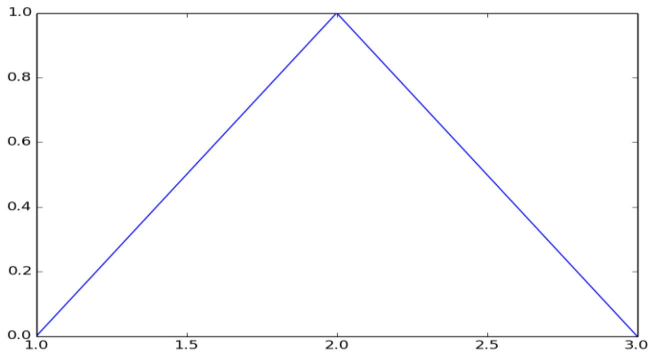


Figure 1: Example of fuzzy triangular $A = (2,1)$.

3. FUZZY LINEAR ORDINARY DIFFERENTIAL SYSTEM OF HIV INFECTION

HIV infection can be described as the disease of the immune system, with vigorous depletion of the defensive cells which is CD4+ T cell. This phenomena will result in immunosuppression and defencelessness to opportunistic infections. When the infection occurs, HIV is transmitted into the body and CD4+ T cell molecule will bind to the HIV receptor as the defending process. HIV is a retrovirus that require host to survive. HIV attached itself to this cell and inserted the genetic material into CD4+ T cell, and then by using the enzyme called reverse transcriptase to convert viral ribonucleic acid (RNA) into deoxyribonucleic acid (DNA) and change the function CD4+ T cell into the HIV factory. Then the new virus particles are release by bursting the infected cell [4]. CD4+ T-cell act as the messenger that sends the signal to the other immune cell by releasing cytokines. CTLs cell usually respond to this message and set out to eliminate HIV cell. In this case, the strong immune system leads to the lower rate of CD4+ T-cell depletion and it vice versa. CD4+ T cell molecule decrease by bursting during the proliferation becomes unable to respond or act against pathogen and the immune system become weak [9]. At this stage the HIV patients turn to AIDS patients. Fuzzy linear system below was proposed by Zarei et al [4].

$$\dot{\tilde{x}}(t) = \tilde{l} \ominus \tilde{s} \otimes \tilde{x}(t) \ominus \tilde{c} \otimes \tilde{v}(t) \tag{1}$$

Equation (1) represents the dynamic concentration of the CD4+ T cell at time *t*. The production of the CD4+ T cell from the source at constant rate represent by $\tilde{l}$. We assume that CD4+ T cell has a finite live span and die at the rate $\tilde{s}$ per cell. The number of these cell which are cause by natural death represent by the term $\tilde{s} \otimes \tilde{x}$. The CD4+ T cell are loss during the infection by the virus particle at a rate $\tilde{c}$ and the term of the free virus destroy CD4+ T cell is $\tilde{c} \otimes \tilde{v}$.

$$\dot{\tilde{v}}(t) = \tilde{k} \otimes \tilde{v}(t) \ominus \tilde{a} \otimes \tilde{z}(t) \tag{2}$$

Equation (2) represents the rate of change virus population. $\tilde{k}$ Is the growth rate of HIV particle that uses the host cell to replicate and proliferate. The total amount of virus produce is given by the term $\tilde{k} \otimes \tilde{v}$. Assuming the CTL eliminate infected cell at the rate $\tilde{a}$ and the total virus eliminate by the CTL or immune respond is given in term $\tilde{a} \otimes \tilde{z}$.

$$\dot{\tilde{z}}(t) = \tilde{h} \otimes \tilde{x}(t) \ominus \tilde{T} \otimes \tilde{v}(t) \quad (3)$$

Equation (3) describes the dynamic of the CTLs during HIV infection. $\tilde{h}$ is the rate of CD4+ T cell stimulate CTLs to proliferate. Hence, CD4+ T cell effect on proliferation of CTLs is expressed by the term $\tilde{h} \otimes \tilde{x}$. Term $\tilde{T} \otimes \tilde{v}$ represent the loss of CTLs due to the increasing the HIV viral load.

Zarei et al [4], has stated that at time, t = 0, the level of CD4+ T cell is normal which is $\dot{\tilde{x}}(0) = (100,0)$ and there is no immune response from CTL-mediated which is $\dot{\tilde{z}}(0) = (0,0)$. The value $\tilde{v}\,\dot{(0)}$ and the other parameter corresponding to patients weak, moderate and strong are shown in the fuzzy triangular membership function as follow.

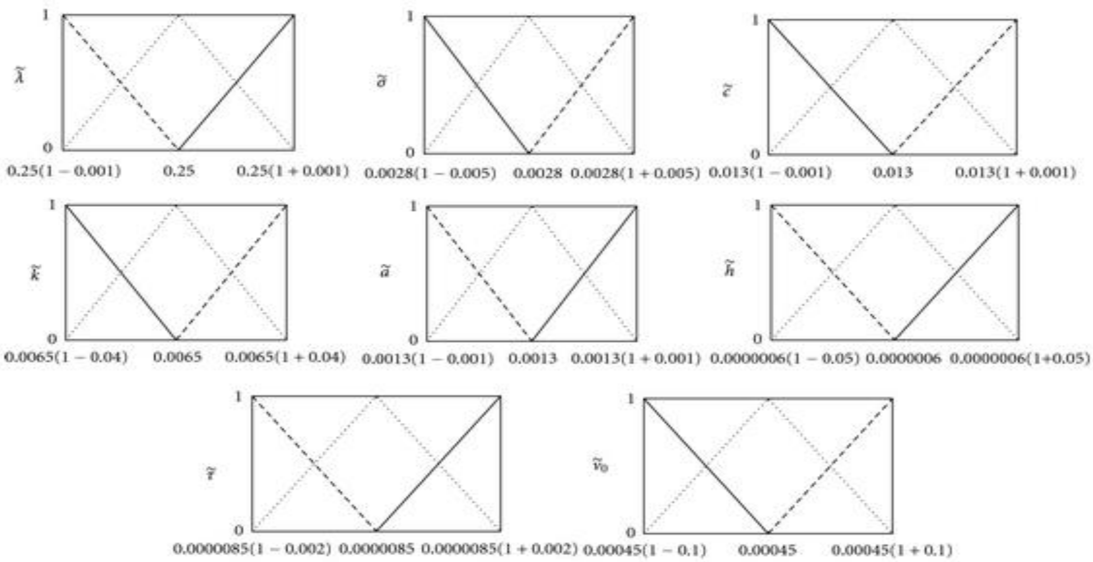


Figure 2: The values of the parameters according to weak (- - -), moderate (…) and strong (__) patients

By implying fuzzy arithmetic, Equations (1)-(3) become

$$\dot{\overline{x}}_\alpha(t) = \overline{\lambda_\alpha} - \underline{\sigma_\alpha}\,\underline{x_\alpha}(t) - \underline{c_\alpha}\,\underline{v_\alpha}(t), \quad \dot{\underline{x}}_\alpha(t) = \underline{\lambda}_\alpha - \overline{\sigma_\alpha}\,\overline{x_\alpha}(t) - \overline{c_\alpha}\,\overline{v_\alpha}(t)$$
$$\dot{\overline{v}}_\alpha(t) = \overline{\overline{k_\alpha}}\,\overline{v_\alpha}(t) - \underline{a_\alpha}\,\underline{z_\alpha}(t), \quad \dot{\underline{v}}_\alpha(t) = \underline{k_\alpha}\,\underline{v_\alpha}(t) - \overline{a_\alpha}\,\overline{z_\alpha}(t)$$
$$\dot{\overline{z}}_\alpha(t) = \overline{h_\alpha}\,\overline{x_\alpha}(t) - \underline{\tau_\alpha}\,\underline{v_\alpha}(t), \quad \dot{\underline{z}}_\alpha(t) = \underline{h_\alpha}\,\underline{x_\alpha}(t) - \overline{\tau_\alpha}\,\overline{v_\alpha}(t)$$
$$\overline{x}_\alpha(0) = \overline{x}_{0\alpha}, \; \underline{x}_\alpha(0) = \underline{x}_{0\alpha}$$
$$\overline{v}_\alpha(0) = \overline{v}_{0\alpha}, \; \underline{v}_\alpha(0) = \underline{v}_{0\alpha}$$
$$\overline{z}_\alpha(0) = \overline{z}_{0\alpha}, \; \underline{z}_\alpha(0) = \underline{z}_{0\alpha}$$

These linear ODEs will be solved using Runge-Kutta Fourth-Order in Matlab for each $\alpha \in [0,1]$. Step size 0.5 and the iteration is up to t = 15000 are considered in this simulation.

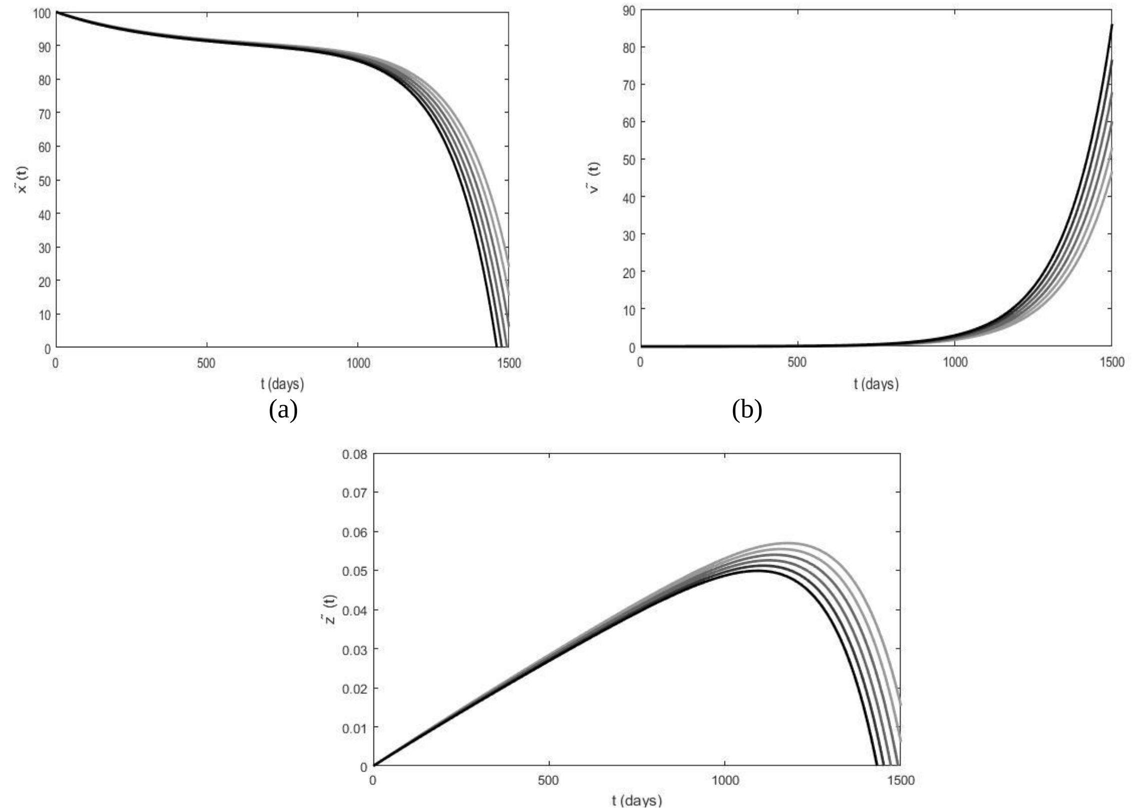
4. NUMERICAL RESULTS AND DISCUSSION

This simulation considers three different immune system's strength which are weak, strong and moderate immune strength patients.

4.1 Dynamic behaviour of the immune cell level and the viral load in weak patient

Figure 3: (a), (b), and (c) show the level of immune system which are CD4+ T cell and CTLs and HIV viral load at the time interval from 0 to 1500 days for weak immune system patients. The dark colour shows the highest possibility to occur while the light dark colour shows the low possibility to occur. Figure 2 (a) shows the slowly decline of CD4+ T cell level at the beginning. The curves show that there are rapid decreases in the number of CD4+ T cells

after slowly incline and the progression to AIDS have the highest possibility to occur. Figure 2 (b) shows that there is very slow increment in the HIV viral load at the beginning. Besides, if we observe the curves there are highest probability that HIV viral load increases rapidly after slowly increase. Moreover, we can say that, the speed of HIV virus increase corresponding to the speed depletion of CD4+ T cells. This is due to proliferation of new HIV cell by bursting the CD4+ T cell. Figure 2 (c) shows the level of CTLs gradually increases when the CD4+ T cell gradually decrease at early stage but decline at the latter stage which is due to virus induce the impairment to CD4+ T cell.



(a) (b)

(c)

Figure 3: (a) CD4+ T cell level, (b) HIV viral load, (c) CTLs level in weak patient

4.2 Dynamic behavior of the immune cell level and the viral load in strong patient

Figure 4 (a) shows the gradual decline of CD4+ T cell in the duration of 1500. The curves show that, there is highest probability that the CD4+ T cell will continue gradual deccreasing. In addition, the slow decline in CD4+ T cell will cause the progression to AIDS become slow. Figure 4 (b) indicates the gradually increase in the HIV viral load level. There is high possibility that HIV viral load will increase gradually. Figure 4 (c) shows that, the high probability that the CTLs cell will last longer. It indicates that the least of the virus induce impairment with the CD4+ T cell.

4.3 Dynamic behavior of the immune cell level and the viral load in moderate patient

Figure 5 (a) shows the level of CD4+ T cell is gradually decline in number but in the moderate rate. Besides, there is high probability that the number of CD4+ T cell decrease in the moderate rate at the later stage after gradual decrease stage. From figure 5 (b) it can be observed that the level of viral load also gradually increase at the moderate rate at later stage of HIV infection. Figure 5 (c) indicates that lasting immune respond in this case also at moderate rate depending on the CD4+ T cell and HIV viral load level. The possibility for this to happen is also at the moderate rate.

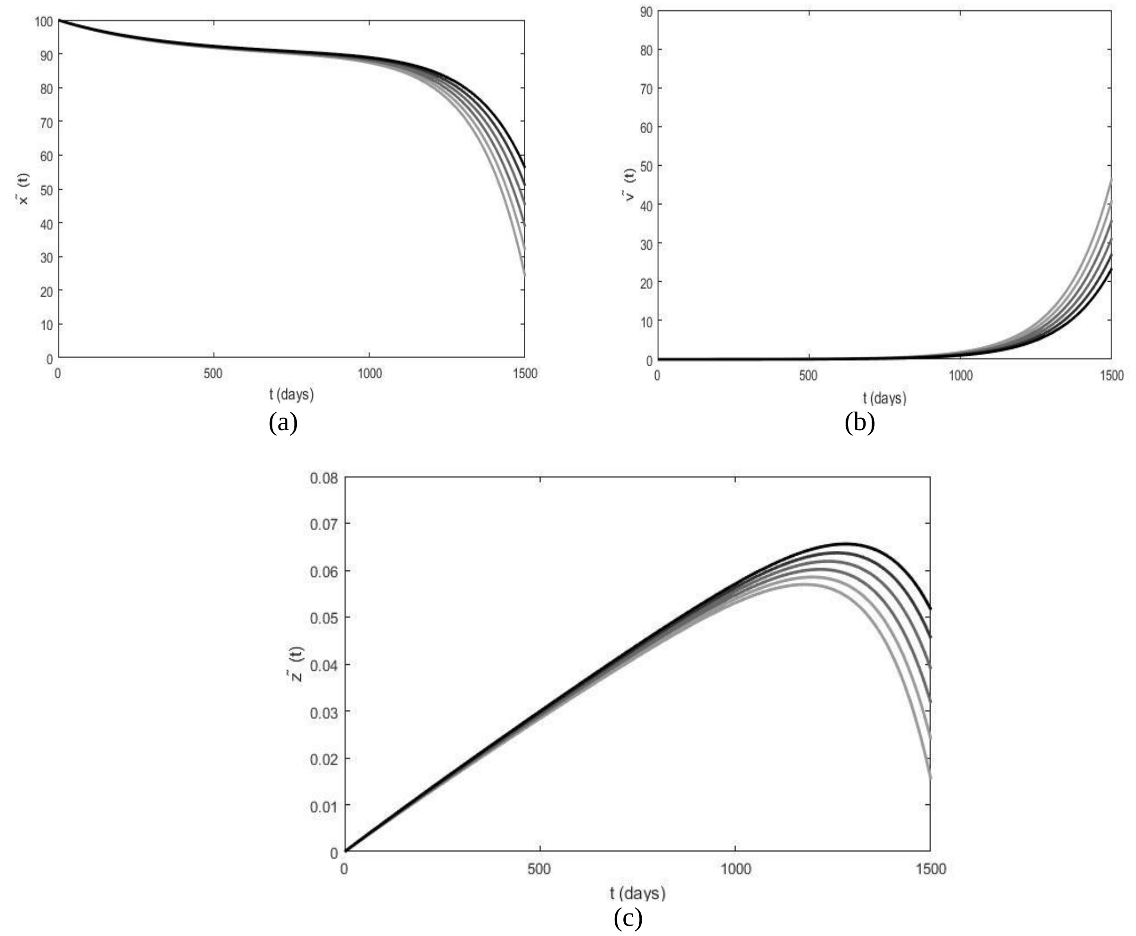
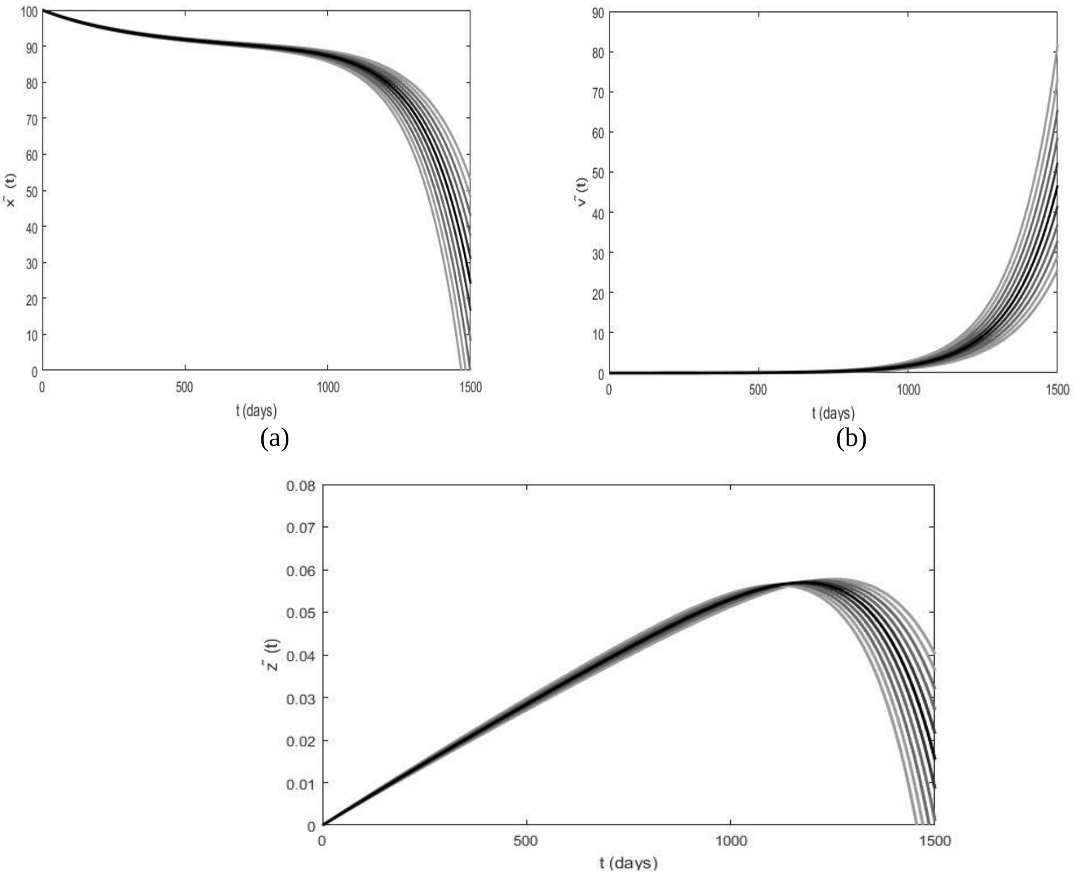


Figure 4: (a) CD4+ T cell level, (b) HIV viral load, (c) CTLs level in strong patient

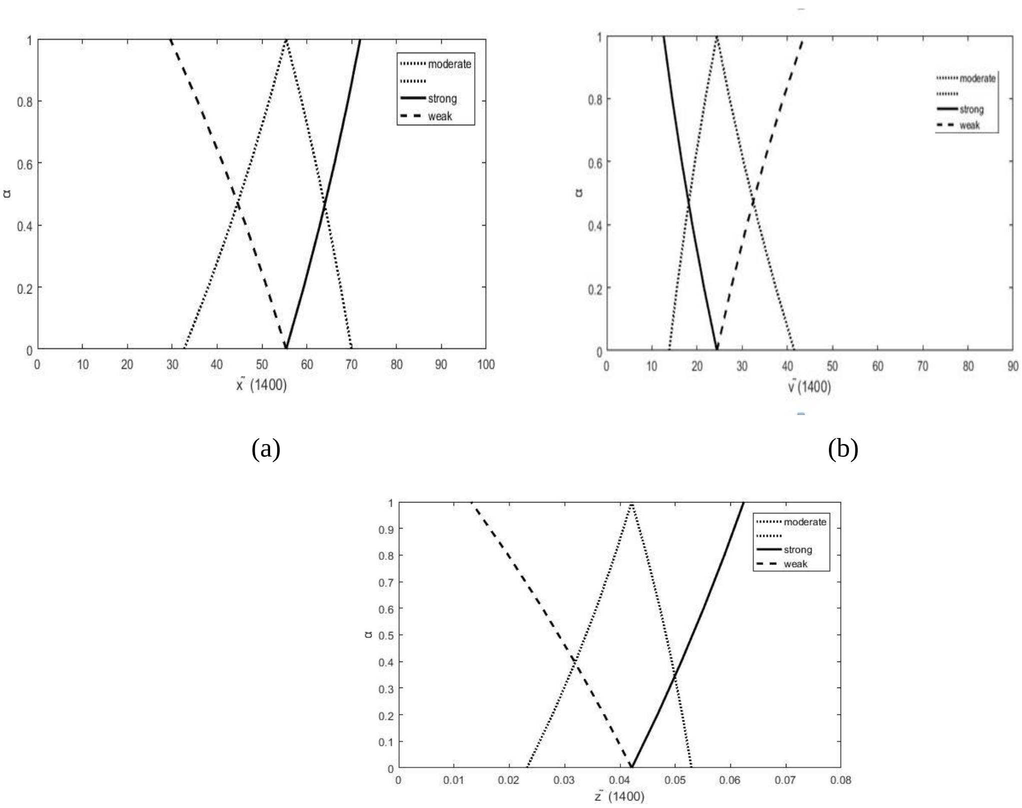
4.4 Cut Indicating the Level of Immune Cell and Viral Load

Figure 6 (a), (b), (c) are obtained by plotting the alpha cut value against number of the cells at t = 1400. In this figure the number of CD4+ T cell for the weak immune patient is less when α = 1 compare to the number of those cells when α = 0. But it is different with the strong immune patient, it shows that the number of those cell is more when α =1 compare when α = 0. For moderate immune system, the numbers of CD4+ T cell are in between the weak and strong. This indicate that at t =1400 the number CD4+ T cell are more in strong immune patients compare to patients who have weak immune strength. As we discussed in 4.3 the increment in the HIV viral load will drop the number of CD4+ T cell. Figure 6 (b) shows that the number of HIV virus based on the α-cut. If we observe, it is completely contrast on what happened in Figure 6 (a). Lastly Figure 6 (c) indicate the α-cut level for CTLs cell. The pattern is same with the Figure 6 (a).



(a) (b) (c)

Figure 5: (a) CD4+ T cell level, (b) HIV viral load, (c) CTLs level in moderate



(a) (b) (c)

Figure 6: (a) α-cut level for CD4+ T cell (b) α-cut level for HIV viral load (c) a) α-cut level for CTLs cell

5. CONCLUSION

We proposed the numerical solution for the mathematical model of HIV dynamic by Runge-Kutta Method of order four. The simulation results show that the fuzzy differential equation can be used in describing the uncertainty immune cell level and the viral load which are due to existing patients with different strength of immune system.

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