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DYNAMICS OF CANCER CELLS WITH IMMUNOTHERAPY AND VIROTHERAPY

MARIEM ELKAF[1,*], ADIL MESKAF[2], KARAM ALLALI[1]

[1]Laboratory of Mathematics and Applications, Faculty of Sciences and Techniques Mohammedia, University Hassan-II Casablanca, Mohammedia, Morocco

[2]Department of SEG, Faculty of Ecomonic and Social Legal Sciences, University Chouaib Doukkali, EL Jadida, Morocco

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Abstract. Oncology is the science that deals with the prevention, diagnosis and study the different possible remedies in order to treat and fight the cancer disease. In this paper, immunotherapy and virotherapy are included to mathematical new model which expresses the interaction between tumor, immunity elements (Cytotoxic T cell and Interleukin-2 (IL-2)) and oncolytic virus. After the well-posedness of model, we show that the disease-free equilibrium point (DFE) and the endemic equilibrium point can exist under specific conditions depending on treatment parameters: adoptive cellular therapy (ACT) or IL-2 treatment or the case of oncolytic virus treatment (OVT) and combined treatments. We will also discuss the local stability of the equilibrium points. The oncolytic dynamic will be analyzed numerically by using MATLAB software in order to interpret the different cancer evolution situations. A set of numerical results are obtained in order to show the performance of each treatment to reduce the size and the speed of tumor proliferation, although it leaves treatment residues for a long time.

Keywords: cancer immunotherapy; oncolytic virotherapy; ordinary differential equations; cancer modeling.

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*Corresponding author

E-mail address: elkaf.mariem@gmail.com

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1. INTRODUCTION

Cancer remains one of the diseases that researchers still discover day by day. It is an illness that can affect all members of the body. The mathematical modeling is used as efficient tool to recognize the cancer cell's progression and to predict its growth. Many works were done using several techniques such as system of ordinary differential equations (ODEs) [1–4] or partial differential equation (PDEs) [5,6]. In some other works, we can find the diffusion of cancer [6–8] or stochastic behavior of the disease [9]. Combined therapies have shown significant promise for treating cancers [3, 10–12]. For example, recent work [13] provides an overview of the clinical status of CAR-T cell and OV therapies and confirm that immunity and virus have an important impact on oncolytic dynamics. The optimal control of cancer model is studied using the metaheuristics approaches [14], the authors have used the external sources of immunotherapies to reduce the cancer growth. With the introduction of virotherapy [15], the work have studied the effect of this new treatment to prevent cancer growth. It was shown that treatment with virus can replace or support the traditional treatments due to potent oncolytic efficacy of virus. Therefore, it remains essential to develop model in order to understand the therapeutic impact of such dynamics. In this paper, we will combine the effect of immunotherapy and virotherapy, we will consider the logistic growth of tumor and the standard incidence functions, with these approaches, we will study the role of the cellular immune system and the role of the oncolytic virus on cancer dynamics. For this purpose, the formulation of the model is inspired from the previous works [6,14,16], and our new model will be given by the following nonlinear system of differential equations:

$$\left\{\begin{array}{rcl} \dfrac{dx}{dt} &=& cy+\dfrac{p_1xz}{g_1+z}-\mu_1x+s_1,\\ \dfrac{dy}{dt} &=& ry(1-by)-\dfrac{p_2xy}{g_2+y}-\beta yv,\\ \dfrac{dz}{dt} &=& \dfrac{p_3xy}{g_3+y}-\mu_2z+s_2,\\ \dfrac{dv}{dt} &=& \alpha\beta yv-\mu_3v+s_3. \end{array}\right. \tag{1}$$

The model (1) describes the dynamics of cancer evolution. The variables x, y, z and v correspond to effector cells, tumor cells, IL-2 and free viruses, respectively. The parameters s_1, s_2 and s_3 express the external sources (injections) of effector cells, IL-2 and virus respectively, μ_1,μ_2

and μ_3 mean the natural loss of effector cells, IL-2 and of the virus respectively. The natural degradation of the tumor is calculated with its progression in the logistic equation $ry(1-by)$ which expresses the evolution of the tumor. The parameter c represents the antigenicity of the tumor in the effector cells. The term $\frac{p_1xz}{g_1+z}$ indicates the effect of saturation on effector cells by IL-2 (noted by f_1 in Fig. 1), while the term $\frac{p_2xy}{g_2+y}$ (noted by f_2 in Fig. 1) indicates the interaction of cancer cells with effectors controlled by tumor and the term $\frac{p_3xy}{g_3+y}$ (noted by f_3 in Fig. 1) indicates the natural production of IL-2 due to the interaction between the effectors and the tumor. Finally, the remaining terms are related to the oncolytic virus which kills tumor cells, βyv is the rate and the amount of virus increases at $\alpha\beta yv$ rate.

The schematic behavior of the interactions between the variables of our model (1) previously is illustrated in Fig. 1.

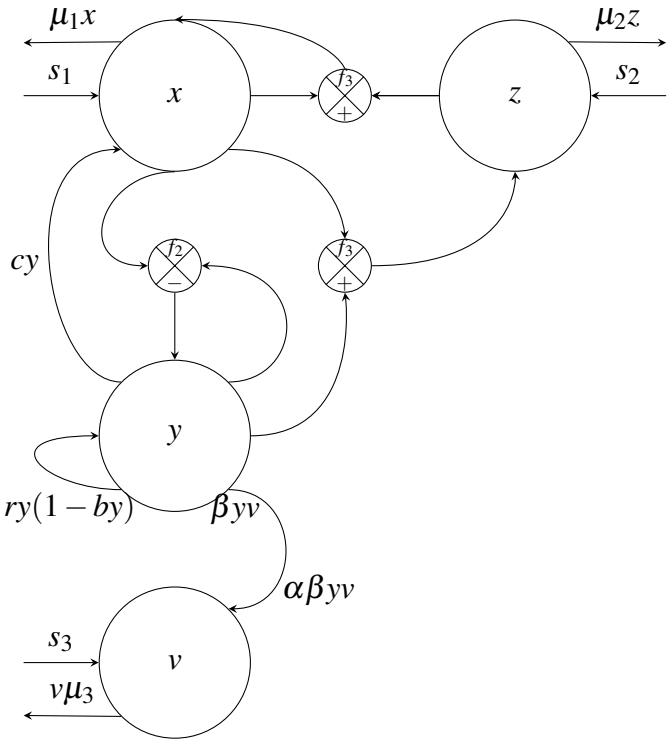

FIGURE 1. Cancer cells evolution with treatment diagram.

This work is organized as follows: The next section is dedicated to the well-posedness of our mathematical formulation in terms of positivity and boundedness of solutions; also the equilibria and their stability is established in the same section. Section 3 deals with the effect of

immunotherapy and virothepary on cancer evolution. Finally, the article ends with a conclusion which sums up all the results of this work.

2. WELLPOSEDNESS AND EQUILIBRUIA STABILITY

Since modeling cells in population evolution requires that the variables should remain non-negative and bounded, we will establish the positivity and boundedness of model (1) solutions. Also, the stability of equilibrium points is discussed.

2.1. Positivity and boundedness of solutions. For biological reasons, the parameters x_0, y_0, z_0 and v_0 must be larger than or equal 0.
Hence, we have the following results:

Proposition 1. *The solutions of the problem* (1) *are non-negative.*

Proof. We will show the non-negativity of the solution.

First, lets show that $\mathbb{R}^4_+ = \{(x(t),y(t),v(t),z(t)) \in \mathbb{R}^4 : x \geq 0, y \geq 0, v \geq 0 \text{ and } z \geq 0\}$ is a positively invariant region.

Indeed, for $(x(t),y(t),v(t),z(t)) \in \mathbb{R}^4_+$ we have:

$$\frac{dy}{dt}_{|y=0} = 0 \geq 0,$$
$$\frac{dx}{dt}_{|x=0} = cy + s_1 \geq 0,$$
$$\frac{dz}{dt}_{|z=0} = \frac{p_3 xy}{g_3 + y} + s_2 \geq 0,$$
$$\frac{dv}{dt}_{|v=0} = s_3 \geq 0.$$

Therefore, all solutions initiating in $\mathbb{R}^4_+$ are positive. □

Proposition 2. *The solutions of the problem* (1) *are bounded.*

Proof. We will show the boundlessness of the solution.

From equation $\frac{dy}{dt} = ry(1-by) - \frac{p_2 xy}{g_2 + y} - \beta yv$, we have : $\frac{dy}{dt} \leq ry(1-by)$.

Thus

$$y \leq \frac{1}{b}$$

So, y is bounded.

From equation $\frac{dx}{dt} = cy + \frac{p_1 xz}{g_1+z} - \mu_1 x + s_1$, we have : $\frac{dx}{dt} + (\mu_1 - p_1)x \leq +cy + s_1$.

Thus

$$x \leq x_0 e^{-(\mu_1 - p_1)t} + \int_0^t (cy + s_1) e^{-(\mu_1 - p_1)(t-\zeta)} \, d\zeta$$

Since y is bounded, thus x is also bounded.

From equation $\frac{dz}{dt} = \frac{p_3 xy}{g_3+y} - \mu_2 z + s_2$, we have : $\frac{dz}{dt} + \mu_2 z \leq +p_3 x + s_2$.

Thus

$$z \leq z_0 e^{-\mu_2 t} + \int_0^t (p_3 x + s_2) e^{-\mu_2 (t-\zeta)} \, d\zeta$$

Since x is bounded, thus z is also bounded.

From equations $\frac{dv}{dt} = \alpha\beta yv - \mu_3 v + s_3$ and $\frac{dy}{dt} = ry(1-by) - \frac{p_2 xy}{g_2+y} - \beta yv$, we have :

$\frac{dv}{dt} + \mu_3 v \leq \alpha(ry - \frac{dy}{dt} + \frac{s_3}{\alpha})$.

Thus

$$v \leq (\alpha(y_0 - \frac{s_3}{\alpha\mu_3}) + v_0) e^{-\mu_3 t} + \alpha(\frac{s_3}{\alpha\mu_3} - y + \int_0^t (\mu_3 + r) y e^{-\mu_3 (t-\zeta)} dt)$$

Since y is bounded, thus v is also bounded. □

3. Existance and Local Stability Analysis

At any equilibrium instant, the variations of the different variables are zero.

Hence, the equilibrium point $E^*(x^*, y^*, z^*, v^*)$ should verify the following system:

$$\begin{cases} 0 &= cy^* + \frac{p_1 x^* z^*}{g_1+z^*} - \mu_1 x^* + s_1, \\ 0 &= y^*[r(1-by^*) - \frac{p_2 x^*}{g_2+y^*} - \beta v^*], \\ 0 &= \frac{p_3 x^* y^*}{g_3+y^*} - \mu_2 z^* + s_2, \\ 0 &= v^*[\alpha\beta y^* - \mu_3] + s_3. \end{cases} \quad (2)$$

The Jacobian matrix of the system (1) at E^*, is given by:

$$J_{E^*} = \begin{pmatrix} -\mu_1 + \frac{p_1 z^*}{g_1+z^*} & c & \frac{p_1 g_1 x^*}{(g_1+z^*)^2} & 0 \\ \frac{-p_2 y^*}{g_2+y^*} & r - \beta v^* - 2bry^* - \frac{p_2 g_2 x^*}{(g_2+y^*)^2} & 0 & -\beta y^* \\ \frac{p_3 y^*}{g_3+y^*} & \frac{p_3 g_3 x^*}{(g_3+y^*)^2} & -\mu_2 & 0 \\ 0 & \alpha\beta v^* & 0 & \alpha\beta y^* - \mu_3 \end{pmatrix}$$

We recall that the absence of virus ($v^* = 0$), the situation is already studied in S. Ahrabi and A. Momenzadeh [14]. In this paper we will consider non-zero virus ($v^* \neq 0$).

The Jacobian becomes:

$$J_{E^*} = \begin{pmatrix} -a_i & c & b_i & 0 \\ -d_i & r-e_i & 0 & -f \\ g & h_i & -\mu_2 & 0 \\ 0 & k_i & 0 & 0 \end{pmatrix}$$

With :

$a_i = \dfrac{p_1 z^*}{g_1 + z^*} - \mu_1 = \dfrac{1}{x^*}(s_1 + \dfrac{c\mu_3}{\alpha\beta})$,

$b_i = \dfrac{p_1 g_1 x^*}{(g_1 + z^*)^2}$,

$d = \dfrac{p_2 \mu_3}{\alpha\beta g_2 + \mu_3}$,

$e_i = \beta v^* + 2br\dfrac{\mu_3}{\alpha\beta} + \dfrac{\alpha^2\beta^2 p_2 g_2 x^*}{(\alpha\beta g_2 + \mu_3)^2}$,

$f = \dfrac{\mu_3}{\alpha}$,

$g = \dfrac{p_3 \mu_3}{\alpha\beta g_3 + \mu_3}$,

$h_i = \dfrac{\alpha^2\beta^2 p_3 g_3 x^*}{(\alpha\beta g_3 + \mu_3)^2}$,

$k_i = \alpha\beta v^*$.

The eigenvalues of the Jacobian matrix are the roots of the characteristic polynomial:

$$P_{E_i}(X) = det(XI - J_{E_i}) = m_4 X^4 + m_3 X^3 + m_2 X^2 + m_1 X + m_0.$$

With: m_i^+ the positive part and m_i^- the absolute value of negative part of the parameter m_i, $i \in \{0,1,2,3\}$.

$m_0 = fk_i a_i \mu_2 - fk_i bg = m_0^+ - m_0^-$, with $m_0^+ = fk_i a_i \mu_2$ and $m_0 = fk_i bg$.

$m_1 = fk_i a_i + fk\mu_2 + b_i dh_i + b_i gr + cd\mu_2 + a_i e_i \mu_2 - b_i e_i g - a_i r\mu_2 = m_1^+ - m_1^-$,

with $m_1^+ = fk_i a_i + fk\mu_2 + b_i dh_i + b_i gr + cd\mu_2 + a_i e_i \mu_2$ and $m_1^- = b_i e_i g + a_i r\mu_2$.

$m_2 = fk_i + cd + a_i\mu_2 + e_i\mu_2 + a_i e_i - b_i g - r\mu_2 - a_i r = m_2^+ - m_2^-$,

with $m_2^+ = fk_i + cd + a_i\mu_2 + e_i\mu_2 + a_i e_i$ and $m_2^- = b_i g + r\mu_2 + a_i r$.

$m_3 = e_i + \mu_2 + a_i - r = m_3^+ - m_3^-$, with $m_3^+ = e_i + \mu_2 + a_i$ and $m_3^- = r$.

$m_4 = 1,$

From the Routh-Hurwitz Theorem applied to the fourth order polynomial in the characteristic equation since $(m_1 m_2 m_3 > m_1^2 m_4 + m_0 m_3^2)$ the eigenvalues of the jacobian matrix have negative real parts.

So, the system is stable since the condition of the of the parameter H_{E^*} is fulfilled, we set the following parameter to discuss this stability :

$$H_{E^*} = \frac{m_0^- m_3^2 + \sum\limits_{(*_i \in \{-,+\}; \prod_{i=1}^3 *_i = +)} (\prod_{i=1}^3 m_i^{*_i})}{m_1^2 + m_0^+ m_3^2 + \sum\limits_{(*_i \in \{-,+\}; \prod_{i=1}^3 *_i = -)} (\prod_{i=1}^3 m_i^{*_i})}$$

So, if $H_{E^*} > 1$ the equilibrium point E_i is stable, else it is unstable.

Now, we can easily state the following result:

Theorem 1. *The point of equilibrium E^* is stable when $H_{E^*} > 1$.*

3.1. Initial conditions and parameters. After properly justified our formulation of the model and discussing the equilibrium. In this section, we will study the effect of immunotherapy and virotherapy separately and jointly with numerical simulations. The variables, their descriptions and the intial conditions are given in Table 1.

Variable	Description	Initial condition
x	Effector	x_0
y	Tumor	y_0
z	IL-2	z_0
v	Virus	v_0

TABLE 1. The model variables descriptions and initial conditions.

For our numerical simulations, we will use the parameters given in Table 2

Parameter	Description	Value	Source
μ_1	Multiplicative inverse of the natural lifespan for effector cells	3.00×10^{-2}	[14, 16]
μ_2	Multiplicative inverse of the natural lifespan for IL-2	1.00×10^{1}	[14, 16]
μ_3	Multiplicative inverse of the natural lifespan for virus	8.00×10^{-3}	[6]
p_1	Proliferation rate of effector cells	1.25×10^{-1}	[14, 16]
p_2	Proliferation rate of tumor	1.00	[14, 16]
p_3	Proliferation rate of IL-2	5.00	[14, 16]
g_1	Threshold for proliferation of effector cells stimulated by IL-2	2.00×10^{5}	[14, 16]
g_2	Threshold for cancer removal	1.00×10^{5}	[14, 16]
g_3	Threshold for production of IL-2 due to cancer cells and effector cells	1.00×10^{3}	[14, 16]
s_1	External source of effector cells	-	
s_2	External source of IL-2	-	
s_3	External source of virus	-	
r	Logistic growth rate of tumour	1.80×10^{-1}	[14, 16]
b	Multiplicative inverse of the tumour's carrying capacity	1.00×10^{-9}	[14, 16]
c	Antigenicity of tumour	5.00×10^{-2}	[14, 16]
β	Infection rate of tumor	1.00×10^{-1}	[6]
α	Elimination rate of virus due to tumor infection	5.00×10^{-1}	[6]

TABLE 2. The model parameters, their descriptions and values.

3.2. Immunotherapy treatment. This subsection is devoted to discuss the existence and the stability analysis of the disease-free equilibrium and the endemic equilibrium points, in case of immunotherapy treatment with ACT and IL-2. Also, we will give numerical simulations for each case.

3.2.1. *Case of adoptive cell immunotherapy treatment.* In this part, we will consider the case of of adoptive cell immunotherapy treatment which means that $s_1 > 0$, $s_2 = 0$ and $s_3 = 0$.

Proposition 3. *The following parameters:*
$T_1 = \dfrac{p_1}{\mu_1}$, $R_1 = \frac{cp_3\mu_3^2}{\alpha\beta g_1\mu_1\mu_2(\mu_3+\alpha\beta g_3)}$, $E_1 = \frac{cp_2\mu_3}{\mu_1 r(\mu_3+\alpha\beta g_2)}$, $E_2 = \frac{b\mu_3}{\alpha\beta}$, $E_3 = \frac{c\mu_3}{\alpha\beta}$ *and* $S_1 = 1+\dfrac{s_1}{E_3}$
will allow to discuss the possibility of having equilibrium points.

Hence, we have the following results:

(1) The disease-free equilibrium $E_{A_0}(\frac{s_1}{\mu_1},0,0,0)$ *always exists.*

(2) *If* $T_1 = 1$ *and* $R_1S_1 < 1$ *and* $E_2 + \dfrac{E_1S_1}{1-R_1S_1} < 1$, *one equilibrium point* $E_{A_1}(x_1, y_1, z_1, v_1)$ *exists.*

(3) *If* $T_1 < 1$ *and* $E_2 + \dfrac{E_1}{2R_1(T_1-1)}(1-R_1S_1 - \sqrt{(R_1S_1+1)^2 - 4T_1R_1S_1}) < 1$, *one equilibrium point* $E_{A_2}(x_2, y_2, z_2, v_2)$ *exists.*

(4) *If* $T_1 > 1$ *and* $R_1S_1 < (\sqrt{T_1} - \sqrt{T_1-1})^2$ *and* $E_2 + \dfrac{E_1}{2R_1(T_1-1)}(1-R_1S_1 + \sqrt{(R_1S_1+1)^2 - 4T_1R_1S_1}) < 1$, *two equilibrium points* $E_{A_2}(x_2, y_2, z_2, v_2)$ *and* $E_{A_3}(x_3, y_3, z_3, v_3)$ *exist.*

Proof. First case, when $y^* = 0$ we get $E_{A_0}(\frac{s_1}{\mu_1}, 0, 0, 0)$.

Other case, when $y^* \neq 0$, we can get $E_{A_i}(x_i, y_i, z_i, v_i), i \in \{1,2,3\}$ with: $y_i = \frac{\mu_3}{\alpha\beta}$.

And x_i is positive solution of the following equation:

$$A_1x^2 + B_1x + C_1 = 0 \tag{3}$$

With:

$A_1 = \mu_1(T_1 - 1) = A,$

$B_1 = E_3(1 - \dfrac{1}{R_1}) + s_1 = B + (S_1 - 1)E_3,$

$C_1 = \dfrac{E_3^2}{\mu_1 R_1}S_1 = CS_1.$

Second case, if $T_1 = 1$ the equation (3) becomes a first order equation and if $R_1S_1 < 1$ we get a positive solution of component x:

$x_1 = \dfrac{E_3S_1}{\mu_1(1-R_1S_1)}.$

And if $E_2 + \dfrac{E_1S_1}{1-R_1S_1} < 1$ we get a positive solution of component v:

$v_1 = \dfrac{r}{\beta}\Big(1 - E_2 - \dfrac{E_1S_1}{1-R_1S_1}\Big),$

$z_1 = \dfrac{g_1R_1S_1}{1-R_1S_1}.$

Third case, if $T_1 < 1$ the equation (3) has just one positive solution x:

$x_2 = \dfrac{E_3}{2R_1\mu_1(T_1-1)}\Big(1 - R_1S_1 - \sqrt{(1+R_1S_1)^2 - 4T_1R_1S_1}\Big).$

And if $E_2 + \dfrac{E_1}{2R_1(T_1-1)}\Big(1 - R_1S_1 - \sqrt{(1+R_1S_1)^2 - 4T_1R_1S_1}\Big) < 1$ we get a position solution of v:

$v_2 = \dfrac{r}{\beta}(1 - E_2 - \dfrac{E_1}{2R_1(T_1-1)}\Big(1 - R_1S_1 - \sqrt{(1+R_1S_1)^2 - 4T_1R_1S_1}\Big),$

$$z_2 = \frac{g_1}{2(T_1-1)}\Big(1-R_1S_1-\sqrt{(1+R_1S_1)^2-4T_1R_1S_1}\Big).$$

Fourth cases, if $T_1 > 1$ and $R_1S_1 < (\sqrt{T_1}-\sqrt{T_1-1})^2$ the equation (3) has just two positive solutions x:

$$x_2 = \frac{E_3}{2\mu_1R_1(T_1-1)}\Big(1-R_1S_1-\sqrt{(1+R_1S_1)^2-4T_1R_1S_1}\Big),$$

and

$$x_3 = \frac{E_3}{2\mu_1R_1(T_1-1)}\Big(1-R_1S_1+\sqrt{(1+R_1S_1)^2-4T_1R_1S_1}\Big).$$

And if $E_2+\dfrac{E_1}{2R_1(T_1-1)}\Big(1-R_1S_1+\sqrt{(1+R_1S_1)^2-4T_1R_1S_1}\Big) < 1$ we get a positive component of v, for $i \in \{2,3\}$:

$$v_i = \frac{r}{\beta}(1-E_2-\frac{E_1}{2R_1(T_1-1)}\Big(1-R_1S_1-(-1)^i\sqrt{(1+R_1S_1)^2-4T_1R_1S_1}\Big),$$

$$z_i = \frac{g_1}{2(T_1-1)}\Big(1-R_1S_1-(-1)^i\sqrt{(1+R_1S_1)^2-4T_1R_1S_1}\Big).$$

In the case of treatment with injection of adoptive (effector) cells, we can steady that state, if the external source is more than the minimum value s_{min_1}, and that is demonstrated at the following theorem. □

Theorem 2. *The disease-free equilibrium in the case of treatment with only effector cell's external source $E_{A_0}(\frac{s_1}{\mu_1},0,0,0)$ is stable when $s_1 > s_{min_1}$, with $s_{min_1} = \dfrac{rg_2\mu_1}{p_2}$.*

Proof. The Jacobian matrix for the point E_{A_0} is the following:

$$J_{E_{A_0}} = \begin{pmatrix} -\mu_1 & c & \frac{p_1s_1}{g_1\mu 1} & 0 \\ 0 & r-\frac{p_2s_1}{g_2\mu 1} & 0 & 0 \\ 0 & \frac{p_3s_1}{g_3\mu 1} & -\mu_2 & 0 \\ 0 & 0 & 0 & -\mu_3 \end{pmatrix}$$

The eigenvalues are $-\mu_1,-\mu_2,-\mu_3$ and $r-\dfrac{p_2s_1}{g_2\mu_1}$, if $s_1 > s_{min_1}$, they are all negative, then we have the stability . □

Form figure 2, we can observe that the proliferation of tumor cells for different values of the external source s_1. First, when we increase the ACT dose the amount of the cancer cells is reduced significantly. In addition, with high value of ACT we observe the damping of the resulting oscillations. This confirms the important role of the first kind of immunotherapy in reducing the cancer cells proliferation.

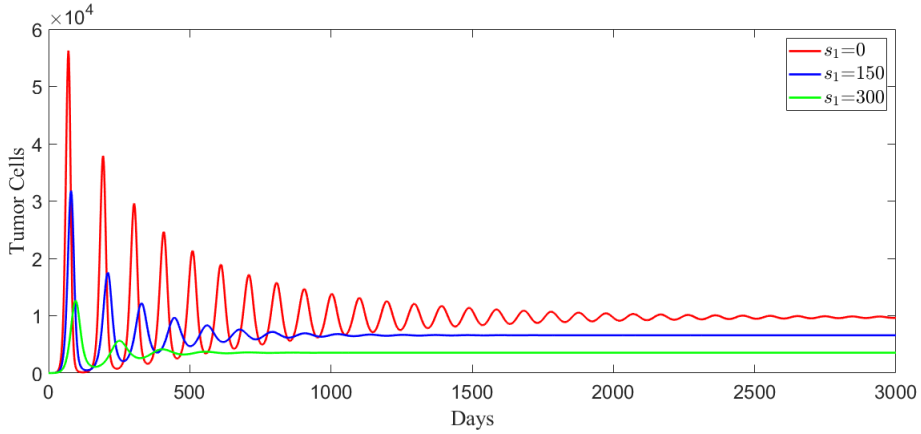

FIGURE 2. Numerical simulation results of tumor in case of ACT only with different doses of external source s_1.

Theorem 3. *The endemic equilibrium points in the case of treatment with only effector cell's external source $E_{A_i}, i \in \{1,2,3\}$ are stable when $H_{E_{A_i}} > 1$.*

Proof. See Theorem 1. □

3.2.2. *Case of Interleukin-2 treatment.* In this part, we will consider the case of IL-2 immunotherapy treatment which means that $s_1 = 0$, $s_2 > 0$ and $s_3 = 0$ and we will discuss the existence and the stability of the equilibrium points in the following proposition and theorems:

Proposition 4. *The following parameters: T_1, R_1, E_1, E_2, E_3 recently declared and $S_2 = 1 + \frac{s_2}{g_1 \mu_2}$ will allow to discuss the possibility of having equilibrium points. Hence, we have the following results:*

(1) The disease-free equilibrium $E_{I_0}(0,0,\frac{s_2}{\mu_2},0)$ always exists.

(2) If $T_1 = 1$ and $R_1 < 1$ and $E_2 + \frac{E_1 S_2}{1-R_1} < 1$, one equilibrium point $E_{I_1}(x_1,y_1,z_1,v_1)$ exists.

(3) If $T_1 < 1$ and
$$E_2 + \frac{E_1}{2R_1(T_1-1)}(1-R_1-(S_2-1)(T_1-1)-\sqrt{(R_1+(S_2(T_1-1)-T_1))^2-4(T_1-1)S_2R_1}) < 1,$$
one equilibrium point $E_{I_2}(x_2,y_2,z_2,v_2)$ exists.

(4) If $T_1 > 1$ and $R_1 < (\sqrt{T_1} - \sqrt{S_2(T_1-1)})^2$ and
$$E_2 + \frac{E_1}{2R_1(T_1-1)}(1-R_1-(S_2-1)(T_1-1)+\sqrt{(R_1+(S_2(T_1-1)-T_1))^2-4(T_1-1)S_2R_1}) < 1,$$
two equilibrium points $E_{I_2}(x_2,y_2,z_2,v_2)$ and $E_{I_3}(x_3,y_3,z_3,v_3)$ exist.

Proof. First case, when $y^* = 0$ we get $E_{I_0}(0,0,\frac{s_2}{\mu_2},0)$.

Other case, when $y^* \neq 0$, we can get $E_{I_i}(x_i,y_i,z_i,v_i), i \in \{1,2,3\}$ with: $y_i = \frac{\mu_3}{\alpha\beta}$.

And x_i is positive solution of the following equation:

$$A_2x^2 + B_2x + C_2 = 0 \tag{4}$$

With:

$A_2 = \mu_1(T_1 - 1) = A$,

$B_2 = B + (S_2 - 1)(T_1 - 1)\frac{E_3}{R_1}$,

$C_2 = CS_2$.

Second case, if $T_1 = 1$, the equation (4) becomes a first order equation.

And if $R_1 < 1$ we get a positive solution of component x:

$x_1 = \frac{E_3S_2}{\mu_1(1-R_1)}$.

And if $E_2 + \frac{E_1S_2}{1-R_1} < 1$ we get a positive solution of component v:

$v_1 = \frac{r}{\beta}(1 - E_2 - \frac{E_1S_2}{1-R_1})$,

$z_1 = g_1(\frac{R_1S_2}{1-R_1} + S_2 - 1)$.

Third case, if $T_1 < 1$ the equation (4) has just one positive solution x:

$x_2 = \frac{E_3}{2\mu_1R_1(T_1-1)}(1 - R_1 - (S_2-1)(T_1-1) - \sqrt{(S_2(T_1-1)+T_1-R_1)^2 - 4T_1S_2(T_1-1)})$.

And if $E_2 + \frac{E_1}{2R_1(T_1-1)}(1 - R_1 - (S_2-1)(T_1-1) - \sqrt{(S_2(T_1-1)+T_1-R_1)^2 - 4T_1S_2(T_1-1)}) < 1$ we get a position solution of v:

$v_2 = \frac{r}{\beta}\big(1 - E_2 - \frac{E_1}{2R_1(T_1-1)}(1 - R_1 - (S_2-1)(T_1-1) - \sqrt{(S_2(T_1-1)+T_1-R_1)^2 - 4T_1S_2(T_1-1)})\big)$,

$z_2 = \frac{g_1}{2(T_1-1)}\big(1 - R_1 + (S_2-1)(T_1-1) - \sqrt{(S_2(T_1-1)+T_1-R_1)^2 - 4T_1S_2(T_1-1)}\big)$.

Fourth cases, if $T_1 > 1$ and $R_1 < \big(\sqrt{T_1} - \sqrt{S_2(T_1-1)}\big)^2$ we get two positive solutions for equation (4):

$x_2 = \frac{E_3}{2\mu_1R_1(T_1-1)}(1 - R_1 - (S_2-1)(T_1-1) - \sqrt{(S_2(T_1-1)+T_1-R_1)^2 - 4T_1S_2(T_1-1)})$,

and

$x_3 = \frac{E_3}{2\mu_1R_1(T_1-1)}(1 - R_1 - (S_2-1)(T_1-1) + \sqrt{(S_2(T_1-1)+T_1-R_1)^2 - 4T_1S_2(T_1-1)})$.

And if $E_2 + \frac{E_1}{2R_1(T_1-1)}(1 - R_1 - (S_2 - 1)(T_1 - 1) + \sqrt{(S_2(T_1-1)+T_1-R_1)^2 - 4T_1S_2(T_1-1)}) < 1$ we get a position solution of v:

$v_i = \frac{r}{\beta}\big(1 - E_2 - \frac{E_1}{2R_1(T_1-1)}(1 - R_1 - (S_2 - 1)(T_1 - 1) - (-1)^i\sqrt{(S_2(T_1-1)+T_1-R_1)^2 - 4T_1S_2(T_1-1)})\big)$,

$z_i = \frac{g_1}{2(T_1-1)}\big(1-R_1+(S_2-1)(T_1-1)-(-1)^i\sqrt{(S_2(T_1-1)+T_1-R_1)^2-4T_1S_2(T_1-1)}\big)$.

Any injection of IL-2 still useless, because it is not possible for immune system to eliminate the cancer cells even if with external source of IL-2, and that is proved by the following theorem .

Theorem 4. *The disease-free equilibrium in the case of IL-2 therapy treatment only* $E_{I_0}(0,0,\frac{s_2}{\mu_2},0)$ *is always unstable.*

Proof. The Jacobian matrix for the point E_{I_0} is the following:

$$J_{E_{I_0}} = \begin{pmatrix} -\mu_1 + \frac{p_1 s2}{g_1\mu_2+s_2} & c & 0 & 0 \\ 0 & r & 0 & 0 \\ 0 & 0 & -\mu_2 & 0 \\ 0 & 0 & 0 & -\mu_3 \end{pmatrix}$$

The eigenvalues are $-\mu_1 + \frac{p_1 s2}{g_1\mu_2+s_2}, -\mu_2, -\mu_3$ and r, they are not all negative.

So E_{I_0} is unstable. □

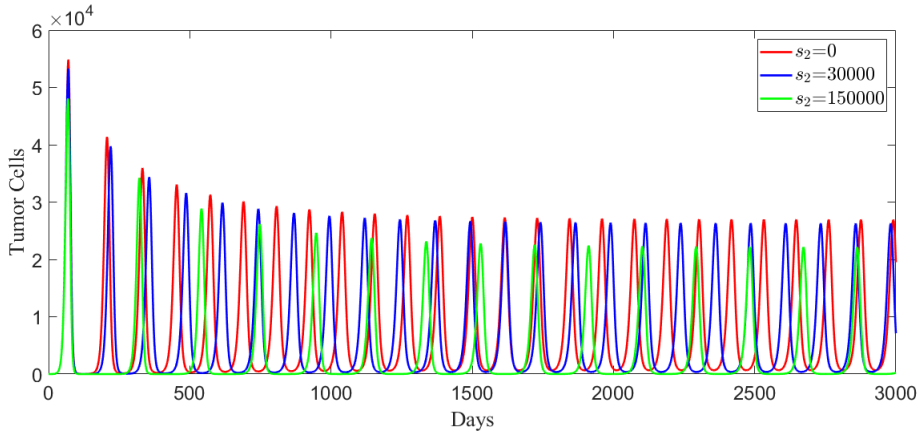

FIGURE 3. Numerical simulation results in case of IL-2 treatment only with different doses of external source s_2.

We can obtain from figure 3 the proliferation of tumor cells for different values of the external source s_2. First, when we rise the IL-2 dose the amount of the cancer cells is reduced significantly. With high value of IL-2 we can observe also the damping of the resulting oscillations but not as well as it is at figure 2 with ACT. In addition, we notice a time lag in the oscillations of tumor cells. With this we confirm the important role of the second kind of immunotherapy in reducing the cancer cells proliferation.

Theorem 5. *The endemic equilibrium points in the case of IL-2 therapy treatment only* $E_{I_i}, i \in \{1,2,3\}$ *are stable when* $H_{E_{I_i}} > 1$.

Proof. See Theorem 1. □

3.3. Virotherapy treatment. In this subsection of virotherapy treatment, we will discuss the existence and the stability of the disease-free equilibrium point when $s_1 = 0$, $s_2 = 0$ and $s_3 > 0$.

Theorem 6. *In case of virothepary only, the disease-free equilibrium point* $E_{V_{03}}(0,0,0,\frac{s_3}{\mu_3})$ *always exist and it is stable when* $s_3 > s_{min_3}$, *with* $s_{min_3} = \dfrac{r\mu_3}{\beta}$.

Proof. To prove the existence of DFE, we replace $y^* = 0$ at (2). We get in evidence $E_{V_{03}}(0,0,0,\frac{s_3}{\mu_3})$.

The Jacobian matrix for the point $E_{V_{03}}$ is the following:

$$J_{E_{V_{03}}} = \begin{pmatrix} -\mu_1 & c & 0 & 0 \\ 0 & r-\beta\frac{s_3}{\mu_3} & 0 & 0 \\ 0 & 0 & -\mu_2 & 0 \\ 0 & \alpha\beta\frac{s_3}{\mu_3} & 0 & -\mu_3 \end{pmatrix}$$

The eigenvalues are $-\mu_1, -\mu_2, -\mu_3$ and $r-\beta\dfrac{s_3}{\mu_3}$, they are all negative, if $s_3 > s_{min_3}$, then we have the stability. □

Figure 4 gives also the behavior of tumor cells proliferation with different values of the external source s_3. We can observe that rising the dose of that external source can eliminate cancer in less then one month [3]. In addition, we can also observe that time of illness can be reduced with upper value. Form that and comparing with figures 2 and figure 3, we confirm the very important role of OVT in reducing the cancer cells proliferation and time of illness.

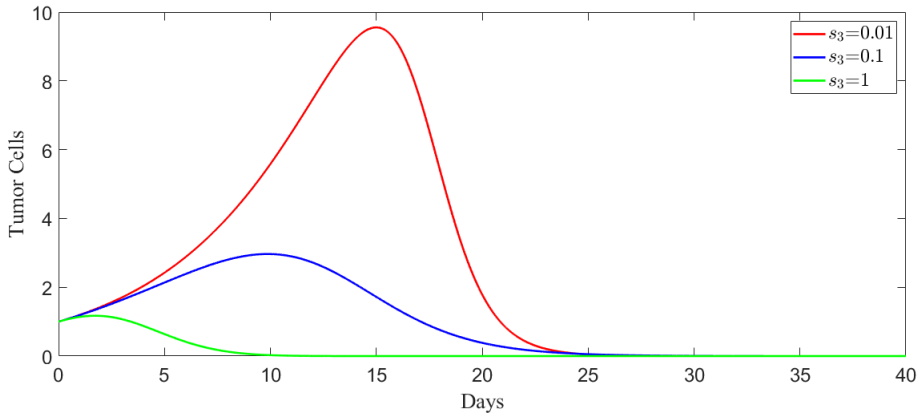

FIGURE 4. Numerical simulation results of tumor in case of OVT only with different doses of external source s_3

3.4. Combined treatment. In this subsection, the existence and the stability of the equilibrium points in case of combined treatment are discussed in the following propositions and theorems with their numerical simulations.

3.4.1. *Case of adoptive cell and IL-2 immunotherapy treatment.* In this part, we will consider the case of adoptive cell and IL-2 immunotherapy treatment which means that $s_1 > 0$, $s_2 > 0$ and $s_3 = 0$.

Proposition 5. *The parameters T_1 , R_1 , E_1 , E_2 , E_3, S_1 and S_2 previously declared will allow to discuss the possibility of having equilibrium points. Hence, we have the following results:*

(1) The disease-free equilibrium $E_{C_0}\big(\frac{s_1}{\mu_1 - \frac{p_1 s_2}{g_1\mu_2+s_2}}, 0, \frac{s_2}{\mu_2}, 0\big)$ *exists if :*

$T_1 = 1$ *or* $T_1 < 1$ *or* ($T_1 > 1$ *and* $s_2 < s_{max_2}$ *with* $s_{max_2} = \frac{g_1\mu_2}{T_1 - 1}$).

(2) If $T_1 = 1$ *and* $R_1 < 1$ *and* $E_2 + \frac{E_1 S_2}{1-R_1} < 1$, *one equilibrium point* $E_{C_1}(x_1, y_1, z_1, v_1)$ *exists.*

(3) If $T_1 < 1$ *and*

$E_2 + \frac{E_1}{2R_1(T_1-1)}(1 - S_1R_1 - (S_2 - 1)(T_1 - 1) - \sqrt{(S_1R_1 + (S_2(T_1-1) - T_1))^2 - 4(T_1-1)S_2T_1}) < 1$, *one equilibrium point* $E_{C_2}(x_2, y_2, z_2, v_2)$ *exists.*

(4) If $T_1 > 1$ *and* $S_1R_1 < (\sqrt{T_1} - \sqrt{S_2(T_1-1)})^2$ *and*

$E_2 + \frac{E_1}{2R_1(T_1-1)}(1 - S_1R_1 - (S_2 - 1)(T_1 - 1) +$

$\sqrt{(S_1R_1+(S_2(T_1-1)-T_1))^2-4(T_1-1)S_2T_1)} < 1$, *two equilibrium points* $E_{C_2}(x_2,y_2,z_2,v_2)$ *and* $E_{C_3}(x_3,y_3,z_3,v_3)$ *exist.*

Proof. First case, when $y=0$, if $T_1=1$ or $T_1<1$ or ($T_1>1$ and $s_2<\frac{g_1\mu_2}{T_1-1}$) we obtain a positive x component and we get $E_{C_0}(\frac{s_1}{\mu_1-\frac{p_1s_2}{g_1\mu_2+s_2}},0,\frac{s_2}{\mu_2},0)$.

Other case, when $y\neq 0$, we can get $E_{C_i}(x_i,y_i,z_i,v_i), i\in\{1,2,3\}$ with:$y_i=\frac{\mu_3}{\alpha\beta}$.

And x_i is positive solution of the following equation:

$$A_3x^2+B_3x+C_3=0 \tag{5}$$

With:

$A_3=\mu_1(T_1-1)=A$,

$B_3=B+(S_1-1)E_3+(S_2-1)(T_1-1)\frac{E_3}{R_1}$,

$C_3=CS_1S_2$.

Second case, if $T_1=1$ the equation (5) becomes a first order equation.

And if $S_1R_1<1$ we get a positive solution of component x:

$x_1=\frac{E_3S_1S_2}{\mu_1(1-S_1R_1)}$.

And if $E_2+\frac{E_1S_1S_2}{1-S_1R_1}<1$ we get a positive solution of component v:

$v_1=\frac{r}{\beta}\big(1-E_2-\frac{E_1S_1S_2}{1-S_1R_1}\big)$,

$z_1=g_1\big(\frac{R_1S_1S_2}{1-S_1R_1}+S_2-1\big)$.

Third case, if $T_1<1$ the equation (5) has just one positive solution x:

$x_2=\frac{E_3}{2R_1\mu_1(T_1-1)}(1-R_1S_1-(S_2-1)(T_1-1)-\sqrt{(S_2(T_1-1)+T_1-R_1S_1)^2-4T_1S_2(T_1-1)})$.

And if $E_2+\frac{E_1}{2R_1(T_1-1)}(1-S_1R_1-(S_2-1)(T_1-1)-\sqrt{((S_2(T_1-1)+T_1-S_1R_1))^2-4T_1S_2(T_1-1))}<1$ we get a position solution of v:

$v_2=\frac{r}{\beta}[1-E_2-\frac{E_1}{2R_1(T_1-1)}(1-S_1R_1-(S_2-1)(T_1-1)-\sqrt{((S_2(T_1-1)+T_1-S_1R_1))^2-4T_1S_2(T_1-1))}]$,

$z_2=\frac{g_1}{2(T_1-1)}[1-S_1R_1+(S_2-1)(T_1-1)-\sqrt{((S_2(T_1-1)+T_1-S_1R_1))^2-4T_1S_2(T_1-1))}]$.

Fourth cases, if $T_1>1$ and $S_1R_1<(\sqrt{T_1}-\sqrt{S_2(T_1-1)})^2$ we get two positive solutions for equation (5):

$$x_2 = \frac{E_3}{2\mu_1 R_1(T_1-1)}(1-S_1R_1-(S_2-1)(T_1-1)-\sqrt{((S_2(T_1-1)+T_1-S_1R_1))^2-4T_1S_2(T_1-1)}),$$
and
$$x_3 = \frac{E_3}{2\mu_1 R_1(T_1-1)}(1-S_1R_1-(S_2-1)(T_1-1)+\sqrt{((S_2(T_1-1)+T_1-S_1R_1))^2-4T_1S_2(T_1-1)}).$$
And if $E_2 + \frac{E_1}{2R_1(T_1-1)}(1 - S_1R_1 - (S_2 - 1)(T_1 - 1) + \sqrt{((S_2(T_1-1)+T_1-S_1R_1))^2-4T_1S_2(T_1-1)}) < 1$ we get a position solution of v:
$$v_i = \frac{r}{\beta}\big(1 - E_2 - \frac{E_1}{2R_1(T_1-1)}(1 - S_1R_1 - (S_2 - 1)(T_1 - 1) - (-1)^i\sqrt{((S_2(T_1-1)+T_1-S_1R_1))^2-4T_1S_2(T_1-1)})\big),$$
$$z_i = \frac{g_1}{2(T_1-1)}\big(1 - S_1R_1 + (S_2-1)(T_1-1) - (-1)^i\sqrt{((S_2(T_1-1)+T_1-S_1R_1))^2-4T_1S_2(T_1-1)})\big).$$
□

Theorem 7. *The disease-free equilibrium in the case of immunotherapy treatment* $E_{C_0}(\frac{s_1}{\mu_1-\frac{p_1s_2}{g_1\mu_2+s_2}},0,\frac{s_2}{\mu_2},0)$ *is stable when it exists and when* $1 < \frac{T_1s_2}{(T_1-1)s_{max_2}+s_2} + \frac{s_1}{s_{min_1}}$.

Proof. The Jacobian matrix for the point E_{C_0} is the following:

$$J_{E_{C_0}} = \begin{pmatrix} -\mu_1 + \frac{p_1 s2}{g_1\mu_2+s_2} & c & \frac{p_1g_1}{g_1+\frac{s_2}{\mu_2}}\frac{s_1}{\mu_1-\frac{p_1s_2}{g_1\mu_2+s_2}} & 0 \\ 0 & r-\frac{p_2}{g_2}\frac{s_1}{\mu_1-\frac{p_1s_2}{g_1\mu_2+s_2}} & 0 & 0 \\ 0 & \frac{p_3}{g_3}\frac{s_1}{\mu_1-\frac{p_1s_2}{g_1\mu_2+s_2}} & -\mu_2 & 0 \\ 0 & 0 & 0 & -\mu_3 \end{pmatrix}$$

The eigenvalues are $-\mu_2, -\mu_3, -\mu_1 + \frac{p_1 s2}{g_1\mu_2+s_2}$ and $r-\frac{p_2}{g_2}\frac{s_1}{\mu_1-\frac{p_1s_2}{g_1\mu_2+s_2}}$, they are negative when the fourth one is, namely $1 < \frac{p_2}{rg_2}\frac{s_1}{\mu_1-\frac{p_1s_2}{g_1\mu_2+s_2}}$.
So E_{C_0} is stable when the condition is verified. □

Figure 5 expresses the proliferation of tumor cells for different values of the external source s_1 and s_2. First, when we increase the ACT dose the amount of the cancer cells is reduced and the damping of the oscillations decrease in time. However, when we increase the IL-2 dose the oscillations slow significantly and make more time to waver. We can observe that the high values of s_1 and s_2 can eliminate cancer. That can confirm the impact of combining immunotherapy treatment to fight cancer growth.

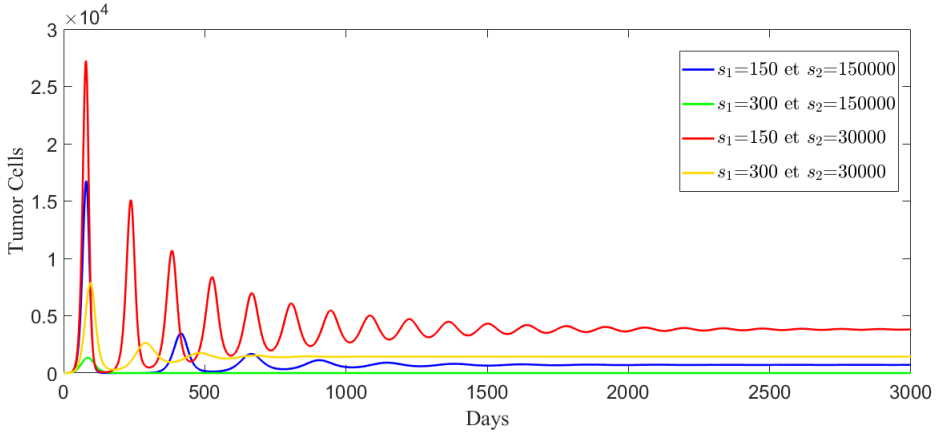

FIGURE 5. Numerical simulation results of tumor in case of combined ACT and IL-2 treatment with different doses of external sources s_1 and s_2

Theorem 8. *The endemic equilibrium points in the case of immunotherapy treatment* $E_{C_i}, i \in \{1,2,3\}$ *are stable when* $H_{E_{C_i}} > 1$.

Proof. See Theorem 1. □

3.4.2. *Case of adoptive cell immunotherapy and virotherapy treatment.* In this part, we will consider the case of adoptive cell immunotherapy and virotherapy which means that $s_1 > 0$, $s_2 = 0$ ans $s_3 > 0$.

Theorem 9. *In case of combined treatment of adoptive cell immunotherapy and virothepary, the equilibrium point* $E_{V_{013}}(\frac{s_1}{\mu_1}, 0, 0, \frac{s_3}{\mu_3})$ *always exist and it is stable when* $\dfrac{s_1}{s_{min_1}} + \dfrac{s_3}{s_{min_3}} > 1$.

Proof. To prove the existence of DFE, we replace $y^* = 0$ at (2). We get in evidence $E_{V_{013}}(\frac{s_1}{\mu_1}, 0, 0, \frac{s_3}{\mu_3})$.

The Jacobian matrix for the point $E_{V_{013}}$ is the following:

$$J_{E_{V_{013}}} = \begin{pmatrix} -\mu_1 & c & \frac{s_1 p_1 g_1 \mu_3^2}{\mu_1(\mu_3 g_1 + s_3)^2} & 0 \\ 0 & r - \beta\frac{s_3}{\mu_3} - \frac{p_2 s_1}{g_2 \mu_1} & 0 & 0 \\ 0 & \frac{p_3 s_1}{g_3 \mu_1} & -\mu_2 & 0 \\ 0 & \alpha\beta\frac{s_3}{\mu_3} & 0 & -\mu_3 \end{pmatrix}$$

We pose: $s_{min_1} = \dfrac{r g_2 \mu_1}{p_2}$.

The eigenvalues are $-\mu_1, -\mu_2, -\mu_3$ and $r(1-\frac{\beta}{r\mu_3}s_3-\frac{p_2}{rg_2\mu_1}s_1)$, they are all negative, if $\frac{s_1}{s_{min_1}}+\frac{s_3}{s_{min_3}}>1$, then we have the stability. □

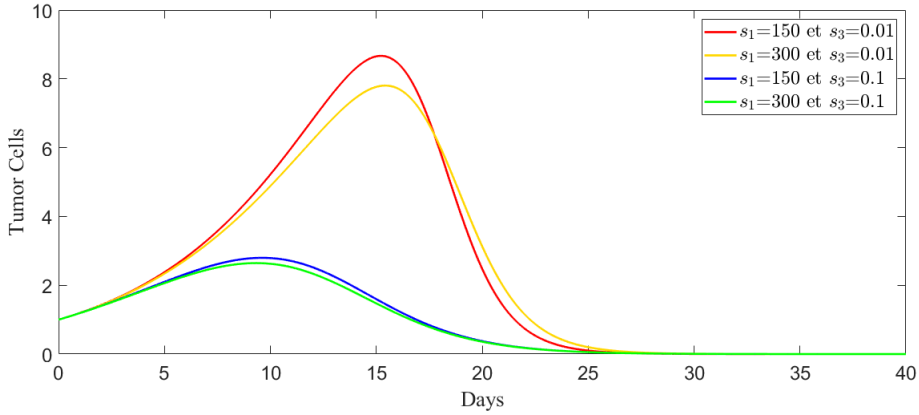

FIGURE 6. Numerical simulation results of tumor in case of combined ACT and OVT with different doses of external sources s_1 and s_3

Form figure 6, we can observe that the proliferation of tumor cells for different values of the external source s_1 and s_2. First, when we rise ACT dose the proliferation of tumor cells decrease softly with virotheapy and the illness make more time to be attenuated. However, when we increase OVT dose the proliferation subsides much more and the time for cancer development is shortened. That confirm the significant role of combined treatment under ACT and OVT.

3.4.3. *Case of IL-2 immunotherapy and virotherapy treatment.* In this part, we will consider the case of IL-2 immunotherapy and virotherapy treatment which means that $s_1 = 0$, $s_2 > 0$ and $s_3 > 0$.

Theorem 10. *In case of combined treatment of IL-2 immunotherapy and virothepary, the equilibrium point* $E_{V_{023}}(0,0,\frac{s_2}{\mu_2},\frac{s_3}{\mu_3})$ *always exist and it is stable when:* $(s_3 > s_{min_3})$ *and* $((T_1 = 1)$ *or* $(T_1 < 1)$ *or* $(T_1 > 1$ *and* $s_2 < s_{max_2}))$.

Proof. To prove the existence of DFE, we replace $y^* = 0$ at (2). We get in evidence $E_{V_{023}}(0,0,\frac{s_2}{\mu_2},\frac{s_3}{\mu_3})$.

The Jacobian matrix for the point $E_{V_{023}}$ is the following:

$$J_{E_{V_{023}}} = \begin{pmatrix} -\mu_1 + \frac{p_1 s_2}{g_1\mu_2+s_2} & c & 0 & 0 \\ 0 & r-\beta\frac{s_3}{\mu_3} & 0 & 0 \\ 0 & 0 & -\mu_2 & 0 \\ 0 & \alpha\beta\frac{s_3}{\mu_3} & 0 & -\mu_3 \end{pmatrix}$$

The eigenvalues are $-\mu_1 + \dfrac{p_1 s_2}{g_1\mu_2+s_2}, -\mu_2, -\mu_3$ and $r-\beta\dfrac{s_3}{\mu_3}$, they are all negative, if $r < \beta\dfrac{s_3}{\mu_3}$ and $\mu_1 > \dfrac{p_1 s_2}{g_1\mu_2+s_2}$, then we have the stability. □

Case of adoptive cell, IL-2 immunotherapy and virotherapy treatment

In this last part, we will consider the case of combined treatment with all therapies which means that $s_1 > 0$, $s_2 > 0$ and $s_3 > 0$.

Proposition 6. *The disease-free equilibrium points* $E_{V_{0123}}(\dfrac{s_1}{\mu_1 - \frac{p_1 s_2}{g_1\mu_2+s_2}}, 0, \dfrac{s_2}{\mu_2}, \dfrac{s_3}{\mu_3})$ *with adoptive cell, IL-2 immunotherapy and the oncolytic virus external sources exist when* $(T_1 = 1)$ *or* $(T_1 < 1)$ *or* $(T_1 > 1$ *and* $s_2 < s_{max_2})$.

Proof. To prove the existence of DFE, we replace $y = 0$ at (2) and we get: $z = \frac{s_2}{\mu_2}$, $v = \frac{s_3}{\mu_3}$ and if $T_1 = 1$ or $T_1 < 1$ or $(T_1 > 1$ and $s_2 < \dfrac{g_1\mu_2}{T_1 - 1})$ we obtain a positive x component. We get $E_{V_{0123}}(\dfrac{s_1}{\mu_1 - \frac{p_1 s_2}{g_1\mu_2+s_2}}, 0, \dfrac{s_2}{\mu_2}, \dfrac{s_3}{\mu_3})$. □

Theorem 11. *The equilibrium point* $E_{V_{0123}}(\dfrac{s_1}{\mu_1 - \frac{p_1 s_2}{g_1\mu_2+s_2}}, 0, \dfrac{s_2}{\mu_2}, \dfrac{s_3}{\mu_3})$ *is stable when it is exist and* $\dfrac{s_1}{s_{min_1}} + \dfrac{T_1 s_2}{(T_1-1)(s_{max_2}-s_2)}\dfrac{s_1}{s_{min_1}} + \dfrac{s_3}{s_{min_3}} > 1.$

Proof. The Jacobian matrix for the point $E_{V_{0123}}$ is the following:

$$J_{E_{V_{0123}}} = \begin{pmatrix} -\mu_1 + \frac{p_1 s_2}{\mu_2 g_2+s_2} & c & \frac{s_1 p_1 g_1 \mu_3^2}{\mu_1(\mu_3 g_1+s_3)^2}(\frac{S_2}{1-(S_2-1)(T_1-1)}) & 0 \\ 0 & r-\beta\frac{s_3}{\mu_3} - \frac{p_2 s_1}{g_2\mu_1}(\frac{S_2}{1-(S_2-1)(T_1-1)}) & 0 & 0 \\ 0 & \frac{p_3 s_1}{g_3\mu_1}(\frac{S_2}{1-(S_2-1)(T_1-1)}) & -\mu_2 & 0 \\ 0 & \alpha\beta\frac{s_3}{\mu_3} & 0 & -\mu_3 \end{pmatrix}$$

The eigenvalues are $-\mu_1 + \frac{p_1 s_2}{\mu_2 g_2 + s_2}, -\mu_2, -\mu_3$ and $r - \beta\frac{s_3}{\mu_3} - \frac{p_2 s_1}{g_2 \mu_1}(\frac{S_2}{1-(S_2-1)(T_1-1)})$, they are all negative, if $-\mu_1 > \frac{p_1 s_2}{\mu_2 g_2 + s_2}$ and $r < \beta\frac{s_3}{\mu_3} - \frac{p_2 s_1}{g_2 \mu_1}(\frac{S_2}{1-(S_2-1)(T_1-1)})$, then we have the stability. □

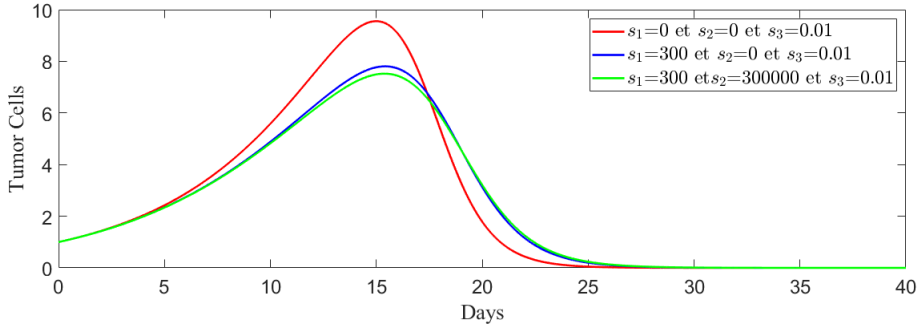

FIGURE 7. Numerical simulation results of tumor in case of combined ACT, IL-2 treatment and OVT with different doses of external sources s_1, s_2 and s_3

The last figure, figure 7 shows the proliferation of tumor cells for different values of the external sources s_1, s_2 and s_3. We already prove the impact of rising one external source at figures 2, 3 and 4 or rising two external sources at figures 5 and 6. At that final case, we can observe that increasing immunotherapy doses in the presence of virotherapy decrease lightly the proliferation of tumor cells and increase softly the time of illness. With this results, we confirm that the combined treatment under ACT, IL-2 and OVT has a better impact in reducing thecancer cells proliferation.

4. CONCLUSION

Cancer treatment often requires a combination of treatment regimens, combining immunotherapy and virotherapy can emerge as promising tools in fighting cancer. In this paper, the evolution of cancer is studied with one or combined treatments whether immunotherapy, virotherapy or both. The dynamics of the disease is formulated by ODE's system which expresses the variations over time of participating elements in this dynamic. We firstly validated the model's plausibility and we have analysed the equilibria of the model when the variations of tumor, oncolytic virus and immunotherapy variables (CTLs and IL-2) are zero. We have found the

necessary conditions for the equilibrium points' existence at the following scenarios: with ACT only, with IL-2 only, with OVT only, with ACT and IL-2, with ACT and OVT, with IL-2 and OVT and the last scenario combined the all. The stability analysis proves that a tumor can grow to its maximum size in case of no-treatment. It is also shown that in the case of ACT only, the treatment requires a minimum dose of CTLs and in the case of IL-2 only, the injection is almost useless if it is not combined with ACT, in the last case of OVT, a minimum dose of virus is require also which can decrease by combining with immunotherapy treatment. Model analysis and numerical simulations suggest some recommendations in order to select the most appropriate treatment strategy. It is shown that the immunotherapy helps a lot to reduce the size of tumor and the speed of the cancer proliferation. With the virotherapy cancer may be eliminated. Numerical simulations shown that increasing the dose of external sources in different treatments have the same positive effect in the course of cancer. The combined treatment makes it possible to reduce the doses of the OVT and the ACT drug which is better, because with the external source of CLTs or IL-2 or oncolytics virus, residues of the external sources still exist even if the tumor disappears and that existence can react with other illness or with some elements of the body. However, cancer evolution in human body is also depending on the each patient's conditions but these existing two way of therapies represent a promising solution to fight cancer.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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