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On fractional approaches to the dynamics of a SARS-CoV-2 infection model including singular and non-singular kernels

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A B S T R A C T

Covid-19 (2019-nCoV) disease has been spreading in China since late 2019 and has spread to various countries around the world. With the spread of the disease around the world, much attention has been paid to epidemiological knowledge. This knowledge plays a key role in understanding the pattern of disease transmission and how to prevent a larger population from contracting it. In the meantime, one should not overlook the significant role that mathematical descriptions play in epidemiology. In this paper, using some known definitions of fractional derivatives, which is a relatively new definition in differential calculus, and then by employing them in a mathematical framework, the effects of these tools in a better description of the epidemic of a SARS-CoV-2 infection is investigated. To solve these problems, efficient numerical methods have been used which can provide a very good approximation of the solution of the problem. In addition, numerical simulations related to each method will be provided in solving these models. The results obtained in each case indicate that the used approximate methods have been able to provide a good description of the problem situation.

Introduction

Infectious diseases are one of the oldest enemies of human health, and the outbreak of terrible epidemics and pandemics that have killed millions of people around the world has made these diseases frightening. The advent of effective vaccines and the development of numerous antibiotics had given the medical community the hope that infectious diseases would soon be eradicated and that these old human enemies would no longer pose a problem for the health of human societies. Unfortunately, the resistance of microorganisms to antibiotics and the emergence of new infectious diseases that did not exist before, such as Covid-19, hepatitis C [1], HIV/AIDS [2], SARS [3], and avian influenza [4], showed that the complete eradication of infectious diseases is still a very difficult path ahead.

In the study of infectious diseases, a certain factor (even the main vector virus) cannot be considered as the only cause of the disease; Rather, a chain of environmental and biological factors are always effective in causing, exacerbating, or stopping the disease. This has caused the study of these diseases to be always associated with problems and difficulties. To successfully prevent disease, it is not necessary to know all the mechanisms of disease. Even if we know the pathogen completely, we can prevent the disease by changing other aspects of the environment and humans. This feature is very important and effective in diseases such as malaria. It should also be noted that infectious diseases are not subject to geographical boundaries and can be easily transmitted from one country to another within a few hours. For this reason, the World Health Organization has called for the strengthening of the disease care system at the national level of the member states. The member countries of this organization should upgrade the capacity of their disease care system at the national level in such a way that it can identify and report the occurrence of infectious diseases of international importance as soon as possible based on the same rules and standards.

The main purpose of mathematical modeling of infectious diseases is to study the prevalence of such diseases in society. In these models, the mechanism of disease transmission and effective characteristics in predicting the behavior of disease transmission is examined and macro strategies for disease control are introduced.

In particular, in recent years, the global outbreak of coronavirus (COVID-19) worldwide has affected all normal routines of life. The main cause of this disease is SARS-CoV-2 [5]. For this reason, mathematical modeling of this disease is one of the most important tools in describing and expressing its mechanism [6–10]. These models enable us to accelerate the control of the outbreak of the disease and even find a drug or vaccine for it. For example, the following mathematical model has been used to study the within-host dynamics of SARS-CoV-2...
infection [11]

\[
\begin{align*}
\frac{dI_{0}(t)}{dt} &= d_{I} (E_{I}(0) - E_{I}(t)) - \beta E_{I}(t)C(t), \\
\frac{dN(t)}{dt} &= \sigma_{2} A(t)N(t) - \eta_{2} A(t)C(t), \\
\frac{dC(t)}{dt} &= \sigma_{2} \eta_{1} A(t)C(t) - \eta_{2} C(t)W(t) - (\theta_{3} + \theta_{2}) C(t), \\
\frac{dV(t)}{dt} &= \sigma_{2} \eta_{1} (1 - \mu) C(t)W(t) - (\theta_{3} + \theta_{2}) W(t), \\
\end{align*}
\]

(1)

Moreover, some important properties of the model, like the nonnegativity of solutions and their boundedness, are established. To get some more information about existing parameters in the model, please refer to the work in [11].

In [12], the authors have investigated a SARS-CoV-2/cancer model with two types of immune responses: SARS-CoV-2-specific antibody immune response and cancer-specific CTL immune response. Mathematical description of these interactions is done using the following nonlinear equation system

\[
\begin{align*}
\frac{dA(t)}{dt} &= \mu - \theta A(t) - \eta_{1} A(t)(N(t) - \eta_{2} A(t)C(t)), \\
\frac{dN(t)}{dt} &= \sigma_{1} A(t)N(t) - \eta_{1} A(t)V(t) - (\theta_{1} + \eta_{1}) N(t), \\
\frac{dC(t)}{dt} &= \sigma_{1} \eta_{1} A(t)C(t) - \eta_{1} C(t)W(t) - (\theta_{1} + \theta_{2}) C(t), \\
\frac{dV(t)}{dt} &= \sigma_{1} \eta_{1} (1 - \mu) C(t)W(t) - (\theta_{1} + \theta_{2}) W(t), \\
\frac{dW(t)}{dt} &= \sigma_{1} \eta_{1} (1 - \mu) V(t)Z(t) - (\theta_{1} + \theta_{2}) Z(t),
\end{align*}
\]

(2)

To get more information about existing parameters in the model, please refer to the work in [12]. The authors have established the Global stability of the equilibria for the model through Lyapunov functions.

By following this path of research, we focus on the following nonlinear system [13]

\[
\begin{align*}
U'(t) &= \lambda - d_{U} U(t) - \beta_{U} U(t)V(t) - \frac{\beta_{U} U(t)}{1 + q_{C} U(t) C(t)} - \frac{\beta_{U} U(t)}{1 + q_{C} U(t) C(t)}, \\
I'(t) &= \frac{\beta_{U} U(t)}{1 + q_{C} U(t) C(t)} + \frac{\beta_{U} U(t)}{1 + q_{C} U(t) C(t)} - d_{I} I(t) - \rho IC, \\
V'(t) &= kI(t) - d_{V} V(t), \\
C'(t) &= \sigma I(t)C(t) - d_{C} C(t).
\end{align*}
\]

In this model \(U(t)\) indicates the concentration of uninfected pulmonary epithelial cells, \(I(t)\) indicates the concentration of uninfected pulmonary epithelial cells. Moreover, \(V(t)C(t)\) denotes free virus particles of SARS-CoV-2 and CTL cells, respectively. We have used \(\lambda\) to indicate the rate at which uninfected pulmonary epithelial cells are generated. We assume that these cells die at rate \(d_{U}\) and become infected by free virus particles at rate \(\beta_{U}\)UV. In case of direct contact with infected pulmonary epithelial cells become infected at rate \(\beta_{I}\)UV. Both cases of infection are inhibited by the non-lymic immune response at rates \(1 + q_{C} C\) and \(1 + q_{C} C\), respectively. Moreover, \(d_{I}\) is the death rate of infected pulmonary epithelial cells, and \(d_{C}\) is their killing rate by the lytic immune response. The production rate of virus from infected pulmonary epithelial cells is denoted by \(k\), the clearance rate of the virus by \(d_{V}\), the immune responsiveness rate by \(\sigma\). Finally, the death rate of CTL cells is represented by \(d_{C}\). More details about this model can be found in Ref. [13]. Moreover, [14–19] are useful references for further investigation of nonlinear models and techniques.

Taking the idea of new efforts in fractional models in the field of epidemiology, we intend to use three important known definitions of fractional derivatives in the model (3). These new assumptions are the main novelty of this article that has not been reported in literature for this model. The remaining parts of the article are compiled as follows. In Section “Some basic properties of model (3)”, some other basic properties of the model are outlined. In Section “The model via the Liouville-Caputo fractional derivative”, the model via the Liouville-Caputo fractional derivative is considered. Further, an efficient numerical method for this particular structure of the model is also implemented in this section. The model via the Caputo-Fabrizio-Caputo fractional derivative has been also studied in the next section. In the fifth section of the paper, the definition of the Atangana-Baleanu-Caputo fractional derivative in the model is employed. Finally, at the end of the present article, the general concluding remarks are drawn.

Some basic properties of model (3)

Following discussions in [13], model (3) is a generalized form of some existing models in the literature:

- In absence of immune response in model (3), we derive

\[
\begin{align*}
U'(t) &= \lambda - d_{U} U(t) - \beta_{U} U(t)V_{(t)}, \\
I'(t) &= \beta_{U} U(t)V_{(t)} - d_{I} I(t), \\
V'(t) &= kI(t) - d_{V} V(t), \\
C'(t) &= \sigma I(t)C(t) - d_{C} C(t).
\end{align*}
\]

which is indeed a special form of what is presented in [20].

- Taking \(\beta_{2} = 0\), \(\beta_{2} = 0\) in (3) yields the model used by Li et al. in [21].

- Taking \(q_{C} = \beta_{2} = 0\) in (3) yields the model analyzed by Nowak et al. in [22].

- If we consider classical virus-to-cell mode in (3), the model reduces to what was studied by Dhar et al. in [23].

Some other basic properties of model (3) are listed below

- The basic reproduction number of the model (3) is calculated as [13]

\[
R_{0} = \frac{\lambda \left( k \beta_{1} + d_{V} q_{C} \right)}{d_{I} q_{C}}. \tag{5}
\]

- The system (3) attains two possible equilibrium points, which are giving by

\[
\begin{align*}
E_{1} &= (U = d_{U} U(t), I = 0, V = 0, C = 0), \\
E_{2} &= \left( \frac{d_{I} q_{C}}{d_{U} q_{C}}, \frac{d_{I} q_{C}}{d_{U} q_{C}}, \frac{d_{I} q_{C}}{d_{U} q_{C}}, 1 - \frac{d_{I} q_{C}}{d_{U} q_{C}}, 1 - \frac{d_{I} q_{C}}{d_{U} q_{C}} \right). \tag{6}
\end{align*}
\]

- The Jacobi matrix corresponding to the model is defined as

\[
J_{U,L,V,C} = \begin{bmatrix}
-d_{U} & -\frac{\beta_{U} V}{C(1 + q_{C})} & -\frac{\beta_{U} V}{C(1 + q_{C})} & -\frac{\beta_{U} V}{C(1 + q_{C})} & 0 \\
\frac{\beta_{U} U}{C(1 + q_{C})} & \frac{\beta_{U} U}{C(1 + q_{C})} & \frac{\beta_{U} U}{C(1 + q_{C})} & \frac{\beta_{U} U}{C(1 + q_{C})} & -\frac{\beta_{U} U}{C(1 + q_{C})} \\
\frac{\beta_{U} U}{C(1 + q_{C})} & \frac{\beta_{U} U}{C(1 + q_{C})} & \frac{\beta_{U} U}{C(1 + q_{C})} & \frac{\beta_{U} U}{C(1 + q_{C})} & -\frac{\beta_{U} U}{C(1 + q_{C})} \\
0 & k & -d_{V} & 0 \\
0 & C\sigma & 0 & \sigma I - d_{C}
\end{bmatrix}
\]

The model via the Liouville-Caputo fractional derivative

In this part, we consider the model (3) with the Liouville–Caputo (LC) fractional derivative giving by

\[
\begin{align*}
\frac{d^{\alpha}_{L} U(t)}{dt^{\alpha}} &= \lambda - d_{U} U(t) - \frac{\beta_{U} U(t)V_{(t)}}{1 + q_{C} U(t) C(t)} - \frac{\beta_{U} U(t)}{1 + q_{C} U(t) C(t)}, \tag{7}
\end{align*}
\]

where the LC fractional derivative is defined as [24]

\[
\frac{d^{\alpha}_{L} \psi(t)}{dt^{\alpha}} = \frac{1}{\Gamma(\alpha)} \int_{0}^{t} (t - \eta)^{\alpha - 1} \psi'(\eta) d\eta, \quad 0 < \alpha \leq 1. \tag{8}
\]

The numerical method used in this section will be the Adams–Bashforth–Moulton (ABM) method [25]. Here, we will follow the steps to apply this method in solving the following fractional-order problem

\[
\frac{d^{\alpha}_{L} \psi(t)}{dt^{\alpha}} = \Theta(t, \psi(t)), \quad \psi^{(k)}(0) = \psi^{k}_{0}, \quad k = 0, 1, \ldots, n - 1. \tag{9}
\]
Fig. 1. Simulations for solving (7) using (13) using different $\rho$'s.

Fig. 2. Simulations for solving (7) using (13) using different $q_1$'s.
Now, taking Liouville–Caputo fractional integration on (9) yields
\[
\psi(t) = \sum_{k=0}^{n_1} \binom{n_1}{k} \frac{t^k}{k!} + \frac{1}{\Gamma(k+1)} \int_0^t (t-\eta)^{k-1} \Theta(\eta, \psi(\eta)) d\eta. 
\]
(10)

The following predictor–corrector form will determine the approximate solution to the problem
\[
\psi_{k+1}^p = \sum_{n=0}^{m_1} \binom{m_1}{n} \psi_0^{(n)} + \frac{1}{\Gamma(m_1+1)} \int_0^t (t-\eta)^{m_1} \Theta(\eta, \psi(\eta)) d\eta, 
\]
where
\[
\psi_{k+1} = \sum_{n=0}^{m_1} \binom{m_1}{n} \psi_0^{(n)} + \frac{1}{\Gamma(m_1+1)} \int_0^t (t-\eta)^{m_1} \Theta(\eta, \psi(\eta)) d\eta, 
\]

Utilizing the numerical algorithm presented in (11), the approximate solution to the fractional problem (7) will be determined from the following formulae
\[
U(t) = \sum_{k=0}^{n_1} \binom{n_1}{k} \frac{t^k}{k!} + \frac{1}{\Gamma(k+1)} \int_0^t (t-\eta)^{k-1} \Theta(\eta, \psi(\eta)) d\eta, 
\]
(13)

In all performed numerical simulations in this paper, the following values are considered for the constants in the model \( a_1 = 0.001, \lambda = 500, \beta_1 = 1.12e-7, \gamma_1 = 0.3, \beta_2 = 1.1e-7, \gamma_2 = 1.6, d_4 = 0.56, \rho = 0.06, k = 230, \sigma = 4.5e-3, \Delta = 10, \gamma_3 = 0.85. \) Figs. 1–3 are displayed to demonstrate the variation of state variables in model (7). In Fig. 1, we have displayed the effect of \( \rho \) on results. While Fig. 2 shows the model’s solution for different \( q_1 \)’s. The plots for different \( k \) have been displayed in Fig. 3.

### The model via the Caputo–Fabrizio–Caputo fractional derivative

In this section, we will study the following model
\[
CFC^D_t^\rho U(t) = \lambda - d_4 U(t) - \frac{\theta_1 U(t)}{1 + \theta_1 C(t)} - \frac{\theta_2 U(t)}{1 + \theta_2 C(t)}, 
\]
\[
CFC^D_t^\rho I(t) = \frac{\theta_1 U(t)}{1 + \theta_1 C(t)} + \frac{\theta_2 U(t)}{1 + \theta_2 C(t)} - d_4 I(t) - \beta I(t), 
\]
\[
CFC^D_t^\rho V(t) = kI(t) - d_4 V(t), 
\]
\[
CFC^D_t^\rho C(t) = \alpha I(t) C(t) - d_4 C(t). 
\]
\( \rho \)
(14)

The fractional derivative operator used in this model, \( CFC^D_t^\rho \), is Caputo–Fabrizio–Caputo (CFC) which is given by \( \rho \)
\[
CFC^D_t^\rho \psi(t) = \frac{M(\rho)}{n - \rho} \int_0^t \psi'(\eta) \eta^{(1 - \rho)} d\eta, 
\]
(15)

where
\[
M(\rho) = \frac{2}{2 - \rho}, 
\]
(16)

The CFC fractional integral is also defined by \( \rho \)
\[
CFC^I_t^\rho \psi(t) = \frac{2(1 - \rho)}{(2 - \rho) M(\rho)} \psi(t) + \frac{2 \rho}{(2 - \rho) M(\rho)} \int_0^t \psi'(\eta) d\eta, 
\]
(17)

Now, let us focus on determining the approximate solution to the following CFC fractional Cauchy problem of
\[
CFC^D_t^\rho \psi(t) = \Theta(t, \psi(t)). 
\]
(18)

Utilizing the corresponding fractional integral operator yields
\[
\psi(t) = \psi(0) + \frac{2(1 - \rho)}{(2 - \rho) M(\rho)} \Theta(t, \psi(t)) + \frac{2 \rho}{(2 - \rho) M(\rho)} \int_0^t \Theta(\eta, \psi(\eta)) d\eta, 
\]
(19)

Taking \( t = t_{n_1} \) in (19), one has
\[
\psi(t_{n_1}) - \psi(0) = \frac{2(1 - \rho)}{(2 - \rho) M(\rho)} \Theta(t_{n_1}, \psi(t_{n_1})) + \frac{2 \rho}{(2 - \rho) M(\rho)} \int_0^{t_{n_1}} \Theta(\eta, \psi(\eta)) d\eta. 
\]
(20)

Inserting Eq. (21) into Eq. (20), one gets
\[
\psi(t_{n_1}) = \psi(0) + \frac{2(1 - \rho)}{(2 - \rho) M(\rho)} \Theta(t_{n_1}, \psi(t_{n_1})) + \frac{2 \rho}{(2 - \rho) M(\rho)} \int_0^{t_{n_1}} \Theta(\eta, \psi(\eta)) d\eta. 
\]
(21)

So we will have
\[
f_{n_1+1} = f_s + \frac{(2 - \rho)(1 - \rho)}{2} \Theta(t_{n_1}, f_s) - \frac{3 \rho}{2} \Theta(t_{n_1}, f_{n_1-1}). 
\]
(23)

As a result, the following recursive relations are determined to approximate the CFC problem (14) as
\[
U_{n_1+1}(t) = U(0) + \frac{2(1 - \rho)}{2} \Theta(t_{n_1}, U(t)) - \frac{3 \rho}{2} \Theta(t_{n_1}, U(t)) \Theta(t_{n_1}, V(t)) - \Theta(t_{n_1}, C(t)) - \Theta(t_{n_1}, C(t)) 
\]
(24)

Figs. 4–6 are displayed to demonstrate the variation of state variables in model (14). In Fig. 4, we have displayed the effect of \( k \) on results. Moreover, Fig. 5 demonstrates the model’s solution for different \( \sigma \)’s. The plots for different \( \beta_2 \) have been displayed in Fig. 6.
Fig. 3. Simulations for solving (7) using (13) using different $k$’s.

Fig. 4. Simulations for solving (14) using (25) using different $k$’s.
Fig. 5. Simulations for solving (14) using (25) using different $\sigma$’s.

Fig. 6. Simulations for solving (14) using (25) using different $\beta_2$’s.
Fig. 7. Simulations for solving (26) using (32) using different $\lambda$'s.

Fig. 8. Simulations for solving (26) using (32) using different $k$'s.
Fig. 9. Simulations for solving (26) using (32) using different $q_1$'s.

Fig. 10. Simulations for solving (26) using (32) using different $q_2$'s.
The model via the Atangana–Baleanu–Caputo fractional derivative

Now, let us consider the model via Atangana–Baleanu–Caputo fractional derivative as

\[
\begin{align*}
\mathcal{ABC}D^\rho_t U(t) &= \lambda - d_1 U(t) - \frac{\beta_1 U(t)V(t)}{1 + q_1 C(t)} - \frac{\beta_2 U(t)I(t)}{1 + q_2 C(t)}, \\
\mathcal{ABC}D^\rho_t I(t) &= \frac{\beta_1 U(t)V(t)}{1 + q_1 C(t)} + \frac{\beta_2 U(t)I(t)}{1 + q_2 C(t)} - d_2 I(t) - \rho I(t), \\
\mathcal{ABC}D^\rho_t V(t) &= k_1(t) - d_3 V(t), \\
\mathcal{ABC}D^\rho_t C(t) &= \sigma I(t) C(t) - d_4 C(t).
\end{align*}
\]

(26)

where the Atangana–Baleanu–Caputo fractional integral of order \(\rho\) of a function \(\psi(t)\) is defined as [27]

\[
\mathcal{ABC}I^\rho_0 \psi(t) = \frac{B(\rho)}{\Gamma(\rho)} \int_0^t \psi(\eta) E_{\rho} \left[ \frac{-\rho}{\rho - \eta} (t - \eta)^{\rho - 1} \right] d\eta.
\]

(27)

where \(B(\rho) = 1 - \rho + \frac{\rho}{\Gamma(\rho)}\) is a normalization function.

The model via the Atangana–Baleanu–Caputo fractional derivative is also defined as [27]

\[
\mathcal{ABC}D^\rho_0 \psi(t) = \frac{1}{B(\rho)} \psi(t) + \frac{\rho}{B(\rho) \Gamma(\rho)} \int_0^t \psi(\eta) (t - \eta)^{\rho - 1} d\eta.
\]

(28)

Consider the following fractional initial value problem

\[
\mathcal{ABC}D^\rho_0 \psi(t) = \Theta(t, \psi(t)),
\]

(29)

Employing the product-integration rule, Ghanbari and his collaborators [28] have developed an efficient scheme to obtain the approximate solution of (29), giving by

\[
\psi_0(t) = \psi_0 + \frac{\rho}{B(\rho)} \int_0^t \psi_0(\eta) E_{\rho} \left[ \frac{-\rho}{\rho - \eta} (t - \eta)^{\rho - 1} \right] d\eta,
\]

(30)

where

\[
\rho = \frac{(n - 1) \beta + n q - 1}{\Gamma(n + 1)}.
\]

(31)

Using the above numerical approximation, we get the following iterative scheme, we have

\[
\begin{align*}
U_n &= U_0 + \frac{\rho}{B(\rho)} \left[ \lambda - d_1 U_0 - \frac{\beta_1 U_0 V_0}{1 + q_1 C_0} - \frac{\beta_2 U_0 I_0}{1 + q_2 C_0} \right] + \sum_{\xi = 1}^{n} \left( d_1 U_0 - \beta_1 U_0 V_0 \right),
I_n &= I_0 + \frac{\rho}{B(\rho)} \left[ \frac{\beta_1 U_0 V_0}{1 + q_1 C_0} + \frac{\beta_2 U_0 I_0}{1 + q_2 C_0} - d_2 I_0 - \rho I_0 C_0 \right] + \sum_{\xi = 1}^{n} \left( \beta_1 U_0 V_0 \right),
V_n &= V_0 + \frac{\rho}{B(\rho)} \left[ \lambda I_n - d_3 V_0 \right] + \sum_{\xi = 1}^{n} \left( \lambda I_n \right),
C_n &= C_0 + \frac{\rho}{B(\rho)} \left[ \sigma I_n C_0 - d_4 C_0 \right] + \sum_{\xi = 1}^{n} \left( \sigma I_n \right).
\end{align*}
\]

Figs. 7–10 are displayed to demonstrate the variation of state variables in model (26). In Fig. 7, we have displayed the effect of \(\lambda\) on results. Also, Fig. 8 depicts the model’s solution for different values of \(q_1, q_2\) have been displayed in Figs. 9 and 10, respectively.

Conclusion

Mathematical models describe the progression of infectious diseases to illustrate the possible consequences of an epidemic and to assist public health interventions. The models use some basic and mathematical hypotheses to find threshold parameters for epidemics and use these parameters to calculate the effects of various factors such as vaccination. In this paper, we have considered some fractional versions of a computational model of dynamics for a SARS-CoV-2 infection. The fractional derivatives used in these definitions are the Liouville–Caputo, the Caputo–Fabrizio–Caputo and the Atangana–Baleanu–Caputo. As it has been proven, the presence of fractional order parameter in these models increases the flexibility of models in describing phenomena, and this is one of the main advantages of these definitions compared to standard structures. In each case, an approximate scheme in finding the numerical solutions for these models is proposed, which approximates the numerical behavior of the model with appropriate accuracy. In some performed numerical simulations, we measure the sensitivity of the model by examining the solutions produced by the model through changing a specific parameter in the model and simultaneously fixing the other parameters. By using the employed methods in this contribution, we will be able to determine the approximate solution of some other models in the field of infectious disease modeling, which is our future research plans in the field.

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