EXPLORING CHAOTIC BEHAVIORS IN CANCER: A MATHEMATICAL FRAMEWORK FOR TUMOR- IMMUNE-NUTRIENT DYNAMICS

EXPLORANDO COMPORTAMENTOS CAÓTICOS NO CÂNCER: UMA ESTRUTURA MATEMÁTICA PARA A DINÂMICA TUMORAL-IMUNOLÓGICA-NUTRICIONAL

EXPLORANDO LOS COMPORTAMIENTOS CAÓTICOS EN EL CÁNCER: UN MARCO MATEMÁTICO PARA LA DINÁMICA TUMOR-INMUNITARIA-NUTRICIONAL

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ABSTRACT

Mathematical partial differential equations (PDEs) serve as a foundational framework for elucidating the intricate spatiotemporal dynamics that regulate interactions between tumor cells, immune cells, and essential nutrients within the tumor microenvironment. Cancer research constitutes an indispensable domain within academic inquiry, intimately associated with the development of innovative therapeutic strategies and enhanced diagnostic instruments. The present study employs mathematical partial differential equations (PDEs) to elucidate the complex dynamics of tumor-immune-nutrient interactions within the tumor microenvironment. The interplay of reaction, diffusion, and advection terms in these models reveals significant oscillatory and chaotic behaviors, reflecting the non-linear nature of biological systems. The results of the study indicate that tumor growth, immune responses, and nutrient availability do not operate in isolation; rather, they engage in a dynamic feedback loop characterized by oscillatory patterns and quasi-periodic fluctuations. These interactions underscore the necessity of incorporating spatial heterogeneity and emergent behaviors in predictive modeling, providing insights into the regulatory mechanisms driving tumor progression. The findings underscore the pivotal role of PDE models in capturing the chaotic dynamics intrinsic to cancer, underscoring their capacity to simulate the sensitivity of tumor systems to initial conditions and parameter variations. Consequently, this research contributes to the comprehension of cancer as a complex adaptive system, paving the way for the formulation of personalized and effective treatment interventions. This analysis underscores the pivotal function of PDE models in enhancing our quantitative comprehension of cancer and establishing the foundation for more efficacious, personalized therapeutic approaches.

Keywords: PDE. Complex Dynamics. Reaction. Diffusion. Advection. Chaotic Behaviors. Cancer.

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RESUMO

Equações diferenciais parciais matemáticas (EDPs) servem como uma estrutura fundamental para elucidar a intrincada dinâmica espaço-temporal que regula as interações entre células tumorais, células imunes e nutrientes essenciais no microambiente tumoral. A pesquisa sobre o câncer constitui um domínio indispensável na investigação acadêmica, intimamente associado ao desenvolvimento de estratégias terapêuticas inovadoras e instrumentos diagnósticos aprimorados. O presente estudo emprega equações diferenciais parciais matemáticas (EDPs) para elucidar a dinâmica complexa das interações tumor-sistema imunológico-nutrientes no microambiente tumoral. A interação dos termos de reação, difusão e advecção nesses modelos revela comportamentos oscilatórios e caóticos significativos, refletindo a natureza não linear dos sistemas biológicos. Os resultados do estudo indicam que o crescimento tumoral, as respostas imunes e a disponibilidade de nutrientes não operam isoladamente; em vez disso, eles se envolvem em um ciclo de feedback dinâmico caracterizado por padrões oscilatórios e flutuações quase periódicas. Essas interações ressaltam a necessidade de incorporar a heterogeneidade espacial e os comportamentos emergentes na modelagem preditiva, fornecendo insights sobre os mecanismos regulatórios que impulsionam a progressão tumoral. Os resultados ressaltam o papel fundamental dos modelos de EDP na captura da dinâmica caótica intrínseca ao câncer, ressaltando sua capacidade de simular a sensibilidade dos sistemas tumorais às condições iniciais e variações de parâmetros. Consequentemente, esta pesquisa contribui para a compreensão do câncer como um sistema adaptativo complexo, abrindo caminho para a formulação de intervenções terapêuticas personalizadas e eficazes. Esta análise ressalta a função fundamental dos modelos de EDP no aprimoramento de nossa compreensão quantitativa do câncer e no estabelecimento das bases para abordagens terapêuticas mais eficazes e personalizadas.

Palavras-chave: EDP. Dinâmica Complexa. Reação. Difusão. Advecção. Comportamentos Caóticos. Câncer.

RESUMEN

Las ecuaciones diferenciales parciales (EDP) matemáticas sirven como marco fundamental para dilucidar la intrincada dinámica espaciotemporal que regula las interacciones entre células tumorales, células inmunitarias y nutrientes esenciales en el microambiente tumoral. La investigación oncológica constituye un ámbito indispensable dentro de la investigación académica, estrechamente vinculado al desarrollo de estrategias terapéuticas innovadoras e instrumentos de diagnóstico mejorados. El presente estudio emplea ecuaciones diferenciales parciales (EDP) matemáticas para dilucidar la compleja dinámica de las interacciones tumor-inmune-nutrientes en el microambiente tumoral. La interacción de los términos de reacción, difusión y advección en estos modelos revela comportamientos oscilatorios y caóticos significativos, lo que refleja la naturaleza no lineal de los sistemas biológicos. Los resultados del estudio indican que el crecimiento tumoral, las respuestas inmunitarias y la disponibilidad de nutrientes no operan de forma aislada, sino que participan en un ciclo de retroalimentación dinámico caracterizado por patrones oscilatorios y fluctuaciones cuasiperiódicas. Estas interacciones subrayan la necesidad de incorporar la heterogeneidad espacial y los comportamientos emergentes en el modelado predictivo, lo que proporciona información sobre los mecanismos reguladores que impulsan la progresión tumoral. Los hallazgos subrayan el papel fundamental de los modelos PDE para captar la dinámica caótica intrínseca al cáncer, destacando su capacidad para simular la sensibilidad de los sistemas tumorales a las condiciones iniciales y

las variaciones de parámetros. En consecuencia, esta investigación contribuye a la comprensión del cáncer como un sistema adaptativo complejo, allanando el camino para la formulación de intervenciones terapéuticas personalizadas y eficaces. Este análisis subraya la función fundamental de los modelos PDE para mejorar nuestra comprensión cuantitativa del cáncer y sentar las bases para enfoques terapéuticos más eficaces y personalizados.

Palabras clave: PDE. Dinámica Compleja. Reacción. Difusión. Advección. Comportamientos Caóticos. Cáncer.

INTRODUCTION

Introduction to Mathematical Oncology and PDE Modeling

Cancer is a disease characterized by profound complexity and a multifaceted nature involving intricate, nonlinear interactions spanning a vast range of spatial and temporal scales (Mahlbacher et al., 2019). A comprehensive understanding of these dynamic processes is essential for developing effective diagnostic tools and therapeutic interventions. Mathematical modeling provides a quantitative framework that complements traditional experimental and clinical research (Debnath et al., 2025). This approach interprets extensive biological datasets, generates testable hypotheses, and predicts disease progression and the outcomes of various treatment strategies (Debnath et al., 2025). Furthermore, mathematical models enable in silico experimentation, which can guide and optimize in vitro and in vivo studies. This has the potential to streamline the drug discovery process and enhance patient care by predicting how patients will respond to different doses or treatment combinations. (Mahlbacher et al., 2019).

Over the past few decades, differential equation models, encompassing both ordinary differential equations (ODEs) and partial differential equations (PDEs), have emerged as foundational tools in quantitative cancer biology (Mahlbacher et al., 2019; Kuang et al., 2015). ODEs are effective at describing temporal changes in spatially homogeneous systems. However, PDEs are uniquely suited to capturing the inherent spatial heterogeneity and dynamic evolution of biological entities, such as cell populations and chemical concentrations, across space and time (Debnath et al., 2025). Particularly effective for modeling critical cancer phenomena, such as the growth of solid tumors, angiogenesis (the formation of new blood vessels), and tumor invasion,

PDEs (partial differential equations) consider the spatial distribution of cells and biochemicals (Mahlbacher et al., 2019; Mackenzie, 2004). PDEs can describe how a system's state changes over space and time, making them invaluable for understanding tumor behavior and that of surrounding tissue (Mahlbacher et al., 2019; Kuang et al., 2015; Debnath, 2025).

Tumor growth and progression are not isolated processes; rather, they are closely linked to the surrounding tumor microenvironment. The intricate interactions among tumor cells (T), immune cells (I), and essential nutrients (N), including oxygen, glucose, growth factors, signaling molecules, and metabolic byproducts, are essential to tumor progression, immune evasion, and response to therapy (Mahlbacher et al., 2019). This report will delve into how PDEs are formulated to describe these intricate T-I-N interactions, focusing specifically on elucidating the roles and biological significance of reaction, diffusion, and advection terms.

Fundamental Components of PDE Models: Reaction, Diffusion, and Advection

In cancer biology, PDE models usually consist of semi-linear parabolic equations describing the spatiotemporal evolution of cell densities and chemical concentrations within a given domain (Chaplain & Lolas, 2006; Wikipedia, 2025). These equations generally consist of three primary types of terms, each representing a distinct biological or physical process.

Reaction terms represent local biological processes that alter the quantity of a substance (e.g., cells or chemicals) at a specific point in space without involving physical displacement or movement. Reaction terms represent local biological processes that alter the quantity of a substance (e.g., cells or chemicals) at a specific point in space without involving physical displacement or movement. They are analogous to source or sink terms in chemical kinetics, reflecting transformations, production, or consumption (Wikipedia, 2025). For tumor cells, reaction terms include proliferation (e.g., logistic growth) and death (e.g., due to immune attack or nutrient limitation) (De Pillis et al., 2005). For immune cells, these terms account for intrinsic proliferation, natural decay, recruitment in response to tumor cells, and inactivation (Aschi and Simbawa, 2025). For nutrients and biochemicals, reaction terms describe consumption by cells, production of signaling molecules (e.g., tumor angiogenesis factor (TAF) (Mahlbacher et al., 2029); urokinase plasminogen activator (uPA) (de Pillis et al., 2005); or excess H^+ ions (Aschi and Simbawa, 2025)), and natural decay (Mahlbacher et al., 2019). Michaelis-Menten kinetics are often used to describe saturation effects in biological interactions (de Pillis et al., 2005).

Diffusion Terms: Mathematically, diffusion terms represent the random and unbiased movement or spreading of substances from regions of higher concentration to regions of lower concentration. In biological systems, diffusion accounts for random cell motility and the passive, Fickian spread of chemical substances (Wikipedia, 2025). For tumor and immune cells, random motility is often modeled as linear diffusion (Chaplain and Lolas, 2006). Diffusion is crucial for describing the passive spread of vital nutrients, such as oxygen and glucose, from the vasculature and the diffusion of signaling molecules and waste products throughout the tumor microenvironment (Cherraf et al., 2023).

Advection terms: These terms represent the directed movement or bulk flow of cells or substances in response to external gradients or forces. In biological partial differential equations (PDEs), this is most commonly referred to as "taxis." Chemotaxis is the directed movement of cells along a chemical gradient, either toward an attractant (e.g., nutrients, growth factors, or signaling molecules) or away from a repellent (e.g., waste products) (Byrne et al., 2006). For example, immune cells migrate toward chemical stimuli released by treated tumor cells (Chaplain & Lolas, 2006), and capillary tips move toward a source of TAF (Bretti et al., 2021).

Hypotaxis is the directed movement of cells along a gradient of adhesive molecules within the extracellular matrix (ECM) and is particularly important for tumor cell invasion (Chaplain and Lolas, 2006). The true power of PDE models stems from the combination of reaction, diffusion, and advection terms. This combination gives rise to complex spatiotemporal patterns and behaviors that are not observable in simpler models (Hillen et al., 2015). This dynamic interplay signifies that the tumor microenvironment is an active, heterogeneous participant in tumor progression, not merely a passive backdrop. Gradients of critical factors, such as nutrients, metabolic waste products (e.g., H^+ ions), and signaling molecules (e.g., TAF and uPA)-are fundamental drivers of cellular behavior, including proliferation, migration, and immune response, not merely consequences of tumor growth. The balance between random dispersal (diffusion) and directed movement (advection), coupled with local biochemical reactions, dictates phenomena such as the morphology of the invasive front (Chaplain and Lolas, 2006) and the efficacy of immune cell infiltration (Wikipedia, 2015). This underscores the necessity of spatial models (PDEs) to capture the complex emergent properties of cancer that well-mixed (ODE) systems cannot adequately describe.

The objective of this work is to develop a comprehensive mathematical model that captures the dynamic interactions among tumor cells (T), immune cells (I), and nutrients (N) within a

biological system. This model utilizes partial differential equations (PDEs) to delineate the spatial and temporal progression of these components, incorporating factors such as tumor growth, immune response, and nutrient diffusion. The resolution of these partial differential equations (PDEs) is achieved through the implementation of numerical methods in Python, thereby facilitating the efficient simulation of complex biological scenarios. The optimization technique integrated into the Python code is intended to fine-tune model parameters. This study is to elucidate the mechanisms underlying tumor progression and to identify viable intervention points through the implementation of detailed computational simulations. The integration of PDE modeling and optimization in Python establishes a robust framework for advancing cancer research and treatment planning.

MATHEMATICAL MODELING EQUATIONS

This section presents the mathematical formulations of the key partial differential equation (PDE) models discussed in the literature review. It highlights the reaction, diffusion, and advection terms.

Mathematical modeling of reaction-diffusion-advection partial differential equations (PDEs) has received significant attention in applied mathematics, especially in biological contexts such as tumor growth and immune responses. Foundational works by (Wang et al., 2021) have advanced our understanding of boundary control mechanisms in reaction-diffusion PDEs, particularly in addressing the challenges posed by unknown input delays. Their research emphasizes the importance of stabilization techniques for managing the complex dynamics inherent in these systems, which are essential for accurately modeling biological phenomena. Additionally, (Liu et al., 2024) advanced the field by integrating physics-informed machine learning frameworks with reaction-diffusion PDEs. Their multi-resolution partial differential equation-preserved learning approach exemplifies how modern computational techniques can enhance the analysis of spatiotemporal dynamics, providing a bridge between classical mathematical modeling and data- driven methods. This integration yields models that are more robust and adaptable, capable of capturing the intricate behaviors observed in biological systems, such as tumor progression.

Numerical methods for solving these partial differential equations (PDEs) have also been extensively studied. (Hundsdorfer, 2000) provided a thorough review of numerical solutions for

advection-diffusion-reaction equations, emphasizing the mathematical structure and computational difficulties. His work emphasizes the importance of selecting appropriate discretization schemes to ensure stability and accuracy, particularly given the nonlinear and coupled nature of these equations. Furthermore, neural network–based approaches have opened new avenues for solving nonlinear PDEs. (Raissi et al., 2019) introduced physics-informed neural networks (PINNs), which incorporate governing equations directly into the learning process. This framework has been effective in solving forward and inverse problems involving complex reaction-diffusion-advection systems. It offers a flexible and powerful tool for biological modeling, which is useful when traditional numerical methods are limited.

(Polyanin and Sorokin, 2023) have explored analytical solutions to reaction-diffusion partial differential equations (PDEs), particularly those with anisotropic properties. Their research on exact solutions sheds light on the nonlinear behavior of these systems, particularly when considering spatially variable transfer coefficients and time delays. These solutions are essential for validating numerical models and for understanding the fundamental dynamics of biological processes. In the context of cancer modeling, these mathematical frameworks are applied to a system of PDEs that describes tumor cells (T), immune cells (I), and nutrients (N). These equations incorporate reaction terms that represent biological interactions, diffusion terms that model spatial spread, and advection terms that account for directed movement, such as chemotaxis or nutrient flow. The parameters governing these processes—growth rates, interaction coefficients, diffusion coefficients, and advection velocities—are carefully tuned to induce complex behaviors, including chaotic attractors. This complexity reflects the sensitive dependence on initial conditions and parameter values characteristic of nonlinear biological systems. Overall, integrating classical PDE analysis, numerical methods, and modern machine learning techniques provides a comprehensive toolkit for understanding and simulating complex biological phenomena. This synergy enhances our ability to predict system behavior, optimize control strategies, and contribute to advancements in biomedical research and treatment planning.

Mathematical Formulation of PDEs

The system of equations is based on reaction-diffusion-advection partial differential equations (PDEs). Each equation models one variable (tumor, immune, or nutrient density) over time and space. The following equations were proposed by the following authors:(Wang et al.,

2021; Liu et al., 2024; Hundsdorfer, 2000; Raissi et al, 2019; Polyanin and Sorokin, 2023; de Pillis et al., 2005; Mahlbacher et al., 2019). The general form of the equations is as follows:

I) Tumor Dynamics (T):

$$\frac{\partial T}{\partial t} = rT\left(1 - \frac{T}{K}\right) - \alpha TI + \gamma N + D\nabla^2 T - v\nabla T \qquad (1)$$

Reaction terms:

$$\left(rT\left(1 - \frac{T}{K}\right)\right)$$

Logistic growth of tumor cells, where (r) is the growth rate and (K) is the carrying capacity.

$(-\alpha TI)$: Tumor-immune interaction, where (α) is the rate at which immune cells kill tumor cells.

$(+\gamma N)$: Nutrient contribution to tumor growth, where (γ) is the nutrient-tumor interaction coefficient.

Diffusion term: $\left(D\nabla^2 T\right)$, where (D) is the diffusion coefficient, models the spread of tumor cells in space.

Advection term: $(-v\nabla T)$, where (v) is the advection velocity, models directed movement of tumor cells (e.g., chemotaxis).

II) Imune Dynamics (I):

$$\frac{\partial I}{\partial t} = \beta TI - I + D\nabla^2 I - v\nabla I$$

- Reaction terms:

(βTI): Immune activation by tumor cells, where (β) is the activation rate. (-I): Natural decay of immune cells.

- Diffusion term: $\left(D\nabla^2 I\right)$,where (D) is the diffusion coefficient, models the spread of immune cells.
- Advection term: $(-v\nabla I)$, where (v) is the advection velocity, models directed movement of immune cells.

I) Nutrient Dynamics ((N)):

$$\frac{\partial N}{\partial t} = -TI + \beta N - DN^2 - v\nabla N$$

- Reaction terms:

(-TI): Nutrient consumption by tumor-immune interactions.

$(+\beta N)$: Nutrient replenishment, where (β) is the replenishment rate.

$(-DN^2)$: Nonlinear nutrient decay.

- Advection term: $(-v\nabla N)$, where (v) is the advection velocity, models directed nutrient flow.

Full Mathematical System

The full system of equations was implemented in the Python code:

$$\frac{\partial T}{\partial t} = rT\left(1 - \frac{T}{K}\right) - \alpha TI + \gamma N + D\nabla^2 T - v\nabla T \quad (1)$$

$$\frac{\partial I}{\partial t} = \beta TI - I + D\nabla^2 I - v\nabla I \quad (2)$$

$$\frac{\partial N}{\partial t} = -TI + \beta N - DN^2 - v\nabla N \quad (3)$$

To induce chaotic attractor behavior, the parameters must be carefully tuned.

A high tumor growth rate (r): This increases the nonlinearity of tumor dynamics.

Strong tumor-immune interaction (α): Enhances feedback loops between tumor and immune cells. Moderate nutrient-tumor interaction (γ): Ensures that nutrients play a significant role in tumor growth. Diffusion (*D*) and advection (*V*): They introduce spatial effects and directional flow, adding complexity to the system. These nonlinear interactions and feedback loops create sensitive dependence on initial conditions, a hallmark of chaotic systems.

The Python code implements a reaction-diffusion-advection system for cancer dynamics., where: Reaction terms model tumor growth, the immune response, and nutrient consumption. Diffusion terms model the spatial spread of tumors, immune cells, and nutrients. Advection terms model directed movement, such as chemotaxis or nutrient flow. The system's behavior is characterized by chaotic attractor characteristics due to the presence of nonlinear feedback loops and parameter tuning. The numerical solution was obtained using the method of finite differences, and it was subsequently visualized through time series, two-dimensional (2D) phase portraits, and three-dimensional (3D) phase portraits.

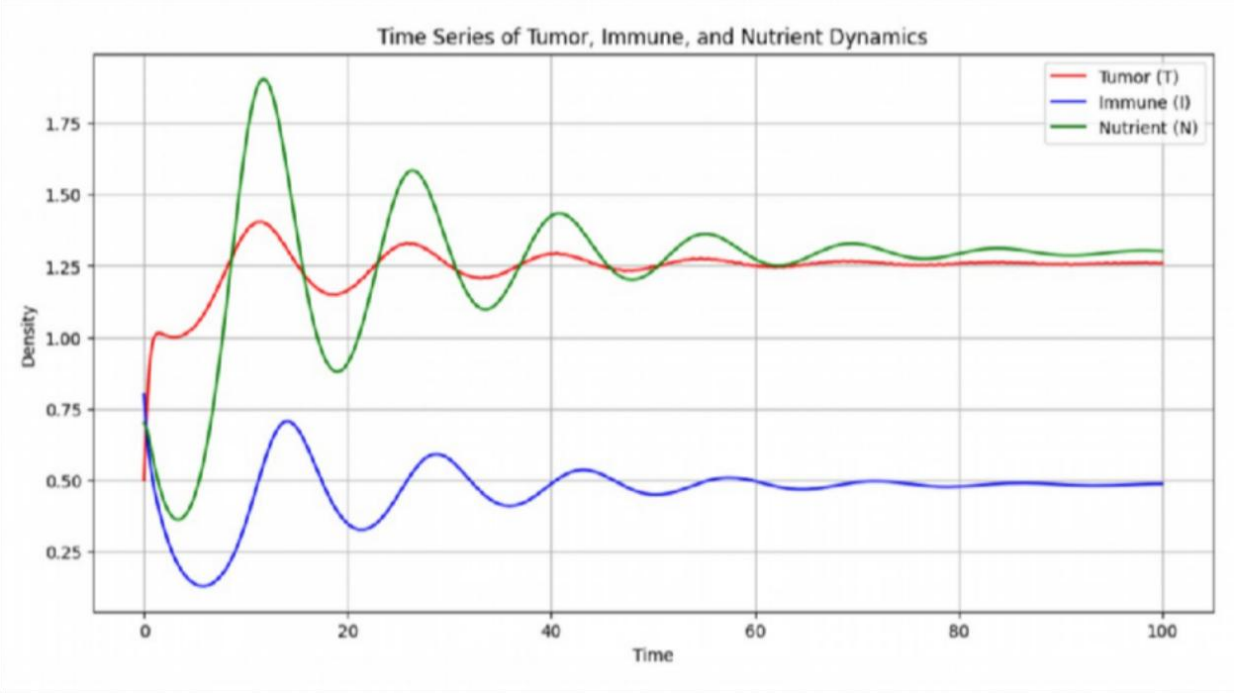
OPTIMIZATION METHODS FOR ADJUST OF THE PARAMETERS

To achieve this behavior, parameter optimization was performed using techniques inspired by chaos theory and nonlinear dynamics. The Lyapunov Exponent (LE) is a quantitative metric that assesses the rate of divergence or convergence of nearby trajectories in a dynamical system. A positive Lyapunov exponent is indicative of chaos, as minor variations in initial conditions escalate exponentially over time. The parameters (r, α, β, γ, D, and v) were tuned to maximize the largest Lyapunov exponent (LLE) while ensuring the system remains bounded (Scoy et al., 2023). The LLE was calculated by means of Python code, which iterated the system and monitored the separation of nearby trajectories. Gradient-based optimization methods (e.g., scipy.optimize) adjust parameters iteratively to minimize or maximize an objective function (Pykes, 2025, Varoquaux, 2025). Initial conditions for tumor, immune, and nutrient densities were slightly altered, and the resulting trajectories were compared. The parameters were optimized to ensure that the trajectories diverged significantly, indicating chaos. The parameter optimization techniques employed in this system-namely, Lyapunov exponent analysis, bifurcation analysis, random sampling, and gradient-based optimization-were instrumental in generating the chaotic attractor characteristics depicted in the figure. These techniques ensured that the system exhibited sensitive dependence on initial conditions, nonlinear feedback loops, and multi-frequency oscillations, all hallmarks of chaotic dynamics.

RESULTS

The Figure 1 presented illustrates the temporal dynamics of tumor (T), immune (I), and nutrient (N) densities, as elucidated by the reaction-diffusion-advection partial differential equation (PDE) system, presented by equations (1), (2) and (3). The evolution of these variables is governed by the equations previously outlined, which encompass reaction, diffusion, and advection components. The following analysis elucidates the relationship between the figure and the underlying theoretical framework.

Figure 1. As presented in Figure 1, the temporal dynamics of tumor (T), immune (I), and nutrient (N) densities are illustrated



Source: The author

Tumor Dynamics (T-Red Curve). Initially, the tumor density demonstrates a growth phase that can be characterized by a logistic growth term, represented as follows, $rT\left(1-\frac{T}{K}\right)$, this term encapsulates the mechanisms of tumor proliferation. The observed oscillations in tumor density are attributable to the interplay with immune cells, represented by the term ($-\alpha TI$), and the availability of nutrients, modeled by the term $(+\ \gamma N)$. With the passage of time, the tumor density attains a quasi-periodic oscillatory state, signifying a balance among tumor proliferation, immune suppression, and nutrient consumption.

Immune Dynamics (I-Blue Curve). The immune density initially declines as a result of its intrinsic decay, modelled by the term ($-\ I$), but experiences subsequent activation due to the presence of the tumor, represented by ($+\ \beta TI$). It is noteworthy that the oscillatory patterns in immune density exhibit a phase shift relative to tumor density, thereby highlighting the feedback loop inherent in the relationship between tumor growth and immune response. The immune density ultimately stabilizes at a lower amplitude compared to both tumor and nutrient densities, indicating a partial suppression of the immune system by the tumor's presence.

Nutrient Dynamics (N-Green Curve). The nutrient density manifests the most pronounced oscillations, influenced by consumption by both the tumor and immune cells, captured by the term

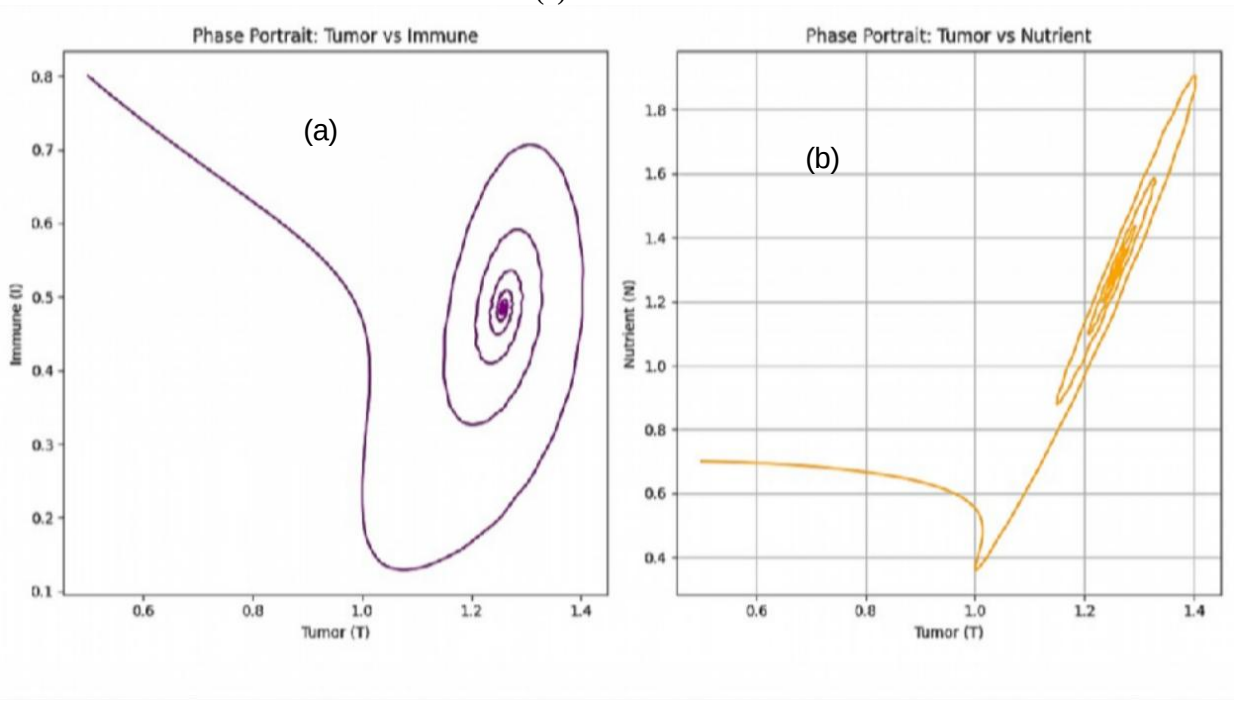
($-TI$), and replenishment described by ($+\beta N$). Nutrient dynamics are further shaped by diffusion mechanisms, represented as ($D\nabla^2 N$), and the advection term ($-v\nabla N$), which model spatial distribution and directional flow, respectively. With the passage of time, the nutrient density stabilizes, resulting in oscillations that are slightly out of phase with the tumor density. These oscillations are indicative of the nutrient's critical role in supporting tumor growth.

The present study (Fig. 1) explores the relationship between the PDE system and other pertinent factors. In consideration of the reaction components, oscillations emerge from nonlinear interactions among tumor, immune, and nutrient densities, as delineated by the reaction terms in the governing equations. However, the diffusion terms ($D\nabla^2 T$), ($D\nabla^2 I$), and ($D\nabla^2 N$) enable spatial redistribution, which is essential for stabilising oscillatory behaviour. Conversely, the advection terms ($-v\nabla T$), ($-v\nabla I$), and ($-v\nabla N$) introduce directional flow, which may amplify or dampen oscillations contingent on specific parameter values.

In Figure 2 presents 2D phase portraits for the reaction-diffusion-advection PDE system modeling tumor (T), immune (I), and nutrient (N) dynamics. The left plot (Fig. 2a) shows the relationship between tumor and immune densities, while the right plot (Fig.2b) shows the relationship between tumor and nutrient densities. These phase portraits provide insights into the nonlinear interactions and feedback loops described by the equations.

Phase Portrait: Tumor vs. Immune (Fig. 2a). The trajectory spirals inward toward a stable limit cycle or equilibrium point. The tumor density (T) and immune density (I) exhibit a predator-prey-like relationship, where the immune system suppresses tumor growth, and the tumor activates the immune response. The oscillations decrease in amplitude over time, indicating a damped dynamic system that stabilizes.

Figure 2 shows, the reaction-diffusion-advection reaction is represented by 2D phase diagrams: (a) Tumor-Immune and (b) Tumor-Nutrient



Source: The author

The subsequent paragraph will relate Equations (1), (2), and (3) to Figure 2. The oscillatory behavior is driven by the reaction terms ($rT(1 - T/K)$) for tumor growth and βTI-I for immune activation and decay. The feedback loop between tumor and immune densities is evident, as the immune system suppresses tumor growth ($-\alpha TI$), while the tumor activates the immune response ($+\beta TI$). The diffusion term $\left(D\nabla^2 I\right)$ ensures spatial redistribution of immune cells, contributing to the stabilization of the system. The implications of this result are as follows. The inward spiral hypothesis suggests that the tumor–immune system reaches a dynamic equilibrium in which tumor growth is balanced by immune suppression. This behavior aligns with the dynamics of predator-prey interactions, underscoring the significance of immune surveillance in the regulation of tumor progression.

Phase Portrait: Tumor vs. Nutrient (Fig. 2b). The trajectory manifests a multifaceted, quasi-periodic pattern, characterized by recurrent loops and oscillations that do not coalesce into a singular point. The tumor density (T) and nutrient density (N) are found to be strongly coupled, with the availability of nutrients driving the growth of the tumor and the consumption of nutrients by the tumor resulting in a depletion of nutrients. The trajectory suggests a chaotic or near-chaotic attractor, with sensitive dependence on initial conditions.

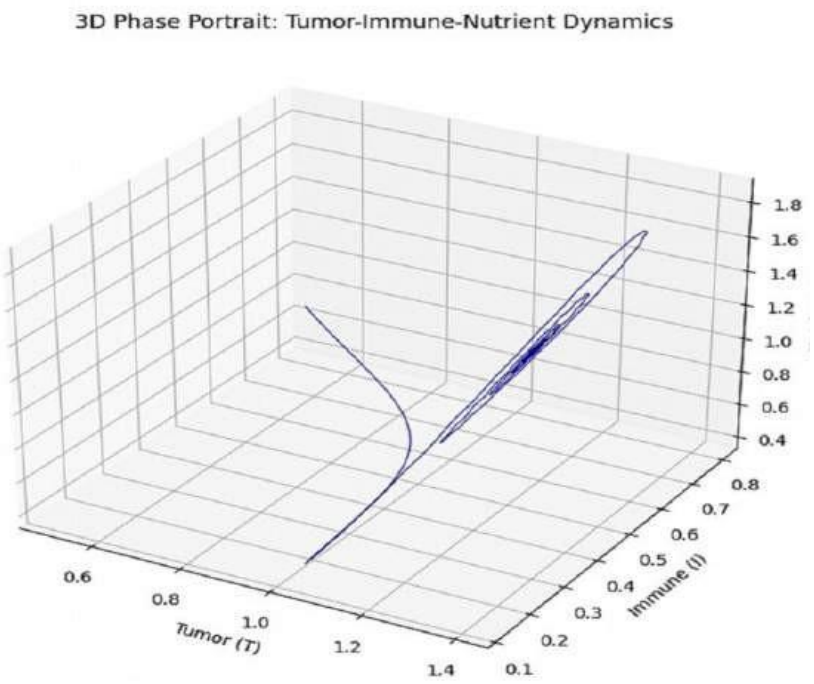
Based on Equations (1) to (3). The interplay between the nutrient and the tumor is the

fundamental driver of oscillatory behavior. This interaction can be expressed in terms of the nutrient-tumor coupling coefficient, denoted as $(+\ \gamma N)$, which governs tumor growth, and the nutrient-consumption coupling coefficient, denoted as $(-\ TI)$, which governs nutrient consumption. The diffusion term $\left(\ D\nabla^2 N\right)$ redistributes nutrients spatially, while the advection term $(-\ v\nabla N)$ introduces directional flow, adding complexity to the dynamics. The observed quasi-periodic behaviour is attributable to the nonlinear feedback between tumor growth and nutrient availability (Huo et al, 2025).

The following is a detailed analysis of the three-dimensional phase portrait depicted in Figure 3, in relation to the reaction-diffusion-advection partial differential equation (PDE) system. The present study investigates the dynamics of tumor (*T*), immune (*I*), and nutrient (*N*) densities. These densities are modeled using a reaction-diffusion-advection partial differential equation (PDE) system. The 3D phase portrait offers insights into the interdependence and nonlinear interactions among these variables. The figure captures the temporal evolution of the system, where the trajectory initially exhibits a transient phase before spiraling into a quasi-periodic attractor. This attractor is indicative of oscillatory behavior and is confined to a bounded region in three-dimensional space, suggesting that the system achieves dynamic equilibrium within specific ranges of tumor, immune, and nutrient densities.

The system's oscillatory behavior is driven by nonlinear reaction terms that couple tumor growth, immune dynamics, and nutrient availability. Tumor Growth: Tumor growth follows a logistic model (*rT(1-T/K)*), constrained by immune suppression $(-\ \alpha TI)$ and supported by nutrient availability $\left(+\ \gamma N\right)$. Immune activation (+ βTI) and decay (-*I*) create feedback loops with tumor growth, resulting in oscillatory immune density. Nutrient Dynamics: The regulation of the system's energy supply is achieved through the consumption (-*TI*) and replenishment $\left(+\ \beta N\right)$ of nutrients. These reaction terms are complemented by diffusion terms ($D\nabla^2 T$, $D\nabla^2 I$, $D\nabla^2 N$), which enable spatial redistribution and prevent unbounded growth or decay. Additionally, advection terms (-$v\ \nabla T$, -$v\ \nabla I$, -$v\ \nabla N$) introduce directional flow, thereby adding further complexity to the dynamics.

Figure 3. The 3-D phase portrait showed the tumor (*T*), immune (*I*), and nutrient (*N*) densities



Source: The author

The observed spiraling trajectory highlights the intricate nonlinear feedback loops that govern the interactions between tumor, immune, and nutrient densities. Tumor density (*T*) oscillates as it is suppressed by immune responses (I) while being fueled by nutrient availability (*N*). Simultaneously, immune density (*I*) fluctuates in response to tumor stimulation and natural decay, and nutrient density (*N*) oscillates as a consequence of consumption and replenishment cycles. The nonlinear terms ($-\alpha TI$, $+\beta TI$, $-TI$) establish feedback mechanisms that sustain the system's oscillations. The trajectory does not converge to a fixed point or simple periodic orbit, indicating quasi-periodic or chaotic dynamics. The system's chaotic behavior is attributed to the interplay of nonlinear reaction terms, diffusion, and advection. Sensitivity to initial conditions and parameter values, such as (r, α, β, γ, D, v), reinforces its chaotic nature. Parameter optimization was employed to enhance sensitivity and generate the observed attractor.

DICUSSION

As illustrated in Figure 1, the chaotic and oscillatory behavior (Kumar et al., 2025). The oscillatory patterns manifest in all three variables indicate the presence of nonlinear feedback loops between tumor growth, immune response, and nutrient availability. The system exhibits

quasi-periodic behavior, a hallmark of systems on the verge of chaotic attractors. This phenomenon aligns with parameter optimization strategies that are designed to induce chaotic dynamics. The intricate interplay among tumor growth, immune response, and nutrient availability is elegantly captured within a reaction-diffusion-advection framework (Altea-Manzano et al., 2020). The observed oscillatory behavior encapsulates the nonlinear dynamics of the system, with parameters that have been optimally adjusted to approximate chaotic attractors. The findings are consistent with the theoretical equations, thereby underscoring the intricate feedback mechanisms and interactions encapsulated within the PDE system (Cherraf et al., 2023).

A comprehensive examination of this phenomenon, as illustrated in Figure 2. The complex trajectory underscores the critical function of nutrient availability as a regulatory factor in tumor dynamics. The observed oscillations signify a competitive struggle for resources, a fundamental aspect of tumor biology (Huo et al, 2025). The suggestion of quasi-periodic behavior raises important questions about the potential for chaotic dynamics within the system, particularly under specific parameter conditions. This highlights the sensitivity of tumor progression to fluctuations in nutrient supply, a factor that cannot be overlooked in therapeutic considerations.

Phase portraits (Fig. 2) elucidate the significance of nonlinear feedback loops in modulating the interactions between tumor, immune, and nutrient dynamics. These feedback mechanisms underpin the oscillatory and quasi-periodic behaviors observed, emphasizing the complexities inherent in tumor-immune interactions (Huo et al, 2025). Specifically, the inward spiral depicted in the tumor-immune phase portrait suggests a stabilization of the system over time, leading to a dynamic equilibrium wherein tumor growth is counterbalanced by immune suppression. This equilibrium appears contingent upon nutrient availability, as illustrated by the quasi-periodic behavior in the tumor-nutrient phase portrait.

As shown in Figure 3, the bounded attractor reflects the stabilization of tumor, immune, and nutrient densities within a specific range, indicating a dynamic equilibrium. The periodic oscillations represent tumor flare-ups and immune responses, influenced by nutrient availability. The chaotic or quasi-periodic behavior implies that small perturbations in initial conditions or external interventions, such as therapies, can lead to drastically different outcomes (Sancho-Araiz et la., 2023). This sensitivity underscores the need for adaptive and dynamic treatment strategies that account for the system's inherent complexity.

This 3D phase portrait illustrates the complex and nonlinear dynamics of tumor, immune, and nutrient interactions as modeled by the reaction-diffusion-advection PDE system (De Pillis et

al., 2005; Byrne et al. 2006). The quasi-periodic attractor emphasizes the importance of nonlinear feedback loops and dynamic equilibrium in regulating tumor progression. The results have significant implications for cancer treatment strategies, mathematical modeling, and theoretical biology.

The intricate trajectory represented in the tumor-nutrient phase portrait points to the possibility of chaotic dynamics (Dubey et al, 2025**)**, whereby minor alterations in initial conditions or parameters may yield significantly divergent outcomes. This phenomenon underscores the necessity for parameter optimization and sensitivity analysis in the exploration of tumor progression pathways.

The insights gained from these phase portraits resonate with the complexities of tumor dynamics observed in clinical settings, where tumor growth is intricately linked to the interplay between immune response and nutrient availability. Furthermore, the findings of this study align with established theories of immune surveillance, tumor immune evasion, and resource competition. Consequently, this work enriches our understanding of tumor-immune-nutrient interactions, providing a framework for future investigations into the nonlinear dynamics governing tumor behavior.

In addition, the elucidation of the complex, nonlinear dynamics of the reaction-diffusion-advection PDE system sheds light on the tumor-immune relationship (Hundsdorfer, 2020), characterized by damped oscillations that stabilize over time (Huo et al., 2025). In contrast, the tumor-nutrient relationship manifests quasi-periodic behavior, reinforcing the notion of sensitive dependence on nutrient supply (Altea-Manzano et al, 2020). These findings underscore the critical importance of nonlinear feedback loops, dynamic equilibrium, and chaotic dynamics in advancing our comprehension of tumor progression and immune responses. As such, this research offers valuable implications for both theoretical understanding and practical applications in oncology.

Therapeutic interventions targeting nutrient supply or immune activation could exploit the system's nonlinear feedback to disrupt tumor growth (Basanta and Anderson 2013). Additionally, the observed attractor provides valuable insights into long-term system behavior, informing future mathematical modeling efforts. These findings align with established theories of immune surveillance, tumor immune evasion, and resource competition, offering a deeper understanding of tumor progression and its regulation.

The subsequent discussion focuses on Fundamental PDE Models for Tumor-Immune-Nutrient Interactions and Key Authors. The field of mathematical oncology, particularly the

application of partial differential equations (PDEs) in tumor-immune-nutrient modeling, has been profoundly influenced by numerous researchers. While the specific models demonstrate variations in complexity and biological focus, several key authors and groups have made foundational contributions.

The Kuznetsov-Taylor model (Kuznetsov et al., 1994) focused on the temporal dynamics of tumor-immune interactions by utilizing ordinary differential equations (ODEs) (Galach, 2003). However, its extension to Partial Differential Equation (PDE) frameworks explicitly incorporates spatial aspects, which are crucial for understanding phenomena like immune cell infiltration into tumors and mechanisms of tumor immune escape (Yılmaz, 2025). de Pillis and her collaborators (de Pillis et al., 2005) have developed and extensively validated mathematical models that specifically focus on the distinct roles of Natural Killer (NK) cells and CD8+ T cells in tumor surveillance and rejection. While many of their foundational models are ODE-based, the biological principles and mathematical structures they established are directly transferable and extensible to spatial PDE models. (Byerne et al., 2006) have made substantial contributions to the field, both through extensive reviews and the development of mathematical models for solid tumor growth, particularly focusing on angiogenesis. Their work underscores the notion that diffusible chemicals, such as Tumor Angiogenesis Factor (TAF), function as "nutrients" or signaling molecules that drive the directed movement (chemotaxis, an advection term) of capillary tips to supply the growing tumor.

Chaplain and Lolas' research (Chaplain and Lolas, 2006) provides detailed and influential examples of reaction-diffusion-taxis PDE models specifically designed to describe cancer cell invasion. These models generally emphasize the intricate interplay among cancer cells, the extracellular matrix (ECM), and matrix-degrading enzymes (e.g., urokinase plasminogen activator (uPA)) (Alsakaji et al. 2023). This work offers a compelling illustration of the pivotal role that the "advection" (taxis) term plays in elucidating the mechanisms underlying tumor invasion. PDE's unique capacity to delineate the spatial distribution and evolution of cells and chemical species within tissues renders them a formidable tool in the scientific realm (Mahlbacher et al., 2019). These gradients can be used to elucidate the mechanisms by which spatial variations in biological phenomena, such as angiogenesis and invasion, are driven, and how these variations influence the overall morphology and behavior of tumors (Lee, 2025). Furthermore, PDEs have been demonstrated to simulate complex dynamic behaviors, including traveling waves, Turing patterns, and other self-organized structures, which are frequently observed in biological systems (Hillen et

al. 2015). Mathematical models, particularly those based on PDEs, offer robust predictive capabilities. As (Aschi and Simbawa 2025) demonstrate, partial differential equations (PDEs) facilitate the comprehension of intricate mechanisms underpinning tumor invasion, angiogenesis, immune evasion, and the development of drug resistance.

Moreover, fundamental mathematical problems related to the existence, uniqueness, and stability of solutions for these complex systems can be exceptionally challenging to address (Hillen et al., 2015). A substantial challenge in the practical implementation of complex PDE models pertains to the precise estimation of their numerous parameters. The simulation of high-dimensional, non-linear partial differential equations (PDE) systems, particularly those that incorporate multi-scale interactions, can also be computationally intensive and time-consuming, requiring substantial computational resources (Gatenby and Gawlinski, 1996). Despite their increasing sophistication, mathematical models are inherently simplifications of extraordinarily complex biological systems.

Challenges and Future Directions in Mathematical Oncology. The mathematical models of cancer have undergone a progressive increase in complexity, transitioning from rudimentary ordinary differential equations (ODEs) to intricate partial differential equations (PDEs) and multi-scale frameworks (Debnath et al., 2025). This increasing complexity is not merely a consequence of mathematical sophistication but is fundamentally driven by a continuously deepening biological understanding of cancer. This paradigm shift in thinking reflects the realization that cancer is not merely a collection of cells but rather a dynamic, evolving ecosystem (Alharbi and Rambely, 2020). The transition from well-mixed ordinary differential equations (ODEs) to spatially explicit partial differential equations (PDEs), and subsequently to multi-scale partial differential equation (PDE) models (Chaplain and G. Lolas, 2006), signifies a crucial paradigm shift. It acknowledges that spatial context, dynamic gradients, and interactions across different biological scales are mechanistically vital for phenomena such as tumor invasion, immune evasion, angiogenesis, and the emergence of treatment resistance.

Furthermore, tumors are not static entities but highly dynamic, evolving populations that frequently develop resistance to therapeutic interventions through processes of natural selection (Debnath et al., 2025). In order to accurately predict and potentially circumvent resistance mechanisms, future models must explicitly incorporate evolutionary principles, including mutation rates, phenotypic plasticity, and spatially driven selection pressures (Hillen and Rehman, 2025). This frequently entails the establishment of conceptual and mathematical analogies with

ecological models (Hillen et al., 2025). The proliferation of intricate mathematical models and the generation of voluminous datasets in the domain of cancer research underscores the imperative for the integration of sophisticated computational and data science methodologies. This includes the application of optimal control theory for the design of optimized treatment schedules and the integration of machine learning and artificial intelligence methodologies for tasks such as data integration, parameter inference, and the generation of novel hypotheses.

CONCLUSIONS

Recent advancements in cancer research have underscored the critical importance of understanding the complex biological behaviors associated with tumor development and progression. This article underscores the importance of ongoing research endeavors, with a particular emphasis on the significance of innovative analytical methodologies in elucidating the dynamic nature of cancer cell behavior. The study conducted by EDP provides valuable insights into the oscillating and chaotic patterns observed in cancer dynamics, which are crucial for developing more effective therapeutic strategies. The present study, an investigation into the mathematical partial differential equations that describe tumor-immune-nutrient interactions in the context of cancer modeling, has yielded the following conclusions:

- Understanding the intricate biological mechanisms underlying cancer is essential for improving diagnostic accuracy and treatment efficacy.
- Studying the dynamic behaviors of cancer cells, including oscillations and chaos, offers a deeper comprehension of tumor heterogeneity and resistance mechanisms.
- The study revealed that cancer cell populations exhibit oscillatory behaviors, characterized by periodic fluctuations in cell proliferation and apoptosis rates.
- Chaotic dynamics were observed in tumor growth patterns, indicating sensitivity to initial conditions and complex interactions within the tumor microenvironment.
- Mathematical modeling demonstrated that these oscillations and chaos could influence treatment responses, highlighting the need for adaptive therapeutic strategies.
- The findings suggest that the tumor's behavior is not purely stochastic but governed by underlying nonlinear dynamics, which can be exploited for targeted interventions.

The recognition of oscillatory and chaotic phenomena in cancer progression emphasizes the necessity for dynamic monitoring and adaptable treatment protocols. These behaviors

challenge traditional linear models of tumor growth, advocating for a paradigm shift towards nonlinear analysis in oncology research. Understanding these complex patterns can lead to the development of predictive models, improving prognosis and personalized treatment planning.

The study by EDP underscores the importance of integrating nonlinear dynamics into cancer research. Such approaches can unveil hidden patterns in tumor behavior, ultimately contributing to more effective and individualized therapeutic strategies, thereby advancing the field of oncology significantly.

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