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Spatiotemporal dynamics of RNA viruses in the presence of immunity and treatment: case of SARS-CoV-2

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In this paper, we develop a mathematical model using partial differential equations to investigate the behavior of RNA viruses in the presence of antiviral treatment. The developed model includes both cell-to-cell and virus-to-cell modes of transmission. Initially, we establish the well-posedness of the model by demonstrating the existence and uniqueness of solutions, as well as their positivity and boundedness. Additionally, we identify and analyze the stable equilibrium states, their global stability depending on specific threshold parameters, using Lyapunov functions. To corroborate our theoretical findings, we provide illustrations through numerical simulations.

Keywords: *reaction–diffusion; RNA viruses; modes of transmission; mathematical modeling; stability analysis.*

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1. Introduction

Coronavirus disease 2019 (COVID-19) resulted from an infection with the SARS-CoV-2 virus. This pandemic has profoundly affected public health, the global economy, and our daily routines. The SARS-CoV-2 virus is part of the RNA virus family, known for causing various infectious diseases such as hepatitis C that is an infection caused by the hepatitis C virus (HCV). On a global scale, roughly 58 million individuals suffer from a chronic HCV infection, with approximately 1.5 million new cases emerging annually [1]. There are about 3.2 million young individuals and children living with a chronic HCV infection [1]. According to the World Health Organization (WHO) [1], in 2019, an estimated 290 000 lives were lost due to hepatitis C, primarily attributed to conditions like cirrhosis and hepatocellular carcinoma, the most common form of liver cancer. The human immunodeficiency virus (HIV) is classified as an RNA virus as well. It continues to be a significant global public health concern, having resulted in the loss of approximately 40.4 million lives thus far, with ongoing transmission occurring in all countries worldwide [2]. As of the end of 2022, it is estimated that there were around 39 million individuals living with HIV, with two-thirds of them (25.6 million) located in the WHO African Region [2]. In the same year, approximately 630 000 (ranging from 480 000 to 880 000) people succumbed to HIV-related causes, while 1.3 million (ranging from 1.0 million to 1.7 million) individuals acquired the virus [2].

The SARS-CoV-2 is a novel coronavirus responsible for the COVID-19 pandemic. It belongs to the coronavirus family, including other viruses such as SARS-CoV and MERS-CoV. It has a higher morbidity compared to other coronaviruses and can cause acute respiratory tract infections with extrapulmonary involvement, such as cardiovascular complications and multi-organ failure [3]. The virus has a genomic organization similar to other coronaviruses, with a set of core genes that encode replicase-structure proteins and has a high transmission rate [3]. It is worth mentioning that this virus persists

in its transmission through emerging variants, one of which is EG5. The latter has been classified as a variant of interest by WHO [4]. Due to this high transmission, over 70 million cases have been so far attacked by COVID-19, 7 million of whom have died [5]. Efforts are underway to develop effective antiviral drugs and vaccines to control and eradicate SARS-CoV-2.

Mathematical modeling is of importance for comprehending and characterizing the dynamics of RNA virus-induced infectious diseases. One of the first model was introduced by Perelson et al. [6]. Nowak and May [7] have also come up with another model to investigate the behavior of HIV infection. In 2020, Hattaf and Yousfi [8] proposed a new mathematical model that investigate the dynamics of SARS-CoV-2. In 2023, Hattaf et al. [9] introduced an additional model exploring the dynamics of the SARS-CoV-2 virus, incorporating the influence of antiviral treatment. All these models are based on systems only governed by ordinary differential equations (ODEs). Undoubtedly, they have contributed to the understanding of viruses-related issues. However, they assumed that cells and viruses are uniformly distributed and their mobility was neglected.

To understand the above factors, we propose a mathematical model governed by partial differential equations (PDEs) with reaction-diffusion to provide a description of the temporal and spatial pattern of RNA viruses like SARS-CoV-2. Our model takes into account the lytic and non-lytic effects of the humoral immunity and both cell-to-cell and virus-to-cell modes of transmission in the presence of the cure of infected cells and the antiviral treatment. The following system of nonlinear PDEs is used to define this model:

$$\begin{cases} \dfrac{\partial S}{\partial t} = d_1\Delta S + \sigma - \mu_1 S(x,t) - \dfrac{\beta_1 S(x,t)V(x,t)}{1+q_1W(x,t)} - \dfrac{\beta_2 S(x,t)I(x,t)}{1+q_2W(x,t)} + \rho L(x,t), \\ \dfrac{\partial L}{\partial t} = d_2\Delta L + \dfrac{\beta_1 S(x,t)V(x,t)}{1+q_1W(x,t)} + \dfrac{\beta_2 S(x,t)I(x,t)}{1+q_2W(x,t)} - (\mu_2+\delta+\rho)L(x,t), \\ \dfrac{\partial I}{\partial t} = d_3\Delta I + \delta L(x,t) - \mu_3 I(x,t), \\ \dfrac{\partial V}{\partial t} = d_4\Delta V + k(1-\varepsilon)I(x,t) - \mu_4 V(x,t) - pV(x,t)W(x,t), \\ \dfrac{\partial W}{\partial t} = d_5\Delta W + rV(x,t)W(x,t) - \mu_5 W(x,t), \end{cases} \tag{1}$$

where $S(x,t)$, $L(x,t)$, $I(x,t)$, $V(x,t)$ and $W(x,t)$ are the densities of uninfected cells, latently infected cells, infected cells, free viruses and antibodies at position x and time t, respectively. Uninfected cells are produced at rate σ, die at rate $\mu_1 S$ and return into infected through exposure to free virus particles at a rate $\beta_1 SV$ or by direct contact with infected cells at rate $\beta_2 SI$. The two modes of transmission are inhibited by non-lytic humoral immune response at rate $1+q_1W$ and $1+q_2W$, respectively. The latently infected cells (L) die at rate $\mu_2 L$, return to the uninfected state at rate ρL, which occurs through the clearance of the virus via a non-cytolytic process and transform into productively infected cells with a rate determined by δL. The productively infected cells (I) die at rate $\mu_3 I$. Free viruses are generated as a result of infected cells at a rate of kI. The virus rate clearance is $\mu_4 V$. The viruses are neutralized by antibodies at a rate of pVW. Antibodies are generated in response to free viruses at a rate of rVW and degrade at a rate of $\mu_5 W$. The parameter ε signifies the efficacy of the antiviral treatment, which inhibits the production of viral particles. The diffusion coefficients for uninfected cells, latently infected cells, infected cells, free viruses, and antibodies are denoted as d_1, d_2, d_3, d_4, and d_5, respectively.

We consider the initial values and Neumann boundary conditions as follows

$$\begin{cases} S(x,0) = \Phi_1(x) \geqslant 0, \quad L(x,0) = \Phi_2(x) \geqslant 0, \quad I(x,0) = \Phi_3(x) \geqslant 0, \quad V(x,0) = \Phi_4(x) \geqslant 0 \\ \text{and } W(x,0) = \Phi_5(x) \geqslant 0, \quad x \in \overline{\Omega}, \\ \dfrac{\partial S}{\partial \boldsymbol{n}} = \dfrac{\partial L}{\partial \boldsymbol{n}} = \dfrac{\partial I}{\partial \boldsymbol{n}} = \dfrac{\partial V}{\partial \boldsymbol{n}} = \dfrac{\partial W}{\partial \boldsymbol{n}} = 0, \quad t > 0, \quad x \in \partial\Omega, \end{cases} \tag{2}$$

where Ω is a bounded domain in $\mathbb{R}^n$ with smooth boundary $\partial\Omega$ and $\frac{\partial}{\partial \boldsymbol{n}}$ is an outward normal vector of $\partial\Omega$.

The rest of the paper is organized as follows. The well-posedness of our model demonstrated by showing the existence and uniqueness of solutions and establishing their non-negativity and boundedness as well as the threshold parameters and equilibria are the main concerns of the next section. The stability analysis is the focus of the third section. The final one is about the numerical illustration of the results of our paper.

2. Equilibria and threshold parameters

We consider the Banach space $C = [C(\overline{\Omega})]^5$, where $C(\overline{\Omega})$ is a set of real valued functions on the $\overline{\Omega}$, equipped with the supremum norm. Furthermore, we require the following lemma (see [10]).

Lemma 1. *Let consider the system as follows*

$$\begin{cases} \dfrac{\partial u}{\partial t} - d\Delta u \leqslant a - bu, & x \in \Omega,\ t > 0, \\ \dfrac{\partial u}{\partial n} = 0, & x \in \partial\Omega,\ t > 0, \\ u(x,0) = u_0(x), & x \in \overline{\Omega}, \end{cases} \tag{3}$$

where a, b and d are the constants with $b \neq 0$. Then

$$u(x,t) \leqslant \max_{x\in\overline{\Omega}} u_0(x)e^{-bt} + \frac{a}{b}(1 - e^{-bt}).$$

Moreover, if $b > 0$, we have

$$u(x,t) \leqslant \max\left\{\frac{a}{b}, \max_{x\in\overline{\Omega}} u_0(x)\right\} \text{ and } \limsup_{t\to+\infty} u(x,t) \leqslant \frac{a}{b}.$$

Theorem 1. *For any initial state $\Phi = (\Phi_1, \Phi_2, \Phi_3, \Phi_4, \Phi_5) \in C$ that satisfies the condition (2), there exists a unique solution to the problem (1)–(2). When cells have equal diffusion coefficients ($d_1 = d_2 = d_3$) and $d_4 = d_5$, this solution is defined over the interval $[0, +\infty)$ and remains both non-negative and bounded for all $t \geqslant 0$.*

Proof. We define the function $G = (G_1, G_2, G_3, G_4)$: $C \to C$ by:

$$\begin{cases} G_1(\phi) = \sigma - \mu_1\phi_1 - \dfrac{\beta_1\phi_1\phi_4}{1 + q_1\phi_5} - \dfrac{\beta_2\phi_1\phi_3}{1 + q_2\phi_5} + \rho\phi_2, \\ G_2(\phi) = \dfrac{\beta_1\phi_1\phi_4}{1 + q_1\phi_5} + \dfrac{\beta_2\phi_1\phi_3}{1 + q_2\phi_5} - (\mu_2 + \delta + \rho)\phi_2, \\ G_3(\phi) = \delta\phi_2 - \mu_3\phi_3, \\ G_4(\phi) = k(1 - \varepsilon)\phi_3 - \mu_4\phi_4 - p\phi_4\phi_5, \\ G_5(\phi) = r\phi_4\phi_5 - \mu_5\phi_5, \end{cases}$$

for any $\phi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5) \in C$. Then the system (1)–(2) is equivalent to

$$\begin{cases} X'(t) = AX(t) + G(t), \quad t > 0 \\ X(0) = \Phi \in C, \end{cases} \tag{4}$$

where $X(t) = (S(t), L(t), I(t), V(t), W(t))^T$ and $AX = (d_1\Delta S, d_2\Delta L, d_3\Delta I, d_4\Delta V, d_5\Delta W)^T$. It is clear that G is locally Lipschitz in C. According to [11], we deduce that system (4) have a unique local solution on its maximal interval of existence $[0, t_{\max})$. Since $0 = (0, 0, 0, 0, 0)$ is a lower-solution of the problem (1)–(2), we have $S \geqslant 0$, $L \geqslant 0$, $I \geqslant 0$, $V \geqslant 0$ and $W \geqslant 0$.

Let $Y = S + L + I$. We assume that $d_1 = d_2 = d_3 = d$ and $d_4 = d_5 = d'$. From the equations (1), we obtain

$$\begin{cases} \dfrac{\partial Y}{\partial t} - d\Delta Y \leqslant \sigma - \mu Y, \\ \dfrac{\partial Y}{\partial n} = 0, \\ Y(x,0) = \Phi_1(x) + \Phi_2(x) + \Phi_3(x), \quad x \in \overline{\Omega}, \end{cases} \tag{5}$$

where $\mu = \min\{\mu_1, \mu_2, \mu_3\}$. By Lemma 1, we get

$$Y(x,t) \leqslant \frac{\sigma}{d} + \max_{x\in\overline{\Omega}}(\Phi_1(x) + \Phi_2(x) + \Phi_3(x)) = M, \quad \forall (x,t) \in \overline{\Omega} \times [0, t_{\max}).$$

Hence Y is bounded on $\overline{\Omega} \times [0, t_{\max})$ which it follows that S, L and I are bounded as well. If we set $H = V + \frac{p}{r}W$, then we have

$$\begin{cases} \dfrac{\partial H}{\partial t} - d'\Delta H \leqslant B - vH, \\ \dfrac{\partial H}{\partial n} = 0, \\ H(x,0) = \Phi_4(x) + \dfrac{p}{r}\Phi_5(x), \quad x \in \overline{\Omega}, \end{cases} \tag{6}$$

where $B = k(1-\varepsilon)M$ and $v = \min\{\mu_4, \mu_5\}$. From Lemma 1, we deduce that H is bounded. This implies both V and W are also bounded. Therefore, it has been established that S, L, I, V and W are bounded on $\overline{\Omega} \times [0, t_{\max})$. Hence, according to the standard theory for semi-linear parabolic systems [12] that $t_{\max} = +\infty$. This concludes the proof. ∎

It is evident that system (1) possesses one infection-free equilibrium $E_0 = (\sigma/\mu_1, 0, 0, 0, 0)$. Then we define the basic reproduction number for our PDE model as follows

$$\mathcal{R}_0 = \frac{\sigma\delta[k(1-\varepsilon)\beta_1 + \mu_4\beta_2]}{\mu_1\mu_3\mu_4(\mu_2+\delta+\rho)}. \tag{7}$$

In biological terms, this threshold parameter signifies the average number of secondary infections generated by a single productively infected cell at the onset of infection. It can be expressed as the sum of $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$, where $\mathcal{R}_{01} = \frac{k\delta\sigma\beta_1(1-\varepsilon)}{\mu_1\mu_2\mu_4(\mu_2+\delta+\rho)}$ represents the basic reproduction number for the virus-to-cell transmission mode and $\mathcal{R}_{02} = \frac{\sigma\delta\beta_2}{\mu_1\mu_3(\mu_2+\delta+\rho)}$ represents the basic reproduction number for the cell-to-cell transmission mode. If $R_0 > 1$ then model (1) admits an other equilibrium $E_1 = (S_1, L_1, I_1, V_1, 0)$, where $S_1 = \frac{\sigma}{\mu_1\mathcal{R}_0}$, $L_1 = \frac{\sigma(\mathcal{R}_0-1)}{(\mu_2+\delta)\mathcal{R}_0}$, $I_1 = \frac{\delta\sigma(\mathcal{R}_0-1)}{\mu_3(\mu_2+\delta)\mathcal{R}_0}$ and $V_1 = \frac{k\delta\sigma(1-\varepsilon)(\mathcal{R}_0-1)}{\mu_3\mu_4(\mu_2+\delta)\mathcal{R}_0}$.

When the humoral immune response has not been established, we have $rV_1 - \mu_5 \leqslant 0$. Therefore, we introduce another threshold parameter known as the reproduction number for humoral immunity, which is defined as follows:

$$\mathcal{R}_1^W = \frac{rV_1}{\mu_5}, \tag{8}$$

where $\frac{1}{\mu_5}$ is the average life span of antibodies and V_1 is the quantity of viruses at the steady state E_1. So, the number $\mathcal{R}_1^W$ can biologically determine the average number of antibodies activated by viral particles.

Based on the findings of the paper [9], we demonstrate that if $\mathcal{R}_1^W > 1$ then the model (1) has an equilibrium point $E_2 = (S_2, L_2, I_2, V_2, W_2)$, where $S_2 \in \left(0, \frac{\sigma}{\mu_1} - \frac{\mu_3\mu_4\mu_5(\mu_2+\delta)}{rk\delta\mu_1(1-\varepsilon)}\right)$, $L_2 = \frac{\sigma-\mu_1S_2}{\mu_2+\delta}$ $I_2 = \frac{\delta(\sigma-\mu_1S_2)}{\mu_3(\mu_2+\delta)}$, $V_2 = \frac{\mu_5}{r}$ and $W_2 = \frac{rk\delta(1-\varepsilon)(\sigma-\mu_1S_2)-\mu_3\mu_4\mu_5(\mu_2+\delta)}{p\mu_3\mu_5(\mu_2+\delta)}$.

Summarizing the above discussions in the following theorem.

Theorem 2. 1. *If $\mathcal{R}_0 \leqslant 1$, then model (1) has a unique infection-free equilibrium $E_0 = (S_0, 0, 0, 0, 0)$, where $S_0 = \dfrac{\sigma}{\mu_1}$.*

2. *If $\mathcal{R}_0 > 1$, then model (1) has a unique infection equilibrium without humoral immunity $E_1 = (S_1, L_1, I_1, V_1, 0)$ besides E_0, where $S_1 = \frac{\sigma}{\mu_1\mathcal{R}_0}$, $L_1 = \frac{\sigma(\mathcal{R}_0-1)}{(\mu_2+\delta)\mathcal{R}_0}$, $I_1 = \frac{\delta\sigma(\mathcal{R}_0-1)}{\mu_3(\mu_2+\delta)\mathcal{R}_0}$ and $V_1 = \frac{k\delta\sigma(1-\varepsilon)(\mathcal{R}_0-1)}{\mu_3\mu_4(\mu_2+\delta)\mathcal{R}_0}$.*

3. *If $\mathcal{R}_1^W > 1$, then model (1) has a unique infection equilibrium with humoral immunity $E_2 = (S_2, L_2, I_2, V_2, W_2)$ besides E_0 and E_1, where $S_2 \in \left(0, \frac{\sigma}{\mu_1} - \frac{\mu_3\mu_4\mu_5(\mu_2+\delta)}{rk\delta\mu_1(1-\varepsilon)}\right)$, $L_2 = \frac{\sigma-\mu_1S_2}{\mu_2+\delta}$ $I_2 = \frac{\delta(\sigma-\mu_1S_2)}{\mu_3(\mu_2+\delta)}$, $V_2 = \frac{\mu_5}{r}$ and $W_2 = \frac{rk\delta(1-\varepsilon)(\sigma-\mu_1S_2)-\mu_3\mu_4\mu_5(\mu_2+\delta)}{p\mu_3\mu_5(\mu_2+\delta)}$.*

3. Stability analysis

In this section, we analyze the stability of equilibria.

First, we have the following result.

Theorem 3. *The infection-free steady state E_0 is globally asymptotically stable if $\mathcal{R}_0 \leqslant 1$ and becomes unstable if $\mathcal{R}_0 > 1$.*

Proof. Given the results established by Hattaf and Yousfi in [13], we consider the following Lyapunov function:

$$\mathcal{L}_0 = \int_\Omega \mathcal{F}_0(E(x,t))\,dx,$$

where $E = (S, L, I, V, W)$ is a solution of (1)–(2) and

$$\mathcal{F}_0(E) = S_0\Phi\left(\frac{S}{S_0}\right) + L + \frac{\mu_2+\delta+\rho}{\delta}I + \frac{\beta_1 S_0}{\mu_4}V + \frac{p\beta_1 S_0}{r\mu_4}W + \frac{\rho(S-S_0+L)^2}{2S_0(\mu_1+\mu_2+\delta)},$$

with $\Phi(x) = x - 1 - \ln x$, for $x > 0$. By a simple computation, we have

$$\begin{aligned}\frac{d\mathcal{L}_0}{dt} = \int_\Omega \Bigg\{ &-\mu_1\left(\frac{1}{S} + \frac{\rho}{S_0(\mu_1+\mu_2+\delta)} + \frac{\rho L}{SS_0}\right)(S-S_0)^2 - \frac{\rho(\mu_2+\delta)L^2}{S_0(\mu_1+\mu_2+\delta)} \\ &- \frac{q_1\beta_1 S_0}{1+q_1W}VW - \frac{q_2\beta_2 S_0}{1+q_2W}IW + \frac{\mu_3(\mu_2+\delta+\rho)}{\delta}I(\mathcal{R}_0-1) - \frac{p\mu_5\beta_1 S_0}{r\mu_4}W\Bigg\}\,dx.\end{aligned}$$

If $\mathcal{R}_0 \leqslant 1$, then $\frac{d\mathcal{L}_0}{dt} \leqslant 0$ with equality if and only if $E = E_0$. By LaSalle invariance principle [14], we deduce that E_0 is globally asymptotically stable when $\mathcal{R}_0 \leqslant 1$.

Now, we establish the instability of E_0 when $R_0 > 1$. To achieve this, we determine the characteristic equation around this equilibrium.

The eigenvalues of operator $-\Delta$ on Ω with homogeneous Neumann boundary conditions can be denoted by $0 = \lambda_1 < \lambda_2 < \ldots < \lambda_n < \ldots$. Let $E(\lambda_i)$ represents the eigenspace corresponding to λ_i in $C^1(\Omega)$. Consider $\{\psi_{ij} : j = 1, 2, \ldots, \dim E(\lambda_i)\}$ as an orthonormal basis for $E(\lambda_i)$, $Y = C^1(\Omega)^5$ and $Y_{ij} = \{c\psi_{ij} : c \in \mathbb{R}^5\}$. Then

$$Y = \bigoplus_{i=1}^{\infty} Y_i \quad \text{and} \quad Y_i = \bigoplus_{j=1}^{\dim E(\lambda_i)} Y_{ij}.$$

The linearized system of system (1) at $E_0 = (S_0, 0, 0, 0, 0,)$ is given by

$$\begin{cases} \dfrac{\partial S}{\partial t} = d_1\Delta S - \mu_1 S(x,t) + \rho L(x,t) - \beta_2 S_0 I(x,t) - \beta_1 S_0 V(x,t), \\ \dfrac{\partial L}{\partial t} = d_2\Delta L - (\mu_2+\delta+\rho)L(x,t) + \beta_2 S_0 I(x,t) + \beta_1 S_0 V(x,t), \\ \dfrac{\partial I}{\partial t} = d_3\Delta I + \delta L(x,t) - \mu_3 I(x,t), \\ \dfrac{\partial V}{\partial t} = d_4\Delta V + k(1-\varepsilon)I(x,t) - \mu_4 V(x,t), \\ \dfrac{\partial W}{\partial t} = d_5\Delta W - \mu_5 W(x,t). \end{cases} \tag{9}$$

Let $\mathcal{N}Z = DZ + A_0Z$, where $Z = (S, L, I, V, W)^T$ and the square matrices D and A_0 are given by

$$D = \operatorname{diag}(d_1, d_2, d_3, d_4, d_5) \quad \text{and} \quad A_0 = \begin{pmatrix} -\mu_1 & \rho & -\beta_2 S_0 & -\beta_1 S_0 & 0 \\ 0 & -(\mu_2+\delta+\rho) & \beta_2 S_0 & \beta_1 S_0 & 0 \\ 0 & \delta & -\mu_3 & 0 & 0 \\ 0 & 0 & k(1-\varepsilon) & -\mu_4 & 0 \\ 0 & 0 & 0 & 0 & -\mu_5 \end{pmatrix}.$$

Then the system (9) is equivalent to $\mathcal{N}Z = DZ + A_0Z$. Note that, for every $i \geqslant 1$, Y_i is invariant under operator $\mathcal{N}$ and the set of eigenvalues of $\mathcal{N}$ is $X = \cup_{i\geqslant 1} X_i$, where X_i represents the set of roots of the characteristic equation $\det(-\lambda_i D + A - xI)$. For $i = 1$, we have $\lambda_1 = 0$ and the characteristic

equation of the restriction of $\mathcal{N}$ to Y_1, is given by

$$(\mu_1 + x)(\mu_5 + x)Q_0(x) = 0, \tag{10}$$

where

$$Q_0(x) = x^3 + (\mu_2 + \mu_3 + \mu_4 + \delta + \rho)x^2 + \big(\mu_3\mu_4 - \delta\beta_2 S_0 + (\mu_3 + \mu_4)(\mu_2 + \delta + \rho)\big)x + \mu_3\mu_4(\mu_2 + \delta + \rho)(1 - R_0).$$

As $\lim\limits_{x\to+\infty} Q_0(x) = +\infty$ and $Q_0(0) = \mu_3\mu_4(\mu_2 + \delta + \rho)(1 - \mathcal{R}0) < 0$ for $\mathcal{R}0 > 1$, it follows that if $R_0 > 1$, the characteristic equation (10) possesses at least one positive eigenvalue. Consequently, E_0 is unstable when $R_0 > 1$. This concludes the proof. ∎

Following this, we demonstrate the asymptotic stability of the infection steady states E_1 and E_2, assuming that $\mathcal{R}_0 > 1$ and under the additional hypothesis:

$$q_1\big(W - W_i\big)\left(\frac{1 + q_1W}{1 + q_1W_i} - \frac{V}{V_i}\right) \leqslant 0, \quad q_2\big(W - W_i\big)\left(\frac{1 + q_2W}{1 + q_2W_i} - \frac{I}{I_i}\right) \leqslant 0, \tag{H}$$

where I_i, V_i, and W_i represent the respective components of productively infected cells, viruses, and antibodies in the infection equilibrium E_i for $i = 1, 2$.

Theorem 4. *If condition (H) holds true for E_1 and $\mathcal{R}_1^W \leqslant 1 < \mathcal{R}_0 \leqslant 1 + \frac{\mu_2+\delta}{\rho}$, then the infection steady state without humoral immunity is globally asymptotically stable and unstable if $\mathcal{R}_1^W > 1$.*

Proof. We define a Lyapunov function as follows

$$\mathcal{L}_1 = \int_\Omega \mathcal{F}_1(E(x,t))\,dx,$$

where $E = (S, L, I, V, W)$ is a solution of (1)–(2) and

$$\mathcal{F}_1(E) = S_1\Phi\left(\frac{S}{S_1}\right) + L_1\Phi\left(\frac{L}{L_1}\right) + \frac{\mu_2 + \delta + \rho}{\delta}I_1\Phi\left(\frac{I}{I_1}\right) + \frac{\beta_1 S_1 V_1}{k(1-\varepsilon)I_1}V_1\Phi\left(\frac{V}{V_1}\right) + \frac{p\beta_1 S_1 V_1}{rk(1-\varepsilon)I_1}W + \frac{\rho\,(S - S_1 + L - L_1)^2}{2S_1(\mu_1 + \mu_2 + \mu_3)}.$$

Then

$$\begin{aligned}\frac{d\mathcal{L}_1}{dt} = \int_\Omega \Bigg\{ &\left(1 - \frac{S_1}{S}\right)\left(\sigma - \mu_1 S - \frac{\beta_1 SV}{1 + q_1W} - \frac{\beta_2 SI}{1 + q_2W} + \rho L\right) \\ &+ \left(1 - \frac{L_1}{L}\right)\left(\frac{\beta_1 SV}{1 + q_1W} + \frac{\beta_2 SI}{1 + q_2W} - (\mu_2 + \delta + \rho)L\right) + \frac{\mu_2 + \delta + \rho}{\delta}\left(1 - \frac{I_1}{I}\right)(\delta L - \mu_3 I) \\ &+ \frac{\beta_1 S_1 V_1}{k(1-\varepsilon)I_1}\left(1 - \frac{V_1}{V}\right)\big(k(1-\varepsilon)I - \mu_4 V - pVW\big) + \frac{p\beta_1 S_1 V_1}{rk(1-\varepsilon)I_1}\big(rVW - \mu_5 W\big) \\ &+ \frac{\rho}{(\mu_1 + \mu_2 + \mu_3)S_1}(S - S_1 + L - L_1)\big(\sigma - \mu_1 S - (\mu_2 + \delta)L\big)\Bigg\}\,dx.\end{aligned}$$

By $k(1-\varepsilon)I_1 = \mu_4 V_1$, $\delta L_1 = \mu_3 I_1$ and $\sigma = \mu_1 S_1 + \beta_1 S_1 V_1 + \beta_2 S_1 I_1 - \rho L_1 = \mu_1 S_1 + (\mu_2 + \delta)L_1$, we get

$$\begin{aligned}\frac{d\mathcal{L}_1}{dt} = \int_\Omega \Bigg\{ &-\frac{1}{SS_1}\left(\mu_1 S_1 - \rho L_1 + \frac{\rho\mu_1 S}{\mu_1 + \mu_2 + \mu_3} + \rho L\right)\big(S - S_1\big)^2 - \frac{\rho(\mu_2 + \delta)(L - L_1)^2}{(\mu_1 + \mu_2 + \mu_3)S_1} \\ &+ \frac{p\mu_5\beta_1 S_1}{r\mu_4}\big(\mathcal{R}_1^W - 1\big)W + \beta_1 S_1 V_1\left[-1 - \frac{V}{V_1} + \frac{V}{(1 + q_1W)V_1} + (1 + q_1W)\right] \\ &+ \beta_2 S_1 I_1\left(-1 - \frac{I}{I_1} + \frac{I}{(1 + q_2W)I_1} + (1 + q_2W)\right) \\ &- \beta_1 S_1 V_1\left[\Phi\left(\frac{S_1}{S}\right) + \Phi\left(\frac{I_1 L}{IL_1}\right) + \Phi\left(\frac{SVL_1}{(1 + q_1W)S_1V_1L}\right) + \Phi\left(\frac{IV_1}{I_1V}\right) + \Phi(1 + q_1W)\right] \\ &- \beta_2 S_1 I_1\left[\Phi\left(\frac{S_1}{S}\right) + \Phi\left(\frac{I_1 L}{IL_1}\right) + \Phi\left(\frac{SIL_1}{(1 + q_2W)S_1I_1L}\right) + \Phi(1 + q_2W)\right]\Bigg\}\,dx.\end{aligned}$$

From (H), we have

$$\begin{aligned} -1-\frac{V}{V_i}+\frac{(1+q_1W_i)V}{(1+q_1W)V_i}+\frac{1+q_1W}{1+q_1W_i}&=\frac{q_1\big(W-W_i\big)}{1+q_1W}\left(\frac{1+q_1W}{1+q_1W_i}-\frac{V}{V_i}\right)\leqslant 0,\\ -1-\frac{I}{I_i}+\frac{(1+q_2W_i)I}{(1+q_2W)I_i}+\frac{1+q_2W}{1+q_2W_i}&=\frac{q_2\big(W-W_i\big)}{1+q_2W}\left(\frac{1+q_2W}{1+q_2W_i}-\frac{I}{I_i}\right)\leqslant 0. \end{aligned} \tag{11}$$

If $\mathcal{R}_0\leqslant 1+\frac{\mu_2+\delta}{\rho}$, then it follows that $\rho L_1\leqslant \mu_1 S_1$. Additionally assuming $\mathcal{R}_1^W\leqslant 1$, we can conclude that $\frac{d\mathcal{L}_1}{dt}\leqslant 0$ with equality if and only if $S=S_1$, $L=L_1$, $I=I_1$, $V=V_1$ and $W=0$. This implies that E_1 is globally asymptotically stable when $\mathcal{R}_1^W\leqslant 1<\mathcal{R}_0\leqslant 1+\frac{\mu_2+\delta}{\rho}$.

Now, we assumed that $\mathcal{R}_1^W>1$. The linearized system of system (1) at $E_1=(S_1,L_1,I_1,V_1,0,)$ is given by

$$\begin{cases} \dfrac{\partial S}{\partial t}=d_1\Delta S-(\mu_1+\beta_1V_1+\beta_2I_1)S(x,t)+\rho L(x,t)-\beta_2S_1I(x,t)-\beta_1S_1V(x,t)\\ \qquad\qquad +(\beta_1q_1S_1V_1+\beta_2q_2S_1I_1)W(x,t),\\ \dfrac{\partial L}{\partial t}=d_2\Delta L+(\beta_1V_1+\beta_2I_1)S(x,t)-(\mu_2+\delta+\rho)L(x,t)+\beta_2S_1I(x,t)+\beta_1S_1V(x,t)\\ \qquad\qquad -(\beta_1q_1S_1V_1+\beta_2q_2S_1I_1)W(x,t),\\ \dfrac{\partial I}{\partial t}=d_3\Delta I+\delta L(x,t)-\mu_3I(x,t),\\ \dfrac{\partial V}{\partial t}=d_4\Delta V+k(1-\varepsilon)I(x,t)-\mu_4V(x,t)-pV_1W(x,t),\\ \dfrac{\partial W}{\partial t}=d_5\Delta W+(rV_1-\mu_5)W(x,t). \end{cases} \tag{12}$$

Let $\mathcal{N}_1Z=DZ+A_1Z$, where $Z=(S,L,I,V,W)^T$ and the square matrices D and A_1 are given by

$$D=\operatorname{diag}(d_1,d_2,d_3,d_4,d_5),$$

and

$$A_1=\begin{pmatrix} -(\mu_1+\beta_1V_1+\beta_2I_1) & \rho & -\beta_2S_1 & -\beta_1S_1 & \beta_1q_1S_1V_1+\beta_2q_2S_1I_1\\ \beta_1V_1+\beta_2I_1 & -(\mu_2+\delta+\rho) & \beta_2S_1 & \beta_1S_1 & -(\beta_1q_1S_1V_1+\beta_2q_2S_1I_1)\\ 0 & \delta & -\mu_3 & 0 & 0\\ 0 & 0 & k(1-\varepsilon) & -\mu_4 & -pV_1\\ 0 & 0 & 0 & 0 & (rV_1-\mu_5) \end{pmatrix}.$$

Then the system (12) is equivalent to $\mathcal{N}_1Z=DZ+A_1Z$. Using the spectral decomposition and the symbols introduced in the proof of Theorem 3, we find that the characteristic equation of the restriction of $\mathcal{N}_1$ to Y_1 has $x=rV_1-\mu_5$ as eigenvalue. Since $\mathcal{R}_1^W=\frac{rV_1}{\mu_5}>1$, we have $x>0$. We conclude that E_1 is unstable if $\mathcal{R}_1^W>1$. ∎

Theorem 5. *Assume that (H) is satisfied for E_2. Then the infection steady state with humoral immunity E_2 is globally asymptotically stable if $\mathcal{R}_1^W>1$.*

Proof. Consider the Lyapunov function define by:

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

where $E=(S,L,I,V,W)$ is a solution of (1)–(2) and

$$\begin{aligned} \mathcal{F}_2(E)=S_2\Phi\left(\frac{S}{S_2}\right)+L_2\Phi\left(\frac{L}{L_2}\right)+\frac{\mu_2+\delta+\rho}{\delta}I_2\Phi\left(\frac{I}{I_2}\right)+\frac{\beta_1S_2V_2}{k(1-\varepsilon)(1+q_1W_2)I_2}V_2\Phi\left(\frac{V}{V_2}\right)\\ +\frac{p\beta_1S_2V_2}{rk(1-\varepsilon)(1+q_1W_2)I_2}W_2\Phi\left(\frac{W}{W_2}\right)+\frac{\rho\,(S-S_2+L-L_2)^2}{2S_2(\mu_1+\mu_2+\mu_3)}. \end{aligned}$$

By using the equalities $\sigma=\mu_1S_2+\frac{\beta_1S_2V_2}{1+q_1W_2}+\frac{\beta_2S_2I_2}{1+q_2W_2}-\rho L_2=\mu_1S_2+(\mu_2+\delta)L_2$, $\delta L_2=\mu_3I_2$, $k(1-\varepsilon)I_2=\mu_4V_2+pV_2W_2$ and $rV_2=\mu_5$, we obtain

$$\frac{d\mathcal{L}_2}{dt}=\int_\Omega\left\{-\frac{1}{SS_2}\left(\mu_1S_2-\rho L_2+\frac{\rho\mu_1S}{\mu_1+\mu_2+\mu_3}+\rho L\right)\big(S-S_2\big)^2+\frac{-\rho(\mu_2+\delta)}{(\mu_1+\mu_2+\mu_3)S_2}(L_2-L)^2\right.$$

$$
\begin{aligned}
&- \frac{\beta_1 S_2 V_2}{1+q_1 W_2}\left[\Phi\left(\frac{I_2 L}{L_2 I}\right)+\Phi\left(\frac{S_2}{S}\right)+\Phi\left(\frac{V_2 I}{I_2 V}\right)+\Phi\left(\frac{S L_2 V(1+q_1 W_2)}{S_2 L V_2(1+q_1 W)}\right)+\Phi\left(\frac{1+q_1 W}{1+q_1 W_2}\right)\right]\\
&+\frac{\beta_1 S_2 V_2}{1+q_1 W_2}\left(-1-\frac{V}{V_2}+\frac{V(1+q_1 W_2)}{V_2(1+q_1 W)}+\frac{1+q_1 W}{1+q_1 W_2}\right)\\
&- \frac{\beta_2 S_2 I_2}{1+q_2 W_2}\left[\Phi\left(\frac{I_2 L}{L_2 I}\right)+\Phi\left(\frac{S_2}{S}\right)+\Phi\left(\frac{S L_2 I(1+q_2 W_2)}{S_2 L I_2(1+q_2 W)}\right)+\Phi\left(\frac{1+q_2 W}{1+q_2 W_2}\right)\right]\\
&+\frac{\beta_2 S_2 I_2}{1+q_2 W_2}\left(-1-\frac{I}{I_2}+\frac{I(1+q_2 W_2)}{I_2(1+q_2 W)}+\frac{1+q_2 W}{1+q_2 W_2}\right)\Bigg\}\,dx.
\end{aligned}
$$

From (11) and the condition $\mu_1 S_2 - \rho L_2 \geqslant 0$, we deduce that $\frac{d\mathcal{L}_2}{dt} \leqslant 0$ with equality if and only if $S = S_2$, $L = L_2$, $I = I_2$, $V = V_2$ and $W = W_2$. Thus, E_2 is globally asymptotically stable. ■

4. Numerical simulation

In order to illustrate the results presented earlier, we perform numerical simulations using the parameters specified and referenced in [9]. These parameters are given as follows

$$
\begin{gathered}
\sigma = 60, \quad d_1 = 0.001, \quad d_2 = 0.001, \quad d_3 = 0.001, \quad d_4 = 0.001, \quad d_5 = 0.001, \quad \mu_1 = 0.001,\\
\varepsilon = 0.2, \quad \mu_2 = 0.09, \quad \delta = 1.5, \quad \mu_3 = 0.75, \quad p = 0.5, \quad \mu_4 = 15, \quad \mu_5 = 0.3,\\
\beta_2 = 1.2 \times 10^{-8}, \quad q_1 = 0.01, \quad q_2 = 0.02, \quad \rho = 0.01, \quad k = 50,
\end{gathered}
$$

and the values of r and β_1 are adjusted to obtain the three cases of global stability identified earlier.

When $r = 2.4 \times 10^{-3}$ and $\beta_1 = 4.6 \times 10^{-6}$ we achieve $\mathcal{R}_0 = 0.9209 \leqslant 1$ and $E_0 = (60000, 0, 0, 0, 0)$. Figure 1 illustrates that E_0 is globally asymptotically stable. In the case where $r = 2.4 \times 10^{-3}$ and $\beta_1 = 1.3 \times 10^{-5}$, we obtain $\mathcal{R}_0 = 2.6009 > 1$, $\mathcal{R}_1^W = 0.9910 \leqslant 1$ and $E_1 = (23069, 23, 46, 124, 0)$. Figure 2 demonstrates the global asymptotic stability of E_1. For $r = 4 \times 10^{-3}$ and $\beta_1 = 1.3 \times 10^{-5}$, we obtain $\mathcal{R}_1^W = 1.6517 > 1$ and $E_2 = (3.1263 \times 10^4, 18.0990, 36.2015, 75.0259, 8.6286)$. Figure 3 also confirms the global asymptotic stability of E_2. These numerical simulations align seamlessly with the assertions in Theorems 3, 4 and 5.

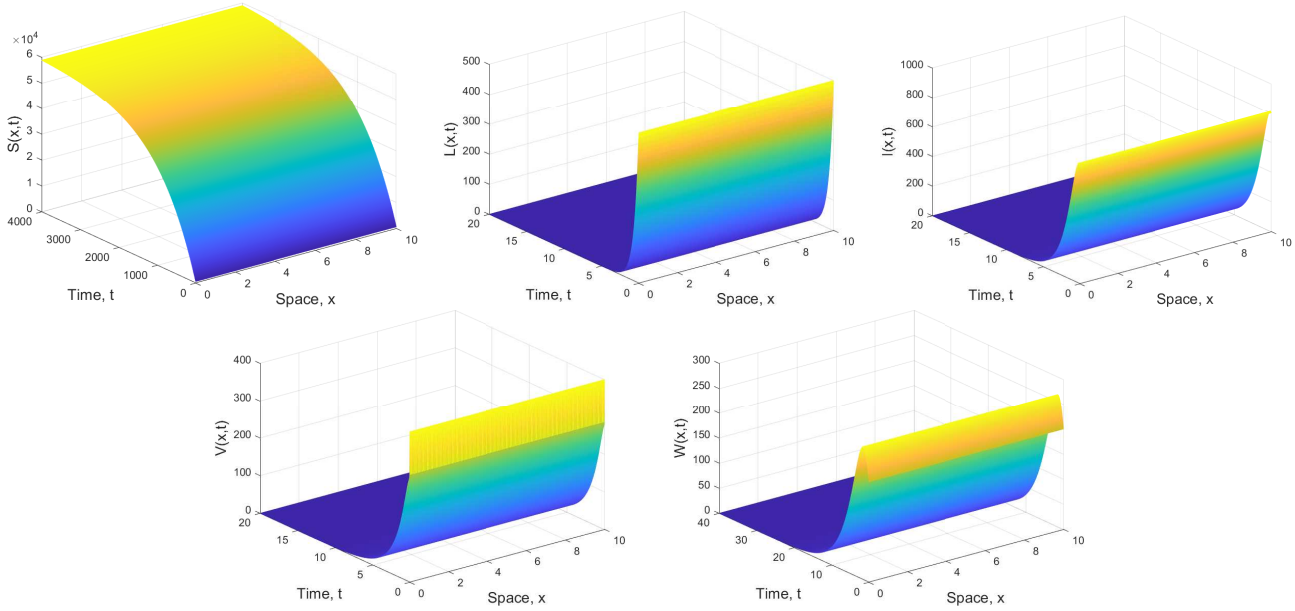

Fig. 1. Behaviour of model (1) when $\mathcal{R}_0 = 0.9209 \leqslant 1$.

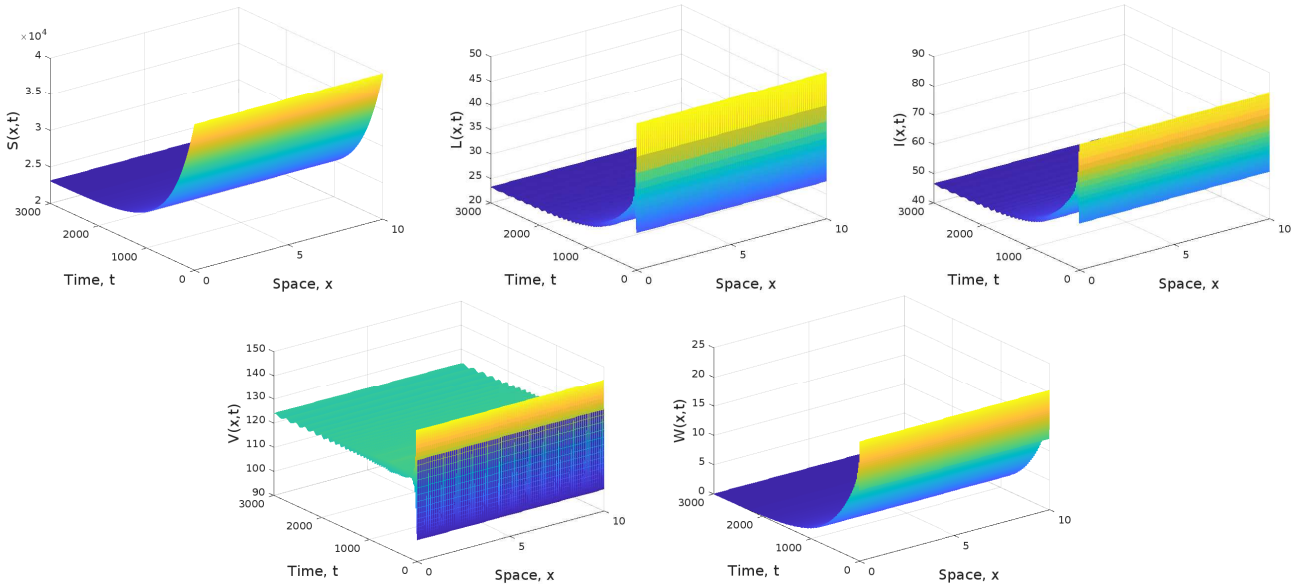

Fig. 2. Behaviour of model (1) for $\mathcal{R}_0 = 2.6009 > 1$ and $\mathcal{R}_1^W = 0.9910 \leqslant 1$.

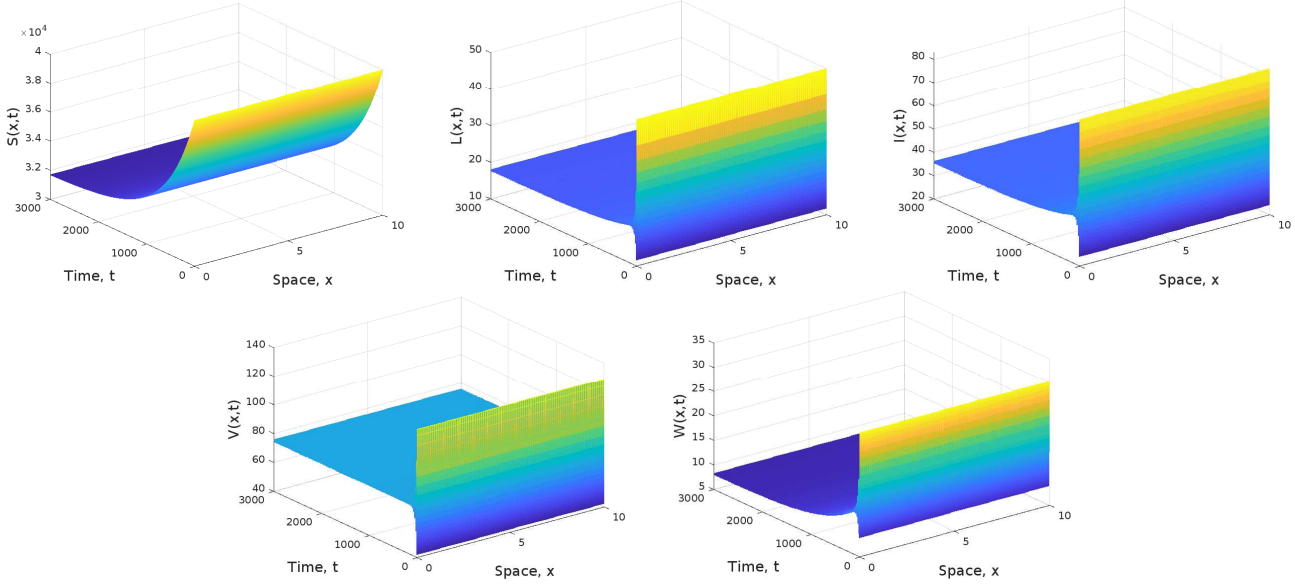

Fig. 3. Behaviour of model (1) for $\mathcal{R}_0 = 2.6009 > 1$ and $\mathcal{R}_1^W = 1.6517 > 1$.

5. Conclusion

In this work, we have studied the spatiotemporal dynamics of RNA viruses in the presence of humoral immunity and antiviral treatment, with a focus on the case of SARS-CoV-2. We have proposed a mathematical model based on partial differential equations with reaction-diffusion. This model accounts for both cellular and viral modes of transmission and incorporates both lytic and non-lytic responses of humoral immunity, as well as the effects of antiviral treatment. Additionally, it includes a non-cytolytic healing process. We have demonstrated that the proposed model is well-posed. Specifically, we have established that under realistic conditions, the system possesses unique, positive, and bounded solutions. We have provided threshold parameters, the basic reproduction number $\mathcal{R}_0$ and the reproduction number of humoral immunity $\mathcal{R}_1^W$. We have established the existence and uniqueness of three equilibrium points: a disease-free equilibrium E_0, a second equilibrium E_1 when $\mathcal{R}_0 > 1$, and a third equilibrium E_2 when $\mathcal{R}_1^w > 1$. We studied the global stability of these three equilibria, showing that E_0 is globally stable if $\mathcal{R}_0 \leqslant 1$ and unstable if $\mathcal{R}_0 > 1$, while E_1 is globally asymptotically stable if $\mathcal{R}_1^W < 1$, and E_2 is globally asymptotically stable if $\mathcal{R}_1^W > 1$.

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Просторово-часова динаміка РНК-вірусів за наявності імунітету та лікування: випадок SARS-CoV-2

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У статті розробляється математична модель, використовуючи диференціальні рівняння в частинних похідних, щоб дослідити поведінку РНК-вірусів за наявності противірусного лікування. Розроблена модель включає способи передачі як від клітини до клітини, так і від вірусу до клітини. Спочатку встановлено коректність моделі, показуючи існування та єдиність рішень, а також їх додатність та обмеженість. Крім того, ідентифіковано та проаналізовано стійкі рівноважні стани, їх глобальну стійкість залежно від конкретних порогових параметрів за допомогою функцій Ляпунова. Щоб підтвердити теоретичні висновки, наведено ілюстрації за допомогою чисельного моделювання.

Ключові слова: *реакція–дифузія; РНК-віруси; способи передачі; математичне моделювання; аналіз стійкості.*