

The Notion of Stability of a Differential Equation and Delay Differential Equation Model of HIV Infection of CD4⁺ T-Cells

¹Normah Maan

¹Department of Mathematical Sciences, Faculty of Science,
 Universiti Teknologi Malaysia, Skudai, Johor Darul
 Takzim, Malaysia.

¹normahmaan@utm.my, normahmaan@gmail.com.

²Izaz Ullah Khan, ³Nor Atirah Izzah Zulkefli

²CIIT Abbottabad, Pakistan.

³Department of Mathematical Sciences, Faculty of Science,
 Universiti Teknologi Malaysia, Skudai, Johor Darul
 Takzim, Malaysia.

²izaz1982@yahoo.co.uk, ³noratirahizzah@gmail.com.

Abstract—This research presents a deep insight to address the notion of stability of an epidemical model of the HIV infection of CD4⁺ T-Cells. Initially, the stability of an ordinary differential equation (ODE) model is studied. This is followed by studying a delay differential equation (DDE) model the HIV infection of CD4⁺ T-Cells. The available literature on the stability analysis of the ODE model and the DDE model of the CD4⁺ T-Cells shows that the stability of the models depends on the basic reproduction number “R₀”. Accordingly, for the basic reproduction number R₀ < 1, the model is asymptotically stable, whereas, for R₀ > 1, the models are globally stable. This research further studies the stability of the models and address the lower possible stability limits for the infection rate of CD4⁺ T-Cells with virus and the reproduction rate of infectious CD4⁺ T-Cells, respectively. Accordingly, the results shows that the lower possible limits for the infection rate of CD4⁺ T-Cells with virus are 0.0000027 mm⁻³ and 0.000066 mm⁻³ for the ODE and DDE models, respectively. Again, the lower stability limits for the reproduction rate of infectious CD4⁺ T-Cells with virus are 12 mm³day⁻¹ and 273.4 mm³day⁻¹ for the ODE and DDE models, respectively. The research minutely studies the stability of the models and gives a deep insight of the stability of the ODE and DDE models of the HIV infection of CD4⁺ T-Cells with virus.

Keywords—HIV infection, Stability analysis, CD4⁺ T-Cells, ODE and DDE Models of HIV infections.

I. INTRODUCTION

In order to address the immunological response to infection with human immunodeficiency virus (HIV), many mathematical models have been developed [1–11]. These models address the infection with human immunodeficiency virus (HIV) as linear / nonlinear ordinary differential equation models, with or without delay. Most of them focus to explain the interactions among immune cells, infected cells, viruses, and target cells at inter molecular level. The simple HIV models can help better understand the disease and the underlying kinetics behind the various drug therapies to cure it. Thus the simplest HIV model is given as:

$$\frac{dV}{dt} = P - cV \quad (1)$$

The variables P , c and V denote the rate of virus production, clearance rate constant and concentration of the virus, respectively. A more reasonable model for the dynamics of the CD4⁺ T-cells is given in equation (2).

$$\dot{T} = s - dT + aT\left(1 - \frac{T}{T_{\max}}\right) \quad (2)$$

In equation (2), “ s ” denotes the production rate of new immune T-cells in the body and “ d ” represents the death rate of virus per T-cell. Note that the immune T-cells can also be produced by proliferation of the available T-cells in the body. Thus in (2), “ a ” represents the maximum proliferation rate and “ T_{\max} ” denotes the maximum population of the immune T-cells. Note that this the maximum threshold population of the immune T- Cells and the proliferation automatically shuts off at this level.

The reproduction process of most of the viruses is simple and straight forward. Most of the viruses copies their Deoxyribonucleic Acid (DNA) and insert a copy into the DNA of the host cells. On stimulation, the copies of the viruses are reproduced. The reproduction of the HIV virus does not take place independently [12]. The HIV virus targets the CD4⁺ T-Cells, when they are in close contact. A special kind of protein on the surface of the HIV virus has a great attraction for the CD4⁺ protein on the surface of the immune T-Cells. Due to the process of binding, the HIV viruses are injected into the T-Cells. An unanswered mystery of the medical science is the retroviral nature of the HIV virus. Unlike most of the viruses, the HIV virus first carries a copy of its RNA, which is then transcribed into DNA. After duplication of DNA of the viruses by the host cells, the viruses reassemble and new virus particles bud from the surface of the host cells. The process of budding is slow paced, sparing, bursting and killing the host cells.

The process of HIV virus infection is not simply clear and straight forward. The medical sciences still have to address the final collapse of the immune system due to the infection of the

virus causing death. However, it is collectively agreed upon, that the process take place in four stages. Firstly, the introduction of the virus into the body. Secondly, the initial short period transient state, when the T-Cells and the virus concentrations are very high. This is followed by the disease steady state, called clinical latency, with extremely large number of viruses and T-Cells with incredible interactions and dynamics. The final stage is the called AIDS, in which, the population of the T-Cells drops to very low numbers (zero), whereas, that of viruses grows without bounds, causing death. However, a controversy still exists to address whether the HIV virus directly kills all the immune T-Cells in the last stage or some of mechanism is at work.

To cure the disease, the widely used methodologies are the anti-retroviral therapies. An evident example is the chemotherapy, through which an adequate part of the infected cells are transformed into target cells at the initial introduction of the viruses in the T-Cells. The dynamics between the effects of drugs on the virus was also studied [13]. At the initial first phase of one / two weeks, the virus population fell down dramatically, followed by a slower second phase [13]. The reason for this may be the noncytopathic nature of HIV virus, meaning that the infectious cells can be lost through death, immune killing or via proper cure, e.g. loss of cccDNA. The second phase slow dynamics is due to the fact that antiviral therapy only partially stops the production of the new viruses, resulting in a drop in the HIV RNA, but in reality an active immune response is required for the second phase decline and loss of cells producing virus [13].

This research tries to present a deep insight for the stability of an epidemic model of the HIV infection of CD4⁺ T-Cells. Initially, the stability of an ordinary differential equation (ODE) model is studied. This is followed by studying a delay differential equation (DDE) model the HIV infection of CD4⁺ T-Cells. The stability of these models was addressed in [12]. The hallmark of the study is that it further studies the stability of the models and addresses the lower possible stability limits for the infection rate of CD4⁺ T-Cells with virus and the reproduction rate of infectious CD4⁺ T-Cells, respectively. Thus the results suggest the lower possible limits for the infection rate of CD4⁺ T-Cells with virus for the ODE and DDE models, respectively. Furthermore, it also gives the lower stability limits for the reproduction rate of infectious CD4⁺ T-Cells with virus for the ODE and DDE models, respectively. In this way, the research deeply studies the stability of the ODE and DDE models of the HIV infection of CD4⁺ T-Cells with virus.

II. THE ODE MODEL

An epidemic model of HIV infection of CD4⁺ T-Cells along with a cure rate is presented as:

$$\frac{dT}{dt} = s - dT + aT\left(1 - \frac{T}{T_{max}}\right) - \beta TV + \rho I \tag{3}$$

$$\frac{dI}{dt} = \beta TV - (\delta + \rho)I \tag{4}$$

$$\frac{dV}{dt} = qI - cV \tag{5}$$

Along with the initial conditions, $T(0) > 0, I(0) > 0, V(0) > 0$.

Here, “ T ” represent the target cells, which, after an interaction with virus “ V ”, get infected. Furthermore, “ I ” represents the number of infected cells. The variable β denotes the infection rate constant, whereas, βTV , is the rate of infection of CD4⁺ T-Cells with virus. Moreover, “ s ” denotes the production rate of new immune T-cells in the body and “ d ” represents the death rate of virus per T-cell. Also “ a ” represents the maximum proliferation rate and “ T_{max} ” denotes the maximum population of the immune T-cells. The other model parameters of the model are given in Table I.

TABLE I. PARAMETERS FOR THE VIRAL SPREAD MODEL.

Parameter	Description	Value
T	Target CD4 ⁺ T-Cells	50 mm^{-3}
V	Infected CD4 ⁺ T-Cells.	80
I	Population of HIV RNA.	100 mm^{-3}
s	Birth rate of CD4 ⁺ T-Cells.	$5 \text{ mm}^{-3} \text{ day}^{-1}$
d	Death rate of CD4 ⁺ T-Cells.	0.01 day^{-1}
a	Growth rate of CD4 ⁺ T-Cells.	0.8 day^{-1}
T_{max}	Maximum population of CD4 ⁺ T-Cells.	$1200 \text{ mm}^3 \text{ day}^{-1}$
β	Infection rate of CD4 ⁺ T-Cells with virus.	0.00024 mm^{-3}
ρ	Cure rate of the disease.	0.01 day^{-1}
δ	Death rate of the infectious CD4 ⁺ T-Cells.	0.4 day^{-1}
q	Reproduction rate of infectious CD4 ⁺ T-Cells.	$1000 \text{ mm}^3 \text{ day}^{-1}$
c	Death rate of free virus.	8 day^{-1}

III. THE DDE MODEL

To describe the dynamics of the interaction of the healthy cells with virus a discreet time delay model given as follows:

$$\frac{dT}{dt} = s - dT + aT\left(1 - \frac{T}{T_{max}}\right) - \beta T(t-\tau)V(t-\tau) + \rho I \tag{6}$$

$$\frac{dI}{dt} = \beta T(t-\tau)V(t-\tau) - (\delta + \rho)I \tag{7}$$

$$\frac{dV}{dt} = qI - cV \tag{8}$$

This model assumes that at time t , only the healthy infected by the HIV virus τ time before “ $(t-\tau)$ ” get infected. This restriction changed the incidence term for the healthy cells from βTV to $\beta T(t-\tau)V(t-\tau)$ in the model. Moreover, the model in Equations (6-8) satisfy the initial conditions: $T(\theta_0) > T_0$, $I(\theta_0) > I_0$, $V(\theta_0) > V_0$ with $\theta_0 \in [-\tau, 0]$. Note that all the parameters of the model in (3-5) and (6-8) are the same except the introduction of discrete time delay τ .

IV. STABILITY OF THE ODE AND DDE MODELS

This section is devoted to analyze the stability of the ODE and DDE models of the HIV infection of CD4⁺ T-Cells with virus.

The ODE model presented in equations (3-5) is asymptotically stable according as the basic reproduction number $R_0 < 1$, whereas, for $R_0 > 1$, the models are globally

stable [12]. Here, $R_0 = \frac{T_0}{\bar{T}} = \frac{(T_{max}\beta q)[(a-d) + \sqrt{(a-d)^2 + (\frac{4as}{T_{max}})}]}{2ac(\delta + \rho)}$, with, $T_0 = (\frac{T_{max}}{2a})[(a-d) + \sqrt{(a-d)^2 + (\frac{4as}{T_{max}})}]$, and $\bar{T} = \frac{c(\delta + \rho)}{\beta q}$.

On analysis, we come to know that stability of the model can be disturbed by a very small number or a large number. For the very small number, this research takes the infection rate of CD4⁺ T-Cells with virus “ β ” and for the large number the reproduction rate of infectious CD4⁺ T-Cells “ q ”, respectively. Table (II) summaries the lower possible stability limits for these parameters and are visualized in Fig. 1 and Fig. 2, respectively. Table (II) shows that the lower possible stability limit for the infection rate of CD4⁺ T-Cells with HIV virus is 0.0000027 mm⁻³ and the lower limit for the reproduction rate of infectious CD4⁺ T-Cells with virus is 12 mm³day⁻¹ for the ODE model.

TABLE II. STABILITY ANALYSIS FOR THE ODE MODEL.

Parameter	Value	$R_0 = \frac{T_0}{\bar{T}} = \frac{(T_{max}\beta q)[(a-d) + \sqrt{(a-d)^2 + (\frac{4as}{T_{max}})}]}{2ac(\delta + \rho)}$
$\beta \text{ mm}^{-3}$ Infection rate of CD4 ⁺ T-Cells with virus.	0.000001	0.726 (Unstable)
	0.000002	0.907 (Unstable)
	0.0000025	0.944 (Unstable)
	0.0000026	0.980 (Unstable)
	0.0000027	1.016 (Stable)
	0.000003	1.089 (Stable)
$q \text{ mm}^3 \text{ day}^{-1}$ Reproduction rate of infectious CD4 ⁺	11	0.958 (Unstable)
	12	1.045 (Stable)
	25	2.17 (Stable)

T-Cells.	50	2.74 (Stable)
	100	8.71 (Stable)
	500	43.57 (Stable)

Again, the DDE model in equations (6-8) is asymptotically stable according as the basic reproduction number $R_0 < 1$, whereas, for $R_0 > 1$, the models are globally stable [12].

In this case, the basic reproduction number $R_0 = \frac{T_0}{\bar{T}} = \frac{(T_0\beta q)}{c(\delta + \rho)}$.

Table (III) summaries the lower possible stability limits for the infection rate of CD4⁺ T-Cells with virus “ β ” and for the reproduction rate of infectious CD4⁺ T-Cells “ q ”, respectively. The lower possible stability limits for these parameters are visualized in Fig. 3 and Fig. 4, respectively. From Table (III), the lower stability limit for the infection rate of CD4⁺ T-Cells with virus is 0.000066 mm⁻³, whereas, for the reproduction rate of infectious CD4⁺ T-Cells with virus is 273.4 mm³day⁻¹ for the DDE model.

TABLE III. STABILITY ANALYSIS FOR THE ODE MODEL.

Parameter	Value	$R_0 = \frac{T_0}{\bar{T}} = \frac{(T_0\beta q)}{c(\delta + \rho)}$
$\beta \text{ mm}^{-3}$ Infection rate of CD4 ⁺ T-Cells with virus.	0.000024	0.365 (Unstable)
	0.00005	0.7621 (Unstable)
	0.00006	0.914 (Unstable)
	0.000065	0.990 (Unstable)
	0.000066	1.006 (Stable)
	0.00007	1.06 (Stable)
$q \text{ mm}^3 \text{ day}^{-1}$ Reproduction rate of infectious CD4 ⁺ T-Cells.	255	0.932 (Unstable)
	260	0.95 (Unstable)
	270	0.98 (Unstable)
	273.3	0.999 (Unstable)
	273.4	1.00024 (Stable)
	273.5	1.00060 (Stable)

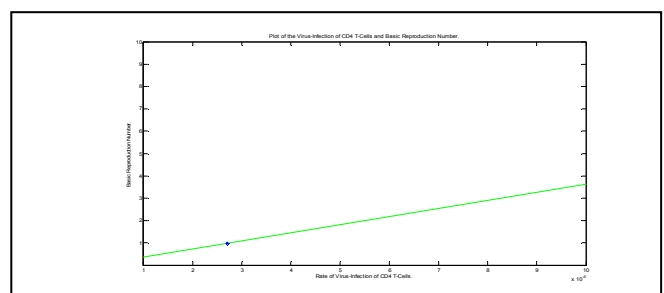


Fig. 1. Plot of the lower possible stability limit of Infection rate of CD4⁺ T-Cells with virus for the ODE model.

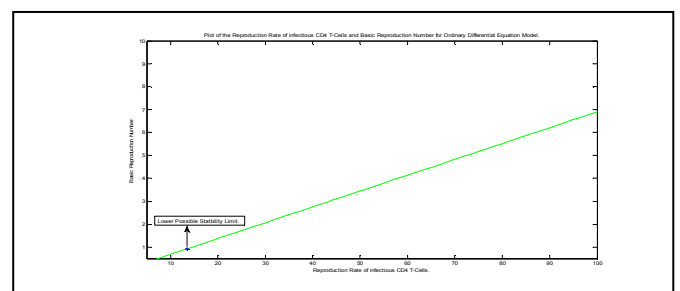


Fig. 2. Plot of the lower possible stability limit for reproduction rate of infectious CD4+ T-Cells for ODE model.

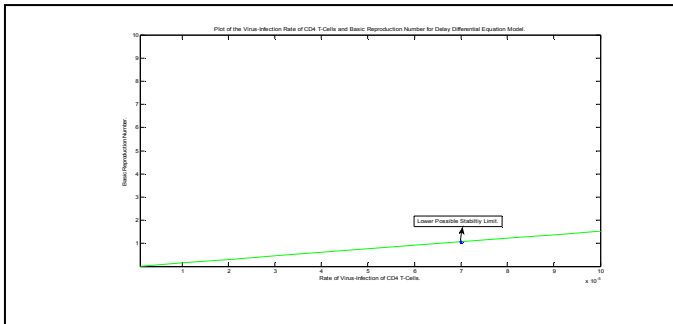


Fig. 3. Plot of the lower possible stability limit of Infection rate of CD4+ T-Cells with virus for the DDE model.

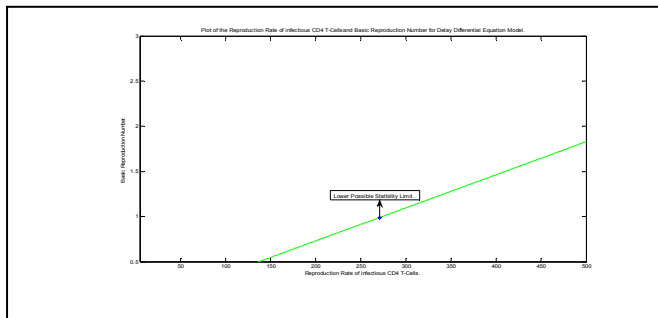


Fig. 4. Plot of the lower possible stability limit for reproduction rate of infectious CD4+ T-Cells for DDE model.

V. CONCLUSIONS

The stability of an ODE and DDE epidemic models of the HIV infection of CD4⁺ T-Cells was studied. The research investigated the lower possible stability limits for the infection rate of CD4⁺ T-Cells with HIV virus and the reproduction rate of infectious CD4⁺ T-Cells, respectively. The research is significant, for every useful system needs to be stable. The main contribution is the study of stability of the ODE and DDE models of the HIV infection of CD4⁺ T-Cells with virus.

ACKNOWLEDGMENT

This research is supported by Research Management Centre – UTM and Malaysian Organization High Education (MOHE) Grants through votes 4F127 and 07J77. The authors are thankful to financial support.

REFERENCES

- [1] R. J. De Boer, and A. S. Perelson, "Target cell limited and immune control models of HIV infection: a comparison," *J.Theor. Biol.*, vol. 190, no. 3, pp. 201–214, 1998.
- [2] T. B. Kepler, and A. S. Perelson, "Cyclic re-entry of germinal center *B* cells and the efficiency of affinity maturation," *Immunol. Today.*, vol. 14, no. 8, pp. 412–415, 1993.
- [3] J. K. Percus, O. E. Percus, and A. S. Perelson, "Predicting the size of the T-cell receptor and antibody combining region from consideration of efficient self-nonself discrimination," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 90, no. 5, pp. 1691–1695, 1993.
- [4] X. Zhou, X. Song, and X. Shi, "A differential equation model of HIV infection of CD4₊T-cells with cure rate," *J. Math. Anal. Appl.*, vol. 342, no. 2, pp. 1342–1355, 2008.
- [5] A. R. McLean, M. M. Rosado, F. Agenes, R. Vasconcellos, and A. A. Freitas, "Resource competition as a mechanism for B cell homeostasis," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 94, no. 11, pp. 5792–5797, 1997.
- [6] X. Song, and A. U. Neumann, "Global stability and periodic solution of the viral dynamics," *J. Math. Anal. Appl.*, vol. 329, no. 1, pp. 281–297, 2007.
- [7] A. L. Lloyd, "The dependence of viral parameter estimates on the assumed viral life cycle: limitations of studies of viral load data," *Proc. Royal Soc. B.*, vol. 268, no. 1469, pp. 847–854, 2001.
- [8] D. Li, and W. Ma, "Asymptotic properties of a HIV-1 infection model with time delay," *J. Math. Anal. Appl.*, vol. 335, no. 1, pp. 683–691, 2007.
- [9] A. R. McLean, and T. B. L. Kirkwood, "A model of human immunodeficiency virus infection in T helper cell clones," *J. Theor. Biol.*, vol. 147, no. 2, pp. 177–203, 1990.
- [10] A. R. McLean and M. A. Nowak, "Models of interactions between HIV and other pathogens," *J. Theor. Biol.*, vol. 155, no. 1, pp. 69–86, 1992.
- [11] J. E. Mittler, B. Sulzer, A. U. Neumann, and A. S. Perelson, "Influence of delayed viral production on viral dynamics in HIV-1 infected patients," *Math. Biosciences.*, vol. 152, no. 2, pp. 143–163, 1998.
- [12] J. Yang, X. Wang, and F. Zhang, "A differential equation model of HIV infection of CD4⁺ T-Cells with delay," *Discrete. Dynamics. Nature Soc.*, vol. 2008, pp. 1–16, 2008.
- [13] A. S. Perelson, P. Essunger, Y. Cao, et al., "Decay characteristics of HIV-1-infected compartments during combination therapy," *Nature.*, vol. 387, no. 6629, pp. 188–191, 1997.

**Creative Commons Attribution License 4.0
 (Attribution 4.0 International, CC BY 4.0)**

This article is published under the terms of the Creative Commons Attribution License 4.0

https://creativecommons.org/licenses/by/4.0/deed.en_US