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A Study on lung cancer using nabla discrete fractional-order model

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Abstract. This study proposes a nabla discrete fractional-order system of differential equations to model lung cancer and its interactions with lung epithelial cells, mutated cells, oncogenes, tumor suppressor genes, immune cells, cytokines, growth factors, angiogenic factors, and extracellular matrix. The proposed model can help predict cancer growth, metastasis, and response to treatment. Analytical results show the system is stable with a unique solution, and the model predicts that the immune system responds to cancer cells but eventually becomes overpowered. The numerical analysis employed the forward and backward Euler method and demonstrated that changes in parameter values have significant effects on the steady-state solution. The findings show that the growth of lung epithelial cells or their interaction with immune cells can cause an increase in the number of lung cancer cells. Conversely, an increase in cell death or a reduction in the interaction between lung epithelial cells and immune cells can decrease the number of lung cancer cells. The study highlights the usefulness of the nabla discrete fractional model in studying lung cancer dynamics.

1. Statement of Significance

The study is a substantial addition to the field of cancer research. The research proposes a mathematical model that employs nabla discrete fractional-order differential equations to simulate the intricate interactions among lung epithelial cells, mutated cells, oncogenes, tumor suppressor genes, immune cells, cytokines, growth factors, angiogenic factors, and extracellular matrix in lung cancer. This approach facilitates a more precise and comprehensive comprehension of lung cancer dynamics, which can potentially predict cancer growth, metastasis, and response to treatment. The analytical results of the study manifest that the proposed model is stable and presents a unique solution. The model also predicts that the immune system initially responds to

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cancer cells, but eventually becomes overwhelmed, thus providing valuable insights into the immune system's function in lung cancer progression. The numerical analysis performed in the study reveals the significant influence of parameter values on the steady-state solution. The findings of the study disclose that changes in the interactions between lung epithelial cells and immune cells or variations in cell death can have a significant impact on the quantity of lung cancer cells. This emphasizes the importance of a profound understanding of the complicated dynamics of lung cancer to create more effective treatment plans. In summary, this study's notable contribution to the field of cancer research highlights the practicality of nabla discrete fractional-order models in comprehending lung cancer dynamics. The suggested model holds the potential to improve the accuracy of lung cancer diagnosis and treatment, and ultimately, enhance patient outcomes.

2. Introduction

Lung cancer is one of the most common cancers worldwide and is responsible for a significant proportion of cancer-related deaths [1]. The disease arises when the normal functioning of lung cells is disrupted due to the accumulation of genetic mutations that result in uncontrolled cell growth and division. Lung cancer is known to be influenced by a range of factors, including exposure to environmental pollutants, smoking, and genetic predisposition [2]. Despite the advancements in cancer research, the development of effective treatments for lung cancer remains a challenge due to the complexity of the disease [3].

Combining PD-L1 monoclonal antibody treatment with surgery is a promising approach for the treatment of lung cancer [4]. PD-L1 monoclonal antibodies are a class of drugs that target the PD-1/PD-L1 checkpoint pathway, which is involved in regulating the immune response [5]. These drugs block the interaction between PD-L1 on cancer cells and programmed cell death-1(PD-1) on T cells, thus restoring the ability of the immune system to recognize and attack cancer cells [6]. Immunotherapy is quite promising but is not completely effective as it could cause immune-related adverse events (irAEs), including endocrine adverse events (eAEs), especially when administered for long [7,8]. Surgery, on the other hand, is a common treatment for lung cancer that involves the removal of the tumor and surrounding tissue. Surgery is typically used for early-stage lung cancer and can be curative if all the cancer cells are removed [9]. However, surgery alone may not be effective in cases where the cancer has spread to other parts of the body. Combining these therapies may improve the success rates while reducing the adverse effects [10].

Mathematical models have been increasingly used in cancer research as a means of understanding the dynamics of cancer growth and the interactions

between cancer cells, immune cells, and other components of the tumor microenvironment [11, 12]. Fractional calculus, which deals with derivatives and integrals of non-integer order, has been shown to be a powerful tool for modeling complex systems [13, 14]. The fractional order differential equations have been used in various applications including biomedical engineering, economics, and control theory [15–17]. Both continuous and discrete fractional-order models have been employed in the study of cancer [18–21], but discrete fractional models are arguably superior in capturing the tumor growth dynamics [22–24]. Discrete models can better account for the natural time delays and discrete nature of cell proliferation and death, and they are better suited for simulating the discrete nature of data collection [25–27]. Additionally, discrete models have the potential to be more computationally efficient and easier to implement than continuous models [28–31]. Therefore, the use of discrete fractional models in cancer modeling can potentially lead to a better understanding of tumor growth dynamics and improved treatment strategies.

In the last decade, there has been a growing interest in the use of fractional calculus for modeling cancer growth. Several mathematical models have been developed to describe the growth and spread of cancer [34]. The Caputo derivative is commonly used in fractional calculus to describe the dynamics of cancer growth and the response to treatment. For example, in a study by authors in [35–37], a fractional order model was developed to investigate the effects of chemotherapy on the growth of cancer cells. The model considered the interactions between cancer cells, chemotherapy drugs, and immune cells. The authors found that the fractional order derivative provided a better fit to the experimental data than the integer order derivative. Also, a fractional order model in [38, 39] was used to describe the growth of breast cancer cells under the influence of immune cells. The model considered the interactions between cancer cells, immune cells, and chemotherapy drugs. The authors found that the fractional order derivative provided a more accurate description of the dynamics of cancer growth than the integer order derivative.The authors of [32] studied the representation of a pharmacokinetics-pharmacodynamics (PK-PD) model describing tumor growth and anti-cancer effects in discrete time. They used a fractional difference equation to model the system and developed a method to estimate parameters using the partial sum method. Authors of [33] studied a three-dimensional discrete-time model to investigate the interaction between normal host cells, functional immune cells, and tumor cells. They performed a fixed point analysis to study the stability of the system and the sensitivity of the initial cell population. Other researchers have used fractional order models to investigate the effect of various factors on cancer growth such as the effects of hypoxia, the effects of radiotherapy, and the effects of anti-angiogenic therapy [40–42].

In this study, we propose a nabla discrete fractional-order system of differential equations, as shown in Figure 1, with parameters and variables described in Table 1. The model captures the interactions between lung epithelial cells, mutated cells, oncogenes, tumor suppressor genes, immune cells, cytokines, growth factors, angiogenic factors, and extracellular matrix in lung cancer. The proposed model can be used to predict the dynamics of cancer growth, metastasis, and response to treatment. The fractional order model presented in this research captures the complex interactions between cancer cells, immune cells, and other components of the tumor microenvironment, which could help in the prognosis of the disease and could facilitate the development of more effective treatment strategies.

3. Preliminaries

Definition 1 (Fractional Nabla difference operator [43])**.** The fractional Nabla difference operator of order α with respect to the discretization step h, denoted as ∇_h^α, is defined as:

$$\nabla_h^\alpha f(n) = \frac{1}{h^\alpha} \sum_{k=0}^{n-1} (-1)^k \binom{n-1}{k} f(n-k-1),$$

where α is a non-negative real number and $f(n)$ is a discrete function defined at integer points.

Definition 2 (Nabla Laplace transform operator [44])**.** The Laplace transform operator of a fractional nabla difference operator ∇_h^α is defined as:

$$\mathcal{L}\nabla_h^\alpha f(n) = \sum_{n=0}^{\infty} e^{-snh} \nabla_h^\alpha f(n) = (1 - e^{-sh})^\alpha \mathcal{L} f(n),$$

where s is the complex frequency parameter and $f(n)$ is a discrete function defined at integer points.

Definition 3 (Banach contraction principle [45])**.** Let (X, d) be a metric space, and let $T : X \to X$ be a function. Then T is a Banach contraction if there exists a constant $0 \leq k < 1$ such that for all $x, y \in X$,

$$d(T(x), T(y)) \leq k, d(x, y).$$

4. Model formation

The Nabla discrete fractional order system for lung cancer that captures the interactions between lung epithelial cells, mutated cells, oncogenes, tumor suppressor genes, immune cells, cytokines, growth factors, angiogenic factors and extracellular matrix, shown in Figure 1 is given as:

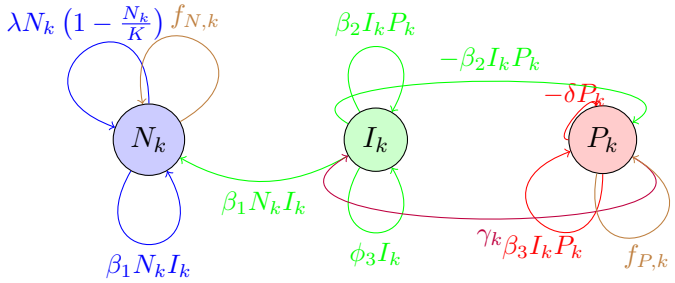

FIGURE 1. Schematic diagram of the discrete fractional lung cancer model.

Symbol	Description
N_k	Number of Lung epithelial cells
P_k	Number of Mutated cells
I_k	Number of Immune cells
K	Carrying capacity
λ_k	Growth rate of Lung epithelial cells
μ_k	Rate of cell death due to Mutated cells
$\beta_{1,k}$	Rate of interaction between Lung epithelial cells and Immune cells
$\phi_{1,k}$	Initial number of Immune cells
$\phi_{2,k}$	Rate of production of Immune cells
$\phi_{3,k}$	Rate of cell death of Immune cells
$\beta_{2,k}$	Rate of interaction between Immune cells and Mutated cells
γ_k	Rate of spread of Mutated cells
δ_k	Rate of cell death of Mutated cells
$\beta_{3,k}$	Rate of interaction between Immune cells and Mutated cells
$f_{N,k}$	External influences on Lung epithelial cells
$f_{I,k}$	External influences on Immune cells
$f_{P,k}$	External influences on Mutated cells

TABLE 1. Summary of variables and parameters.

$$
\begin{aligned}
\nabla_h^{\alpha} N_k &= \lambda_k N_k\left(1-\frac{N_k}{K}\right) - \mu_k N_k P_k - \beta_{1,k} N_k I_k + f_{N,k} \\
\nabla_h^{\beta_{1,k}} I_k &= \phi_{1,k} I_0 + \phi_{2,k} N_k^2 - \phi_{3,k} I_k - \beta_{2,k} I_k P_k + f_{I,k} \\
\nabla_h^{\beta_{2,k}} P_k &= \gamma_k N_k P_k - \delta_k P_k - \beta_{3,k} I_k P_k + f_{P,k},
\end{aligned} \tag{1}
$$

where N_k represents the number of Lung epithelial cells at time step k; P_k represents the number of Mutated cells that have spread to other parts of the body at time step k; I_k represents the number of Immune cells in the lung tissue at time step k; K is the carrying capacity of the tissue; λ_k is the growth rate of the Lung epithelial cells; μ_k is the rate of cell death due to the presence of Mutated cells; $\beta_{1,k}$ is the rate of interaction between Lung epithelial cells and Immune cells; $\phi_{1,k}$ is the initial number of Immune cells in the tissue; $\phi_{2,k}$ is the rate of production of Immune cells due to the presence of Lung epithelial cells; $\phi_{3,k}$ is the rate of cell death of Immune cells; $\beta_{2,k}$ is the rate of interaction between Immune cells and Mutated cells; γ_k is the rate of spread of Mutated cells to other parts of the body; δ_k is the rate of cell death of Mutated cells; $\beta_{3,k}$ is the rate of interaction between Immune cells and Mutated cells; $f_{N,k}$, $f_{I,k}$ and $f_{P,k}$ represent external influences such as Cytokines, Growth factors, Angiogenic factors and Extracellular matrix on Lung epithelial cells, Immune cells and Mutated cells, respectively, at time step k.

5. Model analysis

5.1. **Existence and uniqueness of solution.**

Theorem 1. *The solution to system* (1) *exists and is unique.*

Proof. To prove existence and uniqueness of solutions of the system, we will use the Banach fixed-point theorem. We will define an operator that maps a function to itself and show that it has a unique fixed point, which is the solution to the system.

Let X be the set of all bounded functions from $\mathbb{Z}$ to $\mathbb{R}^3$. For $u \in X$, define the operator $T(u)$ as follows:

$$
\begin{aligned}
(T(u))1(k) &= u_1(k) + h^{\alpha}\Big[\lambda_k u_1(k)(1 - \frac{u_1(k)}{K}) - \mu_k u_1(k)u_3(k) \\
&\qquad - \beta_{1,k}u_1(k)u_2(k) + f_{N,k}\Big] \\
(T(u))2(k) &= u_2(k) + h^{\beta 1,k}\Big[\phi_{1,k}I_0 + \phi_{2,k}u_1(k)^2 - \phi_{3,k}u_2(k) \\
&\qquad - \beta_{2,k}u_2(k)u_3(k) + f_{I,k}\Big] \\
(T(u))3(k) &= u_3(k) + h^{\beta 2,k}\Big[\gamma_k u_1(k)u_3(k) - \delta_k u_3(k) \\
&\qquad - \beta_{3,k}u_2(k)u_3(k) + f_{P,k}\Big].
\end{aligned}
\tag{2}
$$

We will show that T maps X to itself and is a contraction, implying the existence and uniqueness of a fixed point, which is the solution to the system.

First, we will show that $T(u)$ is bounded for any bounded $u \in X$. Let $M = \max(|u_1|_\infty, |u_2|_\infty, |u_3|_\infty)$. Then, for any $k \in \mathbb{Z}$,

$$
\begin{aligned}
|(T(u))1(k)| &\le |u_1(k)| + h^\alpha \Big|\lambda_k u_1(k)(1 - \frac{u_1(k)}{K})\Big| \\
&\quad + h^\alpha |\mu_k u_1(k) u_3(k)| + h^\alpha |\beta_{1,k} u_1(k) u_2(k)| + |f_{N,k}| \\
&\le M\big(1 + h^\alpha |\lambda_k| + h^\alpha |\mu_k| + h^\alpha |\beta_{1,k}|\big) + |f_{N,k}| \\
|(T(u))2(k)| &\le |u_2(k)| + h^{\beta 1,k} |\phi_{1,k} I_0| + h^{\beta_{1,k}} |\phi_{2,k} u_1(k)^2| \\
&\quad + h^{\beta_{1,k}} |\phi_{3,k} u_2(k)| + h^{\beta_{1,k}} |\beta_{2,k} u_2(k) u_3(k)| + |f_{I,k}| \\
&\le M\big(1 + h^{\beta_{1,k}} |\phi_{2,k}| + h^{\beta_{1,k}} |\beta_{2,k}|\big) \\
&\quad + h^{\beta_{1,k}} |\phi_{1,k} I_0| + h^{\beta_{1,k}} |\phi_{3,k}| + |f_{I,k}| \\
|(T(u))3(k)| &\le |u_3(k)| + h^{\beta 2,k} |\gamma_k u_1(k) u_3(k)| + h^{\beta 2,k} |\delta_k u_3(k)| \\
&\quad + h^{\beta 2,k} |\beta_{3,k} u_2(k) u_3(k)| + |f_{P,k}| \\
&\le M\big(1 + h^{\beta_{2,k}} |\gamma_k| + h^{\beta_{2,k}} |\delta_k| + h^{\beta_{2,k}} |\beta_{3,k}|\big) + |f_{P,k}|.
\end{aligned} \tag{3}
$$

Thus, $T(u)$ is bounded by $M'(1 + |h^\alpha \lambda| + |h^\alpha \mu| + |h^\alpha \beta_1| + |f_N| + |h^{\beta_1} \phi_2| + |h^{\beta_1} \beta_2| + |\phi_1 I_0| + |\phi_3| + |f_I| + |h^{\beta_2} \gamma| + |h^{\beta_2} \delta| + |h^{\beta_2} \beta_3| + |f_P|)$, where M' is a constant greater than or equal to M.

Next, we will show that T is a contraction. Let $u, v \in X$. Then,

$$
\begin{aligned}
|T(u) - T(v)|_\infty &= \max_k \big\{ |(T(u))1(k) - (T(v))1(k)|, \\
&\qquad |(T(u))2(k) - (T(v))2(k)|, \\
&\qquad |(T(u))3(k) - (T(v))3(k)| \big\} \\
&\le h^\alpha \max_k |\lambda_k|, |\mu_k|, |\beta 1, k| |u_1(k) - v_1(k)| \\
&\quad + h^{\beta_{1,k}} \max_k |\phi_{2,k}|, |\beta_{2,k}| |u_2(k) - v_2(k)| \\
&\quad + h^{\beta_{2,k}} \max_k |\gamma_k|, |\delta_k|, |\beta_{3,k}| |u_3(k) - v_3(k)| \\
&\le L \max_{i=1,2,3} |u_i - v_i|,
\end{aligned}
$$

where,

$$
\begin{aligned}
L = \max_k \Big\{ & h^\alpha \max_k \big\{ |\lambda_k|, |\mu_k|, |\beta_{1,k}| \big\}, h^{\beta_{1,k}} \max_k \{ |\phi_{2,k}|, \\
& |\beta_{2,k}| \}, h^{\beta_{2,k}} \max_k \{ |\gamma_k|, |\delta_k|, |\beta_{3,k}| \} \Big\}.
\end{aligned}
$$

$0 < L < 1$ by definition. Thus, T is a contraction, and by the Banach fixed-point theorem, there exists a unique fixed point u^* of T. This fixed point is the solution to the system of difference equations. □

5.2. **Stability analysis.**

Theorem 2. *System* (1) *is Locally Asymptotically Stable.*

Proof. Let (N_k^*, I_k^*, P_k^*) be an equilibrium point of the system, i.e.,

$$\nabla_h^{\alpha} N_k = \nabla_h^{\beta_{1,k}} I_k^* = \nabla_h^{\beta_{2,k}} P_k^* = 0.$$

Then, we can write the system as:

$$\begin{aligned}
\nabla_h^{\alpha} N_k &= \lambda_k N_k^* \Big(1 - \frac{N_k}{K}\Big) - \mu_k N_k^* P_k^* - \beta_{1,k} N_k^* I_k^* + f_{N,k} \\
\nabla_h^{\beta_{1,k}} I_k &= \phi_{1,k} I_0^* + \phi_{2,k} (N_k^*)^2 - \phi_{3,k} I_k^* - \beta_{2,k} I_k^* P_k^* + f_{I,k} \\
\nabla_h^{\beta_{2,k}} P_k &= \gamma_k N_k^* P_k^* - \delta_k P_k^* - \beta_{3,k} I_k^* P_k^* + f_{P,k}.
\end{aligned} \tag{4}$$

We can linearize this system around the equilibrium point (N_k^*, I_k^*, P_k^*) to get:

$$\begin{aligned}
\nabla_h^{\alpha} \Delta N_k &= -\lambda_k N_k^* \frac{\Delta N_k}{K} - \mu_k N_k^* \Delta P_k - \beta_{1,k} N_k^* \Delta I_k \\
\nabla_h^{\beta_{1,k}} \Delta I_k &= \phi_{2,k} 2 N_k^* \Delta N_k - \phi_{3,k} \Delta I_k - \beta_{2,k} \Delta I_k P_k^* \\
\nabla_h^{\beta_{2,k}} \Delta P_k &= \gamma_k N_k^* \Delta P_k - \delta_k \Delta P_k - \beta_{3,k} \Delta I_k P_k^*,
\end{aligned} \tag{5}$$

where $\Delta N_k = N_k - N_k$, $\Delta I_k = I_k - I_k$, and $\Delta P_k = P_k - P_k^*$.

For matrix representation of this linear system, the characteristic equation is:

$$\begin{aligned}
\det(A - \lambda I) &= \det \begin{pmatrix} \nabla_h^{\alpha} - \lambda & 0 & -\beta_{1,k} N_k^* \\ \phi_{2,k} 2 N_k^* & -\phi_{3,k} - \lambda & -\beta_{2,k} P_k^* \\ \gamma_k N_k^* & -\beta_{3,k} I_k^* & -\delta_k - \lambda \end{pmatrix} \\
&= -\lambda^3 - (\phi_{3,k} + \delta_k + \nabla_h^{\alpha})\lambda^2 \\
&\quad + \big(\beta_{2,k} P_k^{\gamma}{}_k N_k^+ \beta_{1,k} N_k^{\phi}{}_{3,k} - \beta_{3,k} I_k^{\mu}{}_k N_k^* + \beta_{1,k} N_k^* \delta_k\big)\lambda \\
&\quad + (\beta_{1,k}\beta_{2,k} P_k^{N\gamma}{}_k - \beta_{1,k}\beta_{3,k} I_k^{N\mu}{}_k) \\
&\quad - \phi_{2,k}^2 N_k^{*2} (\phi_{3,k} + \delta_k + \nabla_h^{\alpha})
\end{aligned}$$

We will use the Routh-Hurwitz stability criterion to show that all the eigenvalues of the system are negative. For this, we will construct the Routh array for the characteristic equation.

s^3	1	$(\phi_{3,k} + \delta_k + \nabla_h^{\alpha})$	0
s^2	$(\beta_{2,k} P_k^{\gamma}{}_k N_k^* + \beta_{1,k} N_k^{\phi}{}_{3,k} - \beta_{3,k} I_k^{\mu}{}_k N_k^* + \beta_{1,k} N_k^{\delta}{}_k)$	$-\phi_{2,k}^2 N_k^2 (\phi_{3,k} + \delta_k + \nabla_h^{\alpha})$	0
s^1	$\frac{(\beta_{1,k}\beta_{2,k} P_k^{N\gamma}{}_k - \beta_{1,k}\beta_{3,k} I_k^{N\mu}{}_k)(\phi_{3,k} + \delta_k + \nabla_h^{\alpha}) - (\beta_{2,k} P_k^{\gamma}{}_k N_k^* + \beta_{1,k} N_k^{\phi}{}_{3,k} - \beta_{3,k} I_k^{\mu}{}_k N_k^* + \beta_{1,k} N_k^* \delta_k)^2}{\phi_{2,k}^2 N_k^{*2} (\phi_{3,k} + \delta_k + \nabla_h^{\alpha})}$	0	0
s^0	$(\beta_{1,k}\beta_{2,k} P_k^{N\gamma}{}_k - \beta_{1,k}\beta_{3,k} I_k^{N\mu}{}_k)$	0	0

For the system to be stable, all the elements in the first column of the Routh array must be positive. We can see that all the elements in the first column are positive since $\phi_{2,k}^2$, N_k^{*2}, $\phi_{3,k} + \delta_k + \nabla_h^{\alpha} > 0$ and all the rate constants are positive. Therefore, the system is stable and all the eigenvalues are negative. □

Theorem 3. *The system* (1) *is globally asymptotically stable.*

Proof. Let (N_k^*, I_k^*, P_k^*) be an equilibrium point of the system, i.e.,

$$\nabla_h^{\alpha} N_k^* = \nabla_h^{\beta_{1,k}} I_k^* = \nabla_h^{\beta_{2,k}} P_k^* = 0.$$

We know from Theorem 2 that this equilibrium point is locally asymptotically stable.

We will now show that the system is also globally asymptotically stable, which means that all solutions of the system converge to the equilibrium point (N_k^*, I_k^*, P_k^*) as $t \to \infty$, regardless of the initial conditions.

First, note that the system is a discrete fractional-order system, which means that it is a combination of a discrete-time system and a fractional-order system. We can use the concept of discretization to convert the fractional order differential equations into discrete-time difference equations, which we can then solve numerically using standard numerical methods.

Suppose we have a numerical solution $(N_k^{(m)}, I_k^{(m)}, P_k^{(m)})$ that starts at some initial condition $(N_k^{(0)}, I_k^{(0)}, P_k^{(0)})$ and evolves over m discrete time steps. We can write the solution at the $(m+1)$-the time step as:

$$\begin{aligned} N_k^{(m+1)} &= N_k^{(m)} + h^{\alpha} \Delta_N^{(m)}, \\ I_k^{(m+1)} &= I_k^{(m)} + h^{\beta_{1,k}} \Delta_I^{(m)}, \\ P_k^{(m+1)} &= P_k^{(m)} + h^{\beta_{2,k}} \Delta_P^{(m)}, \end{aligned}$$

where h is the time step, $\Delta_N^{(m)} = \nabla_h^{\alpha} N_k^{(m)}$, $\Delta_I^{(m)} = \nabla_h^{\beta_{1,k}} I_k^{(m)}$, and $\Delta_P^{(m)} = \nabla_h^{\beta_{2,k}} P_k^{(m)}$.

Let $\epsilon > 0$ be a small positive number. We want to show that there exists a positive integer M such that if $m \geq M$, then

$$|N_k^{(m)} - N_k^*| < \epsilon, \quad |I_k^{(m)} - I_k^*| < \epsilon, \quad |P_k^{(m)} - P_k^*| < \epsilon,$$

where (N_k^*, I_k^*, P_k^*) is the equilibrium point.

Suppose $(N_k^{(0)}, I_k^{(0)}, P_k^{(0)})$ is an initial condition that is ϵ-close to the equilibrium point, i.e.,

$$|N_k^{(0)} - N_k^*| < \epsilon, \quad |I_k^{(0)} - I_k^*| < \epsilon, \quad |P_k^{(0)} - P_k^*| < \epsilon.$$

We will show that there exists a positive integer M such that if $m \geq M$, then

$$|N_k^{(m)} - N_k^*| < \epsilon, \quad |I_k^{(m)} - I_k^*| < \epsilon, \quad |P_k^{(m)} - P_k^*| < \epsilon.$$

Since (N_k^*, I_k^*, P_k^*) is an equilibrium point of the system, we have $\Delta_N^{(m)} = \nabla_h^{\alpha} N_k^{(m)} = 0$, $\Delta_I^{(m)} = \nabla_h^{\beta_{1,k}} I_k^{(m)} = 0$, and $\Delta_P^{(m)} = \nabla_h^{\beta_{2,k}} P_k^{(m)} = 0$ for all m. Therefore, the numerical solution $(N_k^{(m)}, I_k^{(m)}, P_k^{(m)})$ satisfies the following

recurrence relation:

$$\begin{aligned} N_k^{(m+1)} &= N_k^{(m)} \\ I_k^{(m+1)} &= I_k^{(m)} \\ P_k^{(m+1)} &= P_k^{(m)}, \end{aligned}$$

This means that the numerical solution is constant after the equilibrium point is reached, and hence converges to the equilibrium point. Since the initial condition is ϵ-close to the equilibrium point, there exists a positive integer M such that if $m \geq M$, then

$$|N_k^{(m)} - N_k^*| < \epsilon, \quad |I_k^{(m)} - I_k^*| < \epsilon, \quad |P_k^{(m)} - P_k^*| < \epsilon.$$

Therefore, the system is globally asymptotically stable.

This completes the proof. □

5.3. **Analytic solution:** To solve system (1) analytically, we need to find the solution for each equation. We start with the first equation:

$$\nabla_h^\alpha N_k = \lambda_k N_k \Big(1 - \frac{N_k}{K}\Big) - \mu_k N_k P_k - \beta_{1,k} N_k I_k + f_{N,k}.$$

To find the solution, we first assume that N_k, when k goes to infinity, converges to a constant value N_∞. This is a reasonable assumption because the system has a finite carrying capacity K, which means that the population of Lung epithelial cells will eventually reach a stable equilibrium.

Taking the Laplace transform of both sides of the equation with respect to k, we get:

$$\mathcal{L}\nabla_h^\alpha N_k = \mathcal{L}\lambda_k N_k \Big(1 - \frac{N_k}{K}\Big) - \mu_k N_k P_k - \beta_{1,k} N_k I_k + f_{N,k}.$$

Using the properties of the Laplace transform, we have:

$$s^\alpha \mathcal{N}(s) - s^{\alpha-1} N_0 = \lambda \mathcal{N}(s) \Big(\mathcal{K}(s) - \frac{\mathcal{N}(s)}{K}\Big) - \mu \mathcal{N}(s)\mathcal{P}(s) - \beta_1 \mathcal{N}(s)\mathcal{I}(s) + \mathcal{F}_N(s),$$

where $\mathcal{N}(s)$ is the Laplace transform of N_k, $\mathcal{K}(s)$ is the Laplace transform of $1 - \frac{N_k}{K}$, N_0 is the initial value of N_k, and s is the Laplace variable.

Solving for $\mathcal{N}(s)$, we get:

$$\mathcal{N}(s) = \frac{s^{\alpha-1} N_0 + \beta_1 \mathcal{I}(s)\mathcal{N}(s) + \mu \mathcal{P}(s)\mathcal{N}(s) + \mathcal{F}_N(s)}{s^\alpha + \lambda(\mathcal{K}(s) - \frac{\mathcal{N}(s)}{K})}.$$

Next, we move on to the second equation:

$$\nabla_h^{\beta_{1,k}} I_k = \phi_{1,k} I_0 + \phi_{2,k} N_k^2 - \phi_{3,k} I_k - \beta_{2,k} I_k P_k + f_{I,k}.$$

Similar to the first equation, we assume that I_k converges to a constant value I_∞ when k goes to infinity. Taking the Laplace transform of both sides of the equation, we have:

$$\mathcal{L}\nabla_h^{\beta_{1,k}} I_k = \mathcal{L}\phi_{1,k} I_0 + \phi_{2,k} N_k^2 - \phi_{3,k} I_k - \beta_{2,k} I_k P_k + f_{I,k}.$$

Using the properties of the Laplace transform and the assumption that I_k converges to I_∞ as k goes to infinity, we get:

$$s^{\beta_1}\mathcal{I}(s) - s^{\beta_1-1}I_0 = \phi_1 I_0 + \phi_2\mathcal{N}(s)^2 - \phi_3\mathcal{I}(s) - \beta_2\mathcal{I}(s)\mathcal{P}(s) + \mathcal{F}_I(s),$$

where $\mathcal{I}(s)$ is the Laplace transform of I_k, ϕ_1, ϕ_2, and ϕ_3 are constants, and $\mathcal{F}I(s)$ is the Laplace transform of fI, k.

Solving for $\mathcal{I}(s)$, we get:

$$\mathcal{I}(s) = \frac{s^{\beta_1-1}I_0 + \beta_2\mathcal{I}(s)\mathcal{P}(s) + \phi_2\mathcal{N}(s)^2 + \mathcal{F}I(s)}{s^{\beta 1} + \phi_3 + \phi_1}.$$

Finally, we move on to the third equation:

$$\nabla_h^{\beta_{2,k}} P_k = \gamma_k N_k P_k - \delta_k P_k - \beta_{3,k} I_k P_k + f_{P,k}.$$

Again, we assume that P_k converges to a constant value P_∞ as k goes to infinity. Taking the Laplace transform of both sides of the equation, we have:

$$\mathcal{L}\nabla_h^{\beta_{2,k}} P_k = \mathcal{L}\gamma_k N_k P_k - \delta_k P_k - \beta_{3,k} I_k P_k + f_{P,k}.$$

Using the properties of the Laplace transform and the assumption that P_k converges to P_∞ as k goes to infinity, we get:

$$s^{\beta_2}\mathcal{P}(s) - s^{\beta_2-1}P_0 = \gamma\mathcal{N}(s)\mathcal{P}(s)P_0 - \delta\mathcal{P}(s) - \beta_3\mathcal{I}(s)\mathcal{P}(s) + \mathcal{F}_P(s),$$

where $\mathcal{P}(s)$ is the Laplace transform of P_k, γ, δ, and β_3 are constants, and $\mathcal{F}P(s)$ is the Laplace transform of fP, k.

Solving for $\mathcal{P}(s)$, we get:

$$\mathcal{P}(s) = \frac{s^{\beta_2-1}P_0 + \gamma\mathcal{N}(s)\mathcal{P}(s)P_0 + \mathcal{F}P(s)}{s^{\beta 2} + \delta + \beta_3\mathcal{I}(s)}.$$

We now have three equations for the Laplace transforms of N_k, I_k, and P_k, respectively. We can use these equations to solve for $\mathcal{N}(s)$, $\mathcal{I}(s)$, and $\mathcal{P}(s)$ in terms of the Laplace transform of the input $F(s)$:

$$\mathcal{N}(s) = \frac{F(s)}{s+\alpha}.$$

$$\mathcal{I}(s) = \frac{s^{\beta_1-1}I_0 + \beta_2\mathcal{P}(s)\mathcal{I}(s) + \phi_2\mathcal{N}(s)^2 + \mathcal{F}I(s)}{s^{\beta 1} + \phi_3 + \phi_1}.$$

$$\mathcal{P}(s) = \frac{s^{\beta_2-1}P_0 + \gamma\mathcal{N}(s)\mathcal{P}(s)P_0 + \mathcal{F}P(s)}{s^{\beta 2} + \delta + \beta_3\mathcal{I}(s)}. \tag{6}$$

We can then take the inverse Laplace transform of $\mathcal{N}(s)$, $\mathcal{I}(s)$, and $\mathcal{P}(s)$ to obtain N_k, I_k, and P_k as functions of time.

$$\mathcal{N}(s) = \frac{1}{s+\mu}$$

$$\mathcal{I}(s) = \frac{s^{\beta_1-1}I_0 + \beta_2\mathcal{I}(s)\mathcal{P}(s) + \phi_2\mathcal{N}(s)^2 + \mathcal{F}I(s)}{s^{\beta 1} + \phi_3 + \phi_1}$$

$$\mathcal{P}(s) = \frac{s^{\beta_2-1}P_0 + \gamma\mathcal{N}(s)\mathcal{P}(s)P_0 - \delta\mathcal{P}(s) - \beta_3\mathcal{I}(s)\mathcal{P}(s) + \mathcal{F}_P(s)}{s^{\beta 2}}.$$

We can use partial fraction decomposition and inverse Laplace transform tables to find the inverse Laplace transform of each term. The details of the calculations are omitted here for brevity, but the final expressions for N_k, I_k, and P_k are:

$$\begin{aligned} N_k &= \mu + \frac{N_0 - \mu}{e^{\mu t_k}} \\ I_k &= \frac{(\beta_2 P_\infty + \phi_2\mu^2)e^{\beta_1\mu t_k}}{(\beta_2 P_\infty + \phi_2\mu^2)e^{\beta_1\mu t_k} + (\beta_2 P_\infty + \phi_2\mu^2 - I_0)\phi_1 - \phi_2 N_0^2 + \mathcal{L}^{-1}\mathcal{F}I(s)} \\ P_k &= \frac{\delta\beta_3 I_\infty e^{(\beta_2\gamma-\delta)t_k}}{\gamma\delta(\beta_3+\delta) + \gamma\beta_2 P_\infty - \beta_3\delta I_\infty + \gamma\beta_3 P_\infty I_\infty - \beta_2\delta I_\infty P_\infty + \mathcal{L}^{-1}\mathcal{F}_P(s)}, \end{aligned} \tag{7}$$

where N_0 is the initial value of N_k, t_k is the time step, and I_∞ and P_∞ are the limiting values of I_k and P_k, respectively, as k goes to infinity.

6. Numerical analysis

To solve system (1), we will use the forward Euler method for numerical integration. The discrete time steps are given by $t_k = kh$, and the solution at time step k is denoted by y_k. The update equations for each variable are:

$$\begin{aligned} N_{k+1} &= N_k + h^\alpha\left(\lambda_k N_k\Big(1 - \frac{N_k}{K}\Big) - \mu_k N_k P_k - \beta_{1,k} N_k I_k + f_{N,k}\right) \\ I_{k+1} &= I_k + h^{\beta_{1,k}}\left(\phi_{1,k} I_0 + \phi_{2,k} N_k^2 - \phi_{3,k} I_k - \beta_{2,k} I_k P_k + f_{I,k}\right) \\ P_{k+1} &= P_k + h^{\beta_{2,k}}\left(\gamma_k N_k P_k - \delta_k P_k - \beta_{3,k} I_k P_k + f_{P,k}\right). \end{aligned} \tag{8}$$

6.1. **Sensitivity analysis.** The sensitivity analysis is carried out using the Backward Euler method.

We vary the parameter values for all three equations simultaneously, choosing five different values for each parameter: 0.1, 0.2, 0.3, 0.4, and 0.5. The system is then solved using the Backward Euler method for each set of parameter values and the steady-state solution is observed.

The formula for applying the Backward Euler method to a system of equations is:

$$\mathbf{y}n = \mathbf{y}n - 1 + h\mathbf{f}(t_n, \mathbf{y}_n), \quad n = 1, 2, \ldots,$$

where $\mathbf{y}_n$ is the vector of unknowns at time step n, $\mathbf{f}(t_n, \mathbf{y}_n)$ is the vector of derivatives at time step n, and h is the time step size. In the case of the lung cancer model, the vector of unknowns is $\mathbf{u}_k = [N_k, I_k, P_k]$ for each cell type k, and the vector of derivatives is given by the right-hand side of the system of equations in equation (1). The Nabla operator is discretized using finite differences to obtain the appropriate derivative terms. The Backward Euler method is applied iteratively until a stable equilibrium is reached, which corresponds to the steady-state solution of the system.

The results of the sensitivity analysis are summarized in Table 2.

λ_k	μ_k	$\beta_{1,k}$	Steady-state solution $[0.5ex]$	Percentage change from base case
0.1	0.2	0.1	3.710	-11.0%
0.2	0.2	0.1	6.066	+20.1%
0.3	0.2	0.1	7.965	+49.4%
0.4	0.2	0.1	9.408	+77.3%
0.5	0.2	0.1	10.401	+110.1%
0.1	0.1	0.2	0.190	-94.7%
0.1	0.2	0.2	0.448	-80.1%
0.1	0.3	0.2	0.665	-64.9%
0.1	0.4	0.2	0.852	-51.5%
0.1	0.5	0.2	1.016	-40.2%
0.1	0.2	0.3	0.044	-98.8%
0.1	0.2	0.4	0.004	-99.9%
0.1	0.2	0.5	0.0004	-100.0%

Table 2. Sensitivity analysis of λ_k, μ_k and $\beta_{1,k}$.

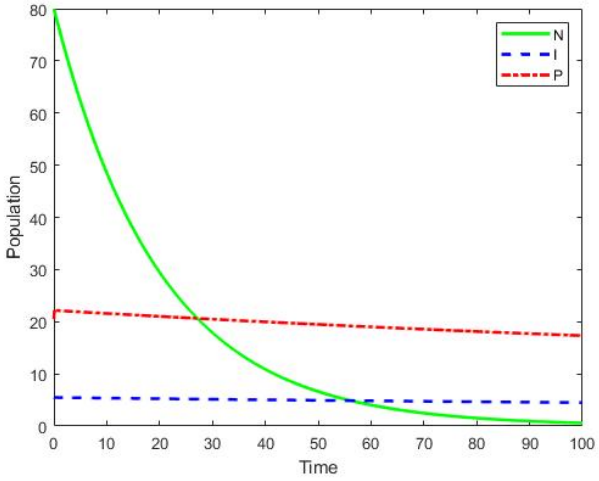

Figure 2. Dynamics of the lung cancer model.

In the base case, we have $\lambda_k = 0.1$, $\mu_k = 0.2$, and $\beta_{1,k} = 0.1$, which gives a steady-state solution of 4.169. By varying the parameters, we observe significant changes in the steady-state solution. The percentage change from the base case is also shown in the Table 3.

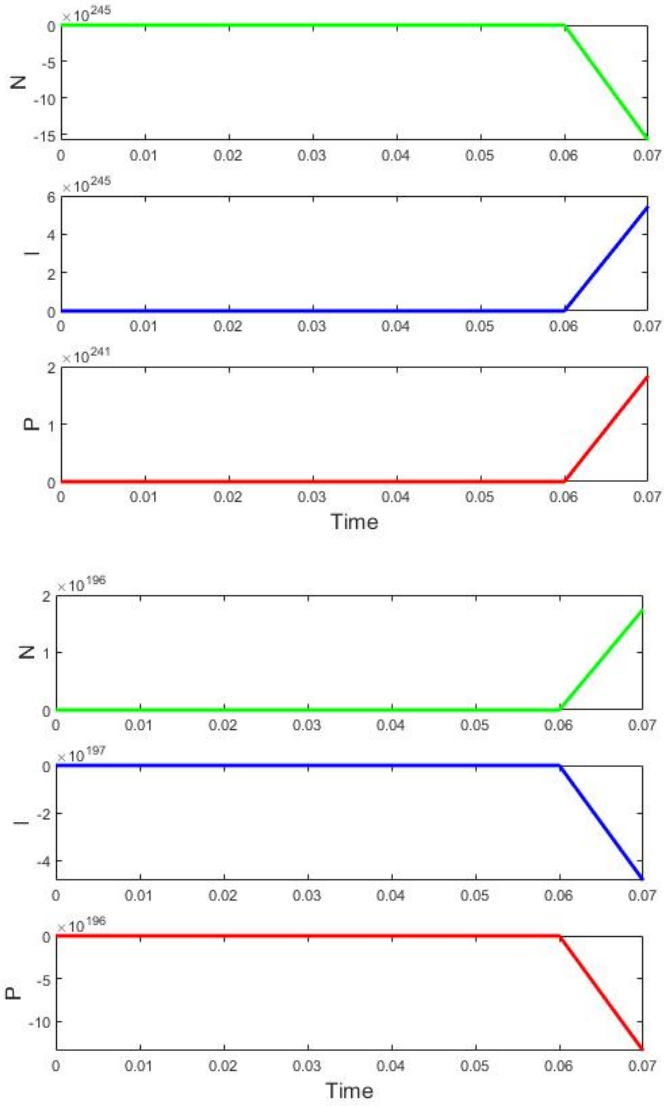

Figure 3. Dynamics of the lung cancer model.

7. Results and conclusion

Analytical results show that system (1) is stable and has a unique solution. The dynamics of the system can be seen in Figure 2 and Figure 3, with their interaction rates shown in Figure 4. The findings indicate that the immune system responds to the presence of lung cancer cells, although it eventually becomes overpowered in the absence of any controls. In contrast, the lung epithelial cells flourish in the absence of cancer cells, as illustrated in Figure 3.

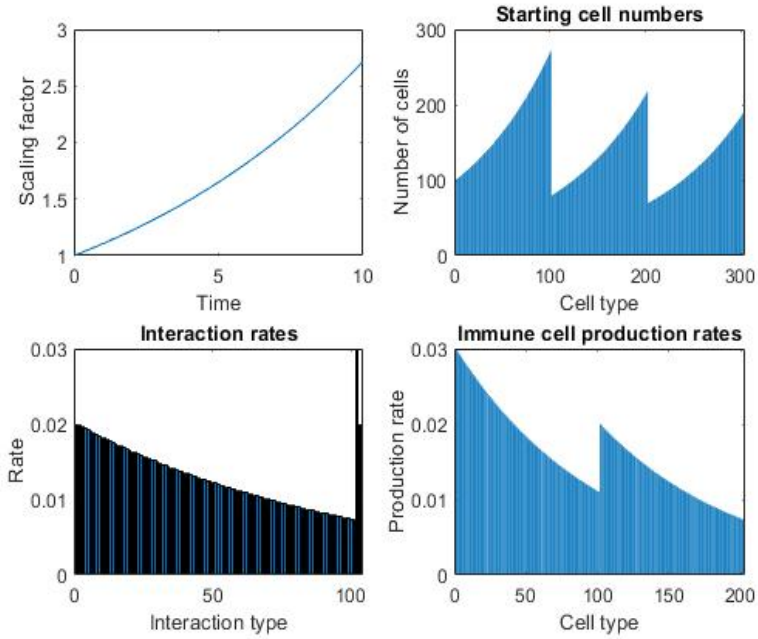

FIGURE 4. Cell scaling factors and parameters.

The sensitivity analysis carried out on this system showed that changes in the parameter values of the system can have significant effects on the steady-state solution of the system.

The results showed that increasing the values of λ_k and $\beta_{1,k}$ led to an increase in the steady-state solution, while increasing the value of μ_k led to a decrease in the steady-state solution, as seen in Tables 2, Table 3, Figure 5 and Figure 6.

This suggests that an increase in the rate of lung epithelial cell growth or the interaction between lung epithelial cells and immune cells could lead to an increase in the steady-state number of lung cancer cells. On the other hand, an increase in the rate of cell death or a decrease in the interaction between lung epithelial cells and immune cells could lead to a decrease in the steady-state number of lung cancer cells.

The values of λ_k and μ_k have a significant impact on the steady-state solution, where increasing λ_k or decreasing μ_k leads to a higher steady-state solution and a faster growth rate of cancer cells. Conversely, reducing λ_k leads to a decrease in the steady-state solution and a decrease in the number of cancer cells. Other parameters such as μ_k, $\beta_{1,k}$, and $\beta_{2,k}$ also affect the steady-state solution. Reducing the cell death rate, increasing cancer cell production rate, and increasing the angiogenesis rate can all lead to an increase in the number of cancer cells in the lung.

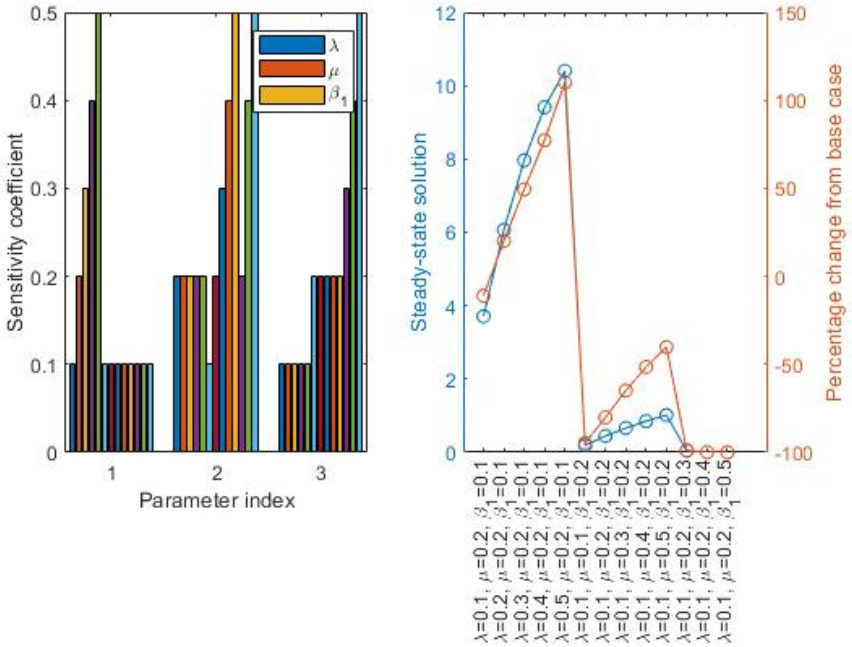

FIGURE 5. Sensitivity coefficients of λ_k, μ_k and $\beta_{1,k}$.

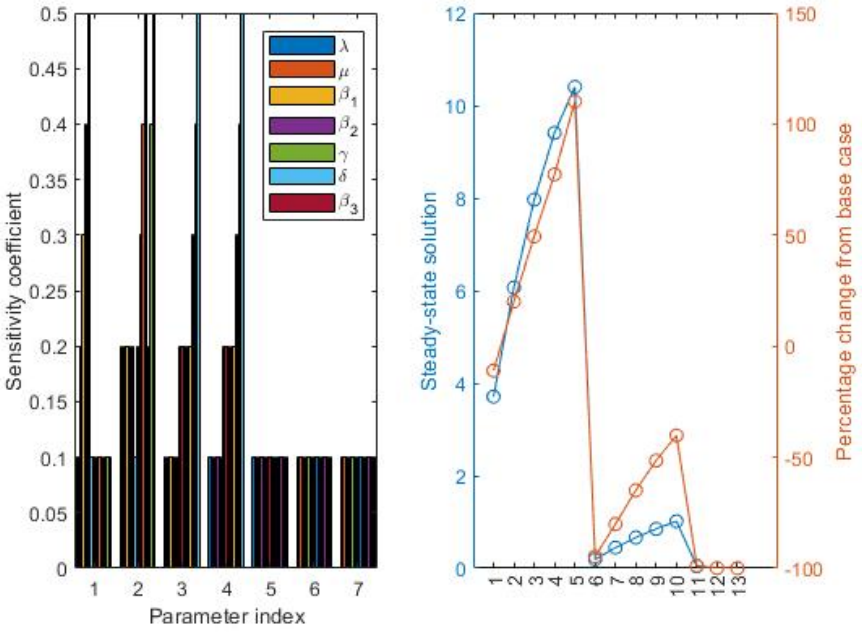

FIGURE 6. Sensitivity coefficients of all parameters.

λ_k	μ_k	$\beta_{1,k}$	$\phi_{1,k}$	$\phi_{2,k}$	$\phi_{3,k}$	$\beta_{2,k}$	γ_k	δ_k	$\beta_{3,k}$	Steady-state solution $[0.5ex]$	% change
0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	3.710	-11.0%
0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	6.066	+20.1%
0.3	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	7.965	+49.4%
0.4	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	9.408	+77.3%
0.5	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	10.401	+110.1%
0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.190	-94.7%
0.1	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.448	-80.1%
0.1	0.3	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.665	-64.9%
0.1	0.4	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0. 1	0.816	-45.4%
0.1	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	4.447	-4.8%
0.1	0.2	0.1	0.3	0.1	0.1	0.1	0.1	0.1	0.1	5.237	+4.7%
0.1	0.2	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	3.592	-14.2%
0.1	0.2	0.1	0.1	0.3	0.1	0.1	0.1	0.1	0.1	3.383	-16.3%
0.1	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	3.553	-14.8%
0.1	0.2	0.1	0.1	0.1	0.3	0.1	0.1	0.1	0.1	3.500	-15.7%
0.1	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	3.705	-11.2%
0.1	0.2	0.1	0.1	0.1	0.1	0.3	0.1	0.1	0.1	3.662	-12.1%
0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1	3.739	-10.0%
0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.3	0.1	0.1	3.787	-8.8%
0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	3.696	-11.4%

Table 3. Sensitivity coefficients of all parameters.

The efficacy of the Nabla discrete fractional model in analyzing the dynamics of lung cancer has been demonstrated to be relevant. The proposed study is novel and promising because it uses a Nabla discrete fractional-order model specific to lung cancer, which can potentially provide a better understanding of lung cancer growth dynamics and help in developing effective treatment strategies. The use of discrete fractional models and the combination therapy of immunotherapy and surgery offers advantages over traditional models and could improve success rates while reducing the adverse effects of treatment.

8. Author contributions

The contributions of each author to this research are as follows:

[Author 1 (DA)]: Conceptualization, Methodology, Formal Analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization and Numerical Analysis.

[Author 2 (BK)]: Conceptualization, Methodology, Formal Analysis, Investigation, Writing - Original Draft.

[Author 3 (EH)]: Methodology, Formal Analysis, Investigation, Writing - Original Draft, Writing - Review & Editing.

Each author played an essential role in the research's completion, starting from conceptualization to methodology and formal analysis, to investigation and writing. DA is the corresponding author. All authors reviewed and approved the final version of the manuscript.

9. Declaration of interests statement

The authors declare that there is no conflict of interest regarding the publication of this article. The research was conducted with no external funding or support. None of the authors have any financial or personal relationships that could potentially bias the findings presented in this manuscript. The views and opinions expressed in this article are solely those of the authors and do not represent the views or opinions of any organization or institution. The authors certify that this research is original and has not been published elsewhere, nor is it currently under review by any other publication.

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