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A reaction–diffusion model for oncolytic M1 virotherapy with distributed delays

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Abstract Oncolytic virotherapy (OVT) is a promising treatment for cancer which can replace or support the traditional treatments like chemotherapy and radiotherapy. Mathematical models have been considered as a powerful tool to develop oncolytic viral treatments and predict the possible outcomes. We study a spatial model for OVT with cytotoxic T lymphocyte immune response and distributed delays. This model is an extended version of the model studied by Wang et al. (Math Biosci 276:19–27, 2016). We study the basic properties of the model including the existence, nonnegativity, and boundedness of solutions. We carefully analyze all equilibrium points and determine the conditions for their existence. We show the global stability of each one of these points by constructing suitable Lyapunov functionals. We use the characteristic equations to confirm the corresponding instability conditions. We carry out some numerical simulations to support the theoretical results and draw some important conclusions. The results show that the distributed delay can have a large impact on the efficacy and amount of OVT. When the immune response is present, the concentration of oncolytic viruses is decreased and the efficiency of treatment is reduced. Changing the diffusion coefficients does not affect the long-time behavior of solutions.

1 Introduction

Despite the great advances in medicine, finding a crucial cure for cancer that has no side effects is still under investigation. The traditional cancer treatments like chemotherapy and radiotherapy may damage healthy cells besides cancer cells. This may cause many side effects such as hair loss, nausea, fatigue, and mouth sores [1]. Oncolytic virotherapy (OVT) is an experimental cancer treatment which uses oncolytic viruses to destroy tumor. The oncolytic viruses can selectively infect and replicate in cancer cells without targeting healthy cells. When the infected cancer cell is lysed, many oncolytic viruses are released and continue to infect other tumor cells [2,3]. If the treatment works successfully, it can reduce the size of tumor and eventually eradicate it [3]. Thus, OVT can be an ideal treatment for some types of tumor which show resistance to standard treatments [4,5]. A variety of oncolytic viruses have been tested in clinical trials including vesicular stomatitis virus (VSV), herpes

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simplex virus (HSV), adenovirus, reovirus [6–8], and M1 virus [9]. Nevertheless, talimogene laherparepvec (T-VEC) is the only oncolytic virus which was approved by the US Food and Drug Administration (FDA) to treat melanoma. T-VEC is a genetically modified HSV which means that it does not cause herpes, but it selectively targets tumor cells [10]. Actually, the approval of T-VEC has increased the motivation to develop oncolytic viruses to treat other types of cancer like lung cancer, pancreatic cancer, glioblastoma, and prostate cancer [11,12].

Although promising results have been reported by clinical studies, the complete potential of oncolytic viruses to remove the tumor has not been achieved yet [13,14]. The initiation of different immune responses against tumor cells during the treatment is one of the major obstacles in OVT. The immune system may attack and destroy the infected tumor cells before the release of new oncolytic viruses. Also, macrophages of the innate immune system can attack oncolytic viruses. These attacks can limit the replication of oncolytic viruses and decrease the efficacy of OVT [3,6,15]. However, there is an evidence that the success of oncolytic viral treatment depends on the induction of strong immune responses against tumor cells [6]. Hence, the immune system is a double-edged sword in OVT, and understanding its complicated role is an active area of research. Another challenge in OVT is the ability of oncolytic viruses to spread through the tumor and infect more cells [14]. The current research efforts aim to resolve the different challenges and design effective oncolytic virotherapies with maximum safety and minimum cost [10,12]. Thus, these efforts work on enhancing the tumor selectivity of oncolytic viruses and determining the significant amount of dosage needed to cure tumor [4,10].

Mathematical modeling has been considered as a powerful tool to develop oncolytic viral treatments and predict the possible outcomes. Also, it helps to understand the complex virus–tumor–immune response interactions. Oncolytic modeling uses approaches that are similar to those used in virus dynamics models (see for example, [16–23]). Oncolytic virotherapy models have been formulated using different types of differential equations. Many of these models are based on the use of ordinary differential equations (ODEs). For example, a basic model for OVT was proposed by Tian [24]. The model consists of three ODEs which reflect the interactions between uninfected tumor cells, infected tumor cells and free virus population. Moreover, Komarova and Wodarz [25] performed a mathematical analysis of a general ODE model to shed light on some conditions needed for the success of OVT. Okamoto et al. [26] developed a mathematical model in which viruses are allowed to infect normal cells besides tumor cells. They argued that reducing the specificity of oncolytic viruses can lead to faster tumor elimination before the presence of an adaptive immune response. Ratajczyk et al. [27] formulated an ODE model to study the effect of combining virotherapy with TNF-α inhibitor. TNF-α is a protein produced by macrophages to destroy tumor cells. Ratajczyk and his colleagues proved that the inhibition of TNF-α can give a chance for oncolytic viruses to replicate, and thus it increases the effectiveness of OVT. Then, the same model was analyzed in [3] as an optimal control problem with two controls, one for the amount of OVT and the other for the amount of TNF-α. Jenner et al. [7] performed a local stability and bifurcation analysis of a system of three ODEs which capture the interaction between oncolytic viruses, uninfected and infected tumor cells populations. Malinzi et al. [28] developed a mathematical model to determine the optimal dosage of chemovirotherapy that is needed to eliminate a tumor. They showed that, under certain conditions, virotherapy can be used to enhance chemotherapy in treating cancer patients.

As mentioned above, the spatial spread of oncolytic viruses plays a vital role in the success of OVT. This has motivated to use partial differential equations (PDEs) to take into account the spatial variations in the distribution of oncolytic viruses and cells during the treatment [29]. For example, Tao and Guo [5] investigated a spherical-symmetric oncolytic virotherapy

PDE model with immune response. They found that the immune response can have a negative impact on the effectiveness of treatment. Malinzi et al. [1] got analytical traveling wave solutions of a PDE model that studies the interaction dynamics between oncolytic viruses, cytotoxic T lymphocytes (CTLs), and tumor cells. Alzahrani et al. [29] introduced a new multiscale modeling approach based on systems of reaction–diffusion equations both at macroscale and microscale. This approach addresses the complex interactions between tumor and oncolytic viruses, where the two scales are connected through a double feedback loop.

It has been shown that time delay is a pivotal element that should be carefully controlled to guarantee the success of oncolytic virotherapy in experimental and clinical trials [30,31]. This has raised the need to extend ODEs to delay differential equations (DDEs) where the effect of time delay of some biological processes is included. Many mathematical models with DDEs have been rigorously analyzed. For instance, Wang et al. [32] determined critical values for the time delay τ at which Hopf bifurcation occurs in OVT model. Wang et al. [30] showed by means of DDEs that the time delay associated with the viral lytic cycle and the number of viruses released from the infected cancer cells are two important factors in OVT. Ashyani et al. [31] showed that the CTL immune response against infected cancer cells causes the fail of virotherapy in the second injection except for a short delay interval $[0, \tau_0^+)$. Kim et al. [33] proved the existence of Hopf bifurcation and formulated an optimal control problem with two controls for DDE model with CTLs. They studied the effect of a time delay on the amount of OVT. Wang et al. [8] proposed a model with intracellular delay and CTL immune response. They suggested many strategies to enhance the effect of oncolytic viruses based on the results of their model.

Due to the sensitive role of time delay in virus dynamics models, PDEs have been extended to delay partial differential equations (DPDEs) to account for both spatial diffusion and time delay effects [34–37]. As an example, Zhao and Tian [14] formulated a delay reaction–diffusion model for OVT. They highlighted many medical implications of their results which cannot be obtained from ODE models. Wang et al. [38] determined the optimal dosage needed for complete tumor eradication in different cases depending on different gene mutations. The models in [14,38] incorporate discrete time delays. A discrete time delay means that each individual within a population is subject to the same delay during a certain biological process [39]. On the other hand, a distributed time delay assumes that the delay is continuously distributed by a continuous distribution function. Hence, the distributed time delay is considered more general and realistic [22,39,40]. In this paper, we deal with PDEs with distributed delays.

In 2014, Lin et al. [9] identified a naturally occurring alphavirus M1 as a selective oncolytic virus that targets cancer cells with Zinc-finger antiviral protein (ZAP) deficiency. More recently, Zhang et al. [41] have found that tumor cells may impair the removal of oncolytic M1 virus by tumor-associated macrophages. This impairment may enhance the tumor selectivity of M1 virus and improve its efficacy. In [42], Wang et al. formulated an ODE model to show the effect of M1 virus on the growth of normal cells and tumor cells. Their model takes the form

$$
\begin{cases}
\dfrac{dH(t)}{dt} = \kappa - dH(t) - \beta_1 H(t)N(t) - \beta_2 H(t)Y(t), \\[2mm]
\dfrac{dN(t)}{dt} = \alpha_1 \beta_1 H(t)N(t) - (d+\eta_1)N(t), \\[2mm]
\dfrac{dY(t)}{dt} = \alpha_2 \beta_2 H(t)Y(t) - \beta_3 Y(t)V(t) - (d+\eta_2)Y(t), \\[2mm]
\dfrac{dV(t)}{dt} = \mu + \alpha_3 \beta_3 Y(t)V(t) - (d+\eta_3)V(t),
\end{cases}
\tag{1}
$$

where $H(t)$, $N(t)$, $Y(t)$ and $V(t)$ denote the concentrations of nutrient, normal cells, tumor cells, and free M1 virus particles, respectively. The model is considered in the chemostat, where the normal and tumor cells compete on a limited nutrient source. Therefore, there is a prey–predator relationship between nutrient and the normal or tumor cells. Also, there is a competition relationship between the normal cells and tumor cells. In model (1), the parameter κ represents the recruitment rate of nutrient, and μ represents the M1 virotherapy dosage. The parameter d is the washout rate constant of nutrient and bacteria. The parameters η_1, η_2, and η_3 are the natural death rate constants of normal cells, tumor cells, and M1 virus, respectively. The nutrient is consumed by the normal cells and tumor cells at rates $\beta_1 H N$ and $\beta_2 H Y$, respectively. The contribution rates of nutrient to biomass of normal cells and tumor cells are given by $\alpha_1 \beta_1 H N$ and $\alpha_2 \beta_2 H Y$, respectively. The M1 virus kills tumor cells at rate $\beta_3 Y V$ and grows at rate $\alpha_3 \beta_3 Y V$.

To the best of our knowledge, none of the previous works of OVT combine the effects of distributed delay and CTL immune response in their models. In order to design better oncolytic treatments, we need to understand the different factors that may affect the efficacy of these treatments including delays, immune responses, and spatial diffusion. Since M1 has shown high tumor selectivity and efficacy [41], forming a model to study its role might be quite beneficial to the oncolytic studies. The authors in [42] focused on one equilibrium point of model (1) corresponding to tumor elimination, and they determined the minimum effective dosage of M1 required to remove the tumor. They neglected the other equilibrium points of system (1), the effect of delays, immune responses, and diffusion. Thus, our purpose in this paper is (i) to extend model (1) to include distributed delay in the dynamics of normal and tumor cells; (ii) to study the effect of CTLs on the efficiency of OVT in the presence of delay; (iii) to include the diffusivity of all model's components; (iv) to study the basic properties of the extended model; (v) to study the global properties of the model; (vi) to study the spatiotemporal behavior of solutions; (vii) to discuss the minimum effective dosage of M1 required to eradicate the tumor in the presence of delay. The effect of innate immune response is not included in the model due to the impairment effect exerted by tumor cells as mentioned above. The paper is organized as follows. In Sect. 2, a detailed description of the model is given. In Sect. 3, the nonnegativity and boundedness of solutions are discussed. In addition, all possible equilibrium points and their existence conditions are investigated. In Sect. 4, the global stability and local instability of these equilibrium points are proved. In Sect. 5, some numerical simulations that verify the theoretical results are provided. In Sect. 6, the results of our work are highlighted.

2 A delayed reaction–diffusion oncolytic M1 virotherapy model

In this section, we take model (1) to further destination by studying the effect of adaptive immunity, particularly CTLs, on the efficacy of OVT. We achieve this goal by considering the following reaction–diffusion model with distributed delays

$$
\begin{cases}
\frac{\partial H(x,t)}{\partial t} = D_H \Delta H(x,t) + \kappa - dH(x,t) - \beta_1 H(x,t)N(x,t) - \beta_2 H(x,t)Y(x,t), \\[2mm]
\frac{\partial N(x,t)}{\partial t} = D_N \Delta N(x,t) + \alpha_1 \beta_1 \int_0^\infty g_1(\varsigma)e^{-a_1\varsigma} H(x,t-\varsigma)N(x,t-\varsigma)\,\mathrm{d}\varsigma \\[2mm]
\qquad\qquad - (d+\eta_1)N(x,t), \\[2mm]
\frac{\partial Y(x,t)}{\partial t} = D_Y \Delta Y(x,t) + \alpha_2 \beta_2 \int_0^\infty g_2(\varsigma)e^{-a_2\varsigma} H(x,t-\varsigma)Y(x,t-\varsigma)\,\mathrm{d}\varsigma \\[2mm]
\qquad\qquad - \beta_3 Y(x,t)V(x,t) \\[1mm]
\qquad\qquad\qquad - \beta_4 Y(x,t)Z(x,t) - (d+\eta_2)Y(x,t), \\[2mm]
\frac{\partial V(x,t)}{\partial t} = D_V \Delta V(x,t) + \mu + \alpha_3 \beta_3 Y(x,t)V(x,t) - (d+\eta_3)V(x,t), \\[2mm]
\frac{\partial Z(x,t)}{\partial t} = D_Z \Delta Z(x,t) + \alpha_4 \beta_4 Y(x,t)Z(x,t) - (d+\eta_4)Z(x,t),
\end{cases}
\tag{2}
$$

for $t > 0$ and $x \in \Omega$, where $Z(x,t)$ denotes the concentration of CTLs at position x and time t. All components of the model are assumed to diffuse in a continuous and bounded domain Ω with a smooth boundary $\partial\Omega$. The diffusion term of any component ν of the model is given by $D_\nu \Delta \nu(x,t)$, where D_ν is the diffusion coefficient and Δ is the Laplacian operator. CTLs kill tumor cells at rate $\beta_4 YZ$ and proliferate at rate $\alpha_4 \beta_4 YZ$. We assume that the normal and tumor cells consume nutrient at time $t - \varsigma$ and benefit from it at time t, where the delay ς is a random variable taken from a continuous probability distribution function $g_i(\varsigma)$ for $i = 1, 2$. The factor $e^{-a_1\varsigma}$ accounts for the probability of survival of normal cells during the delay period with death rate a_1. The factor $e^{-a_2\varsigma}$ accounts for the probability of survival of tumor cells during the delay period with death rate a_2. Thus, the term $\alpha_1 \beta_1 \int_0^\infty g_1(\varsigma)e^{-a_1\varsigma} H(x,t-\varsigma)N(x,t-\varsigma)\,\mathrm{d}\varsigma$ gives the contribution of nutrient to biomass of normal cells at time t. Similarly, the term $\alpha_2 \beta_2 \int_0^\infty g_2(\varsigma)e^{-a_2\varsigma} H(x,t-\varsigma)Y(x,t-\varsigma)\,\mathrm{d}\varsigma$ gives the contribution of nutrient to biomass of tumor cells at time t. The probability distribution functions $g_1(\varsigma)$ and $g_2(\varsigma)$ are assumed to satisfy

$$
g_i(\varsigma) > 0, \quad \int_0^\infty g_i(\varsigma)\,\mathrm{d}\varsigma = 1, \quad 0 < \int_0^\infty g_i(\varsigma)e^{-a_i\varsigma}\,\mathrm{d}\varsigma \le 1, \quad \text{for } i = 1, 2.
$$

The initial conditions of model (2) are given by

$$
\begin{aligned}
H(x,\theta) = \omega_1(x,\theta), \quad N(x,\theta) = \omega_2(x,\theta), \quad Y(x,\theta) = \omega_3(x,\theta), \\
V(x,\theta) = \omega_4(x,\theta), \quad Z(x,\theta) = \omega_5(x,\theta), \quad \text{for } (x,\theta) \in \bar{\Omega} \times (-\infty, 0],
\end{aligned}
\tag{3}
$$

where $\omega_i(x,\theta)(i = 1,\ldots,5)$ are nonnegative and continuous functions in $\bar{\Omega} \times (-\infty, 0]$. Also, we consider the homogeneous Neumann boundary conditions (NBCs)

$$
\frac{\partial H}{\partial \vec{n}} = \frac{\partial N}{\partial \vec{n}} = \frac{\partial Y}{\partial \vec{n}} = \frac{\partial V}{\partial \vec{n}} = \frac{\partial Z}{\partial \vec{n}} = 0, \quad \text{for } (x,t) \in \partial\Omega \times (0, +\infty),
\tag{4}
$$

where $\frac{\partial}{\partial \vec{n}}$ is the outward normal derivative on the boundary $\partial\Omega$. The NBCs indicate that the cells and viruses are confined within the boundary and do not cross it.

Remark 1 A model with discrete delays can be obtained from model (2) by considering special forms of $g_1(\varsigma)$ and $g_2(\varsigma)$ as

$$g_i(\varsigma) = \delta(\varsigma - \varsigma_i), \quad \text{for } i = 1, 2,$$

where $\delta(.)$ is the Dirac delta function and ς_i are finite time delays. Then, the delay terms in the second and third equations of model (2) are given by $\alpha_1\beta_1 e^{-a_1\varsigma_1} H(x, t - \varsigma_1)N(x, t - \varsigma_1)$ and $\alpha_2\beta_2 e^{-a_2\varsigma_2} H(x, t - \varsigma_2)Y(x, t - \varsigma_2)$, respectively.

3 Basic properties

In this section, we show the well-posedness of model (2)–(4). Also, we identify all possible equilibrium points and establish their existence conditions.

Let $\mathbb{X} = C(\bar{\Omega}, \mathbb{R}^5)$ be the Banach space of continuous functions from $\bar{\Omega}$ to $\mathbb{R}^5$. Define the Banach space of fading memory type [43] $\mathbb{C}_\alpha = \{\psi \in C((-\infty, 0], \mathbb{X}) : \psi(\theta)e^{\alpha\theta}$ is uniformly continuous for $\theta \in (-\infty, 0]$ and $\sup_{\theta \leq 0} |\psi(\theta)|e^{\alpha\theta} < \infty\}$, where $\|\psi\| = \sup_{\theta \leq 0} |\psi(\theta)|e^{\alpha\theta}$ and α is a positive constant. Then, we identify an element $\omega \in \mathbb{C}_\alpha$ as a function from $\bar{\Omega} \times (-\infty, 0]$ into $\mathbb{R}^5$ defined by $\omega(x, \theta) = \omega(\theta)(x)$. For any continuous function $A : (-\infty, \bar{\varrho}) \to \mathbb{X}$, we define $A_t \in \mathbb{C}_\alpha$ by $A_t(\theta) = A(t + \theta)$, for $\bar{\varrho} > 0$ and $\theta \leq 0$. It is not hard to see that $t \to A_t$ is a continuous function from $[0, \bar{\varrho})$ to $\mathbb{C}_\alpha$.

Theorem 1 *Suppose that $D_H = D_N = D_Y = D_V = D_Z$. Then, there exists a unique nonnegative and bounded solution defined on $\bar{\Omega} \times [0, +\infty)$ for any given initial data satisfying* (3).

Proof For any $\omega = (\omega_1, \omega_2, \omega_3, \omega_4, \omega_5)^T \in \mathbb{C}_\alpha$ and $x \in \bar{\Omega}$, we define $F = (F_1, F_2, F_3, F_4, F_5) : \mathbb{C}_\alpha \to \mathbb{X}$ by

$$
\begin{cases}
F_1(\omega)(x) = \kappa - d\omega_1(x, 0) - \beta_1\omega_1(x, 0)\omega_2(x, 0) - \beta_2\omega_1(x, 0)\omega_3(x, 0), \\
F_2(\omega)(x) = \alpha_1\beta_1 \int_0^\infty g_1(\varsigma)e^{-a_1\varsigma}\omega_1(x, -\varsigma)\omega_2(x, -\varsigma) \, d\varsigma - (d + \eta_1)\omega_2(x, 0), \\
F_3(\omega)(x) = \alpha_2\beta_2 \int_0^\infty g_2(\varsigma)e^{-a_2\varsigma}\omega_1(x, -\varsigma)\omega_3(x, -\varsigma) \, d\varsigma - \beta_3\omega_3(x, 0)\omega_4(x, 0) \\
\qquad\qquad - \beta_4\omega_3(x, 0)\omega_5(x, 0) - (d + \eta_2)\omega_3(x, 0), \\
F_4(\omega)(x) = \mu + \alpha_3\beta_3\omega_3(x, 0)\omega_4(x, 0) - (d + \eta_3)\omega_4(x, 0), \\
F_5(\omega)(x) = \alpha_4\beta_4\omega_3(x, 0)\omega_5(x, 0) - (d + \eta_4)\omega_5(x, 0).
\end{cases}
$$

Then, we can rewrite problem (2)–(4) as the following abstract ordinary differential equation

$$
\begin{cases}
\frac{dA}{dt} = MA + F(A_t), \ t > 0, \\
A(0) = \omega \in \mathbb{C}_\alpha,
\end{cases}
$$

where $A = (H, N, Y, V, Z)^T$ and $MA = (D_H\Delta H, D_N\Delta N, D_Y\Delta Y, D_V\Delta V, D_Z\Delta Z)^T$. It is clear that F is locally Lipschitz in $\mathbb{C}_\alpha$. According to [44–47], we conclude that problem (2)–(4) has a unique local solution on its maximal existence time interval $[0, T_{max})$. Also, we have $H(x, t) \geq 0$, $N(x, t) \geq 0$, $Y(x, t) \geq 0$, $V(x, t) \geq 0$ and $Z(x, t) \geq 0$ since $\mathbf{0} = (0, 0, 0, 0, 0)$ is a lower solution of problem (2)–(4).

The next step is to show the boundedness of solutions. From the first equation of (2), we get

$$
\begin{cases}
\frac{\partial H(x,t)}{\partial t} - D_H\Delta H(x, t) \leq \kappa - dH(x, t), \\
\frac{\partial H}{\partial n} = 0, \\
H(x, 0) = \omega_1(x, 0) \geq 0.
\end{cases}
$$

Let $\widetilde{H}(t)$ be a solution to the following ODE system

$$\begin{cases} \dfrac{d\widetilde{H}(t)}{dt} = \kappa - d\widetilde{H}(t), \\ \widetilde{H}(0) = \max\limits_{x\in\Omega} \omega_1(x, 0). \end{cases}$$

This implies that $\widetilde{H}(t) \leq \max\left\{\dfrac{\kappa}{d}, \max\limits_{x\in\Omega} \omega_1(x, 0)\right\}$. From the comparison principle [48], we have $H(x, t) \leq \widetilde{H}(t)$. Hence, we get

$$H(x, t) \leq \max\left\{\frac{\kappa}{d}, \max_{x\in\Omega} \omega_1(x, 0)\right\}, \quad \text{for } (x, t) \in \bar{\Omega} \times [0, T_{\max}).$$

This implies that $H(x, t)$ is bounded. Let

$$G_i = \int_0^\infty g_i(\varsigma)e^{-a_i\varsigma} \, d\varsigma, \quad \text{for } i = 1, 2. \tag{5}$$

Then, we define

$$\Gamma(x, t) = \int_0^\infty g_1(\varsigma)e^{-a_1\varsigma} H(x, t - \varsigma) \, d\varsigma + \int_0^\infty g_2(\varsigma)e^{-a_2\varsigma} H(x, t - \varsigma) \, d\varsigma$$

$$+ \frac{1}{\alpha_1} N(x, t) + \frac{1}{\alpha_2} Y(x, t) + \frac{1}{\alpha_2\alpha_3} V(x, t) + \frac{1}{\alpha_2\alpha_4} Z(x, t).$$

When $D_H = D_N = D_Y = D_V = D_Z$, we get

$$\frac{\partial \Gamma(x, t)}{\partial t} - D_H \Delta\Gamma(x, t)$$

$$\leq \frac{\mu}{\alpha_2\alpha_3} + \kappa \int_0^\infty g_1(\varsigma)e^{-a_1\varsigma} \, d\varsigma + \kappa \int_0^\infty g_2(\varsigma)e^{-a_2\varsigma} \, d\varsigma - d \int_0^\infty g_1(\varsigma)e^{-a_1\varsigma} H(x, t - \varsigma) \, d\varsigma$$

$$- d \int_0^\infty g_2(\varsigma)e^{-a_2\varsigma} H(x, t - \varsigma) \, d\varsigma$$

$$- \frac{(d + \eta_1)}{\alpha_1} N(x, t) - \frac{(d + \eta_2)}{\alpha_2} Y(x, t) - \frac{(d + \eta_3)}{\alpha_2\alpha_3} V(x, t)$$

$$- \frac{(d + \eta_4)}{\alpha_2\alpha_4} Z(x, t)$$

$$\leq \frac{\mu}{\alpha_2\alpha_3} + \kappa(G_1 + G_2) - d\Gamma(x, t)$$

$$\leq \frac{\mu}{\alpha_2\alpha_3} + 2\kappa - d\Gamma(x, t).$$

Thus, $\Gamma(x, t)$ satisfies the following system

$$\begin{cases} \frac{\partial \Gamma(x,t)}{\partial t} - D_H \Delta \Gamma(x, t) \leq \frac{\mu}{\alpha_2 \alpha_3} + 2\kappa - d\Gamma(x, t), \\ \frac{\partial \Gamma}{\partial n} = 0, \\ \Gamma(x, 0) = \int\limits_0^\infty g_1(\varsigma) e^{-a_1\varsigma} \omega_1(x, -\varsigma) \, d\varsigma + \int\limits_0^\infty g_2(\varsigma) e^{-a_2\varsigma} \omega_1(x, -\varsigma) \, d\varsigma + \frac{1}{\alpha_1} \omega_2(x, 0) \\ \qquad\quad + \frac{1}{\alpha_2} \omega_3(x, 0) + \frac{1}{\alpha_2 \alpha_3} \omega_4(x, 0) \\ \qquad\quad + \frac{1}{\alpha_2 \alpha_4} \omega_5(x, 0) \geq 0. \end{cases}$$

Hence, we can deduce from the comparison principle [48] that

$$\Gamma(x, t) \leq \max \left\{ \frac{\mu}{\alpha_2 \alpha_3 d} + \frac{2\kappa}{d}, \max_{x \in \bar{\Omega}} \Gamma(x, 0) \right\}, \quad \text{for } (x, t) \in \bar{\Omega} \times [0, T_{\max}).$$

This implies that $N(x, t)$, $Y(x, t)$, $V(x, t)$ and $Z(x, t)$ are bounded on $\bar{\Omega} \times [0, T_{\max})$. Thus, all solutions are bounded on $\bar{\Omega} \times [0, T_{\max})$. Then, the boundedness of the solutions on $\bar{\Omega} \times [0, +\infty)$ are deduced from the standard theory for semi-linear parabolic systems [49].
□

For the sake of simplicity, we let

$$d_1 = (d + \eta_1), \quad d_2 = (d + \eta_2), \quad d_3 = (d + \eta_3), \quad d_4 = (d + \eta_4),$$
$$\nu = \nu(x, t) \text{ for } \nu \in \{H, N, Y, V, Z\}.$$

Theorem 2 *There exist positive parameters $\mathcal{R}_0$, $\mathcal{R}_1$, $\mathcal{R}_l$, $\mathcal{R}_m$, $\mathcal{R}_n$, ξ_1, ξ_2 and ρ such that model* (2) *has six possible equilibrium points whenever the following conditions are hold:*

(a) *The competition-free equilibrium $E_0 = (H_0, 0, 0, V_0, 0)$ always exists;*
(b) *The treatment failure immune-free equilibrium $E_1 = (H_1, 0, Y_1, V_1, 0)$ exists if $\mathcal{R}_0 > \mathcal{R}_l$;*
(c) *The tumor-free equilibrium $E_2 = (H_2, N_2, 0, V_2, 0)$ exists if $\mathcal{R}_1 > 1$;*
(d) *The treatment failure equilibrium $E_3 = (H_3, 0, Y_3, V_3, Z_3)$ exists if $\rho > 1$ and $\mathcal{R}_0 > \mathcal{R}_m + \dfrac{\mu \xi_2}{\alpha_3 dd_2 d_4 (\rho - 1)}$;*
(e) *The partial success immune-free equilibrium $E_4 = (H_4, N_4, Y_4, V_4, 0)$ exists if $\mathcal{R}_0/\mathcal{R}_1 > 1$, $\mathcal{R}_n < \mathcal{R}_1 + \dfrac{\mu \beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{dd_1 d_2 d_3}$;*
(f) *The coexistence equilibrium $E_5 = (H_5, N_5, Y_5, V_5, Z_5)$ exists if $\rho > 1$, $\mathcal{R}_1 > \mathcal{R}_m$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \alpha_4 \beta_4}{\alpha_3 dd_1 d_2 d_4 (\rho - 1)}$.*

Proof Any equilibrium point $E = (H, N, Y, V, Z)$ of model (2) satisfies the following system

$$\begin{cases} \kappa - dH - \beta_1 HN - \beta_2 HY = 0, \\ \alpha_1 \beta_1 G_1 HN - d_1 N = 0, \\ \alpha_2 \beta_2 G_2 HY - \beta_3 YV - \beta_4 YZ - d_2 Y = 0, \\ \mu + \alpha_3 \beta_3 YV - d_3 V = 0, \\ \alpha_4 \beta_4 YZ - d_4 Z = 0. \end{cases} \qquad (6)$$

By solving system (6) algebraically, we get the following equilibrium points:

(a) The competition-free equilibrium $E_0 = (H_0, 0, 0, V_0, 0)$ with

$$H_0 = \frac{\kappa}{d}, \quad V_0 = \frac{\mu}{d_3}.$$

The equilibrium point is biologically admissible if all of its components are nonnegative. Hence, E_0 always exists since $H_0 > 0$ and $V_0 > 0$.

(b) Define $\xi_1 = \beta_2 d_3 + \alpha_3 \beta_3 d$, $\mathcal{R}_0 = \dfrac{\kappa \alpha_2 \beta_2 G_2}{d d_2}$ and $\mathcal{R}_l = 1 + \dfrac{\mu \beta_3}{d_2 d_3}$.

The treatment failure immune-free equilibrium is given by $E_1 = (H_1, 0, Y_1, V_1, 0)$, where

$$H_1 = \frac{\beta_2 \beta_3 (\mu + \kappa \alpha_2 G_2 \alpha_3) + d_2 \xi_1 + \sqrt{(\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1)^2 + \mu \beta_2 \beta_3 [\beta_2 \beta_3 (\mu + 2\kappa \alpha_2 G_2 \alpha_3) + 2 d_2 \xi_1]}}{2 \alpha_2 \beta_2 G_2 \xi_1},$$

$$Y_1 = \frac{\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1 + \beta_2 (\mu \beta_3 + 2 d_2 d_3) - \sqrt{(\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1)^2 + \mu \beta_2 \beta_3 [\beta_2 \beta_3 (\mu + 2\kappa \alpha_2 G_2 \alpha_3) + 2 d_2 \xi_1]}}{2 \beta_2 \alpha_3 \beta_3 d_2},$$

$$V_1 = \frac{\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1 + \mu \beta_2 \beta_3 + \sqrt{(\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1)^2 + \mu \beta_2 \beta_3 [\beta_2 \beta_3 (\mu + 2\kappa \alpha_2 G_2 \alpha_3) + 2 d_2 \xi_1]}}{2 \beta_3 \xi_1}.$$

It is easy to note that $H_1 > 0$ and $V_1 > 0$. Thus, the existence condition of E_1 is determined by $Y_1 > 0$. We find

$$Y_1 > 0 \Longleftrightarrow \kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1 + \beta_2 (\mu \beta_3 + 2 d_2 d_3)$$
$$> \sqrt{(\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1)^2 + \mu \beta_2 \beta_3 [\beta_2 \beta_3 (\mu + 2\kappa \alpha_2 G_2 \alpha_3) + 2 d_2 \xi_1]}$$
$$\Longleftrightarrow 2\beta_2 (\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1)(\mu \beta_3 + 2 d_2 d_3) + \beta_2^2 (\mu \beta_3 + 2 d_2 d_3)^2$$
$$> \mu \beta_2 \beta_3 [\beta_2 \beta_3 (\mu + 2\kappa \alpha_2 G_2 \alpha_3) + 2 d_2 \xi_1]$$
$$\Longleftrightarrow \frac{\kappa \alpha_2 \beta_2 G_2}{d d_2} > 1 + \frac{\mu \beta_3}{d_2 d_3}$$
$$\Longleftrightarrow \mathcal{R}_0 > \mathcal{R}_l.$$

Hence, E_1 exists if $\mathcal{R}_0 > \mathcal{R}_l$.

(c) Take $\mathcal{R}_1 = \dfrac{\kappa \alpha_1 \beta_1 G_1}{d d_1}$. The tumor-free equilibrium is given by $E_2 = (H_2, N_2, 0, V_2, 0)$, where

$$H_2 = \frac{d_1}{\alpha_1 \beta_1 G_1}, \quad N_2 = \frac{d}{\beta_1}(\mathcal{R}_1 - 1), \quad V_2 = \frac{\mu}{d_3}.$$

It is clear that $H_2 > 0$, $N_2 > 0$ if $\mathcal{R}_1 > 1$, and $V_2 > 0$. Hence, the existence condition of E_2 is $\mathcal{R}_1 > 1$.

(d) Define $\xi_2 = \beta_2 d_4 + \alpha_4 \beta_4 d$, $\rho = \dfrac{\alpha_4 \beta_4 d_3}{\alpha_3 \beta_3 d_4}$ and $\mathcal{R}_m = 1 + \dfrac{\beta_2 d_4}{\alpha_4 \beta_4 d}$.

The treatment failure equilibrium is given by $E_3 = (H_3, 0, Y_3, V_3, Z_3)$, where

$$H_3 = \frac{\kappa \alpha_4 \beta_4}{\xi_2}, \quad Y_3 = \frac{d_4}{\alpha_4 \beta_4}, \quad V_3 = \frac{\mu \alpha_4 \beta_4}{\alpha_3 \beta_3 d_4 (\rho - 1)},$$
$$Z_3 = \frac{\kappa \alpha_2 \beta_2 G_2 \alpha_3 \alpha_4 \beta_4 d_4 (\rho - 1) - \xi_2 [\mu \alpha_4 \beta_4 + \alpha_3 d_2 d_4 (\rho - 1)]}{\alpha_3 \beta_4 d_4 \xi_2 (\rho - 1)}.$$

Clearly, $H_3 > 0$, $Y_3 > 0$, and $V_3 > 0$ if $\rho > 1$. Now, we need to find the condition for which $Z_3 > 0$. Indeed,

$$
\begin{aligned}
Z_3 > 0 &\iff \kappa\alpha_2\beta_2 G_2\alpha_3\alpha_4\beta_4 d_4(\rho-1) > \xi_2\left[\mu\alpha_4\beta_4 + \alpha_3 d_2 d_4(\rho-1)\right] \\
&\iff \frac{\kappa\alpha_2\beta_2 G_2}{dd_2} > 1 + \frac{\beta_2 d_4}{\alpha_4\beta_4 d} + \frac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho-1)} \\
&\iff \mathcal{R}_0 > \mathcal{R}_m + \frac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho-1)}.
\end{aligned}
$$

Hence, the existence conditions of E_3 are $\rho > 1$ and $\mathcal{R}_0 > \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho-1)}$.

(e) Take $\mathcal{R}_n = 1 + \dfrac{\beta_2 d_3}{\alpha_3\beta_3 d}$. The partial success immune-free equilibrium is given by $E_4 = (H_4, N_4, Y_4, V_4, 0)$, where

$$
\begin{aligned}
H_4 &= \frac{d_1}{\alpha_1\beta_1 G_1}, \quad N_4 = \frac{\beta_3\left[\kappa\alpha_1\beta_1 G_1\alpha_3 d_2(\mathcal{R}_0/\mathcal{R}_1 - 1) + \mu\beta_2 d_1\right] - d_1 d_2\xi_1(\mathcal{R}_0/\mathcal{R}_1 - 1)}{\beta_1\alpha_3\beta_3 d_1 d_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}, \\
Y_4 &= \frac{d_2 d_3(\mathcal{R}_0/\mathcal{R}_1 - 1) - \mu\beta_3}{\alpha_3\beta_3 d_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}, \quad V_4 = \frac{d_2}{\beta_3}(\mathcal{R}_0/\mathcal{R}_1 - 1).
\end{aligned}
$$

As we can see, $H_4 > 0$, and $V_4 > 0$ if $\mathcal{R}_0/\mathcal{R}_1 > 1$. Next, we need to determine the conditions for which $N_4 > 0$ and $Y_4 > 0$. We have

$$
\begin{aligned}
N_4 > 0 &\iff \beta_3\left[\kappa\alpha_1\beta_1 G_1\alpha_3 d_2(\mathcal{R}_0/\mathcal{R}_1 - 1) + \mu\beta_2 d_1\right] > d_1 d_2\xi_1(\mathcal{R}_0/\mathcal{R}_1 - 1) \\
&\iff \frac{\kappa\alpha_1\beta_1 G_1}{dd_1} + \frac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} > 1 + \frac{\beta_2 d_3}{\alpha_3\beta_3 d} \\
&\iff \mathcal{R}_1 + \frac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} > \mathcal{R}_n.
\end{aligned}
$$

Also, we get

$$
\begin{aligned}
Y_4 > 0 &\iff d_2 d_3(\mathcal{R}_0/\mathcal{R}_1 - 1) > \mu\beta_3 \\
&\iff \frac{\kappa\alpha_2\beta_2 G_2}{dd_2} > \frac{\kappa\alpha_1\beta_1 G_1}{dd_1} + \frac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3} \\
&\iff \mathcal{R}_0 > \mathcal{R}_1 + \frac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3}.
\end{aligned}
$$

Hence, the existence conditions of E_4 are $\mathcal{R}_0/\mathcal{R}_1 > 1$, $\mathcal{R}_n < \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3}$.

(f) The coexistence equilibrium is given by $E_5 = (H_5, N_5, Y_5, V_5, Z_5)$, where

$$
\begin{aligned}
H_5 &= \frac{d_1}{\alpha_1\beta_1 G_1}, \quad N_5 = \frac{\kappa\alpha_1\beta_1 G_1\alpha_4\beta_4 - d_1\xi_2}{\beta_1\alpha_4\beta_4 d_1}, \quad Y_5 = \frac{d_4}{\alpha_4\beta_4}, \quad V_5 = \frac{\mu\alpha_4\beta_4}{\alpha_3\beta_3 d_4(\rho-1)}, \\
Z_5 &= \frac{\alpha_1\beta_1 G_1\alpha_3 d_2 d_4(\mathcal{R}_0/\mathcal{R}_1 - 1)(\rho-1) - \mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_1\beta_1 G_1\alpha_3\beta_4 d_4(\rho-1)}.
\end{aligned}
$$

It is clear that $H_5 > 0$, $Y_5 > 0$, and $V_5 > 0$ if $\rho > 1$. Then, we need to investigate the existence conditions corresponding to $N_5 > 0$ and $Z_5 > 0$. We get

$$N_5 > 0 \iff \kappa\alpha_1\beta_1 G_1\alpha_4\beta_4 > d_1\xi_2$$
$$\iff \frac{\kappa\alpha_1\beta_1 G_1}{dd_1} > 1 + \frac{\beta_2 d_4}{\alpha_4\beta_4 d}$$
$$\iff \mathcal{R}_1 > \mathcal{R}_m.$$

On the other hand, we have

$$Z_5 > 0 \iff \alpha_1\beta_1 G_1\alpha_3 d_2 d_4(\mathcal{R}_0/\mathcal{R}_1 - 1)(\rho - 1) > \mu\alpha_1\beta_1 G_1\alpha_4\beta_4$$
$$\iff \frac{\kappa\alpha_2\beta_2 G_2}{dd_2} > \frac{\kappa\alpha_1\beta_1 G_1}{dd_1} + \frac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho - 1)}$$
$$\iff \mathcal{R}_0 > \mathcal{R}_1 + \frac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho - 1)}.$$

Hence, the existence conditions of E_5 are $\rho > 1$, $\mathcal{R}_1 > \mathcal{R}_m$ and $\mathcal{R}_0 > \mathcal{R}_1 + \frac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho - 1)}$. $\qquad\square$

4 Global properties

In this section, we show the global stability of all equilibrium points computed in Theorem 2. In addition, we check the local instability conditions of these points.

Define a function $\Phi : (0, +\infty) \to [0, +\infty)$ by $\Phi(v) = v - 1 - \ln v$. Clearly, $\Phi(v) = 0$ if and only if $v = 1$.

Theorem 3 (a) *The competition-free equilibrium E_0 is globally asymptotically stable if $\mathcal{R}_1 \leq 1$ and $\mathcal{R}_0 \leq \mathcal{R}_l$.*
(b) *The equilibrium E_0 is unstable if $\mathcal{R}_1 > 1$ or $\mathcal{R}_0 > \mathcal{R}_l$.*

Proof (a) We define the following Lyapunov functional

$$\mathcal{U}_0(t) = \int_\Omega \left\{ H_0\Phi\left(\frac{H}{H_0}\right) + \frac{1}{\alpha_1 G_1}N + \frac{1}{\alpha_2 G_2}Y + \frac{1}{\alpha_2 G_2\alpha_3}V_0\Phi\left(\frac{V}{V_0}\right) + \frac{1}{\alpha_2 G_2\alpha_4}Z \right.$$
$$+ \frac{\beta_1}{G_1}\int_0^\infty g_1(\varsigma)e^{-a_1\varsigma}\int_0^\varsigma H(x, t - \theta)N(x, t - \theta)\, d\theta\, d\varsigma$$
$$\left. + \frac{\beta_2}{G_2}\int_0^\infty g_2(\varsigma)e^{-a_2\varsigma}\int_0^\varsigma H(x, t - \theta)Y(x, t - \theta)\, d\theta\, d\varsigma \right\} dx.$$

By taking the time derivative of $\mathcal{U}_0(t)$ along the solutions of (2), we get

$$
\frac{d\mathcal{U}_0}{dt} = \int_{\Omega} \left\{ \left(1 - \frac{H_0}{H}\right) [D_H \Delta H + \kappa - dH - \beta_1 HN - \beta_2 HY] \right.
$$

$$
+ \frac{1}{\alpha_1 G_1} \left[D_N \Delta N + \alpha_1 \beta_1 \int_0^{\infty} g_1(\varsigma) e^{-a_1\varsigma} H(x, t - \varsigma) N(x, t - \varsigma)\, d\varsigma - d_1 N \right]
$$

$$
+ \frac{1}{\alpha_2 G_2} \left[D_Y \Delta Y + \alpha_2 \beta_2 \int_0^{\infty} g_2(\varsigma) e^{-a_2\varsigma} H(x, t - \varsigma) Y(x, t - \varsigma)\, d\varsigma \right.
$$

$$
\left. - \beta_3 YV - \beta_4 YZ - d_2 Y \right]
$$

$$
+ \frac{1}{\alpha_2 G_2 \alpha_3} \left(1 - \frac{V_0}{V}\right) [D_V \Delta V + \mu + \alpha_3 \beta_3 YV - d_3 V]
$$

$$
+ \frac{1}{\alpha_2 G_2 \alpha_4} [D_Z \Delta Z + \alpha_4 \beta_4 YZ - d_4 Z]
$$

$$
+ \frac{\beta_1}{G_1} \int_0^{\infty} g_1(\varsigma) e^{-a_1\varsigma} [HN - H(x, t - \varsigma) N(x, t - \varsigma)]\, d\varsigma
$$

$$
\left. + \frac{\beta_2}{G_2} \int_0^{\infty} g_2(\varsigma) e^{-a_2\varsigma} [HY - H(x, t - \varsigma) Y(x, t - \varsigma)]\, d\varsigma \right\} dx
$$

$$
= \int_{\Omega} \left\{ \left(1 - \frac{H_0}{H}\right) D_H \Delta H - \frac{d (H - H_0)^2}{H} + \left(\beta_1 H_0 - \frac{d_1}{\alpha_1 G_1}\right) N \right.
$$

$$
+ \left(\beta_2 H_0 - \frac{d_2}{\alpha_2 G_2} - \frac{\beta_3 V_0}{\alpha_2 G_2}\right) Y
$$

$$
+ \frac{\mu}{\alpha_2 G_2 \alpha_3} \left(2 - \frac{V_0}{V} - \frac{V}{V_0}\right) - \frac{d_4}{\alpha_2 G_2 \alpha_4} Z + \frac{1}{\alpha_1 G_1} D_N \Delta N + \frac{1}{\alpha_2 G_2} D_Y \Delta Y
$$

$$
\left. + \frac{1}{\alpha_2 G_2 \alpha_3} \left(1 - \frac{V_0}{V}\right) D_V \Delta V + \frac{1}{\alpha_2 G_2 \alpha_4} D_Z \Delta Z \right\} dx.
$$

$$(7)$$

By using the divergence theorem and NBCs (4), we have

$$
0 = \int_{\partial\Omega} \nabla v \cdot \vec{n}\, dx = \int_{\Omega} \mathrm{div}(\nabla v)\, dx = \int_{\Omega} \Delta v\, dx,
$$

$$
0 = \int_{\partial\Omega} \frac{1}{v} \nabla v \cdot \vec{n}\, dx = \int_{\Omega} \mathrm{div}(\frac{1}{v}\nabla v)\, dx = \int_{\Omega} \left[\frac{\Delta v}{v} - \frac{\|\nabla v\|^2}{v^2}\right] dx,
$$

$$
\text{for } v \in \{H, N, Y, V, Z\}.
$$

Thus, we obtain

$$
\int_{\Omega} \Delta v\, dx = 0,
$$

$$
\int_{\Omega} \frac{\Delta v}{v}\, dx = \int_{\Omega} \frac{\|\nabla v\|^2}{v^2}\, dx, \quad \text{for } v \in \{H, N, Y, V, Z\}.
$$

$$(8)$$

Therefore, Eq. (7) is reduced to

$$
\begin{aligned}
\frac{d\mathcal{U}_0}{dt} = \int_\Omega \Bigg\{ & -\frac{d\,(H-H_0)^2}{H} + \frac{d_1}{\alpha_1 G_1}\,(\mathcal{R}_1 - 1)\,N + \frac{d_2}{\alpha_2 G_2}\,(\mathcal{R}_0 - \mathcal{R}_l)\,Y \\
& -\frac{\mu}{\alpha_2 G_2 \alpha_3}\,\frac{(V-V_0)^2}{V V_0} - \frac{d_4}{\alpha_2 G_2 \alpha_4} Z \Bigg\}\, dx \\
& - D_H H_0 \int_\Omega \frac{\|\nabla H\|^2}{H^2}\, dx - \frac{D_V V_0}{\alpha_2 G_2 \alpha_3} \int_\Omega \frac{\|\nabla V\|^2}{V^2}\, dx.
\end{aligned}
$$

We conclude that $\dfrac{d\mathcal{U}_0}{dt} \le 0$ if $\mathcal{R}_1 \le 1$ and $\mathcal{R}_0 \le \mathcal{R}_l$. Moreover, $\dfrac{d\mathcal{U}_0}{dt} = 0$ when $H = H_0$, $N = 0$, $Y = 0$, $V = V_0$ and $Z = 0$. Thus, the largest invariant set $\Psi_0 \subseteq \Psi = \{(H, N, Y, V, Z) \mid \frac{d\mathcal{U}_0}{dt} = 0\}$ is the singleton $\{E_0\}$. By LaSalle's invariance principle [50,51, Theorem 5.3], E_0 is globally asymptotically stable when $\mathcal{R}_1 \le 1$ and $\mathcal{R}_0 \le \mathcal{R}_l$.

(b) To prove the local instability of E_0, we need to find the characteristic equation. Let $0 = \zeta_1 < \zeta_2 < \cdots < \zeta_k < \cdots$ be the eigenvalues of the Laplace operator $-\Delta$ with the homogeneous NBCs. Let $\mathcal{E}(\zeta_i)$ be the eigenfunction space corresponding to the eigenvalues ζ_i $(i = 1, 2, \ldots)$. Let $\{\rho_{ij} : j = 1, 2, \ldots, \dim \mathcal{E}(\zeta_i)\}$ be an orthonormal basis of $\mathcal{E}(\zeta_i)$, where $\dim \mathcal{E}(\zeta_i)$ is the dimension of the space $\mathcal{E}(\zeta_i)$. Define

$$
\mathbb{S} = \{(H, N, Y, V, Z) \in \left[C^1(\bar{\Omega})\right]^5 : \frac{\partial H}{\partial \vec{n}} = \frac{\partial N}{\partial \vec{n}} = \frac{\partial Y}{\partial \vec{n}} = \frac{\partial V}{\partial \vec{n}} = \frac{\partial Z}{\partial \vec{n}} = 0 \text{ on } \partial\Omega\},
$$

$$
\mathbb{S}_{ij} = \{a\rho_{ij} \mid a \in \mathbb{R}^5\}.
$$

Then, we have

$$
\mathbb{S}_i = \bigoplus_{j=1}^{\dim \mathcal{E}(\xi_i)} \mathbb{S}_{ij} \quad \text{and} \quad \mathbb{S} = \bigoplus_{i=1}^{\infty} \mathbb{S}_i.
$$

Let $E_e = (H_e, N_e, Y_e, V_e, Z_e)$ be an arbitrary equilibrium point of system (2)–(4). Then, the linearization of system (2) at E_e is given by

$$
\frac{\partial W}{\partial t} = \mathcal{D}\Delta W + \mathcal{J}_1 W(x, t) + \mathcal{J}_2 W(x, t - \varsigma),
$$

where $W = (H, N, Y, V, Z)^T$, $\mathcal{D} = diag(D_H, D_N, D_Y, D_V, D_Z)$,

$$
\mathcal{J}_1 = \begin{bmatrix} -d - \beta_1 N_e - \beta_2 Y_e & -\beta_1 H_e & -\beta_2 H_e & 0 & 0 \\ 0 & -d_1 & 0 & 0 & 0 \\ 0 & 0 & -\beta_3 V_e - \beta_4 Z_e - d_2 & -\beta_3 Y_e & -\beta_4 Y_e \\ 0 & 0 & \alpha_3 \beta_3 V_e & \alpha_3 \beta_3 Y_e - d_3 & 0 \\ 0 & 0 & \alpha_4 \beta_4 Z_e & 0 & \alpha_4 \beta_4 Y_e - d_4 \end{bmatrix},
$$

and

$$
\mathcal{J}_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ \alpha_1 \beta_1 G_1 N_e & \alpha_1 \beta_1 G_1 H_e & 0 & 0 & 0 \\ \alpha_2 \beta_2 G_2 Y_e & 0 & \alpha_2 \beta_2 G_2 H_e & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}.
$$

Define $\mathcal{L} W = \mathcal{D}\Delta W + \mathcal{J}_1 W(x, t) + \mathcal{J}_2 W(x, t - \varsigma)$. For each $i \ge 1$, $\mathbb{S}_i$ is invariant under the operator $\mathcal{L}$. In addition, λ is an eigenvalue of $\mathcal{L}$ if and only if it is a root of the characteristic equation

$$det(\lambda I + \mathcal{D}\zeta_i - \mathcal{J}_1 - \mathcal{J}_2 e^{-\lambda\varsigma}) = 0, \tag{9}$$

for some $i \geq 1$, for which there is an eigenvector in $\mathbb{S}_i$. Here, I is the identity matrix. To prove the instability of any equilibrium point, it is enough to find i such that the characteristic equation (9) has a positive root. Let

$$\overline{G}_i = \int_0^\infty g_i(\varsigma)e^{-(a_i+\lambda)\varsigma}\,d\varsigma, \quad \text{for } i = 1, 2.$$

Now, the characteristic equation at E_0 is given by

$$f_{0,1}(\lambda) f_{0,2}(\lambda) (\lambda + d + D_H\zeta_i) (\lambda + d_3 + D_V\zeta_i) (\lambda + d_4 + D_Z\zeta_i) = 0, \tag{10}$$

where

$$f_{0,1}(\lambda) = \lambda - \alpha_1\beta_1\overline{G}_1 H_0 + d_1 + D_N\zeta_i,$$
$$f_{0,2}(\lambda) = \lambda - \alpha_2\beta_2\overline{G}_2 H_0 + d_2 + \beta_3 V_0 + D_Y\zeta_i.$$

From Eq. (10), two roots of the characteristic equation are given by $f_{0,1}(\lambda) = 0$ and $f_{0,2}(\lambda) = 0$. We can see that

$$\lim_{\lambda\to+\infty} f_{0,1}(\lambda) = +\infty, \quad \lim_{\lambda\to+\infty} f_{0,2}(\lambda) = +\infty.$$

In addition, we have

$$f_{0,1}(0)|_{i=1} = -\alpha_1\beta_1 G_1 H_0 + d_1 = -d_1 (\mathcal{R}_1 - 1) < 0 \quad \text{if } \mathcal{R}_1 > 1,$$
$$f_{0,2}(0)|_{i=1} = -\alpha_2\beta_2 G_2 H_0 + d_2 + \beta_3 V_0 = -d_2 (\mathcal{R}_0 - \mathcal{R}_l) < 0 \quad \text{if } \mathcal{R}_0 > \mathcal{R}_l.$$

Hence, the characteristic equation (10) has positive roots if $\mathcal{R}_1 > 1$ or $\mathcal{R}_0 > \mathcal{R}_l$. Thus, the equilibrium E_0 is unstable if $\mathcal{R}_1 > 1$ or $\mathcal{R}_0 > \mathcal{R}_l$.

In the next theorems, we will need the following quantities

$$\ln\frac{H(x, t-\varsigma)N(x, t-\varsigma)}{HN} = \ln\frac{H(x, t-\varsigma)N(x, t-\varsigma)}{H_i N} + \ln\frac{H_i}{H}, \quad \text{for } i = 2, 4, 5,$$
$$\ln\frac{H(x, t-\varsigma)Y(x, t-\varsigma)}{HY} = \ln\frac{H(x, t-\varsigma)Y(x, t-\varsigma)}{H_j Y} + \ln\frac{H_j}{H}, \quad \text{for } j = 1, 3, 4, 5.$$
$$\tag{11}$$

Theorem 4 *Assume that $\rho > 1$, $\mathcal{R}_0/\mathcal{R}_1 > 1$ and $\mathcal{R}_0 > \mathcal{R}_l$. Then, we have the following two situations:*

(a) *The treatment failure immune-free equilibrium E_1 is globally asymptotically stable if*
$$\mathcal{R}_n \geq \mathcal{R}_1 + \frac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} \text{ and } \mathcal{R}_0 \leq \mathcal{R}_m + \frac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}.$$
(b) *The equilibrium E_1 is unstable if $\mathcal{R}_n < \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$ or $\mathcal{R}_0 > \mathcal{R}_m +$*
$$\frac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}.$$

Proof (a) We take the following Lyapunov functional

$$\mathcal{U}_1(t) = \int_\Omega \left\{ H_1 \Phi\left(\frac{H}{H_1}\right) + \frac{1}{\alpha_1 G_1} N + \frac{1}{\alpha_2 G_2} Y_1 \Phi\left(\frac{Y}{Y_1}\right) \right.$$

$$+ \frac{1}{\alpha_2 G_2 \alpha_3} V_1 \Phi\left(\frac{V}{V_1}\right) + \frac{1}{\alpha_2 G_2 \alpha_4} Z$$

$$+ \frac{\beta_1}{G_1} \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} \int_0^\varsigma H(x, t-\theta) N(x, t-\theta) \, d\theta \, d\varsigma$$

$$\left. + \frac{\beta_2}{G_2} H_1 Y_1 \int_0^\infty g_2(\varsigma) e^{-a_2 \varsigma} \int_0^\varsigma \Phi\left(\frac{H(x, t-\theta) Y(x, t-\theta)}{H_1 Y_1}\right) d\theta \, d\varsigma \right\} dx.$$

By taking the time derivative of $\mathcal{U}_1(t)$ along the solutions of (2), we obtain

$$\frac{d\mathcal{U}_1}{dt} = \int_\Omega \left\{ \left(1 - \frac{H_1}{H}\right) [D_H \Delta H + \kappa - dH - \beta_1 HN - \beta_2 HY] \right.$$

$$+ \frac{1}{\alpha_1 G_1} \left[D_N \Delta N + \alpha_1 \beta_1 \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} H(x, t-\varsigma) N(x, t-\varsigma) \, d\varsigma - d_1 N \right]$$

$$+ \frac{1}{\alpha_2 G_2} \left(1 - \frac{Y_1}{Y}\right) \left[D_Y \Delta Y + \alpha_2 \beta_2 \int_0^\infty g_2(\varsigma) e^{-a_2 \varsigma} H(x, t-\varsigma) Y(x, t-\varsigma) \, d\varsigma \right.$$

$$\left. - \beta_3 YV - \beta_4 YZ - d_2 Y \right]$$

$$+ \frac{1}{\alpha_2 G_2 \alpha_3} \left(1 - \frac{V_1}{V}\right) [D_V \Delta V + \mu + \alpha_3 \beta_3 YV - d_3 V]$$

$$+ \frac{1}{\alpha_2 G_2 \alpha_4} [D_Z \Delta Z + \alpha_4 \beta_4 YZ - d_4 Z]$$

$$+ \frac{\beta_1}{G_1} \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} [HN - H(x, t-\varsigma) N(x, t-\varsigma)] \, d\varsigma$$

$$+ \frac{\beta_2}{G_2} H_1 Y_1 \int_0^\infty g_2(\varsigma) e^{-a_2 \varsigma} \left[\frac{HY}{H_1 Y_1} - \frac{H(x, t-\varsigma) Y(x, t-\varsigma)}{H_1 Y_1} \right.$$

$$\left. + \ln \frac{H(x, t-\varsigma) Y(x, t-\varsigma)}{HY} \right] d\varsigma \right\} dx.$$

From (6), we can see that E_1 satisfies the following equilibrium conditions

$$\begin{cases} \kappa = dH_1 + \beta_2 H_1 Y_1, \\ \frac{\beta_3}{\alpha_2 G_2} Y_1 V_1 = \frac{d_3}{\alpha_2 G_2 \alpha_3} V_1 - \frac{\mu}{\alpha_2 G_2 \alpha_3}, \\ \beta_2 H_1 Y_1 = \frac{\beta_3}{\alpha_2 G_2} Y_1 V_1 + \frac{d_2}{\alpha_2 G_2} Y_1. \end{cases} \tag{12}$$

By using (12), the time derivative of $\mathcal{U}_1(t)$ is simplified to

$$
\begin{aligned}
\frac{d\mathcal{U}_1}{dt} = \int_\Omega \Bigg\{ & \left(1 - \frac{H_1}{H}\right)(dH_1 - dH) + \left(\beta_1 H_1 - \frac{d_1}{\alpha_1 G_1}\right) N \\
& + \frac{\mu}{\alpha_2 G_2 \alpha_3}\left(2 - \frac{V_1}{V} - \frac{V}{V_1}\right) + \left(\frac{\beta_4}{\alpha_2 G_2} Y_1 - \frac{d_4}{\alpha_2 G_2 \alpha_4}\right) Z \\
& + \beta_2 H_1 Y_1 \left(2 - \frac{H_1}{H} - \frac{1}{G_2}\int_0^\infty g_2(\varsigma) e^{-a_2\varsigma} \frac{H(x, t - \varsigma)Y(x, t - \varsigma)}{H_1 Y}\, d\varsigma\right) \\
& + \frac{\beta_2}{G_2} H_1 Y_1 \int_0^\infty g_2(\varsigma) e^{-a_2\varsigma} \ln \frac{H(x, t - \varsigma)Y(x, t - \varsigma)}{HY}\, d\varsigma \\
& + \left(1 - \frac{H_1}{H}\right) D_H \Delta H + \frac{1}{\alpha_1 G_1} D_N \Delta N + \frac{1}{\alpha_2 G_2}\left(1 - \frac{Y_1}{Y}\right) D_Y \Delta Y \\
& + \frac{1}{\alpha_2 G_2 \alpha_3}\left(1 - \frac{V_1}{V}\right) D_V \Delta V \\
& + \frac{1}{\alpha_2 G_2 \alpha_4} D_Z \Delta Z \Bigg\}\, dx.
\end{aligned}
\tag{13}
$$

After using (8) and (11), the time derivative in (13) is transformed to

$$
\begin{aligned}
\frac{d\mathcal{U}_1}{dt} = \int_\Omega \Bigg\{ & -\frac{d(H - H_1)^2}{H} + \beta_1 (H_1 - H_4) N \\
& - \frac{\mu}{\alpha_2 G_2 \alpha_3}\frac{(V - V_1)^2}{V V_1} + \frac{\beta_4}{\alpha_2 G_2}(Y_1 - Y_3) Z \\
& - \frac{\beta_2}{G_2} H_1 Y_1 \int_0^\infty g_2(\varsigma) e^{-a_2\varsigma}\left[\Phi\left(\frac{H_1}{H}\right)\right. \\
& \left. + \Phi\left(\frac{H(x, t - \varsigma)Y(x, t - \varsigma)}{H_1 Y}\right)\right] d\varsigma \Bigg\}\, dx \\
& - D_H H_1 \int_\Omega \frac{\|\nabla H\|^2}{H^2}\, dx - \frac{D_Y Y_1}{\alpha_2 G_2}\int_\Omega \frac{\|\nabla Y\|^2}{Y^2}\, dx \\
& - \frac{D_V V_1}{\alpha_2 G_2 \alpha_3}\int_\Omega \frac{\|\nabla V\|^2}{V^2}\, dx.
\end{aligned}
$$

We can see that $\dfrac{d\mathcal{U}_1}{dt} \leq 0$ if $(H_1 - H_4) \leq 0$ and $(Y_1 - Y_3) \leq 0$. From the equilibrium points, we have

$$
H_1 - H_4 \leq 0 \iff \frac{\beta_2 \beta_3 (\mu + \kappa \alpha_2 G_2 \alpha_3) + d_2 \xi_1 + \sqrt{(\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1)^2 + \mu \beta_2 \beta_3 [\beta_2 \beta_3 (\mu + 2\kappa \alpha_2 G_2 \alpha_3) + 2 d_2 \xi_1]}}{2\alpha_2 \beta_2 G_2 \xi_1}
$$

$$
\leq \frac{d_1}{\alpha_1 \beta_1 G_1}
$$

$$
\iff \sqrt{(\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1)^2 + \mu \beta_2 \beta_3 [\beta_2 \beta_3 (\mu + 2\kappa \alpha_2 G_2 \alpha_3) + 2 d_2 \xi_1]}
$$

$$
\leq \frac{2\alpha_2 \beta_2 G_2 d_1 \xi_1}{\alpha_1 \beta_1 G_1} - [\kappa \alpha_2 \beta_2 G_2 \alpha_3 \beta_3 - d_2 \xi_1 + 2 d_2 \xi_1 + \mu \beta_2 \beta_3]
$$

$$
\iff \kappa \alpha_1 \beta_1 G_1 \alpha_3 \beta_3 d_2 (\mathcal{R}_0/\mathcal{R}_1 - 1) + \mu \beta_2 \beta_3 d_1
$$

$$
\leq (\beta_2 d_1 d_2 d_3 + \alpha_3 \beta_3 dd_1 d_2)(\mathcal{R}_0/\mathcal{R}_1 - 1)
$$

$$\Longleftrightarrow \frac{\kappa\alpha_1\beta_1 G_1}{dd_1} + \frac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} \le 1 + \frac{\beta_2 d_3}{\alpha_3\beta_3 d}$$

$$\Longleftrightarrow \mathcal{R}_1 + \frac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} \le \mathcal{R}_n.$$

Also, we have

$$
Y_1 - Y_3 \le 0 \Longleftrightarrow \kappa\alpha_2\beta_2 G_2\alpha_3\beta_3 - d_2\xi_1 + \mu\beta_2\beta_3 + 2\beta_2 d_2 d_3 - \frac{2\beta_2\alpha_3\beta_3 d_2 d_4}{\alpha_4\beta_4}
$$

$$
\le \sqrt{(\kappa\alpha_2\beta_2 G_2\alpha_3\beta_3 - d_2\xi_1)^2 + \mu\beta_2\beta_3\left[\beta_2\beta_3\left(\mu + 2\kappa\alpha_2 G_2\alpha_3\right) + 2d_2\xi_1\right]}
$$

$$
\Longleftrightarrow \kappa\alpha_2\beta_2 G_2\alpha_3\alpha_4\beta_4 d_4(\rho - 1)
$$

$$
\le \alpha_3 d_2 d_4\left(\beta_2 d_4 + \alpha_4\beta_4 d\right)(\rho - 1) + \mu\alpha_4\beta_4\xi_2
$$

$$
\Longleftrightarrow \frac{\kappa\alpha_2\beta_2 G_2}{dd_2} \le 1 + \frac{\beta_2 d_4}{\alpha_4\beta_4 d} + \frac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}
$$

$$
\Longleftrightarrow \mathcal{R}_0 \le \mathcal{R}_m + \frac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}.
$$

Hence, $\dfrac{d\mathcal{U}_1}{dt} \le 0$ if $\mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} \le \mathcal{R}_n$ and $\mathcal{R}_0 \le \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}$.
Also, one can show that $\dfrac{d\mathcal{U}_1}{dt} = 0$ when $H = H_1$, $N = 0$, $Y = Y_1$, $V = V_1$ and $Z = 0$.
Thus, the largest invariant set $\Psi_1 \subseteq \Psi = \{(H, N, Y, V, Z) \mid \frac{d\mathcal{U}_1}{dt} = 0\}$ is the singleton $\{E_1\}$.
When $\rho > 1$, $\mathcal{R}_0/\mathcal{R}_1 > 1$ and $\mathcal{R}_0 > \mathcal{R}_l$, LaSalle's invariance principle [50,51] ensures that
the equilibrium E_1 is globally asymptotically stable for $\mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} \le \mathcal{R}_n$

and $\mathcal{R}_0 \le \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}$.

(b) From (9), the characteristic equation at E_1 is given by

$$
\begin{aligned}
f_1(\lambda) & (\lambda - \alpha_4\beta_4 Y_1 + d_4 + D_Z\zeta_i)\Big(\alpha_3\beta_3^2 Y_1 V_1 (\lambda + \beta_2 Y_1 + d + D_H\zeta_i) \\
& + (\lambda - \alpha_3\beta_3 Y_1 + d_3 + D_V\zeta_i) \\
& \times \big[\alpha_2\beta_2^2 \overline{G}_2 H_1 Y_1 + (\lambda + \beta_2 Y_1 + d + D_H\zeta_i) \\
& \quad (\lambda - \alpha_2\beta_2 \overline{G}_2 H_1 + \beta_3 V_1 + d_2 + D_Y\zeta_i)\big]\Big) = 0,
\end{aligned}
\tag{14}
$$

where

$$f_1(\lambda) = \lambda - \alpha_1\beta_1\overline{G}_1 H_1 + d_1 + D_N\zeta_i.$$

Two roots of the characteristic equation (14) are given by $f_1(\lambda) = 0$ and $(\lambda - \alpha_4\beta_4 Y_1 + d_4 + D_Z\zeta_i) = 0$. We have

$$\lim_{\lambda \to +\infty} f_1(\lambda) = +\infty,$$

$$f_1(0)|_{i=1} = -\alpha_1\beta_1 G_1 H_1 + d_1 = -\alpha_1\beta_1 G_1 (H_1 - H_4).$$

From the proof of part (a), we can see that $f_1(0)|_{i=1} < 0$ if $\mathcal{R}_n < \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$. The other root at $i = 1$ is given by

$$\lambda|_{i=1} = \alpha_4\beta_4 Y_1 - d_4 = \alpha_4\beta_4 (Y_1 - Y_3) > 0 \quad \text{if } \mathcal{R}_0 > \mathcal{R}_m + \frac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}.$$

Thus, the characteristic equation has positive roots if $\mathcal{R}_n < \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$ or $\mathcal{R}_0 > \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}$. In this situation, the equilibrium E_1 is unstable. $\qquad\square$

Theorem 5 *Assume that $\mathcal{R}_1 > 1$. Then, we have the following two situations:*

(a) *The tumor-free equilibrium E_2 is globally asymptotically stable if $\mathcal{R}_0 \leq \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3}$.*

(b) *The equilibrium E_2 is unstable if $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3}$.*

Proof (a) We consider the following Lyapunov functional

$$
\mathcal{U}_2(t) = \int_\Omega \left\{ H_2\Phi\left(\frac{H}{H_2}\right) + \frac{1}{\alpha_1 G_1}N_2\Phi\left(\frac{N}{N_2}\right) + \frac{1}{\alpha_2 G_2}Y \right.
$$
$$
+ \frac{1}{\alpha_2 G_2\alpha_3}V_2\Phi\left(\frac{V}{V_2}\right) + \frac{1}{\alpha_2 G_2\alpha_4}Z
$$
$$
+ \frac{\beta_1}{G_1}H_2 N_2 \int_0^\infty g_1(\varsigma)e^{-a_1\varsigma}\int_0^\varsigma \Phi\left(\frac{H(x,t-\theta)N(x,t-\theta)}{H_2 N_2}\right)\,d\theta\,d\varsigma
$$
$$
\left. + \frac{\beta_2}{G_2}\int_0^\infty g_2(\varsigma)e^{-a_2\varsigma}\int_0^\varsigma H(x,t-\theta)Y(x,t-\theta)\,d\theta\,d\varsigma \right\}\,dx.
$$

By computing the time derivative of $\mathcal{U}_2(t)$ along the solutions of (2), we have

$$
\frac{d\mathcal{U}_2}{dt} = \int_\Omega \left\{ \left(1 - \frac{H_2}{H}\right)[D_H\Delta H + \kappa - dH - \beta_1 HN - \beta_2 HY] \right.
$$
$$
+ \frac{1}{\alpha_1 G_1}\left(1 - \frac{N_2}{N}\right)\left[D_N\Delta N + \alpha_1\beta_1\int_0^\infty g_1(\varsigma)e^{-a_1\varsigma}H(x,t-\varsigma)N(x,t-\varsigma)\,d\varsigma - d_1 N\right]
$$
$$
+ \frac{1}{\alpha_2 G_2}\left[D_Y\Delta Y + \alpha_2\beta_2\int_0^\infty g_2(\varsigma)e^{-a_2\varsigma}H(x,t-\varsigma)Y(x,t-\varsigma)\,d\varsigma - \beta_3 YV - \beta_4 YZ - d_2 Y\right]
$$
$$
+ \frac{1}{\alpha_2 G_2\alpha_3}\left(1 - \frac{V_2}{V}\right)[D_V\Delta V + \mu + \alpha_3\beta_3 YV - d_3 V]
$$
$$
+ \frac{1}{\alpha_2 G_2\alpha_4}[D_Z\Delta Z + \alpha_4\beta_4 YZ - d_4 Z]
$$
$$
+ \frac{\beta_1}{G_1}H_2 N_2\int_0^\infty g_1(\varsigma)e^{-a_1\varsigma}\left[\frac{HN}{H_2 N_2} - \frac{H(x,t-\varsigma)N(x,t-\varsigma)}{H_2 N_2}\right.
$$
$$
\left. + \ln\frac{H(x,t-\varsigma)N(x,t-\varsigma)}{HN}\right]\,d\varsigma
$$
$$
\left. + \frac{\beta_2}{G_2}\int_0^\infty g_2(\varsigma)e^{-a_2\varsigma}[HY - H(x,t-\varsigma)Y(x,t-\varsigma)]\,d\varsigma \right\}\,dx.
$$

From (6), we can see that E_2 satisfies the following conditions

$$
\begin{cases}
\kappa = d H_2 + \beta_1 H_2 N_2, \\
\beta_1 H_2 N_2 = \frac{d_1}{\alpha_1 G_1} N_2, \\
\frac{\mu}{\alpha_2 G_2 \alpha_3} = \frac{d_3}{\alpha_2 G_2 \alpha_3} V_2.
\end{cases}
\tag{15}
$$

By using (15), the time derivative of $\mathcal{U}_2(t)$ can be simplified to

$$
\begin{aligned}
\frac{d\mathcal{U}_2}{dt} = \int_\Omega \Bigg\{ & \left(1 - \frac{H_2}{H}\right)(d H_2 - d H) + \left(\beta_2 H_2 - \frac{d_2}{\alpha_2 G_2} - \frac{\beta_3}{\alpha_2 G_2} V_2\right) Y \\
& + \frac{\mu}{\alpha_2 G_2 \alpha_3} \left(2 - \frac{V_2}{V} - \frac{V}{V_2}\right) \\
& - \frac{d_4}{\alpha_2 G_2 \alpha_4} Z + \beta_1 H_2 N_2 \Bigg(2 - \frac{H_2}{H} \\
& - \frac{1}{G_1} \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} \frac{H(x, t-\varsigma) N(x, t-\varsigma)}{H_2 N} \, d\varsigma \Bigg) \\
& + \frac{\beta_1}{G_1} H_2 N_2 \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} \ln \frac{H(x, t-\varsigma) N(x, t-\varsigma)}{H N} \, d\varsigma \\
& + \left(1 - \frac{H_2}{H}\right) D_H \Delta H + \frac{1}{\alpha_1 G_1} \left(1 - \frac{N_2}{N}\right) D_N \Delta N \\
& + \frac{1}{\alpha_2 G_2} D_Y \Delta Y + \frac{1}{\alpha_2 G_2 \alpha_3} \left(1 - \frac{V_2}{V}\right) D_V \Delta V \\
& + \frac{1}{\alpha_2 G_2 \alpha_4} D_Z \Delta Z \Bigg\} \, dx.
\end{aligned}
\tag{16}
$$

After using (8) and (11), the time derivative in (16) is transformed to

$$
\begin{aligned}
\frac{d\mathcal{U}_2}{dt} = \int_\Omega \Bigg\{ & -\frac{d\,(H - H_2)^2}{H} + \frac{d d_1 d_2}{\kappa \alpha_1 \beta_1 G_1 \alpha_2 G_2} \left(\mathcal{R}_0 - \mathcal{R}_1 - \frac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{d d_1 d_2 d_3}\right) Y \\
& - \frac{\mu}{\alpha_2 G_2 \alpha_3} \frac{(V - V_2)^2}{V V_2} - \frac{d_4}{\alpha_2 G_2 \alpha_4} Z \\
& - \frac{\beta_1}{G_1} H_2 N_2 \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} \left[\Phi\left(\frac{H_2}{H}\right) + \Phi\left(\frac{H(x, t-\varsigma) N(x, t-\varsigma)}{H_2 N}\right)\right] d\varsigma \Bigg\} \, dx \\
& - D_H H_2 \int_\Omega \frac{\|\nabla H\|^2}{H^2} \, dx - \frac{D_N N_2}{\alpha_1 G_1} \int_\Omega \frac{\|\nabla N\|^2}{N^2} \, dx - \frac{D_V V_2}{\alpha_2 G_2 \alpha_3} \int_\Omega \frac{\|\nabla V\|^2}{V^2} \, dx.
\end{aligned}
$$

We note that $\frac{d\mathcal{U}_2}{dt} \le 0$ if $\mathcal{R}_0 \le \mathcal{R}_1 + \frac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{d d_1 d_2 d_3}$. In addition, It can be easily shown that $\frac{d\mathcal{U}_2}{dt} = 0$ if $H = H_2$, $N = N_2$, $Y = 0$, $V = V_2$ and $Z = 0$. Thus, the largest invariant set $\Psi_2 \subseteq \Psi = \{(H, N, Y, V, Z) \mid \frac{d\mathcal{U}_2}{dt} = 0\}$ is the singleton $\{E_2\}$. Accordingly,

LaSalle's invariance principle [50,51] guarantees the global asymptotic stability of E_2 when $\mathcal{R}_1 > 1$ and $\mathcal{R}_0 \leq \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{dd_1d_2d_3}$.

(b) From (9), the characteristic equation at E_2 is given by

$$
\begin{aligned}
& f_2(\lambda)\,(\lambda + d_3 + D_V \zeta_i)\,(\lambda + d_4 + D_Z \zeta_i) \\
& \times \left[\alpha_1 \beta_1^2 \overline{G}_2 H_2 N_2 + (\lambda + \beta_1 N_2 + d + D_H \zeta_i)\,\big(\lambda - \alpha_1 \beta_1 \overline{G}_1 H_2 + d_1 + D_N \zeta_i\big) \right] = 0,
\end{aligned}
\tag{17}
$$

where

$$
f_2(\lambda) = \lambda - \alpha_2 \beta_2 \overline{G}_2 H_2 + d_2 + \beta_3 V_2 + D_Y \zeta_i.
$$

One root of the characteristic equation (17) is given by $f_2(\lambda) = 0$, where we have

$$
\lim_{\lambda \to +\infty} f_2(\lambda) = +\infty,
$$

$$
f_2(0)|_{i=1} = -\alpha_2 \beta_2 G_2 H_2 + d_2 + \beta_3 V_2 = -\frac{dd_1d_2}{\kappa \alpha_1 \beta_1 G_1} \left(\mathcal{R}_0 - \mathcal{R}_1 - \frac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{dd_1d_2d_3} \right).
$$

We note that $f_2(0)|_{i=1} < 0$ if $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{dd_1d_2d_3}$, and the characteristic equation (17) has a positive root in this case. Hence, the equilibrium E_2 is unstable if $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{dd_1d_2d_3}$.   □

Theorem 6 *Suppose that $\rho > 1$ and $\mathcal{R}_0 > \mathcal{R}_m + \dfrac{\mu \xi_2}{\alpha_3 dd_2d_4(\rho - 1)}$. Then, we have the following two situations:*

(a) *The treatment failure equilibrium E_3 is globally asymptotically stable if $\mathcal{R}_1 \leq \mathcal{R}_m$.*
(b) *The equilibrium E_3 is unstable if $\mathcal{R}_1 > \mathcal{R}_m$.*

Proof (a) We consider the following Lyapunov functional

$$
\begin{aligned}
\mathcal{U}_3(t) = \int_\Omega \Bigg\{ & H_3 \Phi\left(\frac{H}{H_3}\right) + \frac{1}{\alpha_1 G_1} N + \frac{1}{\alpha_2 G_2} Y_3 \Phi\left(\frac{Y}{Y_3}\right) \\
& + \frac{1}{\alpha_2 G_2 \alpha_3} V_3 \Phi\left(\frac{V}{V_3}\right) + \frac{1}{\alpha_2 G_2 \alpha_4} Z_3 \Phi\left(\frac{Z}{Z_3}\right) \\
& + \frac{\beta_1}{G_1} \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} \int_0^\varsigma H(x, t-\theta) N(x, t-\theta)\, d\theta\, d\varsigma \\
& + \frac{\beta_2}{G_2} H_3 Y_3 \int_0^\infty g_2(\varsigma) e^{-a_2 \varsigma} \int_0^\varsigma \Phi\left(\frac{H(x, t-\theta) Y(x, t-\theta)}{H_3 Y_3}\right) d\theta\, d\varsigma \Bigg\}\, dx.
\end{aligned}
$$

By taking the time derivative of $\mathcal{U}_3(t)$ along the solutions of (2), we obtain

$$
\begin{aligned}
\frac{d\mathcal{U}_3}{dt} &= \int_\Omega \left\{ \left(1 - \frac{H_3}{H}\right) \left[D_H \Delta H + \kappa - dH - \beta_1 HN - \beta_2 HY \right] \right. \\
&\quad + \frac{1}{\alpha_1 G_1} \left[D_N \Delta N + \alpha_1 \beta_1 \int_0^\infty g_1(\varsigma) e^{-a_1\varsigma} H(x, t - \varsigma) N(x, t - \varsigma)\, d\varsigma - d_1 N \right] \\
&\quad + \frac{1}{\alpha_2 G_2} \left(1 - \frac{Y_3}{Y}\right) \left[D_Y \Delta Y + \alpha_2 \beta_2 \int_0^\infty g_2(\varsigma) e^{-a_2\varsigma} H(x, t - \varsigma) Y(x, t - \varsigma)\, d\varsigma \right. \\
&\quad \left. - \beta_3 YV - \beta_4 YZ - d_2 Y \right] \\
&\quad + \frac{1}{\alpha_2 G_2 \alpha_3} \left(1 - \frac{V_3}{V}\right) [D_V \Delta V + \mu + \alpha_3 \beta_3 YV - d_3 V] \\
&\quad + \frac{1}{\alpha_2 G_2 \alpha_4} \left(1 - \frac{Z_3}{Z}\right) [D_Z \Delta Z + \alpha_4 \beta_4 YZ - d_4 Z] \\
&\quad + \frac{\beta_1}{G_1} \int_0^\infty g_1(\varsigma) e^{-a_1\varsigma} [HN - H(x, t - \varsigma) N(x, t - \varsigma)]\, d\varsigma \\
&\quad + \frac{\beta_2}{G_2} H_3 Y_3 \int_0^\infty g_2(\varsigma) e^{-a_2\varsigma} \left[\frac{HY}{H_3 Y_3} - \frac{H(x, t - \varsigma) Y(x, t - \varsigma)}{H_3 Y_3} \right. \\
&\quad \left. \left. + \ln \frac{H(x, t - \varsigma) Y(x, t - \varsigma)}{HY} \right]\, d\varsigma \right\}\, dx.
\end{aligned}
\tag{18}
$$

From (6), we can see that E_3 satisfies the following equilibrium conditions

$$
\begin{cases}
\kappa = dH_3 + \beta_2 H_3 Y_3, \\
\frac{\beta_3}{\alpha_2 G_2} Y_3 V_3 = \frac{d_3}{\alpha_2 G_2 \alpha_3} V_3 - \frac{\mu}{\alpha_2 G_2 \alpha_3}, \\
\frac{\beta_4}{\alpha_2 G_2} Y_3 Z_3 = \frac{d_4}{\alpha_2 G_2 \alpha_4} Z_3, \\
\beta_2 H_3 Y_3 = \frac{\beta_3}{\alpha_2 G_2} Y_3 V_3 + \frac{\beta_4}{\alpha_2 G_2} Y_3 Z_3 + \frac{d_2}{\alpha_2 G_2} Y_3.
\end{cases}
\tag{19}
$$

By using (19), (8) and (11), the time derivative in (18) is transformed to

$$
\begin{aligned}
\frac{d\mathcal{U}_3}{dt} &= \int_\Omega \left\{ -\frac{d(H - H_3)^2}{H} + \frac{\alpha_4 \beta_4 dd_1}{\alpha_1 G_1 \xi_2} (\mathcal{R}_1 - \mathcal{R}_m) N - \frac{\mu}{\alpha_2 G_2 \alpha_3} \frac{(V - V_3)^2}{VV_3} \right. \\
&\quad - \frac{\beta_2}{G_2} H_3 Y_3 \int_0^\infty g_2(\varsigma) e^{-a_2\varsigma} \left[\Phi\left(\frac{H_3}{H}\right) \right. \\
&\quad \left. \left. + \Phi\left(\frac{H(x, t - \varsigma) Y(x, t - \varsigma)}{H_3 Y}\right) \right]\, d\varsigma \right\}\, dx \\
&\quad - D_H H_3 \int_\Omega \frac{\|\nabla H\|^2}{H^2}\, dx - \frac{D_Y Y_3}{\alpha_2 G_2} \int_\Omega \frac{\|\nabla Y\|^2}{Y^2}\, dx \\
&\quad - \frac{D_V V_3}{\alpha_2 G_2 \alpha_3} \int_\Omega \frac{\|\nabla V\|^2}{V^2}\, dx - \frac{D_Z Z_3}{\alpha_2 G_2 \alpha_4} \int_\Omega \frac{\|\nabla Z\|^2}{Z^2}\, dx.
\end{aligned}
$$

This implies that $\dfrac{d\mathcal{U}_3}{dt} \leq 0$ if $\mathcal{R}_1 \leq \mathcal{R}_m$. Moreover, $\dfrac{d\mathcal{U}_3}{dt} = 0$ when $H = H_3$, $N = 0$, $Y = Y_3$, $V = V_3$ and $Z = Z_3$. Thus, the largest invariant set $\Psi_3 \subseteq \Psi = \{(H, N, Y, V, Z) \mid \dfrac{d\mathcal{U}_3}{dt} = 0\}$ is the singleton $\{E_3\}$. By LaSalle's invariance principle [50,51], the equilibrium E_3 is globally asymptotically stable if $\mathcal{R}_1 \leq \mathcal{R}_m$ given that the point exists for $\rho > 1$ and $\mathcal{R}_0 > \mathcal{R}_m + \dfrac{\mu \xi_2}{\alpha_3 d d_2 d_4 (\rho - 1)}$.

(b) From (9), the characteristic equation at E_3 is given by

$$
f_3(\lambda)\Bigg((\lambda + \beta_2 Y_3 + d + D_H \zeta_i) \left[\alpha_4 \beta_4^2 Y_3 Z_3 (\lambda - \alpha_3 \beta_3 Y_3 + d_3 + D_V \zeta_i) \right.
$$

$$
\left. + \alpha_3 \beta_3^2 Y_3 V_3 (\lambda - \alpha_4 \beta_4 Y_3 + d_4 + D_Z \zeta_i) \right]
$$

$$
+ (\lambda - \alpha_4 \beta_4 Y_3 + d_4 + D_Z \zeta_i)(\lambda - \alpha_3 \beta_3 Y_3 + d_3 + D_V \zeta_i) \tag{20}
$$

$$
\times \left[\alpha_2 \beta_2^2 \overline{G}_2 H_3 Y_3 + (\lambda + \beta_2 Y_3 + d + D_H \zeta_i) \right.
$$

$$
\left. (\lambda - \alpha_2 \beta_2 \overline{G}_2 H_3 + \beta_3 V_3 + \beta_4 Z_3 + d_2 + D_Y \zeta_i) \right] \Bigg) = 0,
$$

where

$$
f_3(\lambda) = \lambda - \alpha_1 \beta_1 \overline{G}_1 H_3 + d_1 + D_N \zeta_i.
$$

One root of the characteristic Eq. (20) is determined by $f_3(\lambda) = 0$, where

$$
\lim_{\lambda \to +\infty} f_3(\lambda) = +\infty,
$$

$$
f_3(0)|_{i=1} = -\alpha_1 \beta_1 G_1 H_3 + d_1 = -\dfrac{\alpha_4 \beta_4 d d_1}{\xi_2} (\mathcal{R}_1 - \mathcal{R}_m).
$$

When $\mathcal{R}_1 > \mathcal{R}_m$, we can see that $f_3(0)|_{i=1} < 0$ and the characteristic equation (20) has a positive root in this situation. Hence, the equilibrium E_3 is unstable if $\mathcal{R}_1 > \mathcal{R}_m$. □

Theorem 7 *Assume that $\rho > 1$, $\mathcal{R}_0/\mathcal{R}_1 > 1$, $\mathcal{R}_n < \mathcal{R}_1 + \dfrac{\mu \beta_2}{\alpha_3 d d_2 (\mathcal{R}_0/\mathcal{R}_1 - 1)}$ and $\mathcal{R}_0 >$*
$\mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{d d_1 d_2 d_3}$. *Then, we have the following two situations:*

(a) *The partial success immune-free equilibrium E_4 is globally asymptotically stable if $\mathcal{R}_0 \leq$*
$\mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \alpha_4 \beta_4}{\alpha_3 d d_1 d_2 d_4 (\rho - 1)}$.

(b) *The equilibrium E_4 is unstable if $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \alpha_4 \beta_4}{\alpha_3 d d_1 d_2 d_4 (\rho - 1)}$.*

Proof (a) We take the following Lyapunov functional

$$
\mathcal{U}_4(t) = \int_\Omega \Bigg\{ H_4 \Phi\left(\dfrac{H}{H_4}\right) + \dfrac{1}{\alpha_1 G_1} N_4 \Phi\left(\dfrac{N}{N_4}\right) + \dfrac{1}{\alpha_2 G_2} Y_4 \Phi\left(\dfrac{Y}{Y_4}\right)
$$

$$
+ \dfrac{1}{\alpha_2 G_2 \alpha_3} V_4 \Phi\left(\dfrac{V}{V_4}\right) + \dfrac{1}{\alpha_2 G_2 \alpha_4} Z
$$

$$
+ \dfrac{\beta_1}{G_1} H_4 N_4 \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} \int_0^\varsigma \Phi\left(\dfrac{H(x, t-\theta) N(x, t-\theta)}{H_4 N_4}\right) d\theta \, d\varsigma
$$

$$
+ \dfrac{\beta_2}{G_2} H_4 Y_4 \int_0^\infty g_2(\varsigma) e^{-a_2 \varsigma} \int_0^\varsigma \Phi\left(\dfrac{H(x, t-\theta) Y(x, t-\theta)}{H_4 Y_4}\right) d\theta \, d\varsigma \Bigg\} dx.
$$

By computing the time derivative of $\mathcal{U}_4(t)$ along the solutions of (2), we obtain

$$
\begin{aligned}
\frac{\mathrm{d}\mathcal{U}_4}{\mathrm{d}t} = \int_\Omega \Bigg\{ &\left(1 - \frac{H_4}{H}\right)[D_H \Delta H + \kappa - dH - \beta_1 HN - \beta_2 HY] \\
&+ \frac{1}{\alpha_1 G_1}\left(1 - \frac{N_4}{N}\right)\Bigg[D_N \Delta N + \alpha_1 \beta_1 \int_0^\infty g_1(\varsigma)\mathrm{e}^{-a_1\varsigma} H(x, t-\varsigma) \\
&\times N(x, t-\varsigma)\,\mathrm{d}\varsigma - d_1 N\Bigg] \\
&+ \frac{1}{\alpha_2 G_2}\left(1 - \frac{Y_4}{Y}\right)\Bigg[D_Y \Delta Y + \alpha_2 \beta_2 \int_0^\infty g_2(\varsigma)\mathrm{e}^{-a_2\varsigma} H(x, t-\varsigma)Y(x, t-\varsigma)\,\mathrm{d}\varsigma \\
&- \beta_3 YV - \beta_4 YZ - d_2 Y\Bigg] \\
&+ \frac{1}{\alpha_2 G_2 \alpha_3}\left(1 - \frac{V_4}{V}\right)[D_V \Delta V \\
&+ \mu + \alpha_3 \beta_3 YV - d_3 V] \\
&+ \frac{1}{\alpha_2 G_2 \alpha_4}[D_Z \Delta Z + \alpha_4 \beta_4 YZ - d_4 Z] \\
&+ \frac{\beta_1}{G_1} H_4 N_4 \int_0^\infty g_1(\varsigma)\mathrm{e}^{-a_1\varsigma}\Bigg[\frac{HN}{H_4 N_4} - \frac{H(x, t-\varsigma)N(x, t-\varsigma)}{H_4 N_4} \\
&+ \ln\frac{H(x, t-\varsigma)N(x, t-\varsigma)}{HN}\Bigg]\,\mathrm{d}\varsigma \\
&+ \frac{\beta_2}{G_2} H_4 Y_4 \int_0^\infty g_2(\varsigma)\mathrm{e}^{-a_2\varsigma}\Bigg[\frac{HY}{H_4 Y_4} - \frac{H(x, t-\varsigma)Y(x, t-\varsigma)}{H_4 Y_4} \\
&+ \ln\frac{H(x, t-\varsigma)Y(x, t-\varsigma)}{HY}\Bigg]\,\mathrm{d}\varsigma \Bigg\}\,\mathrm{d}x.
\end{aligned}
\tag{21}
$$

From (6), we can see that E_4 satisfies the following equilibrium conditions

$$
\begin{cases}
\kappa = dH_4 + \beta_1 H_4 N_4 + \beta_2 H_4 Y_4, \\
\beta_1 H_4 N_4 = \frac{d_1}{\alpha_1 G_1} N_4, \\
\frac{\beta_3}{\alpha_2 G_2} Y_4 V_4 = \frac{d_3}{\alpha_2 G_2 \alpha_3} V_4 - \frac{\mu}{\alpha_2 G_2 \alpha_3}, \\
\beta_2 H_4 Y_4 = \frac{\beta_3}{\alpha_2 G_2} Y_4 V_4 + \frac{d_2}{\alpha_2 G_2} Y_4.
\end{cases}
\tag{22}
$$

By using (22), (8) and (11), the time derivative in (21) is transformed to

$$
\begin{aligned}
\frac{d\mathcal{U}_4}{dt} = \int_\Omega \Bigg\{ &-\frac{d\,(H-H_4)^2}{H} + \frac{\beta_4}{\alpha_2 G_2}\,(Y_4 - Y_5)\,Z - \frac{\mu}{\alpha_2 G_2 \alpha_3}\,\frac{(V-V_4)^2}{V V_4} \\
&- \frac{\beta_1}{G_1} H_4 N_4 \int_0^\infty g_1(\varsigma) e^{-a_1\varsigma} \left[\Phi\left(\frac{H_4}{H}\right) + \Phi\left(\frac{H(x,t-\varsigma)N(x,t-\varsigma)}{H_4 N}\right) \right] d\varsigma \\
&- \frac{\beta_2}{G_2} H_4 Y_4 \int_0^\infty g_2(\varsigma) e^{-a_2\varsigma} \left[\Phi\left(\frac{H_4}{H}\right) + \Phi\left(\frac{H(x,t-\varsigma)Y(x,t-\varsigma)}{H_4 Y}\right) \right] d\varsigma \Bigg\} dx \\
&- D_H H_4 \int_\Omega \frac{\|\nabla H\|^2}{H^2}\,dx - \frac{D_N N_4}{\alpha_1 G_1} \int_\Omega \frac{\|\nabla N\|^2}{N^2}\,dx \\
&- \frac{D_Y Y_4}{\alpha_2 G_2} \int_\Omega \frac{\|\nabla Y\|^2}{Y^2}\,dx - \frac{D_V V_4}{\alpha_2 G_2 \alpha_3} \int_\Omega \frac{\|\nabla V\|^2}{V^2}\,dx.
\end{aligned}
$$

The sign of $\dfrac{d\mathcal{U}_4}{dt}$ is determined by the sign of $(Y_4 - Y_5)$ since all other terms are negative. From the equilibrium points E_4 and E_5, we find

$$
\begin{aligned}
Y_4 - Y_5 =& \frac{d_2 d_3(\mathcal{R}_0/\mathcal{R}_1 - 1) - \mu\beta_3}{\alpha_3\beta_3 d_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} - \frac{d_4}{\alpha_4\beta_4} \\
=& \frac{\alpha_3 d_4\,(\alpha_2\beta_2 G_2 d_1 - \alpha_1\beta_1 G_1 d_2)\,(\rho-1) - \mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_1\beta_1 G_1\alpha_3\alpha_4\beta_4 d_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} \\
=& \frac{dd_1 d_4(\rho-1)}{\kappa\alpha_1\beta_1 G_1\alpha_4\beta_4(\mathcal{R}_0/\mathcal{R}_1 - 1)}\left[\frac{\kappa\alpha_2\beta_2 G_2}{dd_2} - \frac{\kappa\alpha_1\beta_1 G_1}{dd_1} - \frac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho-1)} \right] \\
=& \frac{dd_1 d_4(\rho-1)}{\kappa\alpha_1\beta_1 G_1\alpha_4\beta_4(\mathcal{R}_0/\mathcal{R}_1)}\left[\mathcal{R}_0 - \mathcal{R}_1 - \frac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho-1)} \right].
\end{aligned}
$$

As a result, we find that $\dfrac{d\mathcal{U}_4}{dt} \le 0$ if $\mathcal{R}_0 \le \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho-1)}$. Also, we can show that $\dfrac{d\mathcal{U}_4}{dt} = 0$ when $H = H_4$, $N = N_4$, $Y = Y_4$, $V = V_4$ and $Z = 0$. Thus, the largest invariant set $\Psi_4 \subseteq \Psi = \{(H, N, Y, V, Z) \mid \dfrac{d\mathcal{U}_4}{dt} = 0\}$ is the singleton $\{E_4\}$. According to LaSalle's invariance principle [50,51], the equilibrium E_4 is globally asymptotically stable if $\mathcal{R}_0 \le \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho-1)}$ provided that the point is defined for $\rho > 1$, $\mathcal{R}_0/\mathcal{R}_1 > 1$, $\mathcal{R}_n < \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3}$.

(b) From (9), the characteristic equation at E_4 is given by

$$
\begin{aligned}
f_4(\lambda)\Big(& \left[\alpha_1\beta_1^2\overline{G}_1 H_4 N_4 + (\lambda + \beta_1 N_4 + \beta_2 Y_4 + d + D_H\zeta_i)\right. \\
& \left(\lambda - \alpha_1\beta_1\overline{G}_1 H_4 + d_1 + D_N\zeta_i\right)\Big] \\
& \times \left[\alpha_3\beta_3^2 Y_4 V_4 + \left(\lambda - \alpha_2\beta_2\overline{G}_1 H_4 + \beta_3 V_4 + d_2 + D_Y\zeta_i\right)\right. \\
& \left(\lambda - \alpha_3\beta_3 Y_4 + d_3 + D_V\zeta_i\right)] \\
& + \alpha_2\beta_2^2\overline{G}_2 H_4 Y_4 \left(\lambda - \alpha_1\beta_1\overline{G}_1 H_4 + d_1 + D_N\zeta_i\right) \\
& \left(\lambda - \alpha_3\beta_3 Y_4 + d_3 + D_V\zeta_i\right)\Big) = 0,
\end{aligned}
\tag{23}
$$

where

$$
f_4(\lambda) = \lambda - \alpha_4\beta_4 Y_4 + d_4 + D_Z\zeta_i.
$$

One root of the characteristic equation (23) is given by $f_4(\lambda) = 0$. In other words, we have the eigenvalue

$$
\lambda|_{i=1} = \alpha_4\beta_4 Y_4 - d_4 = \alpha_4\beta_4 (Y_4 - Y_5).
$$

From the proof of part (a), we can see that $(Y_4 - Y_5) > 0$ if $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho - 1)}$.
In this situation, the characteristic equation has a positive root, and the equilibrium E_4 is unstable. □

Theorem 8 *The coexistence equilibrium E_5 is globally asymptotically stable if $\rho > 1$, $\mathcal{R}_1 > \mathcal{R}_m$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho - 1)}$.*

Proof We take the following Lyapunov functional

$$
\begin{aligned}
\mathcal{U}_5(t) = \int_\Omega \Bigg\{ & H_5\Phi\left(\frac{H}{H_5}\right) + \frac{1}{\alpha_1 G_1} N_5\Phi\left(\frac{N}{N_5}\right) + \frac{1}{\alpha_2 G_2} Y_5\Phi\left(\frac{Y}{Y_5}\right) \\
& + \frac{1}{\alpha_2 G_2\alpha_3} V_5\Phi\left(\frac{V}{V_5}\right) + \frac{1}{\alpha_2 G_2\alpha_4} Z_5\left(\frac{Z}{Z_5}\right) \\
& + \frac{\beta_1}{G_1} H_5 N_5 \int_0^\infty g_1(\varsigma)\mathrm{e}^{-a_1\varsigma} \int_0^\varsigma \Phi\left(\frac{H(x, t-\theta)N(x, t-\theta)}{H_5 N_5}\right) \mathrm{d}\theta\,\mathrm{d}\varsigma \\
& + \frac{\beta_2}{G_2} H_5 Y_5 \int_0^\infty g_2(\varsigma)\mathrm{e}^{-a_2\varsigma} \int_0^\varsigma \Phi\left(\frac{H(x, t-\theta)Y(x, t-\theta)}{H_5 Y_5}\right) \mathrm{d}\theta\,\mathrm{d}\varsigma \Bigg\} \mathrm{d}x.
\end{aligned}
$$

After using the equilibrium conditions at E_5, (8) and (11), the time derivative of $\mathcal{U}_5(t)$ is given by

$$
\begin{aligned}
\frac{d\mathcal{U}_5}{dt} = \int_\Omega \Bigg\{ &-\frac{d\,(H-H_5)^2}{H} - \frac{\mu}{\alpha_2 G_2 \alpha_3} \frac{(V-V_5)^2}{V V_5} \\
&- \frac{\beta_1}{G_1} H_5 N_5 \int_0^\infty g_1(\varsigma) e^{-a_1 \varsigma} \left[\Phi\left(\frac{H_5}{H}\right) + \Phi\left(\frac{H(x, t-\varsigma) N(x, t-\varsigma)}{H_5 N}\right) \right] d\varsigma \\
&- \frac{\beta_2}{G_2} H_5 Y_5 \int_0^\infty g_2(\varsigma) e^{-a_2 \varsigma} \left[\Phi\left(\frac{H_5}{H}\right) + \Phi\left(\frac{H(x, t-\varsigma) Y(x, t-\varsigma)}{H_5 Y}\right) \right] d\varsigma \Bigg\} dx \\
&- D_H H_5 \int_\Omega \frac{\|\nabla H\|^2}{H^2} \, dx - \frac{D_N N_5}{\alpha_1 G_1} \int_\Omega \frac{\|\nabla N\|^2}{N^2} \, dx \\
&- \frac{D_Y Y_5}{\alpha_2 G_2} \int_\Omega \frac{\|\nabla Y\|^2}{Y^2} \, dx - \frac{D_V V_5}{\alpha_2 G_2 \alpha_3} \int_\Omega \frac{\|\nabla V\|^2}{V^2} \, dx \\
&- \frac{D_Z Z_5}{\alpha_2 G_2 \alpha_4} \int_\Omega \frac{\|\nabla Z\|^2}{Z^2} \, dx.
\end{aligned}
$$

This implies that $\dfrac{d\mathcal{U}_5}{dt} \le 0$. Also, one can show that $\dfrac{d\mathcal{U}_5}{dt} = 0$ when $H = H_5$, $N = N_5$, $Y = Y_5$, $V = V_5$ and $Z = Z_5$. Thus, the largest invariant set $\Psi_5 \subseteq \Psi = \{(H, N, Y, V, Z) \mid \frac{d\mathcal{U}_5}{dt} = 0\}$ is the singleton $\{E_5\}$. According to LaSalle's invariance principle [50,51], the equilibrium E_5 is globally asymptotically stable if $\rho > 1$, $\mathcal{R}_1 > \mathcal{R}_m$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \alpha_4 \beta_4}{\alpha_3 d d_1 d_2 d_4 (\rho - 1)}$.

□

Remark 2 It follows from Theorem 5 that the tumor cells will be removed from the body when $\mathcal{R}_1 > 1$ and

$$
\begin{aligned}
\mathcal{R}_0 &\le \mathcal{R}_1 + \frac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{d d_1 d_2 d_3} \\
\Longleftrightarrow \mathcal{R}_0 - \mathcal{R}_1 &\le \frac{\kappa \mu \alpha_1 \beta_1 G_1 \beta_3}{d d_1 d_2 d_3} \\
\Longleftrightarrow \frac{d d_1 d_2 d_3 \, (\mathcal{R}_0 - \mathcal{R}_1)}{\kappa \alpha_1 \beta_1 G_1 \beta_3} &\le \mu \\
\Longleftrightarrow \mu_0 &\le \mu,
\end{aligned}
$$

where

$$
\mu_0 = \frac{d d_1 d_2 d_3 \, (\mathcal{R}_0 - \mathcal{R}_1)}{\kappa \alpha_1 \beta_1 G_1 \beta_3}. \tag{24}
$$

Hence, μ_0 is the minimum effective dosage of M1 virus required to eliminate the tumor. When $\mu < \mu_0$, we see from Theorem 7 that the tumor cells will persist as $t \longrightarrow \infty$.

5 Numerical simulations

In this section, we pursue some numerical simulations in order to verify the results of Theorems 3–8. For this purpose, we choose $g_i(\varsigma)$ in model (2) as

$$
g_i(\varsigma) = b_i e^{-b_i \varsigma}, \quad \text{for } i = 1, 2.
$$

Clearly, $g_i(\varsigma) > 0$ and $\int_0^\infty g_i(\varsigma)\, d\varsigma = \int_0^\infty b_i e^{-b_i \varsigma}\, d\varsigma = 1$. This form of $g_i(\varsigma)$ was taken in [22]. Consequently, the values of G_1 and G_2 defined in Eq. (5) are given by

$$G_i = b_i \int_0^\infty e^{-(a_i+b_i)\varsigma}\, d\varsigma = \frac{b_i}{a_i + b_i}, \quad \text{for } i = 1, 2.$$

The values of $\mathcal{R}_0$ and $\mathcal{R}_1$ are given by

$$\mathcal{R}_0 = \frac{\kappa \alpha_2 \beta_2 b_2}{d d_2 (a_2 + b_2)}, \quad \mathcal{R}_1 = \frac{\kappa \alpha_1 \beta_1 b_1}{d d_1 (a_1 + b_1)}. \tag{25}$$

In order to transform system (2) to PDE system, we introduce the following new variables

$$A(x,t) = \int_0^\infty e^{-(a_1+b_1)\varsigma} H(x, t-\varsigma) N(x, t-\varsigma)\, d\varsigma,$$

$$B(x,t) = \int_0^\infty e^{-(a_2+b_2)\varsigma} H(x, t-\varsigma) Y(x, t-\varsigma)\, d\varsigma. \tag{26}$$

Thus, system (2) is transformed to the following system

$$\begin{cases} \frac{\partial H(x,t)}{\partial t} = D_H \Delta H(x,t) + \kappa - d H(x,t) - \beta_1 H(x,t) N(x,t) - \beta_2 H(x,t) Y(x,t), \\ \frac{\partial A(x,t)}{\partial t} = H(x,t) N(x,t) - (a_1 + b_1) A(x,t), \\ \frac{\partial N(x,t)}{\partial t} = D_N \Delta N(x,t) + \alpha_1 \beta_1 b_1 A(x,t) - d_1 N(x,t), \\ \frac{\partial B(x,t)}{\partial t} = H(x,t) Y(x,t) - (a_2 + b_2) B(x,t), \\ \frac{\partial Y(x,t)}{\partial t} = D_Y \Delta Y(x,t) + \alpha_2 \beta_2 b_2 B(x,t) - \beta_3 Y(x,t) V(x,t) - \beta_4 Y(x,t) Z(x,t) \\ \quad - d_2 Y(x,t), \\ \frac{\partial V(x,t)}{\partial t} = D_V \Delta V(x,t) + \mu + \alpha_3 \beta_3 Y(x,t) V(x,t) - d_3 V(x,t), \\ \frac{\partial Z(x,t)}{\partial t} = D_Z \Delta Z(x,t) + \alpha_4 \beta_4 Y(x,t) Z(x,t) - d_4 Z(x,t). \end{cases} \tag{27}$$

For system (27), we consider the following initial conditions

$$H(x,0) = 0.3 \left(1 + 0.2 \cos^2(\pi x)\right), \quad N(x,0) = 0.2 \left(1 + 0.2 \cos^2(\pi x)\right),$$

$$Y(x,0) = 0.2 \left(1 + 0.2 \cos^2(\pi x)\right),$$

$$V(x,0) = 0.3 \left(1 + 0.2 \cos^2(\pi x)\right), \quad Z(x,0) = 0.02 \left(1 + 0.2 \cos^2(\pi x)\right).$$

The initial conditions for the new variables $A(x,t)$ and $B(x,t)$ can be computed from (26). We take the spatial domain as $\Omega = [0, 2]$ with a step size $\Delta x = 0.02$. We perform the simulations on a time interval $[0, 400]$ with a step size $\Delta t = 0.1$. The values of α_2, β_1, β_2, β_3, β_4, η_1, η_2, η_3 and η_4 are taken as free parameters while the other remaining parameters are listed in Table 1. Some parameter values are taken from [42], while others are taken as an assumption. The results of the numerical simulations are classified into six categories:

(a) We consider $\alpha_2 = 0.8$, $\beta_1 = 0.03$, $\beta_2 = 0.03$, $\beta_3 = 0.1$, $\beta_4 = 0.03$, $\eta_1 = 0.04$, $\eta_2 = 0.01$, $\eta_3 = 0.008$ and $\eta_4 = 0.01$. These values give $\mathcal{R}_1 = 0.3636 < 1$ and $\mathcal{R}_0 = 0.7273 < \mathcal{R}_l = 2.1905$. In this situation, the competition-free equilibrium $E_0 = (1, 0, 0, 0.3571, 0)$ is globally asymptotically stable as shown in Fig. 1. This result coincides with Theorem 3. At this point, both populations of normal and tumor cells are extinct. This extinction might be a result of a severe competition between the normal and

Table 1 List of parameters of model (2)

Parameter	Value	Parameter	Value	Parameter	Value
κ	0.02	α_4	0.8	D_Z	0.03
μ	0.01	D_H	0.02	a_1	0.1
d	0.02	D_N	0.02	a_2	0.1
α_1	0.8	D_Y	0.01	b_1	1
α_3	0.5	D_V	0.04	b_2	1

tumor cells on a limited nutrient source. Hence, the effect of oncolytic virotherapy on tumor growth cannot be examined in this situation.

(b) We consider $\alpha_2 = 0.8, \beta_1 = 0.03, \beta_2 = 0.1, \beta_3 = 0.1, \beta_4 = 0.2, \eta_1 = 0.04, \eta_2 = 0.008,$ $\eta_3 = 0.008$ and $\eta_4 = 0.01$. This set of parameters gives $\rho = 2.9867 > 1$, $\mathcal{R}_0/\mathcal{R}_1 = 7.1429 > 1$, $\mathcal{R}_0 = 2.5974 > \mathcal{R}_l = 2.2755$, $\mathcal{R}_n = 3.8 > \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} = 0.945$ and $\mathcal{R}_0 < \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)} = 5.6527$. As reported in Theorem 4, the treatment failure immune-free equilibrium $E_1 = (0.908, 0, 0.0214, 0.3707, 0)$ is globally asymptotically stable as shown in Fig. 2. The severe competition between the normal and tumor cells led to the extinction of normal cells, where the OVT failed in demolishing the tumor and saving the normal cells. At this stage, the life of cancer's patient can be at a real risk or he/she may die.

(c) We consider $\alpha_2 = 0.8, \beta_1 = 0.1, \beta_2 = 0.03, \beta_3 = 0.1, \beta_4 = 0.03, \eta_1 = 0.008,$ $\eta_2 = 0.01, \eta_3 = 0.006$ and $\eta_4 = 0.01$. For this combination of parameter values, we obtain $\mathcal{R}_1 = 2.5974 > 1$ and $\mathcal{R}_0 = 0.7273 < \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3} = 5.9274$. In agreement with Theorem 5, the solutions of system (2) globally converge to the tumor-free equilibrium $E_2 = (0.385, 0.3195, 0, 0.3846, 0)$ as shown in Fig. 3. This case reflects the success of OVT in reducing tumor load to zero before the initiation of CTL immune response. Thus, the parameters and global stability conditions of this point can help design oncolytic viruses with better efficacy.

(d) We consider $\alpha_2 = 0.9, \beta_1 = 0.04, \beta_2 = 0.5, \beta_3 = 0.1, \beta_4 = 0.6, \eta_1 = 0.05,$ $\eta_2 = 0.008, \eta_3 = 0.005$ and $\eta_4 = 0.02$. These values give $\rho = 6 > 1, \mathcal{R}_0 = 14.6104 > \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)} = 8.369$ and $\mathcal{R}_1 = 0.4156 < \mathcal{R}_m = 3.0833$. As a result, the treatment failure equilibrium $E_3 = (0.3247, 0, 0.0834, 0.4799, 0.0943)$ is globally asymptotically stable as shown in Fig. 4. This result supports Theorem 6. This case reflects the oncolytic virotherapy failure which results in normal cells extinction. At this point, the tumor is controlled by CTL immune response, which may limit the replication of oncolytic M1 virus and lead to therapy failure.

(e) We consider $\alpha_2 = 0.9, \beta_1 = 0.16, \beta_2 = 0.35, \beta_3 = 0.1, \beta_4 = 0.1, \eta_1 = 0.009,$ $\eta_2 = 0.008, \eta_3 = 0.008$ and $\eta_4 = 0.01$. Then, we get the values of the threshold parameters as $\rho = 1.4933 > 1, \mathcal{R}_0/\mathcal{R}_1 = 2.5488 > 1, \mathcal{R}_n = 10.8 < \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)} = 12.0832, \mathcal{R}_0 = 10.2273 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3} = 9.1306$ and $\mathcal{R}_0 < \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho - 1)} = 19.505$. In this case, the partial success immune-free equilibrium $E_4 = (0.2493, 0.1593, 0.0992, 0.4341, 0)$ is globally asymptotically stable. This result supports Theorem 7 and is shown in Fig. 5. At this point and with no
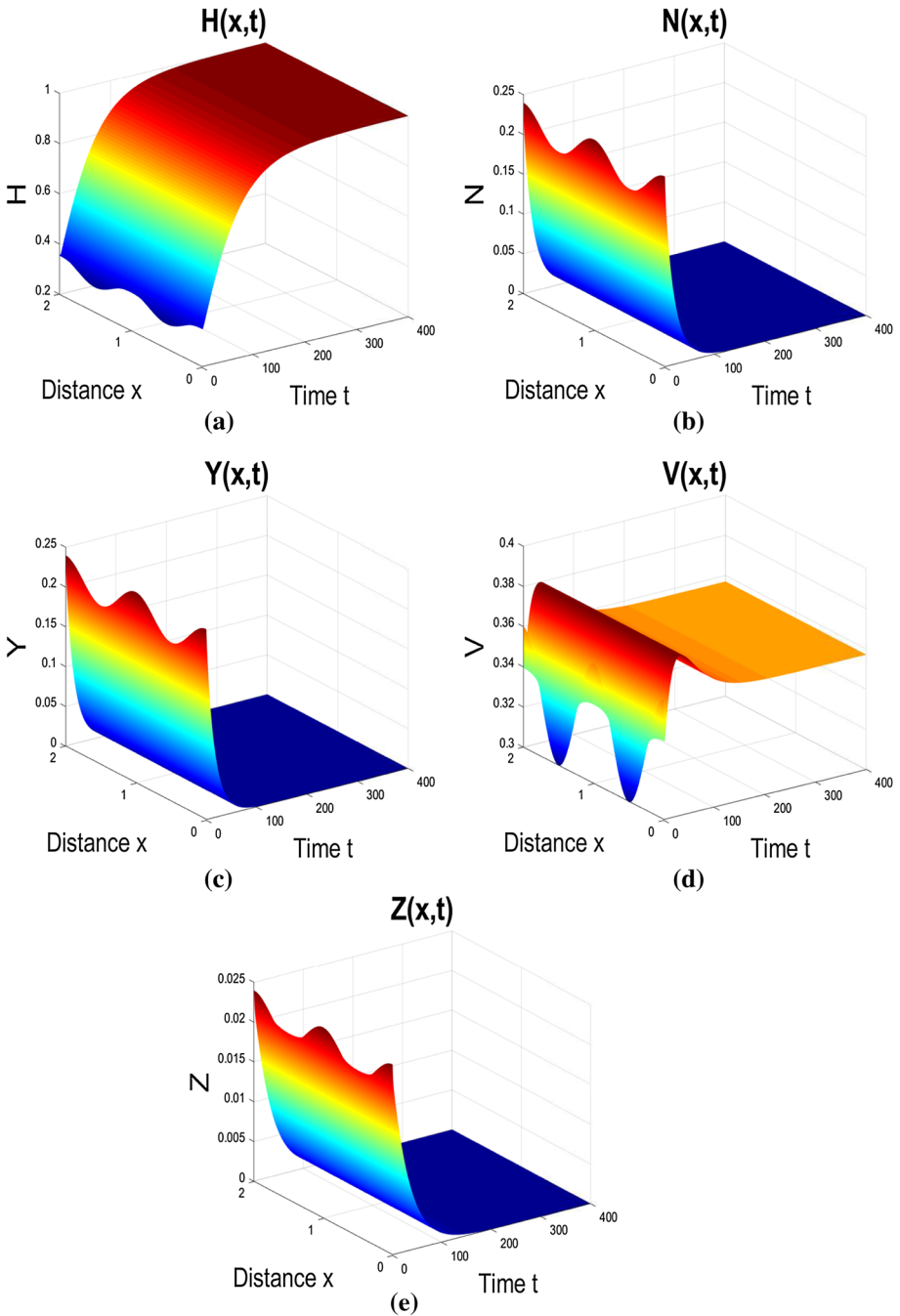
Fig. 1 The numerical simulations of system (2) when $\mathcal{R}_1 \leq 1$ and $\mathcal{R}_0 \leq \mathcal{R}_l$. The competition-free equilibrium E_0 is globally asymptotically stable. The sub-figures show the spatiotemporal distributions of **a** nutrient, **b** normal cells, **c** tumor cells, **d** free M1 virus, and **e** immune response
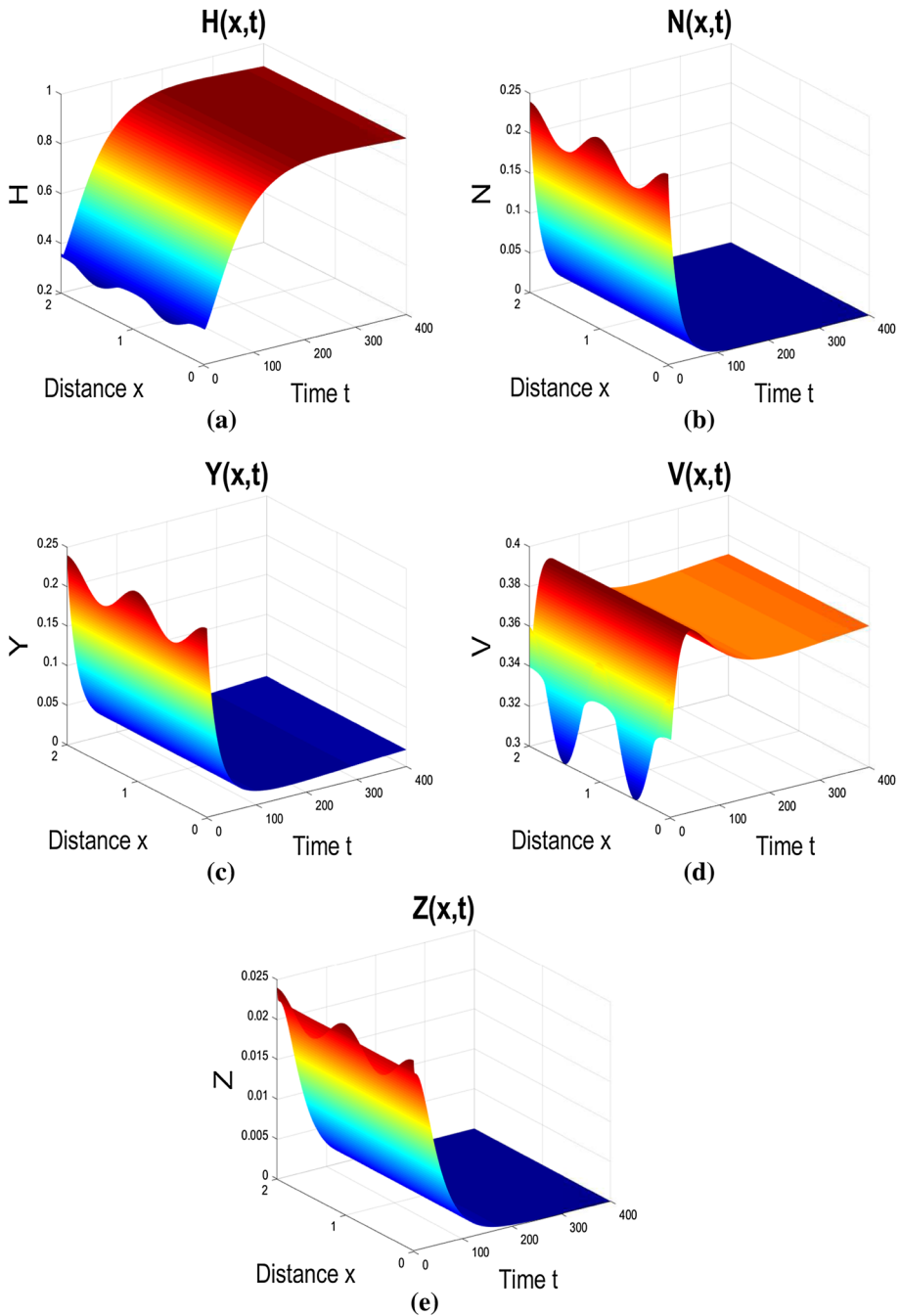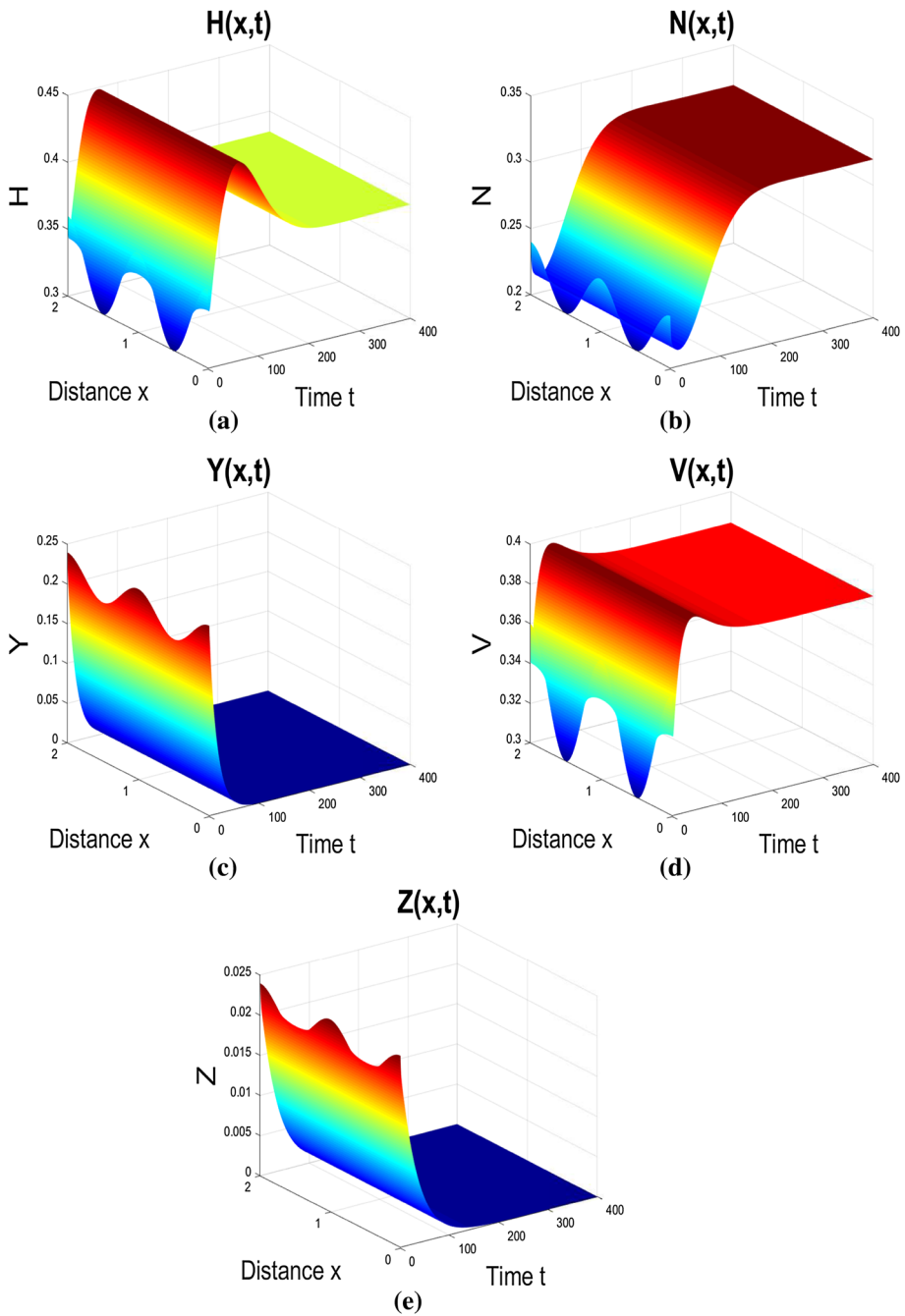
Fig. 2 The numerical simulations of system (2) when $\rho > 1, \mathcal{R}_0/\mathcal{R}_1 > 1, \mathcal{R}_n \geq \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$ and $\mathcal{R}_0 \leq \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}$. The treatment failure immune-free equilibrium E_1 is globally asymptotically stable. The sub-figures show the spatiotemporal distributions of **a** nutrient, **b** normal cells, **c** tumor cells, **d** free M1 virus, and **e** immune response
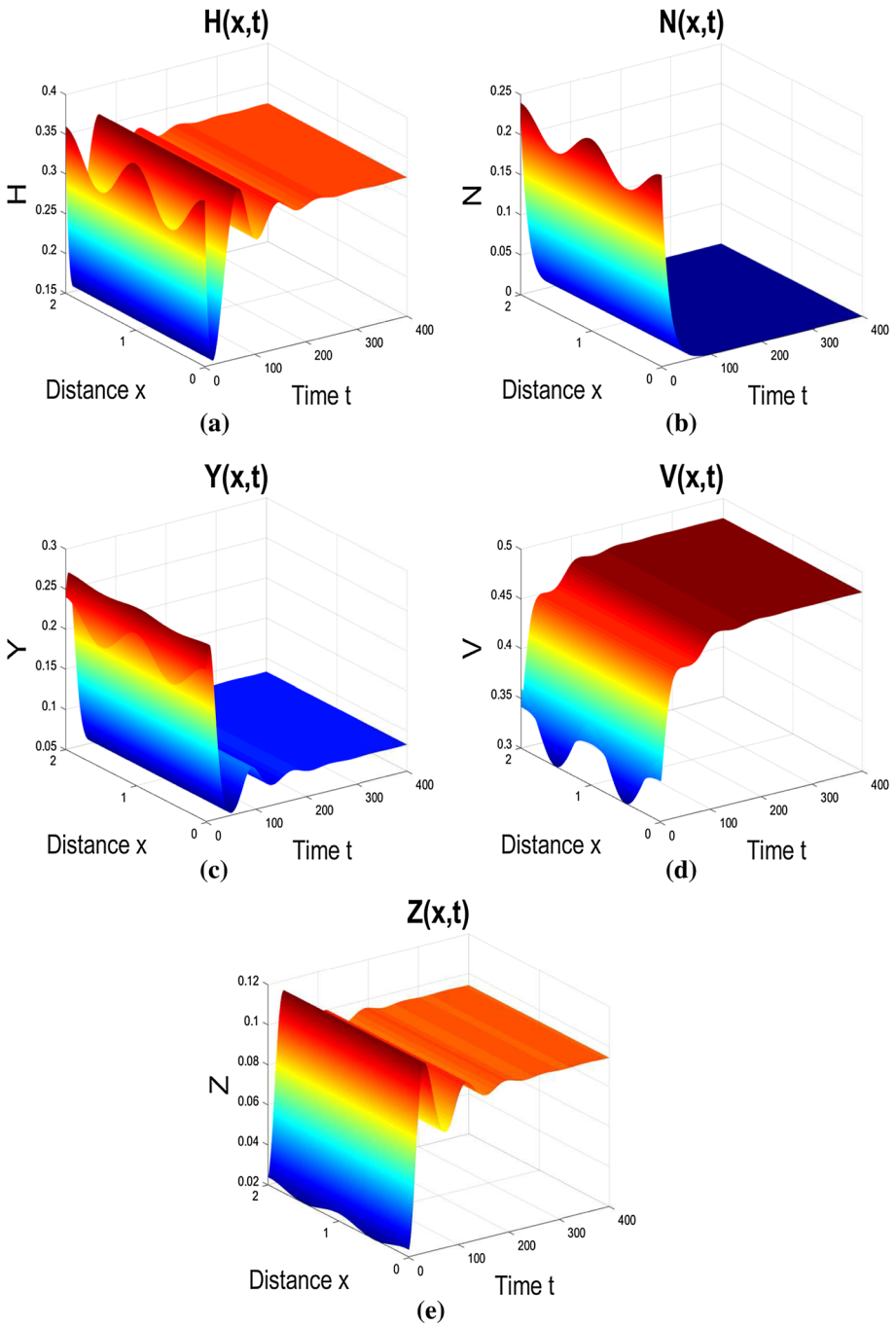
H(x,t)

N(x,t)

Y(x,t)

V(x,t)

Z(x,t)

Fig. 3 The numerical simulations of system (2) when $\mathcal{R}_0 \leq \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1d_2d_3}$. The tumor-free equilibrium E_2 is globally asymptotically stable. The sub-figures show the spatiotemporal distributions of **a** nutrient, **b** normal cells, **c** tumor cells, **d** free M1 virus, and **e** immune response
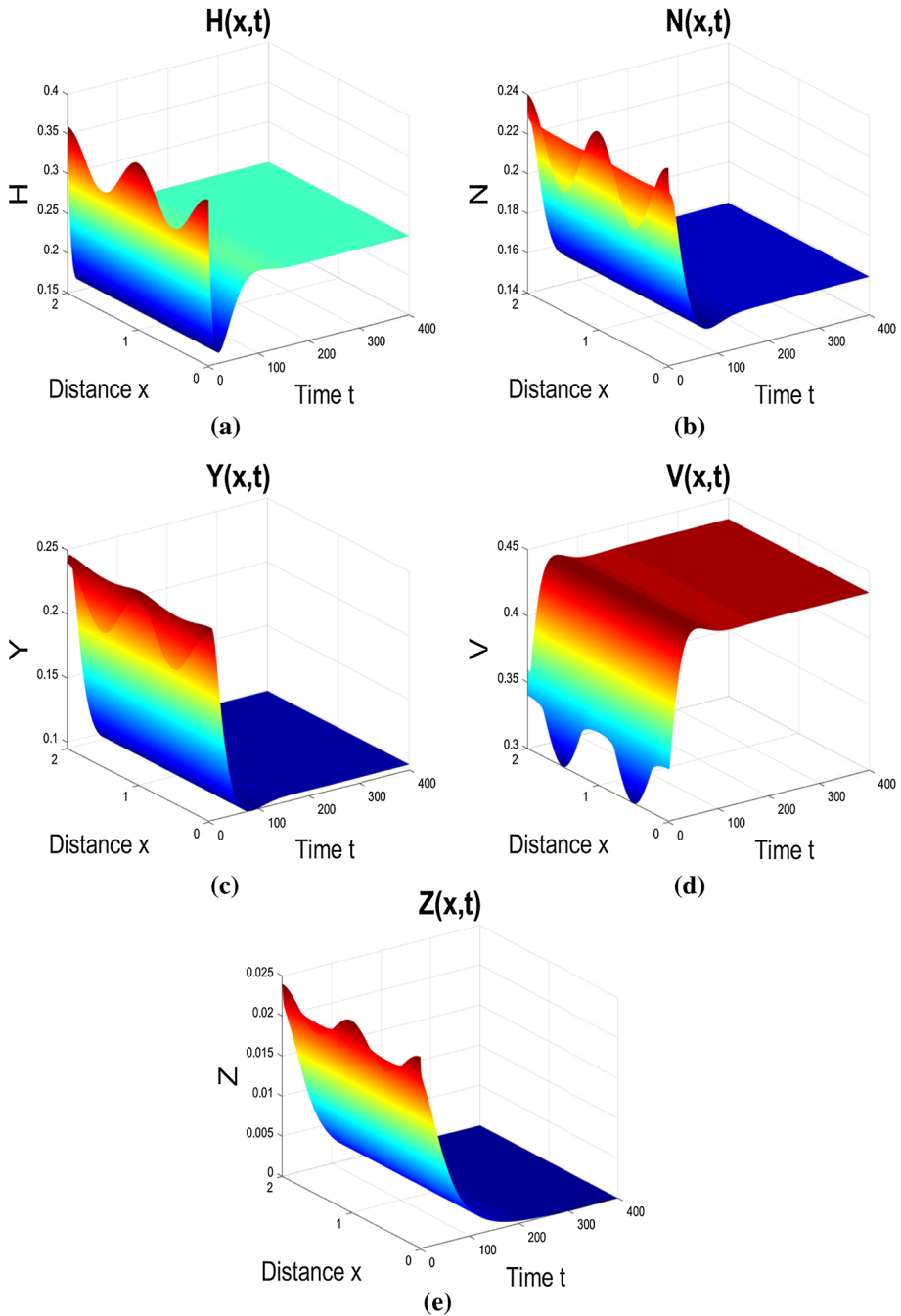
Fig. 4 The numerical simulations of system (2) when $\mathcal{R}_1 \leq \mathcal{R}_m$. The treatment failure equilibrium E_3 is globally asymptotically stable. The sub-figures show the spatiotemporal distributions of **a** nutrient, **b** normal cells, **c** tumor cells, **d** free M1 virus, and **e** immune response

Fig. 5 The numerical simulations of system (2) when $\rho > 1$ and $\mathcal{R}_0 \le \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \alpha_4 \beta_4}{\alpha_3 dd_1 d_2 d_4 (\rho - 1)}$. The partial success immune-free equilibrium E_4 is globally asymptotically stable. The sub-figures show the spatiotemporal distributions of **a** nutrient, **b** normal cells, **c** tumor cells, **d** free M1 virus, and **e** immune response

immune response, the viral therapy partially succeeds in saving the normal cells, but it does not have the full ability to demolish the tumor.

(f) We consider $\alpha_2 = 0.9$, $\beta_1 = 0.19$, $\beta_2 = 0.5$, $\beta_3 = 0.05$, $\beta_4 = 0.8$, $\eta_1 = 0.008$, $\eta_2 = 0.008$, $\eta_3 = 0.005$ and $\eta_4 = 0.03$. With this choice of parameters, we get $\rho = 12.8 > 1$, $\mathcal{R}_1 = 4.9351 > \mathcal{R}_m = 2.9531$ and $\mathcal{R}_0 = 14.6104 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho-1)} = 8.7588$. In agreement with Theorem 8, the coexistence equilibrium $E_5 = (0.2027, 0.2085, 0.0781, 0.4339, 0.0415)$ is globally asymptotically stable in this case as shown in Fig. 6. The tumor is controlled by immune cells and the OVT loses its ability to control the tumor. Thus, the presence of CTL immune response renders the OVT ineffective.

To see the contribution of the distributed delay to the efficacy of OVT, we increase the value of a_2 in model (2). Increasing a_2 means decreasing the survival probability of tumor cells during the delay period. Accordingly, we consider the same parameter values given in (e) except for a_2, where we take it as $a_2 = 0.8$. The solutions in this case tend to the point with $H = 0.2495$, $N = 0.3758$, $Y = 0$, $V = 0.3574$ and $Z = 0$. The associated threshold parameters are $\mathcal{R}_1 = 4.0125 > 1$ and $\mathcal{R}_0 = 6.25 < \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3} = 9.1306$. This means that increasing a_2 switches the system from the partial success equilibrium E_4 to the tumor-free equilibrium E_2. The resulting figure is quite similar to Fig. 3.

In order to examine the effect of the distributed delay on the minimum effective dosage μ_0 required to remove the tumor, we first vary a_1 in Eq. (24) while the conditions $\mathcal{R}_1 > 1$ and $\mathcal{R}_0 \leq \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3}$ are hold. We fix all other parameters in Eq. (24) to the same values considered in case (e) with $a_2 = 0.8$, where the solutions approach the tumor-free equilibrium E_2. The values of $\mathcal{R}_0$ and $\mathcal{R}_1$ are computed from Eq. (25). We see from Fig. 7a that increasing a_1, which means decreasing the survival probability of normal cells during the delay period, increases the minimum amount of dose required to eliminate the tumor. The next step is to vary a_2 in Eq. (24) and fix the values of all other parameters. We observe from Fig. 7b that increasing a_2, which means decreasing the survival probability of tumor cells during the delay period, decreases the minimum effective dosage μ_0. Thus, the delay terms can have a strong impact on the minimum amount of OVT needed to eradicate the tumor.

The effect of CTL immune response on the concentration of M1 virus can be seen by varying α_4 and fixing all other parameters to the same values considered in case (f). The result is shown in Fig. 8. Increasing CTL stimulation rate constant α_4 in model (2) decreases the concentration of oncolytic M1 virus. This supports the result of case (f) that CTLs reduce the efficiency of OVT.

To see the effect of changing diffusion coefficients on global stability, it is sufficient to consider the impact on normal cells. For this purpose, we change the diffusion coefficient of normal cells in case (f) to $D_N = 0.002$ and $D_N = 0.0002$. We note from Fig. 9 that changing the diffusion coefficient does not affect the global stability of the equilibrium, but it only affects the earlier local behavior of solution.

6 Conclusion

Oncolytic virotherapy is a promising cancer treatment depends on attacking cancer cells by viruses. Research efforts have focused on solving the different issues of OVT in order to increase its efficacy. Mathematical models have been used to shorten the path toward the
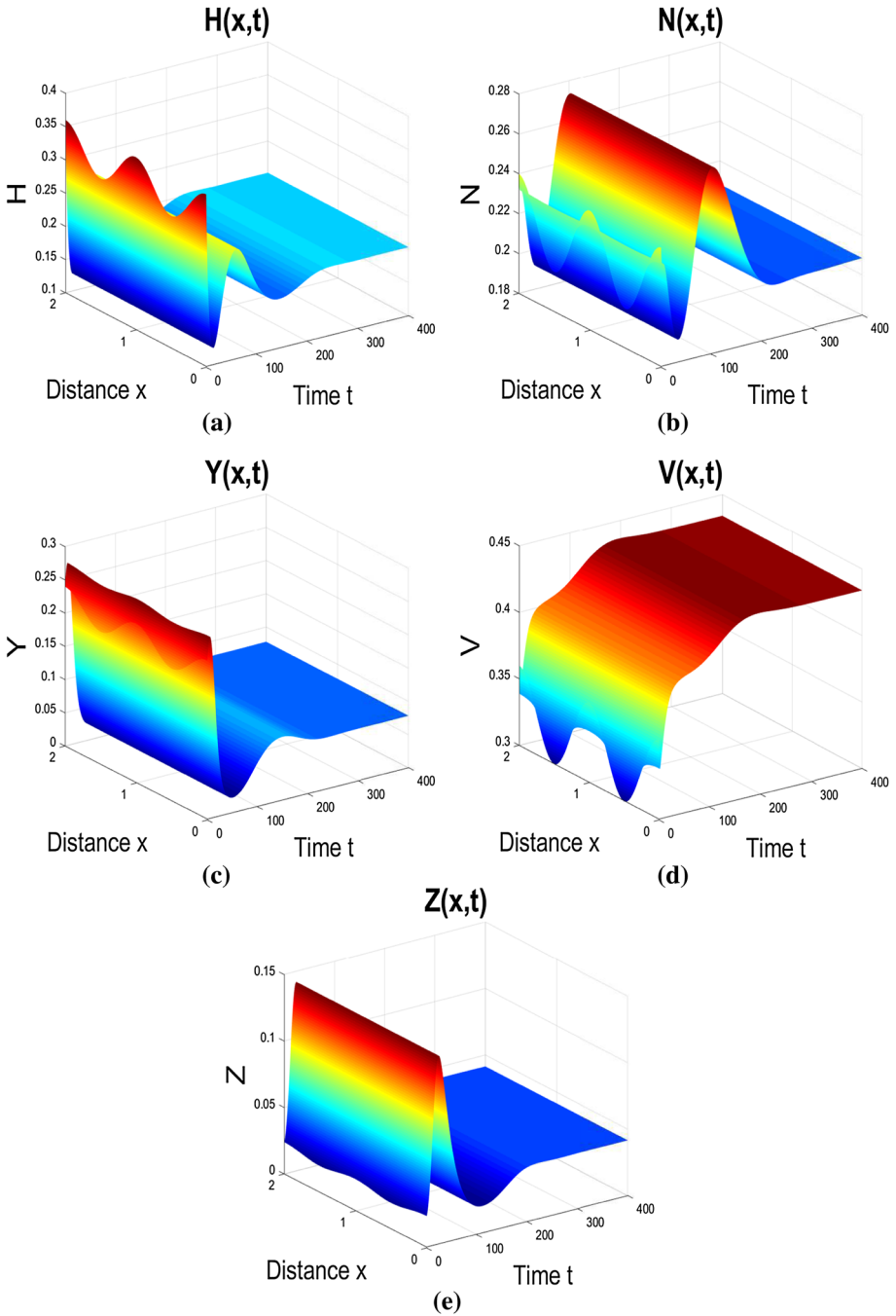
Fig. 6 The numerical simulations of system (2) when $\rho > 1, \mathcal{R}_1 > \mathcal{R}_m$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa \mu \alpha_1 \beta_1 G_1 \alpha_4 \beta_4}{\alpha_3 d d_1 d_2 d_4 (\rho - 1)}$. The coexistence equilibrium E_5 is globally asymptotically stable. The sub-figures show the spatiotemporal distributions of **a** nutrient, **b** normal cells, **c** tumor cells, **d** free M1 virus, and **e** immune response
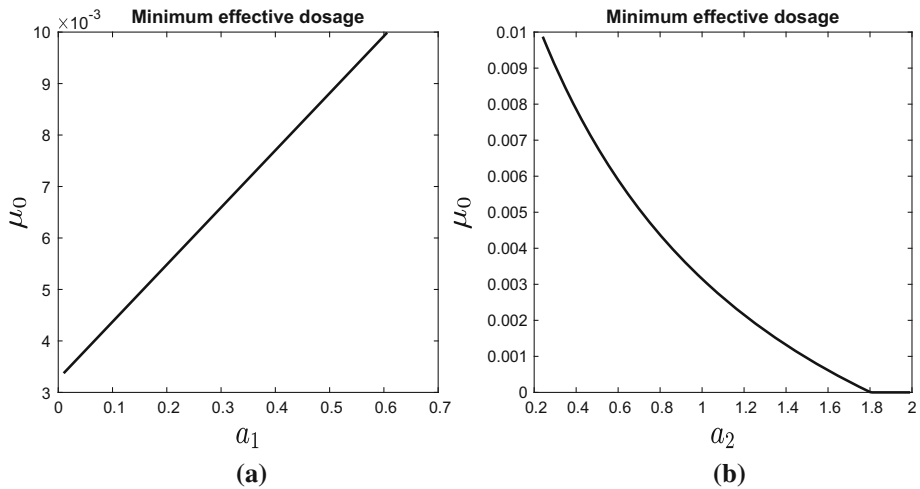
Fig. 7 The effect of varying a_1 and a_2 on the minimum effective dosage μ_0 for the tumor-free equilibrium E_2
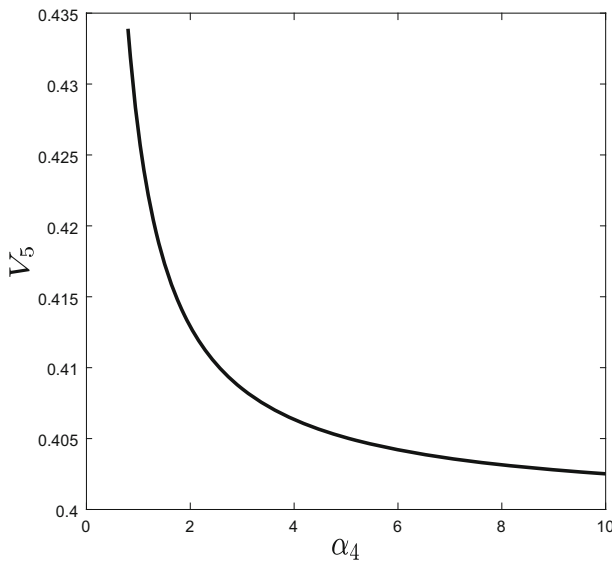

Fig. 8 The effect of varying CTL stimulation rate constant α_4 on the concentration of M1 virus for the coexistence equilibrium E_5

adoption of this treatment. In this paper, we studied a system of five PDEs with distributed delays. The model has six equilibrium points which reflect different possible outcomes of oncolytic virotherapy. These points are

(a) The competition-free equilibrium E_0 which always exists and it is globally asymptotically stable if $\mathcal{R}_1 \leq 1$ and $\mathcal{R}_0 \leq \mathcal{R}_l$. At this point, the normal and tumor cells populations are extinct and the efficacy of oncolytic virotherapy cannot be measured.
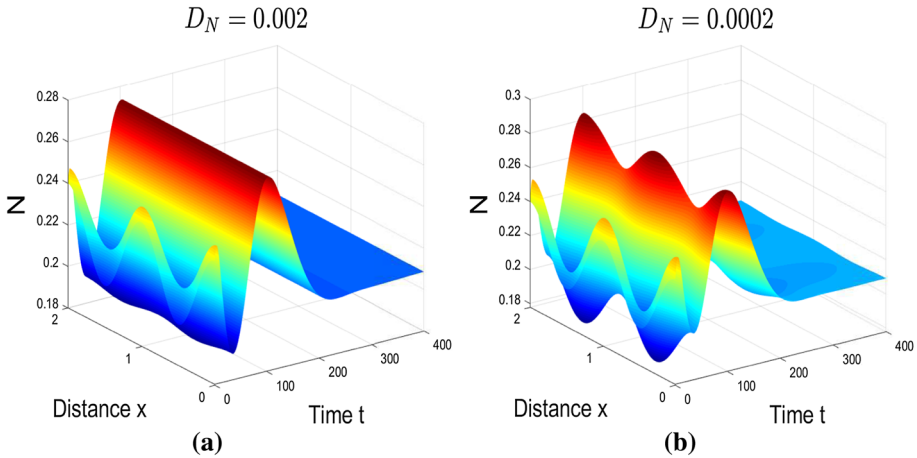
$$D_N = 0.002 \qquad\qquad D_N = 0.0002$$

Fig. 9 The effect of changing the diffusion coefficient on the concentration of normal cells. All parameters are identical to those used in Fig. 6 except for the diffusion coefficient D_N

(b) The treatment failure immune-free equilibrium E_1 which exists if $\mathcal{R}_0 > \mathcal{R}_l$. It is globally asymptotically stable when the conditions $\rho > 1$, $\mathcal{R}_0/\mathcal{R}_1 > 1$, $\mathcal{R}_n \geq \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$ and $\mathcal{R}_0 \leq \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}$ are satisfied. The extinction of normal cells at this point indicates to the fail of oncolytic virotherapy and to the death of patient.

(c) The tumor-free equilibrium E_2 exists when $\mathcal{R}_1 > 1$ and it is globally asymptotically stable if $\mathcal{R}_0 \leq \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3}$. The extinction of tumor cells at this point reflects the success of oncolytic viral therapy. Hence, reaching this point is the goal of viral therapies.

(d) The treatment failure equilibrium E_3 which exists if $\rho > 1$ and $\mathcal{R}_0 > \mathcal{R}_m + \dfrac{\mu\xi_2}{\alpha_3 dd_2 d_4(\rho - 1)}$. It is globally asymptotically stable if $\mathcal{R}_1 \leq \mathcal{R}_m$. This point reflects the fail of oncolytic virotherapy in the presence of CTL immune response.

(e) The partial success immune-free equilibrium E_4 exists if $\mathcal{R}_0/\mathcal{R}_1 > 1$, $\mathcal{R}_n < \mathcal{R}_1 + \dfrac{\mu\beta_2}{\alpha_3 dd_2(\mathcal{R}_0/\mathcal{R}_1 - 1)}$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\beta_3}{dd_1 d_2 d_3}$. It is globally asymptotically stable when the conditions $\rho > 1$ and $\mathcal{R}_0 \leq \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho - 1)}$ are met. At this point, the oncolytic virotherapy does not have the full efficacy to remove the tumor cells.

(f) The coexistence equilibrium E_5 is defined and globally asymptotically stable if $\rho > 1$, $\mathcal{R}_1 > \mathcal{R}_m$ and $\mathcal{R}_0 > \mathcal{R}_1 + \dfrac{\kappa\mu\alpha_1\beta_1 G_1\alpha_4\beta_4}{\alpha_3 dd_1 d_2 d_4(\rho - 1)}$. At this point, the immune response controls the tumor and prevents the oncolytic M1 virus from completing its role.

We found that the global stability of the equilibrium points of model (2) is ensured for any diffusion coefficients as long as the conditions given in (a)-(f) are hold. Additionally, some parameters in the distributed delay terms have a critical impact on the efficacy of oncolytic virotherapy. These parameters can change the fate of OVT or change the minimum amount of the therapy required to remove the tumor (Fig. 7). Hence, the values of these parameters should be carefully chosen and controlled. Moreover, the immune response against tumor

cells decreases the concentration of oncolytic M1 virus (Fig. 8) and reduces the efficiency of cancer viral therapy. Thus, our results support the studies which suggest using some drugs with the oncolytic virotherapy to inhibit the immune response against tumor cells [5,8,13]. This usage of inhibition drugs is equivalent to decreasing the stimulation rate $\alpha_4\beta_4 YZ$ in model (2) or increasing the death rate $(d+\eta_4)Z$. Comparing with the existing models of OVT, the model in this paper is the first model addresses with a complete mathematical analysis the interaction between oncolytic M1 virotherapy and CTLs in the presence of distributed delay. M1 virus has shown great selectivity and efficacy in treating tumor [41]. Thus, our results can be subjected to further investigation in order to be used in the development of M1 virotherapy. The results can be used to determine the minimum effective dosage required to eliminate the tumor in the presence of CTLs and infinite delays (see Remark 2). Our results can help to estimate the parameters and compute the thresholds needed for full eradication of tumor. Further, the model can be extended to study the effect of combining oncolytic M1 virotherapy with chemotherapy. Applying the multiscale modeling approach discussed in [29] may help to better understand the dynamics of oncolytic virotherapy and its role in tumor elimination. Besides, considering model (2) with cross-diffusion may give a deeper insight into some nonlinear features associated with diffusion [52,53]. Performing a linear stability analysis and investigating the occurrence of bifurcation is another possibility to understand the role of oncolytic virotherapy in model (2). These points are left as possible future works.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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