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Combination of virotherapy and chemotherapy with optimal control for combating cancer

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Abstract

The purpose of this paper is to study the behaviors shown by a modified mathematical model representing interactions between immune cells, un-infected tumor cells, infected tumor cells, and normal cells when subjected initially to chemotherapy and virotherapy alone and subsequently a combination of both. Stability analysis is carried out for all steady states in each treatment model. Conditions are derived under which recurrence of tumors can be prevented when the amount of applied drugs are reduced. Analysis of the model shows that the tumor can be eliminated with a lower dose of chemotherapy if it is combined with virotherapy. The existence of an optimal control set, and optimality of the model are discussed. The optimal control problem relative to the model is designed in a way to reduce the number of tumor cells and the amount of chemotherapeutic drugs and at the same time to increase the positive effect of virotherapy to improve the immune system, thereby causing a reduction in patient's recovery time.

Keywords: Immune response; Chemotherapy; Virus therapy; Chemo-virotherapy; Stability analysis; Optimal control

1. Introduction

Cancer is one of the most feared and persistent killer diseases. Cancer can develop in almost any organ or tissue of the body. In the case of cancer patients, abnormal cells grow uncontrollably, exceeding their normal limits, and these abnormal cells invade adjoining parts of the body and thus spread to other organs [22]. According to the 2018 report of WHO [6], 18.1 million people worldwide had cancer, 9.6 million died. By 2040, those figures will be almost doubled [6]. Cancer treatment is, therefore, still a significant field of research. Surgery, chemotherapy, and radiation therapy are traditional methods adopted for cancer treatment. Nevertheless, the major drawback of these therapies is that they involve a high level of toxicity. To overcome this drawback, nowadays, immunotherapy, virotherapy, etc., are used along with chemotherapy. Immunotherapy, which uses genetically engineered cytokines, is used to boost up the immune system. The fundamental goal of virotherapy treatment is selective damage of cancerous cells with virus infection while leaving normal cells undamaged. Virotherapy can replicate viruses within

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infected tumor cells, which ultimately leads to an extensive tumor cell lysis (oncolysis), as well as a high-risk signal. Also, it can stimulate the immune system through the concomitant release of both tumoral and viral antigens [8]. Though this treatment has fewer side effects yet, it cannot eliminate the tumor if used alone. Survival rates on monotherapies alone are generally poor, especially in metastatic or end-stage cases. Treatment of cancer with the combination of multiple therapies has led to significant improvements in the standard of care and cure for different cancer patients.

Most types of cancers often relapse because of their resistance to traditional therapies [39]. So, aggressive combination therapies are the need of the hour for combating cancer. Combination therapies such as radio-immunotherapy [15,35], radio-virotherapy [9,36], immunotherapy combined with other therapies [24,38], etc., are the current types of therapies used for cancer treatment. Recently, chemo-virotherapy, a combination of chemotherapy and oncolytic viruses, has gained increasing importance in clinical settings. The implication of using chemo-virotherapy is that oncolytic viruses either directly target tumor cells or transmit genes that make the tumor cells more susceptible to chemotherapeutic drugs [20]. Mukhopadhyay and Bhattacharya [26] presented a model of tumor-immune-virus interactions and demonstrated the importance of different regulatory parameters in controlling model energy. Malinzi et al. 2017 [20] have shown that chemotherapy alone cannot eradicate tumor cells but can reduce tumor concentration to a much lower level if combined with an oncolytic virus. Phan and Tian [28] modified the works of Malinzi et al. by adding another state variable. They studied the effect of innate immune responses on infected cancer cells and the virus population. Malinzi et al. 2018 [21] showed how virotherapy improves the effect of chemotherapy. They showed that a patient could be cured even by applying half of the maximum tolerable doses in the case of combination. Abernathy et al. [2] studied the necessary and adequate medical conditions for virotherapy to ensure a globally stable treatment model. They showed that when these conditions were violated, relapse of cancer could occur. S. M. Al-Tuwairqi et al. [4] modified the mathematical model in [2] by introducing an interaction between the innate immune system and uninfected tumor cells and showed that the tumor cells and virus are detected by natural killer (NK) cells which are part of the innate immune system [23,25,31,40]. Most authors [1,3,7,12,16,19,27,29] worked with mathematical models that consider interactions between oncolytic virus, uninfected and infected tumor cells. De. Pills et al. [30] tested the limit sets of a steady-state and showed that chemotherapy could be stopped as soon as the orbit enters the basin of attraction of the tumor-free steady state. A few other authors [18,33,34,37] analyzed the combined effect of normal cells and various other therapies in their models. K. J. Mahasa et al. [18] showed that viral infection in normal cells could increase oncolytic virotherapy if the virus replicates rapidly within infected cells. Oncolytic virotherapy infects and destroys tumor cells but does not kill normal cells, and the same has been reported in the NCI report [37]. Some researchers [21,33,34] have developed mathematical models to study the interaction between uninfected–infected tumor growth subjected to chemo-virotherapy and find the best possible result by applying optimal control theory. Optimal control dramatically helps to reduce the tumor cell load with optimal drug administration, which can minimize the time for a patient to get cured with minimum side effects.

The purpose of this paper is to propose and analyze a modified model which has been formulated by modifying the models proposed by Malinzi et al. [21] and De Pillis et al. [30]. We have studied the long-term dynamics arising from the combined treatment of oncolytic virotherapy and chemotherapy on immune-tumor-normal cells. The paper is structured as follows: Section 2 describes the proposed model and the basic assumptions. In Section 3, we examine the positive invariance and boundedness of the model solutions. Description of the treatment methods is stated from a biological point of view. We analyze three sub-models: only chemotherapy model, only virotherapy model, a combined chemotherapy and virus therapy model. Stability analysis has been done for all steady states underestimated parameter values taken from earlier papers. Above mentioned three sub-models are analyzed in Sections 4, 5, and 6, respectively. In Section 7, we set up an optimal control problem related to our study and analyze it. Pontryagin's maximum principle was used for this purpose. In Section 8, simulations and comparison results are explained. Conclusions and references are given in the final section.

2. Model formulation

The use of viruses for cancer treatment began during the 1950s with tissue culture and rodent cancer models development. Viruses that reproduce themselves efficiently within cancer cells without harming normal cells are found in nature and can be modified in the laboratory. Oncolytic viruses have been viewed as a tool by many researchers to kill cancer cells directly. Recent research further suggests that some oncolytic viruses may work at

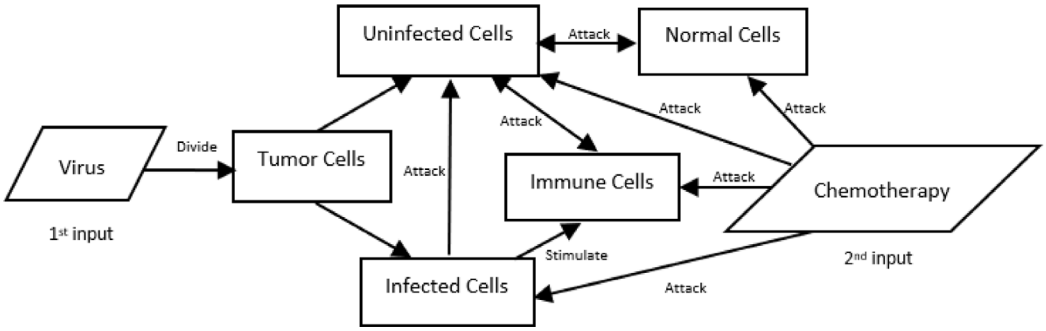

Fig. 1. Symmetric diagram of immune-tumor-normal cells in the presence of virus and chemotherapy drugs.

least in part by triggering an immune response against cancer [21]. When a virus infects a tumor cell, it copies within the tumor cell until it bursts. The dying cancer cell releases tumor antigens which help the immune system to recognize cancer cells. (See Fig. 1.)

One of the main drawbacks of chemotherapy is that it kills both cancerous and healthy normal cells. So, the patient's immune system is weakened in this treatment method, making the patient prone to dangerous diseases [33]. On the contrary, when applied alone, the average duration of virotherapy treatment is three years with scheduled monitoring [2]. However, combination treatment strategies with chemotherapy and virotherapy have shown significant promise for cancer treatment [21]. Under this strategy, the main aim is to kill tumor cells and, at the same time reduction in the amount of drug administration. Thus, it reduces the potentially toxic effects of toxic chemicals caused by the overuse of drugs. Thus, the main goal of chemo-virotherapy is to eradicate tumor cells while maintaining a sufficient level of normal cells so that the patient can withstand side effects and attacks of other opportunistic diseases.

2.1. Model description and assumptions

In this section, we propose and formulate our modified mathematical model describing a tumor's growth when subjected to chemotherapy and oncolytic virotherapy treatments. First, we consider the dynamics of interacting cell populations: immune cells, tumor cells, normal cells, free viruses when subjected to chemotherapy. Then, after injecting with an oncolytic virus, the model presented here subdivides the tumor cell population into uninfected tumor cells $U(t)$ and infected tumor cells $I(t)$. The following assumptions are made in setting up the model.

Without treatment, the tumor grows logistically with a carrying capacity $1/b_1$. Virus infections kill tumor cells, whereas chemotherapy drugs kill all types of cells. Moreover, virus infection kills tumor cells in the Michaelis–Menten form, whereas chemotherapy and immune cells kill tumor cells in the Lotka–Volterra form.

With virus treatment, the virus-specific immune response is proportional to the infected tumor cells population [21], which is represented in the last term of the first equation by the term φI, where φ is the virus-specific immune response. This term has not been applied in the model proposed by De Pillis et al. [30]. Virus production is a function of virus burst size and the death of infected immune cells. The number of viruses, therefore, increases as infected tumor cell density multiplies. Therefore, the infected cells, I, are infected with the virus at a dose of $d_2 I$, thus acting as the source of the virus by releasing free virions into the tissue space by b virions released at the rate of each cell, which has been incorporated in the first term in Eq. (2.5) [11].

We consider both virus and tumor-specific immune responses. These viruses can be modified to provide beneficial properties, including reducing the ability of tumor cells to infect healthy cells and allowing to deliver therapeutic payloads specifically to tumors and infected tumor cells by producing immune-enhancing cells [5]. We also assume that the number of tumor cells grows faster than normal cells.

The presence of tumor cells stimulates the immune response, represented by the Michaelis–Menten term, $\rho(U + I)E/(\sigma + (U + I))$, where $(U + I) = T$, is the total number of tumor cells and ρ and σ are positive constants. This type of response term is the same as the term used in the relevant models of De Pillis et al. [30], Kuznetsov et al. [14], and Kirschner and Panetta [13]. We assume that the term $(\rho_1 UV)/(\sigma_1 + U)$ describes an infection of tumor cells by the virus where ρ_1 is the infection rate and σ_1 is the Michaelis–Menten constants. Infection of tumor cells by the virus is consistent with the assumptions made in Malinzi et al. [21].

2.2. Model equations

We propose the following model describing the interactions between immune cells E, uninfected tumor cells U, infected tumor cells I, normal cells N, virotherapy V and chemotherapy C.

$$\frac{dE}{dt} = \mu + \frac{\rho\,(U+I)\,E}{\sigma + (U+I)} - d_1 E - k_1 EU - a_1 EC + \varphi I, \tag{2.1}$$

$$\frac{dU}{dt} = r_1 U\,(1 - b_1\,(U+I)) - \frac{\rho_1 UV}{\sigma_1 + U} - k_2 EU - k_3 NU - a_2 UC, \tag{2.2}$$

$$\frac{dI}{dt} = \frac{\rho_1 UV}{\sigma_1 + U} - d_2 I - k_4 IE - a_3 IC, \tag{2.3}$$

$$\frac{dN}{dt} = r_2 N\,(1 - N) - k_5 UN - a_4 NC, \tag{2.4}$$

$$\frac{dV}{dt} = b d_2 I - \frac{\rho_1 UV}{\sigma_1 + U} - \delta V, \tag{2.5}$$

$$\frac{dC}{dt} = u - d_3 C, \tag{2.6}$$

The initial conditions for the model are assumed to be:

$$E\,(0) = E_0, U\,(0) = U_0, I\,(0) = I_0, N\,(0) = N_0, V\,(0) = V_0, C\,(0) = C_0,$$

where the constants $E_0, U_0, I_0, N_0, V_0, C_0$ denoted the initial concentration of immune cells, uninfected tumor cells, infected tumor cells, normal cells, free virus particles, chemotherapy drugs respectively. They are assumed to be non-negative to make those biologically meaningful.

In Eq. (2.1), the term μ represents the constant source rate of immune cells already present in our body. The term $\rho(U+I)E/(\sigma+(U+I))$, describes tumor-specific immune response, where $(U+I) = T$, is the total number of tumor cells, ρ is the maximum recruitment of immune cells by tumor cells and σ is the half-saturation for the proliferation term [21]. The term $-d_1 E$ represents the natural decay rate of immune cells. Tumor-specific immune decay and kill rate of immune cells due to drug administration are represented as $-k_1 EU$, $-a_1 EC$ respectively.

In Eqs. (2.2) and (2.3), the term $r_1 U\,(1 - b_1\,(U+I))$ represents tumor growth where r_1 is the intrinsic growth rate of the tumor. The term $(\rho_1 UV)/(\sigma_1 + U)$ describes an infection of tumor cells by the virus where ρ_1 is the infection rate and σ_1 is the Michaelis–Menten constants. The terms $-k_2 EU$, $-k_3 NU$, $-a_2 UC$ are respectively the decay rate of uninfected tumor cells due to immune cells, normal cells, and drug administration. The term $-d_2 I$ is the natural death rate of infected tumor cells and $-k_4 IE$, $-a_3 IC$ are respectively the decay rate of infected tumor cells due to immune cells and drug administration.

In Eq. (2.4), the term $r_2 N\,(1 - N)$ represents normal cell growth where r_2 is the intrinsic growth rate of normal cells with maximum carrying capacity one. The term $-k_5 UN$ represents the decay rate of normal cells due to uninfected tumor cells and $-a_4 NC$ is the killed rate of normal cells due to drug administration.

In Eq. (2.5), the term $b d_2 I$ represents virus proliferation rate where the virus burst size is b and d_2 is the death rate of infected tumor cells. The term $-(\rho_1 UV)/(\sigma_1 + U)$ represents the loss of free virus due to infection of the uninfected tumor cells. Virus deactivation in the body tissue is represented by the term $-\delta V$.

In Eq. (2.6), the dose of chemotherapeutic drug given is represented by u and the term $-d_3 C$ represents the drug administration decay rate.

3. Positive invariance and boundedness

Before we proceed with the mathematical analysis, we need to show that the model with considered parameter values is biologically feasible. According to the standard comparison theory, it follows

$$\frac{dE}{dt} = \mu + \frac{\rho\,(U+I)\,E}{\sigma + (U+I)} - d_1 E - k_1 EU - a_1 EC + \varphi I \leq \mu - d_1 E,$$

Integration of the above leads to

$$E(t) \leq \frac{\mu}{d_1} + e^{-d_1 t} E(0) => \underbrace{\lim}_{t\to\infty} \sup(E(t)) \leq \frac{\mu}{d_1},$$

Again,

$$\begin{aligned}\frac{dU}{dt} + \frac{dI}{dt} &= r_1 U(1 - b_1(U+I)) - \frac{\rho_1 UV}{\sigma_1 + U} - k_2 EU - k_3 NU - a_2 UC + \frac{\rho_1 UV}{\sigma_1 + U} - d_2 I - k_4 IE - a_3 IC \\ &\leq r_1 (U+I)(1 - b_1(U+I)),\end{aligned}$$

Proceeding as above, we have

$$(U+I)(t) \leq \frac{1}{b_1 + (U+I)(0) e^{-r_1 t}} => \underbrace{\lim}_{t\to\infty} \sup((U+I)(t)) \leq \frac{1}{b_1},$$

Similarly, we have

$$\frac{dV}{dt} \leq b - \delta V => \underbrace{\lim}_{t\to\infty} \sup(V(t)) \leq \frac{b}{\delta},$$

$$\frac{dN}{dt} \leq r_2 N(1-N) => \underbrace{\lim}_{t\to\infty} \sup(N(t)) \leq 1,$$

$$\text{and } \frac{dC}{dt} \leq u - d_3 C => \underbrace{\lim}_{t\to\infty} \sup(C(t)) \leq \frac{u}{d_3},$$

Thus, the feasible region is defined as: $\psi = \left\{(E, U, I, N, V, C) \epsilon R_+^6\right\}$.

We assume that the initial values $E(0) \geq 0, U(0) \geq 0, I(0) \geq 0, N(0) \geq 0, V(0) \geq 0$, and $C(0) \geq 0$ then $E(t) \geq 0, U(t) \geq 0, I(t) \geq 0, N(t) \geq 0, V(t) \geq 0$ and $C(t) \geq 0$ for all $t > 0$.

The trajectories evolve in the attracting regions

$$\psi = \left\{(E, U, I, N, V, C) \in R_+^6 | E(t) \leq \frac{\mu}{d_1}, U(t) + I(t) \leq \frac{1}{b_1}, N(t) \leq 1, V(t) \leq \frac{b}{\delta}, C(t) \leq \frac{u}{d_3}\right\}.$$

The domain ψ is positive invariant for the model equations (2.1) to (2.6) and therefore biologically meaningful for the cell concentration. This verifies that the model formed by Eqs. (2.1) to (2.6) is biologically feasible.

3.1. Immune-normal cells response at tumor growth

Initially, we want to check when a patient should be subjected to some treatment method. For this purpose, it is required to look at the growth pattern of the tumor when the interaction takes place between immune and normal cells only (without treatment). Numerical resolutions presented in Fig. 2 show that the immune system can eliminate small tumors, but it is overwhelmed by larger tumors. More specifically, the immune system can eliminate the growth rate of tumor cells up to $r_1 \leq 0.2$ but fails to inhibit the larger growth rate of the tumor i.e., when $r_1 > 0.2$. This shows that some form of treatment method becomes necessary when $r_1 > 0.2$.

4. Dynamic behavior of the model with only chemotherapy

We consider the case $U(t) + I(t) = T(t)$, where $T(t)$ is the total number of tumor cells. As the model is considered with chemotherapy only, $V(t) = 0$ and $\varphi = 0$. Here, the infected tumor density is zero throughout the tissue since there was no virotherapy treatment.

$$\begin{aligned}\frac{dE}{dt} &= \mu + \frac{\rho TE}{\sigma + T} - d_1 E - k_1 ET - a_1 EC, \\ \frac{dT}{dt} &= r_1 T(1 - b_1 T) - k_2 ET - k_3 NT - a_2 TC, \\ \frac{dN}{dt} &= r_2 N(1-N) - k_5 TN - a_4 NC, \end{aligned} \tag{4.1}$$

$$\frac{dC}{dt} = u - d_3 C,$$

The initial conditions for the model are: $E(0) = E_0$, $T(0) = T_0$, $N(0) = N_0$, $C(0) = C_0$ where each initial value is positive.

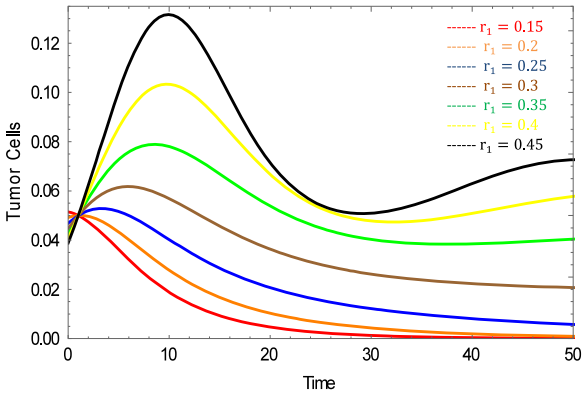

Fig. 2. The plot shows that the dynamics of tumor cells as a result of auto-regulatory cell–cell interactions. Initial points are $E(0) = 0.2$, $T(0) = 0.05$ and $N(0) = 0.6$.

4.1. Analysis of the model

In this section, we show the existence of the steady states for the model (4.1) and study their stabilities. Main advantage of studying stability is to investigate the possibilities of eliminating the tumor and investigate the effect of the chemotherapeutic drug.

4.2. Existence of steady states

Definition 1. Point $\overline{x} \in R^n$ is called the steady state of the model if $f(\overline{x}) = 0$.

From Definition 1, we obtain the following existing steady states:
(i) $P_1(E_1^*, 0, N_1^*, C_1^*)$, where the tumor cells population is zero. Here, $E_1^* = \frac{\mu}{d_1 + a_1 C_1^*}$, $N_1^* = \frac{r_2 - a_4 C_1^*}{r_2}$, $C_1^* = \frac{u}{d_3} = C^*$.
(ii) $P_2(E^*, T^*, N^*, C^*)$, coexisting steady state, where immune-tumor-normal cells co-exist with non-zero population after treatment.

Here,

$$E^* = \frac{\mu(\sigma + T^*)}{(d_1 + k_1 T^* + a_1 C^*)(\sigma + T^*) - \rho T^*}, N^* = \frac{r_2 - k_5 T^* - a_4 C^*}{r_2}, C^* = \frac{u}{d_3} \text{ and}$$

$$T^* = \frac{1}{r_1 b_1}\left(r_1 - k_2 E^* - k_3 N^* - a_2 C^*\right)$$

$$= \frac{1}{b_1} - \frac{k_2}{r_1 b_1}\left(\frac{\mu(\sigma + T^*)}{(d_1 + k_1 T^* + a_1 C^*)(\sigma + T^*) - \rho T^*}\right) - \frac{k_3}{r_1 b_1}\left(\frac{r_2 - k_5 T^* - a_4 C^*}{r_2}\right) - \frac{a_2 C^*}{r_1 b_1},$$

or

$$A_{11} T^{*3} + A_{12} T^{*2} + A_{13} T^* + A_{14} = 0, \tag{4.2}$$

where,

$$A_{11} = k_1 (r_1 r_2 b_1 - k_3 k_5),$$
$$A_{12} = (r_1 r_2 b_1 - k_3 k_5)(d_1 + k_1 \sigma + a_1 C^* - \rho) + k_1 (r_2 k_3 - r_1 r_2 + a_2 r_2 C^* - k_3 a_4 C^*),$$

$$A_{13} = (r_2k_3 - r_1r_2 + a_2r_2C^* - k_3a_4C^*)(d_1 + k_1\sigma + a_1C^* - \rho) + \sigma\,(r_1r_2b_1 - k_3k_5)\,(d_1 + a_1C^*) + \mu r_2k_2,$$
$$A_{14} = \sigma(r_2k_3 - r_1r_2 + a_2r_2C^* - k_3a_4C^*)(d_1 + a_1C^*) + \mu r_2k_2\sigma,$$

For the existence of T^*, discriminate must be positive.

Since $N = 0$ is the death case, so we discard this steady state.

4.3. Stability analysis of the steady states

We investigate the stability of these steady states by linearizing the model (4.1) about each of the steady states. The Jacobian matrix of model (4.1) at an arbitrary point is given by

$$J = \begin{pmatrix} P_{11} & P_{14} & 0 & -a_1E \\ -k_2T & P_{12} & -k_3T & -a_2T \\ 0 & -k_5N & P_{13} & -a_4N \\ 0 & 0 & 0 & -d_3 \end{pmatrix}, \tag{4.3}$$

where, $P_{11} = \frac{\rho T}{\sigma+T} - d_1 - k_1T - a_1C$, $P_{12} = r_1 - 2r_1b_1T - k_2E - k_3N - a_2C$, $P_{13} = r_2 - 2r_2N - k_5T - a_4C$, $P_{14} = \frac{\sigma\rho E}{(\sigma+T)^2} - k_1E$.

As shown in Section 4.2, the model (4.1) has two steady states.

(i) $P_1(E_1^*, 0, N_1^*, C_1^*)$, tumor free state: The eigenvalues of the Jacobian matrix (4.3) evaluated at this steady state P_1 are

$$\lambda_1 = -d_1 - a_1C_1^*, \lambda_2 = r_1 - k_2E_1^* - k_3N_1^* - a_2C_1^*, \lambda_3 = r_2 - 2r_2N_1^* - a_4C_1^* \text{ and } \lambda_4 = -d_3 < 0,$$

So, following standard result (related to eigenvalue and stability) we can conclude that the steady state P_1 is locally asymptotically sable if the following two conditions are satisfied

$$1.\ u < \frac{r_2d_3}{a_4} \text{ and} \tag{4.4}$$
$$2.\ \left(r_2\left(r_1 - a_2C_1^*\right) - k_3\left(r_2 - a_4C_1^*\right)\right)\left(d_1 + a_1C_1^*\right) < \mu k_2r_2, \tag{4.5}$$

otherwise, unstable.

We consider the chemotherapy dose u in between stable range to bring the model to the tumor-free steady state.

(ii) $P_2(E^*, T^*, N^*, C^*)$, coexisting steady state: Here, one eigen value is $\lambda = -d_3 < 0$ and the other eigen values are derived from the Jacobian matrix J.

The characteristic equation at steady state P_2 is

$$\lambda^3 - \left(P'_{11} + P'_{12} + P'_{13}\right)\lambda^2 + (P'_{11}\left(P'_{12} + P'_{13}\right) + P'_{12}P'_{13} - k_3k_5T^*N^* + k_2T^*P'_{14})\lambda + P'_{11}k_3k_5T^*N^*$$
$$- P'_{11}P'_{12}P'_{13} - k_2T^*P'_{13}P'_{14} = 0$$

or

$$d\lambda^3 + X_{11}\lambda^2 + X_{12}\lambda + X_{13} = 0 \tag{4.6}$$

where,

$$P'_{11} = \frac{\rho T^*}{\sigma + T^*} - d_1 - k_1T^* - a_1C^*,$$
$$P'_{12} = r_1 - 2r_1b_1T^* - k_2E^* - k_3N^* - a_2C^*,$$
$$P'_{13} = r_2 - 2r_2N^* - k_5T^* - a_4C^*,$$
$$P'_{14} = \frac{\sigma\rho E^*}{(\sigma + T^*)^2} - k_1E^*,$$
$$X_{11} = -\left(P'_{11} + P'_{12} + P'_{13}\right),$$
$$= \Big(d_1 + k_1T^* + a_1C^* - r_1 + 2r_1b_1T^* + k_2E^* + k_3N^* + a_2C^* - r_2 + 2r_2N^*$$

$$+k_5T^*+a_4C^*-\frac{\rho T^*}{\sigma+T^*}\Big), \tag{4.7}$$

$$\begin{aligned}
X_{12} &= P'_{11}\left(P'_{12}+P'_{13}\right)+P'_{12}P'_{13}-k_3k_5T^*N^*+k_2T^*P'_{14},\\
&=\left(\frac{\rho T^*}{\sigma+T^*}-d_1-k_1T^*-a_1C^*\right)\left(r_1-2r_1b_1T^*-k_2E^*-k_3N^*-a_2C^*+r_2-2r_2N^*\right.\\
&\quad\left.-k_5T^*-a_4C^*\right)+\left(r_1-2r_1b_1T^*-k_2E^*-k_3N^*-a_2C^*\right)\left(r_2-2r_2N^*-k_5T^*-a_4C^*\right)\\
&\quad-k_3k_5T^*N^*+k_2T^*\left(\frac{\sigma\rho E^*}{(\sigma+T^*)^2}-k_1E^*\right),\\
X_{13} &= P'_{11}k_3k_5T^*N^*-P'_{11}P'_{12}P'_{13}-k_2T^*P'_{13}P'_{14}\\
&=\left(\frac{\rho T^*}{\sigma+T^*}-d_1-k_1T^*-a_1C^*\right)k_3k_5T^*N^*-\left(\frac{\rho T^*}{\sigma+T^*}-d_1-k_1T^*-a_1C^*\right)\\
&\quad\times\left(r_1-2r_1b_1T^*-k_2E^*-k_3N^*-a_2C^*\right)\left(r_2-2r_2N^*-k_5T^*-a_4C^*\right)\\
&\quad-k_2T^*\left(r_2-2r_2N^*-k_5T^*-a_4C^*\right)\left(\frac{\sigma\rho E^*}{(\sigma+T^*)^2}-k_1E^*\right),
\end{aligned}$$

and

$$\begin{aligned}
X_{11}X_{12}-X_{13} &= \Big(d_1+k_1T^*+a_1C^*-r_1+2r_1b_1T^*+k_2E^*+k_3N^*+a_2C^*-r_2+2r_2N^*\\
&\quad+k_5T^*+a_4C^*-\frac{\rho T^*}{\sigma+T^*}\Big)\left(\left(\frac{\rho T^*}{\sigma+T^*}-d_1-k_1T^*-a_1C^*\right)\left(r_1-2r_1b_1T^*-k_2E^*\right.\right.\\
&\quad\left.-k_3N^*-a_2C^*+r_2-2r_2N^*-k_5T^*-a_4C^*\right)+\left(r_1-2r_1b_1T^*-k_2E^*-k_3N^*-a_2C^*\right)\\
&\quad\times\left(r_2-2r_2N^*-k_5T^*-a_4C^*\right)-k_3k_5T^*N^*+k_2T^*\left(\frac{\sigma\rho E^*}{(\sigma+T^*)^2}-k_1E^*\right)\Big)\\
&\quad-\left(\left(\frac{\rho T^*}{\sigma+T^*}-d_1-k_1T^*-a_1C^*\right)k_3k_5T^*N^*-\left(\frac{\rho T^*}{\sigma+T^*}-d_1-k_1T^*-a_1C^*\right)\right.\\
&\quad\times\left(r_1-2r_1b_1T^*-k_2E^*-k_3N^*-a_2C^*\right)\left(r_2-2r_2N^*-k_5T^*-a_4C^*\right)\\
&\quad\left.-k_2T^*\left(r_2-2r_2N^*-k_5T^*-a_4C^*\right)\left(\frac{\sigma\rho E^*}{(\sigma+T^*)^2}-k_1E^*\right)\right),
\end{aligned} \tag{4.8}$$

By Routh–Hurwitz stability criteria, if $X_{11}>0$ and $X_{11}X_{12}-X_{13}>0$, then P_2 is locally stable and becomes unstable when conditions are not satisfied. Validity of (4.7) and (4.8) are verified by putting the parameter values from Table 1.

Case 1 Considering $u=0.0260123$ in stable range from conditions Eqs. (4.4) and (4.5).

Using parameter values from Table 1 and considering $u=0.0260123$ in (4.2), we get.

The steady state solution is found to be $(0.164,-0.00000048,0.703,0.52)$, $(-0.49,0.371,0.439,0.52)$ and $(-4.808,2.803,-1.29973,0.52)$. Thus, in this case there are no biologically valid steady states.

Case 2: Considering $u=0.025$ between unstable range from conditions Eqs. (4.4) and (4.5).

Using parameter values from Table 1 and considering $u=0.025$ in (4.2), we get.

The steady state solution is found to be $(0.177,0.008,0.709,0.5)$, $(-0.467,0.371,0.449,0.5)$ and $(-4.827,2.829,-1.306,0.5)$.

The above values show that there is only one biologically valid steady state, which is $(0.177,0.008,0.709,0.5)$ and its eigenvalues are $(-0.279,-0.249,-0.007)$. This guarantees that the equilibrium is locally asymptotically stable since all eigenvalues are negative. Biologically, this signifies that chemotherapy treatment reduce the tumor cells to a low tumor concentration state and it is locally asymptotically stable to the co-existing steady state. Also, as it effects the immune cells and normal cells population.

In the next section, we investigated about the global stability of tumor free equilibrium point P_1 and on the basis of this investigation we forward the following theorem.

Table 1
Parameter values considered for the model.

Parameters	Meaning	Values	Source
μ	Constant source rate of immune cells already presents in the body	0.05	[30]
ρ	Maximum recruitment of immune cells by tumor cells	1	[30]
σ	Half-saturation for the proliferation term	0.4	[30]
φ	Virus-specific immune response	0.1	[2]
r_1	Intrinsic tumor growth rate	0.45 (estimate)	[30]
r_2	Growth rate of normal cell	0.35	[30]
$1/b_1$	Tumor population carrying capacity	2/3	[30]
ρ_1	Infection rate	0.4 (estimate)	[27]
σ_1	Michaelis–Menten constants	0.2 (estimate)	[27]
δ	Virus deactivation in the body tissue	0.001	[1]
d_1	Natural decay rate of immune cells	0.2	[30]
d_2	Natural death rate of infected tumor cells	0.01	[30]
d_3	Natural decay rate of drug	0.05	[30]
a_1	Immune cells kill rate due to drug	0.2	[30]
a_2	Uninfected tumor cell kill rate due to drug	0.5	[30]
a_3	Infected tumor cell kill rate due to drug	0.1	[30]
a_4	Normal cells kill rate due to drug	0.2	[30]
k_1	Decay rate of immune cells due to uninfected tumor cells	0.2	[30]
k_2	Decay rate of uninfected tumor cells due to immune cells	0.3	[30]
k_3	Decay rate of uninfected tumor cells due to normal cells	0.2	[30]
k_4	Decay rate of infected tumor cells due to immune cells	0.05	[30]
k_5	Decay rate of normal cells due to uninfected tumor cells	0.25	[30]
u	Dose of chemotherapy drug	Varied	
b	Virus burst size	Varied	

Theorem 4.1. *The healthy steady state P_1 is globally asymptotically stable if the steady state P_1 is locally stable, and the following conditions*

$$k_2E_1^* + k_3N_1^* + a_2C_1^* > r_1, \quad E = \frac{\mu}{d_1},\ T = \frac{1}{b_1},\ C = \frac{u}{d_3},$$

are satisfied.

Proof of Theorem 4.1 can be found in Appendix A.

Next, we carry out the following numerical resolutions.

Fig. 3 shows evaluation of the model with chemotherapy treatment. At a high dose of chemotherapy drug administration rate i.e., $u = 0.027$, the tumor is eradicated. This model allows complete removal of the tumor only when treatment is introduced with growth rate of the tumor $r_1 = 0.45$. Fig. 3 further shows that this chemotherapeutic drug administration also leads to damage of normal cells and immune cells as side effects. So, it can be concluded that though with increased drug amount, chemotherapy alone is capable of cleaning tumor cells, but it has a serious drawback of reducing the number of normal cells approximately below 70% of the carrying capacity. Further, this treatment method also takes more time to eradicate the tumor cells.

5. Dynamic behavior of the model with only virotherapy

To analyze the effect of virotherapy on immune-tumor-normal cells, we study the model with only virotherapy treatment i.e., $C(t) = 0$.

$$\begin{aligned}
\frac{dE}{dt} &= \mu + \frac{\rho(U+I)E}{\sigma + (U+I)} - d_1E - k_1EU + \varphi I,\\
\frac{dU}{dt} &= r_1U(1 - b_1(U+I)) - \frac{\rho_1UV}{\sigma_1 + U} - k_2EU - k_3NU,\\
\frac{dI}{dt} &= \frac{\rho_1UV}{\sigma_1 + U} - d_2I - k_4IE,
\end{aligned} \tag{5.1}$$

$$\frac{dN}{dt} = r_2 N(1-N) - k_5 U N,$$
$$\frac{dV}{dt} = b d_2 I - \frac{\rho_1 U V}{\sigma_1 + U} - \delta V,$$

with initial conditions $E(0) = E_0, U(0) = U_0, I(0) = I_0, N(0) = N_0, V(0) = V_0$ where each initial value is positive.

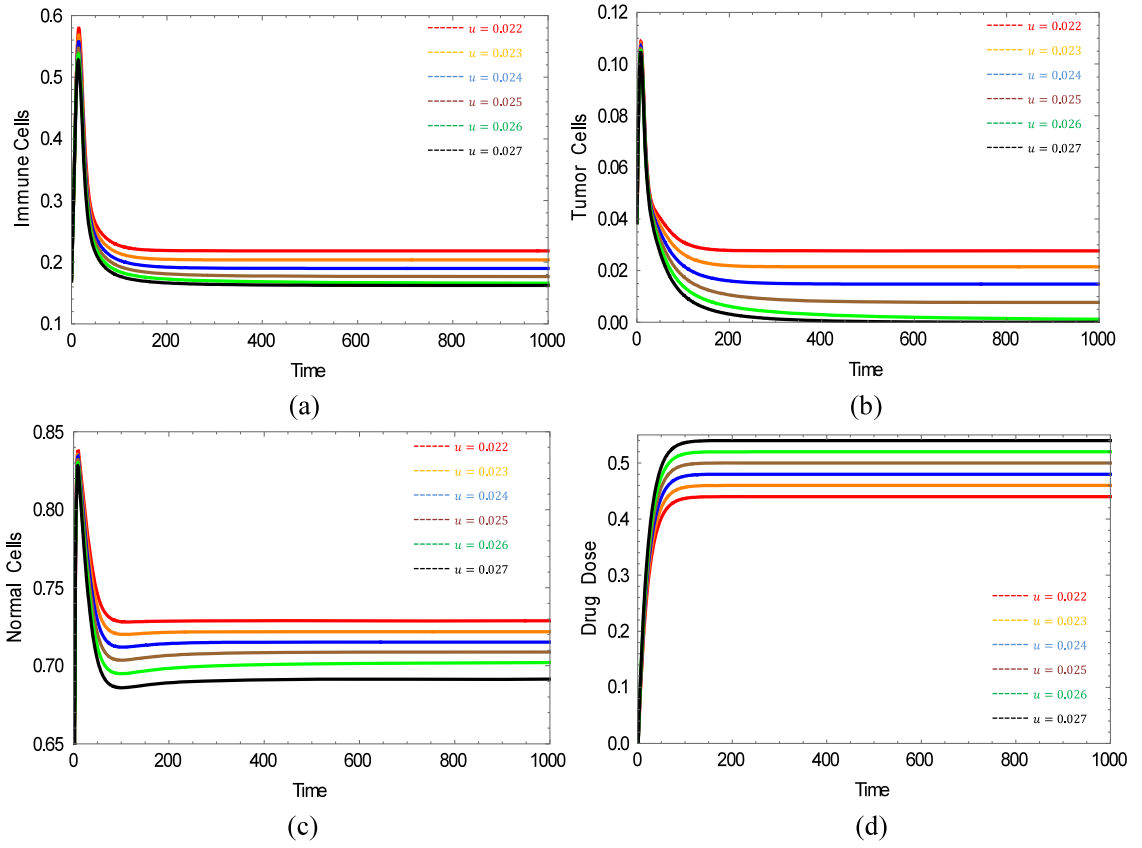

Fig. 3. Time-series solutions of the model (4.1) with initial conditions: $E(0) = 0.2, T(0) = 0.05, N(0) = 0.6, C(0) = 0.001$. Figures (a), (b), and (c) depict the density of immune cells, tumor cells, and normal cells for different drug administration, respectively, and figure (d) represents the administration of the different chemo-drug doses.

5.1. Analysis of the model

In this section, we study the existence of the steady states and their stabilities. As stated earlier, main advantage of studying stability is to investigate the possibilities of eliminating the tumor and investigate the effect of virus therapy.

5.2. Existence of steady states

Following the method in Section 4.2, steady states are found to be
(i) $P_1^*\left(\frac{\mu}{d_1}, 0, 0, 1, 0\right)$, tumor and virus free steady state, where infected and uninfected tumor cells population are zero. This steady state means that model is in a healthy stage.
(ii) $P_2^*(E_2, U_2, 0, N_2, 0)$, infected tumor cells, and virus-free states.

where, $E_2 = \frac{\mu(\sigma+U_2)}{(d_1+k_1U_2)(\sigma+U_2)-\rho U_2}$, $N_2 = \frac{r_2-k_5U_2}{r_2}$ and

$$U_2 = \frac{1}{r_1b_1}(r_1 - k_2E_2 - k_3N_2) = \frac{1}{b_1} - \frac{k_2}{r_1b_1}\left(\frac{\mu(\sigma+U_2)}{(d_1+k_1U_2)(\sigma+U_2)-\rho U_2}\right) - \frac{k_3}{r_1b_1}\left(\frac{r_2-k_5U_2}{r_2}\right),$$

Or

$$B_{11}U_2^3 + B_{12}U_2^2 + B_{13}U_2 + B_{14} = 0, \tag{5.2}$$

where,

$$B_{11} = k_1(r_1r_2b_1 - k_3k_5),$$
$$B_{12} = (r_1r_2b_1 - k_3k_5)(d_1 + k_1\sigma - \rho) + k_1(r_2k_3 - r_1r_2),$$
$$B_{13} = (r_2k_3 - r_1r_2)(d_1 + k_1\sigma - \rho) + \sigma d_1(r_1r_2b_1 - k_3k_5) + \mu r_2k_2,$$
$$B_{14} = \sigma(d_1(r_2k_3 - r_1r_2) + \mu r_2k_2),$$

For existence of U_2, the discriminant must be positive.

(iii) $P_3^*(E_3, U_3, I_3, N_3, V_3)$, coexisting steady state, where immune-tumor-normal cells coexist with the non-zero population after virus is injected.

Here, $E_3 = \frac{(\mu+\varphi I_3)(\sigma+U_3+I_3)}{(d_1+k_1U_3)(\sigma+U_3+I_3)-\rho U_3}$, $I_3 = \frac{\rho U_3V_3}{(d_2+k_4E_3)(\sigma_1+U_3)}$, $N_3 = \frac{r_2-k_5U_3}{r_2}$, $V_3 = \frac{bd_2I_3(\sigma_1+U_3)}{\rho_1U_3+\delta(\sigma_1+U_3)}$ and

$$U_3 = \frac{1}{r_1b_1}\left(r_1 - r_1b_1I_3 - k_2E_3 - k_3N_3 - \frac{\rho_1V_3}{\sigma_1+U_3}\right),$$

or

$$C_{11}U_3^2 + C_{12}U_3 + C_{13} = 0, \tag{5.3}$$

where,

$$C_{11} = r_1b_1,$$
$$C_{12} = r_1b_1\sigma_1 - r_1 + r_1b_1I_3 + k_2E_3 + k_3N_3,$$
$$C_{13} = \rho_1V_3 - \sigma_1(r_1 - r_1b_1I_3 - k_2E_3 - k_3N_3),$$

For existence of U_3, the discriminant must be positive.

Since $N = 0$ biologically means the death of the patient, so we discard the steady states having $N = 0$.

5.3. Stability analysis of the steady states

We investigate the stability of these steady states by linearizing the model (5.1) about each of the steady states. The Jacobian matrix of model (5.1) at an arbitrary point is given by

$$J_1 = \begin{pmatrix} Q_{11} & \frac{\sigma\rho E}{(\sigma+(U+I))^2} - k_1E & \varphi & 0 & 0 \\ -k_2U & Q_{12} & -r_1b_1U & -k_3U & \frac{-\rho_1U}{(\sigma_1+U)} \\ -k_4I & \frac{\sigma_1\rho_1V}{(\sigma_1+U)^2} & Q_{13} & 0 & \frac{\rho_1U}{(\sigma_1+U)} \\ 0 & -k_5N & 0 & Q_{14} & 0 \\ 0 & \frac{-\sigma_1\rho_1V}{(\sigma_1+U)^2} & bd_2 & 0 & Q_{15} \end{pmatrix},$$

where, $Q_{11} = \frac{\rho(U+I)}{\sigma+(U+I)} - d_1 - k_1U$, $Q_{12} = r_1 - 2r_1b_1U - r_1b_1I - \frac{\sigma_1\rho_1V}{(\sigma_1+U)^2} - k_2E - k_3N$, $Q_{13} = -d_2 - k_4E$, $Q_{14} = r_2 - 2r_2N - k_5U$, $Q_{15} = -\delta - \frac{\rho_1U}{(\sigma_1+U)}$.

As shown above, the model (5.1) has three steady states. Below, we investigate the stability of each of these states.

(i) $P_1^*(\frac{\mu}{d_1}, 0, 0, 1, 0)$, uninfected tumor, infected tumor and virus free state: The eigen values at P_1^* state are derived from the Jacobian matrix J_1, which are found to be

$$\lambda_1 = -d_1, \lambda_2 = r_1 - k_2.\frac{\mu}{d_1} - k_3, \lambda_3 = -d_2 - k_4.\frac{\mu}{d_1}, \lambda_4 = -r_2 \text{ and } \lambda_5 = -\delta.$$

So, the equilibrium is locally asymptotically stable if $r_1 - k_2.\frac{\mu}{d_1} - k_3 < 0$, otherwise unstable.

(ii) $P_2^*(E_2, U_2, 0, N_2, 0)$, infected tumor cells and virus-free state:

The characteristics equation at steady state $P_2^* is$

$$\left(\left(Q'_{13}-\lambda\right)\left(Q'_{15}-\lambda\right)-\frac{\rho_1 U_2}{(\sigma_1+U_2)}bd_2\right)\left(\left(Q'_{11}-\lambda\right)\left(\left(\left(Q'_{12}-\lambda\right)\left(Q'_{14}-\lambda\right)+k_3k_5N_2U_2\right)\right)\right.$$
$$\left.-k_2U_2\left(\frac{\sigma\rho E_2}{(\sigma+U_2)^2}-k_1E_2\right)\left(Q'_{14}-\lambda\right)\right)=0 \tag{5.4}$$

where $Q'_{11}=\frac{\rho U_2}{\sigma+U_2}-d_1-k_1U_2,'_{12}=r_1-2r_1b_1U_2-k_2E_2-k_3N_2$, $Q'_{13}=-d_2-k_4E_2$, $Q'_{14}=r_2-2r_2N_2-k_5U_2$, $Q'_{15}=-\delta-\frac{\rho_1U_2}{(\sigma_1+U_2)}$.

In this state, it is difficult to calculate the eigen values from Eq. (5.4) because this equation is non-linear and involving many terms. So, we substitute the parameter values in Table 1.

Using parameter values from Table 1 and considering $b = 3.49$ (depends on other parameter values in Table 1) in Eq. (5.2), we get three steady states as $(0.715, 0.067, 0, 0.952, 0)$, $(-0.182, 0.573, 0, 0.591, 0)$ and $(-5.251, 3.430, 0, -1.450, 0)$. Out of the three, only biologically valid steady state is P_2^* $(0.715, 0.067, 0, 0.952, 0)$.

From the characteristics Eq. (5.4), we get the eigenvalues for P_2^* to be

$$\lambda_1=-0.07009,\ \lambda_2=-0.333,\ \lambda_3=-0.141-0.128i,\ \lambda_4=-0.141+0.128i \text{ and } \lambda_5=0.114.$$

This shows that the virus-free state P_2^* is unstable. Physically it means that without any treatment tumor cells cannot be eradicated.

(iii) $P_3^*(E_3, U_3, I_3, N_3, V_3)$, coexisting steady state:

In steady state P_3^*, it is difficult to calculate the characteristics equation and involving many terms. So, we substitute the parameter values in Table 1.

Using parameter values from Table 1 and considering $b = 3.49$ in Eq. (5.3), we get, five steady states, which are found to be $(0.283, 0.001, 0.007, 0.999, 0.08)$, $(0.466, 0.011, 0.028, 0.992, 0.045)$, $(0.496, -1.56, 1.427, 2.11, 0.108)$, $(0.503, -0.05, -5.009, 1.036, 1.313)$, $(0.496, 1.321, -0.858, 0.056, -0.086)$.

Out of the five, two steady states are biologically feasible, which are

$$P_3^*\,(0.283, 0.001, 0.007, 0.999, 0.08) \text{ and } P_4^*\,(0.466, 0.011, 0.028, 0.992, 0.045)\,.$$

In steady state P_3^*, it is difficult to calculate the characteristics equation and involving many terms. So, we substitute the parameter values in Table 1.

(i) The characteristic equation at steady state P_3^* is

$$\lambda^5+0.165\lambda^4-0.072\lambda^3-0.003\lambda^2+0.000011\lambda-0.000000081=0,$$

From which the eigen values are found to be $\lambda_1=-0.35$, $\lambda_2=-0.043$, $\lambda_3=0.22$, $\lambda_4=0.004-0.015i$ and $\lambda_5=0.22$. The eigenvalues show that the co-existing steady state P_3^* is unstable.

(ii) The characteristic equation at steady state P_4^* is

$$\lambda^5+0.128\lambda^4-0.094\lambda^3-0.005\lambda^2+0.00017\lambda-0.0000041=0,$$

From which the eigen values are found to be $\lambda_1=-0.349$, $\lambda_2=-0.082$, $\lambda_3=0.276$, $\lambda_4=0.014-0.018i$ and $\lambda_5=0.014+0.018i$. The nature of the eigen values show that the co-existing steady state P_4^* is unstable.

From our above discussion it is seen that out of the above steady states, only P_1^* is stable and the remaining are unstable. Further, we have shown above that P_1^* is locally asymptotically stable. We investigated about the global stability of P_1^* and on the basis of this investigation we forward the following theorem.

Theorem 5.1. *The healthy steady state P_1^* is globally asymptotically stable if the steady state P_1^* is locally stable and the following conditions*

$$k_2E_1+k_3N_1>r_1,\ E=\frac{\mu}{d_1},\ U+I=\frac{1}{b_1},\ V=\frac{b}{\delta},$$

are satisfied.

Proof of Theorem 5.1 can be found in Appendix B.

Next, we verify our results numerically.

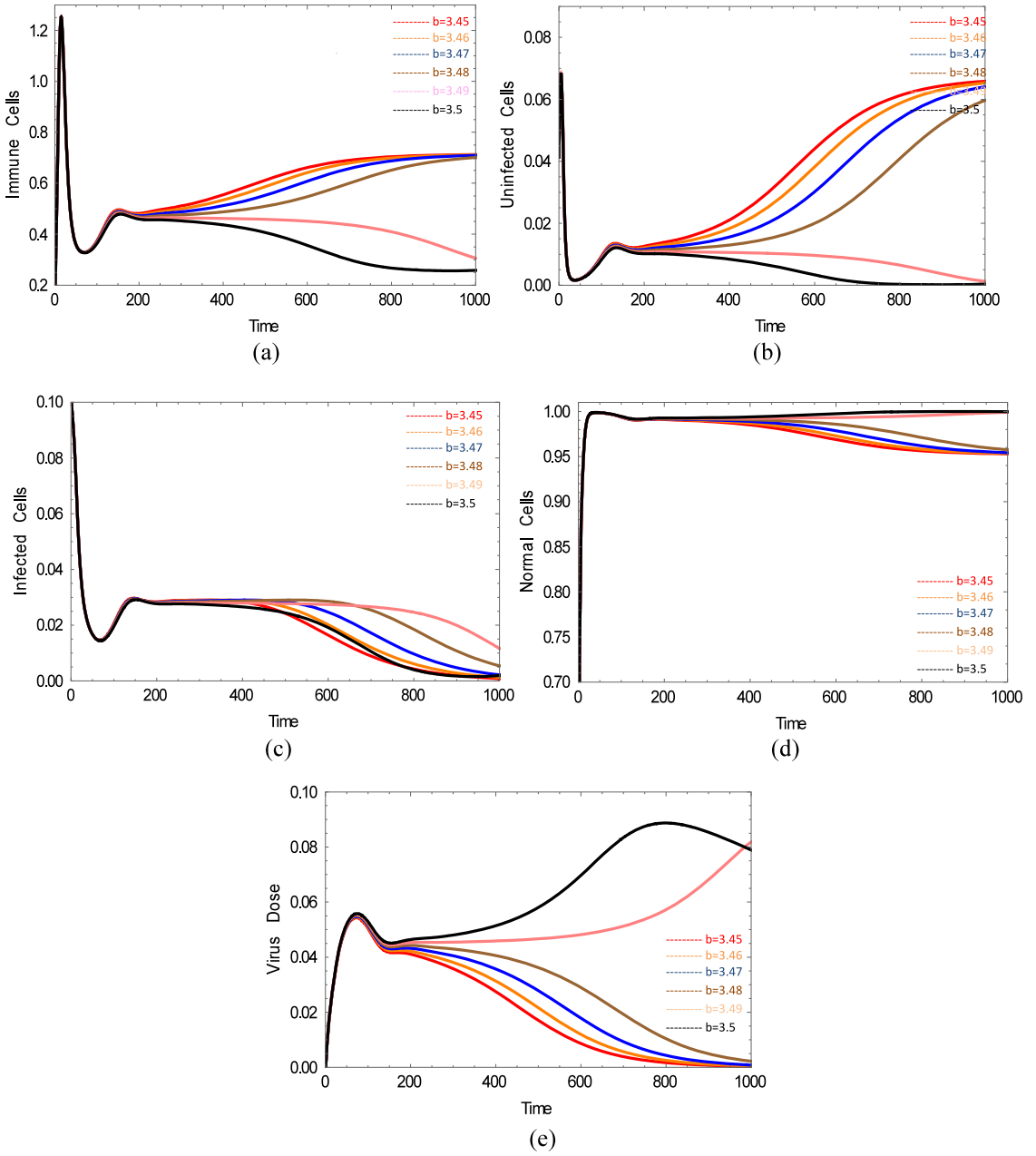

Fig. 4. Time-series solutions of the model (5.1) with initial conditions $E(0) = 0.2, U(0) = 0.05, I(0) = 0.1, N(0) = 0.6, V(0) = 0.001$. Figures (a), (b), (c), and (d) represent the density of immune cells, uninfected tumor cells, infected tumor cells, and normal cells, respectively, for different virus burst sizes, and figure (e) represents the different virus burst sizes.

Fig. 4 shows an evaluation of the model with virotherapy alone. From figures (b) and (c) It is seen that in this mode of therapy, tumor can be eradicated with a high dosage of virus burst size where $b = 3.5$. The time-series solutions of the model (5.1) shows that an increase in the virus burst size reduces the uninfected tumor density and increases the density of immune cells. Further, it is seen that both uninfected and infected tumor cells get reduced to zero in quick succession which is biologically feasible. Another advantage of this mode of treatment is observed to be reduction in tumor size without much loss of normal cells. But this treatment method takes a prolonged (excessive) period to reduce the tumor cells.

6. Dynamic behavior of the combined chemo-virotherapy model

To analyze the effect of the combined treatment of chemotherapy and virotherapy, we now proceed to study the whole model which consist of Eqs. (2.1) to (2.6).

$$\begin{aligned}
\frac{dE}{dt} &= \mu + \frac{\rho\,(U+I)\,E}{\sigma+(U+I)} - d_1E - k_1EU - a_1EC + \varphi I,\\
\frac{dU}{dt} &= r_1U\,(1-b_1\,(U+I)) - \frac{\rho_1UV}{\sigma_1+U} - k_2EU - k_3NU - a_2UC,\\
\frac{dI}{dt} &= \frac{\rho_1UV}{\sigma_1+U} - d_2I - k_4IE - a_3IC,\\
\frac{dN}{dt} &= r_2N\,(1-N) - k_5UN - a_4NC,\\
\frac{dV}{dt} &= bd_2I - \frac{\rho_1UV}{\sigma_1+U} - \delta V,\\
\frac{dC}{dt} &= u - d_3C,
\end{aligned} \tag{6.1}$$

with initial conditions: $E\,(0)=E_0$, $U\,(0)=U_0$, $I\,(0)=I_0$, $N\,(0)=N_0$, $V\,(0)=V_0$, $C\,(0)=C_0$ where each initial value is positive.

6.1. Analysis of the model

In this section, we study about the existence of the steady states related with the model (6.1) and their nature of stabilities. The motivation for doing so is as stated in earlier sections.

6.2. Existence of steady states

Following the method adopted earlier the steady states are found to be
(i) $P_1^{**}(\overline{E}_1,0,0,\overline{N}_1,0,\overline{C}_1)$, tumor cells and virus free steady state, where infected and uninfected tumor cells population are zero. Here, $\overline{E}_1=\frac{\mu}{d_1+a_1\overline{C}_1}$, $\overline{N}_1=\frac{r_1-a_4\overline{C}_1}{r_1}$, $\overline{C}_1=\frac{u}{d_3}=C^*$.
(ii) $P_2^{**}(\overline{E}_2,\overline{U}_2,0,\overline{N}_2,0,\overline{C}_2)$, infected tumor cells and virus free steady state.
Here, $\overline{E}_2=\frac{\mu(\sigma+\overline{U}_2)}{(d_1+k_1\overline{U}_2+a_1C^*)(\sigma+\overline{U}_2)-\rho\overline{U}_2}$, $\overline{N}_2=\frac{r_2-k_5\overline{U}_2-a_4C^*}{r_2}$, $\overline{C}_2=\frac{u}{d_3}=C^*$ and

$$\begin{aligned}
\overline{U}_2 &= \frac{1}{r_1b_1}\left(r_1 - k_2\overline{E}_2 - k_3\overline{N}_2 - a_2C^*\right)\\
&= \frac{1}{b_1} - \frac{k_2}{r_1b_1}\left(\frac{\mu(\sigma+\overline{U}_2)}{(d_1+k_1\overline{U}_2+a_1C^*)(\sigma+\overline{U}_2)-\rho\overline{U}_2}\right) - \frac{k_3}{r_1b_1}\left(\frac{r_2-k_5\overline{U}_2-a_4C^*}{r_2}\right) - \frac{a_2C^*}{r_1b_1},
\end{aligned}$$

or

$$D_{11}\overline{U}_2^3 + D_{12}\overline{U}_2^2 + D_{13}\overline{U}_2 + D_{14} = 0, \tag{6.2}$$

where,

$$\begin{aligned}
D_{11} &= k_1\,(r_1r_2b_1 - k_3k_5)\\
D_{12} &= (r_1r_2b_1 - k_3k_5)\,(d_1+k_1\sigma+a_1C^*-\rho) + k_1(r_2k_3 - r_1r_2 + a_2r_2C^* - k_3a_4C^*)\\
D_{13} &= (r_2k_3 - r_1r_2 + a_2r_2C^* - k_3a_4C^*)(d_1+k_1\sigma+a_1C^*-\rho) + \sigma\,(r_1r_2b_1 - k_3k_5)\,(d_1+a_1C^*) + \mu r_2k_2\\
D_{14} &= \sigma(r_2k_3 - r_1r_2 + a_2r_2C^* - k_3a_4C^*)(d_1+a_1C^*) + \mu r_2k_2\sigma
\end{aligned}$$

For the existence of $\overline{U}_2$, discriminant must be positive.
(iii) $P_3^{**}(\overline{E}_3,0,\overline{I}_3,\overline{N}_3,\overline{V}_3,\overline{C}_3)$, uninfected tumor free steady state:
where, $\overline{E}_3=\frac{-d_2-a_3\overline{C}_3}{k_4}$, $\overline{N}_3=\frac{r_2-a_4\overline{C}_3}{r_2}$, $\overline{V}_3=\frac{bd_2\overline{I}_3}{\delta}$, $\overline{C}_3=C^*$ and

$$\mu + \frac{\rho\overline{I}_3\overline{E}_3}{\sigma+\overline{I}_3} - d_1\overline{E}_3 - a_1\overline{E}_3C^* + \varphi\overline{I}_3 = 0,$$

or

$$E_{11}\overline{I}_3^2 + E_{12}\overline{I}_3 + E_{13} = 0,$$

where,

$$E_{11} = \varphi,$$
$$E_{12} = \rho\overline{E}_3 + \mu - d_1\overline{E}_3 - a_1\overline{E}_3C^* + \varphi\sigma,$$
$$E_{13} = (\mu - d_1\overline{E}_3 - a_1\overline{E}_3C^*)\sigma,$$

For existence of $\overline{I}_3$, discriminant must be positive.

(iii) $P_3^{**}(\overline{E}_3, 0, \overline{I}_3, \overline{N}_3, \overline{V}_3, \overline{C}_3)$, uninfected tumor free steady state:
where, $\overline{E}_3 = \frac{-d_2 - a_3\overline{C}_3}{k_4}$, $\overline{N}_3 = \frac{r_2 - a_4\overline{C}_3}{r_2}$, $\overline{V}_3 = \frac{bd_2\overline{I}_3}{\delta}$, $\overline{C}_3 = C^*$ and

$$\mu + \frac{\rho\overline{I}_3\overline{E}_3}{\sigma + \overline{I}_3} - d_1\overline{E}_3 - a_1\overline{E}_3C^* + \varphi\overline{I}_3 = 0,$$

or

$$E_{11}\overline{I}_3^2 + E_{12}\overline{I}_3 + E_{13} = 0, \tag{6.3}$$

where,

$$E_{11} = \varphi,$$
$$E_{12} = \rho\overline{E}_3 + \mu - d_1\overline{E}_3 - a_1\overline{E}_3C^* + \varphi\sigma,$$
$$E_{13} = (\mu - d_1\overline{E}_3 - a_1\overline{E}_3C^*)\sigma,$$

For existence of $\overline{I}_3$, discriminant must be positive.

(viii) $P_4^{**}(\overline{E}_4, \overline{U}_4, \overline{I}_4, \overline{N}_4, \overline{V}_4, \overline{C}_4)$, co-existing steady state:

$$\overline{E}_4 = \frac{\left(\mu + \varphi\overline{I}_4\right)\left(\sigma + \overline{U}_4 + \overline{I}_4\right)}{(d_1 + k_1\overline{U}_4 + a_1\overline{C}_4)\left(\sigma + \overline{U}_4 + \overline{I}_4\right) - \rho(\overline{U}_4 + \overline{I}_4)}, \overline{I}_4 = \frac{\rho_1\overline{U}_4\overline{V}_4}{\left(\sigma_1 + \overline{U}_4\right)\left(d_2 + k_4\overline{E}_4 + a_3\overline{C}_4\right)},$$
$$\overline{N}_4 = \frac{r_2 - k_5\overline{U}_4 - a_4\overline{C}_4}{r_2},$$
$$\overline{V}_4 = \frac{bd_2\overline{I}_4(\sigma_1 + \overline{U}_4)}{\rho\overline{U}_4 + \delta(\sigma_1 + \overline{U}_4)}, \overline{C}_4 = C^* \text{ and}$$
$$\overline{U}_4 = \frac{1}{r_1b_1}\left(\mathrm{r}_1 - r_1b_1\overline{I}_4 - \frac{\rho_1\overline{V}_4}{\sigma_1 + \overline{U}_4} - k_2\overline{E}_4 - k_3\overline{N}_4 - a_2C^*\right),$$

or

$$F_{11}\overline{U}_4^2 + F_{12}\overline{U}_4 + F_{13} = 0, \tag{6.4}$$

where,

$$F_{11} = r_1b_1,$$
$$F_{12} = r_1b_1\sigma_1 - r_1 + r_1b_1\overline{I}_4 + k_2\overline{E}_4 + k_3\overline{N}_4 + a_2C^*,$$
$$F_{13} = \rho_1\overline{V}_4 - \sigma_1\left(r_1 - r_1b_1\overline{I}_4 - k_2\overline{E}_4 - k_3\overline{N}_4 - a_2C^*\right),$$

For existence of $\overline{U}_4$, the discriminant must be positive.

Since $N = 0$ biologically means the death of the patient, so we discard the steady states having $N = 0$.

6.3. Stability analysis of the steady states

We investigate the stability of these steady states by linearizing the model (6.1) about each of the steady states. The Jacobian matrix of the model (6.1) at an arbitrary point is given by

$$J_2 = \begin{pmatrix} R_{11} & R_{16} & \varphi & 0 & 0 & -a_1E \\ -k_2U & R_{12} & -r_1b_1U & -k_3U & \frac{-\rho_1U}{(\sigma_1+U)} & -a_2U \\ -k_4I & \frac{\sigma_1\rho_1V}{(\sigma_1+U)^2} & \mathrm{R}_{13} & 0 & \frac{\rho_1U}{(\sigma_1+U)} & -a_3I \\ 0 & -k_5N & 0 & R_{14} & 0 & -a_4N \\ 0 & \frac{-\sigma_1\rho_1V}{(\sigma_1+U)^2} & bd_2 & 0 & R_{15} & 0 \\ 0 & 0 & 0 & 0 & 0 & -d_3 \end{pmatrix},$$

where, $R_{11} = \frac{\rho(U+I)}{\sigma+(U+I)} - d_1 - k_1U - a_1C$, $R_{12} = r_1 - 2r_1b_1U - r_1b_1I - \frac{\sigma_1\rho_1V}{(\sigma_1+U)^2} - k_2E - k_3N - a_2C$, $R_{13} = -d_2 - k_4E - a_3C$, $R_{14} = r_2 - 2r_2N - k_5U - a_4C$, $R_{15} = -\delta - \frac{\rho_1U}{(\sigma_1+U)}$, $R_{16} = \frac{\sigma\rho E}{(\sigma+(U+I))^2} - k_1E$. As found above, the model (6.1) has four steady states. Now, we investigate the nature of stability of each of those one by one.
(i) $P_1^{**}(\overline{E}_1, 0, 0, \overline{N}_1, 0, \overline{C}_1)$, tumor and virus free steady state: The eigen values of the Jacobian matrix at P_1^{**} are found as

$$\lambda_1 = -d_1 - a_1\overline{C}_1 < 0, \lambda_2 = r_1 - k_2.\frac{\mu}{d_1 + a_1\overline{C}_1} - k_3.\frac{r_2 - a_4\overline{C}_1}{r_2} - a_2\overline{C}_1,$$

$$\lambda_3 = -d_2 - k_4.\frac{\mu}{d_1 + a_1\overline{C}_1} - a_3\overline{C}_1 < 0, \lambda_4 = -r_2 + a_4\overline{C}_1,$$

$$\lambda_5 = -\delta \text{ and } \lambda_6 = -d_3 < 0.$$

So, using the standard relationship between eigenvalues and nature of stability, it can be concluded that P_1^{**} is locally asymptotically stable if

$$1.\ u < \frac{r_2d_3}{a_4} \text{ and} \tag{6.5}$$

$$2.\ \left\{r_2\left(r_1 - a_2\overline{C}_2\right) - k_3\left(r_2 - a_4\overline{C}_2\right)\right\}\left(d_1 + a_1\overline{C}_2\right) < \mu k_2r_2, \text{ otherwise unstable.} \tag{6.6}$$

We consider the chemotherapy dose u in stable range to bring the model to the at steady state P_1^{**}.
(ii) $P_2^{**}(\overline{E}_2, \overline{U}_2, 0, \overline{N}_2, 0, \overline{C}_2)$, infected tumor and virus free steady state: Here, one eigen value is $\lambda = -d_3 < 0$ and the other eigen values are derived from the Jacobian matrix J_2.

The characteristic equation at steady state P_2^{**} is

$$\begin{aligned}&\left(R'_{11} - \lambda\right)\left(\left(R'_{12} - \lambda\right)\left(R'_{14} - \lambda\right)\left((R'_{13} - \lambda)(R'_{15} - \lambda) - \frac{\rho_1\overline{U}_2}{\left(\sigma_1 + \overline{U}_2\right)}bd_2\right) - k_3k_5\overline{U}_2\overline{N}_2(R'_{13} - \lambda)(R'_{15} - \lambda)\right) \\ &+ R'_{16}\left(k_2\overline{U}_2\left(R'_{14} - \lambda\right)\left(\left(R'_{13} - \lambda\right)\left(R'_{15} - \lambda\right) - \frac{\rho_1\overline{U}_2}{\left(\sigma_1 + \overline{U}_2\right)}bd_2\right)\right) = 0\end{aligned} \tag{6.7}$$

where,

$$R'_{11} = \frac{\rho\overline{U}_2}{\sigma + \overline{U}_2} - d_1 - k_1\overline{U}_2 - a_1\overline{C}_2, R'_{12} = r_1 - 2r_1b_1\overline{U}_2 - k_2\overline{E}_2 - k_3\overline{N}_2 - a_2\overline{C}_2, {}'_{13} = -d_2 - k_4\overline{E}_2 - a_3\overline{C}_2,$$

$$R'_{14} = r_2 - 2r_2\overline{N}_2 - k_5\overline{U}_2 - a_4\overline{C}_2, R'_{15} = -\delta - \frac{\rho_1\overline{U}_2}{\left(\sigma_1 + \overline{U}_2\right)}, R'_{16} = \frac{\sigma\rho\overline{E}_2}{\left(\sigma + \overline{U}_2\right)^2} - k_1\overline{E}_2.$$

It is difficult to calculate the eigen values from Eq. (6.7) because this equation is non-linear and involving many terms. So, we substitute the parameter values in Table 1.

Case1 with $u = 0.0260123$ (in stable range from conditions (6.5) and (6.6)).

Using parameter values from Table 1 and considering $u = 0.0260123$ in Eq. (6.2), we get three steady states as $(0.164, -0.00000048, 0, 0.703, 0, 0.52)$, $(-0.49, 0.369, 0, 0.439, 0, 0.52)$ and $(-4.808, 2.803, 0, -1.3, 0, 0.52)$.

So, no biologically valid steady state exists in this case.

Case2: Consider $u = 0.025$ (in unstable range from conditions (6.5) and (6.6)).

Using parameter values from Table 1 and considering $u = 0.025$ in Eq. (6.2), we get three steady states, which are $(0.177, 0.00076, 0, 0.709, 0, 0.5)$, $(-0.467, 0.371, 0, 0.449, 0, 0.5)$ and $(-4.827, 2.829, 0, -1.306, 0, 0.5)$.

Out of the three, only one is biologically feasible, which is P_2^{**} $(0.179, 0.00076, 0, 0.709, 0, 0.5)$.

The eigen values related to this point are

$$\lambda_1 = -0.05, \lambda_2 = -0.246462, \lambda_3 = -0.297935, \lambda_4 = -0.07, \lambda_5 = -0.002 \text{ and } \lambda_6 = 0.004.$$

This shows that the steady state P_2^{**} at $(0.177, 0.00076, 0, 0.709, 0, 0.5)$ is unstable.

Biologically, it is clear from this that immune system fails to remove tumor cells without a sufficient amount of drug dose.

(iii) $P_3^{**}(\overline{E}_3, 0, \overline{I}_3, \overline{N}_3, \overline{V}_3, \overline{C}_3)$, uninfected tumor free steady state: Here, eigen values are $\lambda_1 = r_1 - r_1 b_1 \overline{I}_3 - \frac{\sigma_1 \rho_1 \overline{V}_3}{\sigma_1} - k_2\overline{E}_3 - k_3\overline{N}_3 - a_2\overline{C}_3$, $\lambda_2 = r_2 - 2r_2\overline{N}_3 - a_4\overline{C}_3$, $\lambda_3 = -\delta$, $\lambda_4 = -d_3 < 0$ and the other eigen values are derived from the Jacobian matrix $J_2(P_3^{**})$.

$$\lambda^2 + \left(-\frac{\rho\overline{I}_3}{\sigma + \overline{I}_3} + d_1 + a_1\overline{C}_3 + d_2 + k_4\overline{E}_3 + a_3\overline{C}_3\right)\lambda + \left(\frac{\rho\overline{I}_3}{\sigma + \overline{I}_3} - d_1 - a_1\overline{C}_3\right)\left(-d_2 - k_4\overline{E}_3 - a_3\overline{C}_3\right) + \varphi k_4\overline{I}_3 = 0$$

or

$$\lambda^2 + X_{22}\lambda + Y_{22} = 0 \tag{6.8}$$

By Routh–Hurwitz criteria, the characteristic Eq. (6.8) has negative roots if $X_{22} > 0$ and $Y_{22} > 0$.

So, using the standard relationship between eigenvalues and nature of stability, it can be concluded that P_3^{**} is locally asymptotically stable if

$$\lambda_1 < 0 = r_1 - r_1 b_1 \overline{I}_3 - \frac{\sigma_1 \rho_1 \overline{V}_3}{\sigma_1} - k_2\overline{E}_3 - k_3\overline{N}_3 - a_2\overline{C}_3 < 0, \ \lambda_2 < 0 = r_2 - 2r_2\overline{N}_3 - a_4\overline{C}_3 < 0,$$

$$d_1 + a_1\overline{C}_3 + d_2 + k_4\overline{E}_3 + a_3\overline{C}_3 > \frac{\rho\overline{I}_3}{\sigma + \overline{I}_3} \text{ and } \left(\frac{\rho\overline{I}_3}{\sigma + \overline{I}_3} - d_1 - a_1\overline{C}_3\right)\left(-d_2 - k_4\overline{E}_3 - a_3\overline{C}_3\right) + \varphi k_4\overline{I}_3 > 0.$$

Case1: Consider $u = 0.0260123$ (in stable range from conditions (6.5) and (6.6)).

Using parameter values from Table 1 and considering $u = 0.0260123$ in Eq. (6.3), steady states are found to be $(-1.24049, 0, 0.227656, 0.702716, 7.945180, 0.520246)$ and $(-1.24049, 0, 7.505558, 0.702716, 261.94399, 0.520246)$. Thus, no biologically valid steady state exists in this case.

Case2: Consider $u = 0.025$ (in unstable range from conditions (6.5) and (6.6)).

Using parameter values from Table 1 and considering $u = 0.025$ in Eq. (6.3), steady states are found to be

$$(-1.2, 0, 0.225443, 0.714286, 7.867970, 0.5) \text{ and } (-1.2, 0, 7.274557, 0.714286, 253.88203, 0.5).$$

So, in this case also no biologically valid steady state exists.

(viii) $P_4^{**}(\overline{E}_4, \overline{U}_4, \overline{I}_4, \overline{N}_4, \overline{V}_4, \overline{C}_4)$, co-existing steady state: Here, one eigen value is $\lambda = -d_3 < 0$ and the other eigen values are derived from the Jacobian matrix J_2.

In steady state P_4^{**}, it is difficult to calculate the characteristics equation and involving many terms. So, we substitute the parameter values in Table 1.

Case1: Consider $u = 0.0260123$ (in unstable range from conditions (6.5) and (6.6)).

Using parameter values from Table 1 and considering $u = 0.0260123$ in Eq. (6.4), steady states are found to be $(-0.543, -0.389, 0.716, 0.98, 0.03, 0.52)$, $(-0.538, -0.06, 2.573, 0.746, -0.521, 0.52)$, $(0.163, -0.001, -0.000013, 0.00045, 0.703, 0.52)$, $(-0.546, 0.241, 0.103, 0.53, 0.0164, 0.52)$, $(-0.544, 6.301, -4.615, -3.798, -0.414, 0.52)$.

So, no biologically valid steady state exists.

Case2: Consider $u = 0.025$ (in unstable range from conditions (6.5) and (6.6)).

Using parameter values from Table 1 and considering $u = 0.025$ in Eq. (6.4), steady states are found to be $(-0.503, -0.307, 0.662, 0.934, 0.02, 0.5)$, $(-0.498, -0.062, 2.29, 0.758, -0.452, 0.5)$, $(0.165, -0.001, -0.00012, 0.715, 0.004, 0.5)$, $(-0.504, 8.66, -6.48, -5.471, -0.577, 0.5)$, $(-0.505, 0.279, 0.075, 0.515, 0.011, 0.5)$.

So, no biologically valid steady state exists in this case also.

From our above discussion it is seen that out of the above steady states, only P_1^{**} is stable and the remaining are unstable. Further, we have shown above that P_1^{**} is locally asymptotically stable. We investigated about the global stability of P_1^{**} and on the basis of this investigation we forward the following theorem.

Theorem 6.1. *The healthy steady state P_1^{**} is globally asymptotically stable if the steady state P_1^{**} is locally asymptotically stable and the conditions*

$$k_2\overline{E}_1 + k_3\overline{N}_1 + a_2\overline{C}_1 > r_1, E = \frac{\mu}{d_1}, U + I = \frac{1}{b_1}, V = \frac{b}{\delta}, C = \frac{u}{d_3},$$

are satisfied.

Proof of Theorem 6.1 can be found in Appendix C.

Now, we verify our result numerically.

Comparing with the results of Figs. 3(b) and 4(b), where chemotherapy and virotherapy treatment methods were used alone respectively, it can be seen from Figs. 5(c) and 5(d) that the uninfected tumor cell population can be eradicated using less amount of chemotherapy in a shorter period when combined chemo-virotherapy mode of treatment is adopted. Fig. 3(b) shows that in absence of virotherapy ($b = 0$), chemotherapeutic drug dose $u = 0.02$ is insufficient to overcome tumor cells of growth rate $r_1 = 0.45$. But, when combined mode of treatment of both chemo-virotherapy is adopted, same amount of chemotherapy drug administration ($u = 0.02$) is sufficient to eradicate the tumor cells at a much higher virus burst size $b = 3.4$ and $r_1 = 0.45$ as seen from Fig. 5(d). Also, from Fig. 4(b) it is seen that the virus therapy alone at virus burst size $b = 3$ is not sufficient to overcome tumor cells of growth rate $r_1 = 0.45$. But, when the same virus burst size ($b = 3$) is subjected to combined therapy with chemotherapy at drug dose $u = 0.025$, it becomes sufficient to eradicate the tumor cells, where tumor cells growth rate $r_1 = 0.45$ as seen from Fig. 5(c).

Thus, combined treatment method can eliminate tumor with lower dose of drug administration rate and virus burst size, which cannot be achieved when either virotherapy or chemotherapy alone is used as mode of treatment.

Figs. 3(b) and 3(c) show that though chemotherapeutic drug dose $u = 0.027$ led to reduction in the burden of tumor cells, but it damaged immune-normal cells populations also, which can put the patient to other health hazards. In contrast, in combined mode of treatment of both chemo-virotherapy, it requires lesser dose of chemotherapy to eradicate the tumor cells, thus reducing the side effect on immune-normal cells. This observation can also be seen in Fig. 5(a), 5(b), 5(g) and 5(h). So, we can conclude that the incorporation of combined therapy to eradicate the tumor cells is more effective as it makes the patients' body tumor-free without putting the patients' health at risk.

Figs. 5(e) and 5(f) further show that both infected and uninfected tumor cells reduces almost simultaneously and it is biologically feasible.

Thus, these simulation results show that the cancer treatment with chemo-virotherapy is more effective than either chemotherapy or virotherapy alone. These results also show that the combined treatment method would take a shorter period to clear all tumor cells from the body.

In the next section, we will analyze the optimal control problem to explicitly determine the optimal combined amount of virus and chemotherapeutic drug dosage necessary for tumor eradication.

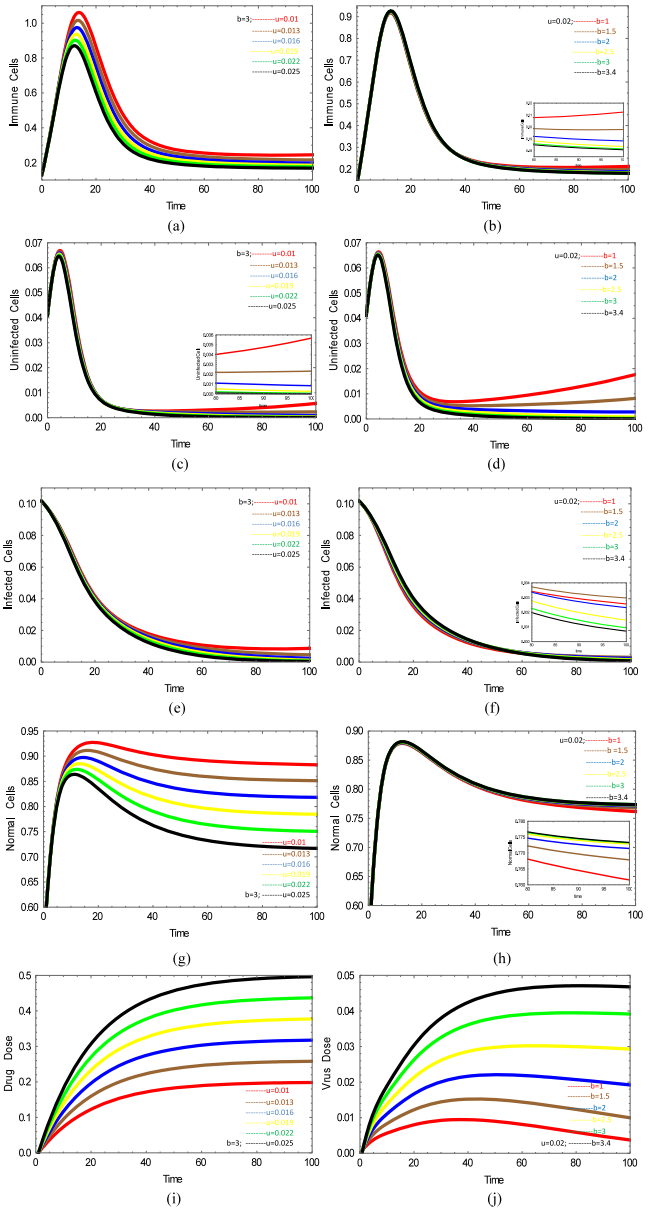

Fig. 5. Time-series solutions of the model (6.1) with the initial conditions for these simulations are: $E(0) = 0.2, U(0) = 0.05, I(0) = 0.1, N(0) = 0.6, V(0) = 0.001, C(0) = 0.001$. Figures (a), (c), (e) and (g) represents the density of immune cells, uninfected tumor cells, infected tumor cells, and normal cells, respectively, for different chemo-drug doses and for virus burst size, $b = 3$. Figures (b), (d), (f), and (h) represents the density of immune cells, uninfected tumor cells, infected tumor cells, and normal cells, respectively, for different virus burst sizes and for chemo-drug dose, $u = 0.02$. Figure (i) represents the different rate of chemo-drug doses with virus burst size, $b = 3$. Figure (j) represents the different rate of virus burst size with chemo-drug dose, $u = 0.02$.

7. Optimal control

This section is dedicated toward the study of the model under investigation when we administer chemo-virotherapy treatment over a fixed time. From a biomedical perspective, we use the concept of optimal control in the model under consideration. As higher doses of chemotherapy cause many side effects in the patients, so, it

is utmost important to keep an eye on how this amount can be minimized. At the same time, we must minimize it in a way so that the tumor can be eradicated because our investigation has already revealed that only virus therapy cannot eradicate tumor. Under such a consideration, we propose and analyze an optimal control problem applied to the chemo-virotherapy model to determine the optimal combination of chemotherapy and virotherapy for controlling the tumor. We set the control variables τ and u respectively to be the supply of viruses and chemotherapy from external sources of drugs, which is incorporated into the model's equations (2.5) and (2.6) to obtain the following control model which is time dependent. For model tractability, we ignore the immune-normal cell responses.

$$\begin{aligned}
\frac{dU}{dt} &= r_1 U\left(1 - b_1\left(U + I\right)\right) - \frac{\rho_1 U V}{\sigma_1 + U} - a_2 U C,\\
\frac{dI}{dt} &= \frac{\rho_1 U V}{\sigma_1 + U} - d_2 I - a_3 I C,\\
\frac{dV}{dt} &= b d_2 I - \frac{\rho_1 U V}{\sigma_1 + U} - \delta V + \tau(t),\\
\frac{dC}{dt} &= u(t) - d_3 C,
\end{aligned} \tag{7.1}$$

Initial conditions for the model are set as:

$$U\left(0\right) = U_0, I\left(0\right) = I_0, V\left(0\right) = V_0, C\left(0\right) = C_0, \tag{7.2}$$

The objective function which is to be minimized is defined as:

$$\Omega\left(\tau, u\right) = \int_0^{t_f} \left[U\left(t\right) + I\left(t\right) - \varepsilon_1 \tau^2(t) + \varepsilon_2 u^2(t)\right] dt, \tag{7.3}$$

The constants $\varepsilon_1, \varepsilon_2$ represent the weight factors of the respective terms. Those are used for balancing the size of the terms. The optimal combination of control variables τ and u will be adequate to minimize the uninfected and infected tumor density ($U(t)$ & $I(t)$) together and also negative side effects over a fixed time. The first two terms of the integrand function represent the total number of tumor cells and the third and fourth terms of the integrand reflect the effectiveness of the applied drugs on the body. Here, we use an optimal control problem relative to the model to maximize the viro-therapeutic effect to boost up the immune system and reduce the duration of recovery time of the patient and minimize chemotherapeutic drug administration to reduce the side effects.

Here, we establish an optimal control τ^*, u^* such that

$$\Omega\left(\tau^*, u^*\right) = \min\left\{\Omega\left(\tau, u\right) : \tau, u \in \Delta\right\}, \tag{7.4}$$

where $\Delta = \left\{\tau, u : \text{measurable}, 0 \leq \tau, u \leq 1, t \in \left[0, t_f\right]\right\}$ is the admissible control set.

7.1. The existence of optimal control

In this sub section, we discuss about the existence of an optimal control of our model (7.1).

The property of super solutions $\overline{U}, \overline{I}, \overline{V}$, and $\overline{C}$ of the model (7.1) is that trajectories given by

$$\begin{aligned}
\frac{d\overline{U}}{dt} &= r_1 \overline{U},\\
\frac{d\overline{I}}{dt} &= \rho_1 \overline{V} - d_2 \overline{I},\\
\frac{d\overline{V}}{dt} &= b d_2 \overline{I} - \delta \overline{V} + \tau,\\
\frac{d\overline{C}}{dt} &= u - d_3 \overline{C},
\end{aligned} \tag{7.5}$$

are bounded. In vector form, we can express the above model (7.5) as:

$$\begin{pmatrix} \overline{U} \\ \overline{I} \\ \overline{V} \\ \overline{C} \end{pmatrix}' \leq \begin{pmatrix} r_1 & 0 & 0 & 0 \\ 0 & -d_2 & \rho_1 & 0 \\ 0 & b d_2 & -\delta & 0 \\ 0 & 0 & 0 & -d_3 \end{pmatrix} \begin{pmatrix} \overline{U} \\ \overline{I} \\ \overline{V} \\ \overline{C} \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ \tau \\ u \end{pmatrix}$$

Since this is a linear model with bounded coefficients and the time frame is limited, so, we can conclude that the solutions $\overline{U}, \overline{I}, \overline{V}$ and $\overline{C}$ of the above model are bounded. Using the theorem proposed by Lukes [10,17], we found that the admissible control class and the corresponding state equations with assumed initial conditions are non-empty. Also, by definition of the set Δ, it is clear that the control set Δ is convex and closed. Since the state solutions are bounded, hence, the right-hand sides of the state model (7.1) are continuous and bounded by a sum of the bounded controls and the states.

Now, we show the convexity of integrand of $\Omega(\tau, u)$ on Δ and that it is bounded below by $\tau_1(u^2 - \tau^2) - \tau_2$ with $\tau_1, \tau_2 > 0$.

Let $p = (p_1, p_2), q = (q_1, q_2)$ be distinct elements of Ω and $0 \leq Y \leq 1$. We have to show that

$$\Omega(p_1 Y + (1-Y) p_2, q_1 Y + (1-Y) q_2) \leq (1-Y)\Omega(p_1, q_1) + Y\Omega(p_2, q_2),$$

where, $\Omega(\tau, u) = U(t) + I(t) - \varepsilon_1 \tau^2(t) + \varepsilon_2 u^2(t)$.

To establish it we proceed as follows:

$$\begin{aligned}
&\Omega(p_1 Y + (1-Y) q_1, p_2 Y + (1-Y) q_2) - (1-Y)\Omega(p_1, p_2) + Y\Omega(q_1, q_2)\\
&= U(t) + I(t) - \varepsilon_1 (p_1 Y + (1-Y) q_1)^2 + \varepsilon_2 (p_2 Y + (1-Y) q_2)^2 - Y\left(U(t) + I(t) - \varepsilon_1 p_1^2 + \varepsilon_2 p_2^2\right)\\
&\quad - (1-Y)\left(U(t) + I(t) - \varepsilon_1 q_1^2 + \varepsilon_2 q_2^2\right)\\
&= U(t) + I(t) - \varepsilon_1\left(p_1^2 Y^2 + 2p_1 q_1 Y(1-Y) + (1-Y)^2 q_1^2\right) + \varepsilon_2\left(p_2^2 Y^2 + 2p_2 q_2 Y(1-Y) + (1-Y)^2 q_2^2\right)\\
&\quad - Y\left(U(t) + I(t) - \varepsilon_1 p_1^2 + \varepsilon_2 p_2^2\right) - (U(t) + I(t) - \varepsilon_1 q_1^2 + \varepsilon_2 q_2^2) + Y\left(U(t) + I(t) - \varepsilon_1 q_1^2 + \varepsilon_2 q_2^2\right)\\
&= -\varepsilon_1 p_1^2 Y^2 - 2\varepsilon_1 p_1 q_1 Y(1-Y) - \varepsilon_1 (1-Y)^2 q_1^2 + \varepsilon_2 p_2^2 Y^2 + 2\varepsilon_2 p_2 q_2 Y(1-Y)\\
&\quad + \varepsilon_2 (1-Y)^2 q_2^2 + \varepsilon_1 p_1^2 Y - \varepsilon_2 p_2^2 Y + \varepsilon_1 q_1^2 - \varepsilon_2 q_2^2 - \varepsilon_1 q_1^2 Y + \varepsilon_2 q_2^2 Y\\
&= -\varepsilon_1 p_1^2 Y^2 - 2\varepsilon_1 p_1 q_1 Y + 2\varepsilon_1 p_1 q_1 Y^2 - \varepsilon_1\left(1 - 2Y + Y^2\right) q_1^2 + \varepsilon_2 p_2^2 Y^2 + 2\varepsilon_2 p_2 q_2 Y - 2\varepsilon_2 p_2 q_2 Y^2\\
&\quad + \varepsilon_2\left(1 - 2Y + Y^2\right) q_2^2 + \varepsilon_1 p_1^2 Y - \varepsilon_2 p_2^2 Y + \varepsilon_1 q_1^2 - \varepsilon_2 q_2^2 - \varepsilon_1 q_1^2 Y + \varepsilon_2 q_2^2 Y\\
&= -\varepsilon_1 p_1^2 Y^2 + 2\varepsilon_1 p_1 q_1 Y^2 - \varepsilon_1 q_1^2 Y^2 + \varepsilon_1 p_1^2 Y - 2\varepsilon_1 p_1 q_1 Y + \varepsilon_1 q_1^2 Y + \varepsilon_2 p_2^2 Y^2 - 2\varepsilon_2 p_2 q_2 Y^2 + \varepsilon_2 q_2^2 Y^2\\
&\quad - \varepsilon_2 q_2^2 Y + 2\varepsilon_2 p_2 q_2 Y - \varepsilon_2 p_2^2 Y\\
&= -(\varepsilon_2 - \varepsilon_1)(p_2 - q_2)^2 Y(1-Y) \quad [\text{Since } (Y-1) \leq 0 \text{ and if } \varepsilon_2 - \varepsilon_1 \geq 0],
\end{aligned}$$

and

$$U(t) + I(t) - \varepsilon_1 \tau^2(t) + \varepsilon_2 u^2(t) \geq -\varepsilon_1 \tau^2(t) + \varepsilon_2 u^2(t) \geq \tau_1\left(u^2(t) - \tau^2(t)\right) \geq \tau_1\left(u^2(t) - \tau^2(t)\right) - \tau_2,$$

This shows that $\tau_1\left(u^2(t) - \tau^2(t)\right) - \tau_2$ is a lower bound of $\Omega(\tau, \mu)$.

This verifies that there exists an optimal control τ^*, u^* for which $\Omega(\tau^*, u^*) = \min\{\Omega(\tau, u) : \tau, u \in \Delta\}$. From above analysis and conclusion, we state the following theorem.

Theorem 7.1. *Subject to the model (7.1), with initial conditions* $U(0) = U_0, I(0) = I_0, V(0) = V_0$, *and* $C(0) = C_0$, *the objective functional*

$$\Omega(\tau, u) = \int_0^{t_f} \left[U(t) + I(t) - \varepsilon_1 \tau^2(t) + \varepsilon_2 u^2(t)\right] dt,$$

admits an optimal control τ^*, u^* *such that* $\Omega(\tau^*, u^*) = \min\{\Omega(\tau, u) : \tau, u \in \Delta\}$, *where* $\Delta = \{(\tau, u) : \tau, u$ *are piecewise continuous*, $0 \leq \tau, u \leq 1, t \in [0, t_f]\}$.

7.2. Characterization of the optimal control

For applying the Pontryagin maximum principle [32], we introduced the four co-state variables $\xi_i (i = 1, 2, 3, 4)$. The Hamiltonian function is given by

$$h = U + I - \varepsilon_1 \tau^2 + \varepsilon_2 u^2 + \xi_1 \dot{U} + \xi_2 \dot{I} + \xi_3 \dot{V} + \xi_4 \dot{C}, \tag{7.6}$$

With substitution from (7.1) into (7.6) we get

$$h = U + I - \varepsilon_1 \tau^2 + \varepsilon_2 u^2 + \xi_1 \left(r_1 U \left(1 - b_1 \left(U + I\right)\right) - \frac{\rho_1 U V}{\sigma_1 + U} - a_2 U C \right) + \xi_2 \left(\frac{\rho_1 U V}{\sigma_1 + U} - d_2 I - a_3 I C \right)$$
$$+ \xi_3 \left(b d_2 I - \frac{\rho_1 U V}{\sigma_1 + U} - \delta V + \tau \right) + \xi_4 \left(u - d_3 C\right),$$

The Hamiltonian equations are:

$$\dot{\xi}_1 = -\frac{\partial h}{\partial U}, \dot{\xi}_2 = -\frac{\partial h}{\partial I}, \dot{\xi}_3 = -\frac{\partial h}{\partial V}, \dot{\xi}_4 = -\frac{\partial h}{\partial C},$$

where, $\xi_i \left(t\right), i = 1, 2, 3, 4$ are the adjoint functions to be determined suitably.

The form of the adjoint equations and transversality conditions are standard results from Pontryagin's maximum principle [32]. The adjoint system can be written in the form:

$$\dot{\xi}_1 = -\frac{\partial h}{\partial U} = -1 - \xi_1 \left(r_1 - 2 r_1 b_1 U - r_1 b_1 I - \frac{\rho_1 \sigma_1 V}{(\sigma_1 + U)^2} - a_2 C \right) - (\xi_2 - \xi_3) \frac{\rho_1 \sigma_1 V}{(\sigma_1 + U)^2},$$
$$\dot{\xi}_2 = -\frac{\partial h}{\partial I} = -1 + \xi_1 r_1 b_1 U + \xi_2 (d_2 + a_3 C) - \xi_3 b d_2,$$
$$\dot{\xi}_3 = -\frac{\partial h}{\partial V} = (\xi_1 - \xi_2) \frac{\rho_1 U}{\sigma_1 + U} + \xi_3 \left(\frac{\rho_1 U}{\sigma_1 + U} + \delta \right),$$
$$\dot{\xi}_4 = -\frac{\partial h}{\partial C} = \xi_1 a_2 U + \xi_2 a_3 I + d_3 \xi_4,$$

The transversality conditions are $\xi_i \left(t_f\right) = 0$, for $i = 1, 2, 3, 4$.

The optimal control functions that must be used are determined from the conditions

$$\frac{\partial h}{\partial \tau} = 0 \text{ and } \frac{\partial h}{\partial u} = 0.$$

Hence, we get

$$\tau^* \left(t\right) = \frac{\xi_3}{2\varepsilon_1}; \tau = \tau^*(t) \text{ and } u^* \left(t\right) = -\frac{\xi_4}{2\varepsilon_2}; u = u^*(t), \tag{7.7}$$

By using the bounds for the control $\tau^*(t)$ and $u^*(t)$ from (7.7), we get

$$\tau^* = \left\{ \begin{array}{c} \frac{\xi_3}{2\varepsilon_1}, \text{ if } 0 \leq \frac{\xi_3}{2\varepsilon_1} \leq 1 \\ 0, \text{ if } \frac{\xi_3}{2\varepsilon_1} \leq 0 \\ 1, \text{ if } \frac{\xi_3}{2\varepsilon_1} \geq 1 \end{array} \right\},$$

and

$$u^* = \left\{ \begin{array}{cc} -\frac{\xi_4}{2\varepsilon_2}, & \text{if } \quad 0 \leq -\frac{\xi_4}{2\varepsilon_2} \leq 1 \\ 0, & \text{if } \quad -\frac{\xi_4}{2\varepsilon_2} \leq 0 \\ 1, & \text{if } \quad -\frac{\xi_4}{2\varepsilon_2} \geq 1 \end{array} \right\},$$

In compact notation, we have

$$\tau^* = \min\left\{\max\left\{0, \frac{\xi_3}{2\varepsilon_1}\right\}, 1\right\}, \tag{7.8}$$

and

$$u^* = \min\left\{\max\left\{0, -\frac{\xi_4}{2\varepsilon_2}\right\}, 1\right\}, \tag{7.9}$$

From above analysis and conclusion, we state the following theorem.

Theorem 7.2. *For optimal control τ^*, u^* and corresponding state variable solutions $U^*(t), I^*(t), V^*(t)$ and $C^*(t)$ that minimize over Δ, there exist specific adjoint variables $\xi_i(t), i = 1, 2, 3, 4$ satisfying the following model:*

$$\begin{aligned}
\dot{\xi}_1 &= -1 - \xi_1\left(r_1 - 2r_1b_1U - r_1b_1I - \frac{\rho_1\sigma_1 V}{(\sigma_1+U)^2} - a_2C\right) - (\xi_2 - \xi_3)\frac{\rho_1\sigma_1 V}{(\sigma_1+U)^2},\\
\dot{\xi}_2 &= -1 + \xi_1 r_1 b_1 U + \xi_2(d_2 + a_3C) - \xi_3 b d_2,\\
\dot{\xi}_3 &= (\xi_1 - \xi_2)\frac{\rho_1 U}{\sigma_1 + U} + \xi_3\left(\frac{\rho_1 U}{\sigma_1 + U} + \delta\right),\\
\dot{\xi}_4 &= \xi_1 a_2 U + \xi_2 a_3 I + d_3\xi_4,
\end{aligned} \tag{7.10}$$

subject to the transversality conditions $\xi_i(t_f) = 0, i = 1, 2, 3, 4$.

In addition, the following properties hold:

$$\tau^* = \min\left\{\max\left\{0, \frac{\xi_3}{2\varepsilon_1}\right\}, 1\right\} \text{ and } u^* = \min\left\{\max\left\{0, -\frac{\xi_4}{2\varepsilon_2}\right\}, 1\right\}.$$

Next, we proceed to numerically solve the proposed model and the optimal control problem.

8. Numerical resolution

In this section, we discuss the numerical solutions of the optimal control model defined in (7.1). We consider the parameter values from Table 1 and the initial conditions are taken as $U(0) = 0.05, I(0) = 0.1, V(0) = 0.001, C(0) = 0.001$. Numerical solutions of the model equations are obtained using MATLAB while those for the optimal model are found using a fourth order Runge–Kutta iterative method. The optimal model (7.1) is associated with conditions (7.8) and (7.9) with separated boundary conditions at times $t = 0$ and $t = t_f$. Forward method is used to solve the optimal model (7.1) and the backward method is used to solve the respective adjoint system (7.10) for $t_f = 50$. The variables associated with optimal models and in the objective functions have different scales. Hence, they are balanced by choosing weight constant $\varepsilon_1 = 2, \varepsilon_2 = 5$ and $b = 3$ in the objective function given in (7.3).

Fig. 7 shows that the combination treatment reduces the tumor density after a few days of treatment. The control model is subjected to a mixed control state constraint with an aim to reduce tumor cells, the amount of chemotherapy drugs and treatment time. For this purpose, we applied the Pontryagin maximum principle, for retarded optimal control problem in the state variables. Numerical method was used to solve the appropriate control problem, based on the degree of variance in the progression of the state model and the model of differentiation back into the combined model. Thus, we identified the best treatment method when reducing the objective function given by (7.3), i.e., reducing the total number of tumor cells and drug dose, $u(t)$ and increasing the virus burst size, $\tau(t)$. From Figs. 6 and 7, we conclude that optimal control is more effective when tumor cells are reduced. Numerical analysis shows that the optimal control variables, $\tau(t)$ and $u(t)$ decrease as the number of tumor cells decreases. The theoretical characterization of the optimal control has also been agreed upon by numerical resolutions.

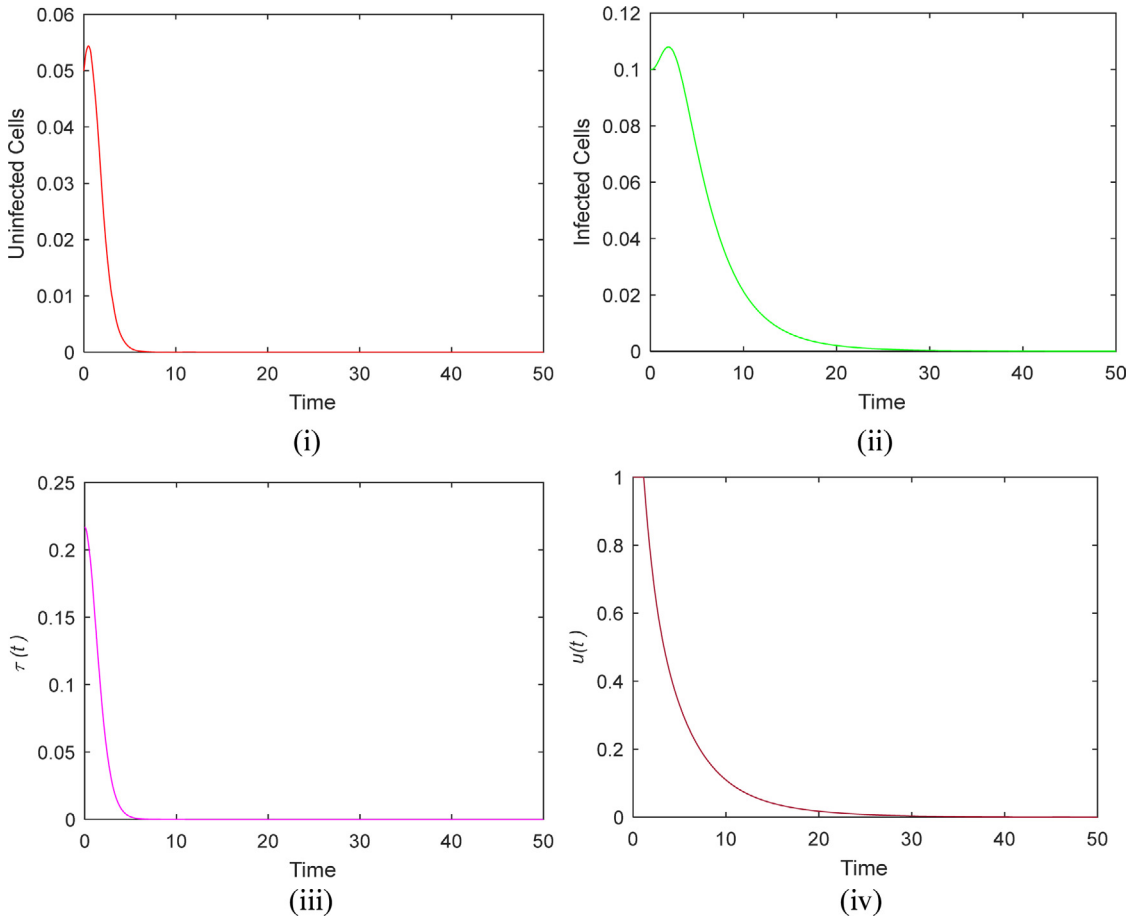

Fig. 6. Figures (i) and (ii) represents the densities of uninfected, infected tumor cells with optimal control, and (iii) and (iv) represents the optimally delivered drugs of virus therapy $\tau(t)$ and chemotherapy $u(t)$.

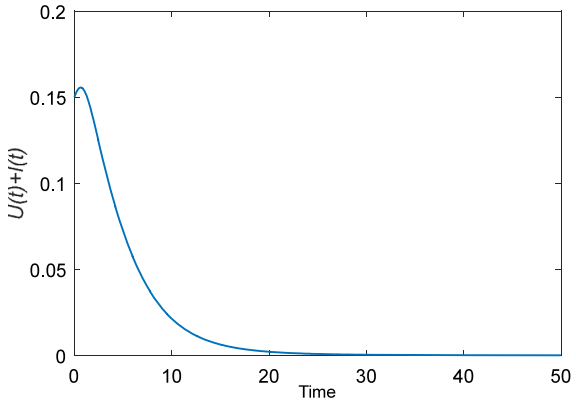

Fig. 7. Time series plot of the total tumor cell population with control.

9. Conclusion

In this study, a modified mathematical model has been proposed in the form of a model of non-linear ordinary differential equations to study the interaction between immune cells, tumor cells and normal cells. The results

derived during the investigation reveal that depending on the parameters and the body's initial immune-tumor-normal cell population, it can be found whether the body's immune system together with the normal cells will be able to tackle the attack of the tumors. It is seen that at a larger tumor growth rate ($r_1 > 0.2$), immune-normal cells fail to overcome tumor cells without treatment and require medical intervention.

So, in the beginning, we investigated the effect of chemotherapy as a treatment measure. In this case, removal of the tumor cells is possible with a high dose of chemotherapy. However, the drawback of this treatment method is that a high dose of chemotherapy kills the patient's normal cells and the tumor cells, making the patient susceptible to many side effects and attacks from other opportunistic diseases. To get rid of this drawback, we investigated the effect of virotherapy alone in the next step. However, in this case, stability analysis has shown that virotherapy alone cannot eradicate tumor cells after the tumors attain a specific size.

In search of a better treatment method, we combined virotherapy with chemotherapy. Stability analysis, in this case, shows that though virotherapy can overcome a small tumor; however, if the tumor is large, virotherapy should be replaced by chemotherapy. A combination of virotherapy with chemotherapy can significantly reduce the dose of chemotherapy required to eradicate the tumor population in comparison to treating with chemotherapy alone. Besides, our data show that the combined therapy also improves the immune system. Thus, the combined therapy mode provides much better results than the single therapy modes of either chemotherapy or virotherapy.

Further, optimal control theory has been applied to an optimal control problem relative to the model to maximize the virotherapy effect to boost the immune system and reduce the duration of the patient's recovery time and minimize chemotherapeutic drug administration to reduce the side effects. Numerical results confirm that optimal treatment strategies effectively achieve the goals mentioned earlier, which should be the component of any best possible mode of treatment.

Appendix A. Global stability analysis of the healthy steady state $P_1\left(E_1^*, 0, N_1^*, C_1^*\right)$ in chemotherapy treatment case

For the behavior of model (4.1) far away from the steady state $P_1(E_1^*, 0, N_1^*, C_1^*)$, we analyze the global stability of P_1 in this section.

Let us define the Lyapunov function of model (4.1) as

$$L_1(E, T, N, C) = \left(E - E_1^* - E_1^* \ln \frac{E}{E_1^*}\right) + T + \left(N - N_1^* - N_1^* \ln \frac{N}{N_1^*}\right) + \left(C - C_1^* - C_1^* \ln \frac{N}{C_1^*}\right)$$

Now, we differentiate w.r.t. time to obtain

$$\begin{aligned}
\frac{dL_1}{dt} &= \left(1 - \frac{E_1^*}{E}\right)\frac{dE}{dt} + \frac{dT}{dt} + \left(1 - \frac{N_1^*}{N}\right)\frac{dN}{dt} + \left(1 - \frac{C_1^*}{C}\right)\frac{dC}{dt} \\
&= \left(1 - \frac{E_1^*}{E}\right)\left(\mu + \frac{\rho T E}{\sigma + T} - d_1 E - k_1 E T - a_1 E C\right) + \left(r_1 T\left(1 - b_1 T\right) - k_2 E T - k_3 N T - a_2 T C\right) \\
&\quad + \left(1 - \frac{N_1^*}{N}\right)\left(r_2 N\left(1 - N\right) - k_5 T N - a_4 N C\right) + \left(1 - \frac{C_1^*}{C}\right)\left(u - d_3 C\right) \\
&= \left(1 - \frac{E_1^*}{E}\right)\left(\frac{\rho T E}{\sigma + T} - d_1\left(E - E_1^*\right) - k_1 E T - a_1 E C + a_1 E_1^* C_1^*\right) \\
&\quad + \left(r_1 T\left(1 - b_1 T\right) - k_2 E T - k_3 N T - a_2 T C\right)\left(1 - \frac{N_1^*}{N}\right)\left(r_2\left(N - N_1^*\right)\right. \\
&\quad \left. - r_2(N^2 - N_1^{*2}) - k_5 T N - a_4 N C + a_4 N_1^* C_1^*\right) + \left(1 - \frac{C_1^*}{C}\right)\left(-d_3\left(C - C_1^*\right)\right) \\
&= \left(\frac{\rho T}{\sigma + T}\left(E - E_1^*\right) - \frac{d_1}{E}\left(E - E_1^*\right)^2 - k_1 T\left(E - E_1^*\right) - a_1\left(C - C_1^*\right)\left(E - E_1^*\right) - \frac{a_1 C_1^*}{E}\left(E - E_1^*\right)^2\right) \\
&\quad - r_1 b_1 T^2 - k_2 T\left(E - E_1^*\right) - k_3 T(N - N_1^*) - a_2 T\left(C - C_1^*\right) \\
&\quad + \left(-r_2\left(N - N_{1\,1}^*\right)^2 - k_5 T\left(N - N_1^*\right) - a_4\left(N - N_1^*\right)\left(C - C_1^*\right)\right) \\
&\quad - \frac{d_3}{C}\left(C - C_1^*\right)^2 + T\left(r_1 - k_2 E_1^* - k_3 N_1^* - a_2 C_1^*\right)
\end{aligned}$$

$$= -Y_1^{T'} M_1 Y_1 - V_1^{T'} Y_1, \tag{4.9}$$

where

$$Y_1^{T'} = \left[E - E_1^*, T, N - N_1^*, C - C_1^*\right], V_2^{T'} = \left[0, -r_1 + k_2 E_1^* + k_3 N_1^* + a_2 C_1^*, 0, 0\right],$$

$$M_1 = \begin{pmatrix} \frac{d_1 + a_1 C_1^*}{E} & \frac{1}{2}(k_1 + k_2) & 0 & \frac{a_1}{2} \\ \frac{1}{2}(k_1 + k_2) & r_1 b_1 & \frac{1}{2}(k_3 + k_5) & \frac{a_2}{2} \\ 0 & \frac{1}{2}(k_3 + k_5) & r_2 & \frac{a_4}{2} \\ \frac{a_1}{2} & \frac{a_2}{2} & \frac{a_4}{2} & \frac{d_3}{C} \end{pmatrix},$$

The second component of the vector V_2 in (4.9), we must have:

$$k_2 E_1^* + k_3 N_1^* + a_2 C_1^* > r_1, \tag{4.10}$$

where such a condition, namely (4.10) results in $V_2^{T'} Y_2 > 0$. Furthermore, by considering the values of parameters from Table 1 and if $E = \mu/d_1$, $T = 1/b_1$, $C = u/d_3$ then $dL_1/dt < 0$.

Therefore, the healthy steady state P_1 is globally asymptotically stable if the steady state P_1 is locally stable, and

$$k_2 E_1^* + k_3 N_1^* + a_2 C_1^* > r_1, E = \frac{\mu}{d_1}, T = \frac{1}{b_1}, C = \frac{u}{d_3},$$

are satisfied. So, the tumor free steady state is globally stable which means the total eradication of the tumor cells.

Appendix B. Global stability analysis of the healthy steady state $P_1^*\left(\frac{\mu}{d_1}, 0, 0, 1, 0\right)$ in virotherapy treatment case

For the behavior of model (5.1) far away from the steady state $P_1^*\left(E_1 = \frac{\mu}{d_1}, 0, 0, N_1 = 1, 0\right)$, we analyze the global stability of P_1^* in this section. Let us define the Lyapunov function of model (5.1) as

$$L_2(E, U, I, N, V) = \left(E - E_1 - E_1 \ln \frac{E}{E_1}\right) + U + I + \left(N - N_1 - N_1 \ln \frac{N}{N_1}\right) + V$$

Now, we differentiate w.r.t. time to obtain

$$\begin{aligned}
\frac{dL_2}{dt} &= \left(1 - \frac{E_1}{E}\right)\frac{dE}{dt} + \frac{dU}{dt} + \frac{dI}{dt} + \left(1 - \frac{N_1}{N}\right)\frac{dN}{dt} + \frac{dV}{dt} \\
&= \left(1 - \frac{E_1}{E}\right)\left(\mu + \frac{\rho(U + I)E}{\sigma + (U + I)} - d_1 E - k_1 E U + \varphi I\right) \\
&\quad + \left(r_1 U(1 - b_1(U + I)) - \frac{\rho_1 U V}{\sigma_1 + U} - k_2 E U - k_3 N U\right) \\
&\quad + \left(\frac{\rho_1 U V}{\sigma_1 + U} - d_2 I - k_4 I E\right) + \left(1 - \frac{N_1}{N}\right)(r_2 N(1 - N) - k_5 U N) + \left(b d_2 I - \frac{\rho_1 U V}{\sigma_1 + U} - \delta V\right) \\
&= \left(\frac{\rho(U + I)}{\sigma + (U + I)}(E - E_1) - \frac{d_1}{E}(E - E_1)^2 - k_1 U(E - E_1) + \frac{\varphi}{E} I(E - E_1)\right) \\
&\quad + \left(r_1 U - r_1 b_1 U^2 - r_1 b_1 U I - k_2 E U - k_3 N U\right) + (-d_2 I - k_4 I E) \\
&\quad + \left(-r_2(N - N_1)^2 - k_5 U(N - N_1)\right) + \left(b d_2 I - \frac{\rho_1 U V}{\sigma_1 + U} - \delta V\right) \\
&= \left(\frac{\rho(U + I)}{\sigma + (U + I)}(E - E_1) - \frac{d_1}{E}(E - E_1)^2 - k_1 U(E - E_1) + \frac{\varphi}{E} I(E - E_1)\right) \\
&\quad - r_1 b_1 U^2 - r_1 b_1 U I - k_2 U(E - E_1) - k_3 U(N - N_1) - k_4 I(E - E_1) \\
&\quad + \left(-r_2(N - N_1)^2 - k_5 U(N - N_1)\right) + \frac{b d_2 I V}{V} - \frac{\rho_1 U V}{\sigma_1 + U} \\
&\quad + U(r_1 - k_2 E_1 - k_3 N_1) + I(-d_2 - k_4 E_1) - \delta V
\end{aligned}$$

$$= -Y_2^{T'} M_2 Y_2 - V_2^{T'} Y_2, \tag{5.5}$$

where

$$Y_2^{T'} = [E - E_1, U, I, N - N_1, V], \; V_2^{T'} = [0, -r_1 + k_2 E_1 + k_3 N_1, d_2 + k_4 E_1, 0, \delta],$$

$$M_2 = \begin{pmatrix} \frac{d_1}{E} & \frac{1}{2}\left(k_1 + k_2 - \frac{\rho}{\sigma+(U+I)}\right) & \frac{1}{2}\left(k_4 - \frac{\varphi}{E}\right) & 0 & 0 \\ \frac{1}{2}\left(k_1 + k_2 - \frac{\rho}{\sigma+(U+I)}\right) & r_1 b_1 & \frac{r_1 b_1}{2} & \frac{k_3+k_5}{2} & \frac{\rho_1}{2(\sigma_1+U)} \\ \frac{1}{2}\left(k_4 - \frac{\varphi}{E}\right) & \frac{r_1 b_1}{2} & 0 & 0 & -\frac{b d_2}{2V} \\ 0 & \frac{k_3+k_5}{2} & 0 & r_2 & 0 \\ 0 & \frac{\rho_1}{2(\sigma_1+U)} & -\frac{b d_2}{2V} & 0 & 0 \end{pmatrix}$$

The second component of the vector V_2 in (5.5), we must have:

$$k_2 E_1 + k_3 N_1 > r_1, \tag{5.6}$$

where such a condition, namely (5.6) results in $V_2^{T'} Y_2 > 0$. Furthermore, by considering the values of parameters from Table 1 and if $E = \mu/d_1$, $U + I = 1/b_1$, $V = b/\delta$, then $dL_2/dt < 0$.

Therefore, the healthy steady state P_1^* is globally asymptotically stable if the steady state P_1^* is locally stable, and

$$k_2 E_1 + k_3 N_1 > r_1, E = \frac{\mu}{d_1}, U + I = \frac{1}{b_1}, V = \frac{b}{\delta},$$

are satisfied. In biological terms, it means that the tumor cells will be killed by virotherapy.

Appendix C. Global stability analysis of the healthy steady state P_1^{**} in chemo-virotherapy treatment case

For the behavior of model (6.1) far away from the steady state $P_1^{**}(\overline{E}_1, 0, 0, \overline{N}_1, 0, \overline{C}_1)$, we analyze the global stability of P_1^{**} in this section. Let us define the Lyapunov function of model (6.1) as

$$L_3(E, U, I, N, V, C) = \left(E - \overline{E}_1 - \overline{E}_1 \ln \frac{E}{\overline{E}_1}\right) + U + I + \left(N - \overline{N}_1 - \overline{N}_1 \ln \frac{N}{\overline{N}_1}\right) + V + \left(C - \overline{C}_1 - \overline{C}_1 \ln \frac{C}{\overline{C}_1}\right).$$

Now, we differentiate w.r.t. time to obtain

$$\begin{aligned} \frac{dL_3}{dt} &= \left(1 - \frac{\overline{E}_1}{E}\right)\frac{dE}{dt} + \frac{dU}{dt} + \frac{dI}{dt} + \left(1 - \frac{\overline{N}_1}{N}\right)\frac{dN}{dt} + \frac{dV}{dt} + \left(1 - \frac{\overline{C}_1}{C}\right)\frac{dC}{dt} \\ &= \left(1 - \frac{\overline{E}_1}{E}\right)\left(\mu + \frac{\rho(U+I)E}{\sigma + (U+I)} - d_1 E - k_1 E U - a_1 E C + \varphi I\right) \\ &\quad + \left(r_1 U(1 - b_1(U+I)) - \frac{\rho_1 U V}{\sigma_1 + U} - k_2 E U - k_3 N U - a_2 U C\right) \\ &\quad + \left(\frac{\rho_1 U V}{\sigma_1 + U} - d_2 I - k_4 I E - a_3 I C\right) + \left(1 - \frac{\overline{N}_1}{N}\right)(r_2 N(1 - N) - k_5 U N - a_4 N C) \\ &\quad + \left(b d_2 I - \frac{\rho_1 U V}{\sigma_1 + U} - \delta V\right) + \left(1 - \frac{\overline{C}_1}{C}\right)(u - d_3 C) \\ &= \left(\frac{\rho(U+I)}{\sigma + (U+I)}(E - \overline{E}_1) - \frac{d_1(E - \overline{E}_1)^2}{E} - k_1 U(E - \overline{E}_1)\right. \\ &\quad \left. - a_1(E - \overline{E}_1)(C - \overline{C}_1) - \frac{a_1 C_1}{E}(E - \overline{E}_1)^2\right. \end{aligned}$$

$$
\begin{aligned}
&+\frac{\varphi I}{E}\left(E-\overline{E}_1\right)\Big)+\Big(r_1U-r_1b_1U^2-r_1b_1UI-\frac{\rho_1UV}{\sigma_1+U}-k_2EU-k_3NU-a_2UC\Big)\\
&+\Big(\frac{\rho_1UV}{\sigma_1+U}-d_2I-k_4IE-a_3IC\Big)+\Big(-r_2\left(N-\overline{N}_1\right)^2-k_5U\left(N-\overline{N}_1\right)\\
&-a_4\left(N-\overline{N}_1\right)\left(C-\overline{C}_1\right)\Big)+\Big(bd_2I-\frac{\rho_1UV}{\sigma_1+U}-\delta V\Big)-\frac{d_3\left(C-\overline{C}_1\right)^2}{C}\\
=&\Big(\frac{\rho\left(U+I\right)}{\sigma+(U+I)}\left(E-\overline{E}_1\right)-\frac{d_1}{E}\left(E-\overline{E}_1\right)^2-k_1U\left(E-\overline{E}_1\right)-a_1\left(E-\overline{E}_1\right)\left(C-\overline{C}_1\right)\\
&+\frac{a_1\overline{C}_1}{E}\left(E-\overline{E}_1\right)\left(C-\overline{C}_1\right)+\frac{\varphi}{E}I\left(E-\overline{E}_1\right)\Big)+\left(-r_1b_1U^2-r_1b_1UI-k_2\left(E-\overline{E}_1\right)U\right.\\
&\left.-k_3\left(N-\overline{N}_1\right)U-a_2U\left(C-\overline{C}_1\right)\right)+\left(-k_4I\left(E-\overline{E}_1\right)-a_3I\left(C-\overline{C}_1\right)\right)\\
&+\Big(-r_2\left(N-\overline{N}_1\right)^2-k_5U\left(N-\overline{N}_1\right)-a_4\left(N-\overline{N}_1\right)\left(C-\overline{C}_1\right)\Big)+\Big(\frac{bd_2IV}{V}-\frac{\rho_1UV}{\sigma_1+U}-\delta V\Big)\\
&-\frac{d_3}{C}\left(C-\overline{C}_1\right)^2+U\left(r_1-k_2\overline{E}_1-k_3\overline{N}_1-a_2\overline{C}_1\right)-I(d_2+k_4\overline{E}_1+a_3\overline{C}_1)\\
=&-Y_3^{T'}M_3Y_3-V_3^{T'}Y_3, \qquad (6.9)
\end{aligned}
$$

where $Y_3^{T'}=\left[E-\overline{E}_1,U,I,N-\overline{N}_1,V,C-\overline{C}_1\right]$,

$$
M_3=\begin{pmatrix}
\frac{d_1+a_1\overline{C}_1}{E} & \frac{1}{2}\left(k_1+k_2-\frac{\rho}{\sigma+(U+I)}\right) & \frac{1}{2}\left(k_4-\frac{\varphi}{E}-\frac{\rho}{\sigma+(U+I)}\right) & 0 & 0 & \frac{a_1}{2}\\
\frac{1}{2}\left(k_1+k_2-\frac{\rho}{\sigma+(U+I)}\right) & r_1b_1 & \frac{r_1b_1}{2} & \frac{k_3+k_5}{2} & \frac{\rho_1}{2(\sigma_1+U)} & \frac{a_2}{2}\\
\frac{1}{2}\left(k_4-\frac{\varphi}{E}-\frac{\rho}{\sigma+(U+I)}\right) & \frac{r_1b_1}{2} & 0 & 0 & -\frac{bd_2}{2V} & \frac{a_3}{2}\\
0 & \frac{k_3+k_5}{2} & 0 & r_2 & 0 & \frac{a_4}{2}\\
0 & \frac{\rho_1}{2(\sigma_1+U)} & -\frac{bd_2}{2V} & 0 & 0 & 0\\
\frac{a_1}{2} & \frac{a_2}{2} & \frac{a_3}{2} & \frac{a_4}{2} & 0 & \frac{d_3}{C}
\end{pmatrix},
$$

$$
V_3^T=\left[0,-r_1+k_2\overline{E}_1+k_3\overline{N}_1+a_2\overline{C}_1,d_2+k_4\overline{E}_1+a_3\overline{C}_1,0,\delta,0\right],
$$

The second component of the vector V_3 in (6.9), we must have:

$$
k_2\overline{E}_1+k_3\overline{N}_1+a_2\overline{C}_1>r_1, \qquad (6.10)
$$

where such a condition, namely (6.10) results in $V_3^{T'}Y_3>0$. Furthermore, by considering the values of parameters from Table 1 and if $E=\mu/d_1$, $U+I=1/b_1$, $V=b/\delta$, $C=u/d_3$, then $dL_3/dt<0$.

Therefore, the healthy steady state P_1^{**} is globally asymptotically stable if the steady state P_1^{**} is locally stable, and

$$
k_2\overline{E}_1+k_3\overline{N}_1+a_2\overline{C}_1>r_1, \quad E=\frac{\mu}{d_1}, \quad U+I=\frac{1}{b_1},V=\frac{b}{\delta}, \quad C=\frac{u}{d_3},
$$

are satisfied. In biological terms, it means that the tumor cells will be killed by chemo-virotherapy.

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