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FRACTIONAL MATHEMATICAL MODEL OF HIV AND CD4+ T-CELLS INTERACTIONS WITH HAART TREATMENT

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Abstract. This study provides the mathematical model of the interaction between the HIV and CD4+ T cells. This research develops other research by formulating a model with the fractional Caputo derivative approach with fractional order α. Based on the model, we obtain the equilibrium point and analyze the stability criterion of the equilibrium point. Furthermore, we perform the *Next Generation Matrix* method to calculate the basic reproduction number (R_0). Then, we apply the *Grunwald-Letnikov Explicit method* to show the numerical result of the model. The result of this study could assist for future improvement, especially for fractional modelling.
Keywords: HIV-Model; Fractional Order; Basic Reproduction Number; Grunwald-Letnikov Method.

I. INTRODUCTION

Human Immunodeficiency Virus (HIV) is a virus that infect lymphocyte cells in the human body. It decreases the immune system of infected person. A set of symptoms that arise due to decreased immunity by HIV infection is called Acquired Immune Deficiency Syndrome (AIDS). HIV can be transmitted through the exchange of various body fluids, such as blood, breast milk, semen and vaginal fluids to a healthy person. In addition, HIV can also be transmitted vertically from a mother to her child during pregnancy and childbirth [1].

Until now, HIV-AIDS has not been cured by the consumption of certain drugs. However, there is a therapy for people with HIV / AIDS which aims to slow down the replication of the virus in the body of an infected person so that it can extend the chance of life and help the body to fight viral infections. It is called *antiretroviral therapy* (ART). In an infected person, the virus begins to attack white blood cells or T lymphocyte cells. When infecting T lymphocytes, the HIV virus will stick to receptors located in the cell wall of T lymphocytes which are known as *Cluster of Differentiation 4* (CD4). The attachment of HIV to the T lymphocyte cell receptor will give the addition to the HIV genetic code into the part of the infected lymphocyte cell. Then, infected T lymphocyte cells will still use themselves when an infection occurs as a form of resistance from any infection that occurs in the body so that HIV attached to T lymphocyte cells will also replicate. A process that repeats over many years will result in many viruses accumulating inside infected cells [2].

Currently, one treatment that is quite effective for HIV-infected individuals to reduce the virus replication is *Highly Active Antiretroviral Therapy* (HAART). The HAART method involves a combination of the use of *Protease Inhibitors* (PI) drugs to inhibit the formation of proteases and *Reverse Transcriptase Inhibitor* (RTI) drugs which are responsible for inhibiting the reverse transcriptase process. The combination of treatments will later inhibit the process of DNA formation from RNA. With the inhibition of the DNA formation process will have an impact on the formation of proteins that are also inhibited so that the formation of viruses becomes slower [2]–[4].

A mathematical model is a set of equations or inequalities that describe the behavior of the problem under review with various types of assumptions given. One of the most researched problems is the mathematical model associated with the spread of disease, including the spread of HIV in the population and its interaction with cells in the body. [1], [2], [5]–[8] The mathematical model in the study uses a model with a system of differential equations with integers order. Research on fractional calculus and fractional differential equations has been carried out in several studies related to models of disease spread. [9]–[20]. Mathematical models of fractional order are used in modeling the spread of HIV disease. For example, in research [9] discusses the model of HIV infection by CD4+ T Lymphocyte cells by considering the effect of drug administration in the treatment process. The model presented is a mathematical model with fractional order. Researchers use the Legendre Wavelet method to determine the solution of a given system. The same goes for research [10], presented a model of HIV dynamics with the fractional order Caputo. This study used data on HIV infection cases in Indonesia from 2006-2018. The solution of this system of equations uses Newton's polynomial numerical approximation.

In addition to HIV, fractional order models are also used to examine the dynamics of the spread of COVID-19 [11]–[13], [16], [20] . For example, research [11] discusses the mathematical model of COVID-19 using the Caputo fractional order. The model considers quarantine to reduce COVID-19 infection rates. The data used in the model was taken from data on COVID-19 infection cases in West Sulawesi, Indonesia. On research [16], researchers use a mathematical model with an integer order which is then reformulated using the definition of fractional derivatives of Caputo. This study examines how fractional order is able to explain the dynamics of COVID-19 in two different places, namely in Spain and Portugal. This is characterized by differences in the results of fractional order estimates obtained for each of these countries.

In this study, the model studied was a mathematical model of the interaction of the HIV virus and CD4+ T lymphocyte cells contained in the study [2] by considering fractional mathematical models using Caputo derivatives. We can observe how the fractional order affect the dynamics of models. In other hand, the background to the use of Caputo derivatives in the model studied because it has advantages in the formulation of initial values. The initial value of the Caputo fractional order derived system is the same as the model with the integer order, so there is no need to define different forms of initial values [21].

This article consists of several subsections. The first part is an introduction that explains the urgency of the study. The second part presents the formulation of the fractional

mathematical model to be studied. In the third part, the results and discussion of this study were obtained. The fourth section contains numerical simulations taking into account various scenarios to see the effect of changes in the values of certain parameters. Numerical simulation using Grunwald Letnikov's Explicit method. This method is a fairly simple method and fits into a model formulation that uses the definition of a Caputo derivative. The final section contains conclusions and development suggestions from this study.

II. PRELIMINARIES

In this section, we recall definitions related to Caputo fractional derivative, sensitivity analysis and a useful theorem for stability of fractional differential system needed for the study of the main result.

Definition 1. Caputo Fractional Derivative [22] *Suppose* $\alpha > 0, t > 0$ *and* $n \in \mathbb{N}$. *Caputo Fractional Derivative* ${}_0^C D_t^\alpha := \frac{d^\alpha}{dt^\alpha}$ *with fractional order* α, *for function* $f(t)$ *is defined by:*

$$ {}_0^C D_t^\alpha f(t) = \begin{cases} \dfrac{1}{\Gamma(n-\alpha)} \displaystyle\int_0^t (t-x)^{n-\alpha-1} f^{(n)}(x)\, dx, & n-1 < \alpha < n, \\ f^{(n)}(t), & \alpha = n. \end{cases} \tag{1} $$

Theorem 1. Local Stability of Fractional Differential System [23]–[25] *Suppose* ${}_a^C D_t^\alpha \boldsymbol{x}(t) = f(\boldsymbol{x}), 0 < \alpha \leq 1$, *and* $\boldsymbol{x} \in \mathbb{R}^n$, *is nonlinear fractional differential system. The equilibrium point* $\bar{\boldsymbol{x}}$ *is solution of* $f(x) = 0$. *The equilibrium point* $\bar{\boldsymbol{x}}$ *is said locally asymptotic stable if for all eigen values* $\lambda_{(j=0,1,\ldots,n)}$ *of Jacobian matrix* $\boldsymbol{A} = \frac{\partial f}{\partial x}$ *evaluated at equilibrium point* $\bar{\boldsymbol{x}}$ *satisfy* $\left|arg\ (\lambda_j)\right| > \frac{\alpha\pi}{2}$.

Definition 2 [26] *The normalized forward sensitivity index of a variable V that depends differentiable on a parameter p, is defined as:*

$$ C_p^V = \frac{\partial V}{\partial p} \times \frac{p}{V}. \tag{2} $$

Grunwald-Letnikov (GL) is one of the numerical methods used to solve fractional order differential equations both linear and nonlinear fractional differential equations. In this method, the derivative used is the definition of the Caputo derivative operator. Suppose a fractional differential equation using Caputo's derivative

$$ D_C^\alpha y(t) = f\big(y(t)\big), \;\; y(\tau_0) = y_0 \;\; (0 < \alpha < 1). \tag{3} $$

Assuming that there is a unique solution $y = y(\tau)$ at interval $[0, T]$ with the initial value can be homogeneous or nonhomogeneous. Then for discretization is selected grid $0 = \tau_0 < \tau_1 < \cdots < \tau_{N+1} = T$ with $\tau_{k+1} - \tau_k = h$ and suppose y_k is an approximation of exact solution $y(\tau_k)$. The approximation by the Grunwald-Letnikov method is then applied to the left hand side of equation (3) where $\tau_{n+1} = (n+1)h$ and the right side is approximated by $f(y_n)$, so the approximation form of the explicit Grunwald-Letnikov method is [27]

$$y_{n+1} - \sum_{v=1}^{n+1} c_v^{\alpha}\, y_{n+1-v} - r_{n+1}^{\alpha} y_0 = h^{\alpha} f(y_n), \tag{4}$$

with

$$r_{n+1}^{\alpha} = h^{\alpha} r_0^{\alpha}(t_{n+1}) = \frac{(n+1)^{1-\alpha}}{\Gamma(1-\alpha)},$$
$$c_v^{\alpha} = \left(1 - \frac{\alpha+1}{v}\right) c_{v-1}^{\alpha}, \qquad c_1^{\alpha} = \alpha.$$

III. THE PROPOSED FRACTIONAL MODEL

In this study, the mathematical model to be studied is a model formulated by Mutiara, et.al [2]. The model is a deterministic model formulated with a system of differential equations using integer order. The mathematical model studied consists of three compartments, namely the number of susceptible cells infected with HIV (x_1), number of HIV-infected cells (x_2) dan the amount of HIV virus in the infected person (x_3). Deterministic model in [2] is reformulated by involving a system of fractional order differential equations as follows

$$\begin{aligned} {}_0^C D_t^{\alpha}(x_1) &= \vartheta - \beta x_1(t) x_3(t) - \mu_1 x_1(t), \\ {}_0^C D_t^{\alpha}(x_2) &= \beta x_1(t) x_3(t) - \mu_2 x_2(t), \\ {}_0^C D_t^{\alpha}(x_3) &= (1-\gamma) k x_2(t) - \mu_3 x_3(t) - \beta x_1(t) x_3(t). \end{aligned} \tag{5}$$

Because of a change from integer derivatives on the left side of the equation system in [2] to Caputo fractional derivative in Equation (5) result the change of dimension *t*. Integer derivatives with operators $\frac{d}{dt}$ has s^{-1} as its dimension, while the fractional derivative $\frac{d^{\alpha}}{dt^{\alpha}} = {}_0^C D_t^{\alpha}$ has $s^{-\alpha}$ dimension, $0 < \alpha \leq 1$ [28]. To accommodate dimensional changes in the left side of the Equation (5), we define the new parameters as follows:

$$\vartheta = \tilde{\vartheta}^{\alpha}, \beta = \tilde{\beta}^{\alpha}, \mu_1 = \widetilde{\mu_1}^{\alpha}, \mu_2 = \widetilde{\mu_2}^{\alpha}, k = \tilde{k}^{\alpha}, \mu_3 = \widetilde{\mu_3}^{\alpha}.$$

By defining these parameters, the system with integer order and system (5) are dimensionally compatible. The dynamics of the interaction of HIV virus with CD4+ T lymphocyte cells can be seen in Figure 1.

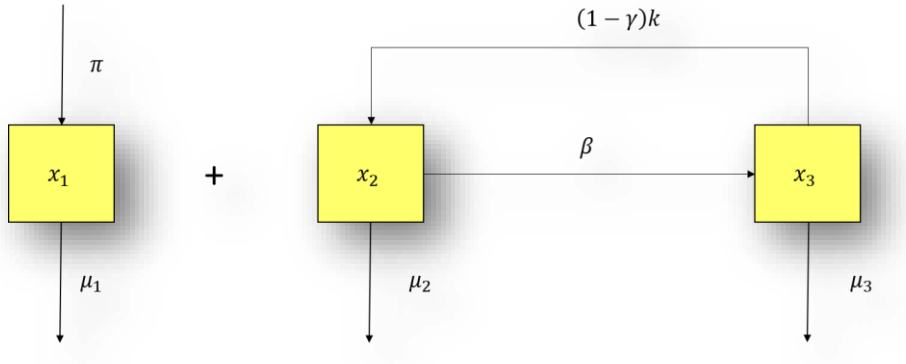

Figure 1. The interaction of HIV virus and T Lymphocyte cells

Based on Figure 1, the model on system (5) is divided into three compartments. x_1 represents a population of cells that are healthy and susceptible to HIV infection, x_2 represents the

population of HIV-infected cells, and x_3 is population of HIV virus in the human body. The population of healthy cells will increase due to the presence of healthy cells produced in a person's body with rate $\tilde{\vartheta}$. Then it will decrease when healthy cells are infected by the HIV virus with an infection rate of $\tilde{\beta}$, so that the healthy cells will move to the HIV-infected cell compartment. Healthy cells that experience natural death or damage will also reduce the number of healthy cells at a natural death rate of $\widetilde{\mu_1}$.

HIV-infected cell populations (x_2) will increase when the HIV virus successfully infects healthy cells and will decrease when HIV-infected cells experience natural death at a rate of $\widetilde{\mu_2}$. HIV virus population (x_3) will increase as infected cells produce new viruses at a rate $\tilde{k}$. To inhibit the growth of virus production, HAART treatment is given which is expressed in proportion γ. HIV virus population will decrease when there is a natural death of the HIV virus at a rate $\widetilde{\mu_3}$ and infection of healthy cells.

In this model it is assumed that $x_1(0) = x_{1_0}, x_2(0) = x_{2_0}, x_3(0) = x_{3_0}$ are the initial value for each compartment with $x_{1_0}, x_{2_0}, x_{3_0} \geq 0$. It is assumed that all parameters used in the model are positive.

Table 1. Model Parameters (5)

Parameters	Description
$\tilde{\lambda}$	The rate of healthy cells produced by the body in a unit of time
$\tilde{\beta}$	The rate of infection of the HIV virus against healthy cells
$\widetilde{\mu_1}$	Natural death rate of healthy cells
$\widetilde{\mu_2}$	Natural death rate of HIV-infected cells
$\widetilde{\mu_3}$	Natural death rate of the HIV virus
$\tilde{k}$	The rate of production of HIV virus by infected cells
γ	Proportion of successful HAART treatment treatments

IV. RESULTS

4.1 The Equilibrium Point of Fractional Model

An equilibrium point is a point that expresses the state of a system that does not change with time. There are two equilibrium points for the system (5), namely the disease-free equilibrium point and the endemic equilibrium point. The equilibrium point for the Caputo fractional model occurs when [29]

$$ {}_0^C D_t^\alpha(x_1) = {}_0^C D_t^\alpha(x_2) = {}_0^C D_t^\alpha(x_3) = 0. \quad (6) $$

A disease-free equilibrium solution is a state in which disease does not spread within a population. This can be interpreted when $x_2 = 0$. Then from (5), we obtained disease-free equilibrium points

$$E^0 = \left(\frac{\vartheta}{\mu_1}, 0,0\right). \tag{7}$$

In addition to disease-free equilibrium points, there are also endemic equilibrium points. The endemic equilibrium point is the state when the disease continues to spread in the population. In this case, the condition occurs when $x_2 \neq 0$. From (5) an endemic equilibrium point is obtained $E^1 = (x_1^*, x_2^*, x_3^*)$, where

$$x_1^* = \frac{\mu_2\mu_3}{\beta\left((1-\gamma)k - \mu_2\right)}, \tag{8}$$

$$x_2^* = \frac{\beta k\vartheta(1-\gamma) - \beta\vartheta\mu_2 - \mu_1\mu_2\mu_3}{\beta\mu_2\left((1-\gamma)k - \mu_2\right)}, \tag{9}$$

$$x_3^* = \frac{\beta\vartheta(k(1-\gamma) - \mu_2) - \mu_1\mu_2\mu_3}{\beta\mu_2\mu_3}. \tag{10}$$

4.2 Basic Reproduction Number

Basic Reproduction number is a threshold for transmission of a disease caused by infected individuals (infectious cells) in a population that are all susceptible to infection. In this section, the basic reproduction number is calculated using the Next Generation Matrix (NGM) method. Suppose Υ is a matrix that expresses the rate at which new infections occurs and Ψ is a matrix that expresses the rate of cell displacement. Based on the compartment infected with the virus, namely: $x_2(t)$ and $x_3(t)$, we obtained Υ and Ψ as follow:

$$\Upsilon = \begin{pmatrix} \beta x_1 x_3 \\ 0 \end{pmatrix} \tag{11}$$

$$\Psi = \begin{pmatrix} \mu_2 x_2 \\ -(1-\gamma)kx_2 + \mu_3 x_3 + \beta x_1 x_3 \end{pmatrix}. \tag{12}$$

Next, we obtain F as a matrix contains partial derivative from matrix Υ in Equation (11) towards x_2 and x_3

$$F = \begin{pmatrix} \frac{\partial\Upsilon_1}{\partial x_2} & \frac{\partial\Upsilon_1}{\partial x_3} \\ \frac{\partial\Upsilon_2}{\partial x_2} & \frac{\partial\Upsilon_2}{\partial x_3} \end{pmatrix} = \begin{pmatrix} 0 & \beta x_1 \\ 0 & 0 \end{pmatrix}. \tag{13}$$

In the same way, matrix V obtained from partial derivatives of matrix Ψ in Equation (12) towards x_2 and x_3 as follow

$$V = \begin{pmatrix} \frac{\partial \Psi_1}{\partial x_2} & \frac{\partial \Psi_1}{\partial x_3} \\ \frac{\partial \Psi_2}{\partial x_2} & \frac{\partial \Psi_2}{\partial x_3} \end{pmatrix} = \begin{pmatrix} \mu_2 & 0 \\ -(1-\gamma)k & \mu_3 + \beta x_1 \end{pmatrix}. \quad (14)$$

Further, we obtain matrix V^{-1} which is the inverse matrix of the Equation (14). We substitute Equation (7) to (13) and (14) so we get

$$F = \begin{pmatrix} 0 & \frac{\beta\vartheta}{\mu_1} \\ 0 & 0 \end{pmatrix}. \quad (15)$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu_2} & 0 \\ -\frac{(1-\gamma)k}{\mu_2(\mu_3 + \frac{\beta\vartheta}{\mu_1})} & \frac{1}{\mu_3 + \frac{\beta\vartheta}{\mu_1}} \end{pmatrix}. \quad (16)$$

From Equation (15) and (16) we obtain Next Generation Matrix as follows

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta\vartheta}{\mu_1} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\mu_2} & 0 \\ -\frac{(1-\gamma)k}{\mu_2(\mu_3 + \frac{\beta\vartheta}{\mu_1})} & \frac{1}{\mu_3 + \frac{\beta\vartheta}{\mu_1}} \end{pmatrix},$$

$$FV^{-1} = \begin{pmatrix} \frac{\beta k\vartheta(1-\gamma)}{\mu_2(\beta\vartheta + \mu_1\mu_3)} & \frac{\beta\vartheta}{\beta\vartheta + \mu_1\mu_3} \\ 0 & 0 \end{pmatrix}. \quad (17)$$

The value of R_0 is obtained from the eigen value of (17)

$$R_0 = \frac{\beta k\vartheta(1-\gamma)}{\mu_2(\beta\vartheta + \mu_1\mu_3)}. \quad (18)$$

4.3 Analysis of parameter sensitivity to R_0

Parameter sensitivity index of R_0 aims to observe how sensitive changes in a parameter affect the changes in the basic reproduction number (R_0). Parameter sensitivity analysis provides an overview of the relationship of a parameter to R_0 value. In this part, sensitivity index will be analyzed from two parameters, namely the parameter of the rate of HIV virus infection to healthy cells or transmission of healthy cells to be infected (β) and parameters of the proportion of treatment HAART (γ).

4.3.1. Sensitivity analysis of parameter β to R_0

Based on Definition 2, sensitivity analysis of parameter β to R_0 is obtained as follow

$$C_{\beta}^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0},$$
$$C_{\beta}^{R_0} = \frac{\mu_1 \mu_3}{\beta\vartheta + \mu_1\mu_3} \geq 0. \tag{19}$$

Assuming all parameter values used in the model are positive, a positive sensitivity index is obtained in Equation (19). In other words, the greater the value of the change β results an increase in the value of the R_0.

4.3.2. Sensitivity analysis of parameter γ to R_0

Based on Definition 2, sensitivity analysis of parameter γ to R_0 is obtained as follow

$$C_{\gamma}^{R_0} = \frac{\partial R_0}{\partial \gamma} \times \frac{\gamma}{R_0},$$
$$C_{\gamma}^{R_0} = \frac{-\gamma}{1-\gamma} \leq 0. \tag{20}$$

Based on parameter sensitivity analysis γ to R_0, assuming all parameter values used in the model are positive, a negative sensitivity index is obtained in Equation (20) so that if the value of γ raise then value R_0 will decrease.

4.4 Stability analysis of Fractional System

In this section, stability analysis of fractional system of two equilibrium points is given. It aims to study the behavior of the system around the equilibrium point. Stability analysis for system (5) begins by forming a Jacobi matrix at E^0 as follows.

$$J(E^0) = \begin{pmatrix} -\mu_1 & 0 & -\frac{\beta\vartheta}{\mu_1} \\ 0 & -\mu_2 & \frac{\beta\vartheta}{\mu_1} \\ 0 & (1-\gamma)k & -\frac{\beta\vartheta}{\mu_1} \end{pmatrix}. \tag{21}$$

Theorem 2. The Equation (7) is an equilibrium point that locally asymptotic stable if $\mu_2 > k(1-\gamma)$ and unstable if $\mu_2 < k(1-\gamma)$.

Proof. From matrix Equation (21) is obtained from characteristic equation

$$(\lambda + \mu_1)\left(\lambda^2 + \left(\frac{\beta\vartheta + \mu_1\mu_2}{\mu_1}\right)\lambda + \beta\vartheta\big(\mu_2 - k(1-\gamma)\big)\right). \tag{22}$$

Based on Equation (22), we obtained an eigen value

$$\lambda_1 = -\mu_1. \tag{23}$$

Because we have $\mu_1 > 0$, it implies $\lambda_1 < 0$ and $|\arg(\lambda_1)| = \pi$. Based on this, it can be guaranteed that $|\arg(\lambda_1)| > \frac{\alpha\pi}{2}$ for all $0 < \alpha \leq 1$. The stability of the equilibrium point will be determined by a quadratic polynomial

$$\lambda^2 + a_1\lambda + a_2 = 0, \tag{24}$$

where

$$\begin{aligned} a_1 &= \frac{\beta\vartheta + \mu_1\mu_2}{\mu_1}, \\ a_2 &= \beta\vartheta\big(\mu_2 - k(1-\gamma)\big). \end{aligned} \tag{25}$$

We have all parameters positive that implies $a_1 > 0$. As a result, Equation (24) has no complex roots with positive real values. Based on Preposition 1 (ii) in [25] , Equation (24) must satisfy $a_1 a_2 > 0$. Because $a_1 > 0$, for a_2 we obtained

$$\beta\vartheta\big(\mu_2 - k(1-\gamma)\big) > 0. \tag{26}$$

For every $\alpha \in (0,1]$, if $\mu_2 > k(1-\gamma)$ then $a_2 > 0$. It implies $\big|\arg\big(\lambda_{2,3}\big)\big| > \frac{\alpha\pi}{2}$. So that, E^0 is locally asymptotic stable. ■

Jacobi matrix evaluated at endemic equilibrium points E^1 as follows

$$J(E^1) = \begin{pmatrix} \dfrac{-\beta\vartheta(k(1-\gamma)-\mu_2)}{\mu_2\mu_3} & 0 & -\dfrac{\mu_2\mu_3}{\big((1-\gamma)k-\mu_2\big)} \\ \dfrac{\beta\vartheta(k(1-\gamma)-\mu_2)-\mu_1\mu_2\mu_3}{\mu_2\mu_3} & -\mu_2 & \dfrac{\mu_2\mu_3}{\big((1-\gamma)k-\mu_2\big)} \\ \dfrac{-\beta\vartheta(k(1-\gamma)-\mu_2)+\mu_1\mu_2\mu_3}{\mu_2\mu_3} & (1-\gamma)k & -\mu_3 - \dfrac{\mu_2\mu_3}{\big((1-\gamma)k-\mu_2\big)} \end{pmatrix}. \tag{27}$$

Suppose

$$\delta_1 = \beta\vartheta(k(1-\gamma)-\mu_2), \tag{28}$$

$$\delta_2 = \frac{\mu_2\mu_3}{\big((1-\gamma)k-\mu_2\big)}, \tag{29}$$

then substitute Equations (28) and (29) into the matrix of Equation (27) so that it is obtained

$$J(E^1) = \begin{pmatrix} \dfrac{-\delta_1}{\mu_2\mu_3} & 0 & -\delta_2 \\ \dfrac{\delta_1-\mu_1\mu_2\mu_3}{\mu_2\mu_3} & -\mu_2 & \delta_2 \\ \dfrac{-\delta_1+\mu_1\mu_2\mu_3}{\mu_2\mu_3} & (1-\gamma)k & -\mu_3-\delta_2 \end{pmatrix} \tag{30}$$

From the matrix of Equation (30) obtained characteristic equations

$$P(\lambda) = \lambda^3 + b_1\lambda^2 + b_2\lambda + b_3$$
$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0, \tag{31}$$

where

$$b_1 = \frac{{\mu_2}^2\mu_3 + \mu_2\mu_3(\mu_3 + \delta_2) + \delta_1}{\mu_2\mu_3},$$
$$b_2 = \frac{{\mu_2}^2\mu_3(\mu_3 + \delta_2) + (\delta_2(\mu_1 - (1-\gamma)k)\mu_3 + \delta_1)\mu_2 + \delta_1\mu_3}{\mu_2\mu_3},$$
$$b_3 = \delta_1 + \delta_2\mu_1\mu_2 - \delta_2\mu_1(1-\gamma)k.$$

Based on Definition 1 on [25], The discriminant of the polynomial (31) follows

$$D(P) = 18b_1b_2b_3 + (b_1b_2)^2 - 4b_3(b_1)^3 - 4(b_2)^3 - 27(b_3)^2.$$

Based on Preposition 1 (iii) on [25] , using Routh-Hurwitz stability criteria. E^1 is locally asymptotic stable with these following condition

(i). For $D(P) > 0$, if $b_1 > 0, b_3 > 0$ and $b_1b_2 - b_3 > 0$ then E^1 is locally asymptotic stable with order $\alpha \in [0,1)$.

(ii). For $D(P) < 0$, if $b_1 \geq 0, b_2 \geq 0, b_3 > 0$ then E^1 is locally asymptotic stable with order $\alpha < \frac{2}{3}$.

(iii). For $D(P) < 0$, if $b_1 > 0, b_2 > 0$ and $b_1b_2 = b_3$ then E^1 is locally asymptotic stable with order $\alpha \in [0,1)$. ■

V. Numerical Simulation Results

In this section, a numerical simulation of the System (5) will be presented. Based on Grunwald Letnikov's explicit form of Equation (4), the numerical equation form of System (5) is

$$x_1^{n+1} = \sum_{v=1}^{n+1} c_v^\alpha\, x_1^{n+1-v} + r_{n+1}^\alpha x_1^0 + h^\alpha(\vartheta - \beta x_1^n x_3^n - \mu_1 x_1^n),$$
$$x_2^{n+1} = \sum_{v=1}^{n+1} c_v^\alpha\, x_2^{n+1-v} + r_{n+1}^\alpha x_2^0 + h^\alpha(\beta x_1^n x_3^n - \mu_2 x_2^n), \tag{32}$$
$$x_3^{n+1} = \sum_{v=1}^{n+1} c_v^\alpha\, x_3^{n+1-v} + r_{n+1}^\alpha x_3^0 + h^\alpha\big((1-\gamma)kx_2^n - \mu_2 x_3^n - \beta x_1^n x_3^n\big),$$

The model parameter values used in this numerical simulation are as follows

Table 2. Parameter and initial values of Model

Variable/Parameters	Descriptions	Values	Source
$x_1(0)$	Initial Values for healthy cells	$10^7\ dm^{-3}$	[2]
$x_2(0)$	Initial Value for HIV-infected cells	$2 \cdot 10^5\ dm^{-3}$	[2]
$x_3(0)$	Initial Values for HIV virus	$10^5\ dm^{-3}$	[2]
ϑ	The rate of production of healthy cells in the body in units of time	$10^6\ day^{-1}dm^{-3}$	[2]
β	The rate of infection of the HIV virus against healthy cells or the transmission of healthy cells becoming infected.	$10^{-8}day^{-1}dm^{-3}$	[2]
k	The rate of production of the virus by infected cells.	$0.055\ day^{-1}$	Assumed
μ_1	Natural death rate of healthy cells	$0.01\ day^{-1}$	Assumed
μ_2	Natural death rate from infected cells	$0.05\ day^{-1}$	Assumed
μ_3	Natural death rate from the HIV virus	$0.02\ day^{-1}$	Assumed
γ	Proportion of HAART treatment	Varied	Assumed

The simulation was given with HAART pre-treatment and post-HAART treatment conditions by considering three fractional orders. We used 200 days interval for this simulation. The results of the HAART pre-treatment simulation can be seen in Figure 2.

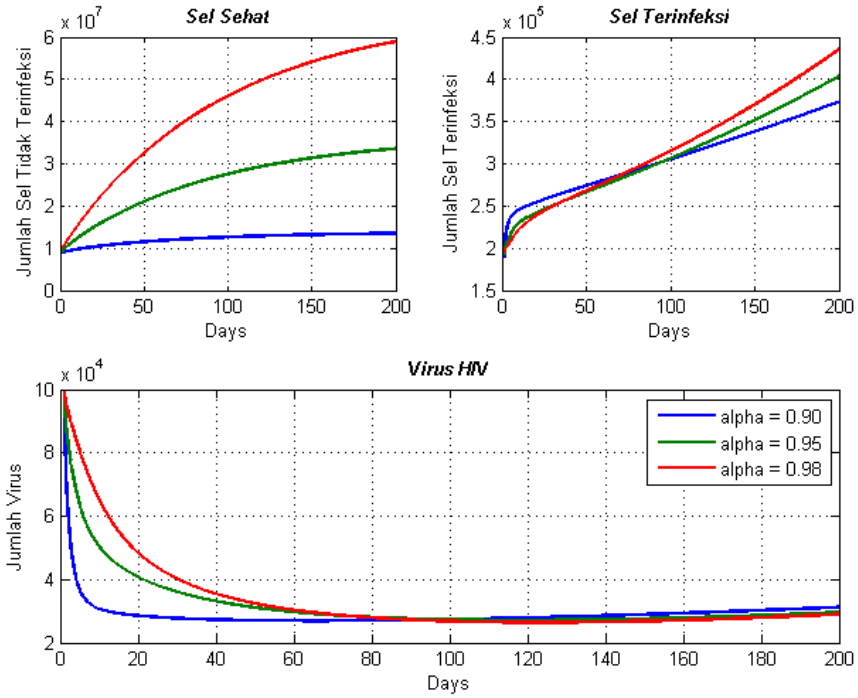

Figure 2. Pre-HAART Model Simulation $\gamma = 0$.

We perform the simulation by the help of MATLAB software. In Figure 2, the simulation results show the dynamics for each compartment. The number of healthy cells shows differences for different fractional order values. The value $\alpha = 0.98$ showed the greatest increase in 200 days of simulation. However, for value $\alpha = 0{,}90$, the number of healthy cells tends to be constant and does not experience a significant increase within 200 days. For the compartment of cells infected with the HIV virus, the results of all three fractional order values showed almost a similar increase. It can be seen that infected cells of order $\alpha = 0.98$ have accelerated in number starting at around day 70. HIV virus compartments for three different fractional orders showed decreased numbers. However, the decline did not reach zero cases. The amount of HIV virus can be observed to be constant throughout the simulation interval. This is also due to the absence of HAART treatment in the simulated model. The reproduction number value in this simulation is for $\alpha = 0.90 \Rightarrow R_0 = 1.0583; \alpha = 0.95 \Rightarrow R_0 = 1.0688; \alpha = 0.98 \Rightarrow R_0 = 1.0747$.

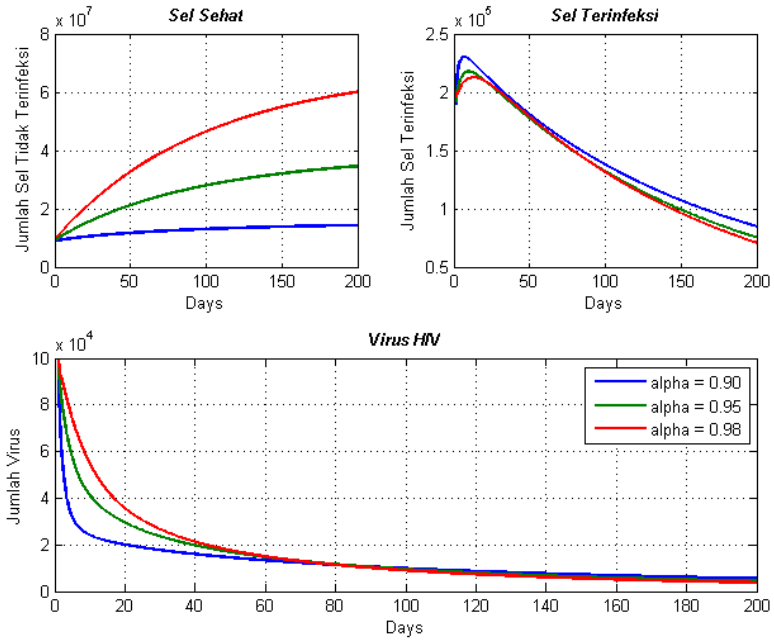

Figure 3. Model Simulation with HAART $\gamma = 0.2$.

Figure 3 provides simulation results with HAART treatment with proportion values $\gamma = 0.2$. Based on the simulations conducted, the existence of HAART treatment has an impact on the dynamics of the number of HIV-infected cells. During the 200 days of simulation, the number of infected cells decreased for each fractional order. The number of infected cells is below $10^5\ dm^{-3}$. For healthy cells, the number of healthy cells produced of fractional order $\alpha = 0.95$ become the highest compared to the other two fractional orders. The amount of HIV virus over the 200 days decreased, with the most significant decrease occurring during the first 20 days of the simulation.

Figure 4 provides simulation results with HAART treatment with proportion values $\gamma = 0.4$. During the 200 days of simulation, the number of infected cells decreased for each fractional order. The number of infected cells is below $0.5 \cdot 10^5\ dm^{-3}$. For healthy cells, the dynamics of the number of healthy cells are not much different from previous simulations. The amount of HIV virus for 200 days has decreased faster than the $\gamma = 0.2$. Based on the graph, the number of HIV viruses is almost 0.

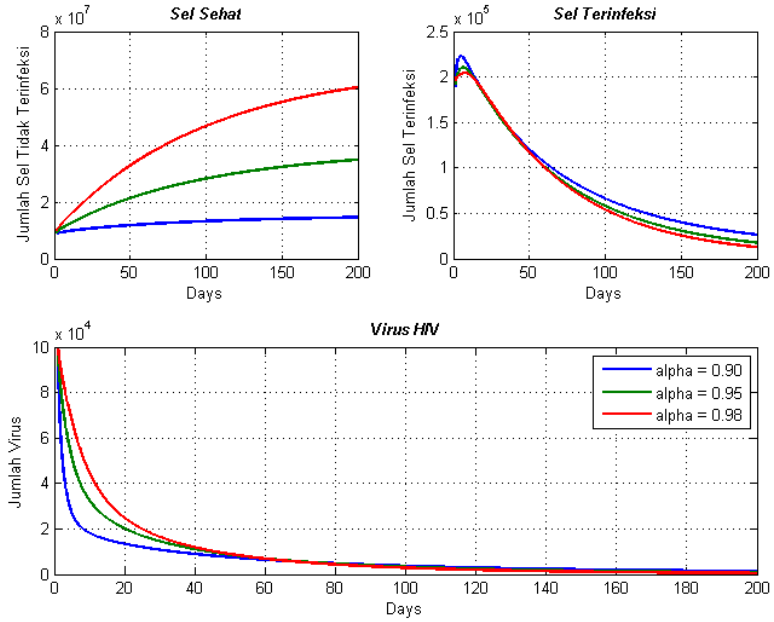

Figure 4. Model Simulation with HAART $\gamma = 0.4$

Figure 5 is the result of a simulation of a combination of two parameters, namely: β and γ towards the value of R_0 by assuming the other parameters are constant according to Table (1). Based on Figure 5 the conditions that produce $R_0 > 1$ occurs when the proportion of treatment tends to be at a lower level as shown in the brown section. These areas are a combination of values of the proportion of HAART treatment below 10% and the value of HIV infection rate above $2 \cdot 10^{-8}$. If an increase in the proportion of HAART treatment is carried out, then the value of R_0 will tend to be below 1. Indirectly, the simulation results in Figure 5 show that changes in the proportion value of HAART treatment tend to have more influence on R_0 compared to the parameters of the rate of HIV infection of healthy cells.

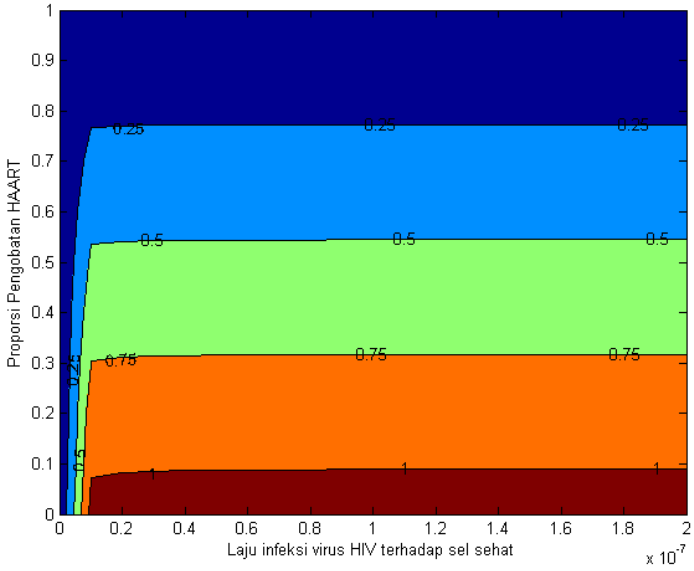

Figure 5. Plot value combinations $\beta - \gamma$ against the R_0 value.

VI. Conclusions

In this study, a fractional model of the interaction of the HIV virus with T Lymphocyte Cells was developed. Based on the sensitivity analysis of two parameters to the base reproduction number (R_0), The infection rate parameter has a directly proportional relationship with R_0. The parameters that represent HAART treatment are inversely proportional to R_0. The results of numerical simulations that considered three fractional orders showed a difference in the number of infected cells between models that did not receive HAART treatment and models that used HAART treatment. With HAART treatment in the form of drug combination administration *Protease Inhibitors* (PI) and *Reverse Transcriptase Inhibitor* (RTI) effect on inhibition of the DNA formation process which has implications for the inhibition of protein formation thereby slowing down the amount of HIV virus production. The slowdown results in the slower formation of the number of HIV-infected cells. For further research, the parameter that describes the HAART treatment is still a constant value parameter, so that in the future it can be considered as a time-dependent parameter so that it can be expanded towards models with optimal control.

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