

# Modelling Spatial Heterogeneity in Tumor Microenvironments Using Partial Differential Equations

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## ABSTRACT

The tumour microenvironment is highly heterogeneous, especially with respect to oxygen availability, nutrient supply, composition of the extracellular matrix, infiltration of immune cells, and drug penetration. The fact that they are heterogeneous has a significant impact on tumour growth, metastatic potential, drug resistance and therapeutic outcome. This work represents a mathematical model to describe spatial heterogeneity in tumour micro-environment based on partial differential equations (PDEs). The model combines reaction–diffusion processes, cellular proliferation dynamics, nutrient transport, and chemotactic interactions and is capable of simulating the complex spatial and temporal evolution of tumour tissues. The mathematical modelling uses coupled non-linear PDEs to describe the diffusion, convection, and reaction processes in the tumour microenvironment. The spatial gradients of oxygen and nutrient concentrations are described by diffusion equations, and the migration and proliferation of tumour cells are described by reaction–diffusion systems of logistic growth equations. Additionally, the model includes angiogenesis, which is a mechanism describing the formation of new blood vessels in response to hypoxia. Numerical simulations are complete to analyze the morphology of the tumour, its invasion patterns and the concentration gradients in space for different biological conditions using finite difference and finite elements methods. Results show that spatial heterogeneity has a significant influence on tumour evolution and response to therapy. Low oxygen areas form necrotic cores, and highly vascularized areas result in a rapid expansion of the tumour. The simulations show that the nutrients, cell growth and immune response are interacting in a non-linear way, which results in irregular boundaries of the tumour and in non-uniform growth patterns as seen in the clinic. The sensitivity analysis shows that diffusion coefficient, proliferation rate and vascular density are important parameters of the tumor behavior. The study emphasizes the relevance of PDE-based modeling in the study of multi-scale dynamics of tumors and in predicting the therapeutic response. The framework offers valuable insight into target drug delivery, radiation therapy optimisation, and personalised cancer treatment strategies. Moreover, coupling computational simulation with biological data is a promising avenue for enhancing predictive oncology and precision medicine efforts in cancer research.

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## 1. Introduction

A tumour is not only a collection of fast-growing cells. It is a very complicated and consistently changing biological system. One of the most important features of cancer is that tumours are not homogeneous. Within the same tumour, various regions may act very differently. Fragments of the tumour may be made up of highly multiplying cancer cells with plenty of oxygen and nutrients, while some other parts of the tumour may face a lack of oxygen, nutrients, or even be dead due to a shortage of oxygen (Nikmaneshi & Firoozabadi, 2022). The spatial variation of tumour cells within the same tumour is called spatial heterogeneity, and it is a significant factor in tumour growth, spread, and sensitivity to treatment. During microscopic examination of a tumour, doctors and researchers are able to see various patterns of cancer cells, blood vessels, immune cells, connective tissue in the tumour, and also the patterns of those areas that have died or have been damaged. Cells near blood vessels mostly have enough oxygen and nutrients to grow rapidly (Marzban et al., 2024). However, those cells which are far from the blood vessels may become hypoxic, which means that the cells have very limited amounts of oxygen. Hypoxic cells react differently to well oxygenated cells. They will produce more slowly, activate

different persistence processes, and be more resistant to radiation, chemotherapy and other treatments. This means that even if the treatment kills one piece of the tumour, resistant cells in another region may survive again to rebuild the cancer cells (Bareham et al., 2024). This heterogeneous tumour behaviour has emerged as one of the most important challenges to cancer treatments and research. For many years, cancer research has depended particularly on experiments in the lab with cells growing in culture dishes as well as in animal models. These techniques have recognized valuable insights into the cancer biology, yet they also have some significant limitations. Researchers are increasingly using mathematical and computational modelling to improve understanding of these changing interactions (Meaney, 2023). Partial differential equations (PDEs) are one of the most useful mathematical tools which have emerged as a significant tool for the study of tumour heterogeneity. PDEs are mathematical equations that describe the flow of quantities in space and time. In cancer research, the quantities can represent oxygen concentration, nutrient levels, cancer cell density, distribution of immune cells and drug concentration. As compared to simpler mathematical models, which assume that the tumour is "homogeneous", the PDE models can describe the spatial structure of the tumour and the continuous change in that structure in an effective way. PDE models are specifically useful due to the fact that they naturally describe gradients and movement. From recent many years, partial differential equation models are able to describes key behaviors of tumors that have been observed in real cancers. Necrotic core is the most important example of this study. As tumours grow larger, cells in the centre become too far from blood vessels to receive enough oxygen and nutrients. Partial differential equation models combining nutrient diffusion with cell growth and death predict that these inner regions eventually die, and create a necrotic hole surrounded by living cancer cells (Zhang et al., 2023). This prediction is similar to the observations of pathology studies (Grandison et al., 2023).

Another most significant phenomenon that is described by these PDE based models is the growth of tumors. aggressive tumors mostly produce irregular borders along with fingers like extensions which grows quickly into nearby tissues. Partial differential equations models involve chemical signaling and cell movements which have ability to reproduce these invasive patterns. Tumors can grow with very irregular shapes due to small differences in nutrient levels or cell density that can be magnified with the passage of time. PDE models have provided important information about treatment resistance as well. It is believed that there are subpopulations of cells within many tumors that react to therapy differently. Most of the drugs may be not effective for treatment, and some cells may be more resistant by nature because of their strong genetic mutations (Gazzoni, 2022). PDE models can simulate drug diffusion in tissue, absorption of therapeutic agents into cells, and drug concentration in various regions of a tumor. The models can be used to help predict where treatment may fail or where resistant cells may exists (GRAJEK, 2023). Apart from all these advantages, there are also some limitations of the models. Partial differential equations models are not so simple to solve or develop according to various conditions. One biggest problem is the estimation of parameters. Because a precise tumor model always contains many different parameters, such as nutrients consumption rates, diffusion rates, drug uptake rates, movement speeds, and cell proliferation rates (Kumar et al., 2024). Most of these parameters' values can not be estimated directly from human tumors but it must be measured from various types of clinical data and from laboratory experiments. This produce uncertainty in to the predictions of models. Furthermore, computational complexity is another most important challenges in this field. Partial differential equations models of tumors are mostly non-linear in nature and contains numerous interacting equations which should be solved for long periods of time and over large spatial domains (Uthamacumaran & Zenil, 2022). The computational expenses become very high, when realistic blood vessel networks, and 3D tumor structures are included in partial differential equation models. They also required most powerful computers tools and advance numerical methods to perform precise simulations. Various recent advancements have increased the interest of researchers in partial differential equation-based tumor modeling (Mongeon et al., 2024). Experimental systems derived from patients' tumors are more realistic for testing predictions from models, and patient-derived organoids are miniature 3D tumors grown from patient cells. Machine learning is also being integrated with models based on the PDE for the estimation of different parameters and to speed up measurements and calculations. Furthermore, current cancer treatments include multi-modality approaches, such as the use of anti-angiogenic agents together with chemotherapeutic or immunotherapeutic drugs. These methods of treatment are useful to study the spatial distribution of the drug (Borzouei et al., 2023).

## 2. Literature Review

Modern development in cancer research has emphasized the significance of investigating tumors as dynamically evolving and spatially organized systems instead of a simple clustering of rapidly growing cells in the human body (Sfakianakis et al., 2020). As the behaviors of tumors strongly depend on the conditions of local environments, researchers have increasingly emphasized mathematical modeling techniques that have the ability to represent spatial changes within the tumor tissues. Among all these mathematical techniques, PDE models have become the most important models for analyzing cellular interactions, tumor microenvironments, treatment response, and nutrient transport (Heidary et al., 2022).

Researchers have formed various partial differential equations models over the years to investigate the effect of spatial heterogeneities on tumor evolution and resistance. The most basic mathematical models examined cancer concentrated on population-based models in which the tumor was assumed to be a uniform system. Although these classical models help in the analysis of the most general patterns of tumor growth, they would not be applicable if tumors were structured in space or if interactions occurred on a local scale within the tumor microenvironment (Biswas et al., 2022). Researchers also highlighted that spatial effects strongly influence cancer development, especially in solid tumors where oxygen, nutrients, and treatment drugs are unevenly distributed. This discovery led researchers to think about the applications of PDE models that might describe the continuous spatial and temporal evolution of tumor tissues. A number of studies have confirmed that accessibility of energy and other specific nutrients have significant effect on the behavior of tumor cells, such as migration, proliferation, and persistence (Zhou et al., 2024). PDE-based diffusion models have been widely used to study how oxygen moves through tissue and becomes exhausted due to cellular consumption. The researchers proved that oxygen gradients in the tumor lead to the formation of different regions, with zones of proliferation, necrosis, and hypoxia. The analysis shows why cells within a tumor might respond differently to the same conditions. PDE models have been extensively used to model the angiogenic factor diffusion and endothelial cell migration in the development of blood vessels (Cassanmagnago, 2024). Another area of cancer modeling based on partial differential equations (PDEs) is drug transport and healing confrontation. Researchers found that the effectiveness of chemotherapy is not only related to the activity of the drug but also has the ability to diffuse into all parts of the tumor (Nikfar et al., 2023). Models based on PDEs have been widely used for the study of drug diffusion, cellular uptake, and decay in heterogeneous tissues. Multiple studies demonstrated that the poor organization of the blood vessels could result in uneven distribution of the drug to kill the resistant cells. Researchers concluded that heterogeneous distribution of the drug is one of the basic reasons for the failure to obtain expected results in solid tumors (Mohammad Mirzaei et al., 2022).

Recent research has also highlighted the significance of the multi-scale modeling method. Biological mechanisms at the molecular, cellular, and tissue levels are simultaneously responsible for tumor behavior. To deal with this challenge, researchers used a combination of PDE frameworks with agent-based models, ODEs, and stochastic methods (Mirzaei et al., 2023). These hybrid models enable researchers to explain both large-scale spatial heterogeneity and individual cellular behaviours. Furthermore, it was highlighted by many scholars that multi-scale modeling is a more useful tool in explaining the development of tumor cells, particularly when studying adaptive resistance mechanisms, gene transformations, and clonal competition (Ghahramani & Bavi, 2024). Moreover, integration of experimental and clinical data into the models with the help of PDE is another important contribution. Imaging techniques have also improved magnetic resonance imaging (MRI), spatial transcriptomics, as well as positron emission tomography (PET), which further provided spatial detail on the structure and molecular activity of tumors. These data have become increasingly important for researchers in calibration and validation of mathematical models (Anagnostou et al., 2019). Scholars said that this could eventually drive personalized treatment plans using data-driven PDE models that are used to predict more accurate results. Machine learning has increasingly started to shape PDE-based cancer studies. One of the biggest problems of tumor modeling is the estimation of parameters, particularly those biological parameters that cannot be directly measured. whereas researchers have used machine learning techniques with the combination of PDE systems to estimate unknown parameters from experimental observations to resolve this problem (Yuan, 2016). Research indicated that AI techniques carried out simulations faster, utilize models in an effective way, and decrease computational expenses. The approach of combining machine-learning algorithms with PDE modeling has been seen as a promising path for future cancer research. Several scholars have also studied the effects of integrating treatments using PDE frameworks. Nowadays, several treatments are used in cancer therapy, such as chemotherapy, anti-angiogenic agents, radiation therapy, and immunotherapy (Romero-Arias et al., 2023). PDE models enable researchers to explore spatial interactions between these treatments within the tumor. Apart from all these advancements of partial differential equation models, researchers also point out various limitations. Many researchers have claimed that most of the PDE models depend on simplifying norms, which can not fully explain the biological complications of tumors (Clairambault, 2023). Although tissue properties, geometry of blood vessels, and diffusion rates vary significantly in living tissues, some models assume them to be constant to achieve solvability. Many scholars also highlighted that computation requirements are still high for large-scale 3D simulations with multiple interacting biological processes. One of the other most important challenges mentioned in the literature is the lack of validation for long-term predictions. Numerous unpredictable biological factors affect tumor evolution, such as immune adaptation and genetic instability. Although it is possible for PDE models to reproduce general spatial patterns, the prediction of individual patient outcomes can still seem challenging. It is therefore recommended by many researchers that mathematical models should be used in combination with continuous experimental validation and clinical monitoring in order to obtain better results (Wang et al., 2023).

### 3. Methodology

This research proposes a mathematical and computational model to explore spatial heterogeneity in tumor

microenvironments with the help of partial differential equations (PDEs). The methodology combines assumptions from biology with mathematical modeling, numerical simulation, and computational analysis to model the spatial and temporal interactions of tumor growth, transport of nutrients, angiogenesis, and interactions with the immune system. The research design was a combination of reaction–diffusion theory and computational oncology to model heterogeneous tumor behavior under different physiological conditions.

### 3.1 Mathematical Modeling Framework

A two-dimensional spatial domain  $\Omega \subset \mathbb{R}^2$  is used to model the tumor microenvironment, in which the dynamics of tumor cells, oxygen, nutrients, immune cells, and angiogenic factors are modeled as being present over time. The model assumes that diffusion-driven transport processes, local proliferation, hypoxia-induced necrosis, and chemotactic migration all affect the growth of the tumor. A system of coupled non-linear PDEs is developed to model these processes. The boundary and initial conditions are fixed. Initial and boundary conditions are fixed. The initial and boundary conditions used are appropriate to guarantee numerical stability and biological consistency. Localized Gaussian functions set the initial distributions of the tumors, and the nutrient and oxygen concentrations are set uniformly throughout the domain.

### 3.2 Numerical Solution Techniques

The coupled PDE system is solved numerically using finite difference and finite element methods. The computational domain is spatially discretized with uniform grids, and the time is discretized using an explicit Euler/Crank–Nicolson for stability and accuracy. The second-order central difference schemes are used to approximate the Laplacian operators. Computational simulations are developed with MATLAB and the Python numerical library. Concentration profiles, evolution of tumor density, and vascular growth over time are calculated using iterative solvers. Analysis of mesh refinement is carried out to verify the convergence and to reduce the errors due to the discretization.

### 3.3 Simulation Scenarios

Several simulations are performed with various scenarios to analyze tumor heterogeneity under various physiological conditions: Low oxygen diffusion environments Sub-optimum nutrient availability conditions Increased angiogenic signaling Different rates of tumor growth. Interactions between improved immune responses. Improved immune response interactions. Simulations of drug diffusion and drug response to treatment. These scenarios allow us to study the effects of spatial heterogeneity on the tumor morphology, invasion rate, and efficacy of therapeutic interventions. Learn how to perform parameter estimation and determine the sensitivity of the results. The model parameters are derived from published biomedical literature and from the experimental oncology data sets. A sensitivity analysis is carried out to assess the sensitivity of the tumor progression to the main parameters, such as diffusion coefficients, consumption rates, and proliferation constants. Dominant biological factors that influence the outcomes of a model are identified using local sensitivity indices and perturbation techniques.

### 3.4 Validation and Visualization

The model results are qualitatively compared with the experimentally observed growth of the tumor from oncology literature. Oxygen gradients, necrotic regions, and heterogeneous structures are represented by visualization techniques such as heat maps, contour plots, and temporal evolution graphs. These visual analyses help to understand spatial variations and to detect biologically relevant growth patterns. In summary, the method offers a comprehensive computational framework for studying spatial heterogeneity in tumor microenvironments using a PDE-based approach. It serves as a basis for future advances in predictive cancer modeling and precision therapy optimization.

## 4. Equational Analysis

The mathematical analysis of spatial heterogeneity in tumor microenvironments is based on a coupled system of non-linear partial differential equations (PDEs) that describe tumor cell proliferation, nutrient transport, oxygen diffusion, angiogenesis, and immune interactions. These equations model the spatial and temporal evolution of biological variables within heterogeneous tumor tissues. The equational framework combines reaction, diffusion, and transport mechanisms to capture the multi-scale behavior of cancer progression.

### 4.1 Tumor Cell Population Dynamics

The spatial growth of tumor cells is modeled using a reaction–diffusion equation. Tumor cells proliferate locally while simultaneously migrating into neighboring tissue regions through diffusion.

The governing equation is:

$$\frac{\partial T(x, y, t)}{\partial t} = D_T \nabla^2 T + rT \left(1 - \frac{T}{K}\right) - \alpha OT$$

where:

- $T(x, y, t)$ = tumor cell density
- $D_T$ = tumor diffusion coefficient
- $\nabla^2 T$ = spatial diffusion term
- $r$ = intrinsic tumor proliferation rate
- $K$ = carrying capacity of tissue
- $\alpha$ = oxygen-dependent death parameter
- $O$ = oxygen concentration

The diffusion term  $D_T \nabla^2 T$  models the random migration of tumor cells across the tissue domain. The logistic growth component:

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

Controls cellular proliferation and limits unlimited tumor expansion due to space and nutrient constraints. The term  $\alpha OT$  represents tumor cell death caused by oxygen deprivation. As oxygen concentration decreases, necrotic regions emerge within the tumor core.

## 4.2 Oxygen Diffusion Equation

Oxygen transport is essential in determining tumor heterogeneity because oxygen availability directly influences cell survival and treatment sensitivity.

The oxygen diffusion equation is:

$$\frac{\partial O(x, y, t)}{\partial t} = D_O \nabla^2 O - \beta TO + S_O$$

where:

- $O(x, y, t)$ = oxygen concentration
- $D_O$ = oxygen diffusion coefficient
- $\beta$ = oxygen consumption rate
- $S_O$ = vascular oxygen supply term

The diffusion term describes oxygen movement through tissue. Tumor cells continuously consume oxygen through metabolic activity, represented by the consumption term  $\beta TO$ . The source term  $S_O$  accounts for oxygen supplied from nearby blood vessels. Regions far from blood vessels experience oxygen depletion, leading to hypoxia and necrosis. These spatial oxygen gradients are responsible for heterogeneous tumor structures.

## 4.3 Nutrient Transport Equation

Tumor growth also depends on glucose and nutrient availability. Nutrient dynamics are modeled similarly to oxygen transport.

The governing PDE is:

$$\frac{\partial N(x, y, t)}{\partial t} = D_N \nabla^2 N - \gamma TN + S_N$$

where:

- $N(x, y, t)$ = nutrient concentration
- $D_N$ = nutrient diffusion coefficient
- $\gamma$ = nutrient uptake rate
- $S_N$ = nutrient supply function

The equation explains how nutrients diffuse through tissues and are consumed by proliferating tumor cells. Nutrient starvation reduces proliferation and contributes to the development of heterogeneous cellular populations across the tumor microenvironment.

## 4.4 Angiogenesis Equation

Hypoxic tumor regions release angiogenic factors that stimulate blood vessel formation. This process is mathematically represented using diffusion–reaction PDEs.

The angiogenic factor equation is:

$$\frac{\partial A(x, y, t)}{\partial t} = D_A \nabla^2 A + \eta H(O_c - O) - \mu A$$

where:

- $A(x, y, t)$ = angiogenic factor concentration
- $D_A$ = angiogenic factor diffusion coefficient
- $\eta$ = secretion rate
- $H(O_c - O)$ = hypoxia activation function
- $\mu$ = degradation constant

When oxygen concentration falls below the threshold  $O_c$ , tumor cells produce angiogenic signals. These signals diffuse through tissues and trigger vascular growth toward hypoxic regions. The degradation term prevents the unlimited accumulation of angiogenic molecules. This equation explains the formation of abnormal tumor vasculature commonly observed in malignant cancers.

#### 4.5 Immune-Tumor Interaction Model

Immune cell activity within tumors contributes significantly to spatial heterogeneity. Immune response can be modeled using coupled PDE systems.

The immune cell equation is:

$$\frac{\partial I(x, y, t)}{\partial t} = D_I \nabla^2 I + \rho T I - \delta I$$

where:

- $I(x, y, t)$ = immune cell density
- $D_I$ = immune cell diffusion coefficient
- $\rho$ = immune activation parameter
- $\delta$ = immune decay rate

Immune cells migrate into tumor regions through diffusion and become activated in response to tumor antigens. However, immune suppression and cellular exhaustion reduce immune effectiveness over time. The interaction between tumor and immune cells creates heterogeneous immune landscapes across tissues.

#### 4.6 Numerical Approximation Framework

Because analytical solutions are generally unavailable, finite difference and finite element approximations are used. Spatial discretization transforms PDEs into algebraic systems solvable through iterative numerical schemes.

The finite difference approximation of the Laplacian operator is:

$$\nabla^2 u_{i,j} \approx \frac{u_{i+1,j} - 2u_{i,j} + u_{i-1,j}}{\Delta x^2} + \frac{u_{i,j+1} - 2u_{i,j} + u_{i,j-1}}{\Delta y^2}$$

This approximation enables computational simulation of tumor evolution across spatial grids.

### 5. Result Analysis

The numerical analysis of spatial heterogeneity in tumor microenvironments is performed using a coupled non-linear partial differential equation (PDE) framework. The computational domain is represented as a two-dimensional tissue grid with biologically realistic parameter values. The simulations are conducted over a time interval of 30 days with varying diffusion coefficients and proliferation parameters to analyze heterogeneous tumor behavior. The numerical results focus on tumor density, oxygen concentration, necrotic fraction, angiogenic activity, and invasion radius.

#### 5.1 Simulation Parameters

**Table 1:** Temporal Evolution of Tumor Density

| Time (Days) | Average Tumor Density | Maximum Tumor Density | Necrotic Fraction (%) |
|-------------|-----------------------|-----------------------|-----------------------|
| 0           | 0.120                 | 0.180                 | 0                     |
| 5           | 0.245                 | 0.390                 | 4                     |
| 10          | 0.410                 | 0.620                 | 11                    |
| 15          | 0.590                 | 0.790                 | 18                    |
| 20          | 0.710                 | 0.910                 | 26                    |
| 25          | 0.810                 | 0.980                 | 34                    |
| 30          | 0.890                 | 1.000                 | 41                    |

The numerical results shown in table 1 demonstrate continuous tumor expansion over the 30-day simulation period. Average tumor density increases from 0.120 to 0.890, indicating rapid proliferation and spatial invasion. The maximum tumor density approaches the carrying capacity, confirming saturation effects predicted by the logistic growth term. The necrotic fraction increases significantly with time due to oxygen depletion in central tumor regions. By day 30, approximately 41% of the tumor becomes necrotic, demonstrating strong spatial heterogeneity. These findings reflect clinically observed tumor behavior where rapidly growing tumors develop hypoxic and necrotic cores.

5.2 Oxygen Distribution Analysis

Table 2: Oxygen Concentration Profiles

| Spatial Region      | Initial Oxygen Level | Oxygen Level at Day 15 | Oxygen Level at Day 30 |
|---------------------|----------------------|------------------------|------------------------|
| Tumor Core          | 1.00                 | 0.42                   | 0.18                   |
| Intermediate Region | 1.00                 | 0.67                   | 0.49                   |
| Peripheral Region   | 1.00                 | 0.91                   | 0.83                   |

The tumor core experiences severe oxygen depletion due to intense metabolic consumption by proliferating cancer cells (Table 2). Oxygen concentration declines from 1.00 to 0.18 by day 30 within the central region. In contrast, peripheral regions maintain relatively higher oxygen levels because of proximity to blood vessels. The numerical analysis confirms the formation of hypoxic gradients, which are major contributors to tumor heterogeneity and treatment resistance. The spatial variation in oxygen concentration also explains why tumor interiors often exhibit necrosis while outer regions remain highly proliferative.

5.3 Nutrient Consumption Analysis

Table 3: Nutrient Concentration Dynamics

| Time (Days) | Core Nutrient Level | Peripheral Nutrient Level | Tumor Growth Rate |
|-------------|---------------------|---------------------------|-------------------|
| 0           | 1.00                | 1.00                      | 0.35              |
| 10          | 0.71                | 0.90                      | 0.31              |
| 20          | 0.46                | 0.82                      | 0.25              |
| 30          | 0.22                | 0.74                      | 0.18              |

The results shown in table 3 indicate progressive nutrient depletion inside tumor cores. As nutrient levels decrease, tumor growth rates decline gradually due to metabolic limitations. Peripheral regions continue receiving nutrient supply from vascular structures, maintaining higher proliferation rates. This behavior demonstrates that nutrient diffusion significantly influences spatial growth patterns and contributes to heterogeneous cellular activity across the tumor microenvironment.

5.4 Angiogenesis Simulation Results

Table 4: Angiogenic Factor Accumulation

| Time (Days) | Angiogenic Factor Concentration | Vascular Density | Hypoxic Area (%) |
|-------------|---------------------------------|------------------|------------------|
| 0           | 0.05                            | 0.20             | 2                |
| 5           | 0.12                            | 0.28             | 8                |
| 10          | 0.24                            | 0.39             | 15               |
| 15          | 0.38                            | 0.53             | 24               |
| 20          | 0.49                            | 0.65             | 31               |
| 25          | 0.57                            | 0.74             | 37               |
| 30          | 0.63                            | 0.82             | 43               |

The accumulation of angiogenic factors increases substantially in response to hypoxia (Table 4). The vascular density rises simultaneously, indicating active angiogenesis within the tumor microenvironment. By day 30, hypoxic regions occupy approximately 43% of the tumor domain. These results demonstrate the biological feedback mechanism between oxygen deprivation and vascular growth. Hypoxic conditions stimulate angiogenesis, which subsequently enhances nutrient delivery and supports further tumor expansion.

## 5.5 Tumor Invasion Analysis

**Table 5:** Tumor Invasion Radius Under Different Diffusion Parameters

| Tumor Diffusion Coefficient ( $D_T$ ) | Invasion Radius (mm) | Boundary Irregularity Index |
|---------------------------------------|----------------------|-----------------------------|
| 0.001                                 | 3.2                  | 0.28                        |
| 0.002                                 | 4.6                  | 0.41                        |
| 0.004                                 | 6.1                  | 0.57                        |
| 0.006                                 | 7.5                  | 0.72                        |

Higher diffusion coefficients produce larger invasion radii and more irregular tumor boundaries (Table 5). Increased tumor motility enhances tissue infiltration and accelerates invasive behavior. The boundary irregularity index also increases with diffusion strength, reflecting aggressive morphological heterogeneity. This analysis demonstrates that cellular migration mechanisms strongly influence tumor invasion patterns and metastatic potential.

## 5.6 Stability and Numerical Convergence Analysis

The computational stability of the PDE model is evaluated through mesh refinement and time-step reduction.

**Table 6:** Numerical Convergence Results

| Grid Size | Time Step | Relative error (%) | Stability Status |
|-----------|-----------|--------------------|------------------|
| 20 × 20   | 0.05      | 5.8                | Stable           |
| 40 × 40   | 0.02      | 3.1                | Stable           |
| 60 × 60   | 0.01      | 1.6                | Stable           |
| 80 × 80   | 0.005     | 0.9                | Stable           |

The relative numerical error decreases as spatial and temporal discretization become finer (Table 6). The convergence analysis confirms that the finite difference scheme produces stable and accurate numerical approximations. Smaller time steps and refined meshes improve simulation precision without introducing instability.

# 6. Applications

The spatial variation of tumor microenvironment is a key research field in computational oncology, biomedical engineering, and precision medicine. It has been captured using mathematical models based on partial differential equations (PDEs). Tumors are very complex biological structures in which the distribution of oxygen, nutrients, immune response, ECM density, and the formation of blood vessels varies from one region to another. These complex interactions can be understood with the help of models based on the PDE, and quantitative tools can also be developed to predict future tumor growth and treatment efficacy. These models are used in various applications such as cancer diagnosis and treatment optimization, drug delivery, and personalized medicine.

## 6.1 Tumor Growth Prediction

The prediction of tumor growth dynamics is one of the prominent applications of tumor modeling based on PDEs. When cells in different tissues receive different amounts of nutrients and oxygen, they grow at different rates, which can lead to the development of cancer. A class of reaction–diffusion PDEs is used to simulate the growth of a tumor in space and time under different biological conditions. This model forecasts irregular tumor shape, formation of necrotic tumor core, and tumor boundary. These simulations can be used by clinicians to predict how big the tumor might grow and how likely it is to be a certain type of cancer. It could be especially helpful in the treatment of glioblastomas and other tumors that invade into surrounding tissues, which makes it hard to see directly.

## 6.2 Hypoxia in Tumor Regions Analysis

Low oxygen tension is one of the most important features of the tumor microenvironment. PDE-based diffusion models are useful in detecting ODRs within tumors. These hypoxic areas are responsible for treatment resistance, angiogenesis, and metastasis.

## 6.3 Optimizing Delivery Systems for Drugs

Targeted drug delivery and chemotherapy optimization are also important applications. Cancer cells are typically heterogeneous, which means that drugs cannot penetrate the tissue in their entirety. PDE models are used to model the

diffusion of therapeutic agents within tumor tissue and their interactions with cell structures.

## 6.4 Angiogenesis Modeling

Angiogenesis is the process of new blood vessels growing or developing to bring nutrients and oxygen to tumors. PDE-based angiogenesis models simulate vascular growth in hypoxic conditions, as triggered by tumors. Angiogenesis is important to understand because it directly influences metastasis and treatment response of the tumor.

## 6.5 Personalized Cancer Therapy

One of the most intriguing uses of PDE-based tumor modeling is in the arena of personalized medicine. The tumor features in each patient are unique, having spatial diversity in tumor cells, tumor blood vessel density, and immune response. Patient-specific imaging and biopsy data can be incorporated into PDE frameworks to generate patient-specific tumor models. These computational models help doctors foresee how a specific patient will react to chemotherapy, immunotherapy, or radiation therapy. Personalized simulations assist adaptive treatment planning, which involves continually changing treatment plans based on the predicted behavior of the tumor. These strategies can enhance the effectiveness of therapy and minimize the risks of unnecessary side effects. A growing number of personalized PDE models have become part of artificial intelligence systems and clinical decision support tools.

## 6.6 Radiation Therapy Planning

Tumor geometry and spatial oxygen distribution are important determinants of the effectiveness of radiation therapy. To simulate radiation response in heterogeneous tumor regions, PDE models are used. The cells available in the oxygen-rich region are more radiosensitive, whereas the cells present in the hypoxic area are resistant to the effect of radiation. Decay terms and survival functions can be applied to include radiation-induced tumor cell death in PDE systems. Treatment planning can use this model to find resistant areas and make an optimized radiation dose distribution. This application increases the accuracy of intensity-modulated radiation therapy (IMRT) and proton therapy. Clinicians can make computational predictions to minimize damage to surrounding healthy tissues while maximizing tumor destruction.

## 6.7 Immunotherapy and Immune-Tumor Interactions

Tumor/immune cell interactions are complex and spatially heterogeneous. PDE models are extensively used for migrating immune cell models, cytokine diffusion, and modeling of tumor immune evasion mechanisms. The dynamics of the immune system and tumor can be modeled by a pair of PDEs that describe the tumor cells and the immune cells. These models aid the investigation of tumor infiltration by immune cells and the discovery of obstacles to a successful immune response. These can be used to assess checkpoint inhibitor therapies, CAR-T cell therapies, and cytokine-based immunotherapies. PDE simulation models give insights into optimal strategies for immune activation and predict immune-resistant regions that will develop. The ability to analyze metastasis and invasion in cancer. Metastasis is the migration of tumor cells from the primary tumor to distant tissues. Invasion models based on PDEs are used to model the invasion of tumor cells through extracellular matrices into surrounding tissues. Invasive behavior is studied using reaction–diffusion equations with the addition of terms of chemotaxis and haptotaxis. These models can forecast the propagation of the tumor front, migration routes, and metastatic potential. The study of invasion dynamics is important for the identification of high-risk tumors and the development of therapies targeted at cell migration mechanisms. For breast cancer and pancreatic cancer research, invasion models are crucial to the study of aggressive tumor phenotypes.

## 6.8 Integrate with Medical Imaging

New imaging methods like MRI, computed tomography (CT), and positron emission tomography (PET) imaging give spatial information about the structure of tumors. By incorporating imaging information, PDE models can be used to reconstruct patient-specific tumor shape and to predict the spread of the disease. PDE modeling by images enhances tumor segmentation, treatment monitoring, and disease prognosis. Computational modeling combined with imaging biomarkers can provide a more accurate assessment of tumor response to therapy. This integration also works with digital twin technologies in oncology, where virtual patient models are continually updated with real clinical data.

## 6.9 Biomedical Research and Experimental Validation

PDE models of tumors are often used in biomedical research laboratories to study theoretical mechanisms of tumors. Experimental scientists use these models to investigate biological hypotheses of nutrient competition, cell proliferation, and vascular remodeling. Computational simulations cut down on the amount of extensive animal experiments needed, as the results give some early predictions of tumor behavior. Treatment strategies can be studied in a laboratory environment.

Still, researchers can do so using a computer in order to analyze the treatment strategies before they go into the laboratory and incur the high cost of the experiments. These applications speed up cancer research and help to create new therapies. Applications of PDE modeling of spatial heterogeneity in tumor microenvironments can be found across a range of disciplines such as oncology, biomedical engineering, pharmaceutical sciences, and precision medicine. The models offer robust tools for comprehending tumor growth, improving therapeutic strategies, forecasting treatment outcomes, and enhancing personalized health approaches. Incorporating clinical data together with mathematical modeling and computationally generated simulations, PDE frameworks are playing a significant role in advancing cancer research and informing the development of more effective and targeted therapeutic interventions.

## 7. Discussion

In the present study, the spatial heterogeneity of the tumor microenvironments was studied with a system of coupled non-linear partial differential equations (PDEs). The mathematical model was able to capture the interplay between tumor cells, oxygen diffusion, nutrient transport, angiogenic signaling, and immune-related phenomena. The numerical simulations showed that the spatial variation of the biological and biochemical quantities inside the tissue domain plays a very strong role in the propagation of a tumor. The results offer valuable insights into the mechanisms that cause tumor heterogeneity, invasion, treatment resistance, and vascular adaptation. A key finding of the study is that the tumors develop heterogeneously, due to imbalanced oxygen and nutrient delivery. Based on the numerical results, the concentration of oxygen in the tumor center decreased markedly because of the high metabolic rate and restricted oxygen supply from the vessels. This decrease in oxygen level created hypoxic and necrotic areas, typical features of malignant tumors seen in clinical oncology. The model showed that oxygen consumption is not evenly distributed across the tumor, and that central regions of the tumor are dead while peripheral regions are very proliferative. These results corroborate the biological evidence that suggests hypoxia is a key component in tumor aggressiveness and therapeutic resistance. The reaction–diffusion model was an appropriate description of the process of tumor invasion and the irregularity of the tumor morphology evolution.

The invasion radius grew significantly with the growing diffusion coefficient of tumors, resulting in irregular and unstable tumor boundaries. These findings suggest that cellular migration and diffusion processes play an important role in the metastatic potential and in tissue infiltration. The irregular shapes that the simulations developed themselves into are reminiscent of invasive phenotypes like glioblastoma and metastatic breast cancer, in which the tumor cells penetrate healthy tissue in an extremely heterogeneous way. The results thus confirm the appropriateness of PDE methods for modeling complex spatial cancer dynamics. The other significant finding of the study is the involvement of a nutrient transport system in controlling tumor growth. The nutrient concentration profiles showed extensive depletion in areas of high cell density, such as tumor regions. As the nutrients decreased, the growth rates of the cells decreased, resulting in non-uniform proliferation patterns throughout the computational domain. The nutrient levels of peripheral areas of the tumor remained high due to the supplies of the vessels, and cellular growth continued. This spatial heterogeneity accounts for the presence of populations of proliferating, quiescent, and necrotic cells in tumors. The findings are consistent with previous biological research indicating that nutrient competition is one of the main factors leading to intratumoral heterogeneity. The angiogenesis simulations also illustrated the adaptive nature of tumors in response to hypoxia. As oxygen levels fell below the critical levels, the amount of angiogenic factors accumulated grew steadily. This resulted in increased vascular density inside the virtual domain of tissue. One of the key mechanisms for tumor survival is the feedback between hypoxia and angiogenesis. When cells are hypoxic, they secrete angiogenic factors that promote the growth of new blood vessels that increase oxygen and nutrient delivery to the damaged areas. The vasculature that is formed, though, is frequently irregular and inefficient, adding to the heterogeneous transport patterns. In conclusion, the discussion demonstrates that the use of PDE-based modeling is a powerful mathematical/computational framework for the understanding of the spatial heterogeneity in a tumor microenvironment. The results show that the interactions between diffusion, proliferation, hypoxia, and angiogenesis give rise to very complicated tumor behaviors that can have a significant impact on disease development and treatment efficacy. The study also brings a quantitative approach that can aid in predictive cancer modeling, therapy optimization, and precision medicine applications, paving the way for advancing computational oncology.

## 8. Conclusion

In this study, a detailed mathematical and computational model of spatial heterogeneity in the tumor microenvironment was developed, based on partial differential equations (PDEs). The model was able to incorporate the proliferation of tumor

cells, transport of oxygen, nutrients, angiogenesis, and immune-related interactions in a coupled non-linear reaction–diffusion system. The study was carried out numerically and using an equational approach to show that significant spatial variations in the biological factors can affect the progression of the tumor, the invasion pattern, the development of hypoxia, and the response to treatment. These findings indeed showed that tumor heterogeneity arises naturally due to the non-linear interactions between diffusion processes, metabolic consumption, vascular adaptation, and cellular proliferation. The oxygen consumption in the core of the tumors resulted in hypoxic and necrotic regions, and nutrient gradients created spatially distinct populations of proliferating and quiescent cells. The angiogenesis simulations also demonstrated how the tumors respond to the inhospitable microenvironmental conditions by promoting new blood vessel growth, which allows for continued tumor growth and invasion.

The numerical analysis showed that a higher tumor diffusivity contributed to higher invasive capability and irregular tumor boundaries, which are characterized by aggressive cancer phenotypes. The reliability and the computational robustness of the PDE framework were established by stability and convergence studies. The research also showed that the transport of the drug, its radiation sensitivity, and the effectiveness of the treatment can be greatly influenced by spatial heterogeneity, highlighting the need to include microenvironmental dynamics in predictive oncology models. In general, the results demonstrate the importance of PDE-based computational modeling for the understanding of the complex behavior of tumors, which is difficult to capture solely from experimental or clinical observations. The framework will lay the groundwork for future progress in computational oncology, precision medicine, treatment optimization, and personalized cancer therapy. The integration of mathematical modeling and biological understanding helps enhance quantitative cancer research and aid in therapeutic choices.

## 9. Recommendations

This study has led to several suggestions for future research and clinical practice: To capture tumor geometry and tissue structure more realistically, future studies are needed to build a three-dimensional PDE model. Simulations in three dimensions would give better visualization of the dynamics of tumor invasion and vascular growth.

1. Medical imaging data, particularly patient-specific data like MRI, CT, and PET imaging, should be incorporated into the PDE framework to enable personalized models of cancer and individualized treatment planning. Future models should be more physiologically accurate by incorporating additional biological mechanisms: mechanical stress, remodeling of the extracellular matrix, genetic mutations, and cellular signaling pathways.

2. Cytokine transport, immune suppression, and response to immunotherapy should be added to the advanced immune system interactions to understand tumor–immune heterogeneity better. The use of hybrid computational methods that integrate PDEs with artificial intelligence/machine learning methods to enhance parameter estimation, prediction accuracy, and adaptive therapy optimization should be investigated.

3. Future research should consider stochastic and multi-scale modeling approaches to account for the random behavior of cells and molecular interactions at the microenvironment level in the tumor. Calibrating model parameters and enhancing the translational accuracy of the computational predictions should be done with experimental validation through laboratory and clinical ONCO data.

4. Simulations of drug transport using PDE need to be expanded to assess targeted drug delivery systems, combination drugs, and nanoparticle therapies to counter therapeutic resistance. Model adaptation is required for specific cancer types that are known to have a critical role for spatial heterogeneity in disease progression, including glioblastoma, breast cancer, pancreatic cancer, and lung cancer. Create clinical decision-support systems using Computational Tumor Modeling to help oncologists make decisions about radiation planning, chemotherapy scheduling, and precision medicine applications. Overall, PDE modeling of the tumor microenvironment is a great interdisciplinary tool for understanding cancer complexity. In the modern era of oncologic medicine, continued development in mathematical modeling, computational simulation, and biomedical integration will create the capacity to predict tumor behavior, optimize treatments more effectively, and improve patient outcomes.

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