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Research Article

Stability Analysis and Numerical Approach to Chemotherapy Model for the Treatment of Lung Cancer

R. Ilakkiya[1*], T. Jayakumar[2], S. Sujitha[3] and E. Vargees Kaviyan[4]

[1]Department of Science and Humanities, Nehru Institute of Technology, Coimbatore -641105,Tamilnadu, India.
* **Corresponding Author Email:** ilakkiyamathematics@gmail.com - **ORCID:** 0009-0006-7054-9025

[2]Department of Mathematics, Sri Ramakrishna Mission Vidyalaya College of Arts and Science, Coimbatore-641020, Tamilnadu, India.
Email: jayakumar.thippan68@gmail.com- **ORCID:** 0000-0002-5276-6775

[3]Department of Science and Humanities, Sree Sakthi Engineering College, Coimbatore - 641104.Tamilnadu, India
Email: sujithaskr5@gmail.com- **ORCID:** 0000-0003-2889-4096

[4]Department of Mathematics, Sri Ramakrishna Mission Vidyalaya College of Arts and Science, Coimbatore-641020, Tamilnadu, India.
Email: vargeeskaviyan@gmail.com- **ORCID:** 0000-0002-8607-7046

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Abstract:

This paper introduces and examines a mathematical model aimed at understand- ing the efficacy of chemotherapy in treating lung cancer. Through the utilization of differential equations, we delve into the intricate interplay between healthy cells, tumor cells, damaged tumor cells, and the impact of chemotherapy. Our analytical deductions are substantiated through extensive numerical simulations, revealing the profound effectiveness of chemotherapy in curbing tumor progression. Addition- ally, stability analysis is discussed and numerical simulations are suggested for the model that we have presented. These findings not only contribute significantly to the realm of lung cancer research but also hold substantial promise for therapeutic advancements. Moreover, the insights gleaned from this study are poised to enrich educational endeavors pertaining to lung cancer modeling, thereby fostering a deeper understanding of its underlying dynamics and treatment strategies.

1. Introduction

This article serves to introduce a comprehensive mathematical model aimed at under- standing lung cancer treatment through chemotherapy, employing intricate differential equations. Through extensive numerical simulations, we delve into the dynamics of both healthy and tumor cells. The insights gleaned from these simulations pave the way for informed decision-making regarding chemotherapy treatments. Liuyong Pang, Lin Shen, and Zhong Zhao explored the efficacy of single immunotherapy, single chemotherapy, and combination treatments. Their research yielded sufficient conditions for the ultimate elimination of tumor cells [1].

Yuting Li et al. objective is to lay the theoretical groundwork for novel lung cancer drug development, with the ultimate aim of improving therapeutic efficacy and patient outcomes [2]. B.M. Alexander, M.othus, H.B.Caglar and A.M. Allen explore the relation- ship between primary tumor and nodal volumes, as measured by chemo-radiotherapy plan- ning scans, and treatment outcomes, including survival and recurrence rate [3]. Chemother- apy stands as a cornerstone in cancer treatment, demonstrating its efficacy in combating malignant cells. By targeting rapidly dividing cells, chemotherapy minimizes its impact on healthy cells with slower reproduction rates. Consequently, our focus lies in elucidat- ing the intricate interplay between healthy and cancerous cells under the influence of chemotherapy.

Non-Small Cell Lung Cancer (NSCLC) presents a multifaceted challenge, not solely confined to its anatomical manifestations but also rooted in its diverse biological under- pinnings [4]. Given that a significant proportion of NSCLC patients face

locally advanced unresectable disease, chemotherapy emerges as the primary therapeutic approach for the majority. Despite strides made in enhancing Overall Survival (OS), long-term outcomes for unresectable stage III NSCLC patients remain disheartening, necessitating continual efforts to refine treatment strategies [5-20]. Lung cancer is studied and reported in the literature [21-23]. S. Sujitha, T.Jayakumar, D.Maheskumar, E. Vargees Kaviyan presents a computational framework for brain tumor treatment using combined therapies. The framework considers interactions between cells and treatment ef- fects, with a stability analysis across treatment categories. Numerical simulations provide insights into therapy effectiveness [5]. Mathematical modeling assumes a pivotal role in this pursuit, aiding in the formulation of hypotheses for prospective clinical trials and opti- mizing trial designs. Notably, in endeavors such as accelerated fractionation, as explored in the CHART and CHARTWEL trials, radiobiological models serve as indispensable tools in trial design and gauging therapeutic efficacy [15]. The ongoing trend of stratifying patients into finer sub-groups and adopting in- treatment adaptation strategies underscores the increasing relevance of patient-specific modeling in lung cancer management. While current assessments of treatment regimens often revolve around potent doses, the sequencing of chemotherapy emerges as a crucial determinant in NSCLC treatment outcomes [4]. Despite this recognition, there exists a dearth of mathematical models elucidating combination therapies, which hold promise in refining patient stratification and optimizing chemotherapy sequencing.

In the realm of malignant glioma management, the amalgamation of surgery and chemotherapy represents the primary course of action. Numerous studies have explored the additive benefits of chemotherapy, with factors such as resection radius, optimal dosing, scheduling, and sequencing (concurrent, adjuvant, or neo-adjuvant) playing pivotal roles in treatment efficacy [24-26]. While further clinical trials are imperative to delineate optimal treatment strategies, the development and validation of mathematical models hold promise in guiding these endeavors. Such meticulously crafted models serve as invaluable tools in formulating hypotheses for future clinical trials and refining trial designs.

The structure of this paper unfolds as follows: a detailed exposition of the tumor growth model and tumor chemotherapy model is presented initially. Subsequently, the outputs of numerical simulations are elucidated, accompanied by Equilibria and local stability analysis and also the global stability analysis with its explanation. Finally, the paper culminates in a discussion section, wherein the implications of our findings are thoroughly explored.

In essence, our endeavor encompasses the development of a sophisticated mathematical framework to comprehensively comprehend lung cancer treatment via chemotherapy. Through meticulous consideration of healthy cells, tumor cells, and their intricate inter- actions, we aim to contribute significantly to the optimization of chemotherapy strategies, ultimately enhancing patient outcomes.

The paper is organized in the following manner. In Section 2, we introduce new system of linear system of differential equations using chemotherapy. In Section 3, stability analysis method is investigated. In Section 4, we discuss the numerical simulations. This paper ends with a brief conclusion and discussion in Section 5.

2. Methodology

As stated in the introduction, the mathematical model described in this study includes chemotherapy. First we introduce a new system of equations in the model (1) - (4). The following system of differential equations provides healthy cells and tumor cells interaction with chemotherapy treatment in the dynamic mode of a lung cancer.

Where x denotes the concentration of healthy cells, y represents the number of tumor cells and z is the damaged tumor cells, w is the amount of chemotherapy drug.

3. Stability Analysis

Our primary focus is on examining the stability properties of the system represented by the equations (1) - (4) [6].

3.1 Equilibria and Local Stability Analysis

The stability of system (1) - (4) around each singular point is characterized by the eigen- values $\lambda_i, (i = 1,2,3,4)$ of the variational matrix, which dictate the local stability of the system.

$$J = = \begin{bmatrix} M_{11} & -c_1 x & 0 & -q_1 x \\ 0 & M_{12} & 0 & 0 \\ 0 & q_2 w & -\alpha & 0 \\ 0 & 0 & 0 & -d_2 \end{bmatrix}. \qquad (5)$$

where,

$M_{11} = -d_1 - q_1 w$, $M_{12} = r - c_2 x - q_2 w$.

The existence and stability of equilibrium points are crucial aspects of understanding the dynamics of the system. In the following sections, we will delve into the analysis of equilibrium points and their stability, considering two distinct scenarios. Firstly, we will examine the system without therapy, providing insights into the natural dynamics of the system. Secondly, we will investigate the system with chemotherapy, analyzing how the introduction of therapy affects the existence and stability of equilibrium points.

Without therapy

System (1) - (4) possesses a trivial equilibrium point, $E_0(0,0,0,0)$ which exists regardless of parameter values, and corresponds to the extinction of all four cell populations.

$$J = \begin{bmatrix} -d_1 & 0 & 0 & 0 \\ 0 & r & 0 & 0 \\ 0 & 0 & -\alpha & 0 \\ 0 & 0 & 0 & -d_2 \end{bmatrix}. \qquad (6)$$

The corresponding eigenvalues for this equilibrium point E_0 are

$$\lambda_1 = -d_1, \lambda_2 = r\,, \lambda_3 = -\alpha, \lambda_4 = -d_2.$$

The fact that one eigenvalue is greater than zero confirms that the equilibrium is unstable.

With Chemotherapy

The system of equations (1) - (4) have "extinct" equilibrium point E_1 (16177.4,0,0,144.259) for any set of parameters

$$J = \begin{bmatrix} M_{11} & -c_1x & 0 & -q_1x \\ 0 & M_{12} & 0 & 0 \\ 0 & q_2w & -\alpha & 0 \\ 0 & 0 & 0 & -d_2 \end{bmatrix}. \qquad (7)$$

where

$$M_{11} = -d_1 - q_1w\,, \qquad M_{12} = r - c_2x - q_2w.$$

The corresponding eigenvalues for this equilibrium point E_1 are

$$\lambda_1 = -d_1 < 0,\ \lambda_2 = M_{11} = -(d_1 + q_1w) < 0\,,$$
$$\lambda_3 = M_{12} = -(c_2x + q_2w - r)0, \lambda_4 = -\alpha < 0.$$

But this time, all of our Eigen values are negative. Our system is locally asymptotically stable.

3.2 Global Stability Analysis of Chemo therapy treatment

Using La Salle's Invariance Principle [27] and a suitable Lyapunov function, this section describes the global stability of the tumor-free equilibrium point E_2=(x̄,0,0,w̄).

We describe the Lyapunov function

$M: R_+^4 \to R$ as $M = \left[x - \bar{x} - \bar{x} ln\left(\frac{x}{\bar{x}}\right)\right] + \frac{1}{2}(w - \bar{w})^2$

It is evident from the formulation of the Lyapunov function that the specified function M is non-negative for the initial circumstances in the first quadrant and vanishes at the tumor-free equilibrium point. The derivative of M concerning time t towards the resolution of the proposed model (1) - (4) is

$$M' = \left[x' - \frac{\bar{x}x'}{x}\right] + w'(w - \bar{w}).$$

On simplification, we get

$$M' = x'\left[1 - \frac{\bar{x}}{x}\right] + w'(w - \bar{w}),$$

where,

$x' = s - c_1xy - d_1x - q_1wx$ and $w' = \emptyset - d_2w$.

Hence,

$$M' = (s - c_1xy - d_1x - q_1wx)\left[1 - \frac{\bar{x}}{x}\right] + (\emptyset - d_2w)(w - \bar{w}).$$

Thus if

$s - c_1xy - d_1x - q_1wx < 0$ *and* $\emptyset - d_2w > (w - \bar{w})$,

then,

$M' \leq 0.$

We calculated $M'(t)$ to verify our above results numerically considering initial values, all parameters given in Table 1. We can summarize the analytical conditions for global asymptotic stability in the following theorem.

Theorem 3.1

If $s - c_1xy - d_1x - q_1wx < 0$ *and* $\emptyset - d_2w > (w - \bar{w})$, then the proposed model (1) - (4) is globally asymptotic stable around the tumor free equilibrium point E_2.

4. Numerical Simulations

The system of equtions (1) - (4) will be discussed in this part, and it will be solved using fourth order Runge-Kutta method. The numerical simulation is also completed by means of select out the parameter values represented in Table 1 with initial conditions x(0),y(0),z(0),w(0). We have chosen two categories to analyze numerically for our model without treatment and with chemotherapy.
First, we now consider without treatment. Figure 1

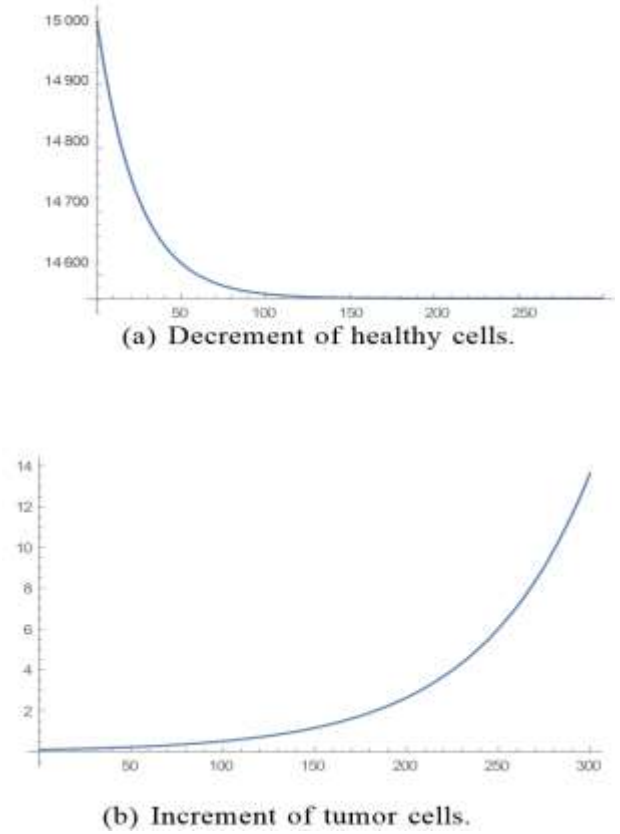

Figure 1. *Numerical Solution of the model without any theraphy.*

illustrates the system's dynamics without treatment. At this stage, the stability analysis shows that the healthy cell population decreases due to the uncontrolled growth of tumor cells, which attain their maximum size, highlighting the need for treatment intervention. This outcome is a direct result of the lack of treatment. To address this, we employ chemotherapy to target tumor cells.

Table 1. *List of symbols and abbreviations [1]*

Parameter	Estimated Values	Description
S	1900	Normal rate of flow of healthy cells into the tumor site [1].
c_1	3.420×10^{-10}	Healthy cells death rate due to interaction with tumor cells [1].
d_1	4.120×10^{-2}	Nature death rate of Healthy cells.
q_1	4×10^{-4}	Fractional healthy cells kill by chemotherapy.
R	9×10^{-2}	Tumor cells growth rate.
B	2.000×10^{-9}	Tumor cells carrying capacity.
c_2	1.100×10^{-5}	Fractional tumor cells kill by healthy cells.
q_2	1.000×10^{-7}	Fractional tumor cells kill by chemotherapy.
d_2	3.466×10^{-1}	Rate of Chemotherapy drug decay.
A	4.120×10^{-2}	Natural death of damaged tumor cells.
Φ	$0 - 400$	Dose per fraction.

5. Conclusions

In this paper, we present a mathematical model to examine the dynamics of cancer cells interacting with chemotherapy. The model considers x(t) as healthy cells, y(t) as tumor cells, z(t) as damaged tumor cells, and w(t) as the amount of chemotherapy drug. The stability of the linear version of the system is analyzed by constructing a characteristic equation, from which we derive the eigenvalues. Since all the eigenvalues are negative, the system is locally asymptotically stable. We then perform a numerical simulation for the system of equations, categorized into two scenarios.
We conclude that this mathematical model, which elucidates the interplay between tumor cells and chemotherapy, is a significant step forward in developing more effective treatments for malignant tumors.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
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