Section A -Research paper

ACHEMOSTAT CANCER MODEL : SIMULATION FOR CHEMOTHERAPY WITH THE EFFECT OF APOPTOSIS

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Abstract

Cancer is one of the most threaten diseases which are prevailing in the world, its fatal outcomes and dangerous side effects of the treatment are making lives miserable of the patients who are suffering from it, and the condition becomes even more severe when it takes the form of metastasis. The aim of this paper is to understand the complexity of cancerous cells by applying chemotherapy along with apoptosis mechanism. The rate of drug incorporate into tumor environment and it is been observed mathematically, with the rate of adhesion between chemotherapy and cancer cell increase the density of tumor cells reduced. Here, we are modelling the problem using Chemostat model with the effect of programmed cell death along with chemotherapy. We have incorporated the rate of apoptosis,it is found that the rate of apoptosis increase, along with induced drug and together they work to increase elimination of cancer cell which leads to wash out the cancer cells.

Keywords: Cancer; Chemostat model, Apoptosis, Chemotherapy, Stability analysis, Hopf bifurcation.

Introduction

Cancer is a disease known for its uncontrollable growth. As per biological significance it comes under the lethal disease in the worldwide nation. According to American cancer society, the number of patients of cancer in USA increases in a drastic manner every year(American cancer Society , www.cancer.org). The accurate reason for cancer is still unknown but (Fares, J., Fares, M.Y.,

Khachfe, H.H. et al(2020)suggested.as per biological morphism there are several factors to induct healthy cells to differentiated cell and further they turned fully mature for malignant stage.The dynamics of the human body are genetically predetermined, not by ageing or unintentional events, but by active cell suicide (death), or Programmed Cell Death(Apoptosis).Apoptosis plays major role by sending signals to cell for any kind of damage in DNA and the cells start healing by repairing themselves or if they found to be incapable of healing or fixing so they choose suicide under apoptosis this is how the mechanism works in the undergo process in apoptosis on the other hand the deprivation of programmed cell death leads the drastic effect that means it creates the environment for the survivals for the cancerous cells and they ignore signal(Yan X, Zhou R, Ma Z.,(2019)). Body mechanism works genetically properly and remove unwanted cell from body. In particular, mathematical model has been used toobserve the intensity of chemotherapy to cure cancer. From mathematical point of view, there are several scientific studies in which chemotherapy has been used to treatcancer(S. Pinho, H. I. Freedman and F. Nani, (2002), E. D. Sontag, (2018),Martin RB, Fisher ME, Minchin RF, Teo KL(1990),H. Knolle, (1988),J.M. Greene, J.L. Gevertz, E.D. Sontag, (2019),A. Świerniak, U. Ledzewicz, H. Schättler, (2003),Ge Song Guizhen Liang , Tianhai Tian and Xinan Zhang (2022)).According toU.S. Food and Drug Administration (www.fda.gov)Chemotherapy medications like Mitotane, Bavencio, and Hydroxyurea are utilised as chemotherapeuticagents.Other methods to treat cancer are radiotherapy, immune response therapy, surgery etc. Dingli D, Michor F. (2006)observed chemotherapeutic agents target malignant cells to limit their excessive growth and the effects of behaviour-induced apoptosis.Chemotherapy and cancer cells have adverse impacts on one another's rates of growth, and hematopoietic mature stem cells suppressed by therapy(Ismail Abdulrashid, Xiaoying(2020)).The Chemostat model, which examines all variables with regard to growth of cell and chemotherapy drug, can be used to understand how chemotherapy and apoptosis interact along with the adhesion.The Complex fiding why chemotherapy fail byKról M, Pawłowski KM, Majchrzak K, Szyszko K, Motyl T.(2010)suggested Chemotherapeutic agent only induced apoptosis in the mature stem cells this process results in a substantial shift in the tumor which leads in the drastic change of tumor burden.If the chemotherapy treatment was halted,the nature of tumor continues enlarged tumor cells and affects the whole treatment leads to fail.

Mathematical Model

The architect ofChemostat is used for bacterialcompetitionmodellingand the continuous growth of microorganisms in the given medium and in specific condition,(Novick A, Szilard L (1950). ,James TW (1961). D Herbert; R Elsworth; RC Telling (1956).)now a days the purpose of Chemostat model is to not only find bacterial growth but also used in chemotherapy (Ismail Abdulrashid, Xiaoying (2020),Nor Afiqah Mohd Aris and Siti Suhana Jamaian Coralie Fritsch, Jérôme Harmand, Fabien Campillo(2014),V. Lemesle, J-L. Gouze´ (2004)), here we have applied Chemostat model to cancer dynamics. InFig (1) cells are occupied into limited amount of stocks i.e. nutrients medium.. Furthermore,the process required the nutrients but due to uncontrolled growth of a cell,nutrients were consumed by cells in a drastic manner, due to the lack of the nutrients the environment changed.The cell volume is assumed to be preoccupying by the cancerous cell but the condition is for model the cell volume is always preoccupied. The cell concentration increased and the washout condition occurs. The assumption we have taken is that the tumor is having the fixed point and here we not include healthy stem cells in this model. We have considered that there are killer cells (cancerous) in the tumor and by the induced of chemotherapeutic agents with the rate of apoptosis .The cancer cells will start dyeing.The cells will also die because of the programmed cell death (apoptosis).The assumption regarding the experimental data for chemotherapy drug BAVENCIO and rate of apoptosis(U.S. Food and Drug Administration www.fda.gov,Prieto A, Díaz D, Barcenilla H, García-Suárez J, Reyes E, Monserrat J, San Antonio E, Melero D, de la Hera A, Orfao A, Alvarez-Mon M. (2002))for the validation for model we consider

- The amplification of tumor cell and the interaction of chemotherapy drug with the rate of adhesion.
- To study the impact of programmed cell death along with chemotherapy the output of the result interlinked between the tumor cells and chemotherapeuticagent.
- To understand the dynamics of the antitumor agent and the effect on the cancer and its uncontrollable growth.

Greenspan, H. P. (1972)suggested that the amplification factor of cancerous cell may affect the result of steady state and equilibrium,i.e. the physiological properties for instance apoptosis and infected cell growth effect into the entire procedure.

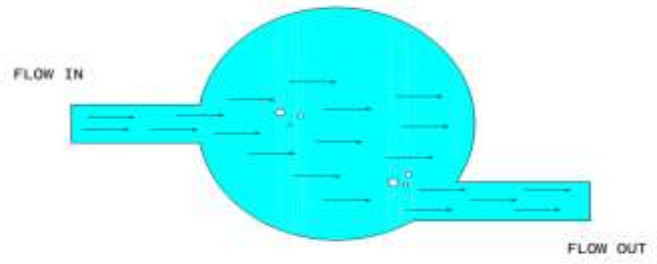


Figure1: Architect of Chemostat

Model Formulation

Here we are considering that tumor cells are occupying the fixed volume V.We are assuming to construct a model which is occupied with cancerous cell only and we are considering that there is no healthy cells in that volume. The main objective is to form Chemostat model with incorporating drug the decay of cancerous cells under the influence of the induced chemotherapy and the termination of dead cell mechanism.It is considered that both the chemotherapeutic drug and the cancerous cells are budding together N_T , C_T are denoted as cancer cells and chemotherapeutic agent respectively. Let the theoretical background of Chemostat with inwards flow and outwards flow for blood stream. $F_{in} = F_{out} = F$ the blood stream ongoing into and coming out from the cancer site, which means $F_{in} = F_{out} = F(t) \neq 0$.The purpose of this work is to study the impact of chemotherapy which are assumed to be diluted in blood stream with respect to time depended concentration. Let there are basic equations and they formed when no interaction between the disease and therapy

$$\frac{dN_T}{dt} = KN_T \text{ and } \frac{dC_T}{dt} = \alpha K C_T N_T$$

$$\frac{dN_T}{dt} = kN_T - \beta_1 N_T C_T - \beta_2 N_T \qquad (1)$$

Where N_T is for the population of tumor cells, β_1 is for the rate by which chemotherapeutic agent is killing the tumor cells. α is the rate of adhesion of chemotherapy and tumor cells. K is the term used for Michaelis Menten, β_2 rate at which naturally the tumor cells are being killed by apoptosis.

$$\frac{dC_T}{dt} = \alpha \frac{k_{\max}}{k_n + c} C_T N_T - \frac{F}{V} C_T + \frac{F}{V} C_{T0} \quad (2)$$

$$\frac{dN_T}{dt} = KN_T \frac{F}{V} - \beta_1 \frac{k_{\max}}{k_n + c} C_T N_T - \beta_2 N_T \frac{F}{V} \quad (3)$$

$\frac{k_{\max}}{k_n + c}$ is term of Michaelis Menten function

$$\frac{dC_T}{dt} = \alpha \frac{k_{\max}}{k_n + c} C_T N_T - \frac{F}{V} C_T + \frac{F}{V} C_{T0} \quad (4)$$

From eq.(1),eq.(2) we add some appropriate terms in eq.(3) and eq.(4) with corresponding flow in the direction of inwards and outwards for chemotherapy and tumor cells. Where $\frac{F}{V} C_{T0}$ is the within-flow into the tumor volume and $\frac{F}{V}$ is the flow per unit volume , N_T ,$-\frac{F}{V} C_T$ outwards flow. We consider this because chemotherapeutic agent and tumor cells will not go with infinite speed. For the dynamically point of view we add constant positive values for C_T ,where $k_{\max}$ is the maximal velocity of escapism.

Non Dimensionalization

Non dimensionalization are ruling tools for analysis the compatibility and the function of the equation for making appropriate and compatible model to solve the mathematical analysis in eq.(3)and (4) . By dropping asterisk sign the dimensionless form of the equation we get the new eq.(5),(6)

$$\gamma_1 = k_{\max} \frac{V}{F}, \gamma_2 = \frac{C_0}{k_n}$$

$$\frac{dN_T}{dt} = N_T - \gamma_1 \frac{C_T}{1 + C_T} N_T - \beta_2 N_T \quad (5)$$

$$\frac{dC_T}{dt} = -\frac{C_T}{1 + C_T} N_T - C_T + \gamma_2 \quad (6)$$

$\frac{C_T}{1+C_T}$ is the new non dimensionlize Michaelis Menten function. γ_1 is the rate of adhesion in chemotherapy and tumor cells whereas, γ_2 is the rate with which the infused chemo (drug) is getting out of tumor in the blood stream without getting attached to the tumor cells. In the below section the units and the terms represent the following parameters

Table1-Parameters and unit for the Model

Parameter	Unit
β_1	0.73 pg/ml ref.[21]
β_2	0.42estimated
γ_1	.6 estimated
γ_2	1.526 estimated
N_T	$10^5 - 10^6$ ref.[15]

Equilibrium State

To findthe exact analyse state of equilibrium we found two relations between tumor and chemotherapy equation:

$\frac{dN_T}{dt}$=0, $\frac{dC_T}{dt} = 0$ in equation (6)we substitute $N_T = 0$

$$-\frac{C_T}{1+C_T} N_T - C_T + \gamma_2 = 0$$

$\frac{C_T}{1+C_T} N_T = \gamma_2$ from$(\bar{N}_T, \bar{C}_T) = (0, \gamma_2)$,now for the non trivial the other condition : $\bar{N}_T > 0$

$$\gamma_1 \frac{\bar{C}_T}{1+\bar{C}_T} = 1 - \beta_2$$

$$\bar{C}_T = \frac{1-\beta_2}{(\gamma_1 - 1 + \beta_2)} = \frac{1}{\frac{\gamma_1}{1-\beta_2} - 1} \qquad (7)$$

$$-\frac{\overline{C}_T}{1+\overline{C}_T}\overline{N}_T-\overline{C}_T+\gamma_2=0$$

$$-$$

$$\overline{N}_T,\overline{C}_T=\left(\left[-\frac{1}{\left(\frac{\gamma_1}{1-\beta_2}\right)-1}+\gamma_2\right]\left(\frac{\gamma_1}{1-\beta_2}\right),\frac{1}{\frac{\gamma_1}{1-\beta_2}-1}\right) \quad (8)$$

Stability Analysis and Linearization

As our model is non linear, to further proceed we must linearize the system in consideration. We use stability analysis and linearization to check closed to steady state the conclusion, can be approximation [17]

$\frac{dx}{dt}=P(N,C)$

$\frac{dy}{dt}=Q(N,C)$, where P and Q are the nonlinear functions.

We assume that $\overline{N}$ and $\overline{C}$ are the solution of steady state, i.e., the equation $P(\overline{N},\overline{C})=Q(\overline{N},\overline{C})$ is satisfied, Now the derivation for the solutions of steady state

$N(t)=\overline{N}+n(t)$

$C(t)=\overline{C}+c(t)$

$\frac{d}{dt}(\overline{N}+n)=P(\overline{N}+n,\overline{C}+c),$

$\frac{d}{dy}(\overline{C}+c)=Q(\overline{N}+n,\overline{C}+c)$

$\frac{dx}{dt}=P(\overline{N},\overline{C})+n\frac{\partial}{\partial x}P(\overline{N},\overline{C})+c\frac{\partial}{\partial y}P(\overline{N},\overline{C})$ where $P_x(\overline{N},\overline{C})$ is $\frac{\partial P}{\partial x}$ evaluated at $(\overline{N},\overline{C})$ and

similarly for P_y, Q_x, Q_y and other terms.Again by definition, $P(\overline{N},\overline{C})=0=P(\overline{N},\overline{C})$ so we left with

$\frac{dx}{dy} = a_{11}x + a_{12}y,$

$\frac{dy}{dt} = a_{21}x + a_{22}y,$ Where the Matrix of coefficients $A = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} = \begin{pmatrix} P_x & P_y \\ Q_x & Q_y \end{pmatrix}_{(\bar{N},\bar{C})}$ is the Jacobian of the systems of the equations.

Local stability in special 2D case

Let $y' = A.y$ where A=$\begin{vmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{vmatrix}$ β = trace $A = a_{11} + a_{22}$,and determinant γ =det $A = a_{11}a_{22} - a_{12}a_{21}$

For the phase portrait the stability is likely to be present at a condition where β <0 and γ >0

$$\frac{dN_T}{dt} = N_T - \gamma_1 \frac{C_T}{1+C_T} N_T - \beta_2 N_T$$

$$\frac{dC_T}{dt} = -\frac{C_T}{1+C_T} N_T - C_T + \gamma_2$$

the value of β and γ is coming out to be $\frac{\gamma_1 C_T - \beta_2(1+C_T)}{1+C_T} < 0$ and $\frac{-1+\beta_2}{(1+C_T)^2} > 0$ respectively. Hence, the model is saddle at the found values and equilibrium state. Furthermore, the System of ODE's with two equations in vector notation is given as[17]

$\frac{d}{dt} y = Ay$ Where $y = [y_1 \; y_2]$,A is the coefficient of the system of ODE given as

$A = \begin{vmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{vmatrix}$ this solution can be given as $y(t) = Ve^{\lambda t}$ Where, V is the vector which is not dependent on time. By incorporating this idea we can write $\frac{dy}{dt} = Ave^{\lambda t}$

$[A - \lambda I]V = 0$. T have an obvious solution at $V = 0$ but besides this obvious solution the second possibility that we may have for the solution is given by $[A - \lambda I] = 0$, which is the characteristics equation for the system of ODEs that we are considering. The Eigen value of the matrix can be given as

$\lambda_i = \frac{\beta \pm \sqrt{\delta}}{2}$ Where β =trace $A = a_{11} + a_{22}$

$\gamma = \det A = a_{11}a_{22} - a_{12}a_{21}$

$\delta = discA = \beta^2 - 4\gamma$,

Biological Interpretation

In this paper we have assumed a tumour of volume V which is having a cell population density of cancer cells and few cells are dying because of the apoptosis i.e. programmed cell death and few more cells are dying because of the induced chemotherapy and the rate of proliferation of cancer cells has reduced to 1 whereas, the rate of apoptosis is (β_2).We have observed In our model that if $1-\beta_2 < 0$, $\beta_2 > 0$, $\beta_2 = 0$ the following condition will be followed

$1-\beta_2 < 0$ All the cancer cells will grow with the rate $(1-\beta_2)$

$1-\beta_2 > 0$ All the cancer cells will die

$1-\beta_2 = 0$ No change point of stagnation, where β_2 is the rate of Apoptosis.

We can see that the rate of apoptosis is playing a key role in controlling the growth and progression of cancer cells and is working positively with the chemo to fight against the infected cell.Here we computing the analysis of the equation and we get $J = \begin{pmatrix} \frac{\partial F_1}{\partial N_T} & \frac{\partial F_1}{\partial C_T} \\ \frac{\partial F_2}{\partial N_T} & \frac{\partial F_2}{\partial C_T} \end{pmatrix} =$

$$\begin{pmatrix} 1-\frac{\gamma_1.C_T}{1+C_T}-\beta_2 & -\frac{\gamma_1 N_T}{(1+C_T)^2} \\ -\frac{C_T}{1+C_T} & \frac{-N_T}{(1+C_T)^2}-1 \end{pmatrix} \begin{vmatrix} 1-\frac{\gamma_1\left[\frac{1-\beta_2}{\gamma_1-(1-\beta_2)}\right]}{1+\gamma_1\left[\frac{1-\beta_2}{\gamma_1-(1-\beta_2)}\right]}-\beta_2 & \frac{-\gamma_1\left[\frac{-\gamma_1}{\gamma_1-(1-\beta_2)}+\frac{\gamma_2\gamma_1}{1-\beta_2}\right]}{\left(1+\gamma_1\left[\frac{1-\beta_2}{\gamma_1-(1-\beta_2)}\right]\right)^2} \\ -\frac{\gamma_1\left[\frac{1-\beta_2}{\gamma_1-(1-\beta_2)}\right]}{1+\gamma_1\left[\frac{1-\beta_2}{\gamma_1-(1-\beta_2)}\right]} & \frac{-\frac{\gamma_1}{\gamma_1-(1-\beta_2)}+\frac{\gamma_2\gamma_1}{1-\beta_2}}{\left(1+\gamma_1\left[\frac{1-\beta_2}{\gamma_1-(1-\beta_2)}\right]\right)^2}-1 \end{vmatrix}$$

$$\beta = \left[1-\frac{\gamma_1.C_T}{1+C_T}-\beta_2\right]+\left[\frac{-N_T}{(1+C_T)^2}-1\right]$$

$$\frac{\left(1+\frac{1-\beta_2}{\gamma_1-1+\beta_2}\right)-\gamma_1\left(\frac{1-\beta_2}{\gamma_1-1+\beta_2}\right)-\beta_2-\beta_2\left(\frac{1-\beta_2}{\gamma_1-1+\beta_2}\right)}{\left(1+\frac{1-\beta_2}{\gamma_1-1+\beta_2}\right)}+$$

$$\frac{\frac{(1-\beta_2-\gamma_2\gamma_1+\gamma_2-\gamma_2\beta_2)\frac{\gamma_1}{1-\beta_2}}{\gamma_1-1+\beta_2}-\left(\frac{1-\beta_2}{\gamma_1-1+\beta_2}\right)^2-1-\left(\frac{2-2\beta_2}{\gamma_1-1+\beta_2}\right)}{\left(1+\frac{1-\beta_2}{\gamma_1-1+\beta_2}\right)^2}$$

$$\frac{\frac{(1-\beta_2-\gamma_2\gamma_1+\gamma_2-\gamma_2\beta_2)\frac{\gamma_1}{1-\beta_2}}{\gamma_1-1+\beta_2}-\left(\frac{1-\beta_2}{\gamma_1-1+\beta_2}\right)^2-1-\left(\frac{2-2\beta_2}{\gamma_1-1+\beta_2}\right)}{\left(1+\frac{1-\beta_2}{\gamma_1-1+\beta_2}\right)^2}$$

$$\frac{\left(\frac{\gamma_1-\gamma_1\beta_2-\gamma_2{\gamma_1}^2+\gamma_2\gamma_1-\gamma_2\gamma_1\beta^2}{1-\beta^2}.(\gamma_1-1+\beta_2)-\gamma_1-1+\beta_2.(\gamma_1-1+\beta_2)\right)}{\left[(\gamma_1-1+\beta_2)^2+1-2\beta_2+{\beta_2}^2-\gamma_1-1+\beta_2.(\gamma_1-1+\beta_2)\right]}$$

$$\frac{-\gamma_2\gamma_1^3+2\gamma_2\gamma_1^2-2\gamma_2\gamma_1^2\beta_2-\gamma_2\gamma_1+2\gamma_2\gamma_1\beta_2-\gamma_2\gamma_1\beta_2^2-\gamma_1+2\gamma_1\beta_2+1-3\beta_2+3\beta_2^2-\beta_2^2\gamma_1-\beta_2^4}{(-2\beta_2^2+\beta_2^2\gamma_1+\beta_2^3-\gamma_1+1).(1-\beta_2)} \quad (9)$$

$$\gamma=\left[\left(1-\frac{\gamma_1.C_T}{1+C_T}-\beta_2\right).\left(\frac{-N_T}{(1+C_T)^2}-1\right)-\left(-\frac{C_T}{1+C_T}\right).\left(-\frac{\gamma_1 N_T}{(1+C_T)^2}\right)\right]$$

$$-\left(-\frac{C_T}{1+C_T}\right).\left(-\frac{\gamma_1 N_T}{(1+C_T)^2}\right)$$

$$\frac{1-\beta_2}{\gamma_1}.\frac{(\gamma_1-{\gamma_1}^2\beta_2+\gamma_2\gamma_1\beta_2)}{\beta_2(1-\beta_2)}.\frac{(\gamma_1-1+\beta_2)}{2\gamma_1-1+\beta_2-\gamma_1\beta_2}$$

$$-\frac{\left[\gamma_1-1+\beta_2-{\gamma_1}^2\beta_2+\gamma_1\beta_2-\gamma_1{\beta_2}^2+\gamma_1\gamma_2\beta_2-\gamma_2\beta_2+\gamma_2{\beta_2}^2\right]}{2\gamma_1\beta_2-\beta_2+{\beta_2}^2-\gamma_1{\beta_2}^2} \quad (10)$$

Routh Hurwitz Criteria

In a system of $n \times n$ order matrix $|A - \lambda I| = 0$ of the characteristics equation of the above will be given $a_o\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-3}.....a_n = 0$ which is a polynomial of degree of n. H_1 is of order 1×1 and H_2 is the order of 2×2 determinants respectively, where $a_0 = 1$

$a_1, a_2.....a_n$ are all constants[17]. Now, for our condition

$$\begin{vmatrix} \dfrac{1-\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)}{1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)} + \theta_2 - 1 - \lambda & \dfrac{-\theta_1\left[\left(\dfrac{-\theta_2}{\theta_1-\theta_2}\right)+\dfrac{\theta_1\theta_3}{\theta_2}\right]}{\left[1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)\right]^2} \\ -\dfrac{\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)}{1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)} & -\dfrac{\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)+\dfrac{\theta_1\theta_3}{\theta_2}}{\left[1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)\right]^2} - 1 - \lambda \end{vmatrix}$$

Where $\theta_1 = \gamma_1,\ \theta_2 = 1-\beta_2\ \theta_3 = \gamma_2$

By solving $\left(\dfrac{1-\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)}{1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)} + \theta_2 - 1 - \lambda\right)\left(\dfrac{\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)+\dfrac{\theta_1\theta_3}{\theta_2}}{\left[1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)\right]^2} - 1 - \lambda\right)$ and $\left(\dfrac{-\theta_1\left[\left(\dfrac{-\theta_2}{\theta_1-\theta_2}\right)+\dfrac{\theta_1\theta_3}{\theta_2}\right]}{\left[1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)\right]^2}\right)$

$$-\frac{\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)}{1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)}$$

We got $\lambda^2 + A\lambda + \beta$ here the characteristic equation is defined for (2×2) matrix and for Routh

Hurtwiz criteria $H_1 = \left|\dfrac{1-\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)}{1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)} + \theta_2 - 1 - \lambda\right|$, (11)

$$H_2 = \begin{vmatrix} \dfrac{1-\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)}{1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)} + \theta_2 - 1 - \lambda & \dfrac{-\theta_1\left[\left(\dfrac{-\theta_2}{\theta_1-\theta_2}\right)+\dfrac{\theta_1\theta_3}{\theta_2}\right]}{\left[1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)\right]^2} \\ -\dfrac{\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)}{1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)} & -\dfrac{\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)+\dfrac{\theta_1\theta_3}{\theta_2}}{\left[1+\theta_1\left(\dfrac{\theta_2}{\theta_1-\theta_2}\right)\right]^2} - 1 - \lambda \end{vmatrix} \quad (12)$$

For the case-

The condition matrix for H_j for (l,m) term can be stated as C_{2l-m} for $0<2l-m<2$ .Here $l=2$ and the eigen values are complex with negative real part ,Hence the solution has unstable steady state.

Hopf Bifurcation

There are some classic rules for bifurcation, suppose there exist a stable equilibrium

(a) $\lambda=0$ Bifurcation occurrence in the saddle node and transcritical pitchfork

(b) $\lambda=\pm i\omega$ condition for Hopf Bifurcation occurs when a pair of complex conjugate appears under Hopf bifurcation **.**If both real parts i.e.$(R_e\lambda_1\lambda_2)<0$ and the appearance of both parts are negative then the fixed point is linearly stable the reason behind is the real parts controls the decay rate of the solution in fixed point and bifurcation happens when Eigen values cross into the half plane. Now, the parameters values of the Chemostat cancer model $(\overline{N}_T,\overline{C}_T)=(\lambda_1,\lambda_2)$,the eigen values for the given term Calculate the Value

$$\lambda_i=\frac{-2.0060\pm\sqrt{-2.0060^2-4*1.08147}}{2}$$

$$\frac{-2.0060\pm\sqrt{-0.30188}}{2}$$

$$\frac{-1.0030\pm.54943i}{2}$$

$$\lambda_1=-1.0030+.274718i$$

$$\lambda_2=-1.0030-.274718i$$

$$\begin{cases}\lambda_1=-1.0030+.274718i\\ \lambda_2=-1.0030-.274718i\end{cases} \qquad (13)$$

Based on the above Eigen value these equation satisfy the condition of the Hopf Birufication (b)

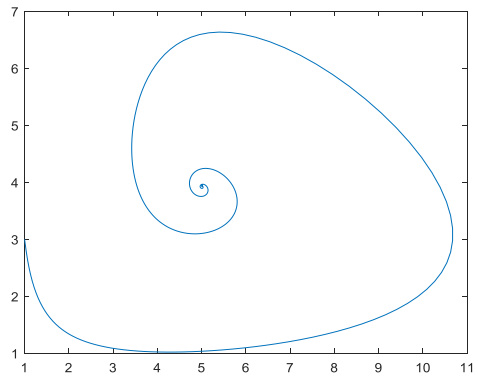


Figure2:Hopf Bifurcation

Numerical Simulation and Result Discussion

The numerical simulation has been carried out using MATLAB for the Phase portrait and also it is shown that how the different rate of chemotherapy along with apoptosis will effect and control the proliferation along with progression of cancerous cell. T is obvious that the region {(x, y1, y2)| x > 0, y1 ≥ 0, y2 ≥ 0|} is positively invariant for model.

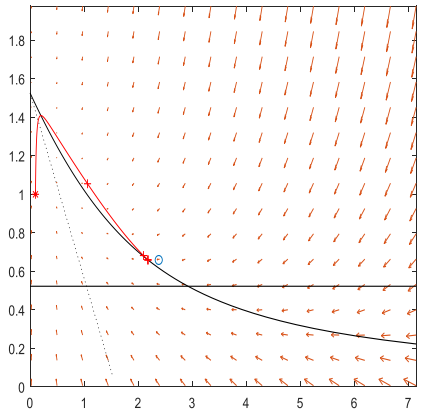


Fig3(a)

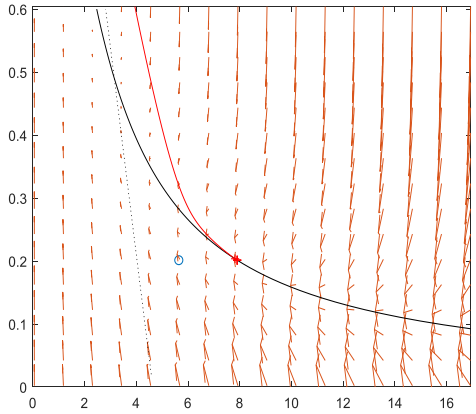


Fig3(b)

Phase portrait for Chemostat figure represents Nullcline and Euler path,red lines shows is the Euler path, The black line are Nullcline for N_T and C_T .Dotted black line represent invariant line and red arrow shows the orientation of vector field in fig3(a) and fig3(b).In fig 3(a) applied the rate of drug .73mg/ml, and in fig 3(b) We increase the rate of drug 1.73pg/ml to check the effect on tumor and apoptosis.

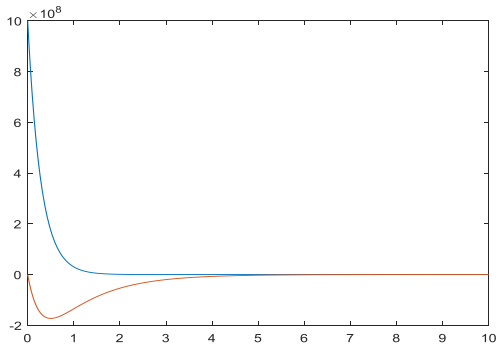


Fig4(a)

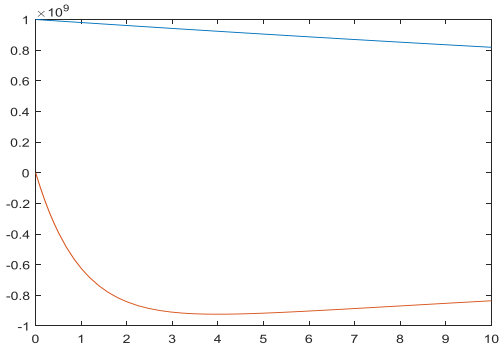
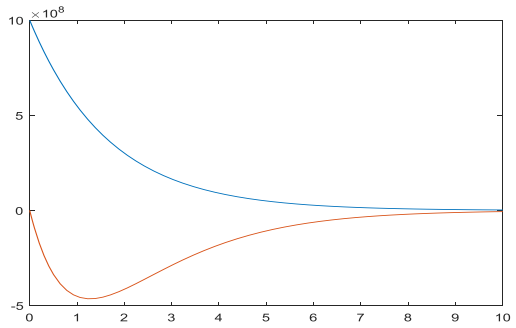


Fig4(b)



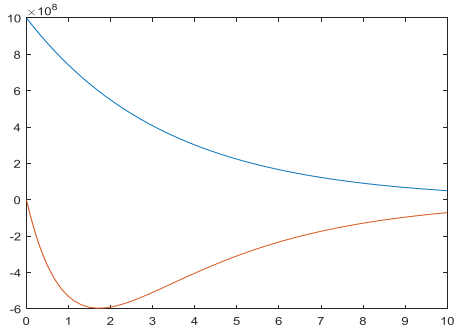


Fig4(c) Fig4(d)

Here,we used the drug BAVENCIO[11]to treat the cancer with the rate $\gamma_1 = .73$ pg/ml and $\beta_2 = .42$ the rate of apoptosis[22].We observed in fig4(a) Cancer cell proliferation and chemotherapy affect the stagnationin tumor growth, cells reached where the proliferation of cancer cell is equal to chemotherapy the rate and it increase rate of which infused chemo is getting out of tumor with blood stream without getting attached to the tumor cells.The drug used to slow down the process of tumor cell with rate of adhesion in chemotherapy and tumor cell also it slightly decrease rate of which infused chemo is getting out of tumor with blood stream without getting attached to the tumor cells . In fig4(b) the rate of adhesion $\gamma_1 = .6$ along the rate of apoptosis increased the number of cell dying with decrease dose rate of chemo .15pg/ml and proliferation of cancer cell increased and action is decline towards the chemotherapy ,the natural defence of the body mechanism like programmed cell death increased into the procedure.In fig4(c) as we decrease the rate of adhesion in chemotherapy and tumor cell $\gamma_1 = 1$along with the rate of apoptosis the rate of chemo and proliferation of cancer cell is closer to chemo ,the natural defence of the body mechanism like programmed cell death increased into the procedure Fig(d)the rate of adhesion in chemotherapy and tumor cell $\gamma_1 = .8$ along with the rate of apoptosis the rate of chemo .73pg/ml and proliferation of cancer cell is the rate of cancer cell is much greater than chemo and the study observe the declinerate of which infused chemo is getting out of tumor with blood stream without getting attached to the tumor cells.

In our study the increase in the chemotherapy concentration along with rate of apoptosis will slowdown the rate of growth of cancer cells which will lead the cancer cell dieand when all the cells will be flushed out from the tumor volume and if there will be more cancer cell than the chemo will

be also be flushed out from the system and the condition of complete washout will be achieved. It is a hypothetical condition forthe model.

Conclusion

In this paper we have modelled cancer dynamics using Chemostat model where a tumour was considered with only the population of cancer cells and how these cells grow and getting killed and being flushed out in the presence of chemotherapy and apoptosis.We have seen that it helps to destroying cancer cells and if the rate of apoptosis is higher along with the induced drug it will help the cancer cells toget controlled proliferation and the death rate will be increased which will ultimately helpin controlling the disease and reducing the cell population in the tumor site.

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