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Research article

A diffusive cancer model with virotherapy: Studying the immune response and its analytical simulation

Noufe H. Aljahdaly* **and Nouf A. Almushaity**

Department of Mathematics, Faculty of Sciences and Arts, King Abdulaziz University, Rabigh, Saudi Arabia

* **Correspondence:** Email: Nhaljahdaly@kau.edu.sa.

Abstract: New cancer therapies, methods and protocols are needed to treat affected patients. Oncolytic viral therapy is a good suggestion for such treatment. This paper proposes a diffusive cancer model with virotherapy and an immune response. This work aims to study the aforementioned model while theoretically including positivity, boundedness and stability, as well as to find the analytical solutions. The analytical solutions are found by using the tanh-expansion method. As a result, we realized that the relative immune cell killing rate can be controlled by the viral burst size. The viral burst size is the number of viruses released from each infected cell during cell lysis. The increasing diffusion of the activated immune system leads to an increase in the uninfected cells. The presented model can be used to study the combination of immunotherapy and virotherapy.

Keywords: cancer mathematical model; oncolytic viruses; immune response
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1. Introduction

Recently, cancer therapies have been heavily developed in order to find a therapy that is able to decay the tumor in a short time without harming the neighboring healthy tissue. In the field of genetic engineering, scientists discovered a new cancer treatment by using genetically altered viruses [1]. Oncolytic viruses are genetically altered viruses that infect cancer cells. They grow in an abnormal tumor cell and destroy it without infecting healthy cells or normal tissue. The oncolytic viruses interact with the tumor cell and generate a burst of an oncolytic virus (see Figure 1). The burst size is the number of new viruses resulting from the lysis of an infected tumor cell, and some of the new viruses may infect nearby tumor cells. The burst size is used to measure the replicability of an oncolytic virus [2].

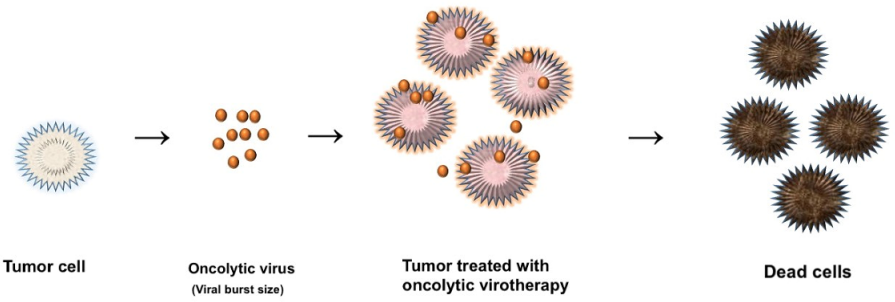


Figure 1. Burst of viruses released from each infected cell during cell lysis.

Mathematical models are able to describe biological and medical problems, such as cancer models with a variety of therapies [3, 4], epidemic models [5], HIV infection models [6–8] and prey-predator models [9]. A few researchers have studied mathematical models of cancer with virotherapy and described the interaction between the virus and the tumor. Wodarz introduced a basic mathematical model that studied tumor growth in the presence of virotherapy treatment [10]. The model has been modified to study the relationship between burst size and virus replicability. The results showed that cancer cells decrease if the burst size is large [11]. On the other hand, some mathematical models have demonstrated the immune system response to virotherapy. Since the immune system treats viruses as foreign bodies and thus destroys them, it shows a negative response to virotherapy that may reduce the quality of viral treatment [12]. Also, many studies describe the interactions between uninfected and infected cells and different kinds of immune responses [13, 14].

Herein, we will review the basic model of oncolytic virus replication which was introduced by Wodarz [15]. The model studies the tumor growth and the infection term and it is given by the following system of ordinary differential equations (ODEs):

$$\begin{aligned} \frac{df}{dt} &= \bar{r}X(f,y) - \bar{\beta}yG(f,y), \\ \frac{dy}{dt} &= \bar{\beta}yG(f,y) - \bar{\delta}y, \end{aligned} \tag{1}$$

where f and y are the uninfected and infected cells, respectively, the function X represents the growth of f and y and the function G denotes the rate at which tumor cells become infected by the virus. The coefficients $\bar{\beta}$ and $\bar{\delta}$ are the infection rate of the virus and the death rate of virus-infected cells, respectively, and the coefficient $\bar{r}$ is the logistical growth rate of uninfected cells. Then, Tian [2] proposed a following common basic model for the virotherapy of three populations:

$$\begin{aligned} \frac{df}{dt} &= \bar{r}f(1 - \frac{f+y}{k}) - \bar{\beta}fv, \\ \frac{dy}{dt} &= \bar{\beta}fv - \bar{\delta}y, \\ \frac{dv}{dt} &= \bar{b}\bar{\delta}y - \bar{\beta}fv - \bar{\gamma}v, \end{aligned} \tag{2}$$

where v is the free virus population and $\bar{\gamma}$ is the death rate of the virus. The coefficient $\bar{b}\bar{\delta}$ refers to the burst size of new viral swarms resulting from killing an infected cell y. The model (2) was also modified in [16] to study the dynamics of oncolytic virotherapy, and it includes four populations, as follows:

$$\begin{aligned}
\frac{df}{dt} =& \bar{r}f(1-\frac{f+y}{C}) - \bar{\beta}fv - \alpha fz - df,\\
\frac{dy}{dt} =& \bar{\beta}fv - \bar{\delta}y - \bar{\mu}yz,\\
\frac{dv}{dt} =& \bar{b}\bar{\delta}y - \bar{\beta}fv - \bar{\gamma}v - \bar{k}vz,\\
\frac{dz}{dt} =& \bar{s}yz - \bar{p}z,
\end{aligned} \tag{3}$$

where z denotes the innate immune cell population, $\bar{s}$ is the rate of stimulation of the innate immune cell and $\bar{p}$ is the rate of immune clearance. Moreover, some models have demonstrated the spread of tumor cells under viral therapy and radiation therapy [17, 18].

The immune response and its impact in both uninfected and infected cells were considered in the model (3) in Reference [19] as follows:

$$\begin{aligned}
\frac{df}{dt} =& \bar{r}f(1-\frac{f+y}{C}) - \bar{\beta}fv - \alpha fz - df,\\
\frac{dy}{dt} =& \bar{\beta}fv - \bar{\delta}y - \bar{\mu}_1yz,\\
\frac{dv}{dt} =& \bar{b}\bar{\delta}y - \bar{\beta}fv - \bar{\gamma}v - \bar{k}vz,\\
\frac{dz}{dt} =& \bar{s}_1yz + \bar{s}_2zf - \bar{p}z,
\end{aligned} \tag{4}$$

where the infected and uninfected cells stimulate the immune response at rates s_1 and s_2, respectively. The novelty of this paper is its study of the mathematical model in [19] by distinguishing between the naive and activated immune system cells. In addition, we study the spread of viruses and cells by taking a diffusion term into account. Thus, we obtain a system of partial differential equations (PDEs). The immune system cells can be activated by immunotherapy or biological therapy. Therefore, it is very important to distinguish between the naive and activated immune system cells in the mathematical model. Thus, the model introduced in this paper can be useful to study the effects of combining immunotherapy with virotherapy.

The paper is organized as follows. The second section introduces the studied mathematical model, the third section is the theoretical study of the system, the fourth section shows the analytical solutions obtained via the tanh-expansion method, the fifth section discuses the results and the last section is a summary of the work.

2. Mathematical model

In this section, we reformulate the mathematical model in [19] by considering the five cell populations, which are uninfected cancer cells f, infected cancer cells y, the free virus v, the naive

immune cells z and the activated immune cells z_a, as follows:

$$\begin{aligned}
\frac{\partial f}{\partial t} =& \bar{r} f(1 - \frac{f+y}{C}) - \bar{\beta} f v - \bar{\alpha_f} f z_a + d_1 \frac{\partial^2 f}{\partial x^2}, \\
\frac{\partial y}{\partial t} =& \bar{\beta} f v - \bar{\delta} y - \bar{\mu}_1 y z_a + d_2 \frac{\partial^2 y}{\partial x^2}, \\
\frac{\partial v}{\partial t} =& \bar{b}\bar{\delta} y - \bar{\beta} x v - \bar{\gamma} v - \bar{k} v z_a + d_3 \frac{\partial^2 z}{\partial x^2}, \\
\frac{\partial z}{\partial t} =& \bar{\lambda}_z - \bar{p} z - \bar{s}_1 y z - \bar{s}_2 z f + d_4 \frac{\partial^2 z}{\partial x^2}, \\
\frac{\partial z_a}{\partial t} =& \bar{s}_1 y z + \bar{s}_2 z f - \bar{\mu}_2 z_a + d_5 \frac{\partial^2 z}{\partial x^2},
\end{aligned} \tag{5}$$

where $d_i, i = 1, 2, 3, 4, 5$ denotes the diffusion terms of f, y, v, z and z_a, respectively. The rest of the parameters are converted to dimensionless parameters in the following system of PDEs and described in Table 1.

Table 1. Descriptions of the parameters in System (6) [17].

Parameters	Description
c	Carrying capacity of the tumor cells
r	Tumor growth rate
λ_z	Stimulation rate of the immune response
b	Burst size of the virus
α_f	Rate of immune-mediated uninfected tumor cell death
δ	Death rate of infected tumor cells
β	Infection rate of the virus
p	Clearance rate of the immune response
κ	Rate of immune-mediated virus death
γ	Clearance rate of the virus
μ_1	Rate of immune-mediated infected tumor cell death
μ_2	Clearance rate of active immune cells
s_1	Stimulation rate of the immune response by infected cells
s_2	Stimulation rate of the immune response by uninfected cells

The system becomes dimensionless by setting $t = \frac{\tau}{\delta}$, $F = Cf$, $Y = Cy$, $V = Cv$, $Z = Cz$ and $Z_a = Cz_a$ and renaming the parameters as follows:

$$r = \frac{\bar{r}}{\delta},\ \beta = \frac{C\bar{\beta}}{\delta},\ \alpha_f = \frac{C\bar{\alpha}}{\delta},\ \mu_1 = \frac{\bar{\mu_1}}{\delta},\ \gamma = \frac{\bar{\gamma}}{\delta},\ k = \frac{\bar{k}}{\delta},\ \lambda_z = \frac{\bar{\lambda}_z}{\delta},\ p = \frac{\bar{p}}{\delta},\ s_1 = \frac{\bar{s_1}}{\delta},$$
$$s_2 = \frac{\bar{s_2}}{\delta}\ \mu_2 = \frac{\bar{\mu_2}}{\delta}.$$

Thus, we obtain the following diffusive PDEs:

$$\frac{\partial F}{\partial t} - d_1 \frac{\partial^2 F}{\partial x} = rF(1 - (F + Y)) - \beta F V - \alpha_f F Z_a,$$

$$\begin{aligned}
\frac{\partial Y}{\partial t} - d_2\frac{\partial^2 Y}{\partial x} =& \beta FV - Y - \mu_1 YZ_a,\\
\frac{\partial V}{\partial t} - d_3\frac{\partial^2 V}{\partial x} =& bY - \beta FV - \gamma V - \kappa VZ_a,\\
\frac{\partial Z}{\partial t} - d_4\frac{\partial^2 Z}{\partial x} =& \lambda_z - pZ - s_1 YZ - s_2 FZ,\\
\frac{\partial Z_a}{\partial t} - d_5\frac{\partial^2 Z_a}{\partial x} =& s_1 YZ + s_2 FZ - \mu_2 Z_a.
\end{aligned} \tag{6}$$

Then, the initial conditions become $F(0) = \frac{f_0}{C}$, $Y(0) = \frac{y_0}{C}$, $V(0) = \frac{v_0}{C}$, $Z(0) = \frac{x_0}{C}$, $Z_a(0) = \frac{x_{a_0}}{C}$.

3. Theoretical study

3.1. Positivity and boundedness of the solutions

Theorem 1. *Let* $(F(x,t), Y(x,t), V(x,t), Z(x,t), Z_a(x,t)) = (\hat{f}(\xi), \hat{y}(\xi), \hat{v}(\xi), \hat{z}(\xi), \hat{z}_a(\xi)) \in R^5_+$, *where* $\xi = kx+ct+\xi_0$*; then, the solutions* $(\hat{f}(\xi), \hat{y}(\xi), \hat{v}(\xi), \hat{z}(\xi), \hat{z}_a(\xi))$ *are nonnegative and bounded in the following region:*

$$\Omega = (\hat{f}, \hat{y}, \hat{v}, \hat{z}, \hat{z}_a) \in R^5_+ \mid, \hat{f} \le 1, \hat{f} + \hat{y} \le 1, \hat{v} \le \frac{b}{\gamma}, \hat{z} + \hat{z_a} \le \frac{\lambda_z}{\zeta},$$

where $\zeta = \min\{p, \mu_2\}$.

Proof. First, we specify the initial value problems for System (6) as follows:

$$\begin{aligned}
\frac{\partial F}{dt} - d_1\frac{\partial^2 F}{\partial x} &= 0,\\
\frac{\partial Y}{dt} - d_2\frac{\partial^2 Y}{\partial x} &= \beta FV, \ge 0,\\
\frac{\partial V}{dt} - d_3\frac{\partial^2 V}{\partial x} &= bY, \ge 0,\\
\frac{\partial Z}{dt} - d_4\frac{\partial^2 Z}{\partial x} &= \lambda_z \ge 0,\\
\frac{\partial Z_a}{dt} - d_5\frac{\partial^2 Z_a}{\partial x} &= s_1 YZ + s_2 FZ, \ge 0.
\end{aligned}$$

As a result, the solutions are non-decreasing. In order to study the boundedness for the aforementioned system of PDEs, we will transfer the system to a system of ODEs using the traveling wave transformation. Let us define $\xi = kx + ct + \xi_0$; then, we get

$$\begin{aligned}
\frac{d\hat{f}}{d\xi} =& \frac{r}{c}\hat{f}(1 - (\hat{f} + \hat{y})) - \frac{\beta}{c}\hat{f}\hat{v} - \frac{\alpha_f}{c}\hat{f}\hat{z_a} + \frac{d_1 k^2}{c}\hat{f}_{\xi\xi},\\
\frac{d\hat{y}}{d\xi} =& \frac{\beta}{c}\hat{f}\hat{v} - \frac{1}{c}\hat{y} - \frac{\mu_1}{c}\hat{y}\hat{z_a} + \frac{d_2 k^2}{c}\hat{y}_{\xi\xi},\\
\frac{d\hat{v}}{d\xi} =& \frac{b}{c}\hat{y} - \frac{\beta}{c}\hat{f}\hat{v} - \frac{\gamma}{c}\hat{v} - \frac{\kappa}{c}\hat{v}\hat{z_a} + \frac{d_3 k^2}{c}\hat{v}_{\xi\xi},
\end{aligned}$$

$$\begin{aligned}\frac{d\hat{z}}{d\xi} =& \frac{\lambda_z}{c} - \frac{p}{c}\hat{z} - \frac{s_1}{c}\hat{y}\hat{z} - \frac{s_2}{c}\hat{f}\hat{z} + \frac{d_4k^2}{c}\hat{z}_{\xi\xi},\\ \frac{d\hat{z_a}}{d\xi} =& \frac{s_1}{c}\hat{y}\hat{z} + \frac{s_2}{c}\hat{f}\hat{z} - \frac{\mu_2}{c}\hat{z_a} + \frac{d_5k^2}{c}\hat{z}_{a\xi\xi}.\end{aligned} \tag{7}$$

From the first equation in System (7), we have

$$\frac{d\hat{f}}{d\xi} = \frac{r}{c}\hat{f}(1-(\hat{f}+\hat{y})) - \frac{\beta}{c}\hat{f}\hat{v} - \frac{\alpha}{c}\hat{f}\hat{z_a} \leq \frac{r}{c}\hat{f}(1-\hat{f}).$$

Let us assume the differential equation $\frac{dF_1}{dt} = r_1F_1(1-F_1)$ with the initial condition $F_1(0) = F_0$, which satisfies

$$F_1(t) = \frac{F_0}{F_0 + (1-F_0)\exp^{-r_1t}};$$

hence,

$$\limsup_{t\to\infty} F_1 = 1.$$

Note that $\frac{d\hat{f}}{dt} \leq \frac{dF_1}{dt}$, which implies that $\lim_{t\to\infty}\sup\hat{f} \leq \lim_{t\to\infty}\sup F_1$. Therefore, we have

$$\limsup_{t\to\infty} \hat{f} \leq 1.$$

From the first and second equations in System (7), we have

$$\begin{aligned}\frac{d\hat{f}}{d\xi} + \frac{d\hat{y}}{d\xi} &\leq \frac{r}{c}\hat{f}(1-(\hat{f}+\hat{y})),\\ &\leq \frac{r}{c}(1-(\hat{f}+\hat{y})),\end{aligned}$$

which satisfy

$$\limsup_{t\to\infty} \hat{f}+\hat{y} \leq 1.$$

Again, from the third equation in System (7), we have

$$\begin{aligned}\frac{d\hat{v}}{d\xi} &\leq \frac{b}{c}\hat{y} - \frac{\gamma}{c}\hat{v},\\ &\leq \frac{b}{c} - \frac{\gamma}{c}\hat{v},\end{aligned}$$

which yields

$$\limsup_{t\to\infty} \hat{v} \leq \frac{b}{\gamma}.$$

Also, from the fourth and fifth equations in System (7), we note that

$$\frac{d\hat{z}}{d\xi} + \frac{d\hat{z_a}}{d\xi} \leq \frac{\lambda_z}{c} - \frac{p}{c}\hat{z} - \frac{\mu_2}{c}\hat{z_a},$$

$$\leq \frac{\lambda_z}{c} - \frac{\zeta}{c}(\hat{z} + \hat{z}_a),$$

where $\zeta = \min\{p, \mu_2\}$. Thus, we obtain

$$\limsup_{t\to\infty} \hat{z} + \hat{z}_a \leq \frac{\lambda_z}{\zeta}$$

and

$$\hat{z} + \hat{z}_a \leq \frac{\lambda_z}{\zeta}.$$

3.2. Equilibrium points

Model (6) has equilibrium points of the form (F, Y, V, Z, Z_a) such that $F \geq 0, Y \geq 0, V \geq 0, Z \geq 0$ and $Z_a \geq 0$. The equilibrium points of the system are the steady-state solutions, which are obtained by setting the following:

$$\begin{aligned}
\frac{\partial F}{dt} - d_1\frac{\partial^2 F}{\partial x} &= 0,\\
\frac{\partial Y}{dt} - d_2\frac{\partial^2 Y}{\partial x} &= 0,\\
\frac{\partial V}{dt} - d_3\frac{\partial^2 V}{\partial x} &= 0,\\
\frac{\partial Z}{dt} - d_4\frac{\partial^2 Z}{\partial x} &= 0,\\
\frac{\partial Z_a}{dt} - d_5\frac{\partial^2 Z_a}{\partial x} &= 0.
\end{aligned}$$

However, with help of Mathematica, we obtained five equilibrium points:

$$\begin{aligned}
E_0 =&(0, 0, 0, 0, 0),\\
E_1 =&(1, 0, 0, 0, 0),\\
E_2 =&\left(\frac{\gamma}{(b-1)\beta}, \frac{\gamma}{(b-1)\beta}\left(\frac{\beta r(b-1) - \gamma r}{(b-1)\beta + \gamma r}\right), \frac{r((b-1)\beta - \gamma)}{\beta((b-1)\beta + \gamma r)}, 0, 0\right),\\
E_3 =&\left(\frac{(\lambda_z - p)}{s_2}, 0, 0, \frac{\mu_2 r\,(-\lambda_z + p + s_2)}{\alpha_f s_2(\lambda_z - p)}, \frac{r\,(-\lambda_z + p + s_2)}{\alpha_f s_2}\right),\\
E_4 =&(F_4, Y_4, V_4, Z_4, Z_{a4}),
\end{aligned}$$

where

$$\begin{aligned}
r\,(1 - (F_4 + Y_4)) - \beta V_4 - \alpha_f Z_{a4} &= 0,\\
Y_4 &= \frac{\beta F_5 V_4}{\mu_1 Z_a 4 + 1},\\
V_4 &= \frac{bY_4}{\beta F_4 + \kappa Z_{a4} + \gamma},
\end{aligned}$$

$$Z_4 = \frac{\lambda_z}{s_1 Y_5 + s_2 F_5 + p},$$
$$Z_{a4} = \frac{s_1 Y_4 + s_2 F_4}{\mu_2} Z_4.$$

E_2 is positive if $b > 1 + (\gamma/\beta)$, and E_3 is positive if $p < \lambda_z < p + s_2$.

3.3. Basic reproduction number

The basic reproduction number is the number of cases that are generated by a signal virus in the population [20]. Let $P = (Y, F, V, Z, Z_a)$, model (7) is rewritten as

$$P' = \upsilon_1(P) - \upsilon_2(P),$$

where

$$\upsilon_1(P) = \begin{pmatrix} \beta FV \\ 0 \\ 0 \\ 0 \end{pmatrix}, \upsilon_2(P) = \begin{pmatrix} \mu_1 Y Z_a \\ -rF(1-(F+Y)) + \beta FV + \alpha_f F Z_a \\ -bY + \beta FV + \kappa V Z_a + \gamma V \\ -\lambda_z + pZ + s_1 YZ + s_2 FZ \\ -s_1 YZ - s_2 FZ + \mu_2 Z_a \end{pmatrix}.$$

Next, the Jacobian matrix for $\upsilon_1(P)$ and $\upsilon_2(P)$ at E_1 are computed as follows:

$$\Upsilon_1 = D(\upsilon_1(E_1)) = \begin{pmatrix} 0 & 0 & \beta & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\Upsilon_2 = D(\upsilon_2(E_1)) = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ r & r & \beta & 0 & \alpha_F \\ -b & 0 & \beta+\gamma & 0 & 0 \\ 0 & 0 & 0 & p+s_2 & 0 \\ 0 & 0 & 0 & -s_2 & \mu_2 \end{pmatrix},$$

$$(\Upsilon_1 \Upsilon_2^{-1}) \begin{pmatrix} \frac{b\beta}{\beta+\gamma} & 0 & \frac{\beta}{\beta+\gamma} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$R_0 = \rho(\Upsilon_1 \Upsilon_2^{-1}) = \frac{b\beta}{\beta+\gamma}, \tag{8}$$

where ρ is the spectral radius. Thus, if $R_0 < 1$, the cancer will decline; if $R_0 = 1$, the cancer will stay alive and stable; if $R_0 > 1$, the cancer will experience growth and outbreak. Therefore, E_0 and E_1 always exist, E_2 exists if $R_0 > 1$, E_3 exists if $p + s_2 > \lambda_z > p$ and E_4 exists if $R_0 > 1$.

3.4. Local stability analysis

We investigate the local stability of the equilibrium points by evaluating the Jacobian matrix of the nonlinear system [21].

Theorem 2. *The trivial equilibrium E_0 of the system is locally unstable.*

Proof. The Jacobian matrix of System (6) at E_0 is

$$J(E_0) = \begin{pmatrix} r & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 \\ 0 & b & -\gamma & 0 & 0 \\ 0 & 0 & 0 & -p & 0 \\ 0 & 0 & 0 & 0 & -\mu_2 \end{pmatrix}. \tag{9}$$

It is obvious that the eigenvalues for $J(E_0)$ are as follows:

$$\lambda_1 = r,\ \lambda_2 = -1,\ \lambda_3 = -\gamma,\ \lambda_4 = -p,\ \lambda_5 = -\mu_2.$$

All eigenvalues are negative if $r < 0$. Hence, E_0 is locally unstable if $r > 0$.

Theorem 3. *The equilibrium point E_1 is locally asymptotically stable if only if $R_0 < 1$.*

Proof. By the calculation of the Jacobian matrix at E_1, we obtain

$$J(E_1) = \begin{pmatrix} -r & -r & -\beta & 0 & -\alpha \\ 0 & -1 & \beta & 0 & 0 \\ 0 & b & -\beta-\gamma & 0 & 0 \\ 0 & 0 & 0 & -p-s_2 & 0 \\ 0 & 0 & 0 & s_2 & -\mu_2 \end{pmatrix}. \tag{10}$$

The characteristic polynomial is

$$det(J(E_1) - \lambda I) = (-\mu_2 - \lambda)(-(p+s_2) - \lambda)(-\lambda - r)\left((-b\beta + \beta + \gamma) + \lambda(\beta + \gamma + 1) + \lambda^2\right).$$

The eigenvalues of $J(E_1)$, which are $\lambda_1 = -\mu_2$, $\lambda_2 = -r$ and $\lambda_3 = -(p + s_2)$, are negative. By the Routh-Hurwitz criteria, since $(\beta + \gamma + 1)$ is positive, $\lambda_{4,5}$ has a real negative part if $b \leq 1 + \frac{\gamma}{\beta}$, which implies that $R_0 < 1$. Biologically, when the viral burst size b is smaller than the critical value which is $1 + \frac{\gamma}{\beta}$, the new produced viruses will be enough to infect tumor cells.

Theorem 4. *The equilibrium point E_2 is locally asymptotically stable if $b > 1$ and $\beta < r$.*

Proof. The jacobian matrix $J(E_2)$ is

$$\begin{pmatrix} \frac{\gamma r}{\beta - b\beta} & \frac{\gamma r}{\beta - b\beta} & -\frac{\gamma}{b-1} & 0 & \frac{\alpha\gamma}{\beta - b\beta} \\ \frac{r((b-1)\beta-\gamma)}{(b-1)\beta+\gamma r} & -1 & \frac{\gamma}{b-1} & 0 & -\frac{\gamma\mu_1 r((b-1)\beta-\gamma)}{(b-1)\beta((b-1)\beta+\gamma r)} \\ \frac{r(-b\beta+\beta+\gamma)}{(b-1)\beta+\gamma r} & b & \frac{b\gamma}{1-b} & 0 & \frac{kr(-b\beta+\beta+\gamma)}{\beta((b-1)\beta+\gamma r)} \\ 0 & 0 & 0 & \frac{\gamma(rs_1(-b\beta+\beta+\gamma)+s_2(-b\beta+\beta-\gamma r))}{(b-1)\beta((b-1)\beta+\gamma r)} & 0 \\ 0 & 0 & 0 & \frac{\gamma(rs_1((b-1)\beta-\gamma)+s_2((b-1)\beta+\gamma r))}{(b-1)\beta((b-1)\beta+\gamma r)} & -\mu_2 \end{pmatrix}, \tag{11}$$

$$det(J(E_2) - \lambda I) = (-\mu_2 - \lambda)(-\beta s_1 F_3 V_3 - s_2 F_3 - p - \lambda)(\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3),$$

where

$$\begin{aligned}
A_1 =& \frac{b\beta\gamma + \beta(b-1) + \beta\gamma r}{(b-1)\beta},\\
A_2 =& \frac{\left(\frac{r}{\beta} - 1\right)(\gamma r(-\beta + \mathrm{b}\beta - \gamma))}{(b-1)(-\beta + \mathrm{b}\beta + \gamma r)} + \frac{r(b\gamma^2 + (b-1)\gamma)}{(b-1)^2\beta},\\
A_3 =& \frac{\gamma r(\beta - \mathrm{b}\beta + \gamma)((b-1)\beta + \gamma r)}{(b-1)\beta(\beta - \mathrm{b}\beta - \gamma r)}.
\end{aligned}$$

The eigenvalues are $\lambda_1 = -\mu_2$ and $\lambda_2 = -\beta s_1 F_3 V_3 - s_2 F_3 - p$, which are both negative, while $\lambda_{3,4,5}$ denotes the zeros of the polynomial $\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3$. It is obvious that $A_1 > 0$ if $b > 1$, $A_2 > 0$ if $b > 1, \beta < r$ and $R_0 > 1$, $A_3 > 0$ if $b > 1$ and $R_0 > 1$, and

$$\begin{aligned}
A_1A_2 - A_3 =& \frac{\beta(b-1)(b\beta - \beta + \mathrm{r}\gamma)}{b\beta\gamma - \beta + \mathrm{b}\beta + \gamma r} - \frac{(b + \gamma r - 1)(\mathrm{b}\beta - \beta + \gamma r)}{(b-1)\beta(\mathrm{b}\beta - \beta + \gamma)}\\
=& \frac{\beta(b-1)(\beta(b-1) + \mathrm{r}\gamma)}{\beta(b\gamma - 1) + \mathrm{b}\beta + \gamma r} - \frac{(b + \gamma r - 1)(\beta(b-1) + \gamma r)}{(b-1)\beta(\beta(b-1) + \gamma)}.
\end{aligned}$$

Therefore, by the Routh-Hurwitz criterion, $\lambda_{3,4,5}$ have negative real parts if $A_1A_2 - A_3 > 0$, which occurs if $b > 1$ and $\beta < r$. Thus, E_2 is locally asymptotically stable.

Biologically, if the viruses are powerful, which means that the burst size is greater than the critical value, then the system has the equilibrium E_2 with the balance of tumor cells, infected tumor cells and viruses.

Theorem 5. *The equilibrium point E_3 is locally asymptotically stable if $b < 1$, $b\beta < R_0$ and $R_0 < 1$. If $\lambda_z = 0$, the point E_3 is locally asymptotically stable under the conditions that $\alpha\beta < \kappa$ and $b\beta < r$.*

To find the eigenvalue, solve the Jacobian $J(E_3)$:

$$\begin{pmatrix}
r(s_2F_3 - 2F_3 + 1) & -rF_3 & -\beta F_3 & 0 & -\alpha_f F_3\\
0 & -\mu_1 Z_{3a} - 1 & \beta F_3 & 0 & 0\\
0 & b & -\gamma - \beta F_3 - \kappa Z_{3a} & 0 & 0\\
s_2Z_3 & s_1Z_3 & 0 & -s_2F_3 - p & 0\\
-s_2Z_3 & -s_1Z_3 & 0 & -s_2F_3 & -\mu_2
\end{pmatrix}.$$

The characteristic polynomial of this matrix is evaluated as follows:

$$P(\lambda) = \lambda^5 + b_4\lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda^1 + b_0 = 0,$$

where b_0, b_1, b_2, b_3 and b_4 are defined in the Appendix. All coefficients are positive if $b < 1$. By using Descartes' rule, the number of sign changes is zero; thus, the point E_3 is locally asymptotically stable if $b < 1$.

Theorem 6. *The equilibrium point E_4 is locally stable if $b < 1$, $b\beta < r$, $s_1 > s_2$, $\lambda_z > Z_{4a}$ and $Z_4 > Z_{4a}$.*

Proof. To find the Jacobian at the equilibrium point E_4, we evaluate $|J(E_4) - \lambda I| = 0$, where $J(E_4)$ is given by

$$\begin{pmatrix} E_{1,1} & -\beta F_4 & 0 & -\alpha F_4 & \\ \beta V_4 & -\mu_1 Z_{4a} - 1 & \beta F_4 & 0 & -\mu_1 Y_4 \\ -\beta V_4 & b & -\gamma - \beta F_4 - \kappa Z_{4a} & 0 & -\kappa V_4 \\ -s_2 Z_4 & -s_1 Z_4 & 0 & -F_4 s_2 - s_1 Y_4 - p & 0 \\ s_2 Z_4 & s_1 Z_4 & 0 & F_4 s_2 + s_1 Y_4 & -\mu_2 \end{pmatrix},$$

where $E_{1,1} = r(1 - Y_4 - 2F_4) - \alpha Z_{4a} - \beta V_4 - rF_4$. The characteristic polynomial is

$$a_0\lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5 = 0,$$

where a_0, a_1, a_2, a_3, a_4 and a_5 are defined in the Appendix. All coefficients are positive if $b < 1$, $b\beta < r$, $\lambda_z > Z_{4a}$, $s_1 > s_2$ and $Z_4 > Z_{4a}$. By using Descartes' rule, the number of sign changes is zero; thus, the point E_4 is locally asymptotically stable if $b < 1$, $b\beta < r$, $\lambda_z > Z_{4a}$,$s_1 > s_2$ and $Z_4 > Z_{4a}$.

3.5. Global stability

In this section, the global stability of the equilibrium points will be investigated by using Lyapunov functions [22], which must be positive definite.

Theorem 7. *E_1 is globally asymptotically stable if* $1 + b \le r \le 2,\ b \le 1$.

Proof. The Lyapunov function is defined at point E_1 as follows:

$$L_1(F, Y, V, Z, Z_a) = F - F_1 - \ln F + Y + \frac{1 - r}{b}V + Z + Z_a.$$

The derivative of L_1 is

$$\begin{aligned} L_1' =& F' - \frac{F'}{F_1} + \frac{(1 - r)V'}{b} + Y' + Z' + Z_a', \\ =& \frac{(1 - r)V'}{b} + Y' + Z' + Z_a', \\ =& A_Y Y + A_V V + A_Z Z + A_{Z_a} Z_a + A_{FV} FV + A_{YZ_a} YZ_a + A_{VZ_a} VZ_a, \end{aligned}$$

where

$$\begin{aligned} A_Y =& -2 + r = -(2 - r), \\ A_V =& \frac{\gamma}{b} - r\frac{\gamma}{b} = \frac{\gamma}{b}(1 - r), \\ A_Z =& -p, \\ A_{Z_a} =& -\mu_2, \\ A_{FV} =& \beta + \frac{\beta}{b} - r\frac{\beta}{b} = 1 + \frac{1}{b}(1 - r), \\ A_{YZ_a} =& -\mu_1, \end{aligned}$$

$$A_{VZ_a} = \frac{\kappa}{b} - \frac{\kappa r}{b} = \frac{1}{b}(1 - r).$$

The equilibrium equations at E_1 are

$$\begin{aligned} rF_1(1 - F_1) &= rF_1 - rF_1^2 = 0, \\ \lambda_z &= 0. \end{aligned}$$

We found that $L_1' \leq 0$ if $1 + b \leq r \leq 2,\ b \leq 1$. Hence, E_1 is globally asymptotically stable if $1 + b \leq r \leq 2, b \leq 1$.

Theorem 8. *E_2 is globally asymptotically stable if $2 < b,\ r > \beta R_0 < 1$ and $2 < Y_2 < \frac{\gamma r}{b\beta}$.*

Proof. The Lyapunov function is defined at E_2 as follows:

$$\begin{aligned} L_2(F, Y, V, Z, Z_a) =& A_1(F - F_2 - F_2 \ln \frac{F}{F_2}) + A_2(Y - Y_2 - Y_2 \ln \frac{Y}{Y_2}) + A_3(V - V_2 - V_2 \ln \frac{V}{V_2}) \\ &+ A_4 Z_2 + A_5 Z_{2a}. \end{aligned}$$

Thus, we have L_2' as follows:

$$L_2' = A_1(1 - \frac{F_2}{F})F' + A_2(1 - \frac{Y_2}{Y})Y' + A_3(1 - \frac{V_2}{V})V' + A_4 Z' + A_5 Z_a'.$$

The equilibrium equations are

$$\begin{aligned} rF_2(1 - (F_2 + Y_2)) - \beta F_2 V_2 &= 0, \\ r - rF_2 - rY_2 &= \beta V_2, \\ \beta F_2 V_2 &= Y_2, \\ \beta F_2 V_2 + \gamma V_2 &= bY_2, \\ \gamma &= \frac{1}{V_2}(b - 1)Y_2, \\ \lambda_z &= 0. \end{aligned} \tag{12}$$

Using the equilibrium equations in L_2' gives

$$\begin{aligned} L_2' =& C_F F + C_Y Y + C_V V + C_Z Z + C_{Z_a} Z_a + C_{\mathrm{FZ}_a} F Z_a + C_{\mathrm{vz}_a} V Z_a + C_{\mathrm{YZ}_a} Y Z_a + C_{F^2} F^2 \\ &+ C_{\mathrm{FV}} FV + C_{\mathrm{FY}} FY + C_{\mathrm{FZ}} FZ + C_{\mathrm{YV}} VY + C_{\mathrm{YZ}} YZ + C_{FYV} FVY + C^*, \end{aligned}$$

where

$$\begin{aligned} C_F &= A_1 F_2 r + A_1 r + A_3 \beta V_2, \\ C_Y &= A_3 b + A_1 F_2 r - A_2, \\ C_V &= A_1 \beta F_2 - A_3 \gamma, \\ C_Z &= -A_4 p, \\ C_{Z_a} &= \alpha A_1 F_2 + A_3 \kappa V_2 + A_2 \mu_1 Y_2 - A_5 \mu_2, \end{aligned}$$

$$
\begin{aligned}
C_{F^2} &= -A_1 r,\\
C_{\mathrm{FY}} &= -A_1 r,\\
C_{\mathrm{FV}} &= -A_3\beta - A_1\beta + A_2\beta,\\
C_{\mathrm{FZ}} &= -A_4 s_2,\\
C_{\mathrm{YZ}} &= -A_4 s_1,\\
C_{\mathrm{FZ}_a} &= -A_1\alpha_f,\\
C_{\mathrm{VZ}_a} &= -A_3\kappa,\\
C_{\mathrm{YZ}_a} &= -A_2\mu_1,\\
C_{\mathrm{YV}} &= -A_3 b V_2,\\
C_{\mathrm{FYV}} &= -A_2\beta Y_2,\\
C^* &= -A_1 F_2 r + A_3\gamma V_2 + A_2 Y_2 + A_4\lambda_z.
\end{aligned}
$$

Note that

$$C_V = A_1\beta F_2 - A_3\gamma = A_1\frac{Y_2}{V_2} - A_3\frac{1}{V_2}(b-1)Y_2 = \frac{Y_2}{V_2}(A_1 - A_3(b-1)),$$

and $C_V = 0$ if $A_3 = \frac{A_1}{b-1}$. Let $A_2 = A_3 = \frac{A_1}{b-1}$; then, $C_{FV} = -A_1\beta$ and $C_F = A_1(r(2-Y_2) - \beta V_2 + \frac{\beta}{b-1}V_2)$. We have that $C_F < 0$ if $Y_2 > 2$. Thus, we obtain C_Y as

$$
\begin{aligned}
C_Y =& \frac{A_1}{b-1}(b-1) + A_1 F_2 r = A_1(1 + r - \beta V_2 - r\beta F_2 V_2),\\
&= A_1(1 + r - \beta V_2 - r\frac{\gamma}{b-1}V_2),\\
=& A_1(1 + r - \frac{(b-1)\beta}{\gamma}Y_2 - rY_2).
\end{aligned}
$$

Since $Y_2 > 2$, $C_Y < 0$. Thus, C_{Z_a} becomes

$$
\begin{aligned}
C_{Z_a} =& A_1(\alpha_f F_2 + \frac{\kappa}{b-1}V_2 + \frac{\mu_1}{b-1}Y_2) - A_5\mu_2,\\
=& \frac{A_1}{b-1}(\frac{\alpha_f\gamma}{\beta} + \kappa V_2 + \mu_1 Y_2) - A_5\mu_2 = 0.
\end{aligned}
$$

If $A_5 = \frac{A_1}{\mu_2(b-1)}(\frac{\alpha_f\gamma}{\beta} + \kappa V_2 + \mu_1 Y_2)$ and we let $A_4 = A_1$, we obtain C^* as follows:

$$
\begin{aligned}
C^* &= -A_1 F_2 r + A_3\gamma V_2 + A_2 Y_2,\\
&= -A_1 F_2 r + \frac{A_1}{b-1}((b-1)Y_2 + Y_2),\\
&= A_1(-F_2 r + \frac{b}{b-1}Y_2).
\end{aligned}
$$

We get that $L_2' \le 0$ if $2 < Y_2 < \frac{\gamma r}{b\beta}$. Hence, E_2 is globally asymptotically stable.

Theorem 9. *E_3 is globally asymptotically stable if $b < 1$; then, $p < \lambda < \frac{p(\mu_2 r + \alpha_f s_2 Z_3)}{\mu_2 r + \alpha_f s_2}$, $\frac{\gamma\left(r + \frac{\alpha_f s_1 Z_3}{\mu_2}\right)}{1-b} < \beta$, and $r > \frac{2\lambda_z\alpha_f}{\mu_2}$.*

Proof. The Lyapunov function at E_3 is defined as follows:

$$\begin{aligned} L_3(F,Y,V,Z,Z_a) =& A_1(F - F_3 - F_3 \ln \frac{F}{F_3}) + A_2 Y + A_3 V + A_4(Z - Z_3 \\ & - Z_3 \ln \frac{Z}{Z_3}) + A_5(Z_a - Z_{a3} - Z_{a3} \ln \frac{Z_a}{Z_{a3}}), \end{aligned}$$

and its derivative is

$$L_3' = A_1(1 - \frac{F_3}{F})F' + A_2 Y' + A_3 V' + A_4(1 - \frac{Z_3}{Z})Z' + A_5(1 - \frac{Z_{a3}}{Z_a})Z_a'.$$

After substituting the points F_3, Z_3 and Z_{a_3} in L_3', we get

$$\begin{aligned} L_3' =& B_F F + B_Y Y + B_V V + B_Z Z + B_{Z_a} Z_a + B_{\mathrm{FZ}_a} F Z_a + B_{\mathrm{vz}_a} V Z_a + B_{\mathrm{YZ}_a} Y Z_a + B_{F^2} F^2 + B_{\mathrm{FV}} FV \\ & + B_{\mathrm{FY}} FY + B_{\mathrm{FZ}} FZ + B_{\mathrm{YZ}} YZ + B_{FZZ_a} FZZ_a + B_{YZZ_a} YZZ_a + B^*, \end{aligned}$$

where

$$\begin{aligned} B_F =& A_1 r + A_1 F_3 r + A_4 s_2 Z_3, \\ B_Y =& A_4 s_1 Z_3 + A_1 r F_3 + A_3 b - A_2, \\ B_V =& -A_3\gamma + A_1\beta F_3, \\ B_Z =& -A_4\lambda_z Z_3 - A_4 p, \\ B_{Z_a} =& -A_5\mu_2 + A_1 F_3 \alpha_f, \\ B_{F^2} =& -A_1 r, \\ B_{\mathrm{FY}} =& -A_1 r, \\ B_{\mathrm{FV}} =& -A_3\beta + A_2\beta - A_1\beta, \\ B_{\mathrm{FZ}} =& A_5 s_2 - A_4 s_2, \\ B_{\mathrm{YZ}} =& A_5 s_1 - A_4 s_1, \\ B_{\mathrm{FZ}_a} =& -A_1\alpha_f, \\ B_{\mathrm{VZ}_a} =& -A_3\kappa, \\ B_{\mathrm{YZ}_a} =& -A_2\mu_1, \\ B_{FZZ_a} =& -A_5 s_2 Z_{3a}, \\ B_{YZZ_a} =& -A_5 s_1 Z_{3a}, \\ B^* =& -A_1 F_3 r + A_5\mu_2 Z_{3a} + A_4\lambda_z + A_4 p Z_3. \end{aligned}$$

The equilibrium equations at $(F_3, 0, 0, Z_3, Z_{a3})$ are

$$\begin{aligned} 0 =& r(1 - F_3) - \alpha_f Z_{3a}, \\ 0 =& \lambda_z - pZ_3 - s_2 F_3 Z_3, \\ 0 =& s_2 F_3 Z_3 - \mu_2 Z_{3a}. \end{aligned} \tag{13}$$

If $A_4 = A_5$, then $B_{FZ} = 0$ and $B_{YZ} = 0$. If $A_3 = A_2$, then $B_{FV} < 0$, $A_3 = \frac{A_1\beta F_3}{\gamma}$ and $B_V = 0$. If $A_5 = \frac{A_1 F_3 \alpha_f}{\mu_2}$, then $B_{Z_a} = 0$. Thus,

$$B_Y = A_4 s_1 Z_3 + A_1 r F_3 + A_3 b - A_2,$$

$$=A_1(\frac{F_3\alpha_f s_1 Z_3}{\mu_2} + rF_3 + \frac{\beta F_3(b-1)}{\gamma});$$

and since $b < 1$, we have that $\frac{\gamma\left(r+\frac{\alpha_f s_1 Z_3}{\mu_2}\right)}{1-b} < \beta$ and

$$\begin{aligned} B_F =& A_1 r + A_1 F_3 r + A_4 s_2 Z_3, \\ =& A_1(r + F_3 r + \frac{\alpha_f F_3 s_2 Z_3}{\mu_2}), \\ =& A_1(2r - \alpha_f Z_{3_a} + \alpha_f Z_{3_a}), \end{aligned}$$

and

$$\begin{aligned} B^* =& - A_1 F_3 r + A_5 \mu_2 Z_{3a} + A_4 \lambda_z + A_4 p Z_3, \\ =& - A_1 F_3 r + \frac{A_1 \alpha_f F_3}{\mu_2}(\mu_2 Z_{3_a} + \lambda_z + p Z_3), \\ =& - A_1 F_3 r + \frac{A_1 F_3 \alpha_f}{\mu_2}(2\lambda_z), \\ =& A_1 F_3(-r + \frac{2\lambda_z \alpha_f}{\mu_2}); \end{aligned}$$

$L_2' \leq 0$ if $r > \frac{2\lambda_z \alpha_f}{\mu_2}$. Hence, E_3 is globally asymptotically stable.

4. Analytical solution

Finding the solutions of the system helps to understand the dynamics of the solutions. Some researchers have found numerical solutions for biological systems by using Galerkin meshless method [23] or traveling wave solutions [24]. Since there are no initial conditions available, the best way is to apply an analytical method which does not require initial or boundary conditions. We shall the use tanh-expansion method to find the solutions [25]. The following are the steps to construct the solution:

(1) Transfer the system of PDEs given by (6) into the system ODEs given by (7) using a traveling wave transformation, which is defined by $\xi = kx + ct + \xi_0$.

(2) Assume that

$$\hat{f} = \eta_1 u(\xi), \quad \hat{y} = \eta_2 u(\xi), \quad \hat{v} = \eta_3 u(\xi), \quad \hat{z} = \eta_4 u(\xi), \quad \hat{z_a} = \eta_5 u(\xi), \tag{14}$$

and substituting (14) into the equation of System (7) gives a polynomial of u and its derivatives:

$$P(u, u', u'', ...) = 0. \tag{15}$$

(3) Assume that

$$u(\xi) = S(\Phi) = \sum_{i=0}^{M} a_i \Phi^i, \tag{16}$$

where M is a positive integer and

$$\Phi = \tanh(\mu\xi), \tag{17}$$

where μ and a_i are constants such that

$$\begin{aligned}\frac{du}{d\xi} =& \frac{dS(\Phi)}{d\Phi} = \mu(1-\Phi^2)\sum_{i=0}^{M} a_i \frac{d\Phi^i}{d\Phi},\\ \frac{d^2u}{d\xi^2} =& \frac{d^2S(\Phi)}{d\Phi^2} = \mu^2(1-\Phi^2)\left(-2\Phi\sum_{i=0}^{M} a_i\frac{d\Phi^i}{d\Phi} + (1-\Phi^2)\sum_{i=0}^{M} a_i\frac{d^2\Phi^i}{d\Phi^2}\right).\end{aligned}$$

(4) Apply the homogeneous balance theorem to find the value of M, i.e., balance the linear terms of highest order in the previous equation with the highest-order nonlinear terms.

(5) Substitute Eq (16) into the equations of System (15) to obtain an equation of Φ^i.

(6) Equate the confections of Φ^i to zero to obtain the a_i's and η's. By following Steps (1) and (2), we obtain the following system of equations:

$$\begin{aligned}\eta_1\frac{d}{d\xi}u =& \eta_1\frac{r}{c}u(1-(\eta_1u+\eta_2u)) - \eta_1\eta_3\frac{\beta}{c}u^2 - \eta_1\eta_5\frac{\alpha_f}{c}u^2 + \eta_1\frac{d_1k^2}{c}u_{\xi\xi},\\ \eta_2\frac{d}{d\xi}u =& \eta_1\eta_3\frac{\beta}{c}u^2 - \eta_2\frac{1}{c}u - \eta_2\eta_5\frac{\mu_1}{c}u^2 + \eta_2\frac{d_2k^2}{c}u_{\xi\xi},\\ \eta_3\frac{d}{d\xi}u =& \eta_2\frac{b}{c}u - \eta_1\eta_3\frac{\beta}{c}u^2 - \eta_3\frac{\gamma}{c}u - \eta_3\eta_5\frac{\kappa}{c}u^2 + \eta_3\frac{d_3k^2}{c}u_{\xi\xi},\\ \eta_4\frac{d}{d\xi}u =& \frac{\lambda_z}{c} - \eta_4\frac{p}{c}u - \eta_2\eta_4\frac{s_1}{c}u^2 - \eta_1\eta_4\frac{s_2}{c}u^2 + \eta_4\frac{d_4k^2}{c}u_{\xi\xi},\\ \eta_5\frac{d}{d\xi}u =& \eta_2\eta_3\frac{s_1}{c}u^2 + \eta_1\eta_3\frac{s_2}{c}u^2 - \eta_5\frac{\mu_2}{c}u + \eta_5\frac{d_5k^2}{c}u_{\xi\xi}.\end{aligned} \tag{18}$$

Then, we sum all of the equations to obtain a single equation, as follows:

$$A_1u + A_2u^2 + A_3u' - k^2A_4u'' - A_5 = 0, \tag{19}$$

where

$$\begin{aligned}A_1 =& \eta_2\frac{1}{c} - \eta_2\frac{b}{c} + \eta_3\frac{\gamma}{c} + \eta_4\frac{p}{c} + \eta_5\frac{\mu_2}{c} - \eta_1\frac{r}{c},\\ A_2 =& \eta_1^2\frac{r}{c} + \eta_1\eta_2\frac{r}{c} + \eta_1\eta_5\frac{\alpha_f}{c} + \eta_2\eta_5\frac{\mu_1}{c} + \eta_1\eta_3\frac{\beta}{c} + \eta_3\eta_5\frac{\kappa}{c},\\ A_3 =& \eta_1 + \eta_2 + \eta_3 + \eta_4 + \eta_5,\\ A_4 =& d_1\eta_1 + d_2\eta_2 + d_3\eta_3 + d_4\eta_4 + d_5\eta_5,\\ A_5 =& -\frac{\lambda_z}{c}.\end{aligned}$$

Next, we follow Steps (3) and (4) and balance between the nonlinear term u^2 and the highest order of the derivative u''; we get $2M = 4 + M - 2$, which satisfies $M = 2$. Thus,

$$u(\xi) = S(\Phi) = a_0 + a_1\Phi + a_2\Phi^2. \tag{20}$$

Substituting Eq (20) into ODE (19) gives

$$A_1S(\Phi) + A_2S^2(\Phi) + A_3\mu(1-\Phi^2)\frac{dS(\Phi)}{d\Phi} - A_4\mu^2(1-\Phi^2)(-2\Phi\frac{dS(\Phi)}{d\Phi} + (1-\Phi^2)\frac{d^2S(\Phi)}{d\Phi^2}) - A_5 = 0. \tag{21}$$

Note that

$$\begin{aligned} S &= a_0 + a_1\Phi + a_2\Phi^2, \\ \frac{dS}{d\Phi} &= a_1 + 2a_2\Phi, \\ \frac{d^2S}{d\Phi^2} &= 2a_2. \end{aligned} \tag{22}$$

Substituting Eq (22) into Eq (21) and collecting all of the terms with the same power of Φ together implies the following:

$$A_1(a_0 + a_1\Phi + a_2\Phi^2) + A_2 + (a_0 + a_1\Phi + a_2\Phi^2)^2 + A_3(a_1 + 2a_2\Phi) - A_4(2a_2) - A_5 = 0;$$

this can be rewritten as

$$b_0 + b_1\Phi + b_2\Phi^2 + b_3\Phi^3 + b_4\Phi^4 = 0.$$

Then, we equate the constant b_i's to zero to obtain the algebraic system of equations and find the a_i's and η's.

Thus, the solutions are in the following form:

$$F = \eta_1 u(x,t), \quad Y = \eta_2 u(x,t), \quad V = \eta_3 u(x,ti), \quad Z = \eta_4 u(x,t), \quad Z_a = \eta_5 u(x,t), \tag{23}$$

where

$$u(x,t) = a_0 + a_1 \tanh(\mu(ct + kx)), \tag{24}$$

and

$$\begin{aligned} d_5 =& \frac{1}{\eta_5^2}\left(\frac{\eta_5(6.58537d_3 - 36.5854d_4)}{a_1c\mu} + \eta_5^2(1.6d_1 - 1.17143d_2 - 6.85366d_3 + 7.42509d_4)\right. \\ & \left. -66.9643d_2 - 423.018d_3 + 489.983d_4\right), \\ \eta_1 =& -1.6, \eta_2 = 1.17143\eta_5 + \frac{66.9643}{\eta_5}, \\ \eta_3 =& -\frac{6.58537}{a_1c\mu} + 6.85366\eta_5 + \frac{423.018}{\eta_5}, \eta_4 = \frac{36.5854}{a_1c\mu} - 7.42509\eta_5 - \frac{489.983}{\eta_5}. \end{aligned}$$

5. Discussion of results

The presented mathematical model aims to elucidate the effects of combining viral therapy with the immune response and its spread. First, we ignored the diffusion terms and solved the problem by using the Runge-Kutta 4th-order method using the values of the non-dimensionless parameters according to Reference [16], as follows:

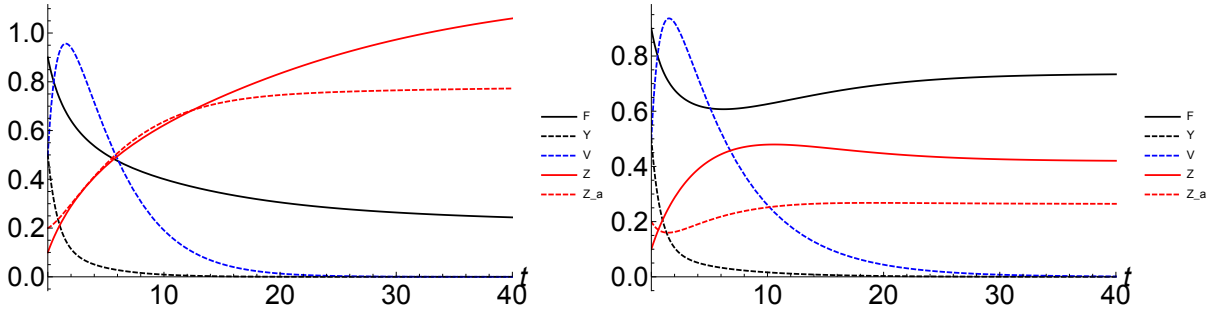
$$\begin{aligned} r = 0.36, \beta = 0.1, \alpha_f = 0.36, \\ \mu_1 = 0.48, b = 2, \gamma = 0.2, \kappa = 0.16, \\ , s_1 = 0.6, s_2 = 0.29, p = 0.036, \\ \lambda_z = 0.2, \mu_2 = 0.036. \end{aligned}$$

We considered two cases: (a) $\mu_1 = \mu_2 = 0.2,\ s_1 = 0.2,\ s_2 = 0.6$ and (b) $\mu_1 = \mu_2 = 0.7\ s_1 = 0.2,\ s_2 = 0.6$, where the initial conditions are $F = 0.9,\ Y = 0.5,\ V = 0.5,\ Z = 0.1$ and $Z_a = 0.2$.

The results in Figure 2 show that, in Case (a), the unaffected cells F decreases during the treatment when the concentration of activated immune system cells is low. On the other hand, the high concentration of Z_a helps to maintain the level of healthy cells in the body. Therefore, we predict that the combination of biological therapy and virotherapy reduces the side effects of the virotherapy, and the patient's body may become less weak during the treatment.

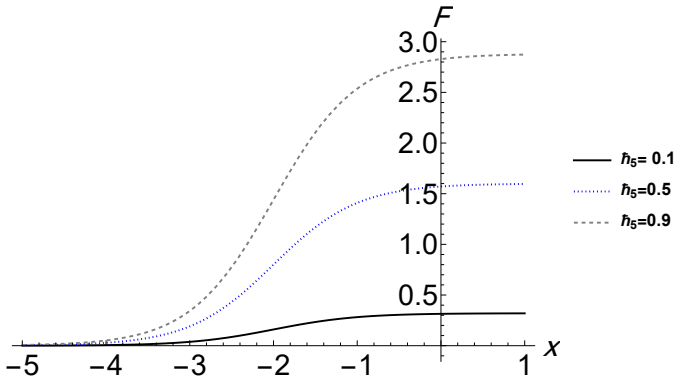
The immune response against cancer cells has been investigated for decades. It has been determined that the immune system actively patrols the body [26]. From this standpoint, we investigate the diffusion coefficient of the immune system d_5. The solutions of Model (6) are found by employing the tanh-expansion method to study the effect of the treatment on cancer growth. The solution is presented in Eq (24), which indicates that d_5 is dependent on $d_1,\ d_2,\ d_3$ and d_4. The diffusion of activated immune system cells (d_5) increases when the diffusion of the unaffected cells (d_1) or naive immune system cells (d_4) increases, while it decreases by increasing the diffusion of the virus (d_2) or infected cells (d_3).

Note that η_5 is another parameter that affects the solution, as we can see in Figures 3–5. The parameter η_5 is a coefficient that is associated with Z_a. When η_5 increases, the concentrations of uninfected cells F and activated immune system cells Z_a increase, while the concentrations of infected cells y, virus v and naive immune system cells Z decrease. We observed that the immune cells Z have the highest concentrations compared to other components in the system, and this indicates the response of the immune system for viral treatment. However, the immunotherapy has been widely used in different protocols to treat cancers [27]. We predict good results of the combination between immune therapy and virotherapy. The results are aligned with the clinical trial in Reference [28]. This clinical trial confirms the possibility of combining the immunotherapy and virotherapy.

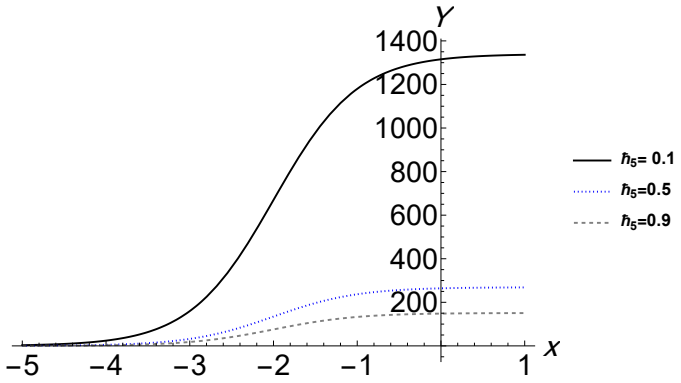


(a) (b)

Figure 2. Solutions obtained by ignoring diffusion terms and considering two cases: (a) the activated immune system (Z_a) has low concentration in the body and (b) Z_a has high concentration.

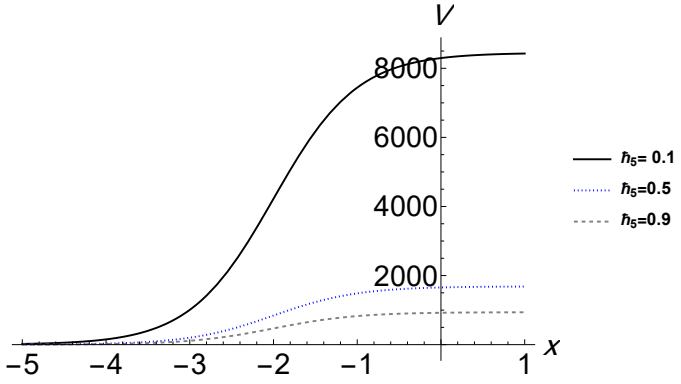


(a) Uninfected cancer cells.



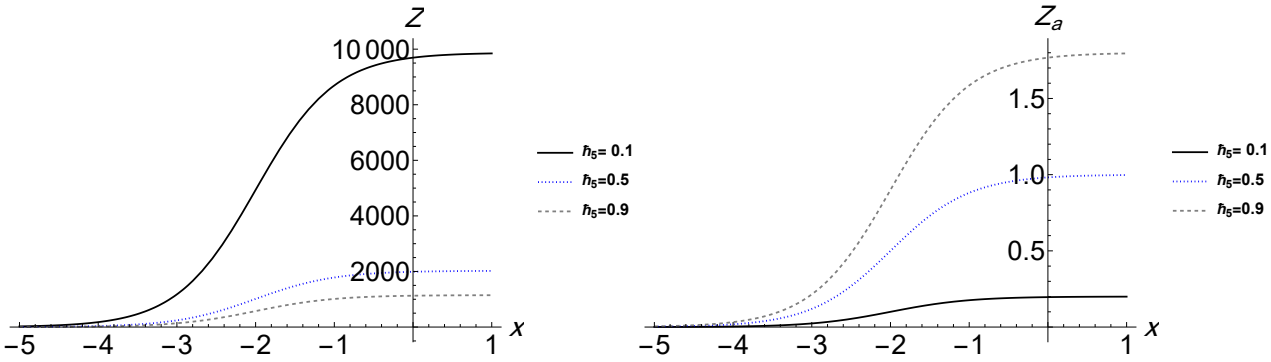
(b) Infected cancer cells.

Figure 3. Solutions for different values of η_5.



(a) Virus.

Figure 4. Solutions for different values of η_5.



(a) Naive immune cells.

(b) Activated immune cells.

Figure 5. Solutions for different values of η_5.

6. Conclusions

In this work, we modified a mathematical model of cancer and virotherapy to study the dynamics of virotherapy with tumor cells and the effects of the immune response. In addition, this modification distinguishes between two types of immune system cells, which are the activated cells and naive cells. The results predict that the high concentration of activated immune cells leads to enhanced results of virotherapy. The activated immune cells can be generated in the patient's body through biological therapy. Moreover, the model was analyzed by using the stability theory of nonlinear systems. We studied the stability of five equilibrium points and determined the conditions of the existence and local and global stability of the equilibrium points. As a result, the success of viral treatment depends on the size of the burst b, the viral infection rate β and the clearance rate of viruses γ, which depend on the type of the virus. The treatment by virotherapy can be more effective by stimulating the activated immune cells. Furthermore, we found the analytical solutions for the studied model by using the tanh-expansion method because of a lack of initial and boundary conditions. We found that, if the concentration of activated immune cells Z_a increases, the unaffected cells f increase, which indicates the improvement of the treatment results.

However, for future work, the studied model can be solved numerically by finding the associated

initial and boundary conditions based on real data, and by using the Galerkin method [23]. Also, diffusion terms can be added in many biological models to study the spread of the model components and deal with a system of PDEs.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Appendix

The definitions of b_0, b_1, b_2, b_3 and b_4 that are related to the characteristic polynomial for E_2 are as follows:

$$
\begin{aligned}
b_0 =&(1-b)\beta F_3+\gamma+\mu_1 Z_{3a}(\gamma+\beta F_3+\kappa Z_{3a})\left(F_3\mu_2 pr+F_3 s_2\left(F_3\mu_2 r+\alpha_f pZ_3\right)\right)\\
&+\kappa Z_{3a},\\
b_1 =&F_3^3((1-b)\beta rs_2+\beta\mu_2 rs_2+\beta\mu_1 rs_2Z_{3a})+F_4^2((1-b)\beta pr+(1-b)\beta\mu_2 r\\
&+(1-b)\beta\mu_2 s_2+\alpha_f(1-b)\beta s_2Z_3+k\mu_1 rs_2Z_{3a}^2+\kappa\mu_2 rs_2Z_{3a}+\kappa rs_2Z_{3a}+\beta pr\\
&+\alpha_f\beta ps_2Z_3+\gamma\mu_2 rs_2+\gamma rs_2+\mu_2 rs_2+\gamma\mu_1 rs_2Z_{3a}+\mu_1\mu_2 rs_2Z_{3a}+2\beta\mu_1\mu_2 rZ_{3a}\\
&+\alpha_f\beta\mu_2 s_2Z_{3a}+\beta\mu_1\mu_2 s_2Z_{3a}+\alpha_f\beta\mu_1 s_2Z_{3a}Z_3)+F_3((1-b)\beta\mu_2 p\\
&+\kappa\mu_2 prZ_{3a}+\alpha_f\kappa ps_2Z_{3a}Z_3+2k\mu_1\mu_2 rZ_{3a}^2+\kappa\mu_2 rZ_{3a}+k\mu_1\mu_2 s_2Z_{3a}^2\\
&+\alpha_f\kappa+\mu_1 s_2Z_{3a}^2Z_{3a}+k\mu_2 s_2Z_{3a}(\alpha_f Z_{3a}+1)+\alpha_f\kappa s_2Z_{3a}Z_3+\gamma\mu_2 pr\\
&+\gamma pr+\mu_2 pr+\mu_1\mu_2 prZ_{3a}+\alpha\mu_1 ps_2Z_{3a}Z_3+\alpha_f\gamma ps_2Z_3+\alpha_f ps_2Z_3\\
&+\beta\mu_1\mu_2 pZ_{3a}+\gamma\mu_2 r+2\gamma\mu_1\mu_2 rZ_{3a}+\gamma\mu_2 s_2+\alpha\gamma\mu_2 s_2Z_{3a}Z_{3a}+\gamma\mu_1\mu_2 s_2Z_{3a}\\
&+\alpha_f\gamma\mu_1 s_2Z_{3a}Z_3+\alpha\gamma s_2Z_3)+\kappa\mu_1\mu_2 pZ_{3a}^2+\gamma\mu_2 p+\alpha_f\mu_2 pZ_{3a}+\gamma\mu_1\mu_2 pZ_{3a},\\
b_2 =&F_3^2((1-b)\beta r+(1-b)\beta s_2+\kappa rs_2Z_{3a}+\mu_1 pr^2Z_{3a}+\beta\mu_1 prZ_{3a}+pr+\mu_1\mu_2 r^2Z_{3a}\\
&+\beta\mu_2 r+\gamma rs_2+\mu_2 rs_2+\mu_1 rs_2Z_{3a}+rs_2+\beta\mu_1 rZ_{3a}+\beta\mu_1\mu_2 rZ_{3a}+\beta\mu_2 s_2\\
&+\beta\mu_1 s_2Z_{3a}+\alpha_f\beta s_2Z_4)+F_3((1-b)\beta\mu_2+(1-b)\beta p+b\beta r+\kappa\mu_1 prZ_{3a}^2+\kappa prZ_{3a}\\
&+k\mu_1 rZ_{3a}^2+\kappa\mu_1\mu_2 rZ_{3a}^2+\kappa\mu_2 rZ_{3a}+\kappa\mu_1 s_2Z_{3a}^2+\kappa\mu_2 s_2Z_{3a}+\alpha_f\kappa s_2Z_{3a}Z_3\\
&+\kappa s_2Z_{3a}+\beta\mu_2 p+\gamma pr+\mu_2 pr+\gamma\mu_1 prZ_{3a}+\mu_1\mu_2 prZ_{3a}+pr+\alpha_f ps_2Z_3\\
&+\gamma\mu_2 r+\gamma r+\mu_2 r+\gamma\mu_1 rZ_{3a}+\gamma\mu_1\mu_2 rZ_{3a}+\gamma\mu_2 s_2+\gamma s_2+\mu_2 s_2\\
&+\gamma\mu_1 s_2Z_{3a}+\mu_1\mu_2 s_2Z_{3a}+\alpha_f\mu_1 s_2Z_{3a}Z_3+\alpha_f\gamma s_2Z_3+\alpha_f s_2Z_3)+\gamma\mu_2\\
&+\alpha_f(1-b)\beta Z_3Z_{3a}+\beta F_3^3rs_2+\kappa\mu_2 pZ_{3a}+\kappa pZ_{3a}+\kappa\mu_2 Z_{3a}+\gamma\mu_2 p+\gamma p+\mu_2 p,\\
b_3 =&F_3((1-b)\beta+\beta\mu_2+\kappa rZ_{3a}+\kappa s_2Z_{3a}+\beta p+pr+\gamma r+\mu_2 r+\mu_1 rZ_{3a}\\
&+r+\gamma s_2+\mu_2 s_2+\mu_1 s_2Z_{3a}+\alpha_f s_2Z_3+s_2+\beta\mu_1 Z_{3a})+\gamma\mu_2+\gamma\\
&+F_3^2(\beta r+rs_2+\beta s_2)+Z_{3a}(\gamma\mu_1+\kappa\mu_2+\kappa p+\kappa+\mu_1\mu_2+\mu_1 p)+\kappa\mu_1 Z_{3a}^2\\
&+\mu_2+\gamma p+\mu_2 p+p,\\
b_4 =&\gamma+\beta F_3+2F_3 r+F_3 s_2+\kappa Z_{3a}+\mu_2+p+\alpha_f Z_{3a}+\mu_1 Z_{3a}+1.
\end{aligned}
$$

The definitions of a_0, a_1, a_2, a_3, a_4 and a_5 that are related to the characteristic polynomial for E_4 are as follows:

$$
\begin{aligned}
a_1 =&\mu_1 Z_4 a + \frac{bY_4}{V_4} + F_4 r + \mu_2 + \frac{\lambda_z}{Z_4} + 1,\\
a_2 =&(1-b)\beta F_4 + Z_{4a}(\frac{b\mu_2 Y_4}{V_4} + \gamma\mu_1 + \beta F_4\mu_1 + F_4\kappa r + F_4\mu_2 r + F_4\mu_1 r\\
&+ \kappa\mu_2 + \kappa p + \kappa + \mu_2^2 + \mu_1\mu_2 + \mu_2 + \mu_1 p + \beta\mu_1 V_4 + \alpha_f\mu_1\mu_2 Z_4)\\
&+ \gamma\mu_2 + \gamma + \beta F_4^2 r + \beta F_4\mu_2 + F_4 pr + \gamma F_4 r + F_4\mu_2 r + F_4 r\\
&+ \mu_2 + \gamma p + \mu_2 p + p + \mu_1\mu_2 Z_{4a}^2,\\
a_3 =&\frac{1}{V_4 Z_4} F_4(V_4(\mu_1 r Z_4 a\lambda_z + \mu_1\mu_2 r Z_4 Z_4 a + \alpha_f s_2 Z_4(\mu_1 Z_4 Z_4 a - \mu_2 Z_4 a\\
&+ \lambda_z + Z_4) + rY_4 Z_4(b\beta + \mu_1 Z_4(s_1 - s_2) - b\beta(\lambda_z + \mu_2 Z_4)\\
&+ \mu_2 r\lambda_z + r\lambda_z + \mu_2 r Z_4) + \beta V_4^2(Z_4(-\beta\mu_1 Z_4 a - (1-b)\beta\\
&+ \mu_2(r-\beta)) + (r-\beta)\lambda_z + Z_4^2(s_1\alpha_f + \kappa(s_1 - s_2))\\
&+ bY_4(rZ_4(\mu_1 Z_4 a + \mu_2 + 1) + r\lambda_z + \alpha_f s_2 Z_4^2))\\
&+ Y_4(\lambda_z(b(\mu_1 Z_4 a + \mu_2 + 1) + \mu_1 s_1 V_4 Z_4) + \mu_2 Z_4(-\mu_1 Z_{4a}(s_1 V_4 - b) + b))\\
&+ \mu_2 V_4\lambda_z(\mu_1 Z_4 a + 1) - \beta(F_4^2 r V_4 Z_4(-V_4 - b) + b\mu_1 s_1 Y_4^2 Z_4^2,\\
a_4 =&\frac{1}{V_4 Z_4} - \beta^2(\kappa F_4 s_1 Z_4^2 V_4^3 + \alpha_f F_4^2 s_1 Z_4^2 V_4^2 - bF_4\lambda_z V_4^2)\\
&- \beta^2 F_4 V_4^2(\lambda_z + Z_{4a}\lambda_z\mu_1 + Z_4\mu_2(1-b) + \lambda_z\mu_2 + Z_4 Z_{4a}\mu_1\mu_2)\\
&- \beta F_4 s_1 Z_4(-((\alpha_f + \kappa)\lambda_z) + \beta Y_4 Z_4\mu_1 + (\alpha_f + \kappa)Z_{4a}\mu_2)V_4^2\\
&- \beta\kappa F_4 s_2 Z_4(\lambda_z + Z_4(Z_{4a}\mu_1 + 1) - Z_a\mu_2)V_4^2 - b\alpha_f\beta F_4^2 s_2 Z_4^2 V_4\\
&+ b\alpha_f\beta F_4 s_1 Y_4 Z_4^2 V_4 + \alpha_f F_4 s_2 Z_4\lambda_z V_4 - b\beta F_4 s_2 Y_4 Z_4^2\mu_1 V_4\\
&+ \alpha_f F_4 s_2 Z_4 Z_{4a}\lambda_z\mu_1 V_4 - b\beta F_4\lambda_z\mu_2 V_4 - \alpha_f F_4 s_2 Z_4 Z_{4a}(Z_{4a}\mu_1 + 1)\mu_2 V_4\\
&+ b\alpha F_4 s_2 Y_4 Z_4^2 + b\alpha_f F_4 s_2 Y_4 Z_4\lambda_z + b\alpha_f F_4 s_2 Y_4 Z_4^2 Z_{4a}\mu_1\\
&- b\alpha_f F_4 s_2 Y_4 Z_4 Z_{4a}\mu_2 + bY_4(\lambda_z(Z_4 a\mu_1 + 1)\mu_2 + s_1 Y_4 Z_4\mu_1(\lambda_z - Z_4 a\mu_2))\\
&+ r(\beta\kappa s_1 V_4^2 Z_4^2 F_4^2 - \beta\kappa s_2 V_4^2 Z_4^2 F_4^2 - \beta V_4(b + \beta V_4)(\lambda_z + Z_4\mu_2)F_4^2\\
&+ bY_4\lambda_z F_4 + b\beta V_4 Y_4\lambda_z F_4 + bs_1 Y_4^2 Z_4^2\mu_1 F_4 - bs_2 Y_4^2 Z_4^2\mu_1 F_4\\
&- s_2 V_4 Y_4 Z_4\lambda_z\mu_1 F_4 + bY_4 Z_{4a}\lambda_z\mu_1 F_4 + bY_4 Z_4\mu_2 F_4 + b\beta V_4 Y_4 Z_4\mu_2 F_4\\
&+ \beta V_4^2\lambda_z\mu_2 F_4 + V_4\lambda_z\mu_2 F_4 + bY_4\lambda_z\mu_2 F_4 + bY_4 Z_4 Z_{4a}\mu_1\mu_2 F_4\\
&+ s_2 V_4 Y_4 Z_4 Z_{4a}\mu_1\mu_2 F_4 + V_4 Z_a\lambda_z\mu_1\mu_2 F_4 + s_1 V_4 Y_4 Z_4\mu_1(\lambda_z - Z_{4a}\mu_2)F_4),\\
a_5 =&\frac{F_4}{V_4 Z_4} F_4 r(-b\mu_1 s_2 Y_4^2 Z_4(-\mu_2 Z_{4a} + \lambda_z) + b\mu_1\mu_2 s_1 Y_4 Z_{4a}(Y_4\lambda_z - s_1 Y_4 Z_4)\\
&+ \beta F_4\kappa s_1 V_4^2 Z_4(\lambda_z - \mu_2 Z_a) - \beta F_4\kappa s_2 V_4^2 Z_4(\lambda_z - \mu_2 Z_{4a}) - \beta F_4\mu_2 V_4\lambda_z(b + \beta V_4)\\
&+ b\mu_1 s_1 Y_4^2 Z_4\lambda_z + b\beta\mu_2 V_4 Y_4\lambda_z + b\mu_2 Y_4\lambda_z + F_4(-\alpha_f b\beta F_4 s_2 V_4 Z_4(\lambda_z - \mu_2 Z_{4a})\\
&- b\beta\mu_1 s_2 V_4 Y_4 Z_4(-\mu_2 Z_{4a} + \lambda_z) - \alpha_f b\beta\mu_2 s_1 V_4 Y_4 Z_4 Z_{4a}\\
&+ \alpha_f bs_2 Y_4 Z_4(\mu_1 Z_{4a} + 1)(-\mu_2 Z_a + \lambda_z) - \alpha_f\beta^2 F_4 s_1 V_4^2 Z_4(\lambda_z - \mu_2 Z_{4a})\\
&+ \beta^2\mu_1\mu_2 s_1 V_4^2 Y_4 Z_4 Z_{4a} - \beta\kappa s_2 V_4^2 Z_4(\mu_1 Z_{4a} + 1)(-\mu_2 Z_{4a} + \lambda_z)
\end{aligned}
$$

$$-\beta^2(-\kappa\mu_2 s_1 V_4^3 Z_4 Z_a + \mu_1\mu_2 V_4^2 Z_a\lambda_z) + \alpha_f b\beta s_1 V_4 Y_4 Z_4\lambda_z$$
$$-\beta^2(\mu_2 V_4^2\lambda_z(1-b) + \mu_1 s_1 Y_4 Z_4 + \kappa s_1 V_4^3 Z_4\lambda_z).$$

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