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The Mathematical Models To Analyze The Impact Of An Adoptive T - Cells Therapy On The Coexistence Of Chronic Lymphocytic And Acute Myelogenous Leukemia.

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Abstract:
Leukemia is a cancerous and progressive disease that affects the myeloid and lymphoid cells of the bone marrow. It causes a lot of problems for families, patients as well as the healthcare systems around the world. This study investigated how adoptive T - cell therapy affects the growth of coexistence of Acute Myelogenous Leukemia (AML) and Chronic Lymphocytic Leukemia (CLL) in a single patient. The methodology involves the development of both classical and fractional differential systems to analyze the coexistence of CLL and AML in a single patient. The numerical simulations were also performed to confirm the results of the analysis. The studies showed that the concentration levels of both types of leukemia cells were very high before the introduction of immunotherapy of the adoptive T cells. The disease free and endemic equilibrium points were proved to be globally asymptotically stable.

Keywords: *Lymphocytic, Myeloid, Leukemia, Reproduction Number, immunotherapy.*

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I. Introduction

An essential component of the immune system, white blood cells (WBCs) work as a natural defense against bacteria, viruses, and other pathogens. WBC are important parts of the immune system which serve as natural weapon to fight off bacteria and other pathogens. A low WBC count which is referred to in Medical terms as Leukopenia is a decreased number of Leucocytes in the blood. Because leukopenia raises the possibility of contracting possibly life-threatening infections, it can be more dangerous [1, 2].

The fast and uncontrolled growth or multiplication of aberrant white blood cells is a hallmark of leukemia [3]. These immature cells hinder the production of the required number of healthy and mature white blood which are necessary for combating infections [4].

In recent years, a lot of clinical case studies have confirmed the association of chronic lymphocytic leukemia (CLL) and acute myelogenous leukemia in a single patient [5, 6, 7]. It has been revealed that most of the associations between AML and CLL are treatment-related and have unfavorable karyotypes [5].
Besides,a great deal of research has been done on how to prevent leukemia cells from spreading.

A comprehensive examination of the challenges,developments,and possible uses of chimeric antigen receptor (CAR)T cell therapy was covered in [8,9,10].The comprehensive studies included clinical trial data and recommendations from experts in the domains of AML and CAR T cell therapy. The study offered suggestions for improving CAR therapy, such as using more receptors or appropriate cytokines. An overview of the difficulties, advancements, and potential uses of chimeric receptor (CAR) T cell therapy was presented using minimal residual hensive. The comprehensive reviews included professional guidance, clinical trial outcomes, and the corpus of research on AML and CAR T cell therapy were all included in the thorough reviews. According to the study, adding more receptors or the right cytokines could enhance CAR therapy. The study in [10] suggested identifying the best clinical conditions, such as minimal residual disease (MRD), low-burden disease, and early salvage, for the application of immunotherapies. [11]. The research verified that unselected donor lymphocyte infusions, or DLIs, are effective in treating post-allogeneic AML and T-ALL patients.

In addition to the many clinical trials on leukemia control, there have been other in-depth studies on mathematical modeling to predict the spread and control of leukemia cells. [12, 13] created mathematical models to distinguish between the sensitivity of normal and mutant stem cells to the bone marrow microenvironment. The three different equilibria of the system correspond to the accelerated-acute phase of the disease, the chronic state, and the normal hematopoietic state. Different classical and fractional differential systems were also constructed by the studies [14–16] to represent the dynamics of myeloid leukemia. In order to demonstrate the worldwide stability of both the endemic and disease-free equilibriums, the proper Lyapunov functions were created [14]. A

classical differential model was developed in [17, 18] to examine the impact of genetically modified patient T lymphocytes against leukemia cells. The outcome demonstrated that the concentration of leukemia cells and infected cells in the blood is decreased by the external infusion of T-cells, or immune cells.

Inspired by the work in [17, 18], the researchers decided to expand on it to include coexistence of AML and CLL in a single patient. The researchers were motivated by the work in [17, 18] and decided to extend it to the coexistence of CLL and AML in a single patient. The classical differential system has also been extended to the Caputo's fractional differential sense in the study.

II. Materials And Methods

The Classical Differential Model

The goal of the study is to identify the impact of an externally engineered adoptive T-cell on the coexistence of CLL and AML in a single patient by developing both a traditional differential system and a Caputo's fractional differential sense. Another leukemic cells compartment was introduced to the system—one for CLL and the other for AML, [4, 17]. Additionally, based on the type of infected cells as indicated in the schematic image, fig.1, below, the researchers included two parameters, φ *and* γ, to describe the rate at which the infected cells travel to CLL and AML compartments, respectively. The following are the models' underlying presumptions:

1. By means of basic intracellular processes of bilinear mass action, healthy cells come into contact with the leukemia cells leading to infections.
2. The infected cells then move from the healthy compartment at the rate of β to the infected compartment.
3. The infected cells then progress and move to the chronic cells or acute cells compartments depending on the types of cells that are infected (i.e. immature or matured cells) at the rates of γ *and* φ respectively. Also $\gamma > \varphi$.
4. It also assumes that the body's entire cell population at any given time is represented by

N = x + y + $z_a + z_c + w$.

Below is the schematic transmission diagram of leukemic cells.

Recruitment Rate (A)

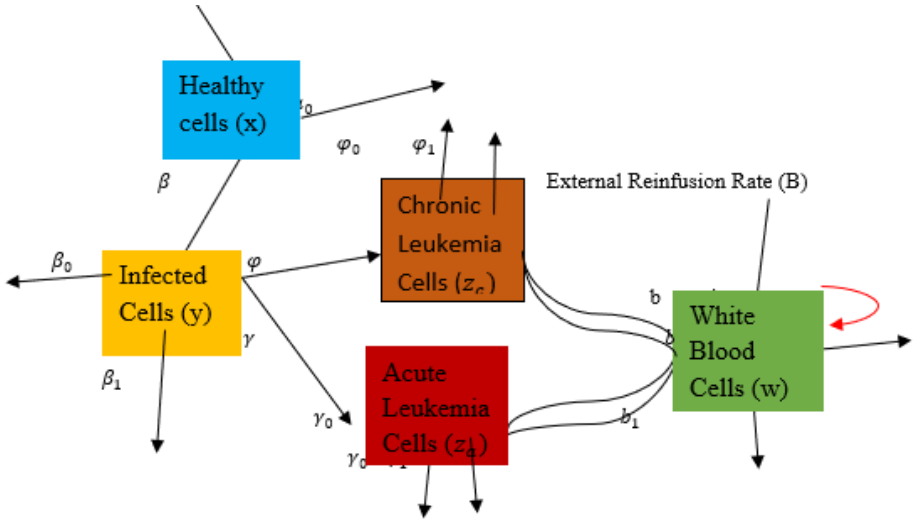

Fig. 1: The Modified Transmission Diagram of Leukemia in the Patients

The smooth curves without arrows in the transmission diagram, Fig. 1 above represent the terms of interaction between the compartments, whereas the red arrows represent the white blood cell self-renewal rates as a result of the leukemia relapse.

The state variables in the schematic diagram are x, y, z_a, z_c *and* w, which stand for the concentration levels of normal or healthy cells, infected cells, AML, CLL and white blood cells respectively. The classical models are given below

$$\begin{aligned}
\frac{dx}{dt} &= \text{A} - a_0 x - \beta xy \\
\frac{dy}{dt} &= \beta xy - \beta_0 y - \gamma y - \varphi y - \beta_1 y(z_a + z_c) \\
\frac{dz_a}{dt} &= \gamma y - \gamma_0 z_a - \gamma_1 z_a w \qquad (1) \\
\frac{dz_c}{dt} &= \varphi y - \varphi_0 z_c - \varphi_1 z_c w \\
\frac{dw}{dt} &= \text{B} + \text{b}(z_a + z_c) - b_0 w - b_1 w(z_a + z_c)
\end{aligned}$$

The table no 1 below gives the descriptions of the parameters and values used the above models.

Table no 1: Summary of Notations

Notations	Definition	Value
A	A Constant rate of healthy blood cell recruitment	1.5
a_0	Natural rate of death of healthy cells	0.01
β	Healthy cells infection rate	0.01
β_0	The infected cells natural death rate	0.005
β_1	The infected cells decayed rate	0.005
γ	The rate of progression of infected cells to AML compartment	0.2
γ_0	Natural rate of death of acute leukemic cells	0.05
γ_1	Decay rate of AML cells due its interaction with immune system	0.005
φ	The transfer rate of infected cells to CLL compartment	0.12
φ_0	Natural death rate of chronic leukemic cells	0.05
φ_1	Decay rate of CLL cells due its interaction with immune system	0.005
B	The rate of adoptive T – Cells reinfusion	2.0
b	The rate of white blood cells proliferation	0.01
b_0	Natural death rate of white blood cells	0.05
b_1	The immune system's deterioration rate as a result of its interactions with leukemia cells	0.001

The Fractional Derivative Model

The researchers extended the developed models (1) to the Caputo's Fractional derivative sense in order to apply the Fractional Derivative techniques to perform the stability test of the system (1).

The Fractional derivative form of the models (1) are given as

$$
\begin{aligned}
{}_0^{\mathrm{C}}\mathbb{D}_t^{\alpha} x(t) &= \mathrm{A} - a_0 x - \beta xy \\
{}_0^{\mathrm{C}}\mathbb{D}_t^{\alpha} y(t) &= \beta xy - \beta_0 y - \gamma y - \varphi y - \beta_1 y(z_a + z_c) \\
{}_0^{\mathrm{C}}\mathbb{D}_t^{\alpha} z_a(t) &= \gamma y - \gamma_0 z_a - \gamma_1 z_a w \qquad (2) \\
{}_0^{\mathrm{C}}\mathbb{D}_t^{\alpha} z_c(t) &= \varphi y - \varphi_0 z_c - \varphi_1 z_c w \\
{}_0^{\mathrm{C}}\mathbb{D}_t^{\alpha} w(t) &= \mathrm{B} + \mathrm{b} z_a + b z_c - b_0 w - b_1 w z_a - b_1 w z_c
\end{aligned}
$$

Subject to the initial condition

$x_0 \geq 0,\ y_0 \geq 0, z_{a(0)} \geq 0, z_c \geq 0\ and\ w_0 \geq 0$

Where ${}_0^{\mathrm{C}}\mathbb{D}_t^{\alpha}$ represents the Caputo's fractional differential operator of order $0 < \alpha \leq 1$.

It's assumed that all the parameters are non-negatives and the functions x(t), y(t), z_a(t), $z_c(t)$, w(t) and their Caputo fractional derivatives are also continuous.

III. The Model Analysis

Positivity Solutions of the System

We defined the system (2) as,

$\Lambda^+ = \{(x, y, z_a, z_c, w) \in R^5 : x(t), y(t), z_a(t), z_c(t), w(t) \geq 0\}$.

Suppose that,

$(x_0, y_0, z_{a(0)}, z_{c(0)}, w_0) \in x$(t)-axis $= \{(x(t), 0, 0, 0, 0) : x(t) \geq 0\}$.

The Laplace transform was applied to the Caputo's fractional derivative system, (2) along with the vector x(t) axis as shown below:

$$\mathcal{L}\left({}_0^{\mathrm{C}}\mathbb{D}_t^{\alpha} x(t)\right) = \mathcal{L}(\mathrm{A} - a_0 x)$$

$$S^{\alpha} X(s) - S^{\alpha-1} x(0) = \frac{A}{S} - a_0 X(s)$$

$$S^{\alpha} X(s) + a_0 X(s) = \frac{A}{S} + S^{\alpha-1} x(0)$$

$$X(s)(S^{\alpha} + a_0) = \frac{A}{S} + S^{\alpha-1} x(0)$$

$$X(s) = \frac{A}{S(S^{\alpha}+a_0)} + \frac{(S^{\alpha-1}x(0)}{(S^{\alpha}+a_0)} = \frac{AS^{\alpha-(\alpha+1)}}{S^{\alpha}+a_0} + \frac{S^{\alpha-1}x(0)}{S^{\alpha}+a_0}$$

Taking the inverse Laplace transform, we have

$x(t) = At^{\alpha}E_{\alpha,(\alpha+1)}(-a_0t^{\alpha}) + x(0)E_{\alpha,1}(-a_0t^{\alpha})$

Hence, system (2) along with the vector $x(t)$ axis, yields

$\{(x, y, z, w) = \{(At^{\alpha}E_{\alpha,(1+\alpha)}(-a_0t^{\alpha}) + x(0)E_{\alpha,1}(-a_0t^{\alpha}), 0, 0, 0, 0): x(t) \geq 0\}$

Similarly system (2) along with the vectors y(t), $z_a(t), z_c(t)$ and w(t) axes also result in the following points: $(x_0, y_0, z_{c(0)}, z_{a(0)}, w_0)$ = (0, $y(0)E_{\alpha,1}(-\beta_0)t^{\alpha}$),0, 0,) ∈ y(*t*)-axis; (*x*(*t*), *y*(*t*), z_a(t), z_c(t), *w*(t)) = (0, 0, $z_a(0)E_{\alpha,1}(-\gamma_0)t^{\alpha}$), 0, 0) ∈ $z_a(t)$-axis; (*x*(*t*), *y*(*t*), $z_a(t)$, $z_c(t)$, *w*(*t*)) = (0, 0, 0, $z_c(0)E_{\alpha,1}(-\varphi_0)t^{\alpha}$) 0,) ∈ $z_c(t)$-axis and (*x*(*t*), *y*(*t*), $z_a(t)$, $z_c(t)$, *w*(*t*)) = (0, 0, 0, 0, $Bt^{\alpha}E_{\alpha,\ \alpha+1}((-b_0)t^{\alpha})$ + w(0)$E_{\alpha,1}(-b_0)t^{\alpha}$)) ∈w(*t*)-axis respectively.

The aforementioned points demonstrate that Λ+ is a positive invariants set since $x(t), y(t), z_a(t), z_c(t)$ *and* $w(t)$ are solutions of the system and positive invariants sets.

The Equilibrium Points

There are two equilibria points in system (2), namely the endemic equilibrium and the disease-free equilibrium points.

At the disease free equilibrium point (DFEP), the infected cells, acute cells, chronic cells, and white blood due to the infusion of adoptive T-cells are absent and therefore set to zero (i.e. y = z_a = z_c = w = 0). blood due to the infusion of adoptive T- cells are absent and hence set to zero, (i.e. y = z_a = z_c = w = 0).

The Endemic equilibrium points (EEP) are the steady state situations where the disease persist in the population [18].

To solve for both equilibria, we set all the derivatives to zero and solve the resulted equations. The system was simplified by letting z = $z_a + z_c$, $z_c = z - z_a$and $\mu_1 = \beta_0 + \gamma + \varphi$. Hence the disease free equilibrium point is, $E^0 = \left(\frac{A}{a_0}, 0, 0, 0, 0\right)$ and the endemic equilibrium point is given by $E^* = (x^*, y^*, z_a{}^*, z_c{}^*, w^*)$, where:

$x^* = \frac{A}{a_0R_0} + \frac{\beta_1 z^*}{\beta}$; $y^* = \frac{a_0\mu_1(R_0-1)-a_0\beta_1z^*)}{\beta(\mu_1+\beta_1z^*)}$; $z^*{}_a = \frac{a_0\gamma\mu_1(R_0-1)-a_0\beta_1\gamma z^*)(b_0+b_1z^*)}{((\gamma_0b_0+\gamma_0b_1z^*)+(B+bz^*)\gamma_1)(\beta_0\beta+\gamma+\varphi+\beta_1\beta z^*)}$; $z_c{}^* = \frac{a_0\varphi\mu_1(R_0-1)-a_0\beta_1\gamma z^*)(b_0+b_1z^*)}{(\omega_0b_0+\varphi_0b_1z^*)+(B+bz^*)\varphi_1)(\beta_0\beta+\gamma+\varphi+\beta_1\beta z^*)}$ $w^* = \frac{B+bz^*}{b_0+b_1z^*}$;

And $R_0 = \frac{\beta A}{a_0(\beta_0-\gamma-\varphi)}$ is the basic reproduction number for (2)

Stability at Disease Free Equilibrium Point, E^0

Lemma 1

Assuming the fractional differential system (2) has α ∈ [0, 1), then the subsequent criteria are satisfied:

i. All of the roots of the characteristic equation, or eigenvalues, of J(E^0), have a negative real portion if the determinants of all Hurwitz matrices (Hj) of the characteristic equations are positive,

ii. When all the eigenvalues are negative, then the DFE point E^0 = ($\frac{A}{a_0}$, 0, 0, 0, 0) is locally asymptotically stable.

Theorem 1

If the basic reproduction number, R_0 < 1, then the DFE point of system (2) is asymptotically stable.

Proof.

The characteristic equation of the Jacobian matrix J(E^0) of (2) at DFE point is given by the equation, $|J(E_0) - \lambda I| = 0$.

$$|J(E^0) - \lambda I| = \begin{vmatrix} -a_0-\lambda & -\frac{\beta A}{a_0} & 0 & 0 & 0 \\ 0 & \mu_1(R_0-1)-\lambda & 0 & 0 & 0 \\ 0 & \gamma & -\gamma_0-\lambda & 0 & 0 \\ 0 & \varphi & 0 & -\varphi_0-\lambda & 0 \\ 0 & 0 & b & b & -b_0-\lambda \end{vmatrix} = 0$$

The characteristic equation can be expressed as,

$$(-a_0-\lambda)[(\beta_0+\gamma+\varphi)(R_0-1)-\lambda](-\gamma_0-\lambda)(-\varphi_0-\lambda)(-b_0-\lambda) = 0$$

Hence, the eigenvalues are, λ_1 =-a_0, $\lambda_2 = \mu_1(R_0-1)$, $\lambda_3 = -\gamma_0$, $\lambda_4 = -\varphi_0$ *and* $\lambda_5 = -b_0$

It can be clearly seen that all the eigenvalues are negative when R_0 < 1. That means that theorem 1 and lemma 1 are proved. Hence DFE, E^0 is asymptotically stable.

Stability at Endemic Equilibrium Point (EEP)

Theorem 2

If the basic reproduction number, $R_0 > 1$, then the Endemic equilibrium point (EEP) is asymptotically stable.

Proof:

The eigenvalues of the characteristic equation at endemic equilibrium point, E^* is given $|J(E^*) - \lambda| = 0$.

$$|J(E^*)| = \begin{vmatrix} T_1 - \lambda & -\beta x^* & 0 & 0 & 0 \\ \beta y^* & T_2 - \lambda & -\beta_1 y^* & -\beta_1 y^* & 0 \\ 0 & \gamma & T_3 - \lambda & 0 & -\gamma_1 {z_a}^* \\ 0 & \varphi & 0 & T_4 - \lambda & -\varphi_1 {z_c}^* \\ 0 & 0 & T_6 & T_6 & T_5 - \lambda \end{vmatrix} = 0$$

Where,

$T_1 = -a_0 - \beta y^*, T_2 = \beta x^* - \beta_0 - \gamma - \varphi - \beta_1({z_a}^* + {z_c}^*), T_3 = -\gamma_0 - \gamma_1 w^*, T_4 = -\varphi_0 - \varphi_1 w^*, T_5 = b_0 + b_1 z^*, T_6 = b - b_1 w^*$

The characteristic equation can be expressed as,

$$k_0 \lambda^5 + k_1 \lambda^4 + k_2 \lambda^3 + k_3 \lambda^2 + k_4 \lambda + k_5 = 0$$

The determinants of Hurwitz's matrices $|H_j|$ of the above characteristic equation, for j = 1, 2, 3, 4, 5, are given below:

$|H_1| = k_1$, $|H_2| = k_1 k_2 - k_3$, $|H_3| = (k_1 k_5 + k_1 k_2 k_3) - (k_1^2 k_4 + k_3^2)$,

$|H_4| = (k_1 k_2 k_3 k_4 + 2k_1 k_4 k_5 + k_2 k_3 k_5) - (k_2^2 k_1 k_5 + k_1^2 k_4^2 + k_3^2 k_4)$,

$|H_5|$ $(H_5) = (k_1 k_2 k_3 k_4 k_5 + 2k_1 k_4 k_5^2 + k_2 k_3 k_5^2) - (k_5^3 + k_1 k_2^2 k_5^2 + k_1^2 k_4^2 k_5 + k_3^2 k_4 k_5)$

For $|H_j| > 0$, then the following inequalities should hold:

$k_1 > 0$; $k_1 k_2 > k_3$; $(k_1 k_5 + k_1 k_2 k_3) > (k_1^2 k_4 + k_3^2)$; $(k_1 k_2 k_3 k_4 + 2k_1 k_4 k_5 + k_2 k_3 k_5) > (k_2^2 k_1 k_5 + k_1^2 k_4^2 + k_3^2 k_4)$ *and* $(k_1 k_2 k_3 k_4 k_5 + 2k_1 k_4 k_5^2 + k_2 k_3 k_5^2) > (k_5^3 + k_1 k_2^2 a_5^2 + k_1^2 k_4^2 k_5 + k_3^2 k_4 k_5)$

Based on Hurwitz's stability criterion, the endemic equilibrium point, E^* would be asymptotically stable when all the above inequalities are met.

Effects of Adoptive T cells on Growth of CLL and AML

Case I: When the immune response is neglected (i.e. w = 0)

In the situation as in [17] when the immune system is so weak in such a way that its response, w to the cancer cells is zero, then the endemic equilibrium values of system (2) becomes:

$$x^* = \frac{\mu_1 + \beta_1 z^*}{\beta}; \quad y^* = \frac{\beta A - a_0\mu_1 - a_0\beta_1 z^*}{\beta(\mu_1 + \beta_1 z^*)}; \quad {z_a}^* = \frac{\gamma y^*}{\gamma_0}; \quad {z_c}^* = \frac{\varphi y^*}{\varphi_0}; \quad w^* = 0 \qquad (3)$$

It was observed from (3) that, the level of concentration of both cancer cells, $(i.e.\ z_a\ and\ z_c)$ are only controlled by the natural death. This could enable the cancer cells to grow out of bound leading to worsening of clinical condition of the patient.

Case II: No dormant membrane or immune response activation cells (i.e. b = 0):

The immune response activator, b activates the immune system or produces the required number of white blood cells when the cancer cells relapse. So we want to consider a situation where there is no immune response activation from professional antigen presenting cells. In that case the endemic equilibrium points of (2) becomes:

$$x^* = \frac{\mu_1 + \beta_1 z^*}{\beta}; \quad y^* = \frac{\beta A - a_0\mu_1 - a_0\beta_1 z^*}{\beta(\mu_1 + \beta_1 z^*}; \quad w^* = \frac{B}{b_0 + b_1 z^*}; \quad {z_a}^* = \frac{\left(\frac{\gamma}{\gamma_0}\right)y^*}{\left(1 + \frac{\frac{\gamma_1}{\gamma_0}B}{b_0 + b_1 z^*}\right.}; \quad {z_c}^* = \frac{\left(\frac{\varphi}{\varphi_0}\right)y^*}{\left(1 + \frac{\frac{\varphi_1}{\varphi_0}B}{b_0 + b_1 z^*}\right)} \qquad (4)$$

It was found that the immune response activation resulting from the infusion of'adoptive T cells,B,in the blood,also checked the level of concentrations of both cancer] cells (i.e.,za,zc). Considering that both of the cancer cells^' equilibrium values in (4) are lower than in (3).As demonstrated in [17],it suggests that immunotherapy using genetically modified T cells affects the spread of cancer cells in the blood even in the absence of antigenicity caused by cancer cells.

Case III: When there no engineered T – cells Therapy (B = 0)

We want to consider a situation when the external engineered adoptive T – cell is not applied to the leukemia patient. In that case, the endemic equilibrium values of (2) are as follows:

$$x^* = \frac{\mu_1 + \beta_1 z^*}{\beta}; \quad y^* = \frac{\beta A - a_0\mu_1 - a_0\beta_1 z^*}{\beta(\mu_1 + \beta_1 z^*)}; \quad w^* = \frac{bz^*}{b_0 + b_1 z^*}; \quad {z_a}^* = \frac{\left(\frac{\gamma}{\gamma_0}\right)y^*}{\left(1 + \frac{\frac{\gamma_1}{\gamma_0}b_1 z}{b_0 + b_1 z^*}\right)}; \quad {z_c}^* = \frac{\left(\frac{\varphi}{\varphi_0}\right)y^*}{\left(1 + \frac{\frac{\varphi_1}{\varphi_0}b_1 z}{b_0 + b_1 z^*}\right)} \qquad (5)$$

It could be seen that the concentration of both CLL and AML cells in (5) are lower than in (3). [17] reported that, in practice, the equilibrium value of immune cells due to the external infusion of engineered T cells

is greater than that in the case without immunotherapy. Hence, adoptive T cells immunotherapy can be a better means of controlling the number of cancer cells in the blood than natural stimulation of immune cells

Numerical Simulations

In order to confirm the above solutions, we simulated the system to determine the behavior or variations of the various compartments. The parameter values in table 1 above were used for the various simulations:

The Algorithm:

The fractional forward Euler method was applied for the simulation algorithm as follows:

We denoted the initial time by $t_1 = 0$; the final time by $t_n = T$ and the step size by h.

The Caputo's fractional differential system (2) was first expressed as:

$${}_{0}^{C}\mathbb{D}_{t}^{\alpha} f(t) = F\big(t, f(t)\big), 0 < \alpha \leq 1,\ 0 \leq t \leq T$$

Subject to the initial conditions,

$x(0) = x_0 \geq 0,\ y(0) = y_0 \geq 0,\ z_a(0) = z_{a(0)} \geq 0,\ z_c(0) = z_{c(0)} \geq 0,\ w(0) = w_0 \geq 0,$

Where, f(t) = $(f_1(t), f_2(t), f_3(t), f_4(t), f_5(t))$ and

$$\begin{aligned} f_1(\mathrm{x}, \mathrm{y}, z_a, z_c, \mathrm{w}) &= \mathrm{A} - a_0 x - \beta x y \\ f_2(\mathrm{x}, \mathrm{y}, z_a, z_c, \mathrm{w}) &= \beta x - \beta_0 - \gamma - \varphi - \beta_1 z \\ f_3(\mathrm{x}, \mathrm{y}, z_a, z_c, \mathrm{w}) &= \gamma y - \gamma_0 z_a - \gamma_1 z_a w \\ f_4(\mathrm{x}, \mathrm{y}, z_a, z_c, \mathrm{w}) &= \varphi \mathrm{y} - \varphi_0 z_c - \varphi_1 z_c w \\ f_5(\mathrm{x}, \mathrm{y}, z_a, z_c, \mathrm{w}) &= \mathrm{B} + \mathrm{bz} - b_0 w - b_1 w z \end{aligned} \quad (6)$$

Letting

N = $\frac{t_n - t_1}{h}$; $h = \frac{T}{N}$, $t_n = nh$, and $n = 1, 2, 3, 4, \ldots, N$

For k = 1: N

j = 1: k

$t_{k+1} = t_k + h$

$$\begin{aligned} x_{(k+1)} &= x_1 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{j=1}^{k} (k-j+1)^\alpha - (k-j)^\alpha) f_1(t_j,\ x_j,\ y_j,\ z_{aj},\ z_{cj},\ w_j) \\ y_{(k+1)} &= y_1 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{j=1}^{k} (k-j+1)^\alpha - (k-j)^\alpha) f_2(t_j,\ x_j,\ y_j,\ z_{aj},\ z_{cj},\ w_j) \\ z_{a(k+1)} &= z_{a(1)} + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{j=1}^{k} (k-j+1)^\alpha - (k-j)^\alpha) f_3(t_j,\ x_j,\ y_j,\ z_{aj},\ z_{cj},\ w_j) \\ z_{c(k+1)} &= z_{c(1)} + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{j=1}^{k} (k-j+1)^\alpha - (k-j)^\alpha) f_4(t_j,\ x_j,\ y_j,\ z_{aj},\ z_{cj},\ w_j) \\ w_{(k+1)} &= w_1 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{j=1}^{k} (k-j+1)^\alpha - (k-j)^\alpha) f_5(t_j,\ x_j,\ y_j,\ z_{aj},\ z_{cj},\ w_j) \end{aligned} \quad (7)$$

Simulation to Determine the Type of Stability at Disease Free Equilibrium (DFE) Point

At the DFE, y = z_a = z_c = w = 0, so we used the initial point, E(x^*, 0, 0, 0, 0)

A = 1.5, $a_0 = 0.01aq1$, and the fractional order,$\alpha = 0.89$

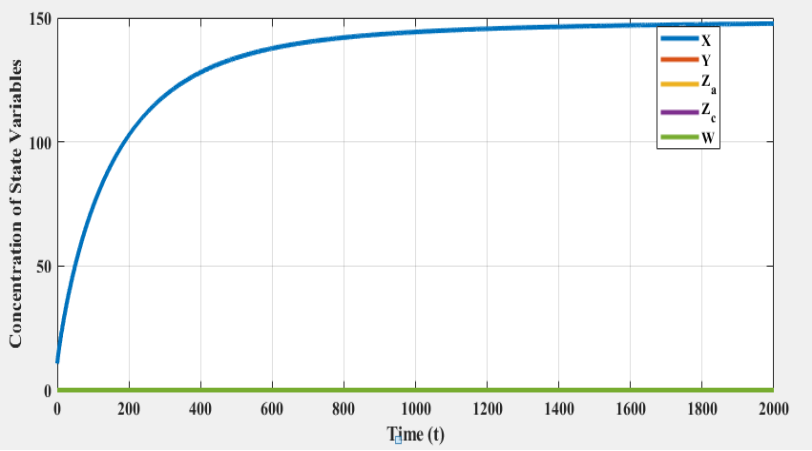

Fig. 2*:* Simulation of the system (2) for t = 2000 days

The Fig. 2 shows that the DFE point is approximately E^o(149.53, 0, 0, 0,0) which occurs at t > 1600. This may suggest that the DFE point is asymptotically stable.

Determine the Stability at the Endemic Equilibrium Point (EEP)

The researchers used the values of the parameters in the table 1 above with the initial values of $x(0)$ = 5, y(0) = 4, $z_a(0)$ = 2, $z_c(0)$ = 3 and w(0) = 0 for the various numerical simulations

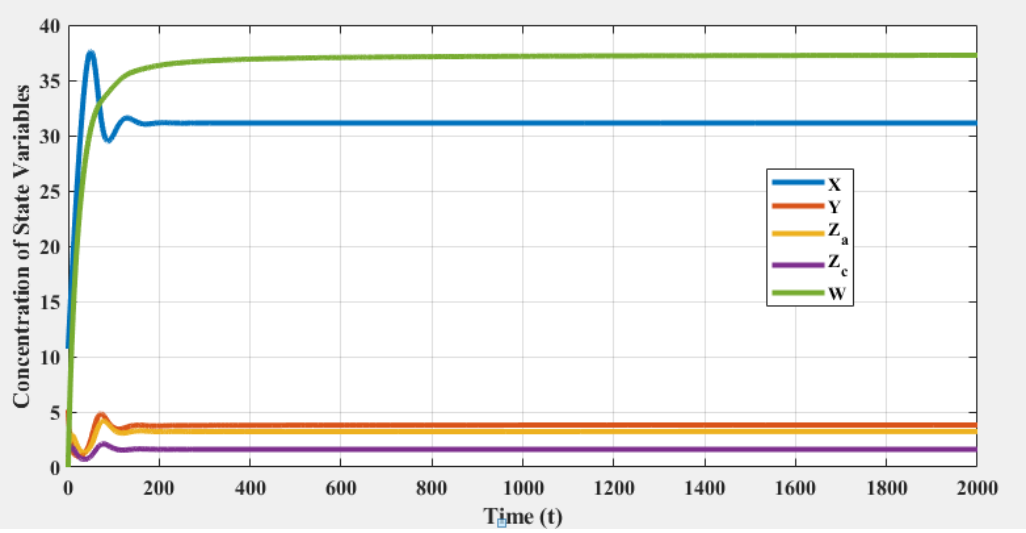

Fig. 3a*:* Simulation of the system

From Fig.3a, the EEP of system (2) is approximately $E^*(31.13, 3.79, 3.22, 3, 1.61, 36.96)$. It could be seen that the transient states of the state variables except the white blood cells occur between the interval, 0 < t < 200. Hence the state variables, x(t), y(t), $z_a(t)$ *and* $z_c(t)$ attained their stability at t ≥ 200 and continues the stability till the end of the process. The white blood cells attained stability at t > 600. The stable state of the system suggests that the EEP is asymptotically stable.

It could be observed that the rate of increment of the concentration level of the immune system (w) is higher than that of the acute and chronic leukemic cells even though it started with the initial concentration of zero (0). The higher concentration of the immune system could be attributed to the reinfusion of an external adoptive T – cells, B and the proliferation rate, b of the white blood cells.

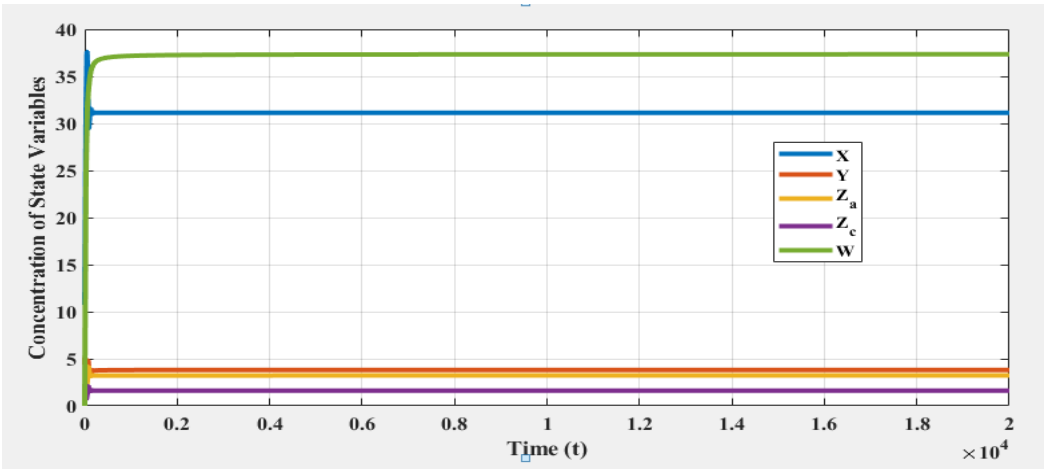

Fig. 3b: Simulation of the system for 0 < t < 20000

The system attains its longest stability point of $E^*(31.13, 3.82, 3.22, 1.61, 37.33)$ at t = 200 1432 and continues till the end of the process at t = 20000. This may suggest that the endemic equilibrium point, $E^*(31.13, 3.82, 3.22, 1.61, 37.33)$ may also be globally stable.

Determine the Effect Proliferation rate, b of Immune System on Spread of AML and CLL Cells

The Fig. 4a and Fig.4b below show the effects of variations of the proliferation rate, b of white blood cells, on the concentration levels of both AML and CLL cells population.

It is revealed that as b increases, the concentration levels of both z_a(t) and z_c(t) also decrease and vice versa. That is the rate of change of the concentration levels of both z_a(t) and z_c(t) are inversely proportional to

the proliferation rate of the immune system. The proliferation of the immune system triggers when cancer cells relapse.

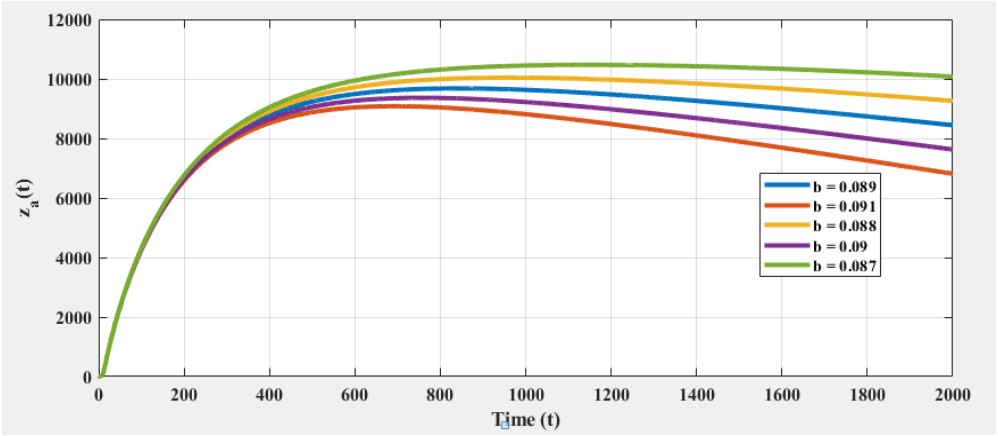

Fig. 4a*:* Effects of Variations of b on Concentration Levels of AML

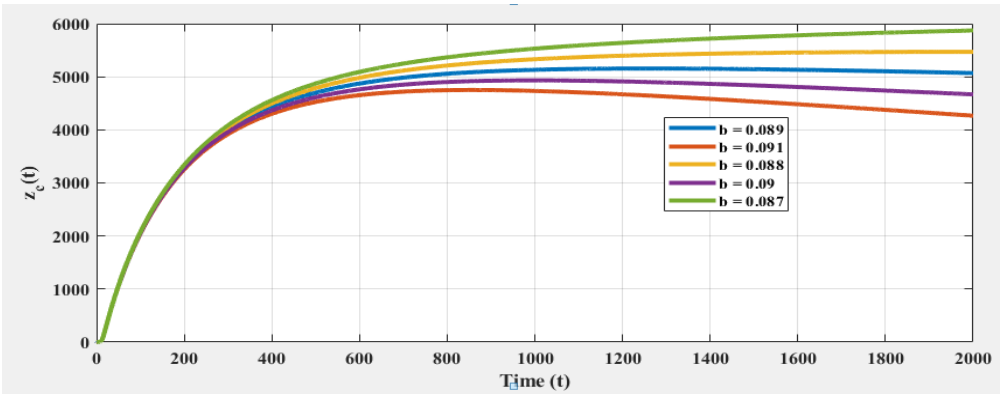

Fig. 4b*:* Effects of Variations of b on Concentration Levels of CLL

Effects of the Rate of adoptive T-Cells Infusion on Cancer Cells

The variations of B on both AML and CLL cells are depicted in Fig 4b and Fig 4b respectively below. It could be seen from both figures that before the introduction of external engineered adoptive T-cells (i.e. when B = 0), the highest concentration levels of both AML and CLL exceed 16500 and 12396 respectively. However, with the introduction of an external engineered T-cells to the system, the concentration levels of AML and CLL started reducing. The concentration levels of both cancer cells decrease as the rate of external engineered T – cells, B increases and vice versa as shown in the fig.5a and fig.5b below. That is the concentration levels of the AML and CLL dropped drastically below 2820 and 1914 respectively.

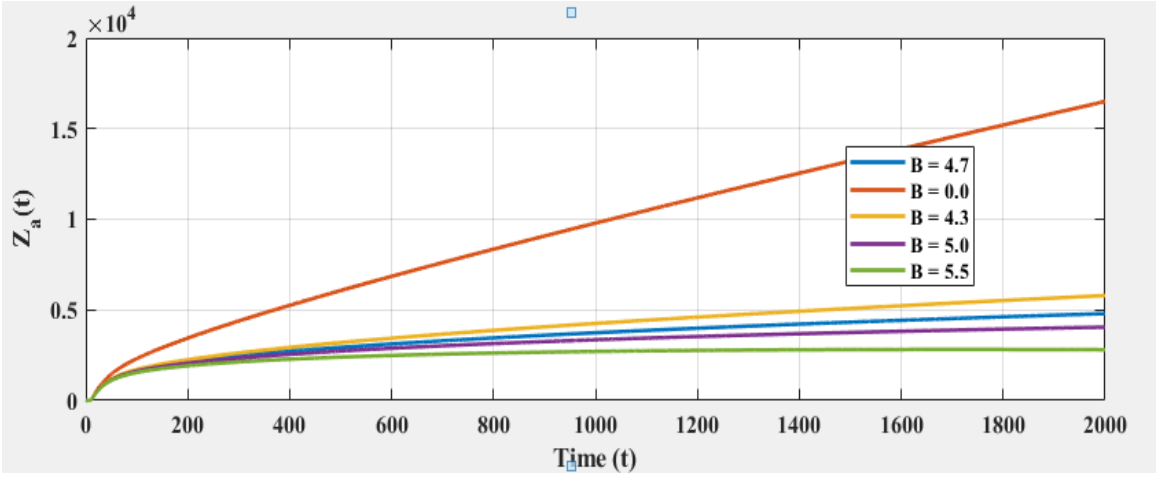

Fig. 5a: Effects of Variations of B on AML

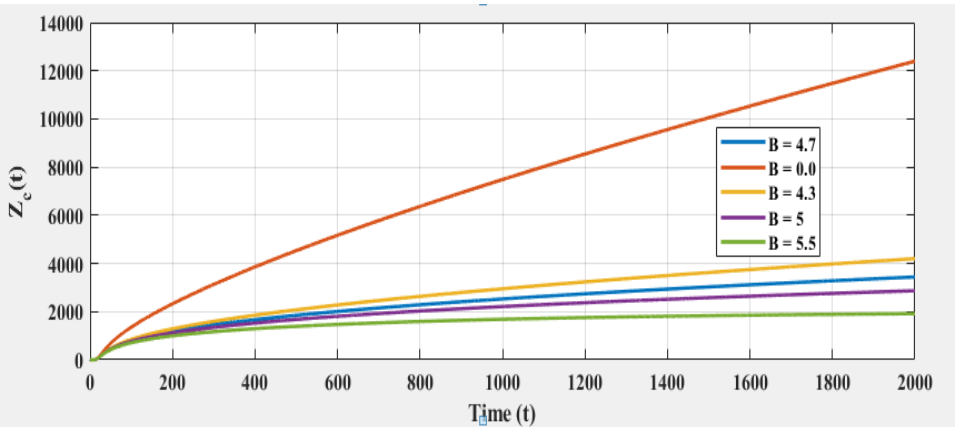

Fig.5b*:* Effects of Variations of B on CLL

The above changes in the concentration levels of both leukemic cells with respect to the variations of B indicates that the external engineered adoptive T – cells can be employed to control both acute and chronic leukemic cells.

Determine the Effects of Fractional Differential Order on the AML and CLL.

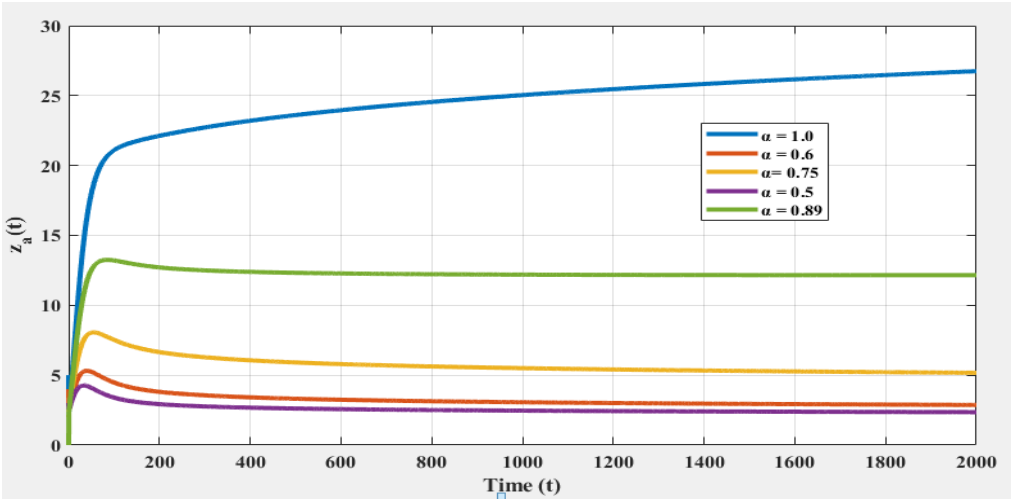

Fig. 6a: Effects of Variation of Fractional differential Order α on AML

From fig. 6a above, it could be observed that the rate of change of the equilibrium concentration of the AML is directly proportional to the differential order, α. For instance, when $\alpha = 0.5$, the equilibrium concentration level of AML was approximately 2.4 but when $\alpha = 0.89$, the equilibrium concentration level of AML increased to 12.2.

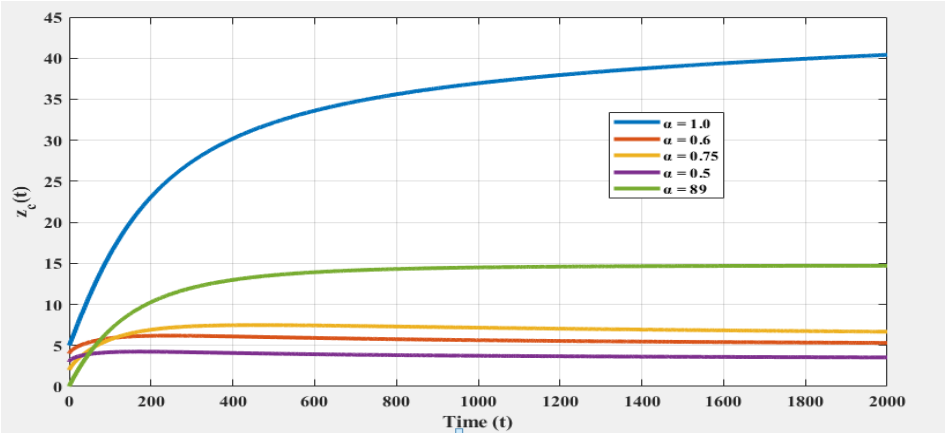

Fig. 6b*:* Effects of Variation of Fractional differential Order (α) on CLL

Similar to fig. 6a, the rate of change of the equilibrium concentration of the CLL is directly proportional to the fractional differential order, α. For fig. 6b, when $\alpha = 0.5$, the equilibrium concentration level of CLL is approximately 3.4, but when $\alpha = 0.89$, the concentration level of CLL also reduced to 13.7.

It is realized from both fig.6a and fig.6b that the AML is more sensitive to the fractional differential order than that of CLL. Then also, when $0 < \alpha < 1$, the equilibrium points of both AML and CLL are reached more faster than when $\alpha = 1$ (i.e. the classical differential system).

IV. Results And Discussions.

The parameter values in table 1 were used to evaluate the analyzed results and compared them to the simulated results. For instance, by evaluating the DFE point, $E^0 = (\frac{A}{a_0}, 0, 0, 0, 0)$ using table 1 above (i.e. A = 1.5, a_0 = 0.01), the approximated DFE point is $E(\frac{1.5}{0.01}, 0, 0, 0, 0) = E(150, 0, 0, 0, 0)$. The result is almost the same as what we got in simulation, Fig. 2 above. The endemic equilibrium point, E^* of system (2) is said to be asymptotically stable if the basic reproduction number, $R_0 > 1$. Evaluating R_0, using table 1, we have $R_0 = \frac{\beta A}{a_0(\beta_0+\gamma+\varphi)} = \frac{0{,}01\times1.5}{0.01(0.05+0.2+0.12)} = 4.054 > 1$. That may suggest that the endemic equilibrium point, E^* is asymptotically stable as proved above . This finding is also supported by the simulations fig.3a and fig.3b.

It could be seen from the simulations, fig.4a and fig.4b that the rate of change of concentration levels of leukemia cells is inversely proportional to that of immune response activator, b which supports the results in case II above. Similarly, from the simulations, fig.5a and fig.5b, the concentration levels of AML and CLL cells before the introduction of reinfusion of an external engineered adoptive T – cells were very high and that also support the results in case III above.

The simulations fig.6a and fig.6b indicate that the stability of the system is achieved more faster when using the fractional order, $0 < \alpha < 1$ than the classical differential system.

V. Conclusion:

The main goal of study was to develop a Mathematical framework to analyze the effects of an adoptive T – cell therapy on spread of CLL and AML that coexist in a single patient. The developed Caputo's Fractional differential model (2) was proved to be asymptotically stable. The results of the analysis and the findings of the performed simulations suggest that the immunotherapy of an adoptive T – cell can control the growth of AML and CLL in a single patient. Researchers recommend that there should be further studies on the applications an adoptive T – cells and the other immunotherapy methods to help control the spread of AML and CLL cells that coexist in a single patient.

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