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RESEARCH ARTICLE

The effect of a psychological scare on the dynamics of the tumor-immune interaction with optimal control strategy

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ABSTRACT

Contracting cancer typically induces a state of terror among the individuals who are affected. Exploring how chemotherapy and anxiety work together to affect the speed at which cancer cells multiply and the immune system's response model is necessary to come up with ways to stop the spread of cancer. This paper proposes a mathematical model to investigate the impact of psychological scare and chemotherapy on the interaction of cancer and immunity. The proposed model is accurately described. The focus of the model's dynamic analysis is to identify the potential equilibrium locations. According to the analysis, it is possible to establish three equilibrium positions. The stability analysis reveals that all equilibrium points consistently exhibit stability under the defined conditions. The bifurcations occurring at the equilibrium sites are derived. Specifically, we obtained transcritical, pitchfork, and saddle-node bifurcation. Numerical simulations are employed to validate the theoretical study and ascertain the minimum therapy dosage necessary for eradicating cancer in the presence of psychological distress, thereby mitigating harm to patients. Fear could be a significant contributor to the spread of tumors and weakness of immune functionality.

1. Introduction

Models are instruments utilized in medicine and science to interpret results, develop hypotheses, and plan experiments to verify them [1]. For instance, mathematical models of population dynamics are frequently represented by differences or differential equations that characterize the temporal evolution of populations [2–9]. Throughout history, ecology has predominantly employed mathematical models to offer qualitative explanations for natural patterns. An exemplary illustration of this methodology was the endeavour to elucidate species diversity through competition models [10–16]. Mathematicsematical modeling is a highly versatile instrument in the field of infectious disease epidemiology, enabling the detection of epidemic patterns, extrapolation of epidemic behaviors, and evaluation of the impact of interventions, including pharmacological treatment, immunization, quarantine, social distance, and hygiene practices, among others [17–22]. An example of a disease model is cancer, which is characterized by the proliferation of malignant cells that infiltrate other anatomical structures and currently ranks as the second most prevalent cause of mortality globally, surpassed only by cardiovascular disease. Developing novel treatment options is a burgeoning study field for scientists seeking to manage cancer effectively. Nevertheless, comprehending the

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intricacies of tumor cell proliferation and their intricate interplay with the immune system is crucial in order to devise novel therapeutic approaches. To accomplish this, researchers extensively depended on mathematical models [23–27]. Several scientists have extensively researched the mathematical modeling of tumor evolution, its interaction with different cells, and the process of tumor growth. They have achieved this by creating multiple models over the past few decades [28–33]. Cancer is amenable to a variety of treatment modalities, including chemotherapy, radiotherapy, and surgery. Chemotherapy, one of the cancer treatments, is a systematic approach that targets and eliminates cancer cells at the site of the tumor while minimizing its impact on effector-normal cells. This eliminates the ability of the tumor cells to metastasize to other anatomical sites [34–36]. For instance, De Pillis and his associates examined multiple mathematical models to quantify the effects of chemotherapy [37]. In addition, Pillis et al. devised a cancer treatment model in which they discovered that combining chemotherapy and immunotherapy can completely eradicate the tumor instead of using either therapy alone [38]. On the other hand, The initial mathematical model that incorporated the influence of fear in a predator-prey system involving two species was presented by Wang et al. in 2016 [39]. Prey animals may alter their grazing location to a more secure area and relinquish their most productive feeding sites due to predator-induced anxiety. The user's text is incomplete and lacks information [40–43]. Further, There has been a recent increase in research focusing on the importance of mathematical models for studying how fear-induced behavioral changes impact the spread of diseases [44–48]. A medical study has demonstrated that psychological stress contributes to the dissemination of cancer cells throughout the patient's body. Psychological stress causes significant dilation and intensification of blood vessels, hence promoting the migration of cancer cells and facilitating the metastasis of the disease [49]. Researchers have discovered that stress-induced hormones exacerbate the proliferation of cancer cells inside the "lymphatic system," thus facilitating their dissemination to other locations, thereby promoting the metastasis of the disease throughout the human body [50].

The present study proposes a psychological scare-cancer-immune-normal-chemotherapy model (PSCINC) regulated by systems of ordinary differential equations, drawing inspiration from the model presented in [51]. We have enhanced the model of De Pillis et al. by replacing the linear functional response with the Holling type II functional response. This modification allows us to accurately depict the eradication of tumor cells by the immune system, considering the possibility of a weakened immune system due to the presence of psychological scare of cancer. Further, there is a lack of study about the influence of fear on the immune-cancer model. Hence, we deem it imperative to examine this phenomenon, as it contributes to reducing the occurrence of catastrophic circumstances.

Further, there is a lack of study about the influence of fear on the immune-cancer model. Hence, we deem it imperative to examine this phenomenon, as it contributes to reducing the occurrence of catastrophic circumstances. Therefore, this study is dedicated to discussing the impact of anxiety on immune cancer patients, which could be a significant contributor to the spread of tumors and weakness of immune functionality. The subsequent sections of this document are organized as follows: section 2 examines the assumptions of the proposed model. The presence of potential equilibrium points is determined in section 3. Next, section 4 discusses the stability conditions of the steady states. The discussion in section 5 focuses on the global stability of equilibriums. In addition, section 6 acknowledges the local bifurcation conditions in close proximity to the fixed points. In section 7, numerical examinations are conducted to validate our analytical findings.

2. Assumptions of the model

Let's examine a system of differential equations (PSCINC) that involves immune cells I (t), tumor cells $C(t)$, normal cells $N(t)$, and chemotherapy treatment $H(t)$ represented as

$$\begin{aligned}
\frac{dI}{dt} &= \frac{\alpha}{1+eC} + \frac{p_1 IC}{\beta_1 + C} - p_2 IC - d_1 I - d_2 IH \\
&= h_1(I, C, H) \\
\frac{dC}{dt} &= m_1 C\,(1 - k_1 C) - \frac{p_3 IC}{\beta_2 + C} - \gamma_1 CN - d_3 HC \\
&= h_2(I, C, N, H) \\
\frac{dN}{dt} &= m_2 N\,(1 - k_2 N) - \gamma_2 CN = h_3(C, N) \\
\frac{dH}{dt} &= \nu - d_4 H = h_4(H)
\end{aligned} \tag{1}$$

In the first equation of the PSCINC model, the term $\frac{\alpha}{1+eC}$ stands for the regular production of immune cells in the body, which is affected by

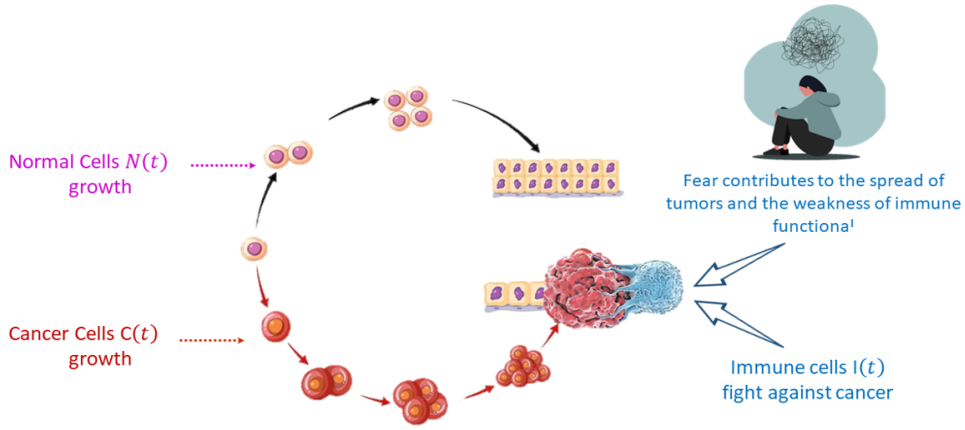
the presence of cancer cells by the psychological scare factor e. Therefore,e the birth-term changes by producing fear function. The fear function is incorporated by the decreasing function $\varphi(e,C) = \frac{1}{1+eC}$, which was initially introduced by Wang et al. [46]. From the biological point of view, $\varphi(e,C)$ is appropriate since

$$\phi(0,C)=1, \phi(e,0)=1,$$
$$\lim_{e\to\infty}\phi(e,C)=0,$$
$$\lim_{C\to\infty}\phi(e,C)=0,$$
$$\frac{\partial\phi(e,C)}{\partial e}<0, \frac{\partial\phi(e,C)}{\partial C}<0.$$

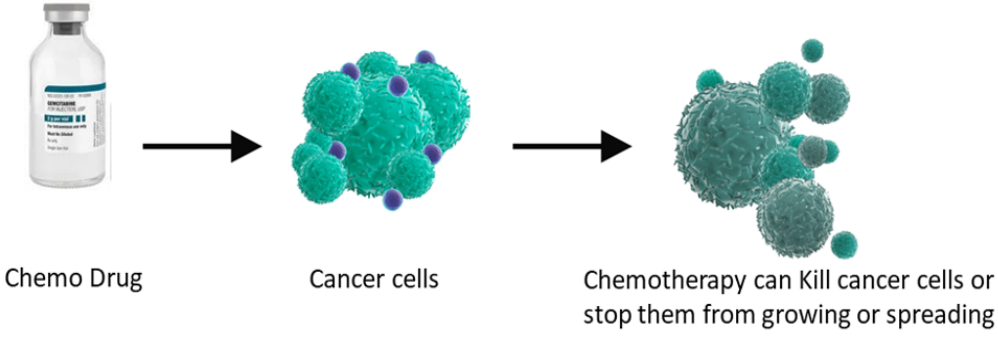
The Michaelis–Menten term $\frac{p_1\ IC}{\beta_1+C}$ signifies the existence of tumor cells that provoke the immune system's response. p_2IC indicates the immune cells' decay rate due to tumor cells. d_1I denotes the effector cells' death rate. d_2IH designates the decay rate of effector cells due to chemo-drug. In the second equation, the $(m_1C(1-k_1C))$ represents the tumor growth term. The term $\frac{p_3IC}{\beta_2+C}$ stands for the eradication of cancerous cells by the body's immune system. γ_1CN indicates the tumor cells' decay rate due to effector cells. d_3HC designates the decay rate of cancer cells due to chemo-drug. In the third equation, $m_2N(1-k_2N)$ denotes the normal cells' growth. γ_2CN represents the rate of disintegration of normal cells caused by the presence of tumor cells. In the last equation, ν is the infusion of chemotherapy drugs externally, and d_4H is the decay rate of the chemo-drug. All parameters were considered non-negative and visibly described in Table 1. Further, Figure 1 illustrates the schematic sketch of the (PSCINC) model.

The subsequent theorem establishes the positivity of all solutions of the (PSCINC) model in the positive orthant of R^4_+.

Theorem 1. *All of the solutions of the (PSCINC) model* $I(t), C(t), N(t)$ *and* $H(t)$ *with the initial conditions* $(I(0), C(0), N(0), H(0)) \in R^4_+$ *are positively invariant.*



(a) Before treatment



(b) After treatment

Figure 1. Schematic diagram of the (PSCINC) model.

Table 1. Description of (PSCINC) system's parameters.

Parameters	Denotation	Values	Source
α	A constant rate of immune cells	0.05	[47]
e	Psychological scare rate from cancer	0.1	Estimated
p_1	Maximum immune cell recruitment by tumor cells	0.1	[53]
β_1	Half-life of effector cells	0.4	[53]
p_2	Efficient elimination rate of malignant cells from effector cells	0.2	[47]
d_1	Effector cells' death rate	0.2	[53]
d_2	Decay rate of effector cells due to chemo-drug	0.09	[53]
m_1	Tumor's intrinsic growth rate	0.4	[53]
k_1	Tumor cells' carrying capacity	1.5	[53]
p_3	Maximum rate of killing the tumor cells by effector cells	0.3	[47]
β_2	Half-life of cancer cells.	0.4	[53]
γ_1	Tumor cell decay rate due to normal cells	0.2	[53]
d_3	Decay rate of cancer cells due to chemo-drug	0.05	[53]
m_2	Normal cell's intrinsic growth rate	0.35	[53]
k_2	Normal cells' carrying capacity	1	[53]
γ_2	Normal cell decay rate due to tumor cells	0.25	[53]
ν	Infusion rate of chemotherapy drugs	0.019	[53]
d_4	Decay rate of the chemo-drug	0.05	[53]

Proof. By integrating the second and third functions of the (PSCINC) model for $C(t)$ and $N(t)$ with a positive initial condition $(I(0), C(0), N(0), H(0))$, we obtain

$$C(t) = C(0)\exp\Big\{\int_0^t \Big[m_1 - m_1 k_1 C(s) - \frac{p_3 I(s)}{\beta_2 + C(s)} - \gamma_1 N(s) - d_3 H(s)\Big] ds\Big\} = Q_C > 0$$

$$N(t) = N(0)\exp\Big\{\int_0^t \Big[m_2 - m_2 k_2 N(s) - \gamma_2 C(s)\Big] ds\Big\} = Q_N > 0$$

From the first equation of the (PSCINC) model, we have

$$dI = \left(\frac{\alpha}{1+eC} + \frac{p_1 IC}{\beta_1 + C} - p_2 IC - d_1 I - d_2 IH\right) dt$$

$$dI \geq \Big[\frac{\alpha}{1+eQ_C} + I\Big(\frac{p_1 Q_C}{\beta_1 + Q_C} - p_2 Q_C - d_1 - \frac{d_2\nu}{d_4}\Big)\Big] dt$$

Therefore, after eliminating the non-negative terms, this produces 0000-0003-4022-8053

$$dI \geq \Big[I\Big(\frac{p_1 Q_C}{\beta_1 + Q_C} - p_2 Q_C - d_1 - \frac{d_2\nu}{d_4}\Big)\Big] dt$$

Consequently, by integrating the equation shown above for $I(t)$, these yields

$$I(t) \geq I(0)\exp\Big\{\int_0^t \Big[\Big(\frac{p_1 Q_C}{\beta_1 + Q_C} - p_2 Q_C - d_1 - \frac{d_2\nu}{d_4}\Big)\Big] ds\Big\}$$

Similarly, from the last equation of the (PSCINC) model, we get

$$dH = (\nu - d_4 H)\, dt \Longrightarrow dH \geq -d_4 H dt$$

By integrating the above equation, we get

$$H(t) \geq H(0)\, exp\left\{\int_0^t -d_4 ds\right\}$$

Thus, $H(t) > 0$ as $t \to \infty$.

As a result of the exponential function's definition, any solution $(I(t), C(t), N(t), H(t))$ that starts inside of R_+^4 with positive initial conditions $(I(0), C(0), N(0), H(0))$ will remain in R_+^4. □

Theorem 2. *All the solutions of the (PSCINC) model are uniformly bounded if the following condition is hold*

Proof. let $(I(0), C(0), N(0), H(0)) \in R_+^4$ be an initial condition for the (PSCINC), then, by using the Bernoulli method, we get

$$\frac{dN}{dt} = m_2 N(1 - k_2 N) - \gamma_2 CN \leq m_2 N(1 - k_2 N)$$
$$\Longrightarrow N(t) \leq \frac{1}{k_2 + N(0)\, e^{-m_2 t}}$$

Thus, $\lim_{t\to\infty} \sup [N(t)] \leq \frac{1}{k_2}$.

Similarly, we get

$$\lim_{t\to\infty} sup\left[C\left(t\right)\right] \leq \frac{1}{k_1},$$

Now, by using the standard comparison theory [48] and the above bound for the cancer cells, we get

$$\begin{aligned}\frac{dI}{dt} &= \frac{\alpha}{1+eC} + \frac{p_1\ IC}{\beta_1 + C} - p_2IC - d_1I - d_2IH \\ &\leq \alpha - d_1I \Longrightarrow \lim_{t\to\infty} sup\left[I\left(t\right)\right] \leq \frac{\alpha}{d_1}\end{aligned}$$

and

$$\lim_{t\to\infty} \sup\left[H\left(t\right)\right] \leq \frac{\nu}{d_4}.$$

Therefore, the corresponding domain region for the (PSCINC) model is

$$\begin{aligned}\varphi = \Big\{ &\left(I, C, N, H\right) \in R_+^4 : I\left(t\right) \leq \frac{\alpha}{d_1}, \\ &C\left(t\right) \leq \frac{1}{k_1}, N\left(t\right) \leq \frac{1}{k_2}, H(t) \leq \frac{\nu}{d_4}\Big\}.\end{aligned}$$

□

3. Equilibria analysis

This section will delve into finding the possible equilibrium and analyzing the system's stability, specifically its stability in the vicinity of equilibrium. To accomplish this, we compute $\frac{dI}{dt} = \frac{dC}{dt} = \frac{dN}{dt} = \frac{dH}{dt} = 0$ and get the following equilibrium in two cases:

(1) No treatment case: in this case, we have two equilibrium points given by
   (a) The cancer-free or healthy point $A_0 = (I_0, 0, N_0)$, where $I_0 = \frac{\alpha}{d_1}$ and $N_0 = \frac{1}{k_2}$.
   (b) The endemic or treatment-free equilibrium point $A_1 = (I_1,\ C_1,\ N_1)$ here $N_1 = \frac{m_2-\gamma_2 C_1}{m_2 k_2}$, $I_1 = \frac{-\alpha(\beta_1+C_1)}{r_1C_1+r_2C_1^2-r_3C_1^3-r_4}$ where

$$\begin{aligned}r_1 &= p_1 - p_2\beta_1 - d_1 - ed_1\beta_1, \\ r_2 &= ep_1 - p_2 - e\beta_1 p_2 - ed_1, \\ r_3 &= ep_2, \\ r_4 &= d_1\beta_1, \\ r_5 &= m_1k_1 - \frac{\gamma_1\gamma_2}{m_2k_2}, \\ r_6 &= m_1 - \frac{\gamma_1}{k_2},\end{aligned}$$

   and C_1 is the root of the following equation

$$f_1\left(C\right) = a_1C^5 + a_2C^4 + a_3C^3 + a_4C^2 + a_5C + a_6, = 0,$$

where,

$$\begin{aligned}a_1 &= r_3r_5, \\ a_2 &= \left(r_5\left(\beta_2r_3 - r_2\right) - r_3r_6\right) \\ a_3 &= -\left(r_5\left(r_1 + r_2\beta_2\right) + r_6\left(\beta_2r_3 - r_2\right)\right). \\ a_4 &= \left(r_5\left(r_4 + r_1\beta_2\right) + r_6\left(r_1 + \beta_2r_2\right)\right). \\ a_5 &= \left(\alpha p_3 - r_6\left(r_4 + r_1\beta_2\right) + \beta_2r_4r_5\right). \\ a_6 &= \left(\alpha\beta_1p_3 - \beta_2r_4r_6\right).\end{aligned}$$

Clearly, $f_1\left(0\right) = \left(\alpha\beta_1p_3 - \beta_2r_4r_6\right)$, and

$$\begin{aligned}f_1\left(k_1\right) = {} & r_3r_5k_1^5 + \left(r_5\left(\beta_2r_3 - r_2\right) - r_3r_6\right)k_1^4 \\ & - \left(\ r_5\left(r_1 + r_2\beta_2\right) + r_6\left(\beta_2r_3 - r_2\right)\right)k_1^3 \\ & + \Big(\ r_5\Big(r_4 - r_1\beta_2\Big) + r_6\left(r_1 + \beta_2r_2\right)\Big)\ k_1^2 \\ & + \left(\alpha p_3 - r_6\left(r_4 - r_1\beta_2\right) + \beta_2r_4r_5\right)k_1 \\ & + \alpha\beta_1p_3 - \beta_2r_4r_6.\end{aligned}$$

Therefore, by the intermediate value theorem [55], $f_1\left(C\right)$ has a positive root, say C_1 in the interval $(0,\ k_1)$ if one of the following conditions is satisfied

$$\begin{aligned}&f_1\left(0\right)\ <\ 0\ and\ f_1\left(k_1\right) > 0, \\ &f_1\left(0\right)\ >\ 0\ and\ f_1\left(k_1\right) < 0.\end{aligned}$$

Now, for I_1 and N_1 to be positive, the following two conditions must be satisfied:

$$\begin{aligned}&m_2 > \gamma_2\ C_1 \\ &r_1C_1 + r_2C_1^2 < r_3C_1^3 + r_4\end{aligned} \tag{2}$$

(2) After treatment case: in this case, we have one positive equilibrium point $A_2 = (I_2, C_2,\ N_2, H_2)$ here

$$\begin{aligned}H_2 = \frac{\nu}{d_4}, N_2 &= \frac{m_2 - \gamma_2C_2}{m_2k_2}, I_2 \\ &= \frac{-\alpha(\beta_1 + C_2)}{-z_0C_2^3 - z_1C_2^2 + z_2C_2 - z_3}\end{aligned}$$

where

$$\begin{aligned}z_0 = ep_2, z_1 &= p_2 - ep_1 + e\beta_1p_2 + ed_1 + \frac{e\nu d_2}{d_4}, \\ z_2 &= p_1 - p_2\beta_1 - d_1 - ed_1\beta_1 - \frac{\nu d_2}{d_4} - \frac{e\nu d_2\beta_1}{d_4}, \\ z_3 &= d_1\beta_1 + \frac{\nu d_2\beta_1}{d_4},\end{aligned}$$

$$z_4 = m_1 k_1 - \frac{\gamma_1 \gamma_2}{m_2 k_2},$$
$$z_5 = \frac{\gamma_1}{k_2} - m_1 + \frac{\nu d_3}{d_4},$$

and C_2 is the root of the following equation

$$f_2(C) = b_1 C^5 + b_2 C^4 + b_3 C^3 + b_4 C^2 + b_5 C + b_6 = 0,$$

where

$$b_1 = z_0 z_4,$$
$$b_2 = (\, z_4 (z_1 + z_0 \beta_2) + z_0 z_5).$$
$$b_3 = (z_4 (z_1 \beta_2 - z_2) + z_5 (z_1 + z_0 \beta_2)).$$
$$b_4 = (\, z_4 (z_3 - \beta_2 z_2) + z_5 (z_1 \beta_2 - z_2)).$$
$$b_5 = (\beta_2 z_3 z_4 + z_5 (z_3 - \beta_2 z_2) + \alpha p_3).$$
$$b_6 = \beta_2 z_3 z_5 + \alpha \beta_1 p_3.$$

Clearly,

$$f_2(0) = \beta_2 z_3 z_5 + \alpha p_3 \beta_1$$

and

$$\begin{aligned} f_2(k_1) = {} & z_0 z_4 k_1^5 \\ & + (\, z_4 (z_1 + z_0 \beta_2) + z_0 z_5) k_1^4 \\ & + (z_4 (z_1 \beta_2 - z_2\,) + z_5 (z_1 + z_0 \beta_2)) k_1^3 \\ & + (z_4 (z_3 - \beta_2 z_2) + z_5 (z_1 \beta_2 - z_2)) k_1^2 \\ & + (\beta_2 z_3 z_4 + z_5 (z_3 - \beta_2 z_2) + \alpha p_3) k_1 \\ & + \beta_2 z_3 z_5 + \alpha \beta_1 p_3. \end{aligned}$$

Therefore, by the intermediate value theorem, $f_2(C)$ has a positive root, say C_2 in the interval $(0, k_1)$ if one of the following conditions is satisfied

$$f_2(0) < 0 \text{ and } f_2(k_1) > 0,$$
$$f_2(0) > 0 \text{ and } f_2(k_1) < 0.$$

For I_2 and N_2 to be positive, the following two conditions must be satisfied:

$$\begin{aligned} & m_2 > \gamma_2 C_2 \\ & z_2 C_2 < z_0 C_2^3 + z_1 C_2^2 + z_3 \end{aligned} \tag{3}$$

Since $N = 0$ indicates that the patients are deceased, we exclude cases where $N = 0$ from consideration. In order to analyze the linear stability of the system at the three equilibrium points mentioned above, it is necessary to calculate the Jacobian matrix of the system, and the Jacobian is

$$J = \begin{bmatrix} j_{11} & j_{12} & 0 & j_{14} \\ j_{21} & j_{22} & j_{23} & j_{24} \\ 0 & j_{32} & j_{33} & 0 \\ 0 & 0 & 0 & j_{44} \end{bmatrix} \tag{4}$$

here.

$$j_{11} = \frac{p_1 C}{\beta_1 + C} - p_2 C - d_1 - d_2 H,$$
$$j_{12} = \frac{-e\alpha}{(1 + eC)^2} + \frac{p_1 \beta_1 I}{(\beta_1 + C)^2} - p_2 I,$$
$$j_{14} = -d_2 I,$$
$$j_{21} = \frac{-p_3 C}{\beta_2 + C},$$
$$j_{22} = m_1 (1 - 2k_1 C) - \frac{p_3 \beta_2 I}{(\beta_2 + C)^2} - \gamma_1 N - d_3 H,$$
$$j_{23} = -\gamma_1 C, j_{24} = d_3 C,$$
$$j_{32} = -\gamma_2 N, j_{33} = m_2 - 2m_2 k_2 N - \gamma_2 C,$$
$$j_{44} = -d_4.$$

- The Jacobian matrix at $A_0 = (I_0, 0, N_0)$ is given as:

$$J(A_0) = \begin{bmatrix} -d_1 & -e\alpha - \frac{p_1 \alpha}{\beta_1 d_1} - \frac{p_2 \alpha}{d_1} & 0 \\ 0 & m_1 - \frac{p_3 \alpha}{\beta_2 d_1} - \frac{\gamma_1}{k_2} & 0 \\ 0 & -\frac{\gamma_2}{k_2} & -m_2 \end{bmatrix} \tag{5}$$

Then, the eigenvalues of $J(A_0)$ are $\lambda_1^0 = -d_1 < 0$, $\lambda_2^0 = m_1 - \frac{p_3 \alpha}{\beta_2 d_1} - \frac{\gamma_1}{k_2}$ and $\lambda_3^0 < 0$. Therefore, A_0 is asymptotic stable whenever if

$$m_1 < \frac{p_3 \alpha}{\beta_2 d_1} + \frac{\gamma_1}{k_2}$$

- The Jacobian matrix at $A_1 = (I_1, C_1, N_1)$ is given as:

$$J(A_1) = \begin{pmatrix} a_{11}^{[1]} & a_{12}^{[1]} & 0 \\ a_{21}^{[1]} & a_{22}^{[1]} & a_{23}^{[1]} \\ 0 & a_{32}^{[1]} & a_{33}^{[1]} \end{pmatrix} \tag{6}$$

where

$$a_{11}^{[1]} = \frac{p_1 C_1}{\beta_1 + C_1} - p_2 C_1 - d_1,$$
$$a_{12}^{[1]} = \frac{-e\alpha}{(1 + eC_1)^2} + \frac{p_1 \beta_1 I_1}{(\beta_1 + C_1)^2} - p_2 I_1,$$
$$a_{21}^{[1]} = \frac{-p_3 C_1}{\beta_2 + C_1},$$
$$a_{22}^{[1]} = m_1 - 2m_1 k_1 C_1 - \frac{p_3 \beta_2 I_1}{(\beta_2 + C_1)^2} - \gamma_1 N_1,$$
$$a_{23}^{[1]} = -\gamma_1 C_1,$$
$$a_{32}^{[1]} = -\gamma_2 N_1,$$
$$a_{33}^{[1]} = m_2 - 2m_2 k_2 N_1 - \gamma_2 C_1.$$

So, the eigenvalues of $J(A_2)$ are the roots of the following equation

$$\left(\lambda^3 + U_1 \lambda^2 + U_2 \lambda + U_3\right) = 0 \tag{7}$$

where:

$$U_1 = -\left(a_{11}^{[1]} + a_{22}^{[1]} + a_{33}^{[1]}\right)$$

$$U_2 = -\Big(-a_{11}^{[1]}\left(a_{22}^{[1]} + a_{33}^{[1]}\right) - a_{22}^{[1]}a_{33}^{[1]} + a_{23}^{[1]}a_{32}^{[1]} + a_{12}^{[1]}a_{21}^{[1]}\Big)$$

$$U_3 = \left(a_{11}^{[1]}\left(a_{23}^{[1]}a_{32}^{[1]} - a_{22}^{[1]}a_{33}^{[1]}\right) + a_{12}^{[1]}a_{21}^{[1]}a_{33}^{[1]}\right)$$

$$U_1U_2 - U_3 = \Big(\left(a_{11}^{[1]} + a_{22}^{[1]} + a_{33}^{[1]}\right)\left(-a_{11}^{[1]}\left(a_{22}^{[1]} + a_{33}^{[1]}\right) - a_{22}^{[1]}a_{33}^{[1]} + a_{23}^{[1]}a_{32}^{[1]} + a_{12}^{[1]}a_{21}^{[1]}\right)\Big) - \left(a_{11}^{[1]}\left(a_{23}^{[1]}a_{32}^{[1]} - a_{22}^{[1]}a_{33}^{[1]}\right) + a_{12}^{[1]}a_{21}^{[1]}a_{33}^{[1]}\right)$$

Thus, according to the Routh-Hurwitz rule [56], A_1 will be asymptotically stable if $U_1 > 0, U_3 > 0$ and $U_1U_2 > U_3$.

- The Jacobian matrix at $A_2 = (I_2, C_2, N_2, H_2)$ is given as:

$$J(A_2) = \begin{bmatrix} a_{11}^{[2]} & a_{12}^{[2]} & 0 & a_{14}^{[2]} \\ a_{21}^{[2]} & a_{22}^{[2]} & a_{23}^{[2]} & a_{24}^{[2]} \\ 0 & a_{32}^{[2]} & a_{33}^{[2]} & 0 \\ 0 & 0 & 0 & a_{44}^{[2]} \end{bmatrix} \tag{8}$$

where,

$$a_{11}^{[2]} = \frac{p_1C_2}{\beta_1 + C_2} - p_2C_2 - d_1 - d_2H_2,$$

$$a_{12}^{[2]} = \frac{-e\alpha}{(1+eC_2)^2} + \frac{p_1\beta_1I_2}{(\beta_1+C_2)^2} - p_2I_2, a_{14}^{[2]} = -d_2I_2,$$

$$a_{21}^{[2]} = \frac{-p_3C_2}{\beta_2 + C_2},$$

$$a_{22}^{[2]} = m_1 - 2m_1k_1C_2 - \frac{p_3\beta_2I_2}{(\beta_2+C_2)^2} - \gamma_1N_2 - d_3H_2,$$

$$a_{23}^{[2]} = -\gamma_1C_2, a_{24}^{[2]} = -d_3C_2,$$

$$a_{32}^{[2]} = -\gamma_2N_2,$$

$$a_{33}^{[2]} = m_2 - 2m_2k_2N_2 - \gamma_2C_2,$$

$$a_{44}^{[2]} = -d_4.$$

So, the eigenvalues of $J(A_2)$ are the roots of the following equation

$$(-d_4 - \lambda)\left(\lambda^3 + D_1\lambda^2 + D_2\lambda + D_3\right) = 0 \tag{9}$$

where,

$$D_1 = -\left(a_{11}^{[2]} + a_{22}^{[2]} + a_{33}^{[2]}\right)$$

$$D_2 = -\Big(-a_{11}^{[2]}\left(a_{22}^{[2]} + a_{33}^{[2]}\right) - a_{22}^{[2]}a_{33}^{[2]} + a_{23}^{[2]}a_{32}^{[2]} + a_{12}^{[2]}a_{21}^{[2]}\Big)$$

$$D_3 = \left(a_{11}^{[2]}\left(a_{23}^{[2]}a_{32}^{[2]} - a_{22}^{[2]}a_{33}^{[2]}\right) + a_{12}^{[2]}a_{21}^{[2]}a_{33}^{[2]}\right)$$

$$D_1D_2 - D_3 = \Big(\left(a_{11}^{[2]} + a_{22}^{[2]} + a_{33}^{[2]}\right)\left(-a_{11}^{[2]}\left(a_{22}^{[2]} + a_{33}^{[2]}\right) - a_{22}^{[2]}a_{33}^{[2]} + a_{23}^{[2]}a_{32}^{[2]} + a_{12}^{[2]}a_{21}^{[2]}\right)\Big) - \left(a_{11}^{[2]}\left(a_{23}^{[2]}a_{32}^{[2]} - a_{22}^{[2]}a_{33}^{[2]}\right) + a_{12}^{[2]}a_{21}^{[2]}a_{33}^{[2]}\right).$$

Thus, according to the Routh-Hurwitz rule, A_2 will be asymptotically stable on the condition that $D_1 > 0, D_3 > 0$ and $D_1D_2 > D_3$.

4. Global stability at the cancer-free steady state

To reach a healthy state, in this section, we will examine the global stability surrounding A_0 to explore the dynamics of the (PSCINC) system at regions far from the equilibrium point A_0.

Theorem 3. *A_0 is a GAS provided the following conditions hold:*

$$m_1k_1 \geq max\left\{\begin{matrix}\frac{2}{d_1}\left(\frac{-\alpha e}{1+eC} + \frac{p_1\ I}{\beta_1+C} - p_2I\right)^2, \frac{2{\gamma_2}^2}{m_2k_2} \\ m_1 < \frac{p_3I}{\beta_2+C} + \gamma_1N\end{matrix}\right\} \tag{10}$$

Proof. Let's define a Lyapunov function [57] for the (PSCINC) model at A_0 as follows: $L(t) = \frac{(I-I_0)^2}{2} + C + \left(N - N_0 - N_0 ln\frac{N}{N_0}\right)$, where $L(t)$ is a positive definite about A_0. Thus,

$$\frac{dL}{dt} = (I - I_0)\frac{dI}{dt} + \frac{dC}{dt} + \left(\frac{N-N_0}{N}\right)\frac{dN}{dt}$$

$$= (I - I_0)\left(\frac{\alpha}{1+eC} + \frac{p_1\ IC}{\beta_1 + C} - p_2IC - d_1I - \alpha + d_1I_0\right) + \left(m_1C - m_1k_1C^2 - \frac{p_3IC}{\beta_2+C} - \gamma_1CN\right) + (N - N_0)\left(m_2(1 - k_2N) - \gamma_2C\right).$$

Therefore,

$$\begin{aligned}\frac{dL}{dt} &= (I-I_0)\\ &\left(\frac{-\alpha eC}{1+eC}+\frac{p_1\ IC}{\beta_1+C}-p_2IC-d_1\left(I-I_0\right)\right)\\ &+\left(m_1C-m_1k_1C^2-\frac{p_3IC}{\beta_2+C}-\gamma_1CN\right)\\ &+\left(N-N_0\right)\left(-m_2k_2\left(N-N_0\right)-\gamma_2C\right).\end{aligned}$$

i.e.,

$$\begin{aligned}\frac{dL}{dt} &= C\left(I-I_0\right)\left(\frac{-\alpha e}{1+eC}+\frac{p_1\ I}{\beta_1+C}-p_2I\right)\\ &-d_1\left(I-I_0\right)^2\\ &+\left(m_1C-m_1k_1C^2-\frac{p_3IC}{\beta_2+C}-\gamma_1CN\right)\\ &-m_2k_2\left(N-N_0\right)^2-\gamma_2C\left(N-N_0\right).\end{aligned}$$

$$\begin{aligned}\Longrightarrow \frac{dL}{dt} &= -\frac{m_1k_1}{2}C^2+C\left(I-I_0\right)\\ &\left(\frac{-\alpha e}{1+eC}+\frac{p_1\ I}{\beta_1+C}-p_2I\right)\\ &-d_1\left(I-I_0\right)^2-\frac{m_1k_1}{2}C^2-\gamma_2C\left(N-N_0\right)\\ &-m_2k_2\left(N-N_0\right)^2\\ &+C\left(m_1-\frac{p_3I}{\beta_2+C}-\gamma_1N\right)\end{aligned}$$

$$\begin{aligned}\Longrightarrow \frac{dL}{dt} \leq &-\left(\sqrt{\frac{m_1k_1}{2}}C+\sqrt{d_1}\left(I-I_0\right)\right)^2\\ &-\left(\sqrt{\frac{m_1k_1}{2}}C+\sqrt{m_2k_2}\left(N-N_0\right)\right)^2\\ &+C\left(m_1-\frac{p_3I}{\beta_2+C}-\gamma_1N\right)\end{aligned}$$

Therefore, $^{dL}/_{dt} < 0$, and hence $L(t)$ is a Lyapunov function under condition 10. □

Thus, the cancer-free steady state A_0 fulfills the requirements for local stability, rendering the point globally stable. From a biological perspective, chemotherapy refers to the process of selectively eliminating tumor cells if conditions (10) are met.

5. Local bifurcation

This section examines the local bifurcation conditions close to steady states by applying Sotomayor's rule for local bifurcation [58, 59].

Theorem 4. *For* $m_1{}^* = \frac{p_3\alpha}{\beta_2 d_1}+\frac{\gamma_1}{k_2}$, *the (PSCINC) model, at* A_0 *has*

(1) *No saddle-node bifurcation (SNB).*
(2) *A transcritical bifurcation (TB) if*

$$\left(T^{[0]}\right)^T\left[D^2h_{m_1}\left(A_0,m_1{}^*\right)\left(S^{[0]},S^{[0]}\right)\right]\neq 0. \quad (11)$$

(3) *A pitchfork bifurcation (PB) if condition (11) is violated where the notation in (11) will be introduced during the proof.*

Proof. At $m_1{}^* = \frac{p_3\alpha}{\beta_2 d_1}+\frac{\gamma_1}{k_2}$, $J(A_0)$ has a zero eigenvalue $\lambda_2^0 = 0$. Therefore, $J(A_0)$ at m_1^* becomes

$$J^*\left(A_0\right)=\begin{bmatrix}-d_1 & -e\alpha-\frac{p_1\alpha}{\beta_1 d_1}-\frac{p_2\alpha}{d_1} & 0\\ 0 & 0 & 0\\ 0 & -\frac{\gamma_2}{k_2} & -m_2\end{bmatrix}$$

Now, let $S^{[0]} = \left(s_1^{[0]},s_2^{[0]},s_3^{[0]}\right)^T$ and $T^{[0]} = \left(t_1^{[0]},t_2^{[0]},t_3^{[0]}\right)^T$ represent the eigenvectors corresponding to the zero eigenvalue of $J^*(A_0)$ and $J^{*T}(A_0)$ respectively. Direct computation gives

$$S^{[0]}=\left(\frac{-\left(\beta_1\left(ed_1+p_2\right)+p_1\right)\ \alpha}{d_1^2\beta_1},1,\frac{-\gamma_2}{m_2k_2}\ \right)^T$$

and

$$T^{[0]}=\left(\ 0,1,0\right)^T.$$

Now, let $h = (h_1(I,C), h_2(I,C,N), h_3(C,N))^T$, then differentiating h with respect to m_1 gives:

$$\frac{\partial h}{\partial m_1}=\left(\frac{\partial h_1}{\partial m_1},\ \frac{\partial h_2}{\partial m_1},\ \frac{\partial h_3}{\partial m_1}\right)=(0,C(1-k_1C,0),$$

$$h_{m_1}\left(A_0,\ m_1{}^*\right)=(0,0,0).$$

Hence,

$$T^{[0]^T}h_{m_1}\left(A_0,m_1{}^*\right)=(0,1,0)\left(0,0,0\right)^T=0$$

That means the (SNB) cannot happen at $m_1{}^*$. Subsequently, since

$$T^{[0]^T}h_{m_1}\left(A_0,m_1{}^*\right)=0$$

$$T^{[0]^T}\left[Dh_{m_1}\left(A_0,m_1{}^*\right)S^{[0]}\right]=(0,1,0)\begin{bmatrix}0&0&0\\0&1&0\\0&0&0\end{bmatrix}$$

$$\begin{pmatrix}\frac{-(\beta_1(ed_1+p_2)+p_1)\ \alpha}{d^2\beta_1}\\ 1\\ \frac{-\gamma_2}{m_2k_2}\end{pmatrix}=1\neq 0$$

$$
\begin{aligned}
&T^{[0]^T}\left[D^2h_{m_1}\left(A_0,{m_1}^*\right)\left(S^{[0]},S^{[0]}\right)\right]\\
&=(0,1,0)\left(2s_1^{[0]}\left(\frac{p_1\left(1-I_0s_1^{[0]}\right)}{\beta_1}-\left(p_2+2e^2\alpha s_1^{[0]}\right)\right),\frac{p_3\left(1+(2I_0-\beta_2)\right)}{\beta_2^2}\right.\\
&\left.-2\left(m_1^*k_1-\gamma_1s_3^{[0]}\right),-s_3^{[0]}\left(\gamma_2+2m_2k_2s_3^{[0]}\right)\right)^T\\
&=\left(\frac{p_3\left(1+s_2^{[0]}\left(2\mathrm{I}_0-\beta_2\right)\right)}{\beta_2^2}-2\left({m_1}^*k_1-\gamma_1s_3^{[0]}\right)\right).
\end{aligned}
$$

This means the required conditions for (TB) are satisfied under condition (11). Finally, if condition (11) is not satisfied, then.

$$\left(T^{[0]}\right)^T D^3h_{m_1}\left(A_0,m_1^*\right)\left(S^{[0]},S^{[0]},S^{[0]}\right)=\frac{2p_3\left(2\beta_2s_1^{[0]}-1-3I_0\right)}{\beta_2^3}.$$

□

Theorem 5. *For*

$$
\begin{aligned}
{\gamma_1}^* &= \frac{-{a_{11}^{[1]}}^2\left(a_{22}^{[1]}+a_{33}^{[1]}\right)-2a_{22}^{[1]}a_{33}^{[1]}a_{11}^{[1]}}{C_1\left(a_{22}^{[1]}a_{32}^{[1]}+a_{32}^{[1]}a_{33}^{[1]}\right)}\\
&-\frac{-{a_{22}^{[1]}}^2\left(a_{11}^{[1]}+a_{33}^{[1]}\right)+\left(a_{11}^{[1]}+a_{22}^{[1]}\right)}{C_1\left(a_{22}^{[1]}a_{32}^{[1]}+a_{32}^{[1]}a_{33}^{[1]}\right)}\\
&-\frac{\left(-{a_{33}^{[1]}}^2+a_{12}^{[1]}a_{21}^{[1]}\right)}{C_1\left(a_{22}^{[1]}a_{32}^{[1]}+a_{32}^{[1]}a_{33}^{[1]}\right)}
\end{aligned}
$$

where ${\gamma_2}^* > 0$*, and the formulas of* $a_{ij}^{[2]}$ *are given in (8), the (PSCINC) model at* A_1 *has a (SNB) if*

$$\left(T^{[1]}\right)^T\left[D^2h_{\gamma_1}\left(A_1,\gamma_1^*\right)\left(S^{[1]},S^{[1]}\right)\right]\neq 0 \quad (12)$$

Proof. According to $J(A_1)$, given by (6), the (PSCINC) model at A_1 has a zero eigenvalue, say $\lambda_2^2=0$, at ${\gamma_1}^*$ and the Jacobian matrix $J^*(A_1)=J(A_1,{\gamma_1}^*)$,becomes:

$$J^*\left(A_1\right)=\begin{bmatrix}\eta_{11}&\eta_{12}&0\\ \eta_{21}&\eta_{22}&\eta_{23}\\ 0&\eta_{32}&\eta_{33}\end{bmatrix},$$

here,

$$
\begin{aligned}
\eta_{11}&=\frac{p_1C_1}{\beta_1+C_1}-p_2C_1-d_1,\\
\eta_{12}&=\frac{-e\alpha}{\left(1+eC_1\right)^2}+\frac{p_1\beta_1I_1}{\left(\beta_1+C_1\right)^2}-p_2I_1,\\
\eta_{21}&=\frac{-p_3}{\beta_2+C_1},\\
\eta_{22}&=m_1-2m_1k_1C_1-\frac{p_3\beta_2I_1}{\left(\beta_2+C_1\right)^2}-{\gamma_1}^*N_1,\\
\eta_{23}&=-{\gamma_1}^*C_1,\\
\eta_{32}&=-\gamma_2N_3,\ \eta_{33}=m_2-2m_2k_2N_1-\gamma_2C_1.
\end{aligned}
$$

Now, let

$$S^{[1]}=\left(s_1^{[1]},s_2^{[1]},s_3^{[1]}\right)^T$$

and

$$T^{[1]}=\left(t_1^{[1]},t_2^{[1]},t_3^{[1]}\right)^T$$

represent the eigenvectors corresponding to the zero eigenvalue of $J^*(A_1)$ and $J^{*T}(A_1)$ respectively. Direct computation gives

$$S^{[1]}=\left(\frac{-\eta_{12}}{\eta_{11}},1,\frac{-\eta_{32}}{\eta_{33}}\right)^T$$

and

$$T^{[1]}=\left(\frac{-\eta_{21}}{\eta_{11}},1,\frac{-\eta_{23}}{\eta_{33}}\right)^T$$

where $\eta_{11}\neq 0$ and $\eta_{33}\neq 0$.
Subsequently, since

$$
\begin{aligned}
{T^{[1]}}^Th_{\gamma_1}\left(A_1,{\gamma_1}^*\right)&=\left(\frac{-\eta_{21}}{\eta_{11}},1,\frac{-\eta_{23}}{\eta_{33}}\right)\\
&(0,-C_1N_1,0)^T=-C_1N_1\neq 0
\end{aligned}
$$

$$
\begin{aligned}
&\left(T^{[1]}\right)^T\left[D^2h_{\gamma_1}\left(A_1,\gamma_1^*\right)\left(S^{[1]},S^{[1]}\right)\right]\\
&=\left(\frac{-\eta_{21}}{\eta_{11}},1,\frac{-\eta_{23}}{\eta_{33}}\right)\\
&\left(\frac{2p_1\beta_1({s_1}^{[1]}-I_1{s_2}^{[1]}){s_2}^{[1]}}{\left(\beta_1+C_1\right)^2}-2p_2{s_1}^{[1]}{s_2}^{[1]}\right.\\
&+\frac{2e^2\alpha\left({s_2}^{[1]}\right)^2}{\left(1+eC_1\right)^3},\frac{p_3{s_2}^{[1]}({s_2}^{[1]}-{s_1}^{[1]}\beta_2)}{\left(\beta_2+C_1\right)^2}\\
&+\frac{2p_3\beta_2I_1\left({s_2}^{[1]}\right)^2}{\left(\beta_2+C_1\right)^3}-2{s_2}^{[1]}({\gamma_1}^*+m_1k_1{s_2}^{[1]},\\
&\left.-\left({s_2}^{[1]}\gamma_2+2m_2k_2\right)\right)^T\\
&=\left(\left(\frac{2p_1\beta_1({s_1}^{[1]}-I_1{s_2}^{[1]}){s_2}^{[1]}}{\left(\beta_1+C_1\right)^2}-2p_2{s_1}^{[1]}{s_2}^{[1]}\right.\right.\\
&\left.+\frac{2e^2\alpha\left({s_2}^{[1]}\right)^2}{\left(1+eC_1\right)^3}\right)\frac{-\eta_{21}}{\eta_{11}}\\
&+\left(\frac{p_3{s_2}^{[1]}({s_2}^{[1]}-{s_1}^{[1]}\beta_2)}{\left(\beta_2+C_1\right)^2}+\frac{2p_3\beta_2I_1\left({s_2}^{[1]}\right)^2}{\left(\beta_2+C_1\right)^3}\right.\\
&\left.-2{s_2}^{[1]}({\gamma_1}^*+m_1k_1{s_2}^{[1]}\right)\\
&\left.-\left({s_2}^{[1]}\gamma_2+2m_2k_2\right)\left(\frac{-\eta_{23}}{\eta_{33}}\right)\right)
\end{aligned}
$$

Hence, condition (12) guarantees that the second condition of saddle-node bifurcation is satisfied. Therefore, the (PSCINC) model has SNB at A_1 with the parameter γ_1^*. □

Theorem 6. *For*

$$\gamma_2{}^* = \frac{-a_{11}^{[2]^2}\left(a_{22}^{[2]}+a_{33}^{[2]}\right)-a_{22}^{[2]^2}\left(a_{11}^{[2]}+a_{33}^{[2]}\right)}{\left(a_{23}^{[2]}a_{33}^{[2]}+a_{22}^{[2]}a_{23}^{[2]}\right)N_2} + \frac{\left(a_{11}^{[2]}+a_{22}^{[2]}\right)\left(-a_{33}^{[2]^2}+a_{12}^{[2]}a_{21}^{[2]}\right)}{\left(a_{23}^{[2]}a_{33}^{[2]}+a_{22}^{[2]}a_{23}^{[2]}\right)N_2} - \frac{2a_{11}^{[2]}a_{22}^{[2]}a_{33}^{[2]}}{\left(a_{23}^{[2]}a_{33}^{[2]}+a_{22}^{[2]}a_{23}^{[2]}\right)N_2}$$

where $\gamma_2{}^* > 0$, *and the formulas of* $a_{ij}^{[2]}$ *are given in (8), the (PSCINC) model at* A_2 *has a (SNB) if*

$$\left(T^{[2]}\right)^T\left[D^2h_{\gamma_2}\left(A_2,\gamma_2^*\right)\left(S^{[2]},S^{[2]}\right)\right]\neq 0 \quad (13)$$

Proof. According to $J(A_2)$, given by (8), the (PSCINC) model at A_2 has a zero eigenvalue, say $\lambda_2^3 = 0$, at $\gamma_2{}^*$ and the Jacobian matrix $J^*(A_2) = J(A_2, \gamma_2{}^*)$, becomes:

$$J^*\left(A_2\right)=\begin{bmatrix}\varsigma_{11}&\varsigma_{12}&0&\varsigma_{14}\\ \varsigma_{21}&\varsigma_{22}&\varsigma_{23}&\varsigma_{24}\\ 0&\varsigma_{32}&\varsigma_{33}&0\\ 0&0&0&\varsigma_{44}\end{bmatrix}$$

$$\begin{aligned}
\varsigma_{11} &= \frac{p_1C_2}{\beta_1+C_2}-p_2C_2-d_1-d_2H_2,\\
\varsigma_{12} &= \frac{-e\alpha}{(1+eC_2)^2}+\frac{p_1\beta_1I_2}{(\beta_1+C_2)^2}-p_2I_2,\\
\varsigma_{13} &= 0,\\
\varsigma_{14} &= -d_2I_4,\\
\varsigma_{21} &= \frac{-p_3}{\beta_2+C_2},\\
\varsigma_{22} &= m_1-2m_1k_1C_2-\frac{p_3\beta_2I_2}{(\beta_2+C_2)^2}\\
&\quad -\gamma_1N_2-d_3H_2,\\
\varsigma_{23} &= -\gamma_1C_2,\\
\varsigma_{24} &= d_3C_2,\\
\varsigma_{32} &= -\gamma_2{}^*N_2,\\
\varsigma_{33} &= m_2-2m_2k_2N_2-\gamma_2{}^*C_2,\\
\varsigma_{44} &= -d_4.
\end{aligned}$$

Now, let

$$S^{[2]}=\left(s_1^{[2]},s_2^{[2]},s_3^{[2]},s_4^{[2]}\right)^T$$

and

$$T^{[2]}=\left(t_1^{[2]},t_2^{[2]},t_3^{[2]},t_4^{[2]}\right)^T$$

represent the eigenvectors corresponding to the zero eigenvalue of $J^*(A_2)$ and $J^{*T}(A_2)$ respectively. Direct computation gives

$$S^{[2]}=\left(\frac{\varsigma_{22}\varsigma_{33}-\varsigma_{23}\varsigma_{32}}{\varsigma_{21}\varsigma_{32}},\frac{-\varsigma_{33}}{\varsigma_{32}},1,0\right)^T$$

and

$$T^{[2]}=\Big(\frac{\varsigma_{22}\varsigma_{33}-\varsigma_{23}\varsigma_{32}}{\varsigma_{12}\varsigma_{23}},\frac{-\varsigma_{33}}{\varsigma_{23}},1,\left[\frac{\varsigma_14(\varsigma_{23}\varsigma_{32}-\varsigma_{22}\varsigma_{33})+\varsigma_{12}\varsigma_{33}\varsigma_{24}}{\varsigma_{12}\varsigma_{23}\varsigma_{44}}\right]\Big)^T$$

where $\varsigma_{12} \neq 0$.

$$T^{[2]^T}h_{\gamma_2}\left(A_2,\gamma_2{}^*\right)=\Big(\frac{\varsigma_{22}\varsigma_{33}-\varsigma_{23}\varsigma_{32}}{\varsigma_{12}\varsigma_{23}},\frac{-\varsigma_{33}}{\varsigma_{23}},1,\left[\frac{\varsigma_14(\varsigma_{23}\varsigma_{32}-\varsigma_{22}\varsigma_{33})+\varsigma_{12}\varsigma_{33}\varsigma_{24}}{\varsigma_{12}\varsigma_{23}\varsigma_{44}}\right]\Big)^T\left((0,0,-C_2N_2,0)^T\right)^T=-C_2N_2\neq 0.$$

$$\begin{aligned}
&\left(T^{[2]}\right)^T\left[D^2h_{\gamma_2}\left(A_2,\gamma_2^*\right)\left(S^{[2]},S^{[2]}\right)\right]\\
&=\left(\frac{\varsigma_{22}\varsigma_{33}-\varsigma_{23}\varsigma_{32}}{\varsigma_{12}\varsigma_{23}},\frac{-\varsigma_{33}}{\varsigma_{23}},1,\left[\frac{\varsigma_{14}(\varsigma_{23}\varsigma_{32}-\varsigma_{22}\varsigma_{33})+\varsigma_{12}\varsigma_{33}\varsigma_{24}}{\varsigma_{12}\varsigma_{23}\varsigma_{44}}\right]\right)\\
&\left(\frac{2p_1\beta_1(s_1{}^{[2]}-I_2s_2{}^{[2]})s_2{}^{[2]}}{(\beta_1+C_2)^2}\right.\\
&-2p_2s_1{}^{[2]}s_2{}^{[2]}+\frac{2e^2\alpha\left(s_2{}^{[2]}\right)^2}{(1+eC_2)^3},\\
&\frac{p_3s_2{}^{[2]}(s_2{}^{[2]}-s_1{}^{[2]}\beta_2)}{(\beta_2+C_2)^2}+\frac{2p_3\beta_2I_2\left(s_2{}^{[2]}\right)^2}{(\beta_2+C_2)^3}\\
&-2s_2{}^{[2]}(\gamma_1+m_1k_1s_2{}^{[2]},\\
&\left.-\left(s_2{}^{[2]}\gamma_2{}^*+2m_2k_2\right),0\right)^T
\end{aligned}$$

□

$$= \left(\left(\frac{2p_1\beta_1(s_1{}^{[2]} - I_2 s_2{}^{[2]})s_2{}^{[2]}}{(\beta_1 + C_2)^2} - 2p_2 s_1{}^{[2]} s_2{}^{[2]} + \frac{2e^2\alpha\left(s_2{}^{[2]}\right)^2}{(1+eC_2)^3} \right) \left(\left(\frac{\varsigma_{22}\varsigma_{33} - \varsigma_{23}\varsigma_{32}}{\varsigma_{12}\varsigma_{23}} \right) + \frac{p_3 s_2{}^{[2]}(s_2{}^{[2]} - s_1{}^{[2]}\beta_2)}{(\beta_2 + C_2)^2} + \frac{2p_3\beta_2 I_2\left(s_2{}^{[2]}\right)^2}{(\beta_2 + C_2)^3} - 2s_2{}^{[2]}(\gamma_1 + m_1 k_1 s_2{}^{[2]}) \right) \left(\frac{-\varsigma_{33}}{\varsigma_{23}} \right) - \left(s_2{}^{[2]}\gamma_2{}^* + 2m_2 k_2 \right) \right).$$

Hence, condition (13) guarantees that the second condition of saddle-node bifurcation is satisfied. Therefore, the (PSCINC) model has SNB at A_2 with the parameter γ_2^*.

6. Optimal control

This section focuses on analyzing the model following the administration of chemotherapy treatment at a certain time. From a biomedical standpoint, we have included the notion of optimum control in the model. For this purpose, we should look into the problem with a control strategy that can lessen the health hazard for the patient. Therefore, we propose and analyze the optimal control problem applicable to model (PSCINC) to determine the optimal dose of chemotherapy to control the tumor. We decide on control inputs v of cellular chemotherapy, included in the fourth equation of the (PSCINC) model, to be supplied from an external source at different times.

So, let us assume that the time-dependent form of our considered model is given in (1) with the following initial conditions for the model set:

So, let us assume that the time-dependent form of our considered model is given in (1) with the following initial conditions for the (PSCINC) system set:

$$I(0) = I_0,\ C(0) = C_0, N(0) = N_0, H(0) = H_0, \tag{14}$$

The objective function, which is to be minimized, is defined as follows:

$$\Omega(\tau) = \int_0^{t_f} [I(t) + C(t) + \varepsilon_1 \nu^2(t)]dt, \tag{15}$$

The constants ε_1 represent the weight factors of the respective terms. These are utilized to equalize the magnitude of the phrases. The ideal selection of control variable ν will effectively reduce tumor density and maximize immune density simultaneously, while also minimizing any unfavorable side effects within a set time frame. The initial component of the integrand function represents the overall quantity of tumor cells, the subsequent component of the integrand function represents the overall quantity of immune cells, and the last component of the integrand function indicates the efficacy of the administered medications on the organism. Here, we employ an optimum control problem to the model to minimize the administration of chemotherapeutic drugs, aiming to mitigate side effects and shorten the patient's recovery period. Here, we set up an optimal control ν^* such that

$$\Omega(\nu^*) = \min\ \{\Omega(\nu) :\ \nu \in \Delta\}, \tag{16}$$

where $\Delta = \{\nu : \text{measurable},\ 0 \le \nu \le 1, t \in [0, t_f]\}$ is the admissible control set.

6.1. The existence of optimal control

In this sub-section, we analyze the existence of an optimal control of the (PSCINC) model (1). The property of super solutions $\bar{I}, \bar{C}, \bar{N}$, and $\bar{H}$ of the model (1) is that trajectories given by

$$\begin{aligned} \frac{d\bar{I}}{dt} &= \alpha - d_1\bar{I}, \\ \frac{d\bar{C}}{dt} &= m_1\bar{C} - p_3 I, \\ \frac{d\bar{N}}{dt} &= m_2\bar{N}, \\ \frac{d\bar{H}}{dt} &= \nu - d_4\bar{H}, \end{aligned} \tag{17}$$

are bounded. In vector form, we can express the above system (17) as:

$$\begin{pmatrix} \bar{I} \\ \bar{C} \\ \bar{N} \\ \bar{H} \end{pmatrix}' \le \begin{pmatrix} -d_1 & 0 & 0 & 0 \\ -p_3 & m_1 & 0 & 0 \\ 0 & 0 & m_2 & 0 \\ 0 & 0 & 0 & -p_4 \end{pmatrix} \begin{pmatrix} \bar{I} \\ \bar{C} \\ \bar{N} \\ \bar{H} \end{pmatrix} + \begin{pmatrix} \alpha \\ 0 \\ 0 \\ \nu \end{pmatrix}$$

Since this is a linear system with bounded coefficients and the time frame is limited, so, we can conclude that the solutions $\bar{I}$, $\bar{C}$,$\bar{N}$, and $\bar{H}$, of the above system are bounded. Using the theorem proposed by Lukes [60], we found that the admissible control class and the corresponding state equations with assumed initial conditions are non-empty. Also, by the definition of the set Δ, it is clear that the control set Δ is convex and closed. Since the state solutions are bounded, hence, the right-hand sides of the state system (1) are continuous and bounded by a sum of the bounded controls and the states.

Now, we examine the convexity of the integrand of $\Omega(\nu)$ on Δ and that it is bounded below by $\tau_1\nu^2(t) - \tau_2$ with $\tau_1, \tau_2 > 0$. Let p, q be distinct

elements of Ω and $0 \leq Y \leq 1$. We have to show that $\Omega\left(p_1 Y+(1-Y) p_2, q_1 Y+(1-Y) q_2\right) \leq (1-Y)\Omega\left(p_1, q_1\right)+Y \Omega\left(p_2, q_2\right)$ where, $\Omega(\nu) = I(t)+C(t)+\varepsilon_1 \nu^2(t)$,

To establish it, we proceed as follows:

$$\begin{aligned}
&\Omega\left(p_1 Y+(1-Y) q_1, p_2 Y+(1-Y) q_2\right) \\
&-(1-Y)\Omega\left(p_1, p_2\right)+Y \Omega\left(q_1, q_2\right) \\
&=C(t)+I(t)+\varepsilon_1\left(p_1 Y+(1-Y) q_1\right)^2 \\
&-Y\left\{C(t)+I(t)+\varepsilon_1 p_1^2\right\}-(1-Y)\{C(t)+I(t) \\
&+\varepsilon_1 q_1^2\}
\end{aligned}$$

$$\begin{aligned}
&=I(t)+C(t)+\varepsilon_1\left(p_1^2 Y^2+2 p_1 q_1 Y(1-Y)\right. \\
&+(1-Y)^2 q_1^2)-Y\left\{I(t)+C(t)+\varepsilon_1 p_1^2\right\} \\
&-\left\{I(t)+C(t)+\varepsilon_1 q_1^2\right\}+Y\left\{I(t)+C(t)+\varepsilon_1 q_1^2\right\}
\end{aligned}$$

$$\begin{aligned}
&=\varepsilon_1 p_1^2 Y^2+2 \varepsilon_1 p_1 q_1 Y(1-Y)+\varepsilon_1(1-Y)^2 q_1^2 \\
&-\varepsilon_1 p_1^2 Y-\varepsilon_1 q_1^2+\varepsilon_1 q_1^2 Y \\
&=\varepsilon_1 p_1^2 Y^2+2 \varepsilon_1 p_1 q_1 Y-2 \varepsilon_1 p_1 q_1 Y^2 \\
&+\varepsilon_1\left(1-2 Y+Y^2\right) q_1^2-\varepsilon_1 p_1^2 Y-\varepsilon_1 q_1^2+\varepsilon_1 q_1^2 Y \\
&=\varepsilon_1 p_1^2 Y^2-\ 2 \varepsilon_1 p_1 q_1 Y^2+\ \varepsilon_1 q_1^2 Y^2 \\
&-\varepsilon_1 p_1^2 Y+2 \varepsilon_1 p_1 q_1 Y-\ \varepsilon_1 q_1^2 Y
\end{aligned}$$

$= -\ \varepsilon_1\left(p_2-q_2\right)^2 Y(1-Y)$ [Since, $(Y-1) \leq 0$, and if $\varepsilon_1 \geq 0$],

and

$$\begin{aligned}
I(t)+C(t)+\varepsilon_1 \nu^2(t) \geq \varepsilon_1 \nu^2(t) &\geq \tau_1 \nu^2(t) \\
&\geq \tau_1 \nu^2(t)-\tau_2 .
\end{aligned}$$

This shows that $\tau_1 \nu^2(t)\ -\tau_2$ is a lower bound of $\Omega(\tau, \mu)$. This verifies that there exists an optimal control ν^* for which $\Omega\left(\nu^*\right)$=min $\Omega\left(\nu^*\right)$ = min $\{\Omega(\nu): \nu \in \Delta\}$ From the above analysis and conclusion, we state the following theorem.

Theorem 7. *Subject to the system (1), with initial conditions* $I(0)=I_0, C(0)=C_0, N(0)=N_0$, *and*$H(0)=\nu_0$, *the objective functional*

$$\Omega(\nu)\ =\int_0^{t_f}\left[I(t)+C(t)+\varepsilon_1 \nu^2(t)\right] dt$$

admits an optimal control ν^* *such that* $\Omega\left(\nu^*\right) = \min\{\Omega(\nu): \nu \in \Delta\}$, *where* $\Delta = (\nu)\nu$are piecewise continuous, $0 \leq \nu \leq 1, t \in [0, t_f]$.

6.2. Characterization of the optimal control

For applying the Pontryagin maximum principle [46], we introduced the four co-state variables ξ_i $(i = 1,2,3,4)$. The Hamiltonian function is given by

$$h = I+C+\varepsilon_1 \nu^2+\ \xi_1 \dot{I}+\ \xi_2 \dot{C}+\ \xi_3 \dot{N}+\xi_4 \dot{H} \quad (18)$$

With substitution from (1) into (18), we get

$$\begin{aligned}
h* &= I+C+\varepsilon_1 \nu^2 \\
&\xi_1\left(\frac{\alpha}{1+eC}+\frac{p_1\ IC}{\beta_1+C}-p_2 IC-d_1 I-d_2 IH\right) \\
&+\xi_2\left(m_1 C\left(1-k_1 C\right)-\frac{p_3 IC}{\beta_2+C}-\gamma_1 CN-d_3 HC\right) \\
&+\xi_3\left(m_2 N\left(1-k_2 N\right)-\gamma_2 CN\ \right)+\xi_4(\nu-d_4 H),
\end{aligned}$$

The Hamiltonian equations are:

$$\dot{\xi}_1=-\frac{\partial h*}{\partial I}, \dot{\xi}_2=-\frac{\partial h*}{\partial C}, \dot{\xi}_3=-\frac{\partial h*}{\partial N}, \dot{\xi}_4=-\frac{\partial h*}{\partial H}, \quad (19)$$

where, $\xi_i(t), i=1,2,3,4$ are the adjoint functions to be determined suitably.

The form of the adjoint equations and transversality conditions are standard results from Pontryagin's Maximum Principle [61]. The adjoint system can be written in the form:

$$\begin{aligned}
\dot{\xi}_1 &= -\frac{\partial h*}{\partial I} \\
&= -1-\xi_1\left(\frac{p_1 C}{\beta_1+C}-p_2 C-d_1-d_2 H\right) \\
&+\xi_2 \frac{p_3 IC}{\beta_2+C},
\end{aligned}$$

$$\begin{aligned}
\dot{\xi}_2 &= -\frac{\partial h*}{\partial C} \\
&= -1+\xi_1\left(\frac{-e\alpha}{(1+eC)^2}+\frac{p_1 \beta_1 I}{(\beta_1+C)^2}-p_2 I\right) \\
&-\xi_2\left(m_1-2 C m_1 k_1-\frac{p_3 \beta_2 I}{(\beta_2+C)^2}-\gamma_1 N-d_3 H\right) \\
&+\xi_3 \gamma_2 N,
\end{aligned}$$

$$\begin{aligned}
\dot{\xi}_3 &= -\frac{\partial h*}{\partial N} \\
&= \xi_2 \gamma_1 C-\xi_3\left(m_2-2 m_2 k_2 N-\gamma_2 C\right),
\end{aligned}$$

$$\dot{\xi}_4 = -\frac{\partial h*}{\partial H} = \xi_1 d_2 I+\xi_2 d_3 C+d_4 \xi_4,$$

The transversality conditions are $\xi_i\left(t_f\right)=0$, for $i=1,2,3,4$.

The condition dictate the necessary optimum control functions is

$\frac{\partial h*}{\partial \nu}=0$.

Hence, we get

$$\nu^*(t)=-\frac{\xi_4}{2\varepsilon_1}; \nu=\nu^*(t) \quad (20)$$

By using the bounds for the control $\nu^*(t)$ from (20), we get

$$\nu^* = \left\{ \begin{array}{ll} -\frac{\xi_4}{2\varepsilon_1}, & if\ 0 \leq -\frac{\xi_4}{2\varepsilon_1} \leq 1 \\ 0, & if\ -\frac{\xi_4}{2\varepsilon_1} \leq 0 \\ 1, & if\ \frac{\xi_4}{2\varepsilon_1} \geq 1 \end{array} \right\}$$

In compact notation, we have

$$\nu^* = \min\left\{\max\left\{0, -\frac{\xi_4}{2\varepsilon_1}\right\}, 1\right\}, \qquad (21)$$

Based on the analysis and conclusion presented above, the subsequent theorem is derived.

Theorem 8. *For optimal control* ν^* *and corresponding state variable solutions* $I^*(t), C^*(t), N^*(t)$ *and* $H^*(t)$ *that minimize over* Δ, *there exist specific adjoint variables* $\xi_i(t)$, $i = 1, 2, 3, 4$ *satisfying the following system:*

$$\begin{aligned} \dot{\xi}_1 &= -1 - \xi_1\left(\frac{p_1\ C}{\beta_1 + C} - p_2 C - d_1 - d_2 H\right) \\ &\quad + \xi_2 \frac{p_3 I C}{\beta_2 + C}, \\ \dot{\xi}_2 &= -1 + \xi_1\left(\frac{-e\alpha}{(1+eC)^2} + \frac{p_1\ \beta_1 I}{(\beta_1 + C)^2} - p_2 I\right) \\ &\quad - \xi_2\left(m_1 - 2C m_1 k_1 - \frac{p_3 \beta_2 I}{(\beta_2 + C)^2}\right. \\ &\quad \left. - \gamma_1 N - d_3 H\right)\ + \xi_3 \gamma_2 N, \\ \dot{\xi}_3 &= \xi_2 \gamma_1 C - \xi_3\left(m_2 - 2m_2 k_2 N - \gamma_2 C\right), \qquad (22) \\ \dot{\xi}_4 &= \xi_1 d_2 I + \xi_2 d_3 C + d_4 \xi_4, \end{aligned}$$

subject to the transversality conditions

$$\xi_i(t_f) = 0,\ i\ = 1, 2, 3, 4.$$

Furthermore, the subsequent properties are valid:

$$\tau^* = \min\left\{\max\left\{0, -\frac{\xi_4}{2\varepsilon_1}\right\}, 1\right\}$$

7. Numerical Analysis

Numerical verification is essential for completing analytical studies. In this section, we visually confirmed the accuracy of our analytical findings for the (PSCINC) system using the software MATLAB. This verification holds significant practical significance. The simulations were conducted using the parameter values specified below [53].

$$\begin{aligned} \alpha =& 0.05,\ e = 0.1, p_1 = 0.1, \beta_1 = 0.4, p_2 = 0.2, \\ & d_1 = 0.2, d_2 = 0.09, m_1 = 0.4,\ k_1 = 1.5, \\ & p_3 = 0.3, \beta_2 = 0.4,\ \gamma_1 = 0.2, d_3 = 0.05, \\ & m_2 = 0.35, k_2 = 1; \gamma_2 = 0.25, \nu = 0.019, \\ & d_4 = 0.05. \end{aligned}$$

Now, we will consider five scenarios to comprehend the dynamic behavior of the (PSCINC) model and assess the influence of chemotherapy treatment and psychological anxiety on tumor suppression. Subsequently, the outcomes of the five cases will be juxtaposed for comparison. The five cases are:

7.1. Case I: the healthy case

In this scenario, we examine the interaction dynamics between healthy cells $N(t)$ and immune cells $I(t)$ in the absence of chemotherapy treatment and psychological nervousness, i.e., where $\nu = 0$ and $e = 0$. Figure 2 depicts the (PSCINC) model with a cancer-free equilibrium point and a single positive equilibrium at $A_0 = (2, 0, 2.38, 0)$ Furthermore, regardless of the initial values, the solution initially experiences growth or decline before converging asymptotically to A_0 after approximately thirty days.

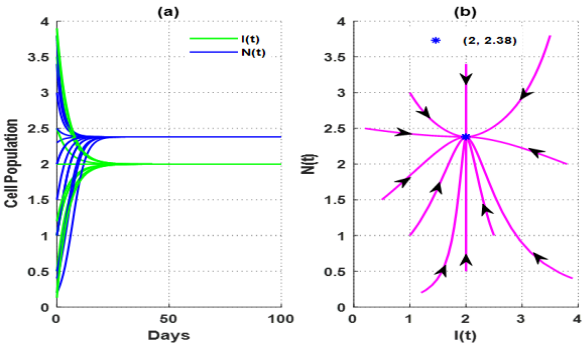


Figure 2. The dynamics of (PSCINC) model with $C = 0, \nu = 0$ and $e = 0$.

7.2. Case II: no treatment case

Here, we examine the behavior of the (PSCINC) model in the absence of treatment and the psychological scare. Figure 3 illustrates the performance of the (PSCINC) model where $\nu = 0$ and $e = 0$. All initial conditions lead to the convergence of the system to a treatment-free equilibrium point $A_1 = (I_1, C_1, N_1, 0) = (0.25, 0.13, 0.9, 0)$. In addition, the population of immune cells steadily diminishes as the number of tumor cells gradually increases. Furthermore, this case clearly demonstrates that eradicating

tumor cells is unattainable without a well-defined therapeutic strategy.

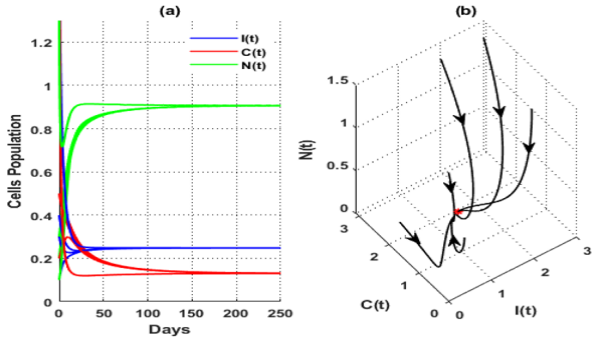


Figure 3. The dynamics of the (PSCINC) model with $\nu = 0$ and $e = 0$.

7.3. Case III: psychological scare case

The objective of this case is to demonstrate the impact of anxiety on the interaction between cancer cells and immune cells in the absence of chemotherapy drugs. Figure 4 explains the performance of the (PSCINC) model where $\nu = 0$ with various values of e. The relationship between rising anxiety and declining immune function is evident. As a result, the tumor cells significantly grow; therefore, external treatment is needed.

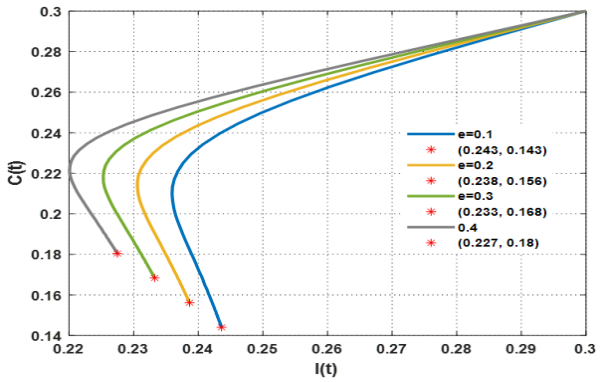


Figure 4. The dynamics of the $(PSCINC)$ model with $\nu = 0$ and various value of e.

7.4. Case IV: a treatment case

In this instance, we will examine the intricacies of the (PSCINC) system when subjected to chemo-drug. Figure.5 clearly depicts the global stability characteristics of the positive steady state $A_2 = (I_2, C_2, N_2, H_2) = (0.2, 0.14, 0.89, 0.38)$. The administration of chemotherapy leads to a substantial decrease in tumor cells within the body compared to past instances. In addition, chemotherapy also adversely affects the immune cells, decreasing the quantity of immune cells compared to the previous cases. Considering those mentioned above, additional doses are necessary to achieve a state devoid of tumors.

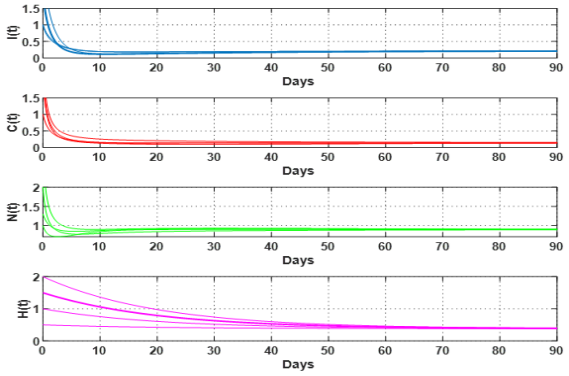


Figure 5. The dynamics of the (PSCINC) model with treatment case.

7.5. Case V: a minimum dosage of chemo-drug

This case aims to examine the effects of modifying the number of chemotherapy doses required to achieve a healthy state. Figure 5 clarifies the performance of the (PSCINC) model with various values of ν. The solution of the (PSCINC) system asymptotically converges to A_2 when v is less than 0.14. Conversely, the system tends towards a cancer-free state A_0 when $\nu = 0.14$. Thus, a value of $\nu = 0.14$ is the minimum dosage of chemotherapy necessary to achieve a condition devoid of cancer.

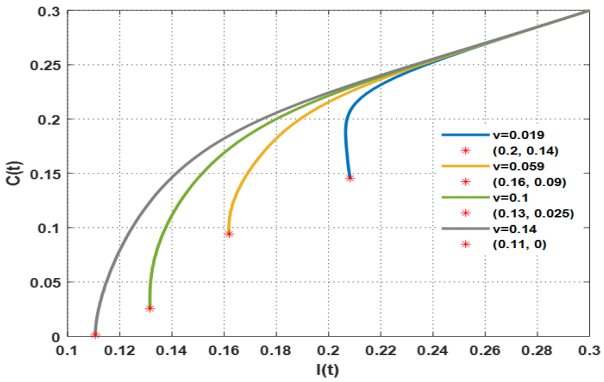


Figure 6. The dynamics of the (PSCINC) model with various values of ν

8. Conclusion

It has been looked at how an ODE mathematical model for tumor growth works, which includes how immune cells interact with tumor cells and how psychological scares and chemotherapy drugs work. The fundamental attributes of the model's

solutions, including positivity and boundedness, were established. A stability analysis was conducted on the system under consideration to investigate the model's dynamic behavior. Our research indicates that the constant state devoid of tumors is stable globally under particular conditions. This suggests that the prescribed treatment can eliminate tumor cells from the body for a specific tumor growth rate.

The numerical simulations validate the analytical findings. Precisely, the threshold values for the transcritical bifurcation are calculated, indicating the point at which cancer transitions from persisting to eradicating. Additionally, numerical analysis reveals that when the tumor size is modest, the prescribed chemotherapy drug can effectively eliminate tumor cells from the body with a minimal minimum dose. Nonetheless, a constraint of our model is that prolonged treatment and a substantial dosage of medications are necessary to eradicate large tumors, both of which can be detrimental to the patient's health.

Our upcoming research will focus on augmenting the immune system by regular vitamin intake or the utilization of stem cells.

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