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DYNAMICS OF A MATHEMATICAL MODEL OF CANCER CELLS, EFFECTOR CELLS WITH CHEMOTHERAPY DRUG

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ABSTRACT:

The research aimed to understand the complex interactions between effector cells, tumor cells, and chemotherapy drugs in the context of cancer treatment. By employing computational simulations and mathematical analyses, the study explored how different chemotherapy regimens and drug doses affected the behavior of these components. Three graphs were used to visually present the findings of the research, highlighting the values of basic parameters and the changes in cancer cell growth rate and drug concentration.

The research developed a mathematical model, consisting of a system of nonlinear differential equations with three sub-populations, to represent the dynamics of cancer with chemotherapy. The model yielded two equilibrium points: the cancer-free equilibrium point and the cancer equilibrium point. Through simulations, it was observed that higher cancer cell growth rates, with other parameters held constant, led to increased cancer cell populations. Conversely, increasing the dosage of chemotherapy drugs within permissible limits resulted in lower cancer cell populations.

Overall, the study provided valuable insights into the effectiveness of chemotherapy in targeting tumor cells, the impact on effector cells, and the overall dynamics of the system. By comprehensively analyzing the interactions and behaviors of these elements, the research contributes to a better understanding of cancer treatment strategies and potential improvements in patient outcomes.

INTRODUCTION

Cancer is a condition characterized by the uncontrolled growth of abnormal cells in the body. It arises from normal cells that divide to maintain cell population equilibrium but undergo unbounded growth or lose the ability to die. Various types of cancers can develop in different organs or tissues, such as the lungs, colon, breast, skin, bones, or nerves. The causes of cancer include exposure to chemicals, excessive alcohol consumption, sunlight exposure, genetic differences, and other factors. Lung cancer is the most common cause of cancer-related death. Certain cancers are more prevalent in specific regions, potentially due to differences in diet and genetic predispositions.

Effector cells, an integral component of the adaptive immune system, encompass diverse cellular subtypes, including cytotoxic T cells, natural killer (NK) cells, and B cells. These specialized immune cells assume paramount importance in orchestrating immune responses against pathogens and aberrant cellular entities within the body. Operating through distinct mechanisms, effector cells execute specific immune functions to combat the presence of infections or abnormal cellular states.

Tumor cells are cells that have undergone uncontrolled proliferation and form a mass or lump of tissue called a tumor. Tumors can be benign (non-cancerous) or malignant (cancerous). Cancerous tumor cells can invade nearby tissues, spread to distant sites in the body through a process called metastasis, and disrupt normal bodily functions.

Chemotherapy is a systemic treatment for cancer that uses cytotoxic drugs to target and eliminate rapidly dividing cells, including cancer cells and some healthy cells. It interferes with essential cellular processes involved in cell division and replication, such as DNA synthesis and replication, enzyme function, and programmed cell death. While the primary target is cancer cells, normal cells with high turnover rates can also be affected, leading to side effects like hair loss, decreased blood cell production, nausea, and gastrointestinal issues. Chemotherapy is a crucial component of cancer management, especially when surgery or radiation is not possible or when the disease has spread. It can be used alone or in combination with other treatments, tailored to the specific cancer type, stage, and individual characteristics of the patient.

The research aimed to examine the dynamics of a mathematical model that captured the intricate interplay among effector cells (immune system components), tumor cells, and chemotherapy drugs. The main objective was to gain a comprehensive understanding of how these elements interacted and influenced one another in the context of cancer treatment. The study employed computational simulations and mathematical analyses to explore the effects of various chemotherapy regimens and drug doses on the behavior of both effector cells and tumor cells. Through this research, valuable insights were obtained regarding the efficacy of chemotherapy in targeting tumor cells, the consequences for effector cells, and the overall dynamics of the system.

RESEARCH METHOD

This study utilized a literature-based approach, leveraging information from multiple journals and reference books. The research process involved several key mathematical steps. Firstly, a mathematical model was developed to represent the system under investigation. This model aimed to capture the dynamics and interactions within the system accurately. Next, the equilibrium points of the model were determined by finding the values of the variables where the system remains unchanged over time. The stability analysis was then performed around these equilibrium points, evaluating how small perturbations in the system variables affect its long-term behavior. Finally, to further investigate the system's behavior, a numerical simulation was conducted, employing the identified parameters to simulate the dynamics and explore different scenarios.

FORMATION

Effector cell population denoted by ‘E’ would experience an increase owing to their steady growth rate 's' in magnitude, while it would decline due to their natural demise rate 'μ' in magnitude. The growth of the effector cell population is affected by the Michaelis-Menten response toward tumor cells at a magnitude rate of 'p'. Again, the population of effector cells is reduced by their interaction with tumor cells at a magnitude rate of 'm', as well as by the chemotherapy drug that causes cell demise at a magnitude rate of 'KE'.

Hence, accounting for all the relevant factors, the change in effector cell population can be described by the following equation:

$$\frac{dE}{dt} = s + p\frac{ET}{h+T} - mET - \mu E - K_E ME$$

With the assumption that the growth rate of tumor cells aligns with the logistics growth rate at a magnitude of 'r', the population of tumor cells experiences an increase. The decline in the tumor cell population can be attributed to the parameter representing tumor clean-up by effector cells, which occurs at a magnitude. This interaction between effector cells and tumor cells can be described using the elegant Michaelis-Menten kinetic form. Additionally, the population of tumor cells diminishes due to the influence of the interaction between tumor cells and the chemotherapy drug, resulting in the demise of tumor cells at a magnitude rate of 'K_T'.

Hence, accounting for all the relevant limitations, the dynamics of tumor cell population over time can be described by the following equation:

$$\frac{dT}{dt} = rT(1 - bT) - \frac{aET}{T+g} - K_T MT$$

The infusion of chemotherapy drugs into the body up to a magnitude of $V_M(t)$ triggers a surge in the concentration of chemotherapy drugs. However, the concentration of chemotherapy drugs gradually declines in proportion due to enzymatic degradation. Consequently, the rate of change in the concentration of chemotherapy drugs with respect to time is influenced.

Thus, the variation of chemotherapy drug concentration can be mathematically expressed by the following equation, representing the rate of change over time:

$$\frac{dM}{dt} = V_M - \frac{\gamma M}{C+M}$$

The equation that represents the mathematical model of chemotherapy is as follows:

$$\frac{dE}{dt} = s + p\frac{ET}{h+T} - mET - \mu E - K_E ME$$

$$\frac{dT}{dt} = rT(1 - bT) - \frac{aET}{T+g} - K_T MT$$

$$\frac{dM}{dt} = V_M - \frac{\gamma M}{c+M}$$

ASSUMPTIONS:

Parameter	Definition	Baseline (Unit)	Unit
p	degree of recruitment of maximum immune-effector cells in relation with cancer cells	0.015	(1/day)
r	rate of tumor growth	4.31×10^{-3}	(1/day)
b	capacity of the tumor cell	10^{-9}	(1/cells)
a	parameter of cancer cleanup	3.41×10^{-10}	(1/cells)
g	half-saturation for cancer cleanup	10^5	(cells)
s	growth rate of normal/effector cells	$1{,}2 \times 10^4$	(cells/day)
m	degree of inactivation of effector cells by tumor cells	2×10^{-11}	(1/cells.day)
μ	rate of natural demise of effector cells	4.12×10^{-2}	(1/day)
γ	rate of decrease in concentration of chemotherapy drug	0.9	(1/day)
h	steepness coefficient of the recruitment curve of effector-immune cells	2.02x10	Cells

EQUILIBRIUM POINTS:

Equilibrium points of the system are obtained when $\frac{dE}{dt} = 0, \frac{dT}{dt} = 0, \frac{dM}{dt} = 0$, i.e.,

$$s + p\frac{ET}{h+T} - mET - \mu E - K_E ME = 0$$

$$rT(1 - bT) - \frac{aET}{T+g} - K_T MT = 0$$

$$V_M(t) - \frac{\gamma M}{c+M} = 0$$

- When T = 0, Consequently, by solving the aforementioned set of equations, we obtain that:

$$\mathbf{E} = \frac{s(\gamma - V_M)}{\mu(\gamma - V_M) - K_E V_M c}, \quad \mathbf{M} = \frac{V_M c}{\gamma - V_M}$$

Existence Criteria:

$$\mu(\gamma - V_M) - K_E V_M c > 0$$

or,

$$(\gamma - V_M) > \frac{K_E V_M c}{\mu}$$

Hence, the system attains a state of equilibrium at $\left(\frac{s(\gamma-V_M)}{\mu(\gamma-V_M)-K_E V_M C}, 0, \frac{V_M c}{\gamma-V_M}\right)$.

- For interior equilibrium point

Let **(E*,T*,M*)** be the interior equilibrium point, where E*≠ 0, T*≠ 0, & M* ≠ 0

So, the system reduces to:

$$s + p\frac{E^*T^*}{h+T^*} - mE^*T^* - \mu E^* - K_E M^* E^* = 0$$

$$rT^*(1 - bT^*) - \frac{aE^*T^*}{T^*+g} - K_T M^* T^* = 0$$

$$V_M(t) - \frac{\gamma M^*}{c+M^*} = 0$$

By similar calculations, $\mathbf{M^*= \frac{V_M c}{\gamma-V_M}}$, $\mathbf{E^*= \frac{-s}{\frac{pT^*}{h+T^*}-mT^*-\mu-\frac{K_E V_M c}{\gamma-V_M}}}$

And T* can be found from the equation;

$$A(T^*)^4+B(T^*)^3+C(T^*)^2+DT^*+F=0$$

Here, $A= -\{rbh + mK_T\left(\frac{V_M c}{\gamma-V_M}\right)\}$

$B = (r-rbg)h - rb(p-h^2+w) - K_T\frac{V_M c}{\gamma-V_M}(p - mh + w + gm)$

$C =(r-rbg)(p-h^2+w) - rbwh + rhg - K_T\frac{V_M c}{\gamma-V_M}\{wh + g(p - mh + w)\}$

$D =wh(r-rbg) + rg(p-h^2+w) - K_T\frac{V_M c}{\gamma-V_M}gwh + as$

Where, F = grwh+as

And, $w = -\mu - K_E\frac{V_M c}{\lambda-V_M}$

Now, for stability analysis:

We calculate the Variational Matrix V(E,T, M) =

$$\begin{pmatrix} T\left(\frac{p}{h+T}-m\right)-\mu-K_E M & \frac{pE}{h+T}-\frac{pET}{(h+T)^2}-mE & -K_E E \\ -\frac{aT}{T+g} & r(1-2bT)-K_T M-\frac{aE}{(T+g)}\left(1-\frac{T}{T+g}\right) & -K_T T \\ 0 & 0 & \frac{\gamma}{(c+M)}\left(\frac{M}{(c+M)}-1\right) \end{pmatrix}$$

The Variational matrix at the equilibrium point $\left(\frac{s(\gamma-V_M)}{\mu(\gamma-V_M)-K_E V_M C}, 0, \frac{V_M c}{\gamma-V_M}\right)$

$$\begin{pmatrix} -\mu-K_E M & \frac{pE}{h}-mE & -K_E E \\ 0 & r-K_T M-\frac{aE}{g} & 0 \\ 0 & 0 & \frac{-\gamma c}{(c+M)^2} \end{pmatrix}$$

For obtaining the eigen values we calculate $|V-\lambda I|=0$

$$\begin{vmatrix} (-\mu-K_E M)-\lambda & \frac{pE}{h}-mE & -K_E E \\ 0 & \left(r-K_T M-\frac{aE}{g}\right)-\lambda & 0 \\ 0 & 0 & \left\{\frac{-\gamma c}{(c+M)^2}\right\}-\lambda \end{vmatrix}$$

Here, $\lambda_1 = -(\mu + K_E M) < 0$

$\lambda_2 = \left(r - K_T M - \frac{aE}{g}\right)$

$\lambda_3 = \frac{-\gamma c}{(c+M)^2} < 0$

Conditional for stability: $\left(r - K_T M - \frac{aE}{g}\right) < 0$

$or, \qquad r < K_T M + \frac{aE}{g}$

Now, at (E*, T*, M*) the variational matrix is given by, V(E*, T*, M*)=

$$\begin{pmatrix} T^*\left(\frac{p}{h+T^*}-m\right)-\mu-K_EM^* & \frac{pE^*}{h+T^*}-\frac{pE^*T^*}{(h+T^*)^2}-mE^* & -K_EE^* \\ -\frac{aT^*}{T^*+g} & r(1-2bT^*)-K_TM^*-\frac{aE^*}{(T^*+g)}\left(1-\frac{T^*}{T^*+g}\right) & -K_TT^* \\ 0 & 0 & \frac{-\gamma c}{(c+M^*)^2} \end{pmatrix}$$

After some substitutions

$$\begin{pmatrix} \frac{-s}{E^*} & \frac{pE^*h}{(h+T^*)^2}-mE^* & -K_EE^* \\ -\frac{aT^*}{T^*+g} & -rbT^*+\frac{aE^*T^*}{(T^*+g)^2} & -K_TT^* \\ 0 & 0 & \frac{-\gamma c}{(c+M^*)^2} \end{pmatrix}$$

For obtaining the eigen values we calculate $|V-\lambda I|=0$

$$\begin{vmatrix} \frac{-s}{E^*}-\lambda & \frac{pE^*h}{(h+T^*)^2}-mE^* & -K_EE^* \\ -\frac{aT^*}{T^*+g} & \left(-rbT^*+\frac{aE^*T^*}{(T^*+g)^2}\right)-\lambda & -K_TT^* \\ 0 & 0 & \frac{-\gamma c}{(c+M^*)^2}-\lambda \end{vmatrix}$$

It is evident that one of the eigenvalues is, $\lambda=\frac{-\gamma c}{(c+M^*)^2}(<0)$.

To conduct further analysis, we utilize the following block matrix and determine its trace and determinant.

$$\begin{pmatrix} \frac{-s}{E^*} & \frac{pE^*h}{(h+T^*)^2}-mE^* \\ \frac{-aT^*}{T^*+g} & -rbT^*+\frac{aE^*T^*}{(T^*+g)^2} \end{pmatrix} = W(\text{say})$$

For the system to exhibit stability, it is necessary for the eigenvalues of the matrix to be negative. This condition is met when the trace of the matrix is negative, and the determinant is positive.

Therefore, Trace(W)<0 and, det (W)>0

Or, $s>\left(\frac{rE^*T^*}{(T^*+g)^2}-rbT^*\right)E^*$ .....(i) Or, $\frac{n^2s}{aq}>\frac{aE^*-rbq^2}{pE^*h-mE^*n^2}$ .....(ii)

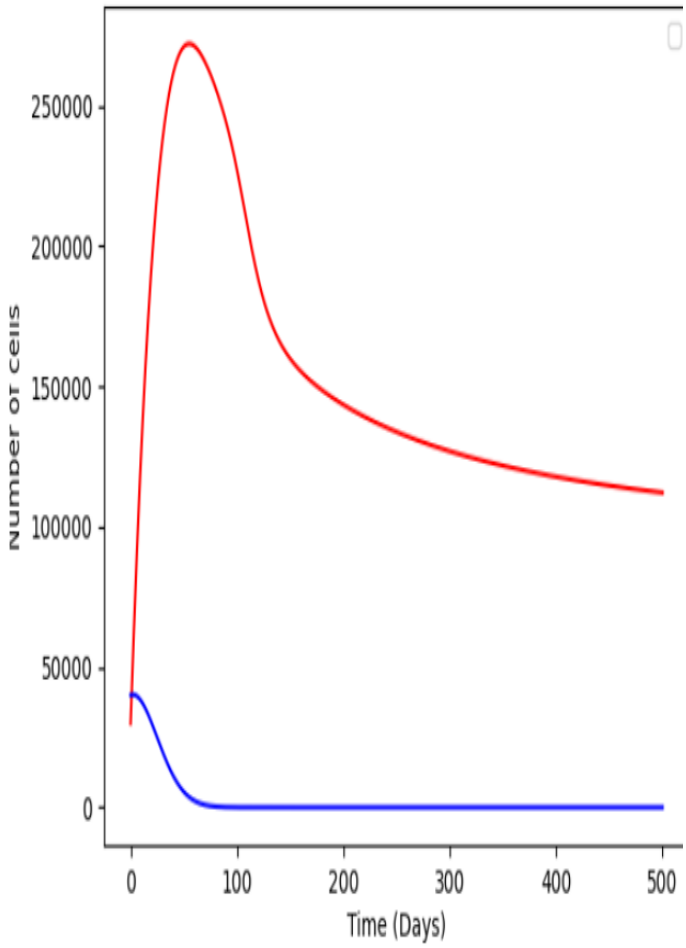
So, the conditions (i) and (ii) are the conditions for stability of the system for the interior point (E*,T*,M*).

NUMERICAL SIMULATION

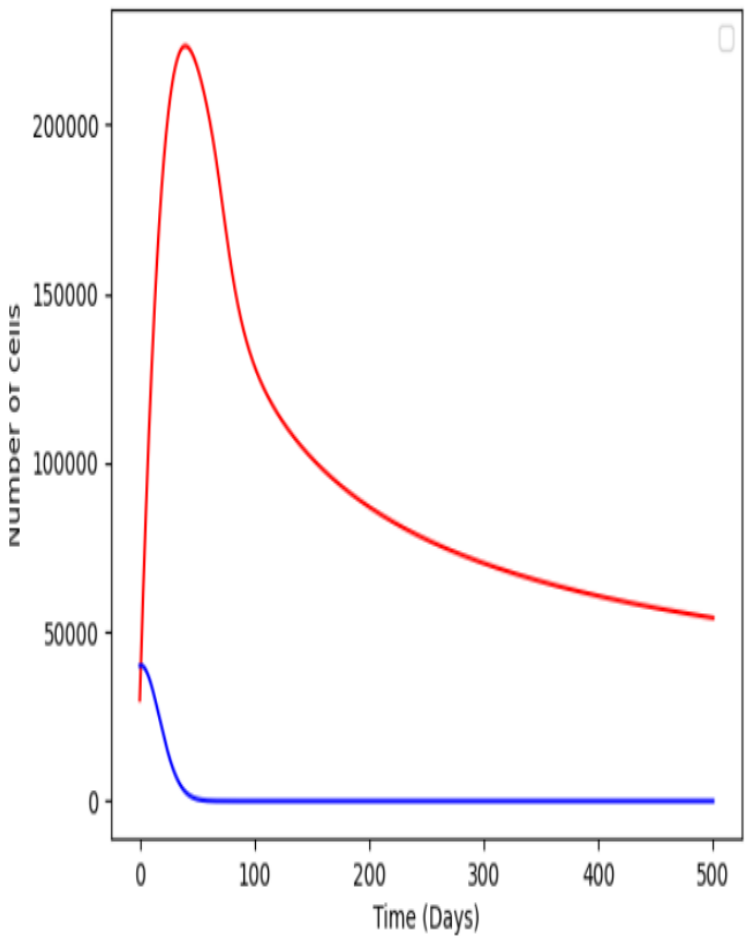
In this research, the simulation is visually presented using three graphs. These graphs serve as illustrations that provide a clear representation of the study's findings.The first aspect depicted in the graphs is the value of the basic parameters. These parameters serve as the foundation of the simulation and play a crucial role in determining its outcomes. By showcasing the values of these fundamental parameters, the graphs provide a reference point for understanding the subsequent changes made to specific parameters.

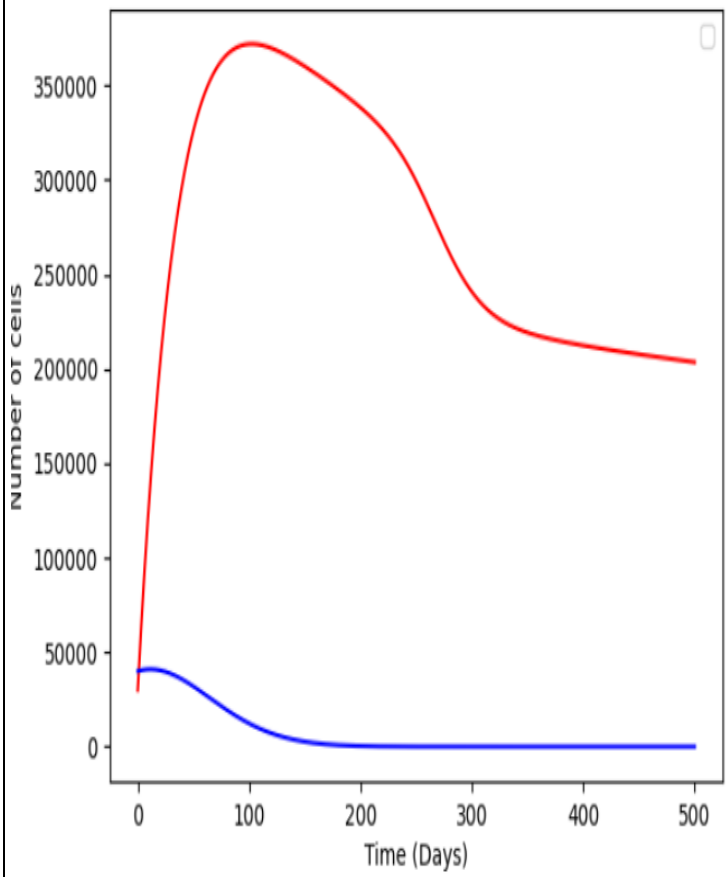
Additionally, the graphs also display modified values of certain parameters. Specifically, two parameters undergo changes in their values throughout the simulation: the rate of cancer cell growth and the rate of concentration of the chemotherapy drugs V. By altering these parameters, researchers aim to observe the effects of different growth rates of cancer cells and varying concentrations of chemotherapy drugs V on the overall outcome of the simulation.

K_E=0.001 ,K_T=0.005 ,V_M = 0.5

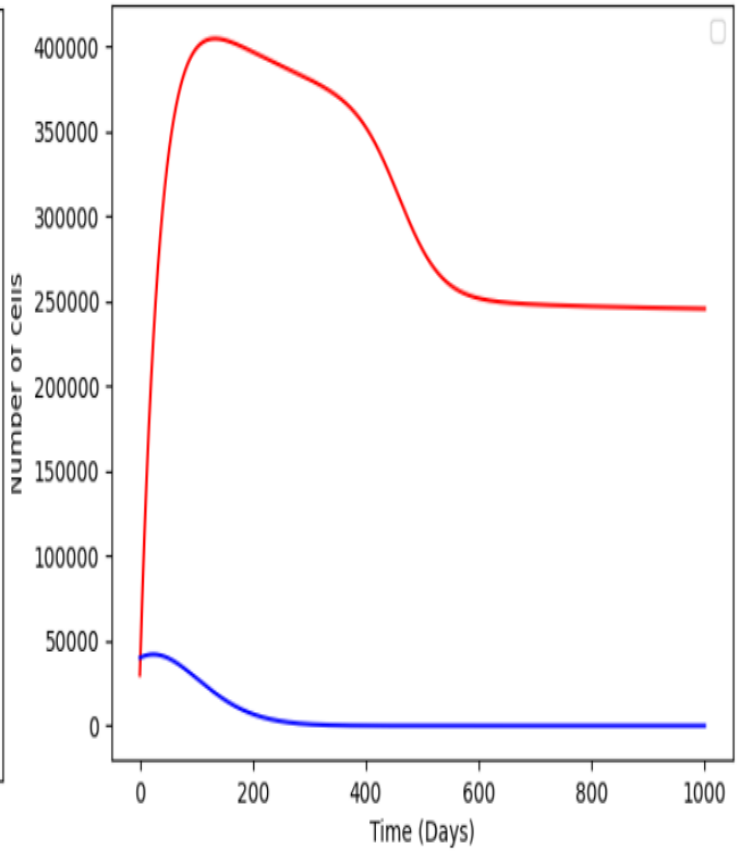


K_E=0.001 ,K_T=0.005 ,V_M = 0.7

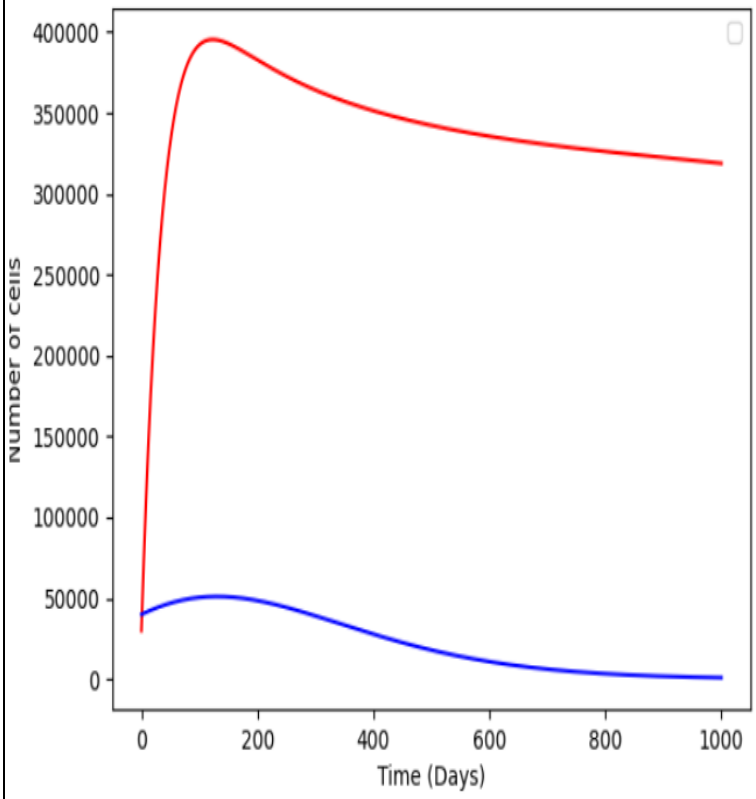




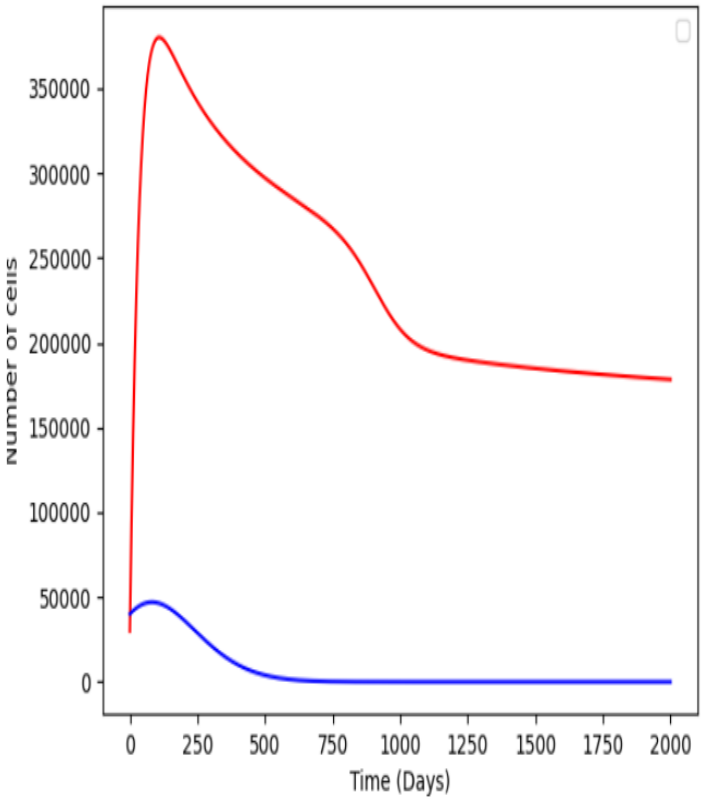
K_E= 0.0001, K_T=0.0005, V_M = 0.5



K_E= 0.0001, K_T=0.0005, V_M = 0.8



K_E=0.0001, K_T=0.0001, V_M = 0.5



K_E= 0.0001, K_T=0.0001, V_M = 0.7

CONCLUSION:

In this research obtained the epidemic model of cancer with chemotherapy in the form of a system of non linear differential equations with three sub-populations. Mathematically, we get equilibrium points are the cancer free equilibrium point and the cancer equilibrium point. Based on the simulation, the greater the growth rate of cancer with other parameter values is constant, the higher the cancer cells. Besides, it is also obtained that the increasing dosage of the drug given with the limits allowed, the lower of those cancer cells.

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