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Piecewise differentiation of the fractional order CAR-T cells-SARS-2 virus model

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A B S T R A C T
The pandemic caused by the SARS-CoV2 virus has prompted research into new therapeutic solutions that can be used to treat the Covid-19 syndrome. As part of this research, immunotherapy, first developed against cancer, is offering new therapeutic horizons also against viral infections. CAR technology, with the production of CAR-T cells (adoptive immunotherapy), has shown applicability in the field of HIV viral infections through second generation CAR-T cells implemented with the “CD4-CAR” system with a viral fusion inhibitor. In addition, to avoid the immunoescape of the virus, bi- or trispecific CAR receptors have been developed. Our research group hypothesizes the use of this immunotherapy system against SARS-CoV2, admitting the appropriate adjustments concerning the target-epitope and a possible remodeling of the nuclease related to the action of this virus. For a more in-depth analysis of this hypothesis, a mathematical model has been developed which, starting from the fractional derivative Caputo, creates a system of equations that describes the interactions between CAR-T cells, memory cells, and cells infected with SARS-CoV2. Through an analysis of the existence and non-negativity of the solutions, the hypothesis is stabilized; then is further demonstrated through the use of the piece-wise derivative and the consequent application of the formula of Newton polynomial interpolation.

Introduction

Biological framework

CAR-T cells are a promising technology that reprograms T cells to overcome the barriers that cancer presents against the action of the immune system: about 90% of individuals treated with CAR (Chimeric Antigen Receptor) technology who selectively target tumors expressing CD-19 such as pediatric acute lymphoblastic lymphoma, go into remission.

Since the CAR receptor allows a reorganization of antigen presentation without requiring the intervention of the molecules of the Major Histocompatibility Complex (MHC), the targets that they can detect are fewer than the T cell receptors (TCR), but they have a rather significant advantage given by a greater specificity that eludes the escape mechanisms that pathogens or the tumor itself can implement. The CAR construct is made according to a panoramic view as shown in Fig. 1 and where the various sectors come from elements of the TCR receptor, the CD28 molecule and from the variable regions of a monoclonal antibody line.

A study by Roberts et al. [1] showed the realization of a construct that directed the specificity of T cells against cells infected with the HIV (fusion of CD4 with the CD3ζ polypeptide chain called “CD4ζ CAR”), exploiting the particular interaction between molecules of the viral envelope with CD4. This experience, however, despite being quite safe, did not allow the observation of a lasting control of the infection in question. This approach, however, has focused on the central action of T cells in the control of viral infections and, thanks to advances in scientific research and biotechnology, numerous advances in the control of chronic HIV inflammation, and the consideration of a subpopulation of T cells that can be engineered, considering their advantages and disadvantages [2].

Thanks to positive experimentation of CAR-T cells in vivo against cancer, advances in the construction technology of the CAR receptor have led to the use of the second generation of this CD4-based receptor optimized by a 4-1BB-CD3 signal domain ζ which was found to be much more efficient in controlling HIV viral replication in vitro and experiments on mouse showed a strong response to the infection [3].

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The second generation of CAR-T cells, thus engineered (Fig. 2), contains a portion that binds the target antigen, that is the single-chain variable fragment (scFv), shows a good antiviral capacity in vitro, but in humans, several factors limit its use and a possible therapy need for a better effectiveness against the diversity of the biochemical characteristics of the HIV and not being immunogenic.

Viral pathogen-specific effector CD8+ T cells play a crucial role in controlling infections in immunocompetent individuals, making adoptive T cell therapy an attractive alternative to currently used anti-infectious therapies. T cells specific for viral pathogens occur at low frequencies in the patient's blood, making them difficult to isolate and expand. Furthermore, these cells have phenotypes subject to depletion and can be rendered inefficient by mutation mechanisms linked to viral escape that lower the expression of the major histocompatibility complex (MHC) or mutate the epitope-target of such cells [4]. Therefore, chimeric antigen receptor (CAR) T cells represent an attractive alternative.

Few anti-infective CARs have been described in the literature so far, most of which target HIV. To improve the function and persistence of CAR-T cells, the “CD44-CAR” system has been redesigned into second and third-generation CARs. While CAR-T cells containing the CD28 co-stimulatory domain promoted increased cytokine production and improved control over HIV replication in vitro, CARs containing 4-1BB were more potent in controlling HIV infection in vivo. Compared to first-generation CAR T cells, second-generation CAR-T cells were more potent in suppressing HIV replication in vitro. Furthermore, in a humanized mouse model of HIV infection, they preserved CD4 + T cell counts, reduced HIV burden, and expanded to a greater extent than first-generation CAR T cells.

However, CAR receptors built on CD4+ T elements have been shown to make CAR-T cells susceptible to HIV infection (Liu et al. 2015). To overcome this potentially harmful situation, the “CD44-CAR” system was equipped with a viral fusion inhibitor (C46 peptide) or small hairpin RNAs to break down the HIV-1 co-receptor (CCR5) and degrade the RNA viral [5].

Our group of analysis and research of Mathematical Models in Biology speculated if similar technology could also be applied in the case of the SARS-CoV2 pandemic that we are currently experiencing, directing a specificity of target similar to what happens for the HIV and where the action of the engineered cells themselves is somewhat simplified by the fact that, at the moment and contrary to HIV, there is no evidence that this type of coronavirus infects T' cells that of using Treg cells, typical of the autoimmunity process, which can proliferate in an antigen-specific way and lead to a sort of subsequent protection for the pathology that expresses that same antigen [6].

In addition, several genome editing techniques have been used to eliminate CCR5 in T cells to give them lifelong resistance to HIV infection [7]. These include the use of various nucleases including ZFN (zinc finger nuclease), which have shown promise in some clinical studies (NCT00842634 and NCT01044654), TALEN (transcription activator-like nuclease) [8], and others nucleases in preclinical studies. These endonucleases were already used to produce universal CAR-T cells by breaking down TCR [9]. At present, it is believed that a test would be needed to verify their ability to break down CCR5 in HIV-CAR T cells.

Finally, to overcome the mechanism of HIV escape from the immune response, T cells expressing bi and tri-specific CARs were designed that target up to three HIV antigens to increase both specificity and affinity. In this case, the CD4 element was fused with a specific “scFv” complex for a CD4-induced epitope on gp120 or the carbohydrate recognition domain (CRD) of a human C-type lectin that binds to glycans stored on virus envelope [10]. The bi-specific CD4-anti-gp120 scFv CAR had better HIV activity than CD4 alone. CARs presenting a CD4 mannose-binding lectin (MBL) showed better activity than both CD4 alone and CD4-anti-gp110. However, as type C lectins can bind glycans that are not specific to HIV-infected cells and can be associated with healthy cells, off-target targets cannot be ruled out and this is an aspect that needs to be analyzed and evaluated carefully.

Computational framework

In the field of computational biology, both the discrete and continuous modeling approaches have remained successful to visualize the biological networks [11–18]. The concept of the fractional operators has been presented simultaneously with the improvement of classical theory. The success of Fractional Calculus applications is that the new fractional order models are frequently more precise than the integer order. The degrees of freedom in the fractional order models are greater than in the corresponding classical. All the fractional operators reflect the entire history of the process being considered. Fractional calculus is consequently an outstanding set of tools for relating memory and transmissible properties of numerous materials and procedures.

In this paper, inspired from the work of Atangana and his coworkers [19,20], we investigate a class of the numerical scheme to approximate time fractional differential equations. The method is consisting on approximations of the Caputo fractional derivative of the order \( a \in (0,1) \) by means of the continuous piecewise polynomials, which are connected to backward differentiation formulae. Additionally, stability and convergence analysis of the numerical method is discussed in detail [11,21,22]. This will encourage additional investigation of this proposed method for solving the time fractional differential equations.

In this manuscript, a fractional order approach [23,24] is used to explore the time dependent interaction rates of the engineered cells with the SARS-CoV2-infected cells. The dynamical analysis of the fractional order model can help to draw useful intervals for the wet-lab, where experimental trials are expensive and crucial to time. Thus the present research can help to demonstrate the impact of fractional order of time, on the sensitive biological interactions and the resulting dynamics. The rest of the paper is designed as follows: In the next section, the fractional order model is presented. Next the dynamical analysis and the intervals are drawn, and finally useful conclusions are drawn based on the limiting intervals for the parameters.

Mathematical model

Preliminaries

The primary definitions about fractional derivative in Caputo sense are describe in [25,26]

Definition. Caputo fractional derivative of the order \( a \in (n-1, n) \) where \( n \in \mathbb{N} \) for the function \( g \in C^a \) defined as

\[
D^a g(t) = \frac{1}{\Gamma(n-a)} \int_0^t (t-\zeta)^{n-a-1} g(\zeta) d\zeta.
\]

where \( \zeta \) represent gamma function. Since \( D^a g(t) -> g^\prime(t) \) as \( a -> 1 \).

Definition. The fractional integral having order \( a > 0 \) of function \( g : R^+ \rightarrow R \) is defined by following

\[
I^a g(t) = \frac{1}{\Gamma(a)} \int_0^t (t-\zeta)^{a-1} g(\zeta) d\zeta.
\]

Definition. A constant point \( \chi^* \) is equilibrium point of a caputo fractional dynamical system

\[
D^a g(\chi^*) = g(t, \chi^*), a \in (0, 1)
\]

if and only if \( g(t, \chi^*) = 0 \).

Model analysis

Consider the action of CAR-T cells (T), memory cells (M) and infected cells (I), in a systematic manner as shown in the schematic 1 (see Table 2 for the parameters description).
We have the fractional differential system of equations as follows:

\begin{align}
\mathcal{C} D^\alpha_T T &= (a - \beta - \gamma) T(t) + (\delta M(t) - c T(t)) I(t), \\
\mathcal{C} D^\alpha_T M &= \beta_\eta T(t) - (\nu + \delta I(t)) M(t), \\
\mathcal{C} D^\alpha_T I &= \kappa (1 - \rho I(t)) I(t) - \sigma T(t) I(t),
\end{align}

with the initial conditions \( T(0) \geq 0, M(0) \geq 0, I(0) \geq 0 \). The description of compartments \( T(t), M(t) \) and \( I(t) \) is in Table 1.

**Existence and non-negativity of solution**

Assume \( R^1_+ \), to present non negativity of model solution as follows

\( R^1_+ = \{ X \in R^1 | X \geq 0 \} \) and \( X(t) = (T, M, I)^T \)

For further process we have following lemma which is the generalized of mean value theorem.

**Lemma.** Assume that \( g(t) \in [a, b] \) and \( \mathcal{C} D^\alpha_T g(t) \in [a, b] \) then,

\[
g(t) = g(a) + \frac{1}{\Gamma(\alpha)} \mathcal{C} D^\alpha_T g(t)(t - a)^\alpha \]

where \( \alpha \leq \zeta \leq t \) for all \( t \in (a, b) \).

| Symbols | Description |
|---------|-------------|
| \( I(t) \) | Infected cells from SARS-CoV-2 virus |
| \( T(t) \) | CAR T cells |
| \( M(t) \) | Memory cells |

**Table 1**

**Table 2**

**The condition for non increasing and non decreasing is give by following corollary.**

**Corollary.** Assume that \( g(t) \in C[a, b] \) and \( \mathcal{C} D^\alpha_T g(t) \in (a, b) \) such that \( \alpha \in (0, 1] \). Then

- if \( \mathcal{C} D^\alpha_T g(t) \leq 0 \) for all \( t \in (a, b) \), then \( g(t) \) is non increasing.
- if \( \mathcal{C} D^\alpha_T g(t) \geq 0 \) for all \( t \in (a, b) \), then \( g(t) \) is non decreasing.

**Theorem 1.** The model possesses a unique solution \( X(t) \in \Omega \) for all \( X(t_0) = (T_0, M_0, I_0) \in \Omega \) with initial condition for all \( t \geq 0 \).

**Proof.** Suppose that the region

\[
\Omega = \{(T, M, I) \in R^3 : \max \{ |T|, |M|, |I| \} \leq P \}
\]

where \( P \) is a finite positive real number. Suppose a map \( F(X) = (F_1(X), F_2(X), F_3(X)) \) where \( X = (T, M, I) \) and \( X' = (T', M', I') \).

\[
F_1(X) = (a - \beta - \gamma) T + (\delta M - c T) I, \\
F_2(X) = \beta_\eta T - (\nu + \delta I) M, \\
F_3(X) = \kappa (1 - \rho I) I - \sigma T I.
\]

For any \( X, X' \in \Omega \)

\[
\| F(X) - F(X') \| = |F_1(X) - F_1(X')| + |F_2(X) - F_2(X')| + |F_3(X) - F_3(X')|.
\]

**Corollary**

\[
|F_1(X) - F_1(X')| \leq \epsilon(T - T') + I|\delta M + c T| - I'| (\delta M' + c T') \\
|F_2(X) - F_2(X')| \leq \epsilon(T - T') + \nu M' + I'| (\nu + \delta I') - \beta_\eta T' \\
|F_3(X) - F_3(X')| \leq \epsilon(T - T') + \nu M' + I'| (\nu + \delta I') - \kappa I' - \sigma T' I' - I'.
\]

**Table 2**

**Summary of parameters.**

| Symbols | Description | Values |
|---------|-------------|--------|
| \( a \) | CAR T cells proliferation rate | \( \text{day}^{-1} \) |
| \( \beta \) | Differentiation rate of CAR T cells into memory cells | \( \text{day}^{-1} \) |
| \( \gamma \) | Death rate of CAR T cells | \( \text{day}^{-1} \) |
| \( \delta \) | Conversion coefficient of M into CAR T cells due to interaction with infected cells from SARS-CoV-2 | (cell day)\(^{-1} \) |
| \( c \) | CAR T cells inhibition coefficient due to interaction with infected cells from SARS-CoV-2 | (cell day)\(^{-1} \) |
| \( \eta \) | Numerical response of conversion of CAR T cells into memory cells | |
| \( \nu \) | Death rate memory cells | \( \text{day}^{-1} \) |
| \( \kappa \) | Maximum growth rate of T cells | \( \text{day}^{-1} \) |
| \( \rho \) | Inverse of infection carrying capacity | \( \text{cell}^{-1} \) |
| \( \sigma \) | CAR T cells induced death coefficient | (cell day)\(^{-1} \) |
Putting the values in from Eq. (10), (11) and (12) in Eq. (9) we have
$$
\| F(X) - F(X') \| \leq (e + c)|T - T'| + \delta |I - I'| + |M| + |I|
$$

Theorem 2. The solution of the model solution.

Local Lipschitz’s. We may concluded that the system possess the unique and
solution.

From the model we can deduce that

$$
\alpha = \frac{c}{\beta + 2\delta P} \quad \beta = \frac{\delta \rho}{\beta + 2\delta P} \\
\gamma = \frac{\delta \rho}{\beta + 2\delta P}
$$

Therefore, $F(X)$ obey condition of Local Lipschitz’s. We may concluded that the system possess the unique solution.

Theorem 2. The solution of the model (4) exists and it remains in $R^+$. Moreover, the solution are non negative.

Proof. From the model we can deduce that

$$
C\frac{d}{d\tau}T|_{\tau=0} \geq 0, \\
C\frac{d}{d\tau}M|_{\tau=0} \geq 0, \\
C\frac{d}{d\tau}I|_{\tau=0} \geq 0.
$$

By using corollary (Section “Existence and non-negativity of solution”), we can concluded that the solution remains in $R^+$. The feasible region is $\Omega$ where $P \geq 0$.

Equilibrium points

The equilibrium point of model (4) obtained by putting equations

$$
\delta_{\tau}T = \alpha T - \beta P + \gamma I + 2\delta P |M| - \delta |I| - |I| + |M|
$$

the model has following equilibrium points. The equilibrium point $(T_0, M_0, I_0)$ is

$$
E_0 = (0, 0, 0),
$$

which is saddle point. The other equilibrium points are defined as

$$
E_1 = (T_1, M_1, I_1) = (0, 0, \frac{1}{\rho})
$$

and the endemic equilibrium point is

$$
E^* = (T^*, M^*, I^*)
$$

where

$$
T^* = \frac{\kappa(\delta \rho(-a + \beta \eta + \gamma + 2\delta) - A \rho + \nu \rho c)}{2\delta \rho c}, \\
M^* = \frac{\kappa(\alpha \delta + \nu \rho)(\delta + \nu \rho)(\alpha + \gamma + \delta - \delta + (q + 1)\nu \rho)}{2\delta \rho c}, \\
I^* = \frac{\kappa \delta \rho(-a + \beta \eta + \gamma + 2\delta) - A \rho + \nu \rho c}{2\delta \rho c}.
$$

As $A = \sqrt{\delta^2(-a - \beta \eta + \gamma)^2 + 2\delta \rho(a - \beta(\eta + 1) - \gamma + \nu \rho c)^2}$. The threshold quantity is known as basic reproduction number for fractional model and it is obtained by using next generation method. The basic reproduction number $R_1$ is biologically important and it determined global dynamics of model. The matrix $F$ and $V^{-1}$ defined as

$$
F = \begin{pmatrix}
-\beta & 0 \\
\beta & 0
\end{pmatrix}, \\
V^{-1} = \begin{pmatrix}
\kappa \frac{2\delta c}{\delta \rho} & \frac{2\delta c}{\delta \rho} \\
\frac{2\delta c}{\delta \rho} & \frac{2\delta c}{\delta \rho}
\end{pmatrix},
$$

The spectral radius of $FV^{-1}$ is basic reproduction which is obtained as

$$
R_1 = \frac{\beta \rho (\delta \rho - \delta - \nu \rho)}{\delta + \nu \rho(\delta + \nu \rho + \epsilon)}.
$$

Stability of equilibrium point

In the literature, the stability analysis is of great significance, while designing a computational model [13,27,28]. The stability analysis of the fractional order model can help to understand the dynamics of the model in detail. The jacobian matrix at equilibrium point is

$$
J_0 = \begin{pmatrix}
\alpha - \beta - \gamma & 0 & 0 \\
\beta \eta & -\nu & 0 \\
0 & 0 & \kappa
\end{pmatrix},
$$

the jacobian matrix $J_0$ is saddle which is always stable. The stability of other equilibrium point is proved by the following theorems.

Theorem 3. Suppose that $r_1$ and $r_2$ be two positive integers such that $gcd(r_1, r_2)$. Assume that $a = \frac{r_1}{r_2}$ and $r_2 = N$, then equilibrium point of model (4) is asymptotically stable gives that $|\arg(\lambda)| > \frac{\pi}{2N}$.

The jacobian matrix at equilibrium point $E_1$ is

$$
J_1 = \begin{pmatrix}
\alpha - \beta - \gamma - \frac{\delta}{\rho} & \frac{\delta}{\rho} & 0 \\
\beta \eta & -\nu - \frac{\delta}{\rho} & 0 \\
0 & 0 & -\kappa
\end{pmatrix},
$$

by expansion we get

$$
(\lambda_1^1 + \kappa_1^1)\lambda_1^2 + \kappa_2^1\lambda_1^2 + \kappa_2
$$

where the coefficients are

$$
\kappa_1 = \frac{(\beta \rho(-a + \beta \eta + \gamma + 2\delta) - A \rho + \nu \rho c)}{2\delta \rho c}, \\
\kappa_2 = \frac{B - (\rho(-a + \beta \rho + \gamma + 2\delta) - \delta + \epsilon)}{2\delta \rho c}, \\
A = \sqrt{\delta^2(-a - \beta \eta + \gamma)^2 + 2\delta \rho(a - \beta(\eta + 1) - \gamma + \nu \rho c)^2} + \delta^2 + 2\delta \epsilon.
$$

Arguments of roots $\lambda_1^1 + \kappa_1 = 0$ and $\lambda_1^1 + \kappa_2 = 0$ also greater than $\frac{\pi}{2N}$. Moreover, if the reproduction number $R_1$ lesser...
than zero, desired conditions fulfilled for all the polynomial (25). But in case if \( R > 1 \) according to Descartes signs rule, there exists at least one root which give positive root, in other word which satisfied \(| \arg(\lambda) | < \frac{\pi}{2N} \). Hence, the equilibrium point is asymptotically stable for \( R < 1 \), otherwise unstable.

**Theorem 4.** For an arbitrary fractional order \( a \) in interval \((0,1)\), and \( R_0 < 1 \), equilibrium point of model (4) is globally asymptotically stable, otherwise unstable.

**Proof.** By the definition of Lyapunov function

\[
V(t) = U_1(t)(T - T_0 - T_0 \ln \frac{T}{T_0}) + U_2(t)(M - M_0 - M_0 \ln \frac{M}{M_0})
\]

\[
+ U_3(t)(I - I_0 - I_0 \ln \frac{I}{I_0}).
\]  (28)

Where \( U_i \) as \( i = 1 \) are positive constants. The time derivative of above Eq. (28) we have

\[
C D_t^a V = U_1 C D_t^a T + U_2 C D_t^a M + U_3 C D_t^a I
\]

\[
= U_1(\alpha - \beta - \gamma)T + (\delta M - cT)I + U_2[\beta \eta T - (\nu + \delta I)M]
\]

\[
+ U_3(1 - \frac{1}{\rho^T})[\kappa(1 - \rho I)I - \sigma I].
\]  (29)

With the help of arithmetical geometrical inequality we have

\[
[(\alpha - \beta - \gamma)T + (\delta M - cT)I] \leq 0,
\]

\[
[\beta \eta T - (\nu + \delta I)M] \leq 0,
\]

\[
(1 - \frac{1}{\rho^T})[\kappa(1 - \rho I)I - \sigma I] \leq 0.
\]  (30)

Hence \( C D_t^a V \) negative for \( R_0 < 1 \). Therefore, the model is globally asymptotically stable at equilibrium point \( E_1 \).

**Stability at endemic equilibrium point**

The Jacobian matrix at endemic equilibrium point is

\[
J^* = \begin{bmatrix}
\alpha - \beta - \gamma - cT^* & \delta I^* & \delta M^* - cT^* \\
\beta \eta & -\nu - cI^* & -cM^* \\
-\sigma I^* & 0 & -2\rho I^* \kappa + \kappa - \sigma T^*
\end{bmatrix}
\]  (31)

The stability of endemic equilibrium point is discussed in **Theorem 3** for \( R_1 > 1 \)

**Theorem 5.** If the basic reproduction number \( R_1 > 1 \), the endemic equilibrium point is globally asymptotically stable.

**Proof.** Suppose the Lyapunov function

\[
L(t) = (T - T^* - T^* \ln \frac{T}{T^*}) + (M - M^* - M^* \ln \frac{M}{M^*}) + (I - I^* - I^* \ln \frac{I}{I^*}).
\]  (32)

By **Theorem 3**, derivative along endemic equilibrium point is

\[
C D_t^a L = (1 - \frac{T^*}{T})C D_t^a T + (1 - \frac{M^*}{M})C D_t^a M + (1 - \frac{I^*}{I})C D_t^a I.
\]  (33)

Where:

\[
(1 - \frac{T^*}{T})C D_t^a T = (1 - \frac{T^*}{T})(\alpha - \beta - \gamma)T + (\delta M - cT)I,
\]

\[
(1 - \frac{M^*}{M})C D_t^a M = (1 - \frac{M^*}{M})[\beta \eta T - (\nu + \delta I)M],
\]

\[
(1 - \frac{I^*}{I})C D_t^a I = (1 - \frac{I^*}{I})[\kappa(1 - \rho I)I - \sigma T I].
\]  (34)

By simplifying

\[
C D_t^a L = I_k \left[ \frac{\delta}{\gamma} \left( \frac{1}{T} - \frac{1}{T^*} \right) \rho + 1 \right] + T \left( a - \beta \eta \left( \frac{1}{\gamma} - 2 \right) - \nu - \sigma \right) \left( \frac{1}{T^*} - \frac{1}{\gamma} + 1 \right)
\]

\[
+ T^* \left( -a + \gamma + \beta \left( -\eta - \frac{\delta M^* T}{M T^*} + 1 \right) - \sigma \right) - I e
\]

\[
+ M^* \left( v + \delta I \left( 1 - \frac{I}{M^*} \right) - 2\nu M \left( \frac{1}{M^*} \right) - \frac{T^*}{T M^*} + 1 \right).
\]  (35)

By arithmetical geometrical inequality

\[
a - \beta \eta \left( \frac{1}{\gamma} - 2 \right) - \nu - \sigma \left( \frac{1}{T^*} - \frac{1}{\gamma} + 1 \right) \leq 0,
\]

\[
-\alpha + \gamma + \beta \left( -\eta - \frac{\delta M^* T}{M T^*} + 1 \right) - \sigma \leq 0
\]

\[
v + \delta I \left( 1 - \frac{I}{M^*} \right) - 2\nu M \left( \frac{1}{M^*} \right) - \frac{T^*}{T M^*} \leq 0
\]

\[
I^* \left( 1 - \frac{1}{T^*} \right) \rho + 1 \leq 0.
\]  (36)

Hence \( C D_t^a L \leq 0 \), therefore by **Theorem 3** the model at endemic equilibrium point is locally asymptotically stable.

**Piece-wise derivative**

To show numerical scheme for model (4), we assume following

\[
\begin{align*}
0 & \quad PG D_t^a T = (a - \beta - \gamma)T(t) + (\delta M - cT(t))I(t), \\
0 & \quad PG D_t^a M = \beta \eta T(t) - (\nu + \delta I(t))M(t), \\
0 & \quad PG D_t^a I = \kappa(1 - \rho I(t))I(t) - \sigma T(t)I(t).
\end{align*}
\]  (37)

Applying the piece-wise derivative, we obtained

\[
T(t) = \begin{cases}
\tilde{T}(0) + \int_0^t (a - \beta - \gamma)T(\tau) + (\delta M - cT(\tau))I(\tau) d\tau \\
\tilde{T}(t_1) + \int_{t_1}^t (a - \beta - \gamma)T(\tau) + (\delta M - cT(\tau))I(\tau) d\tau
\end{cases}
\]

\[
M(t) = \begin{cases}
\tilde{M}(0) + \int_0^t (\beta \eta T(\tau) - (\nu + \delta I(\tau))M(\tau) d\tau \\
\tilde{M}(t_1) + \int_{t_1}^t (\beta \eta T(\tau) - (\nu + \delta I(\tau))M(\tau) d\tau
\end{cases}
\]

\[
I(t) = \begin{cases}
\tilde{I}(0) + \int_0^t \kappa(1 - \rho I(\tau))I(\tau) - \sigma T(\tau)I(\tau) d\tau \\
\tilde{I}(t_1) + \int_{t_1}^t \kappa(1 - \rho I(\tau))I(\tau) - \sigma T(\tau)I(\tau) d\tau
\end{cases}
\]  (38)

At \( t = t_{n+1} \) we can write

\[
T(t_{n+1}) = \begin{cases}
\tilde{T}(0) + \int_0^t (a - \beta - \gamma)T(\tau) + (\delta M - cT(\tau))I(\tau) d\tau \\
\tilde{T}(t_{n+1}) + \int_{t_{n+1}}^t (a - \beta - \gamma)T(\tau) + (\delta M - cT(\tau))I(\tau) d\tau
\end{cases}
\]

\[
M(t_{n+1}) = \begin{cases}
\tilde{M}(0) + \int_0^t (\beta \eta T(\tau) - (\nu + \delta I(\tau))M(\tau) d\tau \\
\tilde{M}(t_{n+1}) + \int_{t_{n+1}}^t (\beta \eta T(\tau) - (\nu + \delta I(\tau))M(\tau) d\tau
\end{cases}
\]

\[
I(t_{n+1}) = \begin{cases}
\tilde{I}(0) + \int_0^t \kappa(1 - \rho I(\tau))I(\tau) - \sigma T(\tau)I(\tau) d\tau \\
\tilde{I}(t_{n+1}) + \int_{t_{n+1}}^t \kappa(1 - \rho I(\tau))I(\tau) - \sigma T(\tau)I(\tau) d\tau
\end{cases}
\]  (39)
Replacing it by formula of Newton polynomial interpolation,

\[
\begin{align*}
T(0) + \sum_{k=1}^{n} \left[ \frac{5}{12} (a - \beta - \gamma T(t_{k-1}) + (\delta M(t_{k-1}) - \epsilon T(t_{k-1}))I(t_{k-1})) \right. &
\left. \times (g(t_{k-1}) - g(t_{k})) \right] \\
+ \sum_{k=1}^{n} \left[ \frac{4}{23} (a - \beta - \gamma T(t_{k-1}) + (\delta M(t_{k-1}) - \epsilon T(t_{k-1}))I(t_{k-1})) \right. &
\left. \times (g(t_{k}) - g(t_{k+1})) \right] \\
\times \left( g(t_{k+1}) - g(t_{k-1}) \right) &
\times (g(t_{k}) - g(t_{k+1})) \\
M(t_{k-1}) + \sum_{k=1}^{n} \left[ \frac{5}{12} (\delta M(t_{k-1}) - (\delta + \epsilon I(t_{k-1}))) I(t_{k-1})) \right. &
\left. \times (g(t_{k-1}) - g(t_{k})) \right] \\
+ \sum_{k=1}^{n} \left[ \frac{4}{23} (\delta M(t_{k-1}) - (\delta + \epsilon I(t_{k-1}))) I(t_{k})) \right. &
\left. \times (g(t_{k}) - g(t_{k+1})) \right] \\
\times \left( g(t_{k+1}) - g(t_{k-1}) \right) &
\times (g(t_{k}) - g(t_{k+1})) \\
I(t_{k-1}) + \sum_{k=1}^{n} \left[ \frac{5}{12} (\epsilon (1 - \rho I(t_{k-1}))) I(t_{k-1})) \right. &
\left. \times (g(t_{k-1}) - g(t_{k})) \right] \\
+ \sum_{k=1}^{n} \left[ \frac{4}{23} (\epsilon (1 - \rho I(t_{k-1}))) I(t_{k})) \right. &
\left. \times (g(t_{k}) - g(t_{k+1})) \right] \\
\times \left( g(t_{k+1}) - g(t_{k-1}) \right) &
\times (g(t_{k}) - g(t_{k+1})) \\
\end{align*}
\]

(40)

Conclusions

To explore complex behavior of SARS-CoV-2 cells infection, here a fractional order model in Caputo sense is explored. Further analysis such as the existence and non-negativity of the solution, basic reproduction number, and equilibrium points of the proposed model is presented. The stability consequences for local and global cases are discussed in detail. The concept of the piece-wise differential and integral operators has been presented in this paper. From numerical results, it is concluded that fractional-order derivative gives more information about the proposed model which is incapable of classical integer order epidemic models. Also, these consequences confirm that including memory effects in the model looks very suitable for such an examination. Some better result is obtained and it progresses and outspreads some current research discovery.

The hypothesis developed by our research group is that there may be a positive action in the use of these adoptive immunotherapy systems also against SARS-CoV2 infection, admitting the need for adjustments concerning the epitope-target (RBD domain of SARS-CoV2 protein S, i.e) and remodeling the action of nucleases within the action of the same virus. The adoption of bi-specific or tri-specific CAR-T could be a solution, even if it is necessary to carefully evaluate the “off-target” objectives and, consequently, to re-engineer the construct to limit any collateral damage.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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