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Global dynamics of a diffusive SARS-CoV-2 model with antiviral treatment and fractional Laplacian operator

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In this paper, we propose and investigate the global dynamics of a SARS-CoV-2 infection model with diffusion and antiviral treatment. The proposed model takes into account the two modes of transmission (virus-to-cell and cell-to-cell), the lytic and nonlytic immune responses. The diffusion into the model is formulated by the regional fractional Laplacian operator. Furthermore, the global asymptotic stability of equilibria is rigorously established by means of a new proposed method constructing Lyapunov functions for a class of partial differential equations (PDEs) with regional fractional Laplacian operator. The proposed method is applied to the classical reaction-diffusion equations with normal diffusion.

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1. Introduction

The COVID-19 pandemic has swept across the globe, affecting millions of people and challenging healthcare systems worldwide. As of the most recent report from the World Health Organization (WHO), there have been over 400 million confirmed cases and over 5 million deaths worldwide. The disease is caused by the novel coronavirus SARS-CoV-2, which primarily spreads through respiratory droplets and close contact with infected individuals. In addition to fever, cough, and difficulty breathing, patients with COVID-19 may experience a wide range of symptoms, including loss of taste and smell, fatigue, and gastrointestinal issues. Understanding the transmission dynamics and clinical features of the disease is crucial for controlling its spread and improving patient outcomes. Mathematical modeling has been used extensively to study the spread of the SARS-CoV-2 virus and to inform public health policies aimed at mitigating its impact. One common approach to modeling the spread of infectious diseases is to use partial differential equations (PDEs) with diffusion terms. However, the diffusion term in these equations is typically assumed to be anomalous, meaning that the spread is not regular in space and time. Many recent studies report the normal spacial diffusion of SARS-CoV-2 virus. For instance Elaiw et al. [1] designed a reaction-diffusion model to depict the dynamic processes of SARS-CoV-2 infection inside cancer patients. Kevrekidis et al. [2] developed a spatially distributed version of a compartmental epidemiological model in the form of reaction-diffusion equations to examine the spatial modeling of the outbreak of COVID-19 in Andalusia (Spain) and the mainland of Greece. Elaiw et al. [3] constructed a model that characterizes the in-host dynamics of HTLV-I and SARS-CoV-2 co-infection.

Recently, PDEs involving fractional Laplacian operator are used to describe the dynamics of systems with anomalous diffusion. This type of operator has received much attention in both pure and applied mathematics. Bucur and Valdinoci [4] observed that some processes occur in nature such as the natural selection can be modeled by the nonlocal fractional Laplacian operator because this natural phenomena

may favour some kind of nonlocal diffusion and that a predator can decide to use a nonlocal dispersive strategy to hunt its preys more efficiently. In [5], the authors proposed a mathematical PDE model with Laplacian operator for pattern formation in coral reefs and they derived the conditions for Turing bifurcation through linear stability analysis of the proposed PDE model. Nezza et al. [6] dealt with the fractional Sobolev spaces and they analyzed the relations among some of their possible definitions and their role in the trace theory. Vázquez [7] described two models of flow in porous media including nonlocal diffusion effects.

The fractional Laplacian is a nonlocal operator and it allows to describe the motions of random particles in the entire set $\mathbb{R}^n$. However, these types of motions can be modeled by the regional fractional Laplacian operator when particles move through a region Ω of $\mathbb{R}^n$ which are not allowed to jump outside Ω but are either reflected back into Ω or killed when they reach the boundary $\partial\Omega$. The last operator was introduced by Bogdan et al. [8] by limiting the integral in the fractional Laplacian in the region Ω. A comparative study about the properties of the fractional Laplacian, regional fractional Laplacian and other nonlocal diffusion operators was carefully investigated in [9].

Most nonlinear systems of PDEs that describe spatiotemporal dynamics of real phenomena in various fields of science and engineering are complex and cannot be solved analytically. It well be more suitable to study the qualitative properties of solutions such as global stability. Accordingly, Hattaf and Yousfi [10] studied the global stability of some reaction-diffusion equations in biology by developing an efficient method for the construction of Lyapunov functions of a class of PDEs with and without delays. Such Lyapunov functions for PDEs are obtained from those for ordinary differential equations (ODEs). Furthermore, the method has been applied by many researchers. For instance, Zhang et al. [11] analyzed the global asymptotic stability of a chemostat model with maintenance energy by constructing a Lyapunov function inspired by the method of [10]. In [12], the authors used the same method to prove the global stability of a nonlocal and time-delayed reaction-diffusion epidemic model. Elaiw and Al Agha [13] also used the method for constructing appropriate Lyapunov functions for a reaction-diffusion model that describes the within-host dynamics of Malaria infection in presence of adaptive immunity. In addition, the method is recently extended in [14] for fractional differential equations (FDEs) with normal diffusion, and in [15] for PDEs with fractional Laplacian operator.

In the literature, most mathematical models formulated by PDEs to describe the diffusion of viral infections like SARS-CoV-2 used normal Laplacian operator. In this paper, we propose a mathematical model for SARS-CoV-2 infection with regional fractional Laplacian operator. To do this, the next section is devoted to SARS-CoV-2 model formulation and their equilibria. A new efficient method for constructing Lyapunov function for a class of PDEs with and without delay is presented in Section 3. Section 4 is devoted to the global stability of the proposed model by mean of the new method. Section 5 establishes numerical simulations. Finally, Section 6 concludes the paper.

2. SARS-CoV-2 model formulation and equilibria

In this section, we propose a mathematical model for SARS-CoV-2 infection with fractional diffusion, antiviral treatment, two modes of transmission, lytic and nonlytic immune response. This model is formulated by the following nonlinear system of PDEs

$$\begin{cases} \dfrac{\partial U}{\partial t} = -d_U(-\Delta)^s_\Omega U(x,t) + \lambda - m_U U(x,t) - \dfrac{\beta_1 U(x,t)V(x,t)}{1+q_1C(x,t)} - \dfrac{\beta_2 U(x,t)I(x,t)}{1+q_2C(x,t)}, \\ \dfrac{\partial I}{\partial t} = -d_I(-\Delta)^s_\Omega I(x,t) + \dfrac{\beta_1 U(x,t)V(x,t)}{1+q_1C(x,t)} + \dfrac{\beta_2 U(x,t)I(x,t)}{1+q_2C(x,t)} - m_I I(x,t) - pI(x,t)C(x,t), \\ \dfrac{\partial V}{\partial t} = -d_V(-\Delta)^s_\Omega V(x,t) + k(1-\varepsilon)I(x,t) - m_V V(x,t), \\ \dfrac{\partial C}{\partial t} = -d_C(-\Delta)^s_\Omega C(x,t) + \sigma I(x,t)C(x,t) - m_C C(x,t), \end{cases} \tag{1}$$

where the concentrations of uninfected pulmonary epithelial cells, infected pulmonary epithelial cells, free virus particles, and CTL cells are denoted by $U(x,t)$, $I(x,t)$, $V(x,t)$, and $C(x,t)$, respectively, at

position x and time t. The generation rate of uninfected pulmonary epithelial cells is given by λ, and their death rate is denoted by $m_U U$. Infection can occur via free virus particles at rate $\beta_1 UV$, which is inhibited by nonlytic immune response at rate $1+q_1C$, or via direct contact with infected pulmonary epithelial cells at rate $\beta_2 UI$, which is also inhibited by nonlytic immune response at rate $1+q_2C$. Infected pulmonary epithelial cells die at rate $m_I I$ and can be targeted by lytic immune responses at rate pIC. The remaining parameters also have specific biological interpretations, k denotes the production rate of virus from infected pulmonary epithelial cells, m_V represents the clearance rate of virus, σ is the immune responsiveness rate, and m_C reflects the death rate of CTL cells. Additionally, non-negative constants d_U, d_I, d_V, and d_C are the coefficients of diffusion. Finally, the parameter ε represents the effectiveness of antiviral treatment that blocks the production of viral particles. It takes values between 0 and 1, where a higher value indicates greater effectiveness.

In the field of biology, the diffusion of virus and cells is known to exhibit an abnormal behaviour, which can be mathematically described by the regional fractional Laplacian operator $(-\Delta)^s_\Omega$. This operator is presented in [16] by

$$\begin{aligned}(-\Delta)^s_\Omega u(x) &= C(n,s)\,\mathrm{PV}\int_\Omega \frac{u(x)-u(y)}{|x-y|^{n+2s}}\,dy \\ &= C(n,s)\lim_{\varepsilon\to 0^+}\int_{\{y\in\Omega,|x-y|>\varepsilon\}}\frac{u(x)-u(y)}{|x-y|^{n+2s}}\,dy,\end{aligned} \tag{2}$$

where the notation PV indicates principal value and $C(n,s)$ is a normalization constant given by

$$C(n,s)=\frac{s\,4^s\Gamma(s+\frac{n}{2})}{\pi^{\frac{n}{2}}\Gamma(1-s)}, \tag{3}$$

with $s\in(0,1)$, Γ is the gamma function. The operator $(-\Delta)^s_\Omega$ describes the random motion of a particle jumping from a point $x\in\Omega$ to another $y\in\Omega$ with intensity proportional to $|x-y|^{-n-2s}$. Furthermore, it should be noted that particles cannot escape from Ω and instead are either reflected back inside or eliminated upon reaching the boundary $\partial\Omega$. Given this constraint, we can now examine the problem stated in (1) with the following generalized Neumann boundary conditions

$$\mathcal{N}^{2-2s}U=\mathcal{N}^{2-2s}I=\mathcal{N}^{2-2s}V=\mathcal{N}^{2-2s}C=0,\quad \text{on}\quad \partial\Omega\times(0,+\infty),$$

where $\mathcal{N}^{2-2s}u$ denotes the fractional normal derivative of u in direction of the outer normal vector defined as in [16] by

$$\mathcal{N}^{2-2s}u(z)=-\lim_{t\to 0^+}\frac{du(z+\boldsymbol{n}(z)t)}{dt}t^{2-2s},$$

$\boldsymbol{n}(z)$ is the inner normal vector of $\partial\Omega$ at the point $z\in\partial\Omega$. In this paper, the initial conditions for model (1) are taken as follows

$$U(x,0)\geqslant 0,\quad I(x,0)\geqslant 0,\quad V(x,0)\geqslant 0,\quad C(x,0)\geqslant 0,\quad x\in\overline{\Omega}.$$

It is important to note that model (1) improves and generalizes the ODE model proposed by Hattaf and Yousfi in [17] by considering the diffusion and antiviral treatment.

The system (1) invariably possesses an infection-free equilibrium, denoted as $P_0(U_0,0,0,0)$, where $U_0=\frac{\lambda}{m_U}$, indicating a healthy state. As a result, we can define the basic reproduction number for our PDE model in the following way

$$\mathcal{R}_0=\frac{\lambda\big(k(1-\varepsilon)\beta_1+m_V\beta_2\big)}{m_U m_I m_V}.$$

As per the biological and referenced [18, 19] perspectives, $\mathcal{R}_0$ can be separated into two constituent parts, namely $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$, where the basic reproduction number of the virus-to-cell infection mode is represented by $\mathcal{R}_{01}$, which is calculated as $\frac{\lambda k(1-\varepsilon)\beta_1}{m_U m_I m_V}$. On the other hand, the basic reproduction number of the second direct cell-to-cell mode is represented by $\mathcal{R}_{02}$, which is calculated as $\frac{\lambda\beta_2}{m_U m_I}$. The remaining steady states of system (1) that are spatially uniform can be described by the following system

$$0=\lambda-m_U U-\frac{\beta_1 UV}{1+q_1C}-\frac{\beta_2 UI}{1+q_2C},$$

$$0 = \frac{\beta_1 UV}{1+q_1C} + \frac{\beta_2 UI}{1+q_2C} - m_I I - pIC,$$
$$0 = k(1-\varepsilon)I - m_V V,$$
$$0 = \sigma IC - m_C C.$$

Based on the last equation, we can deduce that either $C = 0$ or $I = \frac{m_c}{\sigma}$. Hence, we will consider two different cases. In the first case, where there is no immune response ($C = 0$), the following expressions are obtained

$$U_1 = \frac{\lambda}{m_U \mathcal{R}_0}, \quad I_1 = \frac{\lambda(\mathcal{R}_0 - 1)}{m_I \mathcal{R}_0}, \quad V_1 = \frac{k(1-\varepsilon)\lambda(\mathcal{R}_0 - 1)}{m_I m_V \mathcal{R}_0}.$$

Thus, if $\mathcal{R}_0 > 1$, the point $P_1(U_1, I_1, V_1, 0)$ equilibrium of model (1) is called the infection equilibrium without cellular immunity.

In the case of presence of immune response, system (1) has another biological steady state that verify the equalities in flow

$$I = \frac{m_c}{\sigma}, \quad V = \frac{k(1-\varepsilon)m_C}{\sigma m_V}, \quad C = \frac{\sigma(\lambda - m_U U) - m_I m_C}{p m_C}, \quad \frac{k(1-\varepsilon)\beta_1 U}{m_V(1+q_1C)} + \frac{\beta_2 U}{1+q_2C} = m_I + pC.$$

Following the same procedure as described in [17], we can define the reproduction number for cellular immunity as $\mathcal{R}_1^C$, given by

$$\mathcal{R}_1^C = \frac{\sigma I_1}{m_C}.$$

When $\mathcal{R}_1^C > 1$, the model (1) exhibits the infection equilibrium with cellular immunity, which is referred to $P_2 = (U_2, I_2, V_2, C_2)$, where

$$U_2 \in \left(0, \frac{\lambda}{m_U} - \frac{m_I m_C}{\sigma m_U}\right), \quad I_2 = \frac{m_C}{\sigma}, \quad V_2 = \frac{k(1-\varepsilon)m_C}{\sigma m_V}, \quad C_2 = \frac{\sigma(\lambda - m_U U_2) - m_I m_C}{p m_C}.$$

3. Lyapunov functions construction method

This section describes our method for constructing Lyapunov functions for a class of PDEs with and without delays involving the regional fractional Laplacian operator.

Let $m \in \mathbb{N}^*$ and $u = (u_1, \ldots, u_m)$ be a non-negative solution of the following ODE system:

$$\dot{u} = f(u), \tag{4}$$

where $f\colon \mathbb{R}^m \longrightarrow \mathbb{R}^m$ is a C^1 function.

Let Ω be a bounded domain of $\mathbb{R}^n$ with smooth boundary $\partial\Omega$, and $D = \operatorname{diag}(d_1, \ldots, d_m)$ be the diagonal matrix of diffusion coefficients $d_i \geqslant 0$ with $i = 1, \ldots, m$. Obviously, if u^* is an equilibrium point of (4), then u^* is also a steady state of the following PDE system with regional fractional Laplacian operator given by

$$\begin{cases} \dfrac{\partial u}{\partial t} = -D(-\Delta)^s_\Omega u + f(u) \quad \text{in} \quad \Omega \times (0, +\infty), \\ \mathcal{N}^{2-2s} u = 0 \quad \text{on} \quad \partial\Omega \times (0, +\infty), \\ u(x, 0) = u_0(x) \quad \text{in} \quad \Omega. \end{cases} \tag{5}$$

If $L(u)$ is a C^1 function on a domain in $\mathbb{R}^m_+$, consider $u(t)$ a solution of ODE system (4), then $\frac{dL(u(t))}{dt}$ is calculated as follows

$$\frac{dL(u(t))}{dt} = \nabla L(u) \cdot f(u). \tag{6}$$

Let $u(x,t)$ be a solution of PDE system (5). Construct another function defined from L as follows

$$\mathcal{L} = \int_\Omega L(u(x,t))\, dx. \tag{7}$$

Calculating $\frac{d\mathcal{L}}{dt}$, we get

$$\frac{d\mathcal{L}}{dt} = \int_\Omega \nabla L(u) \cdot \big(- D(-\Delta)^s_\Omega u + f(u)\big)\, dx$$

$$= \int_\Omega \nabla L(u)\cdot f(u)\,dx - \int_\Omega \nabla L(u)\cdot D(-\Delta)^s_\Omega u\,dx.$$

Hence,

$$\frac{d\mathcal{L}}{dt} = \int_\Omega \nabla L(u)\cdot f(u)\,dx - \sum_{i=1}^m d_i \int_\Omega \frac{\partial L}{\partial u_i}(u)(-\Delta)^s_\Omega u_i\,dx. \tag{8}$$

According to Theorem 2.3 of [20] and Theorem 3.5 of [16], we have

$$\int_\Omega \frac{\partial L}{\partial u_i}(u)(-\Delta)^s_\Omega u_i\,dx = \frac{C(n,s)}{2}\int_\Omega\int_\Omega \frac{\left(\frac{\partial L}{\partial u_i}(u(x,t)) - \frac{\partial L}{\partial u_i}(u(y,t))\right)\left(u_i(x,t)-u_i(y,t)\right)}{|x-y|^{n+2s}}\,dx\,dy - B_{n,s}\int_{\partial\Omega}\frac{\partial L}{\partial u_i}(u)\mathcal{N}^{2-2s}u_i\,d\sigma, \tag{9}$$

where $B_{n,s}$ is a normalized constant. Since $\mathcal{N}^{2-2s}u = 0$ on $\partial\Omega$, we deduce that

$$\frac{d\mathcal{L}}{dt} = \int_\Omega \nabla L(u)\cdot f(u)\,dx - \frac{C(n,s)}{2}\sum_{i=1}^m d_i\,\mathcal{E}\left(u_i, \frac{\partial L}{\partial u_i}(u)\right),$$

where

$$\mathcal{E}\left(u_i, \frac{\partial L}{\partial u_i}(u)\right) = \int_\Omega\int_\Omega \frac{\left(\frac{\partial L}{\partial u_i}(u(x,t)) - \frac{\partial L}{\partial u_i}(u(y,t))\right)\left(u_i(x,t)-u_i(y,t)\right)}{|x-y|^{n+2s}}\,dx\,dy.$$

Therefore, we construct the function L that satisfied for all $i = 1,\dots,m$, the following condition

$$\int_\Omega\int_\Omega \frac{\left(\frac{\partial L}{\partial u_i}(u(x,t)) - \frac{\partial L}{\partial u_i}(u(y,t))\right)\left(u_i(x,t)-u_i(y,t)\right)}{|x-y|^{n+2s}}\,dx\,dy \geqslant 0, \quad \text{for all} \quad i = 1,\dots,m, \tag{C_1}$$

which is equivalent to $\mathcal{E}\left(u_i, \frac{\partial L}{\partial u_i}(u)\right) \geqslant 0$ for all $i = 1,\dots,m$.

In the literature, many authors (see, for example [18]) constructed the Lyapunov functions of the form

$$L(u) = \sum_{i=1}^m a_i\left(u_i - u_i^* - \int_{u_i^*}^{u_i}\frac{g_i(u_i^*)}{g_i(t)}\,dt\right), \tag{10}$$

where g_i is a non-negative and strictly increasing function on $\mathbb{R}_+$ and $a_i \geqslant 0$. In this case,

$$\mathcal{E}\left(u_i, \frac{\partial L}{\partial u_i}(u)\right) = a_i g_i(u_i^*)\int_\Omega\int_\Omega \frac{\left(g_i((u_i(x,t)) - g_i(u_i(y,t))\right)\left(u_i(x,t)-u_i(y,t)\right)}{g_i(u_i(x,t))\,g_i(u_i(y,t))\,|x-y|^{n+2s}}\,dx\,dy \geqslant 0.$$

When $g_i(z) = z$, the expression of function L becomes

$$L(u) = \sum_{i=1}^m a_i\left(u_i - u_i^* - u_i^*\ln\frac{u_i}{u_i^*}\right), \tag{11}$$

and

$$\mathcal{E}\left(u_i, \frac{\partial L}{\partial u_i}(u)\right) = a_i u_i^*\int_\Omega\int_\Omega \frac{(u_i(x,t)-u_i(y,t))^2}{u_i(x,t)u_i(y,t)|x-y|^{n+2s}}\,dx\,dy \geqslant 0.$$

In summary, we get the following fundamental results.

Theorem 1. *Let L be a Lyapunov function for ODE system (4).*

(i) If the function L satisfies the condition (C_1), then the function $\mathcal{L}$ defined by (7) is a Lyapunov function for PDE system (5) with regional fractional Laplacian operator.

(ii) If the function L is of the form (10) or (11), then $\mathcal{L}$ is a Lyapunov function for PDE system (5) with regional fractional Laplacian operator.

Now, we consider the following delayed PDE system

$$\begin{cases} \dfrac{\partial u}{\partial t} = -D(-\Delta)^s_\Omega u + f(u) + g(u,u_t) \quad \text{in} \quad \Omega\times(0,+\infty), \\ \mathcal{N}^{2-2s}u = 0 \quad \text{on} \quad \partial\Omega\times(0,+\infty), \\ u(x,t) = u_0(x,t) \quad \text{in} \quad \Omega\times[-\tau,0], \end{cases} \tag{12}$$

where $\tau \geqslant 0$ and the function u_t is such that $u_t(x,\theta) = u(x,t+\theta)$ on $\Omega\times[-\tau,0]$, g is a function of u and u_t.

Therefore, along the positive solution of (12), $\frac{d\mathcal{L}}{dt}$ becomes

$$\begin{aligned}\frac{d\mathcal{L}}{dt} &= \int_\Omega \nabla L(u)\cdot\big(-D(-\Delta)^s_\Omega u + f(u) + g(u,u_t)\big)\,dx\\ &= \int_\Omega \nabla L(u)\cdot f(u)\,dx - \int_\Omega \nabla L(u)\cdot D(-\Delta)^s_\Omega u\,dx + \int_\Omega \nabla L(u)\cdot g(u,u_t)\,dx\\ &= \int_\Omega \nabla L(u)\cdot f(u)\,dx - \frac{C(n,s)}{2}\sum_{i=1}^m d_i\,\mathcal{E}\left(u_i,\frac{\partial L}{\partial u_i}(u)\right) + \int_\Omega \nabla L(u)\cdot g(u,u_t)\,dx.\end{aligned}$$

Like in [21], we can modify the integrand of the last term to show the negativeness of $\frac{d\mathcal{L}}{dt}$ for system (12).

Our method extends that in [10]. In fact, consider the following classical reaction-diffusion system with normal diffusion given by

$$\begin{cases} \dfrac{\partial u}{\partial t} = D\Delta u + f(u) \quad \text{in} \quad \Omega\times(0,+\infty),\\ \dfrac{\partial u}{\partial \nu} = 0 \quad \text{on} \quad \partial\Omega\times(0,+\infty),\\ u(x,0) = u_0(x) \quad \text{in} \quad \Omega. \end{cases} \tag{13}$$

Let $u(x,t)$ be a solution of (13). Denote

$$\mathcal{M} = \int_\Omega L(u(x,t))\,dx, \tag{14}$$

where $L(u)$ is a Lyapunov function for the corresponding reaction system of (13). Then, we have

$$\frac{d\mathcal{M}}{dt} = \int_\Omega \nabla L(u)\cdot f(u)\,dx + \sum_{i=1}^m d_i\int_\Omega \frac{\partial L}{\partial u_i}(u)\Delta u_i\,dx. \tag{15}$$

It follows from Proposition 2.5 of [20] that

$$\begin{aligned}\lim_{s\to 1^-}\int_\Omega \frac{\partial L}{\partial u_i}(u)(-\Delta)^s_\Omega u_i\,dx &= \int_\Omega \nabla u_i\nabla\frac{\partial L}{\partial u_i}(u)\,dx\\ &= -\int_\Omega \frac{\partial L}{\partial u_i}(u)\Delta u_i\,dx + \int_{\partial\Omega}\frac{\partial u_i}{\partial\nu}\frac{\partial L}{\partial u_i}(u)\,d\sigma,\end{aligned}$$

Passing to the limit in (8) and using the above equalities, we obtain

$$\begin{aligned}\lim_{s\to 1^-}\frac{d\mathcal{L}}{dt} &= \int_\Omega \nabla L(u)\cdot f(u)\,dx - \sum_{i=1}^m d_i\int_\Omega \nabla u_i\nabla\frac{\partial L}{\partial u_i}(u)\,dx\\ &= \int_\Omega \nabla L(u)\cdot f(u)\,dx + \sum_{i=1}^m d_i\int_\Omega \frac{\partial L}{\partial u_i}(u)\Delta u_i\,dx - \sum_{i=1}^m d_i\int_{\partial\Omega}\frac{\partial u_i}{\partial\nu}\frac{\partial L}{\partial u_i}(u)\,d\sigma.\end{aligned}$$

According to (15),

$$\frac{d\mathcal{M}}{dt} = \int_\Omega \nabla L(u)\cdot f(u)\,dx - \sum_{i=1}^m d_i\int_\Omega \nabla u_i\nabla\frac{\partial L}{\partial u_i}(u)\,dx + \sum_{i=1}^m d_i\int_{\partial\Omega}\frac{\partial u_i}{\partial\nu}\frac{\partial L}{\partial u_i}(u)\,d\sigma.$$

Since $\frac{\partial u}{\partial\nu} = 0$ on $\partial\Omega$, we deduce that

$$\frac{d\mathcal{M}}{dt} = \int_\Omega \nabla L(u)\cdot f(u)\,dx - \sum_{i=1}^m d_i\int_\Omega \nabla u_i\nabla\frac{\partial L}{\partial u_i}(u)\,dx. \tag{16}$$

Thus, the condition (C_1) reduces to

$$\int_\Omega \nabla u_i\cdot\nabla\left(\frac{\partial L}{\partial u_i}\right)dx \geqslant 0 \quad \text{for all} \quad i=1,\dots,m. \tag{17}$$

Additionally, if the function L is of the form (11), then

$$\int_\Omega \nabla u_i\cdot\nabla\left(\frac{\partial L}{\partial u_i}\right)dx = a_i u_i^*\int_\Omega \frac{|\nabla u_i|^2}{u_i^2}\,dx \geqslant 0 \quad \text{for all} \quad i=1,\dots,m.$$

Similarly, if L is of the form (10), then

$$\int_\Omega \nabla u_i\cdot\nabla\left(\frac{\partial L}{\partial u_i}\right)dx = a_i g_i(u_i^*)\int_\Omega g_i'(u_i)\frac{|\nabla u_i|^2}{g_i(u_i)^2}\,dx \geqslant 0 \quad \text{for all} \quad i=1,\dots,m.$$

Consequently, we have the following corollary.

Corollary 1. *If the function L satisfies the condition (17), then the function $\mathcal{M}$ defined by (14) is a Lyapunov function for the classical reaction-diffusion system (13) with normal diffusion.*

4. Global stability of the proposed model

The purpose of this section is to examine the global stability of three equilibria established by the system presented in equations (1). We will achieve this by using the method described in the preceding section.

Theorem 2. *If $\mathcal{R}_0 \leqslant 1$, then the infection-free equilibrium P_0 of model (1) is globally asymptotically stable.*

Proof. Consider the form of the notation for u and the reaction function $F(u)$ as follows

$$u = \begin{pmatrix} U \\ I \\ V \\ C \end{pmatrix} \quad \text{and} \quad F(u) = \begin{pmatrix} \lambda - m_U U - \frac{\beta_1 UV}{1+q_1 C} - \frac{\beta_2 UI}{1+q_2 C} \\ \frac{\beta_1 UV}{1+q_1 C} + \frac{\beta_2 UI}{1+q_2 C} - m_I I - pIC \\ k(1-\varepsilon)I - m_V V \\ \sigma IC - m_C C \end{pmatrix}, \tag{18}$$

let the function $\Psi(x) := x - \ln x - 1$ for $x > 0$ and the following functional

$$L_0(u) = U_0 \Psi\left(\frac{U}{U_0}\right) + I + \frac{\beta_1 U_0}{m_V} V + \frac{p}{\sigma} C,$$

$$\mathcal{L}_0(u) = \int_\Omega L_0(u(x,t))\, dx.$$

Obviously, $L_0(U,I,V,C) > 0$ for $U,I,V,C > 0$ and $L_0(P_0) = 0$. By using the method described in section 3, we get

$$\frac{d\mathcal{L}_0(u)}{dt} = \int_\Omega \nabla L_0(u) \cdot f(u)\, dx - \frac{C(n,s)}{2} \sum_{i=1}^{4} d_i\, \mathcal{E}\left(u_i, \frac{\partial L_0}{\partial u_i}(u)\right),$$

for d_i the diffusion coefficients and u_i the u components.

We can view the negativeness of $\nabla L_0(u) \cdot f(u)$ from [17] such as

$$\begin{aligned} \nabla L_0(u) \cdot f(u) = \frac{dL_0}{dt} &= -\frac{m_U}{U}(U - U_0)^2 + m_I I \left(\frac{k(1-\varepsilon)\beta_1 U_0}{m_I m_V} + \frac{\beta_2 U_0}{m_I(1+q_2 C)} - 1\right) \\ &\quad - \frac{q_1 \beta_1 U_0}{1+q_1 C} VC - \frac{p m_C}{\sigma} C \\ &\leqslant -\frac{m_U}{U}(U - U_0)^2 + m_I I(\mathcal{R}_0 - 1) - \frac{p m_C}{\sigma} C. \end{aligned}$$

Then $\nabla L_0(u) \cdot f(u) \leqslant 0$ when $\mathcal{R}_0 \leqslant 1$. In addition, the functional L_0 satisfies the following conditions of the Theorem 1,

$$\begin{aligned} &\mathcal{E}\left(U, \frac{\partial L_0}{\partial U}(u)\right) = U_0 \int_\Omega \int_\Omega \frac{(U(x,t) - U(y,t))^2}{U(x,t)U(y,t)|x-y|^{n+2s}}\, dx\, dy \geqslant 0, \\ &\mathcal{E}\left(I, \frac{\partial L_0}{\partial I}(u)\right) = 0, \\ &\mathcal{E}\left(V, \frac{\partial L_0}{\partial V}(u)\right) = 0, \\ &\mathcal{E}\left(C, \frac{\partial L_0}{\partial C}(u)\right) = 0. \end{aligned}$$

If $\mathcal{R}_0 \leqslant 1$, we can conclude that $\frac{d\mathcal{L}_0}{dt} \leqslant 0$. Moreover, the equality holds if and only if $U = U_0$, $I = 0$, $V = 0$, and $C = 0$. We conclude that P_0 is globally asymptotically stable when $\mathcal{R}_0 \leqslant 1$, by applying LaSalle's invariance principle. ∎

We will now analyze the asymptotic stability of two infection equilibria P_1 and P_2. For this analysis, we will assume that $\mathcal{R}_0 > 1$ and the following additional hypothesis,

$$q_1(C - C_i)\left(\frac{1+q_1C}{1+q_1C_i} - \frac{V}{V_i}\right) \leqslant 0,$$
$$q_2(C - C_i)\left(\frac{1+q_2C}{1+q_2C_i} - \frac{I}{I_i}\right) \leqslant 0, \tag{H}$$

where I_i, V_i and C_i are infected pulmonary epithelial cell, virus and CTL cell components of the infection equilibrium P_i for $i = 1, 2$.

Theorem 3.

(i) If (H) holds for the infection equilibrium P_1 without cellular immunity, then P_1 is globally asymptotically stable if $\mathcal{R}_1^C \leqslant 1 < \mathcal{R}_0$.

(ii) If (H) holds for the infection equilibrium P_2 with cellular immunity, then P_2 is globally asymptotically stable if $\mathcal{R}_1^C > 1$.

Proof. For (i), let us consider the following functionals

$$L_1(u) = U_1\Psi\left(\frac{U}{U_1}\right) + I_1\Psi\left(\frac{I}{I_1}\right) + \frac{\beta_1 U_1 V_1}{k(1-\varepsilon)I_1}V_1\Psi\left(\frac{V}{V_1}\right) + \frac{p}{\sigma}C,$$

$$\mathcal{L}_1(u) = \int_\Omega L_1(u(x,t))\,dx.$$

According to [17],

$$\begin{aligned}\nabla L_1(u)\cdot f(u) = \frac{dL_1}{dt} = &-\frac{m_U}{U}(U-U_1)^2 + \frac{pm_C}{\sigma}\left(\mathcal{R}_1^C - 1\right)C\\ &+ \beta_1 U_1 V_1\left(-1 - \frac{V}{V_1} + \frac{V}{(1+q_1C)V_1} + (1+q_1C)\right)\\ &+ \beta_2 U_1 I_1\left(-1 - \frac{I}{I_1} + \frac{I}{(1+q_2C)I_1} + (1+q_2C)\right)\\ &+ \beta_1 U_1 V_1\left(4 - \frac{U_1}{U} - \frac{IV_1}{I_1V} - \frac{UVI_1}{(1+q_1C)U_1V_1I} - (1+q_1C)\right)\\ &+ \beta_2 U_1 I_1\left(3 - \frac{U_1}{U} - \frac{U}{(1+q_2C)U_1} - (1+q_2C)\right).\end{aligned}$$

From (H),

$$-1 - \frac{V}{V_i} + \frac{(1+q_1C_i)V}{(1+q_1C)V_i} + \frac{1+q_iC}{1+q_1C_i} = \frac{q_1(C-C_i)}{1+q_1C}\left(\frac{1+q_1C}{1+q_1C_i} - \frac{V}{V_i}\right) \leqslant 0,$$
$$-1 - \frac{1}{I_i} + \frac{(1+q_2C_i)I}{(1+q_2C)I_i} + \frac{1+q_2C}{1+q_2C_i} = \frac{q_2(C-C_i)}{1+q_2C}\left(\frac{1+q_2C}{1+q_2C_i} - \frac{I}{I_i}\right) \leqslant 0.$$

Using the property that the arithmetic mean (AM) is greater than or equal to the geometric mean (GM), we can derive the following inequalities

$$4 - \frac{U_1}{U} - \frac{IV_1}{I_1V} - \frac{UVI_1}{(1+q_1C)U_1V_1I} - (1+q_1C) \leqslant 0$$

and

$$3 - \frac{U_1}{U} - \frac{U}{(1+q_2C)U_1} - (1+q_2C) \leqslant 0.$$

Then $\nabla L_1(u)\cdot f(u) \leqslant 0$ when $\mathcal{R}_1^C \leqslant 1$. Clearly, the functional L_0 satisfies the following conditions of Theorem 1 that are

$$\mathcal{E}\left(U, \frac{\partial L_1}{\partial U}(u)\right) = U_1\int_\Omega\int_\Omega \frac{(U(x,t)-U(y,t))^2}{U(x,t)U(y,t)|x-y|^{n+2s}}\,dx\,dy \geqslant 0,$$
$$\mathcal{E}\left(I, \frac{\partial L_1}{\partial I}(u)\right) = I_1\int_\Omega\int_\Omega \frac{(I(x,t)-I(y,t))^2}{I(x,t)I(y,t)|x-y|^{n+2s}}\,dx\,dy \geqslant 0,$$

$$\mathcal{E}\left(V, \frac{\partial L_1}{\partial V}(u)\right) = \frac{\beta_1 U_1 V_1}{k(1-\varepsilon)I_1} V_1 \int_\Omega \int_\Omega \frac{(V(x,t)-V(y,t))^2}{V(x,t)V(y,t)|x-y|^{n+2s}}\,dx\,dy \geqslant 0,$$
$$\mathcal{E}\left(C, \frac{\partial L_1}{\partial C}(u)\right) = 0.$$

If $\mathcal{R}_1^C \leqslant 1$, then $\frac{d\mathcal{L}_1}{dt} \leqslant 0$. Hence, P_1 is globally asymptotically stable.

For (ii), we consider the Lyapunov function

$$\mathcal{L}_2(u) = \int_\Omega L_2(u(x,t))\,dx,$$

where

$$L_2(u) = U_2\Psi\left(\frac{U}{U_2}\right) + I_2\Psi\left(\frac{I}{I_2}\right) + \frac{\beta_1 U_2 V_2}{(1+q_1C_2)k(1-\varepsilon)I_2} V_2\Psi\left(\frac{V}{V_2}\right) + \frac{p}{\sigma}C_2\Psi\left(\frac{C}{C_2}\right).$$

The computation of $\nabla L_2(u)\cdot f(u)$ gives

$$\begin{aligned}
\nabla L_2(u)\cdot f(u) &= \frac{dL_2}{dt} \\
&= -\frac{m_U}{U}(U-U_2)^2 + \frac{\beta_1 U_2 V_2}{1+q_1C_2}\left(-1 - \frac{V}{V_2} + \frac{(1+q_1C_2)V}{(1+q_1C)V_2} + \frac{1+q_1C}{1+q_1C_2}\right) \\
&\quad + \frac{\beta_2 U_2 I_2}{1+q_2C_2}\left(-1 - \frac{I}{I_2} + \frac{(1+q_2C_2)I}{(1+q_2C)I_2} + \frac{1+q_2C}{1+q_2C_2}\right) \\
&\quad + \frac{\beta_1 U_2 V_2}{1+q_1C_2}\left(4 - \frac{U_2}{U} - \frac{IV_2}{I_2V} - \frac{(1+q_1C_2)UVI_2}{(1+q_1C)U_2V_2I} - \frac{1+q_1C}{1+q_1C_2}\right) \\
&\quad + \frac{\beta_2 U_2 I_2}{1+q_2C_2}\left(3 - \frac{U_2}{U} - \frac{(1+q_2C_2)U}{(1+q_2C)U_2} - \frac{1+q_2C}{1+q_2C_2}\right).
\end{aligned}$$

Since AM is greater than or equal to GM, we have

$$4 - \frac{U_2}{U} - \frac{IV_2}{I_2V} - \frac{(1+q_1C_2)UVI_2}{(1+q_1C)U_2V_2I} - \frac{1+q_1C}{1+q_1C_2} \leqslant 0,$$
$$3 - \frac{U_2}{U} - \frac{(1+q_2C_2)U}{(1+q_2C)U_2} - \frac{1+q_2C}{1+q_2C_2} \leqslant 0.$$

Then $\nabla L_2(u)\cdot f(u) < 0$ when $\mathcal{R}_2^C > 1$.

Moreover, the functional L_2 satisfies the conditions of Theorem 1:

$$\mathcal{E}\left(U, \frac{\partial L_2}{\partial U}(u)\right) = U_2 \int_\Omega \int_\Omega \frac{(U(x,t)-U(y,t))^2}{U(x,t)U(y,t)|x-y|^{n+2s}}\,dx\,dy \geqslant 0,$$
$$\mathcal{E}\left(I, \frac{\partial L_2}{\partial I}(u)\right) = I_2 \int_\Omega \int_\Omega \frac{(I(x,t)-I(y,t))^2}{I(x,t)I(y,t)|x-y|^{n+2s}}\,dx\,dy \geqslant 0,$$
$$\mathcal{E}\left(V, \frac{\partial L_2}{\partial V}(u)\right) = \frac{\beta_1 U_2 V_2}{(1+q_1C_2)k(1-\varepsilon)I_2} V_2 \int_\Omega \int_\Omega \frac{(V(x,t)-V(y,t))^2}{V(x,t)V(y,t)|x-y|^{n+2s}}\,dx\,dy \geqslant 0,$$
$$\mathcal{E}\left(C, \frac{\partial L_2}{\partial C}(u)\right) = \frac{p}{\sigma}C_2 \int_\Omega \int_\Omega \frac{(C(x,t)-C(y,t))^2}{C(x,t)C(y,t)|x-y|^{n+2s}}\,dx\,dy \geqslant 0.$$

If $\mathcal{R}_2^C > 1$, then we have $\frac{d\mathcal{L}_2}{dt} \leqslant 0$, which implies that P_1 is globally asymptotically stable. ∎

5. Numerical simulations

In this section, we first propose a numerical scheme to approximate the solutions of our PDE model (1).

According to [22], the fractional Laplacian given in (2) can be approximated in one dimension, for $u = \{u_j\}_{j\in\mathbb{Z}}$ a function defined on the uniform grid $\Omega_h = \{jh | j \in \mathbb{Z}\} \cap \Omega$ with spacing $h > 0$, by the following discrete operator

$$(-\Delta)^s_\Omega u_j = \sum_{k=-\infty}^{+\infty} (u_j - u_{j-k})w_k = \sum_{k=1}^{+\infty} (-u_{j-k} + 2u_j - u_{j+k})w_k, \tag{19}$$

where $\{w_k\}_{k\in\mathbb{Z}}$ are the positive weights satisfying $\sum_{k\in\mathbb{Z}} w_k = 1$. As in [23], we choose

$$w_k = C(1,s)|k|^{-2s-1} \quad (k \neq 0),$$

with $C(1,s)$ the normalization constant defined in (3). It is natural to require that $w_k = w_{-k}$ since the fractional Laplacian is symmetric. When the explicit Euler scheme used in the discretization of the model (1) is

$$\frac{u_j^{n+1} - u_j^n}{\Delta t} = D(-\Delta_h)^s u_j^n + F(u_j^n),$$

at time $t_{n+1} = (n+1)\Delta t$ the scheme can be also written as

$$\begin{aligned} u_j^{n+1} &= (1 + \Delta t w_0)u_j^n + D\sum_{k\neq 0} \Delta t(u_j^n - u_{j-k}^n)w_k + \Delta t F(u_j^n), \\ &= (1 + \Delta t w_0)u_j^n + D\sum_{k=1}^{+\infty} \Delta t(-u_{j+k}^n + 2u_j^n - u_{j-k}^n)w_k + \Delta t F(u_j^n), \end{aligned}$$

where $F = (F_1, F_2, F_3, F_4)$ is the reaction component given in (18), the weight w_0 can be arbitrary, because it does not enter into (19).

As a result to approximate the model (1), the following recursive relations take place

$$\begin{aligned} U_j^{n+1} &= (1 + \Delta t\, w_0)\, U_j^n + d_U \sum_{k=1}^{N} \Delta t\, (-U_{j+k}^n + 2U_j^n - U_{j-k}^n)w_k + \Delta t\, F_1(u_j^n), \\ I_j^{n+1} &= (1 + \Delta t\, w_0)\, I_j^n + d_I \sum_{k=1}^{N} \Delta t\, (-I_{j+k}^n + 2I_j^n - I_{j-k}^n)w_k + \Delta t\, F_2(u_j^n), \\ V_j^{n+1} &= (1 + \Delta t\, w_0)\, V_j^n + d_V \sum_{k=1}^{N} \Delta t\, (-V_{j+k}^n + 2V_j^n - V_{j-k}^n)w_k + \Delta t\, F_3(u_j^n), \\ C_j^{n+1} &= (1 + \Delta t\, w_0)\, C_j^n + d_C \sum_{k=1}^{N} \Delta t\, (-C_{j+k}^n + 2C_j^n - C_{j-k}^n)w_k + \Delta t\, F_1(u_j^n). \end{aligned}$$

The parameters of the SARS-CoV-2 model are typically determined through biological calculations or estimates, taking into account morphometric data such as the numbers of various pulmonary cells and lung volume. In this study, we analyze the numerical dynamics of model (1) using different parameter values, as classified in [17], presented in Table 1.

Table 1. Parameter values for the SARS-CoV-2 model.

Parameter	Range value
λ	$57.757 - 1.2 \times 10^4$ cells mL^{-1} day $^{-1}$
m_U	10^{-3}day^{-1}
β_1	$0 - 1$ mL virion $^{-1}$ day $^{-1}$
β_2	$0 - 1$ mL cell^{-1} day $^{-1}$
m_I	$0.088 - 0.58$ day^{-1}
k	$88 - 580$ virions cell $^{-1}$ day^{-1}
m_V	$2.4464 - 15.1232$ day^{-1}
σ	$0 - 1$ mL cell^{-1} day $^{-1}$
m_C	$0.05 - 1$ mL cell^{-1} day^{-1}
p	$0.05 - 1$ mL cell^{-1} day^{-1}
q_1	$0 - 1$ mL cell^{-1}
q_2	$0 - 1$ mL cell^{-1}

Based on the given information, Table 1 provides the values for the parameters used: $\lambda = 500$, $m_U = 0.001$, $\beta_1 = 1.12 \times 10^{-7}$, $\beta_2 = 1.1 \times 10^{-7}$, $q_1 = 0.3$, $q_2 = 0.6$, $m_I = 0.56$, $p = 0.06$, $m_V = 10$, and $m_C = 0.85$. The remaining parameters σ and k are considered as free variables.

Infection-free equilibrium P_0: To analyze the dynamics of P_0, we investigate the case where $\mathcal{R}_0 = 0.9782 \leqslant 1$. By selecting $\sigma = 0.05$ and $k = 88$, it can be shown that $P_0(5 \times 10^5, 0, 0, 0)$ is globally asymptotically stable. This theoretical result is visually illustrated in Figure 1, which depicts the convergence of the solutions of model (1) towards P_0.

Infection equilibrium without cellular immunity P_1: Considering $\sigma = 1.1 \times 10^{-3}$ and $k = 230$, we find that $\mathcal{R}_0 = 2.3982 > 1$ and $\mathcal{R}_1^C = 0.6737 \leqslant 1$. Figure 2 illustrates that the trajectories of model (1) converge towards the infection equilibrium $P_1(2.0850 \times 10^5, 520.5563, 1.1973 \times 10^4, 0)$. This confirms the global asymptotic stability of P_1 and validates the analytical result obtained in Theorem 3(i).

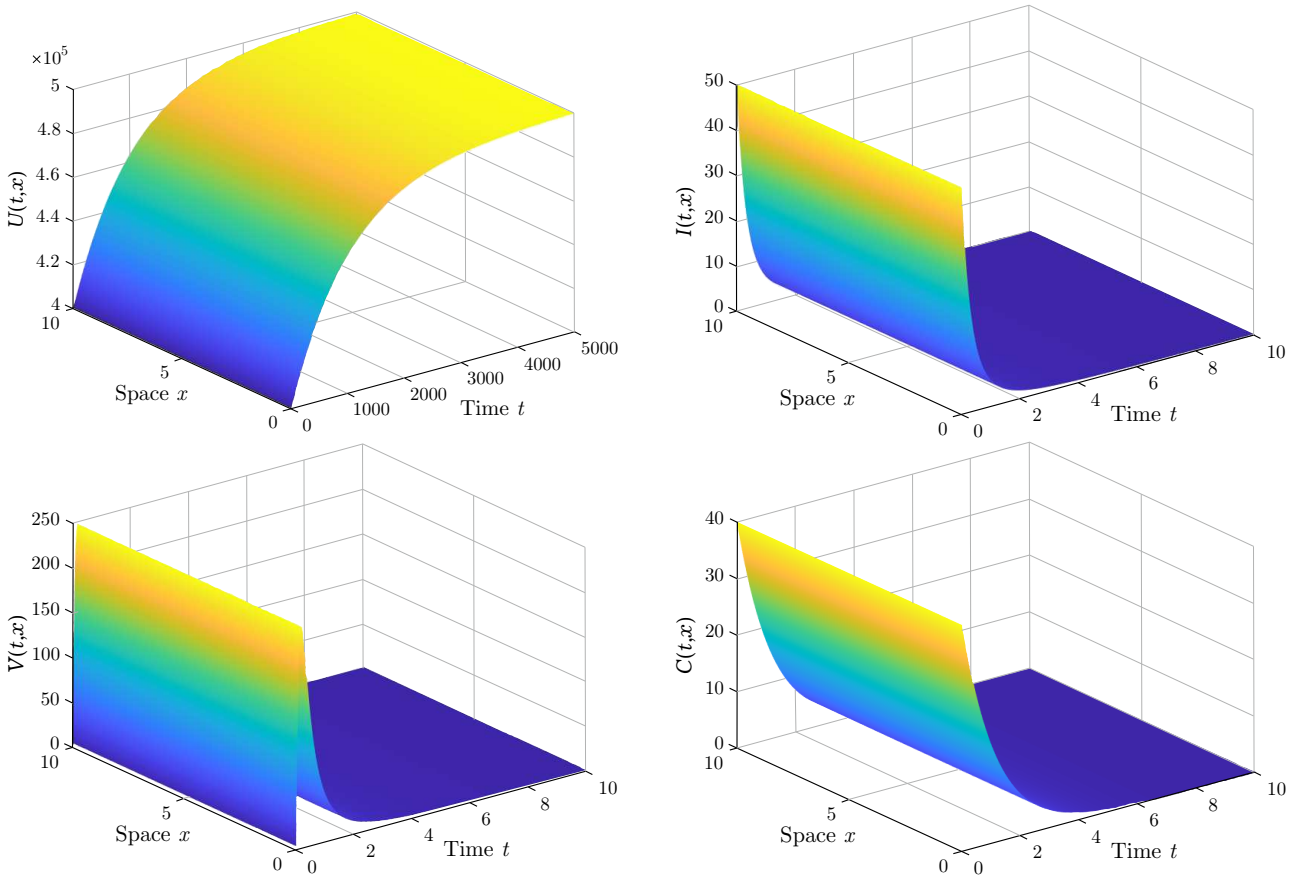

Fig. 1. Dynamics of system (1) at P_0.

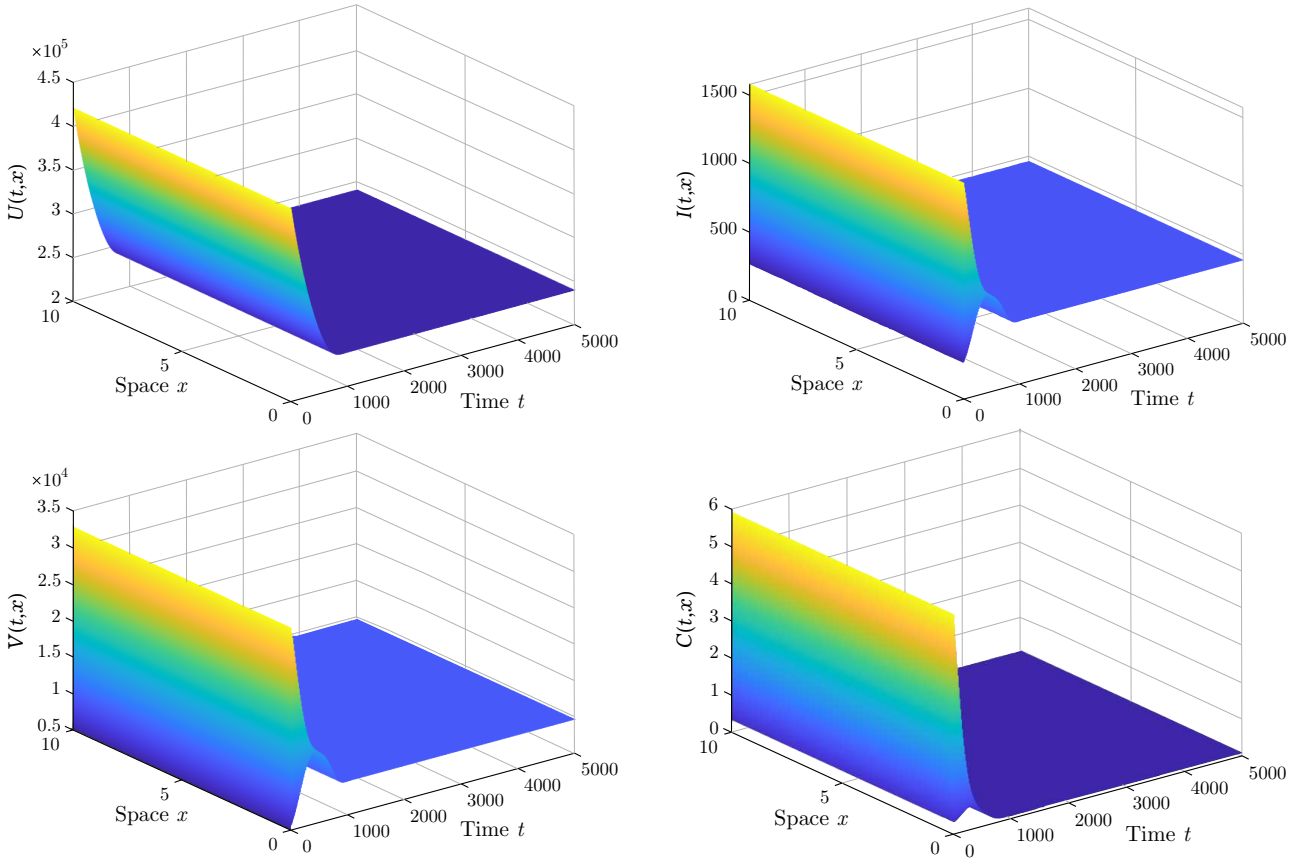

Fig. 2. Dynamics of system (1) at P_1.

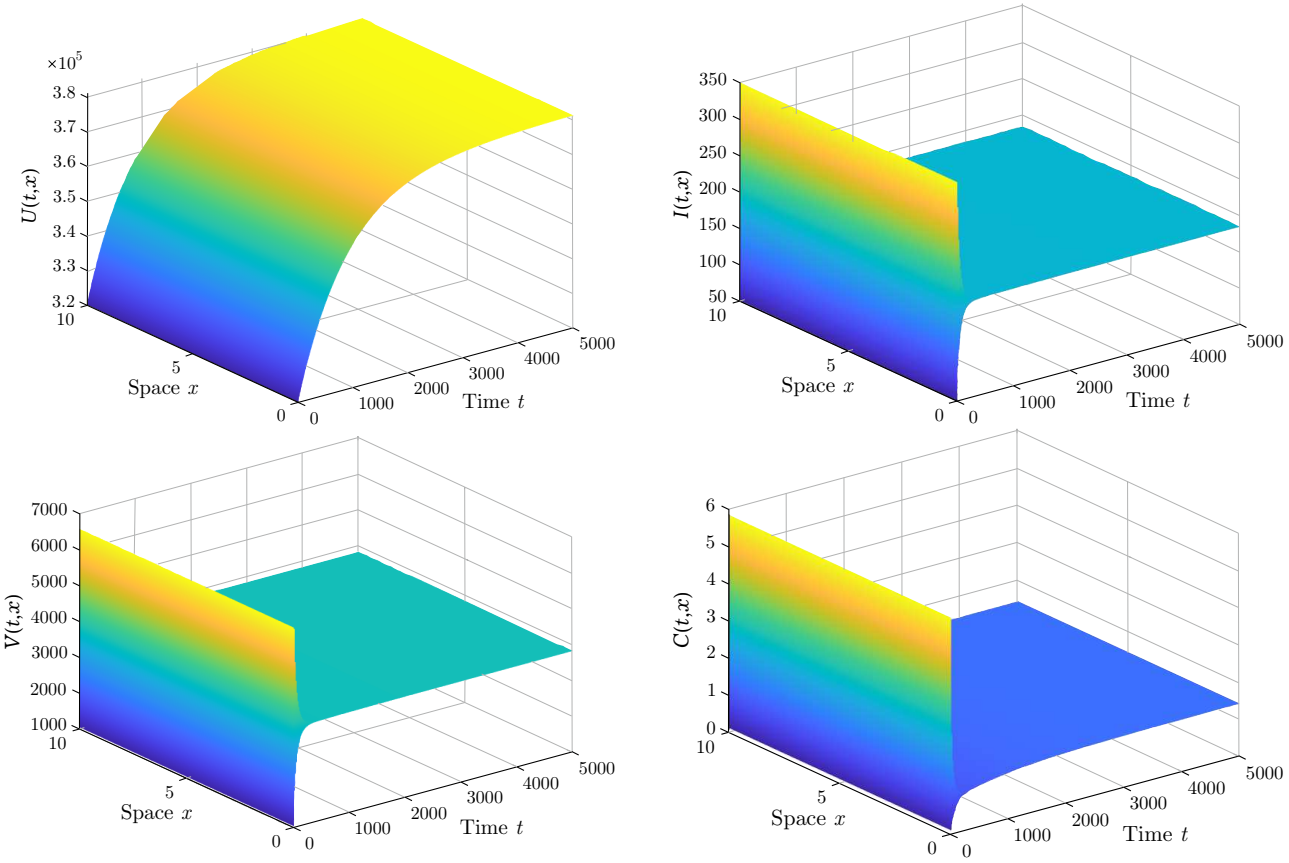

Fig. 3. Dynamics of system (1) at P_2.

Infection equilibrium with cellular immunity P_2: For $\sigma = 4.5 \times 10^{-3}$ and $k = 230$, we have $\mathcal{R}_0 = 2.3982 > 1$ and $\mathcal{R}_1^C = 2.7559 > 1$. In Figure 3, we observe that the trajectories of model (1) converge to the infection equilibrium with cellular immunity $P_2(3.7506 \times 10^5, 188.2088, 4.3292 \times 10^3, 1.6977)$. This illustrates the results of the global asymptotic stability of P_2 given in Theorem 3(ii).

6. Conclusion

In this work, we have proposed a SARS-CoV-2 infection model with diffusion and antiviral treatment. The proposed model incorporates both modes of transmission (virus-to-cell and cell-to-cell), the lytic and nonlytic immune responses. The anomalous diffusion into the model was described by the regional fractional Laplacian operator. We first established the equilibria and the threshold parameters of the model. The global stability of such equilibria has been investigated by means of a new method constructing Lyapunov functions for a class of PDEs with and without delay involving regional fractional Laplacian operator. In addition, the new method extended the case of the classical reaction-diffusion equations with normal diffusion presented in [10].

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Глобальна динаміка дифузійної моделі SARS-CoV-2 з противірусним лікуванням і дробовим оператором Лапласа

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У цій статті пропонується та досліджується глобальна динаміка моделі інфекції SARS-CoV-2 із дифузним та противірусним лікуванням. Запропонована модель враховує два шляхи передачі (від вірусу до клітини та від клітини до клітини), літичну та нелітичну імунні відповіді. Дифузія в модель формулюється регіональним дробовим оператором Лапласа. Крім того, глобальна асимптотична стійкість рівноваги строго встановлена за допомогою нового запропонованого методу побудови функцій Ляпунова для класу рівнянь в частинних похідних (PDE) з регіональним дробовим оператором Лапласа. Запропонований метод застосовано до класичних рівнянь "реакції–дифузії" з нормальною дифузією.

Ключові слова: *SARS-CoV-2; COVID-19; регіональний дробовий оператор Лапласа; дифузія; функції Ляпунова; глобальна стійкість.*