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GLOBAL STABILITY OF REACTION-DIFFUSION EQUATIONS WITH FRACTIONAL LAPLACIAN OPERATOR AND APPLICATIONS IN BIOLOGY

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Abstract. The main objective of this paper is to develop an efficient method to establish the global stability of some reaction-diffusion equations with fractional Laplacian operator. This method is based on Lyapunov functionals for ordinary differential equations (ODEs). A classical case of such types of fractional spacial diffusion equations is rigorously studied. Moreover, the developed method is applied to some biological systems arising from epidemiology and cancerology.

Keywords: fractional diffusion; biological systems; asymptotic stability; Lyapunov functional.

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1. Introduction

The classical reaction-diffusion equations consist of two additive terms, a diffusion process, and a reaction term. Diffusion is the result of the random motion of individuals, and the use of the Laplacian operator is based on the key assumption that this random motion is a stochastic Gaussian (normal) process. However, a large number of works have shown the presence of

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anomalous diffusion processes such as Lévy process. These processes occur widely in physics, chemistry and biology. For instance, Chen and Holm [1] proposed a lossy wave equation based on the fractional Laplacian. Another derivation of wave equations to model acoustic absorption and dispersion in biological tissue was developed by Treeby and Cox [2]. A class of fractional diffusion models was introduced in [3] in order to mathematically describe cardiac tissue with the macroscopic effects of structural heterogeneity on impulse propagation. In addition, Somathilake and Burrage [4] proposed a space fractional reaction-diffusion model for growth of corals in a tank.

The global stability of systems with normal diffusion has attracted the attention of several researchers. In 2009, Xu and Ma [5] investigated the global stability of a delayed hepatitis B virus (HBV) model with spatial diffusion, saturation response of the infection rate and intracellular incubation period. Shaoli et al. [6] proposed a diffused HBV model with cellular immune response and nonlinear incidence for the control of viral infections. They proved that the free diffusion of the virus has no effect on the global stability of such HBV infection problem with Neumann homogeneous boundary conditions. Hattaf and Yousfi [7] developed a method for the construction of Lyapunov functionals of classical reaction-diffusion systems with and without delays. This method has been used by many authors (see, for example, [8, 9, 10, 11, 12, 13]) in order to study the global stability of various models with normal diffusion. Recently, the developed method was extended by the same authors [14] in order to study the global stability of fractional differential equations (FDEs) with normal diffusion and Caputo fractional derivative. An application of this last extended method was recently presented in [15] to establish the global dynamics of a FDE model for M1 oncolytic virotherapy with CTL immune response.

To our knowledge, there is no method aims to study the global stability of systems with anomalous diffusion by using the Lyapunov functionals of the corresponding reaction systems. Therefore, the main objective of this paper is to extend the method presented in [7] to space fractional reaction-diffusion equations with fractional Laplacian operator. To do this, Section 2 deals with the presentation of the method. Section 3 is devoted to the study of a particular and classical case of such types of equations. The paper ends with applications of our method to some biological systems.

2. Description of the Method

In this section, we propose a method of the construction of Lyapunov functionals for space fractional reaction-diffusion equations with and without delay.

First, consider the following reaction equation expressed by ODE as

$$\dot{u} = f(u), \tag{1}$$

where the state variable u is a non-negative vector of concentrations $u_1, ..., u_m$, $m \in \mathbf{N}^*$ and $f : \mathbb{R}^m \longrightarrow \mathbb{R}^m$ is a C^1 function.

Let $D = diag(d_1, ..., d_m)$ be the diagonal matrix of diffusion with $d_i \geq 0$ and Ω be a bounded domain in $\mathbb{R}^n$ with smooth boundary $\partial\Omega$. It is clear that if u^* is a steady state of (1), then u^* is also a steady state of the following reaction-diffusion equation with fractional Laplacian operator given by

$$\begin{cases} \dfrac{\partial u}{\partial t} + D(-\Delta)^s u = f(u) & in\, \Omega \times (0, +\infty), \\ \mathcal{N}_s u = 0 & in\, \mathbb{R}^n \setminus \overline{\Omega} \times (0, +\infty), \\ u(x, 0) = u_0(x) & in\, \Omega, \end{cases} \tag{2}$$

where $s \in (0, 1)$ and $(-\Delta)^s$ is the fractional Laplacian operator defined as in [16] by

$$\begin{aligned} (-\Delta)^s u(x) =& PV \int_{\mathbb{R}^n} \frac{u(x) - u(y)}{|x - y|^{n+2s}} \, dy \\ =& C(n, s) \lim_{\varepsilon \to 0^+} \int_{\mathbb{R}^n \setminus B(x, \varepsilon)} \frac{u(x) - u(y)}{|x - y|^{n+2s}} \, dy, \end{aligned} \tag{3}$$

PV is a commonly used abbreviation for "in the principal value sense", $B(x, \varepsilon)$ is the ball of center $x \in \mathbb{R}^n$ and radius ε, $C(n, s)$ is a normalization constant that depends on n and s and it is given by

$$C(n, s) = \left(\int_{\mathbb{R}^n} \frac{1 - \cos(\zeta_1)}{|\zeta|^{n+2s}} d\zeta \right)^{-1} = \frac{s 4^s \Gamma(s + \frac{n}{2})}{\pi^{\frac{n}{2}} \Gamma(1 - s)}, \tag{4}$$

with $\zeta = (\zeta_1, \zeta')$, $\zeta' \in \mathbb{R}^{n-1}$ and Γ is the gamma function. Further, $\mathcal{N}_s$ is a non-local normal derivative defined in [17] by

$$\mathcal{N}_s u(x) = C(n, s) \int_{\Omega} \frac{u(x) - u(y)}{|x - y|^{n+2s}} \, dy, \quad x \in \mathbb{R}^n \setminus \overline{\Omega}. \tag{5}$$

When $f(u)=0$, we obtain the Neumann problem presented in [17]. Additionally, the probabilistic interpretation of such Neumann problem was given in [17] as follows:

(i) $u(x,t)$ is the particle position probability distribution of moving randomly inside Ω.

(ii) When the particle leaves Ω, it immediately come back to Ω.

(iii) If the particle has gone to $x\in\mathbb{R}^n\setminus\overline{\Omega}$, it may returns to any position $y\in\Omega$ by the probability density of jumping between x and y being proportional to $|x-y|^{-n-2s}$.

Let $V(u)$ be a C^1 function defined on some domain in $\mathbb{R}^m_+$. If $u(t)$ is a solution of (1), then the time derivative of $V(u(t))$ satisfies

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

We assume that the range of $u(t)$ is included in the domain of $V(u)$. We remark that the right-hand side of (6) is given by the gradient of the function $V(u)$ and the vector field $f(u)$. Hence, this side is defined without the consideration that $u(t)$ is a solution of (1), and it is important for our computation of Lyapunov functionals.

Let $u(x,t)$ be a solution of system (2). Denote

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

The computation of the time derivative of W along the positive solution of (2) provides

$$\begin{aligned}\frac{dW}{dt}&=\int_\Omega \nabla V(u)\cdot\big(-D(-\Delta)^s u+f(u)\big)dx\\&=\int_\Omega \nabla V(u)\cdot f(u)dx-\int_\Omega \nabla V(u).D(-\Delta)^s u dx.\end{aligned}$$

Then

$$\frac{dW}{dt}=\int_\Omega \nabla V(u)\cdot f(u)dx-\sum_{i=1}^m d_i\int_\Omega \frac{\partial V}{\partial u_i}(u)(-\Delta)^s u_i dx. \tag{8}$$

We assume the integrand of the first term of (8) is already calculated as (6) for the ODE (1). The second term can be simplified by using Lemma 3.3 of [17] as follows

$$\begin{aligned}\int_\Omega \frac{\partial V}{\partial u_i}(u)(-\Delta)^s u_i\,dx=&\frac{C(n,s)}{2}\int_{\mathbb{R}^{2n}_{\Omega^2}}\frac{\big(\frac{\partial V}{\partial u_i}(u(x,t))-\frac{\partial V}{\partial u_i}(u(y,t))\big)\big(u_i(x,t)-u_i(y,t)\big)}{|x-y|^{n+2s}}dxdy\\&-\int_{\mathscr{C}\Omega}\frac{\partial V}{\partial u_i}(u)\mathscr{N}_s u_i,\end{aligned}$$

where $\mathscr{C}\Omega := \mathbb{R}^n \setminus \Omega$ and $\mathbb{R}^{2n}_{\Omega^2} := \mathbb{R}^{2n} \setminus (\mathscr{C}\Omega)^2$.

Since $\mathscr{N}_s u = 0$ in $\mathbb{R}^n \setminus \overline{\Omega}$, we have

$$\frac{dW}{dt} = \int_\Omega \nabla V(u) \cdot f(u) dx - \frac{C(n,s)}{2} \sum_{i=1}^m d_i \mathscr{I}_{u_i}(V,\Omega)(u), \tag{9}$$

where

$$\mathscr{I}_{u_i}(V,\Omega)(u) := \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{\left(\frac{\partial V}{\partial u_i}(u(x,t)) - \frac{\partial V}{\partial u_i}(u(y,t))\right)\left(u_i(x,t) - u_i(y,t)\right)}{|x-y|^{n+2s}} dxdy.$$

Since the constants d_i and $C(n,s)$ are non-negative, we construct the function V such that

$$\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{\left(\frac{\partial V}{\partial u_i}(u(x,t)) - \frac{\partial V}{\partial u_i}(u(y,t))\right)\left(u_i(x,t) - u_i(y,t)\right)}{|x-y|^{n+2s}} dxdy \geq 0, \quad \text{for } i = 1,\dots,m. \tag{10}$$

On the other hand, most of the authors in literature constructed the explicit Lyapunov functions of the form

$$V(u) = \sum_{i=1}^m a_i(u_i - u_i^* - u_i^* \ln \frac{u_i}{u_i^*}). \tag{11}$$

In this case, we have

$$\mathscr{I}_{u_i}(V,\Omega) = a_i u_i^* \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(u_i(x,t) - u_i(y,t))^2}{u_i(x,t)u_i(y,t)|x-y|^{n+2s}} dxdy \geq 0.$$

For more generality like in [18] and [19], $V(u)$ can be given of the form

$$V(u) = \sum_{i=1}^m a_i \left(u_i - u_i^* - \int_{u_i^*}^{u_i} \frac{g_i(u_i^*)}{g_i(t)} dt \right), \tag{12}$$

where g_i is a non-negative and strictly increasing function on $\mathbb{R}_+$. So, we get

$$\begin{aligned}
\mathscr{I}_{u_i}(V,\Omega) &= \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{\left(\frac{\partial V}{\partial u_i}(u(x,t)) - \frac{\partial V}{\partial u_i}(u(y,t))\right)\left(u_i(x,t) - u_i(y,t)\right)}{|x-y|^{n+2s}} dxdy \\
&= a_i g_i(u_i^*) \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{g_i(u_i(x,t)) - g_i(u_i(y,t))}{u_i(x,t) - u_i(y,t)} \frac{(u_i(x,t) - u_i(y,t))^2}{g_i(u_i(x,t))g_i(u_i(y,t))|x-y|^{n+2s}} dxdy \\
&\geq 0.
\end{aligned}$$

Based on the above discussions, we obtain the following main results.

Theorem 2.1. *Let V be a Lyapunov functional for ODE system* (1).

(i) *If the function V satisfies the condition* (10), *then the function W defined by* (7) *is a Lyapunov functional for the space fractional reaction-diffusion system* (2).

(ii) *If the function V is of the form* (11) *or* (12)*, then W is a Lyapunov functional for the space fractional reaction-diffusion system* (2).

Next and as in [7], consider the following delayed space fractional reaction-diffusion equation

$$
\begin{cases}
\dfrac{\partial u}{\partial t} + D(-\Delta)^s u = f(u) + g(u,u_t) & in\, \Omega \times (0,+\infty), \\
\mathscr{N}_s u = 0 & in\, \mathbb{R}^n \setminus \overline{\Omega} \times (0,+\infty), \\
u(x,t) = u_0(x,t) & in\, \Omega \times [-\tau, 0],
\end{cases} \tag{13}
$$

where $s \in (0,1)$, $\tau \geq 0$, the function u_t is defined on $\Omega \times [-\tau, 0]$ by $u_t(x,\theta) = u(x,t+\theta)$ and g is a functional of u, u_t.

In this case, the time derivative of the function W defined by (7) along the positive solution of (13) satisfies

$$
\begin{aligned}
\frac{dW}{dt} &= \int_\Omega \nabla V(u).\big(-D(-\Delta)^s u + f(u) + g(u,u_t)\big)dx \\
&= \int_\Omega \nabla V(u).f(u)dx - \int_\Omega \nabla V(u).D(-\Delta)^s u\, dx + \int_\Omega \nabla V(u).g(u,u_t)dx.
\end{aligned}
$$

Therefore,

$$
\frac{dW}{dt} = \int_\Omega \nabla V(u).f(u)dx - \frac{C(n,s)}{2}\sum_{i=1}^{m} d_i \mathscr{I}_{u_i}(V,\Omega) + \int_\Omega \nabla V(u).g(u,u_t)dx.
$$

As in [7], the integrands of the first and second terms are already calculated. By means idea of Kajiwara et al. [20], the integrand of the third term can be modified to show the negativeness of the time derivative of a Lyapunov function for (13).

3. Classical Case

In this section, we will show that the method described in the previous section for anomalous diffusion modeled by the fractional Laplacian operator generalizes the one introduced in [7] for the classical reaction-diffusion system given by

$$
\begin{cases}
\dfrac{\partial u}{\partial t} & = D\Delta u + f(u) \quad in\, \Omega \times (0,+\infty), \\
\dfrac{\partial u}{\partial \nu} & = 0 \quad on\, \partial\Omega \times (0,+\infty), \\
u(x,0) & = u_0(x) \quad in\, \Omega.
\end{cases} \tag{14}
$$

First, by Proposition 4.4 in [16], we have that

$$\lim_{s\to 1^-} -(-\Delta)^s u = \Delta u,$$

and Proposition 5.1 in [17] gives

$$\lim_{s\to 1^-} \frac{C(n,s)}{2} \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(v(x)-v(y))(u(x)-u(y))}{|x-y|^{n+2s}}\,dxdy = \int_\Omega \nabla u.\nabla v.$$

Then

$$\lim_{s\to 1^-} \int_{\mathbb{R}^n\setminus\Omega} v\mathcal{N}_s u = \int_{\partial\Omega} v\frac{\partial u}{\partial \nu}.$$

Thus, the integration by parts formula presented in Lemma 3.3 of [17] becomes to the following famous Green's formula

$$\int_\Omega v\Delta u = -\int_\Omega \nabla u.\nabla v + \int_{\partial\Omega} v\frac{\partial u}{\partial \nu}.$$

By a similar computation, the condition (10) reduces to

$$\int_\Omega \nabla u_i.\nabla\left(\frac{\partial V}{\partial u_i}\right)dx \geq 0 \qquad \text{for all } i = 1,\dots,m. \tag{15}$$

We can now conclude that the diffusion system (2) with the fractional Laplacian operator is a general case of the classical diffusion system (14), i.e. when s tends to 1 ($s\to 1^-$), (2) reduces to (14), as well as our method generalizes the one of the system (14), even if we replace the (10) by (15). Therefore, we summarize this result in the following corollary.

Corollary 3.1. *Let V be a Lyapunov functional for ODE system* (1).

(i) *If the function V satisfies the condition* (15)*, then the function W defined by* (7) *is a Lyapunov functional for the reaction-diffusion system* (14).

(ii) *If the function V is of the form* (11) *or* (12)*, then W is a Lyapunov functional for the reaction-diffusion system* (14).

4. Applications

In this section, we apply our method to three biological examples.

Example 1: Like in [21], consider the following SIR epidemic model:

$$\begin{cases} \frac{dS}{dt} = \mu N - \mu S(t) - \beta S(t)I(t), \\ \frac{dI}{dt} = -(\mu+\nu)I(t) + \beta S(t)I(t), \\ \frac{dR}{dt} = \nu I(t) - \mu R(t), \end{cases} \tag{16}$$

where $S(t)$, $I(t)$ and $R(t)$ are the numbers of individual numbers who are susceptible, infectious and recovered, respectively with N is the total population. The parameters μ, ν and β denote the rates of natural death, recovery and transmission, respectively.

Since the state variable R does not appear in the two first equations of model (16), we can reduce (16) to the following system:

$$\begin{cases} \frac{dS}{dt} = \mu N - \mu S(t) - \beta S(t)I(t), \\ \frac{dI}{dt} = -(\mu+\nu)I(t) + \beta S(t)I(t). \end{cases} \tag{17}$$

To model the mobility of individuals, we propose the following fractional model

$$\begin{cases} \frac{\partial S}{\partial t} = -d_S(-\Delta)^s S(x,t) + \mu N - \mu S(x,t) - \beta S(x,t)I(x,t), \\ \frac{\partial I}{\partial t} = -d_I(-\Delta)^s I(x,t) - (\mu+\nu)I(x,t) + \beta S(x,t)I(x,t), \end{cases} \tag{18}$$

where $S(x,t)$ and $I(x,t)$ represent the numbers of susceptible and infectious individuals at location x and time t, respectively. The positive constants d_S and d_I denote the corresponding diffusion coefficients for these two classes of individuals. Here, we consider system (18) with non-local Neumann boundary conditions

$$\mathcal{N}_s S = \mathcal{N}_s I = 0, \quad \text{in } \mathbb{R}^n \setminus \overline{\Omega} \times (0,+\infty), \tag{19}$$

and initial conditions

$$S(x,0) \geq 0,\ I(x,0) \geq 0, \qquad \text{for all } x \in \Omega. \tag{20}$$

Obviously, $e^0 = (N,0)$ is a steady state called disease-free equilibrium, with the basic reproduction number

$$r_0 = \frac{N\beta}{\mu+\nu}.$$

Let $u = \begin{pmatrix} S \\ I \end{pmatrix}$, $f(u) = \begin{pmatrix} \mu N - \mu S - \beta SI \\ -(\mu+\nu)I + \beta SI \end{pmatrix}$ and define a Lyapunov functional for (17) as

$$V_1(u) = \frac{1}{2}\big(S-N\big)^2 + NI.$$

Hence,

$$\frac{dV_1(u(t))}{dt} = \nabla V_1(u).f(u) = -(\mu+\beta I)(S-N)^2 - N(\mu+\nu)(1-r_0)I. \tag{21}$$

If $r_0 < 1$, then $\nabla V_1(u).f(u) < 0$. Therefore, we construct the Lyapunov functional for fractional diffusion model (18) at e^0 as follows:

$$W_1 = \int_\Omega V_1(u(x,t))dx.$$

We have

$$\begin{aligned}
\mathscr{I}_S(V_1,\Omega) &= \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{\big(\frac{\partial V}{\partial S}(u(x,t)) - \frac{\partial V}{\partial S}(u(y,t))\big)\big(S(x,t)-S(y,t)\big)}{|x-y|^{n+2s}} dxdy \\
&= \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(S(x,t)-S(y,t))^2}{|x-y|^{n+2s}} dxdy \geq 0.
\end{aligned}$$

Since $\frac{\partial V}{\partial I} = N$, we get

$$\mathscr{I}_I(V_1,\Omega) = \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{\big(\frac{\partial V}{\partial I}(u(x,t)) - \frac{\partial V}{\partial I}(u(y,t))\big)\big(I(x,t)-I(y,t)\big)}{|x-y|^{n+2s}} dxdy = 0.$$

Therefore, V_1 satisfies the condition (10). By applying (i) of Theorem 2.1, we deduce that W_1 is a Lyapunov functional of reaction-diffusion (18) at the equilibrium point e^0.

Similarly to [21], system (17) has an epidemic equilibrium $e^* = (S^*, I^*)$, where $S^* = \frac{\mu+\nu}{\beta}$ and $I^* = \frac{\mu N}{\mu+\nu} - \frac{\mu}{\beta} = \frac{\mu}{\beta}(r_0 - 1)$.

For the epidemic equilibrium e^*, we define the following functionals

$$\begin{aligned}
V_2(u) &= \left(S - S^* - S^* \ln\frac{S}{S^*}\right) + \left(I - I^* - I^* \ln\frac{I}{I^*}\right), \\
W_2 &= \int_\Omega V_2(u(x,t))dx.
\end{aligned}$$

Since V_2 is of the form (11), it follows from (ii) of Theorem 2.1 that W_2 is a Lyapunov functional for the space fractional reaction-diffusion system (18) at the epidemic equilibrium e^*.

Example 2: Like in [15] and [22], consider the following model

$$\begin{cases} \frac{dS}{dt} &= A - dS(t) - \beta_1 S(t)N(t) - \beta_2 S(t)T(t), \\ \frac{dN}{dt} &= r_1\beta_1 S(t)N(t) - (d+\varepsilon_1)N(t), \\ \frac{dT}{dt} &= r_2\beta_2 S(t)T(t) - (d+\varepsilon_2)T(t) - \beta_3 T(t)V(t) - \beta_4 T(t)Z(t), \\ \frac{dV}{dt} &= B + r_3\beta_3 T(t)V(t) - (d+\varepsilon_3)V(t), \\ \frac{dZ}{dt} &= r_4\beta_4 T(t)Z(t) - (d+\varepsilon_4)Z(t), \end{cases} \tag{22}$$

where $S(t)$, $N(t)$, $T(t)$, $V(t)$ and $Z(t)$ are the concentrations of nutrient, normal cells, tumor cells, M1 virus and CTL cells at time t, respectively. The parameter A is the recruitment rate of nutrient. The parameter B is the recruitment rate of M1 virus which means the minimum effective dosage of medication. The factors $\beta_1 SN$ and $\beta_2 ST$ are the rates of consuming the nutrient by normal and tumor cells, respectively. $r_1\beta_1 SN$ and $r_2\beta_2 ST$ represent the growth rates of normal and tumor cells, respectively. The M1 virus infects and eradicates tumor cells at rate $\beta_3 TV$, while it reproduces at rate $r_3\beta_3 TV$. The constant d is the washout rate of nutrient and bacteria. The parameters ε_1, ε_2 and ε_3 are the natural death rates of normal cells, tumor cells and M1 virus, respectively. CTL immune cells destroy tumor cells at rate $\beta_4 TZ$, and they replicate at rate $r_4\beta_4 TZ$. While ε_4 represents the natural death rate of CTL cells.

By some biological considerations related to cancer treatment, it can be assumed that the diffusion of cells is abnormal, which corresponds to a fractional spatial spread modeled by the operator $(-\Delta)^s$ with $s \in (0,1)$. Thus, system (22) becomes

$$\begin{cases} \frac{\partial S}{\partial t} &= -D_S(-\Delta)^s S(x,t) + A - dS(x,t) - \beta_1 S(x,t)N(x,t) - \beta_2 S(x,t)T(x,t), \\ \frac{\partial N}{\partial t} &= -D_N(-\Delta)^s N(x,t) + r_1\beta_1 S(x,t)N(x,t) - (d+\varepsilon_1)N(x,t), \\ \frac{\partial T}{\partial t} &= -D_T(-\Delta)^s T(x,t) + r_2\beta_2 S(x,t)T(x,t) - (d+\varepsilon_2)T(x,t) \\ & -\beta_3 T(x,t)V(x,t) - \beta_4 T(x,t)Z(x,t), \\ \frac{\partial V}{\partial t} &= -D_V(-\Delta)^s V(x,t) + B + r_3\beta_3 T(x,t)V(x,t) - (d+\varepsilon_3)V(x,t), \\ \frac{\partial Z}{\partial t} &= -D_Z(-\Delta)^s Z(x,t) + r_4\beta_4 T(x,t)Z(x,t) - (d+\varepsilon_4)Z(x,t), \end{cases} \tag{23}$$

where $S(x,t)$, $N(x,t)$, $T(x,t)$, $V(x,t)$ and $Z(x,t)$ are the concentrations of nutrient, normal cells, tumor cells, M1 virus and CTL cells at position x and time t, respectively. The parameters D_S, D_N, D_T, D_V and D_Z are the diffusion coefficients for nutrient, normal cells, tumor cells, M1 virus and CTL cells, respectively. The initial conditions are given by

$$S(x,0)\geq 0,\ N(x,0)\geq 0,\ T(x,0)\geq 0, V(x,0)\geq 0,\ Z(x,0)\geq 0,\ x\in\overline{\Omega}, \tag{24}$$

and the nonlocal Neumann conditions are

$$\mathcal{N}_s S=\mathcal{N}_s N=\mathcal{N}_s T=\mathcal{N}_s V=\mathcal{N}_s Z=0, \quad \text{in } \mathbb{R}^n\setminus\overline{\Omega}\times(0,+\infty). \tag{25}$$

Let

$$\begin{aligned}
a_1 &= \beta_3(r_3\beta_3 d+\beta_2(d+\varepsilon_3)),\\
a_2 &= \frac{a_1}{\beta_3}(d+\varepsilon_2)-\beta_2\beta_3(B+r_2r_3A),\\
a_3 &= -B\beta_2(d+\varepsilon_2),\\
\delta &= a_2^2-4a_1a_3,
\end{aligned}$$

and

$$\mathscr{A}_1=\frac{Ar_1\beta_1}{d(d+\varepsilon_1)},\qquad \mathscr{A}_2=\frac{Ar_2\beta_2}{d(d+\varepsilon_2)},\qquad \textit{and}\qquad \mathscr{A}_3=\frac{r_4\beta_4(d+\varepsilon_3)}{r_3\beta_3(d+\varepsilon_4)}.$$

Similarly to [15], we have the following results:

(i) System (23) has a steady state called a competition-free equilibrium $E_0(S_0,0,0,V_0,0)$, where $S_0=\frac{A}{d}$ and $V_0=\frac{B}{d+\varepsilon_3}$.

(ii) When $\mathscr{A}_1>1$, system (23) has a steady state called tumor-free equilibrium $E_1(S_1,N_1,0,V_1,0)$, where $S_1=\frac{d+\varepsilon_1}{r_1\beta_1}$, $N_1=\frac{d}{\beta_1}(\mathscr{A}_1-1)$ and $V_1=\frac{B}{d+\varepsilon_3}$.

(iii) When $\mathscr{A}_2>1+\frac{B\beta_3}{(d+\varepsilon_2)(d+\varepsilon_3)}$, system (23) has another equilibrium called the treatment failure immune-free equilibrium $E_2(S_2,0,T_2,V_2,0)$, where $S_2=\frac{\beta_3V_2+d+\varepsilon_2}{r_2\beta_2}$, $T_2=\frac{-d}{\beta_2}+\frac{Ar_2}{\beta_3V_2+d+\varepsilon_2}$ and $V_2=\frac{-a_2+\sqrt{\delta}}{2a_1}$.

(iv) When $\mathscr{A}_2>\mathscr{A}_1+\frac{ABr_1\beta_1\beta_3}{d(d+\varepsilon_3)(d+\varepsilon_2)(d+\varepsilon_1)}$ and $\mathscr{A}_1+\frac{B\beta_2}{r_3d(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)}>1+\frac{\beta_2(d+\varepsilon_3)}{r_3\beta_3 d}$, system (23) has a steady state called a partial success immune-free equilibrium $E_3(S_3,N_3,T_3,V_3,0)$ where $S_3=\frac{d+\varepsilon_1}{r_1\beta_1}$, $N_3=\frac{Ar_1r_3\beta_1\beta_3-r_3\beta_3d(d+\varepsilon_1)-\beta_2(d+\varepsilon_1)(d+\varepsilon_3)}{r_3\beta_1\beta_3(d+\varepsilon_1)}+\frac{B\beta_2}{r_3\beta_1(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)}$, $T_3=\frac{-B+(d+\varepsilon_3)V_3}{r_3\beta_3V_3}$, and $V_3=\frac{d+\varepsilon_2}{\beta_3}(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)$.

(v) When $\mathscr{A}_3>1$ and $\mathscr{A}_2>1+\frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4d}+\frac{B(\beta_2(d+\varepsilon_4)+r_4\beta_4d)}{r_3d(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)}$, system (23) has an equilibrium point called a treatment failure equilibrium $E_4(S_4,0,T_4,V_4,Z_4)$ defined by

$S_4 = \frac{Ar_4\beta_4}{\beta_2(d+\varepsilon_4)+r_4\beta_4 d}$, $T_4 = \frac{d+\varepsilon_4}{r_4\beta_4}$, $V_4 = \frac{Br_4\beta_4}{r_3\beta_3(d+\varepsilon_4)(A_3-1)}$ and
$Z_4 = \frac{Ar_2\beta_2 r_3\beta_3 r_4\beta_4(d+\varepsilon_4)(\mathscr{A}_3-1)-(\beta_2(d+\varepsilon_4)+r_4\beta_4 d)(r_3\beta_3(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)+B\beta_3 r_4\beta_4)}{r_3\beta_3\beta_4(\beta_2(d+\varepsilon_4)+r_4\beta_4 d)(d+\varepsilon_4)(\mathscr{A}_3-1)}$.

(vi) When $\mathscr{A}_3 > 1$, $\mathscr{A}_1 > 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d}$ and $\mathscr{A}_2 > \mathscr{A}_1 + \frac{ABr_1\beta_1 r_4\beta_4}{r_3 d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)}$, system (23) has a steady state called a coexistence equilibrium $E_5(S_5,N_5,T_5,V_5,Z_5)$ where $S_5 = \frac{d+\varepsilon_1}{r_1\beta_1}$, $T_5 = \frac{d+\varepsilon_4}{r_4\beta_4}$, $N_5 = \frac{Ar_1\beta_1 r_4\beta_4-(\beta_2(d+\varepsilon_4)+r_4\beta_4 d)(d+\varepsilon_1)}{\beta_1 r_4\beta_4(d+\varepsilon_1)}$, $V_5 = \frac{Br_4\beta_4}{r_3\beta_3(d+\varepsilon_4)(\mathscr{A}_3-1)}$
and $Z_5 = \frac{r_3(r_2\beta_2(d+\varepsilon_1)-r_1\beta_1(d+\varepsilon_2))(d+\varepsilon_4)(\mathscr{A}_3-1)-Br_1\beta_1 r_4\beta_4}{r_1\beta_1 r_3\beta_4(d+\varepsilon_4)(\mathscr{A}_3-1)}$.

Let $u = \begin{pmatrix} S \\ N \\ T \\ V \\ Z \end{pmatrix}$ and $f(u) = \begin{pmatrix} A - dS - \beta_1 SN - \beta_2 ST \\ r_1\beta_1 SN - (d+\varepsilon_1)N \\ r_2\beta_2 ST - (d+\varepsilon_2)T - \beta_3 TV - \beta_4 TZ \\ B + r_3\beta_3 TV - (d+\varepsilon_3)V \\ r_4\beta_4 TZ - (d+\varepsilon_4)Z \end{pmatrix}$.

1) For E_0, consider the following functional

$$L_0(u) = S_0\phi\left(\frac{S}{S_0}\right) + \frac{1}{r_1}N + \frac{1}{r_2}T + \frac{1}{r_2 r_3}V_0\phi\left(\frac{V}{V_0}\right) + \frac{1}{r_2 r_4}Z,$$

where $\phi(z) = z - \ln(z) - 1$ for $z > 0$. L_0 is non-negative. In fact, the strict global minimum of ϕ attained at $x = 1$ and $\phi(1) = 0$. Further, we have

$$\begin{aligned} \frac{dL_0}{dt} &= \nabla L_0(u).f(u) \\ &= \frac{-d}{S}(S-S_0)^2 + \frac{d+\varepsilon_1}{r_1}(\mathscr{A}_1 - 1)N - \frac{d+\varepsilon_4}{r_2 r_4}Z \\ &\quad + \frac{d+\varepsilon_2}{r_2}\left(\mathscr{A}_2 - 1 - \frac{B\beta_3}{(d+\varepsilon_2)(d+\varepsilon_3)}\right)T - \frac{d+\varepsilon_3}{r_2 r_3}\frac{(V-V_0)^2}{V}. \end{aligned}$$

If $\mathscr{A}_2 \le 1 + \frac{B\beta_3}{(d+\varepsilon_2)(d+\varepsilon_3)}$ and $\mathscr{A}_1 \le 1$, then $\frac{dL_0}{dt} \le 0$, and from LaSalle's invariance principle [23], E_0 is globally asymptotically stable for ODE model (22) when $\mathscr{A}_2 \le 1 + \frac{B\beta_3}{(d+\varepsilon_2)(d+\varepsilon_3)}$ and $\mathscr{A}_1 \le 1$. Then we construct the Lyapunov functional at E_0 for fractional diffusion model (23) as follows

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

We have

$$\begin{aligned}
\mathscr{I}_S(L_0,\Omega) &= S_0\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(S(x,t)-S(y,t))^2}{S(x,t)S(y,t)|x-y|^{n+2s}}\,dxdy \geq 0,\\
\mathscr{I}_N(L_0,\Omega) &= 0,\\
\mathscr{I}_T(L_0,\Omega) &= 0,\\
\mathscr{I}_V(L_0,\Omega) &= \frac{V_0}{r_2r_3}\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(V(x,t)-V(y,t))^2}{V(x,t)V(y,t)|x-y|^{n+2s}}\,dxdy \geq 0\\
\mathscr{I}_Z(L_0,\Omega) &= 0.
\end{aligned}$$

Hence, the condition (10) is satisfied and $\mathscr{L}_0$ is a Lyapunov functional for model (23) at E_0 when $\mathscr{A}_2 \leq 1+\frac{B\beta_3}{(d+\varepsilon_2)(d+\varepsilon_3)}$ and $\mathscr{A}_1 \leq 1$.

2) For the tumor-free equilibrium E_1, consider the functional

$$L_1(u) = S_1\phi\left(\frac{S}{S_1}\right)+\frac{1}{r_1}N_1\phi\left(\frac{N}{N_1}\right)+\frac{1}{r_2}T+\frac{1}{r_2r_3}V_1\phi\left(\frac{V}{V_1}\right)+\frac{1}{r_2r_4}Z.$$

We have

$$\begin{aligned}
\nabla L_1(u).f(u) &= -(d+\beta_1N_1)\frac{(S-S_1)^2}{S}-\frac{B}{r_2r_3}\frac{(V-V_1)^2}{VV_1}-\frac{d+\varepsilon_4}{r_2r_4}Z\\
&\quad +\frac{d(d+\varepsilon_1)(d+\varepsilon_2)}{Ar_1r_2\beta_1}\left(\mathscr{A}_2-\mathscr{A}_1-\frac{ABr_1\beta_1\beta_3}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}\right)T.
\end{aligned}$$

Then $\nabla L_1(u).f(u) \leq 0$ when $\mathscr{A}_2 \leq \mathscr{A}_1+\frac{ABr_1\beta_1\beta_3}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$.

Let

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

Obviously, we get

$$\begin{aligned}
\mathscr{I}_S(L_1,\Omega) &= S_1\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(S(x,t)-S(y,t))^2}{S(x,t)S(y,t)|x-y|^{n+2s}}\,dxdy \geq 0,\\
\mathscr{I}_N(L_1,\Omega) &= \frac{N_1}{r_1}\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(N(x,t)-N(y,t))^2}{N(x,t)N(y,t)|x-y|^{n+2s}}\,dxdy \geq 0,\\
\mathscr{I}_T(L_1,\Omega) &= 0,\\
\mathscr{I}_V(L_1,\Omega) &= \frac{V_1}{r_2r_3}\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(V(x,t)-V(y,t))^2}{V(x,t)V(y,t)|x-y|^{n+2s}}\,dxdy \geq 0,\\
\mathscr{I}_Z(L_1,\Omega) &= 0.
\end{aligned}$$

Thus, the condition (10) is satisfied and $\mathscr{L}_1$ is a Lyapunov functional for the diffusion model (23) at E_1 when $\mathscr{A}_2 \leq \mathscr{A}_1 + \frac{ABr_1\beta_1\beta_3}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$.

3) For the equilibrium E_2, consider the functional

$$L_2(u) = S_2\phi\left(\frac{S}{S_2}\right) + \frac{1}{r_1}N + \frac{1}{r_2}T_2\phi\left(\frac{T}{T_2}\right) + \frac{1}{r_2r_3}V_2\phi\left(\frac{V}{V_2}\right) + \frac{1}{r_2r_4}Z.$$

We have

$$\nabla L_2(u).f(u) = -(d+\beta_2T_2)\frac{(S-S_2)^2}{S} - \frac{B}{r_2r_3}\frac{(V-V_2)^2}{VV_2} - \beta_1(\frac{d+\varepsilon_1}{r_1\beta_1} - S_2)N - \frac{\beta_4}{r_2}(\frac{d+\varepsilon_4}{r_4\beta_4} - T_2)Z.$$

Since

$$\frac{d+\varepsilon_4}{r_4\beta_4} - T_2 = 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d} + \frac{B(\beta_2(d+\varepsilon_4)+r_4\beta_4 d)}{r_3d(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)} - \mathscr{A}_2,$$

and

$$\frac{d+\varepsilon_1}{r_1\beta_1} - S_2 = 1 + \frac{\beta_2(d+\varepsilon_3)}{r_3\beta_3 d} - \mathscr{A}_1 - \frac{B\beta_2}{r_3d(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)},$$

we deduce that L_2 is a Lyapunov functional for ODE model (22) at E_2 when $1 + \frac{\beta_2(d+\varepsilon_3)}{r_3\beta_3 d} \geq \mathscr{A}_1 + \frac{B\beta_2}{r_3d(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)}$ and $\mathscr{A}_2 \leq 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d} + \frac{B(\beta_2(d+\varepsilon_4)+r_4\beta_4 d)}{r_3d(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)}$.

Denote

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

We have

$$\begin{aligned}
\mathscr{I}_S(L_2,\Omega) &= S_2\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(S(x,t)-S(y,t))^2}{S(x,t)S(y,t)|x-y|^{n+2s}}\,dxdy \geq 0,\\
\mathscr{I}_N(L_2,\Omega) &= 0,\\
\mathscr{I}_T(L_2,\Omega) &= \frac{T_2}{r_2}\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(T(x,t)-T(y,t))^2}{T(x,t)T(y,t)|x-y|^{n+2s}}\,dxdy \geq 0,\\
\mathscr{I}_V(L_2,\Omega) &= \frac{V_2}{r_2r_3}\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(V(x,t)-V(y,t))^2}{V(x,t)V(y,t)|x-y|^{n+2s}}\,dxdy \geq 0,\\
\mathscr{I}_Z(L_2,\Omega) &= 0.
\end{aligned}$$

Then $\mathscr{L}_2$ is a Lyapunov functional for (23) at E_2 when $1 + \frac{\beta_2(d+\varepsilon_3)}{r_3\beta_3 d} \geq \mathscr{A}_1 + \frac{B\beta_2}{r_3d(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)}$ and $\mathscr{A}_2 \leq 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d} + \frac{B(\beta_2(d+\varepsilon_4)+r_4\beta_4 d)}{r_3d(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)}$.

4) For E_3, consider the functional

$$L_3(u) = S_3\phi\left(\frac{S}{S_3}\right) + \frac{1}{r_1}N_3\phi\left(\frac{N}{N_3}\right) + \frac{1}{r_2}T_3\phi\left(\frac{T}{T_3}\right) + \frac{1}{r_2r_3}V_3\phi\left(\frac{V}{V_3}\right) + \frac{1}{r_2r_4}Z.$$

We have

$$\nabla L_3(u).f(u) = -(d+\beta_2T_3+\beta_1N_3)\frac{(S-S_3)^2}{S} - \frac{B}{r_2r_3}\frac{(V-V_3)^2}{VV_3} - \frac{\beta_4}{r_2}(\frac{d+\varepsilon_4}{r_4\beta_4} - T_3)Z.$$

Since

$$\begin{aligned}\frac{d+\varepsilon_4}{r_4\beta_4} - T_3 &= \frac{((d+\varepsilon_4)r_3\beta_3 - r_4\beta_4(d+\varepsilon_3))V_3 + Br_4\beta_4}{r_3\beta_3r_4\beta_4}\\ &= \frac{d(d+\varepsilon_1)(d+\varepsilon_4)(1-\mathscr{A}_3)}{Ar_1\beta_1r_4\beta_4(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)}\left(\mathscr{A}_2 - \mathscr{A}_1 + \frac{ABr_1\beta_1r_4\beta_4}{r_3d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_4)(1-\mathscr{A}_3)}\right),\end{aligned}$$

we deduce that L_3 is a Lyapunov functional for ODE model (22) at E_3 when $\frac{\mathscr{A}_2}{\mathscr{A}_1} > 1$, $\mathscr{A}_3 > 1$, $\mathscr{A}_2 > \mathscr{A}_1 + \frac{ABr_1\beta_1\beta_3}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$ and $\mathscr{A}_1 + \frac{B\beta_2}{r_3d(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)} > 1 + \frac{\beta_2(d+\varepsilon_3)}{r_3\beta_3d}$.
Let

$$\mathscr{L}_3 = \int_\Omega L_3(x,t)dx.$$

We get

$$\begin{aligned}\mathscr{I}_S(L_3,\Omega) &= S_3\int_{\mathbb{R}^{2n}_{\Omega^2}}\frac{(S(x,t)-S(y,t))^2}{S(x,t)S(y,t)|x-y|^{n+2s}}dxdy \geq 0,\\ \mathscr{I}_N(L_3,\Omega) &= \frac{N_3}{r_1}\int_{\mathbb{R}^{2n}_{\Omega^2}}\frac{(N(x,t)-N(y,t))^2}{N(x,t)N(y,t)|x-y|^{n+2s}}dxdy \geq 0,\\ \mathscr{I}_T(L_3,\Omega) &= \frac{T_3}{r_2}\int_{\mathbb{R}^{2n}_{\Omega^2}}\frac{(T(x,t)-T(y,t))^2}{T(x,t)T(y,t)|x-y|^{n+2s}}dxdy \geq 0,\\ \mathscr{I}_V(L_3,\Omega) &= \frac{V_3}{r_2r_3}\int_{\mathbb{R}^{2n}_{\Omega^2}}\frac{(V(x,t)-V(y,t))^2}{V(x,t)V(y,t)|x-y|^{n+2s}}dxdy \geq 0,\\ \mathscr{I}_Z(L_3,\Omega) &= 0.\end{aligned}$$

Hence, the condition (10) is satisfied and $\mathscr{L}_3$ is a Lyapunov functional for model (23) at E_3 when $\frac{\mathscr{A}_2}{\mathscr{A}_1} > 1$, $\mathscr{A}_3 > 1$, $\mathscr{A}_2 > \mathscr{A}_1 + \frac{ABr_1\beta_1\beta_3}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$ and $\mathscr{A}_1 + \frac{B\beta_2}{r_3d(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)} > 1 + \frac{\beta_2(d+\varepsilon_3)}{r_3\beta_3d}$.

5) For the treatment failure equilibrium E_4, consider the functional

$$L_4(u) = S_4\phi\left(\frac{S}{S_4}\right) + \frac{1}{r_1}N + \frac{1}{r_2}T_4\phi\left(\frac{T}{T_4}\right) + \frac{1}{r_2r_3}V_4\phi\left(\frac{V}{V_4}\right) + \frac{1}{r_2r_4}Z_4\phi\left(\frac{Z}{Z_4}\right).$$

We have

$$
\begin{aligned}
\nabla L_4(u).f(u) &= \frac{d}{S}(2S_4S - S^2 - S_4^2) + \beta_2 T_4(2S_4 - \frac{S_4^2}{S} - S) \\
&\quad + (\beta_1 S_4 - \frac{d+\varepsilon_1}{r_1})N + \frac{B}{r_2 r_3}(2 - \frac{V_4}{V} - \frac{V}{V_4}) \\
&= -(d+\beta_2 T_4)\frac{(S-S_4)^2}{S} + \beta_1(S_4 - \frac{d+\varepsilon_1}{r_1\beta_1})N - \frac{B}{r_2 r_3}\frac{(V-V_4)^2}{VV_4}.
\end{aligned}
$$

Since

$$
\begin{aligned}
S_4 - \frac{d+\varepsilon_1}{r_1\beta_1} &= \frac{Ar_1\beta_1 r_4\beta_4 - (d+\varepsilon_1)(\beta_2(d+\varepsilon_4) + r_4\beta_4 d)}{r_1\beta_1(\beta_2(d+\varepsilon_4) + r_4\beta_4 d)} \\
&= \frac{r_4\beta_4 d(d+\varepsilon_1)}{r_1\beta_1(\beta_2(d+\varepsilon_4) + r_4\beta_4 d)}(\mathscr{A}_1 - 1 - \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d}).
\end{aligned}
$$

Then $\nabla L_4(u).f(u) \geq 0$ when $\mathscr{A}_1 \leq 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d}$. Consider the functional

$$
\mathscr{L}_4 = \int_\Omega L_4(x,t)dx.
$$

We have

$$
\begin{aligned}
\mathscr{I}_S(L_4,\Omega) &= S_4 \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(S(x,t)-S(y,t))^2}{S(x,t)S(y,t)|x-y|^{n+2s}}\,dxdy \geq 0, \\
\mathscr{I}_N(L_4,\Omega) &= 0, \\
\mathscr{I}_T(L_4,\Omega) &= \frac{T_4}{r_2}\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(T(x,t)-T(y,t))^2}{T(x,t)T(y,t)|x-y|^{n+2s}}\,dxdy \geq 0, \\
\mathscr{I}_V(L_4,\Omega) &= \frac{V_4}{r_2 r_3}\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(V(x,t)-V(y,t))^2}{V(x,t)V(y,t)|x-y|^{n+2s}}\,dxdy \geq 0, \\
\mathscr{I}_Z(L_4,\Omega) &= \frac{Z_4}{r_2 r_4}\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(Z(x,t)-Z(y,t))^2}{Z(x,t)Z(y,t)|x-y|^{n+2s}}\,dxdy \geq 0.
\end{aligned}
$$

Then $\mathscr{L}_4$ is a Lyapunov functional for (23) at E_4 when $\mathscr{A}_1 \leq 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d}$.

6) For the equilibrium E_5 let the functional

$$
L_5(u) = S_5\phi\left(\frac{S}{S_5}\right) + \frac{1}{r_1}N_5\phi\left(\frac{N}{N_5}\right) + \frac{1}{r_2}T_5\phi\left(\frac{T}{T_5}\right) + \frac{1}{r_2 r_3}V_5\phi\left(\frac{V}{V_5}\right) + \frac{1}{r_2 r_4}Z_5\phi\left(\frac{Z}{Z_5}\right).
$$

We have

$$
\nabla L_5(u).f(u) = -(d+\beta_1 N_5 + \beta_2 T_5)\frac{(S-S_5)^2}{S} - \frac{B}{r_2 r_3}\frac{(V-V_5)^2}{VV_5}.
$$

Then $\nabla L_5(u).f(u) \leq 0$ when $\mathscr{A}_3 > 1$, $\mathscr{A}_1 > 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d}$ and $\mathscr{A}_2 > \mathscr{A}_1 + \frac{ABr_1\beta_1 r_4\beta_4}{r_3 d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)}$.

Let

$$\mathscr{L}_5 = \int_\Omega L_5(x,t)dx.$$

We have

$$\begin{aligned}
\mathscr{I}_S(L_5,\Omega) &= S_5 \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(S(x,t)-S(y,t))^2}{S(x,t)S(y,t)|x-y|^{n+2s}}\,dxdy \geq 0 \\
\mathscr{I}_N(L_5,\Omega) &= \frac{N_5}{r_1} \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(N(x,t)-N(y,t))^2}{N(x,t)N(y,t)|x-y|^{n+2s}}\,dxdy \geq 0, \\
\mathscr{I}_T(L_5,\Omega) &= \frac{T_5}{r_2} \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(T(x,t)-T(y,t))^2}{T(x,t)T(y,t)|x-y|^{n+2s}}\,dxdy \geq 0, \\
\mathscr{I}_V(L_5,\Omega) &= \frac{V_5}{r_2 r_3} \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(V(x,t)-V(y,t))^2}{V(x,t)V(y,t)|x-y|^{n+2s}}\,dxdy \geq 0, \\
\mathscr{I}_Z(L_5,\Omega) &= \frac{Z_5}{r_2 r_4} \int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{(Z(x,t)-Z(y,t))^2}{Z(x,t)Z(y,t)|x-y|^{n+2s}}\,dxdy \geq 0.
\end{aligned}$$

Thus, the condition (10) is satisfied and $\mathscr{L}_5$ is a Lyapunov functional for model (23) at E_5 when $\mathscr{A}_3 > 1$, $\mathscr{A}_1 > 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d}$ and $\mathscr{A}_2 > \mathscr{A}_1 + \frac{ABr_1\beta_1 r_4\beta_4}{r_3 d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)}$.

We summarize the study of this system in following results.

(i) When $\mathscr{A}_2 \leq 1 + \frac{B\beta_3}{(d+\varepsilon_2)(d+\varepsilon_3)}$ and $\mathscr{A}_1 \leq 1$, the equilibrium E_0 of model (23) is globally asymptotically stable.

(ii) Assume that $\mathscr{A}_1 > 1$. When $\mathscr{A}_2 \leq \mathscr{A}_1 + \frac{ABr_1\beta_1\beta_3}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$, the equilibrium E_1 of model (23) with non-trivial initial functions is globally asymptotically stable.

(iii) Assume that $\mathscr{A}_2 > 1 + \frac{B\beta_3}{(d+\varepsilon_2)(d+\varepsilon_3)}$, $\frac{\mathscr{A}_2}{\mathscr{A}_1} > 1$ and $\mathscr{A}_3 > 1$. Then the treatment failure immune-free equilibrium E_2 of system (23) is globally asymptotically stable if $1 + \frac{\beta_2(d+\varepsilon_3)}{r_3\beta_3 d} \geq \mathscr{A}_1 + \frac{B\beta_2}{r_3 d(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)}$ and $\mathscr{A}_2 \leq 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d} + \frac{B(\beta_2(d+\varepsilon_4)+r_4\beta_4 d)}{r_3 d(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)}$.

(iv) Suppose that $\frac{\mathscr{A}_2}{\mathscr{A}_1} > 1$, $\mathscr{A}_3 > 1$, $\mathscr{A}_2 > \mathscr{A}_1 + \frac{ABr_1\beta_1\beta_3}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$ and $\mathscr{A}_1 + \frac{B\beta_2}{r_3 d(d+\varepsilon_2)(\frac{\mathscr{A}_2}{\mathscr{A}_1}-1)} > 1 + \frac{\beta_2(d+\varepsilon_3)}{r_3\beta_3 d}$. Then, the partial success immune-free equilibrium E_3 of model (23) is globally asymptotically stable if $\mathscr{A}_2 \leq \mathscr{A}_1 - \frac{ABr_1\beta_1 r_4\beta_4}{r_3 d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_4)(1-\mathscr{A}_3)}$.

(v) Assume that $\mathscr{A}_3 > 1$ and $\mathscr{A}_2 > 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d} + \frac{B(\beta_2(d+\varepsilon_4)+r_4\beta_4 d)}{r_3 d(d+\varepsilon_2)(d+\varepsilon_4)(A_3-1)}$. Then the treatment failure equilibrium E_4 of model (23) is globally asymptotically stable if $\mathscr{A}_1 \leq 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d}$.

(vi) When $\mathscr{A}_3 > 1$, $\mathscr{A}_1 > 1 + \frac{\beta_2(d+\varepsilon_4)}{r_4\beta_4 d}$ and $\mathscr{A}_2 > \mathscr{A}_1 + \frac{ABr_1\beta_1 r_4\beta_4}{r_3 d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_4)(\mathscr{A}_3-1)}$, the coexistence equilibrium E_5 for system (23) is globally asymptotically stable.

Example 3: Consider the following delayed SIR model with Hattaf-Yousfi functional response like in [24] given by

$$\begin{cases} \frac{dS}{dt} = A - \mu S(t) - \frac{\beta S(t)I(t)}{\alpha_0+\alpha_1 S(t)+\alpha_2 I(t)+\alpha_3 S(t)I(t)}, \\ \frac{dI}{dt} = \frac{\beta S(t-\tau)I(t-\tau)e^{-\mu\tau}}{\alpha_0+\alpha_1 S(t-\tau)+\alpha_2 I(t-\tau)+\alpha_3 S(t-\tau)I(t-\tau)} - (\mu+\nu+d)I(t), \\ \frac{dR}{dt} = \nu I(t) - \mu R(t), \end{cases} \tag{26}$$

where $S(t), I(t)$, and $R(t)$ are the populations of susceptible, infected, and recovered individuals, respectively. The parameters A, μ, d, and ν are respectively, the recruitment rate, the natural death rate, the death rate due to disease, and the recovery rate. The non-negative constants $\alpha_i, i = 0,1,2,3$, measure the saturation, inhibitory, or psychological effects, and the positive constant β is the infection rate.

Since the state variable R does not appear in the two first equations of model (26), we can reduce (26) to the following system:

$$\begin{cases} \frac{dS}{dt} = A - \mu S(t) - \frac{\beta S(t)I(t)}{\alpha_0+\alpha_1 S(t)+\alpha_2 I(t)+\alpha_3 S(t)I(t)}, \\ \frac{dI}{dt} = \frac{\beta S(t-\tau)I(t-\tau)e^{-\mu\tau}}{\alpha_0+\alpha_1 S(t-\tau)+\alpha_2 I(t-\tau)+\alpha_3 S(t-\tau)I(t-\tau)} - (\mu+\nu+d)I(t). \end{cases} \tag{27}$$

To model the mobility of people within a country or even worldwide like in Example 1, we propose the following model

$$\begin{cases} \frac{\partial S}{\partial t} = -d_S(-\Delta)^s S(x,t) + A - \mu S(x,t) - \psi\big(S(x,t), I(x,t)\big)I(x,t), \\ \frac{\partial I}{\partial t} = -d_I(-\Delta)^s I(x,t) + \psi\big(S(x,t-\tau), I(x,t-\tau)\big)I(x,t-\tau)e^{-\mu\tau} - \eta I(x,t), \end{cases} \tag{28}$$

where $\psi(S,I) = \dfrac{\beta S}{\alpha_0+\alpha_1 S+\alpha_2 I+\alpha_3 SI}$ and $\eta = \mu+\nu+d$. Constants d_S and d_I are the diffusion coefficients for the susceptible and infected individuals. We consider model (28) with non-local Neumann boundary conditions:

$$\mathscr{N}_s S = \mathscr{N}_s I = 0, \quad \text{in } \mathbb{R}^n \setminus \overline{\Omega} \times (0,+\infty), \tag{29}$$

and initial conditions

$$S(x,\theta) = S_0(x,\theta) \geq 0,\ I(x,\theta) = I_0(x,\theta) \geq 0, \text{ in } \Omega \times [-\tau, 0]. \tag{30}$$

Similarly to [25], we can prove that system (28) has always an disease-free equilibrium point $E_f = (S^0, 0)$ with $S^0 = \frac{A}{\mu}$ and the basic reproduction number

$$R_0 = \frac{\psi(\frac{A}{\mu}, 0)e^{-\mu\tau}}{\eta},$$

and if $R_0 > 1$, then the system (28) has a unique endemic equilibrium $E^*(S^*, I^*)$ with $S^* \in \left(0, \frac{A}{\mu}\right)$ and $I^* > 0$.

For E_f, consider the following functional

$$V(u) = S - S^0 - \int_{S^0}^{S} \frac{\psi(S^0, 0)}{\psi(X, 0)} dX + e^{\mu\tau} I + \int_{t-\tau}^{t} \psi\big(S(\theta), I(\theta)\big) I(\theta) d\theta,$$

where $u = (S, I)$. Calculating the time derivative of V along the positive solution of system (27) as in [25] gives

$$\begin{aligned}
\frac{dV}{dt} =& \mu S^0 \left(1 - \frac{S}{S^0}\right)\left(1 - \frac{\psi(S^0, 0)}{\psi(S, 0)}\right) + \eta e^{\mu\tau} I \left(\frac{\psi(S, I)}{\psi(S, 0)} R_0 - 1\right) \\
\leq& \mu S^0 \left(1 - \frac{S}{S^0}\right)\left(1 - \frac{\psi(S^0, 0)}{\psi(S, 0)}\right) + \eta e^{\mu\tau} I (R_0 - 1).
\end{aligned}$$

Then $\frac{dV}{dt} \leq 0$ when $R_0 \leq 1$. Therefore, we construct the Lyapunov functional for fractional diffusion model (28) at E_f as follows:

$$W = \int_\Omega V(u(x,t)) dx.$$

We have

$$\begin{aligned}
\frac{dW}{dt} =& \int_\Omega \left\{ \mu S^0 \left(1 - \frac{S}{S^0}\right)\left(1 - \frac{\psi(S^0, 0)}{\psi(S, 0)}\right) + \eta e^{\mu\tau} I \left(\frac{\psi(S, I)}{\psi(S, 0)} R_0 - 1\right) \right\} dx \\
& - \int_\Omega d_S \left(1 - \frac{\psi(S^0, 0)}{\psi(S(x,t), 0)}\right) (-\Delta)^s S(x,t) dx - \int_\Omega d_I e^{\mu\tau} (-\Delta)^s I(x,t) dx.
\end{aligned}$$

Since $\int_\Omega e^{\mu\tau}(-\Delta)^s I(x,t)dx = 0$ and the function $S \mapsto \psi(S,0)$ is non-negative, increasing on $\mathbb{R}_+$, we have

$$\begin{aligned}
&\int_\Omega \left(1 - \frac{\psi(S^0,0)}{\psi(S(x,t),0)}\right)(-\Delta)^s S(x,t)dx \\
&= \psi(S^0,0)\int_{\mathbb{R}^{2n}_{\Omega^2}} \frac{\psi(S(x,t),0)-\psi(S(y,t),0)}{S(x,t)-S(y,t)} \frac{(S(x,t)-S(y,t))^2}{\psi(S(x,t),0)\psi(S(y,t),0)|x-y|^{n+2s}}dxdy \\
&\geq 0.
\end{aligned}$$

Therefore, $\frac{dW}{dt} \leq 0$ when $R_0 \leq 1$. Then W is a Lyapunov functional for system (28) at equilibrium E_f, which implies that E_f is globally asymptotically stable when $R_0 \leq 1$.

Similarly to the above and based on the results in [25], we can easily construct a Lyaponuv functional to prove that endemic equilibrium E^* is globally asymptotically stable when $R_0 > 1$.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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