A Mathematical Model to Treat for a Cancer Using Chemotherapy and Immunotherapy under Mass Action Kinetics for Immunotherapy

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Abstract: - Cancer is a burning problem in the modern health field. In this research mainly we focused on how we can treat for a cancer by using chemotherapy and immune therapy as individual monotherapies and as a combined therapy. In previously, researchers have constructed mathematical models to analyse the combined therapy treatment with saturation effects for immune therapy treatment but here we introduce mass action kinetics for immune therapy and this model reflects as a continues attacking process to tumour cells by immune cells with the help of chemotherapy drug. We introduce some threshold levels which we can remove cancer completely and control the cancer in a constant level.

Key-Words: - Mass action, Michaelis-Menton, equilibrium point, tumour, asymptotically stable, chemotherapy

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1 Introduction

Cancer causes lots of deaths around the world. Currently, cancer is the second cause of death worldwide and is expected to hit 27.1 million people by 2030 [1],[2].

Food patterns, lack of exercise, using tobacco, radiation mainly caused cancer. Cancer is a disease that the cells of the body grow abnormally. This unusual growth in the body can happen anywhere in the body and can affect people from any age group. When we consider about cancer treatment methods there are lots of strategies that has developed in this era. Chemotherapy, hormone therapy, hyperthermia, immunotherapy, radiation therapy, surgery and targeted therapy are some of prominent treatment methods in the modern world [3]. Among these treatments, chemotherapy, and immunotherapy both are prominent treatment methods in the modern world. When we consider chemotherapy, there are many different types of chemotherapy drugs that can work differently to kill cancer cells. Some may interfere with the growth and division of these cells. Others can help cause cancer cells to self-destruct. Chemotherapy is used for plenty of purposes, it can disturb the growth of cancer cells, sometimes it can stop spreading of cancer cells in the body. Chemotherapy can give to the body as injections, injecting to the muscle, spinal code, skin and sometimes it can give as tablets. This therapy has some side effects. Among them these are the main side effects bone marrow suppression, neuropathies, gastrointestinal disorders, integrating patients' perceptions regarding side effects into decision making process during cancer treatment is always important [4]. The immune system is the body's basic defence against infection and cancer. It is made up of a complex network of cells, molecules, organs and lymph tissues attempting together to defend the body against microorganisms such as bacteria, viruses and fungi, as well as against cancer cells. The immune system plays a crucial role in preventing cancer. It acts in a cascade manner to counter the pathogenic response both by the innate and adaptive immune systems [5]. Immune cells can find cancer cells and kill them and completely eliminate cancer cells but sometimes it can control the growth of cancer. Immune checkpoint inhibitors, adoptive cell transfer, monoclonal antibodies, T-cell therapy, vaccines are some treatment methods [6]. Immunotherapy has some side effects, they are paining, swelling, soreness, redness and rash. In this research, first we consider chemotherapy and Immunotherapy individually and then we consider both of them as a combined therapy [5],[6].

2 Model

Here we construct the mathematical model to represent the interactions between cancer cell population, immune cell population and chemotherapy agents in blood.

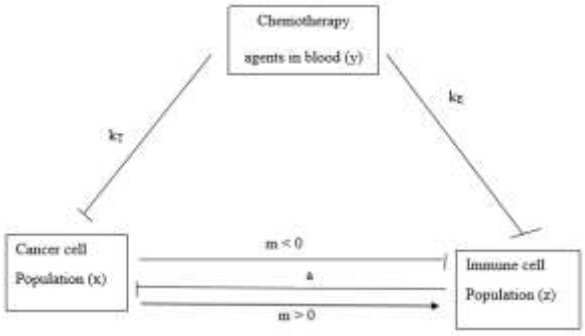


Fig. 1: The interrelationship among x, y and z. In this diagram arrow represents the activation and blunt arrow represents inhibition.

$$x' = rx(1 - bx) - axz - k_T xy \quad (1)$$
$$y' = -y\gamma + h$$
$$z' = s - dz + \frac{mxz}{g + x} - k_E yz$$
$$x(0) \geq 0, y(0) = 0, z(0) \geq 0$$

Consider the parameters of the model.

r = rate of tumour growth.
b = Inverse carrying capacity of tumour cells.
a = parameter of cancer cleans up.
k_T = killing rate of tumour cells by chemotherapy.
γ =rate of decrement in concentration of chemotherapy.
h = supply rate of chemotherapy drug.
s = supply rate of immune cells.
d = death rate of immune cells.
m = proliferation rate of immune cells.
k_E=killing rate of immune cells by chemotherapy.
g=half saturation constant of immune proliferation.

These are the state variables.
x = Cancer cell population.
y =Amount of chemotherapeutic agent in the blood stream.
z = Immune cell population.

m can be negative or positive. Here all the other parameters are positive.

The first equation states the rate of change in the cancer cell population, basically logistic growth model has used to represent the growth of cancer cell population [11]. Here we consider how immunotherapy and chemotherapy attack to cancer cells, axz represent the attack of immune cells to cancer cells and on the other hand $k_T xy$ represent the attack of chemotherapy drug to tumor cells [12], [13], [14],[15]. As this phenomenon is a biochemical reaction, we assume that this reaction happens according to the mass action law [14]. Previous researchers have used the attack of immune cells with saturation effects but in our research work we construct our model as these immune cells attack cancer cells without any saturation effect and this reaction happens according to the Mass action law [14]. If the immunotherapeutic drug can attack cancer cells without decaying its strength, the given model can represent this scenario clearly [9].

The second equation states the rate of change in the amount of chemotherapeutic agent in the bloodstream with time. Here it supplies drug in a constant rate, it is represented by h [13]. Chemotherapy drug concentration is decreasing with time, specialty in [9] introduced model, the drug concentration is decreasing with a constant rate.

The third equation states the rate of change of the immune cell population with time, here immune cells are injected to body from outside. On the other hand, when time is increasing these immune cells die, it can be represented by using the natural death rate of immune cells. Activation of immune cells works according to Michaelis-Menten mechanism [12]. Immune cells can be killed by the chemotherapy drug, that incident is represented in the model by using the killing rate of immune cells by chemotherapy [13]. In the model of [8] they have considered activation and inactivation of immune cells separately but in this model according to the sign of m, it can be decided the activation of immune cells or resistance for immune cells [9,12]. In our research we consider immune cells proliferate without any resistance, so $m > 0$. In [8] the model has used with Viral Therapy and Immune Therapy but here we modified that model replacing Viral Therapy form Chemotherapy by taking concepts form the model [9].

Theorem 1. *Solution of* (1) *exist, remain nonnegative, and are bounded on* $[0, \infty)$.

Proof : Let $F(x,y,v,z)$ be the right hand side of (1). Since F is locally Lipschitz in $\mathbb{R}^3_+$, there exist a unique solution on $[0,t_0)$ for the initial value problem

(1), where $t_0 > 0$ may depend on the initial condition. As $x'|_{x=0} = 0, y'|_{y=0} = 0$, and $z'|_{z=0} \geq 0$, solution of (1) remain nonnegative on $[0,t_0)$ by [7].

We let $w = x + y + z$. Then, $w' \leq \quad rx + s + \frac{mxz}{g+x} + y\gamma \quad \leq rx + s + mz + y\gamma$, where $p_0 = \max\{r, m, \gamma\}$. $w' \leq s + p_0 w$. Consider $X' = s + p_0 X$ with X(0) = $w(0)$. Since the solution of $X(t)$ are defined on [0,∞) and $w(t) \leq X(t)$ on $[0, t_0)$, $w(t)$ can be extended to $t = t_0$. Therefore solutions of (1) are bounded, noticing $x'|_{x \geq 1/b} < 0$ implies $\lim_{t\to\infty} \sup(x(t)) \leq 1/b$.

Consider the second equation in (1). $y' = y\gamma + h$. $y'|_{y \geq h/\gamma} < 0$ implies $\lim_{t\to\infty} \sup(y(t)) \leq h/\gamma$. When m>0, let $k_0 = \min\{r, \gamma, d\}$, suppose $w = x + y + m_0 z$. $W' \leq rx(1 - bx) + h - y\gamma + sm_0 - dzm_0 + \frac{mm_0xz}{g+x} - axz \leq 2rx + h - y\gamma + sm_0 - dzm_0 + \frac{mm_0xz}{g+x} - axz$, then choose m_0 such that $\frac{mm_0}{g+x} - a < 0$ for all $x \geq 0$, then $W' \leq \left(\frac{2r}{b} + h + sm_0\right) - y\gamma - rx - dm_0 z$, then $W' \leq C_1 - k_0 W$,from this we can obtain $\lim_{t\to\infty} \sup\big(W(t)\big) \leq \frac{C_1}{k_0}$.

When $m \leq 0$, Let $W = x + y + z, W' \leq rx(1 - bx) + h - y\gamma + s - dz + \frac{mxz}{g+x} - axz \leq 2rx + h - y\gamma + s - dz + \frac{mxz}{g+x} - axz < (\frac{2r}{b} + h + s) - y\gamma - rx - dz$, then $W' \leq C_2 - k_0 W$, from this we can obtain $\lim_{t\to\infty} \sup\big(W(t)\big) \leq \frac{C_2}{k_0}$. Hence, we can conclude that solutions of (1) are bounded.

2 Chemotherapy

In this section we are going to consider only about chemotherapy treatment. We reduced our model to the following sub-system.

$$\begin{aligned} x' &= rx(1 - bx) - k_T xy \\ y' &= -y\gamma + h \\ 0 \leq x(0) &\leq \frac{1}{b}, y(0) = 0 \end{aligned} \qquad (2)$$

Using Dulac Criteria with $B(x, y) = \frac{1}{xy}$. We consider on the region

$$R_x 1 = \{(x, y) \in \mathbb{R}^2_+ : x > 0, y > 0\} \qquad (3)$$

$$\frac{\partial\left|\frac{r(1-bx)}{y}\right|}{\partial x} + \frac{\partial\left|\frac{-y\gamma+h}{xy}\right|}{\partial y} = \frac{-rb}{y} - \frac{h}{xy^2} < 0 \text{ for } x, y > 0$$

Proposition 2.1. *Consequently* (2) *has no periodic solutions on* $R_x 1$.

Biologically this gives an important idea. There are no periodic orbits means cancer can't occur again and again under this chemotherapy.

Finding equilibrium points for the system (2).

$$rx(1 - bx) - k_T xy = 0$$

$$y\gamma = h$$

Then we can obtain cancer free equilibrium as $(0, \frac{h}{\gamma})$ and further we can find a positive equilibrium point as $(\frac{1}{b}\left(1 - \frac{k_T h}{r\gamma}\right), \frac{h}{\gamma})$, here $k_T h < r\gamma$. Then we are going to discuss about the existence and the stability of these two equilibrium points.

Consider the x isocline, $f(x) = \frac{r(1-bx)}{k_T}$ and consider the z isocline $g(x) = \frac{h}{\gamma}$, where $f(x)$ is strictly decreasing with $f(0) = \frac{r}{k_T}$ and $f\left(\frac{1}{b}\right) = 0$. $g(x)$ is a constant function. The range of x is $0 \leq x \leq \frac{1}{b}$. If $\frac{h}{\gamma} > \frac{r}{k_T}$ then there are no intersections between isoclines. So, it follows that (2) has no positive equilibrium points on the other hand when the opposite of above inequality happens, when $\frac{h}{\gamma} \leq \frac{r}{k_T}$ there is only one intersection in these two isoclines, it gives that there is a unique positive equilibrium point for the system (2). Then let's consider local stability of the cancer free equilibrium point by using the Jacobian.

$$J\left(0, \frac{h}{\gamma}\right) = \begin{pmatrix} r - \frac{k_T h}{\gamma} & 0 \\ 0 & -\gamma \end{pmatrix}$$

Then we can conclude that, $\left(0, \frac{h}{\gamma}\right)$ is locally asymptotically stable if $r\gamma < k_T h$ (both eigenvalues are negative) and otherwise it becomes a saddle point if $r\gamma > k_T h$ (one eigenvalue is negative and the other one is positive). Then let's consider the positive equilibrium point.

$$J\left(\frac{1}{b}\left(1 - \frac{k_T h}{r\gamma}\right), \frac{h}{\gamma}\right) = \begin{pmatrix} r - 2brx - k_T y & -k_T x \\ 0 & -\gamma \end{pmatrix}$$

By using x isocline and $r - 2brx - k_T y$ we can reduce the above jacobian to following form.

$$J\left(\frac{1}{b}\left(1-\frac{k_T h}{r\gamma}\right),\frac{h}{\gamma}\right)=\begin{pmatrix}-brx & -k_T x\\ 0 & -\gamma\end{pmatrix}$$

We are considering on x ≥ 0, y ≥ 0. In this Jacobian matrix trace is negative and determinant is positive. Then we can obtain that positive equilibrium point is locally asymptotically stable.

By using Poincare Bendixen Theorem [7] and the above results we can obtain the following theorem.

$$R_x 1=\{(x,y)\in\mathbb{R}_+^2: x>0\} \quad (4)$$

Theorem 2. *The following statements hold for* (2).

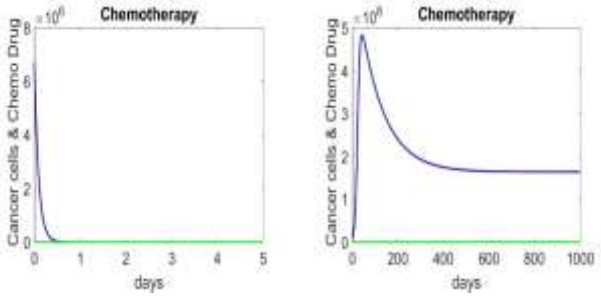
a) *If $hk_T > r\gamma$ then $\left(0,\frac{h}{\gamma}\right)$ is globally asymptotically stable in $\mathbb{R}_+^2$.*

b) *If $hk_T < r\gamma$, then there is a unique positive equilibrium point (x^*,y^*) which is globally asymptotically stable in $R_x 1$.*

When the tumour is not aggressive, so that the immune system is not dysfunctional, the tumour can be eradicated completely if the tumour killing rate is large. On the other hand, if the tumour killing rate is not large, then the tumour cells will be stabilized at a positive level that is smaller than carrying capacity. Further it has an interesting biological phenomenon, when the basic reproduction number of the supply rate of chemotherapy is greater than the basic reproduction number of the supply rate of tumour cells cancer can eliminate. So, we need a strong chemotherapy treatment to cure the cancer completely. On the other hand, if the basic reproduction number of tumour supply rate is greater than the basic reproduction number of the supply rate of chemotherapy, tumour level has to stabilize in a fixed level. Finally, we can conclude that this gives a threshold level that under what condition we can eliminate the tumour completely with the support of only chemotherapy. Then let's move towards the combined therapy and how it works.

Table 1. Parameters values and sources

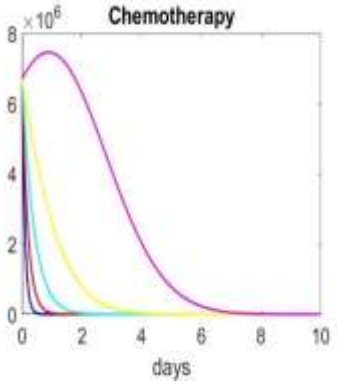
Parameter	Value	Unit	Reference
r	0.2773-0.3466	day^{-1}	estimated
b	1.02×10^{-9}	cell^{-1}	[2]
a	$10^{-5}-10^{-3}$	cell^{-1}day^{-1}	[2]
k_T	0.01-0.7	cell^{-1}day^{-1}	[3]
γ	0.01-0.9	day^{-1}	[3][4]
h	0.003-0.6	mg day^{-1}	[3]
s	5000	cell day^{-1}	[2]
d	2	day^{-1}	[2]
m	-1-1.5$\times 10^{-9}$	cell^{-1}day^{-1}	[2]
k_E	0.06	cell^{-1}day^{-1}	[3]
g	40-10^5	cell	[2]



(a) (b)

Fig. 2: Here Green Curve Represents the Amount of Chemotherapy Drug and Blue Curve Represents the Cancer Cell Population r = 0.3, $b = 1.02\times 10^{-9}$, h = 0.05, γ = 0.01, Initial Tumor Cell Population= 6.7 × 10^6 cells, Initial Chemotherapy Drug Amount= 19.95units, (a) K_T = 0.55 (b) K_T = 0.005.

When we decrease the initial supply amount of chemotherapy, we can observe that it takes a long-time treatment period to eliminate the tumour completely. It reveals that, with a strong initial amount of chemotherapy, we can remove can within a short time period.



(a)

Fig. 3: Here blue, red, cyan, yellow, magenta curves respectively represent the behaviour of tumour cell population according to each initial amount of chemotherapy drug respectively 19.95, 10, 5, 2, 1, r = 0.3, b = 1.02× 10^{-9}, h = 0.05, γ = 0.01, initial tumor cell population= 6.7 × 10^6cells, K_T = 0.55.

3 Immune Therapy

Now the model reduces to the following form.

$$x' = rx(1-bx) - axz$$

$$z' = s - dz + \frac{mxz}{g+x} \qquad (5)$$

$$0 \le x(0) \le \frac{1}{b}, z(0) \ge 0$$

First, we are going to Dulac Criteria to analyse about periodic solutions. Using Dulac Criteria, we can obtain that, there are no periodic orbits in this system.

Using Dulac Criteria with $B(x,z) = \frac{1}{xz}$.

$$\frac{\partial\left[\frac{rx-brx^2-axz}{xz}\right]}{\partial x} + \frac{\partial\left[\frac{s-dz+\left[\frac{mxz}{g+x}\right]}{xz}\right]}{\partial y} = \frac{-rb}{z} - \frac{s}{xz^2} < 0 \; for \; x, y > 0$$

Proposition 3.1. *Consequently* (5) *has no periodic solutions.*

This implies that under immune therapy cancer can't occur again and again because there are no periodic orbits. We proceed to discuss the existence of positive equilibria. The nontrivial x-isocline and the z-isocline of (5) are given respectively by

$$z = \frac{r(1-bx)}{a} =: f(x) \qquad (6)$$

$$z = \frac{s(g+x)}{dg + (d-m)x} =: g(x)$$

Where f is strictly decreasing with $f(0) = r/a$ and $f(1/b) = 0$. The slope of the graph of g is $g'(x) = \frac{msg}{(dg+(d-m)x)^2}$. clearly, we can see the slope depends on the sign of m.

$$g(0) = \frac{s}{d} \qquad g(\infty) = \frac{s}{(d-m)}$$

3.1 m ≥ 0

For m ≥ 0, it needed to be $dg + (d-m)x \ge 0$ to become g(x)>0, when $m \le d$, $g(x)$ becomes positive but when m > d we need x < $\frac{dg}{m-d}$, if m > d then g(x) is positive only on [0, $\frac{dg}{m-d}$). On the other hand, if $0 \le m \le d, g(x)$ is defined and positive on [0, ∞). When m > 0, g(x) is increasing and when x arrives to infinity, curve approach to a constant level $\frac{s}{(d-m)}$. If $\frac{r}{a} > \frac{s}{d}$, then it occurs a positive equilibrium point. Consider the determinant of the jacobian at that point (x^1, z^1).

$$J(x^1, z^1) = \begin{pmatrix} -brx^1 & -ax^1 \\ \frac{mz^1 g}{(g+x^1)^2} & -d + \frac{mx^1}{g+x^1} \end{pmatrix}$$

According to the z^1 in (5),$-d + \frac{mx^1}{g+x^1} < 0$, then we can see $T_r(J) < 0$ and $Det(J) > 0$, so we can conclude that this equilibrium point is locally asymptotically stable. Then consider about the cancer free equilibrium point (0, *s/d*).

$$J(0, z^1) = \begin{pmatrix} r - as/d & 0 \\ \frac{ms}{dg} & -d \end{pmatrix}$$

According to the eigenvalues we can see this equilibrium point is unstable if $\frac{r}{a} > \frac{s}{d}$ and on the other hand If $\frac{r}{a} < \frac{s}{d}$ cancer free equilibrium point become locally asymptotically stable, in this

situation, there doesn't exist a positive equilibrium point. When $m = 0$ the case become trivial. By using Poincar´e-Bendixson Theroem[7] and above details we can obtain bellow theorem.

$$R_x 2 = \{(x, 2) \in \mathbb{R}^2_+ : x > 0\}.$$

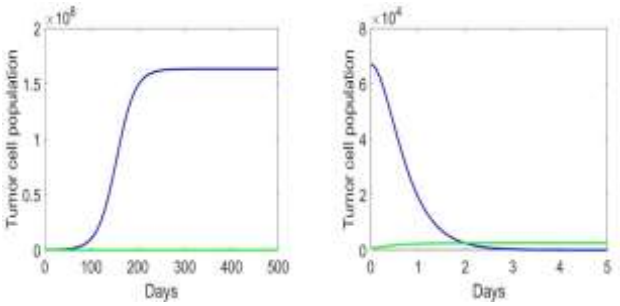
Theorem 3. *The following statements hold for* (5).

a) If $\frac{as}{d} > r$ *then (0, s/d) is globally asymptotically stable in* $R_x 2$.

b) If $\frac{as}{d} < r$ *then there is a unique positive equilibrium point* (x^1, y^1) *which is globally asymptotically stable in* $R_x 2$.

Here also happen a similar situation like chemotherapy in section 3. We can observe when the cancer clean-up rate is greater than the rate of tumour growth, tumour can eliminate completely. On the other hand, when the tumour growth rate is greater than the rate of cancer cleanup we have to stabilize the tumour size in some fixed level. Here it provides a threshold level to eradicate the cancer completely, further we can say, it needs a strong immune therapy treatment to remove the cancer when immune cells proliferate without the resistance of cancer cells.

4.2 Numerical Simulations



(a) (b)

Fig. 4: Here green curve represents the amount of immunotherapy and blue curve represents the cancer cell population r = 0.3, b = 1.02 ×10^{-9}, s = 5000, d = 2, m = 1×10^{-9}, g = 2000 initial tumour cell population = 6.7×10^4 cells, initial immune cell amount = 300, (a)α = 1×10^{-4}, (b) α = 1×10^{-3}.

When we consider about the Theorem 3, according to the details of figure 3(a) we can calculate that $\frac{as}{d}$ = 2.5 and r = 0.3 then $\frac{as}{d}$ < r. It is clear that cancer level arrivers to a fixed level. On the other hand, according to figure 3(b), $\frac{as}{d}$ > r = 0.25 and r =0.3 there $\frac{as}{d}$ < r and cancer free equilibrium point becomes globally asymptotically stable and we can remove the cancer completely. It clearly represents that when the rate of cancer cleanup by immune cells is in a strong level, we can eradicate the cancer by immunotherapy completely. Here we can calculate that if we need to remove the cancer what is the needed cancer cleanup rate. Another important result is if we can identify cancer in early, we can remove it completely otherwise we have to fix the cancer in a stable level.

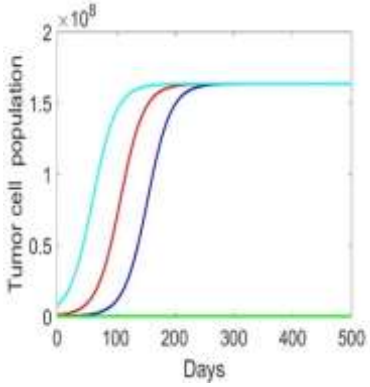


Fig. 5: Here blue, red, cyan, curves respectively represent the behaviour of tumour cell population according to each initial amount of tumour cell population = 6.3×10^4 cells, = 6.3×10^5 cells, = 6.3×10^6 cells.

It is clear that when the tumour cell population is high, it approaches to a constant level more rapidly.

4.3 m < 0

When m < 0, g(x) is defined on (0, ∞] and g(x) is gradually decreasing and approaches to a constant level $\frac{s}{d-m}$. f is strictly decreasing with $f(0) = r/a$ and $f\left(\frac{1}{b}\right) = 0$. Here x is in the range of $0 < x < 1/b$ and z is in the range of 0 < z < s/d. We are going to consider about the existence of the positive equilibrium points and their stability and then supposed to describe about the biological phenomena in each case. Setting $f(x)$ = g(x) and

simplifying, the x component of a positive equilibrium is a positive root of

$$H1(x) =: rb(m-d)x^2 + (rd - rm - rbdg - sa)x + g(rd - sa) \quad (7)$$

$H1(1/b) = -\frac{a}{g} - gsa < 0$. The vertex of H1(x) is at $\left(\frac{rd-rm-rbdg-sa}{2rb(d-m)}, \Delta 1\right)$.

$$\Delta 1 = \frac{(rd-rm-rbdg-sa)^2}{4rb(d-m)} + g(rd - sa) \quad (8)$$

If $rd > sa$,then has a unique positive equilibrium point (x_2 , z_2) where $x_2 <$ 1/b and $z_2 <$ s/d. Notice T r($J(x_2 , z_2)) < 0$ and consider about $Det(J(x_2 , z_2))$.

$$Det(J(x_2 , z_2)) = \frac{x_2}{(g+x_2)^2}[rb(d-m)x_2^2 + 2brg(d-m)x_2 + gr(m+bdg)] \quad (9)$$

$$Det(J(x_2 , z_2)) = \frac{x_2\ rb(d-m)}{(g+x_2)^2}[x_2^2 + g[2x_2 + \frac{rm+rbdg}{rb(d-m)}]]$$

If $g[2x_2 + \frac{rm+rbdg}{rb(d-m)}] > 0$ then $(J(x_2 , z_2))$. > 0, from here we can obtain a sufficient condition that $rd > sa$, then (x_2 , z_2) becomes locally asymptotically stable. As there are no any other stable equilibrium points in R_x2, (x_2 , z_2) becomes globally asymptotically stable in that region.

If $sa > rd$, where the tumor free equilibrium point $(0, s/d)$ is locally asymptotically stable. If $rd - rm - rbdg - sa \leq 0$, It is clear that $H(x)$ has no positive real roots since $H(x) \leq 0$ for all $x \geq 0$ and thus $(0, \frac{s}{d})$ is globally asymptotically stable by the Poincar´e-Bendixson Theorem. Let $rd - rm - rbdg - sa > 0$ and $\Delta 1 < 0$ then there is no positive equilibrium point in the system (5) because there are no any intersections with the quadratic curve with the x axis. If $\Delta 1 = 0$ quadratic curve touches the x axis at one point and it means (5) has one positive equilibrium point and as $\Delta 1 = 0$ implies the equilibrium point become non hyperbolic. If $sa > rd$, $rd - rm - rbdg - sa > 0$ and $\Delta 1 > 0$, there exist two positive equilibrium points $(\bar{x}_i, \bar{z}_i), i =$ 1,2 where $\bar{x}_1 < \bar{x}_2$. We can simplify

$$Det\big(J(\bar{x}_i, \bar{z}_i)\big) = \frac{\bar{x}_i rb(d-m)}{(g+\bar{x}_i)^2}\left[\bar{x}_i^2 + \left[2\bar{x}_i + \frac{rm+rbdg}{rb(d-m)}\right]\right]$$

Theorem 4. *If m<0, then the following statements hold for* (5).

a) If sa < rd there is a unique positive equilibrium point (x_2, z_2) *which is globally asymptotically stable in* R_x2.

b) If sa>rd and $rd - rm - rbdg - sa \leq 0$ *then there is no positive equilibrium points and* $\left(0, \frac{s}{d}\right)$ *is globally asymptotically stable in* $\mathbb{R}^2_+$.

c) If sa>rd and $rd - rm - rbdg - sa > 0$ *and* $\Delta 1 < 0$ *then there is no positive equilibrium points for* (5) *and* $\left(0, \frac{s}{d}\right)$ *is globally asymptotically stable in* $\mathbb{R}^2_+$, *system* (5) *has a unique equilibrium point which is non –hyperbolic if* $\Delta 1 = 0$

d) If sa>rd, $rd - rm - rbdg - sa > 0$ *and* $\Delta 1 > 0$, *there exist two positive equilibrium points* $(\bar{x}_i, \bar{z}_i)$.

5 Combined Therapy

In this section we are going to consider the effects of combined therapy. When we are giving Immune therapy and Chemotherapy together, we need to observe how this dynamical system behaves. Here we are considering the full system on

$$\Gamma = \{(x, y, z) \in \mathbb{R}^3_+ : x > 0, y > 0, z > 0\} \quad (10)$$

$$x' = rx(1 - bx) - axz - k_T xy$$

$$y' = -y\gamma + h \quad (11)$$

$$z' = s - dz + \frac{mxz}{g+x} - k_E yz$$

First let's considered the isoclines of the system.

$$0 = rx(1 - bx) - axz - k_T xy$$

$$0 = -y\gamma + h \quad (13)$$

$$0 = s - dz + \frac{mxz}{g+x} - k_E yz$$

From (6) second equation, we can obtain the value of y component at equilibrium state and we can observe it's a constant value such as $y = \frac{h}{\gamma}$. After substituting for y in first and second equations in (6) we can obtain a two-dimensional equation system.

We can obtain x-isocline and the z-isocline as,

$$x = \frac{1}{a}\left(r - \frac{k_T h}{\gamma}\right) - \frac{rbx}{a} := P(x)$$

$$z = \frac{sg + sx}{\left(dg + \frac{k_E hg}{\gamma}\right) + \left(d - m + \frac{k_E h}{\gamma}\right)x}$$

Suppose $r > \frac{hk_T}{\gamma}$

Where P is strictly decreasing with $P(0) = \frac{r}{a} - \frac{k_T h}{a\gamma}$ and $P\left(\frac{1}{b}\left(1 - \frac{k_T h}{r\gamma}\right)\right)$. The slope of the graph of $Q(x)$ is $Q'(x) = \frac{msg}{\left[\left(dg + \frac{k_E hg}{\gamma}\right) + \left(d - m - \frac{k_E h}{\gamma}\right)x\right]^2}$. Clearly, we can see that the sign of the slope depends on the sign of m.

$$Q(0) = \frac{s}{d + \frac{k_E h}{\gamma}}$$

$$Q(\infty) = \frac{s}{d - m + \frac{k_E h}{\gamma}}$$

5.1 $m \geq 0$

When $m \geq 0$, it needed to be $\left(dg + \frac{k_E hg}{\gamma}\right) + \left(d - m + \frac{k_E h}{\gamma}\right)x \geq 0$ to become $Q(x) > 0$, but when $m > d + \frac{k_E h}{\gamma}$ we need $x < \frac{\left(dg + \frac{k_E hg}{\gamma}\right)}{\left(d - m + \frac{k_E h}{\gamma}\right)}$. If $m > d + \frac{k_E h}{\gamma}$ then $Q(x)$ is positive only on $\left[0, \frac{\left(dg + \frac{k_E hg}{\gamma}\right)}{\left(d - m + \frac{k_E h}{\gamma}\right)}\right)$. On the other hand, if $0 \leq m \leq d + \frac{k_E h}{\gamma}$, $Q(x)$ is defined and positive on $[0, \infty)$. When m > 0, $Q(x)$ is increasing when x arrives to infinity, curve approaches to a constant level $\frac{s}{d - m + \frac{k_E h}{\gamma}}$.

When $Q(0) > P(0)$ there are no intersections of two isoclines in the first quadrant. Then system contains a cancer free equilibrium point. After calculating we can obtain it as $E^* = E^* = E^* = \left(0, \frac{h}{\gamma}, \frac{\gamma h}{d + k_E h}\right)$. Let's consider the Jacobian at that point.

$$J(0, y^*, z^*) = \begin{bmatrix} r - az^* - k_T y^* & 0 & 0 \\ 0 & -\gamma & 0 \\ \frac{mz^* g}{(g + x^*)^2} & -k_E z^* & -d - k_E y^* \end{bmatrix}$$

This is an upper triangular matrix, if all the diagonal elements become negative then this system becomes locally asymptotically stable at E^*. We can obtain a condition that if $r - az^* - k_T y^* < 0$ then (11) becomes locally asymptotically stable at E^*. This (11) is asymptotically autonomous with (5), in that (5) subsystem cancer free equilibrium point is globally asymptotically stable on $R_x 2$ hence we can say E^* is globally asymptotically stable on Γ.

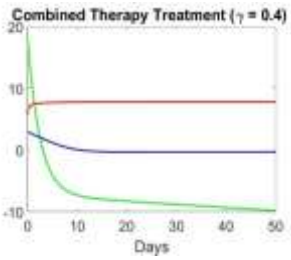
Theorem 5. *The following statement hold for* (11). *If* $r < \frac{as\gamma}{d\gamma + k_E h} + \frac{k_T h}{\gamma}$, *then* E^* *is globally asymptotically stable on* Γ.

From the above theorem we can obtain, when the tumour killing rate of chemotherapy and immune therapy (combined therapy) is greater than the tumour growth rate cancer can eliminate completely. Here it provides a threshold level to eliminate cancer completely. Then let's consider $Q(0) < P(0)$. Here these two isoclines have only one intersection in Γ . In this situation there exist a unique positive equilibrium point in the system and here $> \frac{as\gamma}{d\gamma + k_E h} + \frac{k_T h}{\gamma}$. This (11) is asymptotically autonomous with (5), according to the stability of (5) subsystem we can obtain that this positive equilibrium point is globally asymptotically stable on Γ.

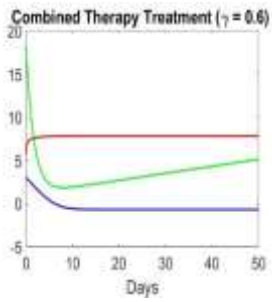
Theorem 6. *The following statement hold for* (11). *If* $r > \frac{as\gamma}{d\gamma + k_E h} + \frac{k_T h}{\gamma}$, *then there exists a unique positive equilibrium point and it is globally asymptotically stable on* Γ.

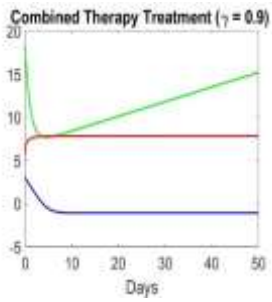
From this theorem we can obtain that if the tumour growth rate is greater than the tumour killing rate of combined therapy, we have to fix the cancer in some stable level but we can't eradicate the cancer completely.

5.2 Numerical Simulations



(a)





(b) (c)

Fig. 6: (a) γ = 0.4 (b) γ = 0.6 (c) γ = 0.9. Here green, blue and red curves represent the logarithm of cancer cell population, concentration of chemotherapy and number of immune cells against number of days. Here r = 0.3465, a = 10^{-5}, K_T = 0.53, h = 0.3, m = 1.3 × 10^{-9} and other values are same as in the Table 1.

It is clear that when we increase the rate of decrement of chemotherapy drug the tumour cell population will increase. It is Important to keep γ in a small level. Then it will be more efficient in the combined therapy.

6 Local Sensitivity Analysis

Table 2. Comparison of cancer cell population change: baseline values

Parameter	Old-Value	New-Value
r	0.3465	0.38115
b	1.02×10^{-9}	1.12×10^{-9}
a	0.0001	0.00011
k_τ	0.53	0.583
γ	0.8	0.88
h	0.3	0.33
s	5000	5500
d	2	2.2
m	1.3×10^{-9}	1.43×10^{-9}
k_g	0.06	0.066
g	10000	11000

Table 3. Comparison of cancer cell population change: For 50 days with X-old value 0.0315 and for 20 days with X-old value 0.0004 for each parameter

t = 50			t = 20		
X-new	Diff.	Per (%)	X-new	Diff.	Per (%)
0.1773	0.1458	462.86	0.0007	0.1458	75.00
0.0314	-0.0001	-0.32	0.0004	-0.0001	0.00
0.0314	-0.0001	-0.32	0.0004	-0.0001	0.00
0.0032	-0.0283	-89.84	0.0001	-0.0283	-75.00
0.247	0.2155	684.13	0.0017	0.2155	325.00
0.0119	-0.0196	-62.22	0.0003	-0.0196	-25.00
0.0315	0	0.00	0.0004	0	0.00
0.0315	0	0.00	0.0004	0	0.00
0.0315	0	0.00	0.0004	0	0.00
0.0315	0	0.00	0.0004	0	0.00
0.0315	0	0.00	0.0004	0	0.00

The primary objective of these calculations is to discern the impact of key parameters on the eradication of cancer cells [17], particularly focusing on their influence during both short (t=20) and extended (t=50) time intervals. The aim is to investigate how variations in these parameters contribute to a 10% increase in the efficacy of

eliminating cancer cells over both brief and prolonged durations.

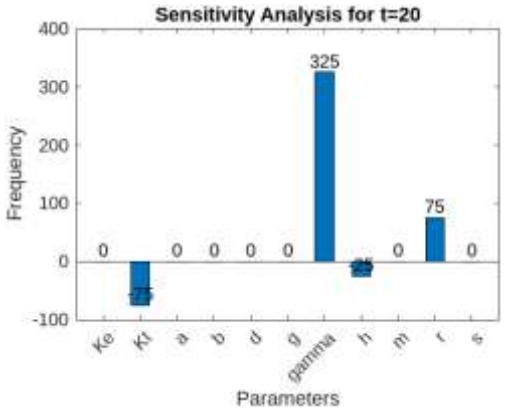


Fig. 7: Percentage difference in cancer cell population change at t=20 days visualization

The depicted figure shows information gathered over a short time period. In this data, the factor that has the biggest effect is γ. What stands out is that when γ values go up, the number of cancer cells in the body also increases. This finding, based on combined therapy results, highlights that higher rate of decrement of concentration of chemotherapy values lead to more cancer cells in the body.

The parameter next most influencing parameter is r, where an increase in its value corresponds to a heightened proliferation of cancer cells within the body. It's clear that when tumours grow faster, getting rid of cancer becomes more challenging. Increasing the Rate of tumour growth makes it harder to eliminate cancer.

The parameters k_t and h play a positive role in the elimination of cancer cells. Increasing k_t by 10% leads to a remarkable 75% improvement in the effectiveness of killing cancer cells, while h contributes a 25% positive impact. Unlike γ, r, h, and k_t the other parameters show no notable impact on the cancer cell population within the 10% of change of itself.

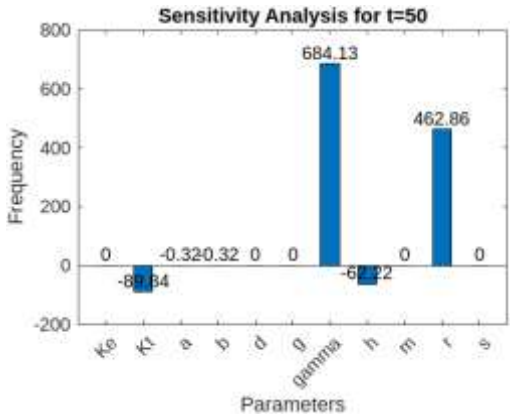


Fig. 8: Percentage difference in cancer cell population change at t=50 days visualization

The presented figure encapsulates an extended duration, revealing key influences. In this dataset, γ emerges as the most impactful factor, while r follows closely in significance, particularly in the short term. This underscores that a higher rate of chemotherapy concentration reduction and accelerated tumour growth present challenges in eliminating cancer cells. Beyond the long-term influence of k_t and h, parameters a and b also contribute positively to cancer cell elimination. However, their impact is notably smaller compared to k_t and h, amounting 0.32%. It's noteworthy that, similar to the short-term scenario, other parameters exhibit no notable impact on the 10% change in the population of cancer cells.

When we compare short-term and long-term treatments, a noticeable trend emerges. The negative impact from γ and r tends to increase over time, signifying that higher values of the rate of chemotherapy reduction γ and tumour growth r become more challenging for cancer elimination as time progresses. On the flip side, the positive impact from k_t and h shows an upward trajectory. This suggests that, with the passage of time, increasing the values of k_t and h becomes more effective in enhancing the process of eliminating cancer cells. In essence, the dynamics indicate a shift where challenges posed by higher γ and r values intensify over time, while the effectiveness of higher k_t and h values becomes more pronounced in the long-term treatment approach.

7 Conclusion

In conclusion, the comprehensive analysis of cancer treatment dynamics presented in this report unveils critical insights that bear significant implications for advancing therapeutic strategies. In this study, we delve into the intricacies of three distinct cancer treatment methodologies: chemotherapy, immunotherapy, and the combined approach integrating both modalities. Our exploration is grounded in a robust mathematical framework, meticulously crafted by amalgamating insights from existing research papers and leveraging mathematical concepts such as the Logistic Growth Model [8],[9],[16], Mass Action Law, and Michaelis-Menten mechanism.

Our mathematical model reveals two equilibrium points. One indicating a cancer-free state and another depicting a situation where cancer persists at a constant level without further growth.

Focusing on chemotherapy as a subsystem, $\left(0, \frac{\mathrm{h}}{\gamma}\right)$ cancer free equilibrium point exists when $\mathrm{k_T h} > \mathrm{r}\gamma$ and proved that positive equilibrium point exists when $\mathrm{k_T h} < \mathrm{r}\gamma$.

Similarly, our examination extends to the immunotherapy subsystem, where in equilibrium points are identified for scenarios representing $(0, \frac{s}{d})$ equilibrium point as absence of cancer when $\frac{as}{d} > r$. And proved that positive equilibrium point exists when $\frac{as}{d} < r$. These findings contribute to obtain threshold levels for parameters as $k_T = 0.54$ and $a = 1.2 \times 10^{-3}$. Leveraging the powerful capabilities of MATLAB software, we translated our mathematical findings into insightful visualizations for the two scenarios involving chemotherapy and immunotherapy subsystems[8],[9].

The two equilibrium points was found in the combined approach as existence of cancer free equilibrium point when $r < \frac{as\gamma}{d\gamma + k_E h} + \frac{k_T h}{\gamma}$ and cancer persists at a constant level equilibrium point when $r > \frac{as\gamma}{d\gamma + k_E h} + \frac{k_T h}{\gamma}$. We generated plots by varying the γ parameter, exploring its impact on the system for the values of γ set at 0.3, 0.8, and 0.9. And final insight was decreasing chemotherapy concentration, as represented by higher γ values, poses a challenge for effectively reducing the cancer cell population.

Finally, a sensitivity analysis was conducted to gauge the influence of parameters [17] on the eradication of cancer cells, with a specific emphasis on short (t=20) and extended (t=50) time intervals. The analysis revealed that γ (Rate of decrement of concentration of chemotherapy) and r (Rate of tumour growth) exhibited a negative impact on cancer elimination, while k_T(Killing rate of tumor cells by chemotherapy) and h (Supply rate of chemotherapy drug) exerted a substantial positive influence. Additionally, parameters a (Parameter of cancer cleanup) and b (Inverse carrying capacity of tumor cells) were found to contribute a very small positive impact to the process of cancer elimination. These findings underscore the nuanced interplay of different parameters in shaping the effectiveness of cancer treatment strategies across varying time frames.

The obtained results indicate the fulfilment of our research objectives, underscoring the effectiveness of the undertaken study in addressing key goals. This achievement not only validates the research methodology but also contributes valuable insights to the field, paving the way for innovative approaches redefine the landscape of hope and healing.

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