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Monte Carlo Simulation of a Nonlinear Subdiffusion Model of Tumor Invasion

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ABSTRACT: The main purpose of this work is to propose a nonlinear non-Markovian model of subdiffusive transportation that involves chemotactic substance affecting the cells' movement. In this case, both of the random waiting time and the escape rate are affected by a chemotactic gradient. We systematically derive the subdiffusive fractional master equation, then we consider the diffusive limit of the fractional master equation. Finally, a Monte-Carlo simulation is run for the model in order to analyse the role of the chemotactic gradient in the diffusion of particles.

Keywords: Subdiffusion, tumor invasion, Monte Carlo simulation.

Contents

1. Introduction

Tumor invasion is a defining hallmark of malignancy and one of the leading causes of cancer-related mortality, with more than 80% of clinical tumor patients dying from invasion and metastasis [1–3]. Certain aggressive cancers, such as gliomas, are capable of infiltrating surrounding tissues at an early stage, making complete surgical resection nearly impossible and leading to inevitable recurrence [4, 5]. The invasive capacity of tumor cells arises from the interplay between their intrinsic migratory properties and the characteristics of the surrounding host tissue microenvironment, including extracellular matrix (ECM) composition, matrix metalloproteinase (MMP) activity, nutrient gradients, and cell–cell adhesion forces [6, 7]. Directed migration toward ECM gradients (haptotaxis) and nutrient sources (chemotaxis), coupled with ECM degradation and modulation of adhesion receptors, can significantly alter the effective diffusion of tumor cells during invasion [8].

Classical reaction–diffusion models based on Fick's law assume that the mean squared displacement (MSD) scales with time as $t^{0.5}$ in homogeneous media. However, experimental evidence in cell biology frequently reveals anomalous diffusion, in which the MSD scales as t^{μ} with $\mu \neq 0.5$ [9, 10]. Subdiffusion ($0 \leq \mu \leq 0.5$) corresponds to slower-than-Fickian spreading and may result from microstructural heterogeneity, trapping effects, or intermittent motility. In the tumor invasion context, such subdiffusive patterns may be driven by complex ECM–cell interactions, intermittent immobilization, and phenotypic switching between motile and proliferative states [11, 12].

A major biological mechanism underlying anomalous transport in tumors is the migration proliferation dichotomy, also referred to as the "go-or-grow" hypothesis [13, 14]. In this paradigm, tumor cells alternate between a migratory phenotype (high motility, no division) and a proliferative phenotype (active division, no migration), with switching rates influenced by microenvironmental conditions such as oxygen and nutrient availability. Fedotov and Iomin [15] modeled this process using a two-component continuous-time random walk (CTRW) framework with general waiting-time distributions for each phenotype. They showed that heavy-tailed proliferative residence times can lead to anomalous subdiffusion of the invasion front, with front position scaling as $\langle r(t) \rangle \sim t^{\mu}$ for $0 < \mu < 1$ [15]. This behaviour arises from long trapping intervals in the proliferative state, which slow the net migration rate relative to classical diffusion models.

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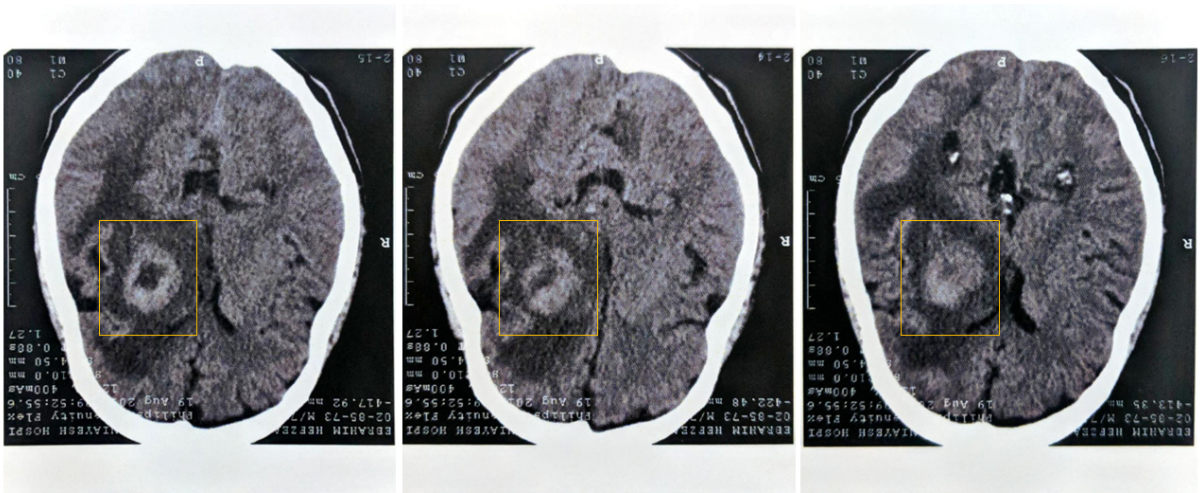

Figure 1: A cross-sectional image of a human brain showing the spread of a brain tumor.

To more fully capture these dynamics in complex tissue environments, Jiang et al. [6] developed a hybrid model combining random motility, haptotaxis, chemotaxis, adhesion, proliferation, and immune response effects. Their simulations demonstrated that tumor invasion can display subdiffusive, superdiffusive, or ballistic spreading depending on the relative strengths of these processes, with subdiffusion often emerging under biologically realistic conditions [6]. In addition to continuum and analytical approaches, Monte Carlo simulations have been used to investigate tumor invasion at the single-cell level, where each cell is represented as an agent that stochastically switches between migration and proliferation according to experimentally motivated waiting-time distributions [6, 15] [7,22]. Such discrete simulations allow direct measurement of scaling exponents, invasion front dynamics, and spatial heterogeneity, providing an independent check on anomalous subdiffusive behavior predicted by CTRW-based and hybrid PDE models.

Taken together, these studies underscore the inadequacy of traditional diffusion assumptions in describing tumor cell invasion and highlight the necessity of incorporating anomalous transport and phenotypic plasticity into predictive models. A more nuanced understanding of tumor diffusion dynamics not only enhances the mathematical fidelity of tumor growth simulations but also informs the design of targeted therapeutic strategies aimed at controlling invasive behavior.

In this work, our attempt is to use Monte Carlo method to simulate the subdiffusion of Tumor Invading in a nonhomologous media. This article is divided into three sections: The introduction, followed by section two, where we present our nonlinear non Markovian model, then the Monte Carlo simulation of this model.

2. Non-Markovian Anomalous Subdiffusion Model

In this section, we examine the growth dynamics of a tumor spheroid, characterized by a densely populated central core and a surrounding invasive zone with comparatively reduced cell density. Cellular motility within the invasive region exhibits a preferential outward, radial orientation away from the spheroid core. This directed migration is primarily governed by spatial heterogeneities in nutrient and oxygen availability, together with chemotactic gradient. The main aim now is to present a 3-Dimensional nonlinear (density dependence) non Markovian model for subdiffision of Tumor invasion. Then we take into account the affection of non homogenous media on the diffusion of the tumor. This study extends the work reported in [16] together with the use of the work in [17, 18].

At this stage, we assume a particle performs a random walk on a 2-Dimensional lattice, making instantaneous jumps of length a from location (x, y) after random waiting times T_{xy}. Falconer et. al. in [16] proposed a new modified escape rates with an additional nonlinear escape rate $\alpha(\rho)$, where

$\rho(x, y, t, \tau)$ is the density of particles at position (x, y) at time t been trapped for time τ. Therefore, the total escape rate is defined as

$$\lambda_\alpha = \lambda(x, y, t) + \alpha(\rho) \tag{2.1}$$

In order to formulate the master equation describing the evolution of the non-Markovian process, we define the structured particle number density $\xi(x, y, t, \tau)$. The balance equation of the model can be written as:

$$\frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -\lambda_\alpha \xi(x, y, t, \tau).$$

Applying the same technique in [16] implies that the fractional master equation (5.5) can be extended to two dimensions as

$$\begin{aligned}
\frac{\partial \rho}{\partial t} &= a\frac{\partial}{\partial x}\left[(\mathtt{L}-\mathtt{R})e^{\Phi(x,y,t)}\mathcal{D}_t^{1-\mu}\rho(x,y,t)e^{-\Phi(x,y,t)} + (\alpha_{\mathtt{L}}(\rho)-\alpha_{\mathtt{R}}(\rho))\rho(x,y,t)\right] \\
&+ \frac{a^2}{2}\frac{\partial^2}{\partial x^2}\left[(\mathtt{R}+\mathtt{L})e^{\Phi(x,y,t)}\mathcal{D}_t^{1-\mu}\rho(x,y,t)e^{\Phi(x,y,t)} + (\alpha_{\mathtt{R}}(\rho)+\alpha_{\mathtt{L}}(\rho))\rho(x,y,t)\right] \\
&+ a\frac{\partial}{\partial y}\left[(\mathtt{D}-\mathtt{U})e^{\Phi(x,y,t)}\mathcal{D}_t^{1-\mu}\rho(x,y,t)e^{-\Phi(x,y,t)} + (\alpha_{\mathtt{D}}(\rho)-\alpha_{\mathtt{U}}(\rho))\rho(x,y,t)\right] \\
&+ \frac{a^2}{2}\frac{\partial^2}{\partial y^2}\left[(\mathtt{U}+\mathtt{D})e^{\Phi(x,y,t)}\mathcal{D}_t^{1-\mu}\rho(x,y,t)e^{\Phi(x,y,t)} + (\alpha_{\mathtt{U}}(\rho)+\alpha_{\mathtt{D}}(\rho))\rho(x,y,t)\right],
\end{aligned} \tag{2.2}$$

where $\Phi(x, y, t) = -\int_0^t \alpha(\rho(x, y, t))dt$ represent the nonlinear exponential factor, and ($\mathtt{R}$, $\mathtt{L}$, $\mathtt{U}$, and $\mathtt{D}$) are the anomalous rate coefficients to each side (right, left, north and south, respectively).

On the other hand, Al-Sabbagh in [17] suggested a new modified escape rates that involve the chemotactic gradient as

$$\lambda_c = \lambda_\alpha + a\chi\Delta\mathtt{S} \tag{2.3}$$

where λ_α is the escape rate defied in 2.1, χ is the chemotaxis coefficient, and $\Delta\mathtt{S} = \mathtt{S}(x-a) - \mathtt{S}(x)$ is the chemotactic gradient. The escape rates (2.3) indicate that the chemotactic gradient $\Delta\mathtt{S}$ significantly influences the enhancement of subdiffusion to the right (when $\Delta\mathtt{S} \geq 0$) or to the left (when $\Delta\mathtt{S} < 0$). However, it has no effect on leaping to the left (if $\Delta\mathtt{S} \geq 0$) or to the right (if $\Delta\mathtt{S} < 0$); in other words, this model exhibits no symmetry regarding the chemotactic substance. The chemotactic gradient also affect the jump probabilities to each side. In this case, the fractional master equation is much more complicated and could be presented as an extension of equation (6.40) in[17].

In the next step, we employ the Monte Carlo method to simulate our models and compare the particle density on a two-dimensional lattice in two cases: the first without any chemical effect, and the second where the chemotactic substance influences the particles during the process.

3. Monte Carlo Simulation of a 3-Dimensional Subdiffusion Model

The Monte Carlo method provides a powerful computational framework for simulating stochastic processes, including anomalous transport phenomena such as subdiffusion. Standard simulation approaches employ a CTRW model. In the CTRW framework, subdiffusion emerges from a particle's trajectory governed by a heavy-tailed probability distribution of waiting times between successive spatial jumps [9]. The CTRW is a widely used Monte Carlo model for simulating subdiffusion. A particle's walk is defined by a sequence of jumps decoupled from a series of waiting times. To generate subdiffusive dynamics, the waiting times (τ) between jumps are drawn from a probability density function with a heavy, power-law tail. The occurrence of very long waiting times, which represent transient trapping events, is the microscopic origin of the macroscopic subdiffusive behavior. The simulation for an ensemble of particles involves iteratively drawing waiting times and jump lengths from their respective distributions to construct trajectories, from which observables like the MSD are calculated [19].

In this section, the Monte Carlo method is run to simulate the tumor invasion in two cases. The first where there is no chemical substance affecting the diffusion. In the second case, the attempt is to notice the influence of chemotaxis on the diffusion.

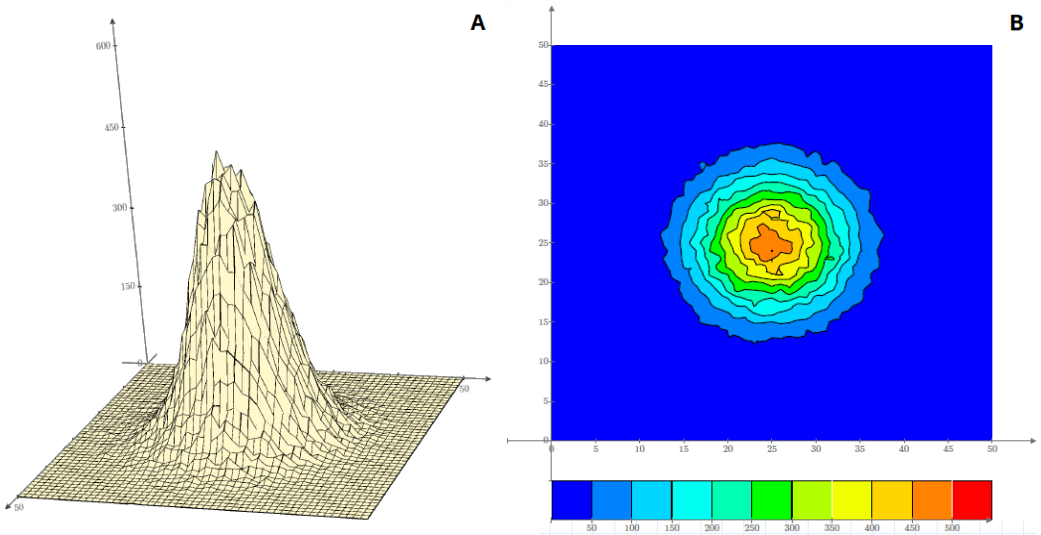

Figure 2: The aggregation of particles with no chemical reaction affecting the diffusion.

Figure2 (A and B) illustrates the distribution of particles in the absence of a chemotactic signal, where the spread remains nearly symmetric and isotropic, reflecting unbiased subdiffusion governed only by random waiting times and nonlinear density effects. In contrast, Figure3 (A and B) shows the distribution when a chemotactic gradient is introduced, producing a clear directional bias in particle movement. The symmetry observed in Figure2 is lost, and particles preferentially diffuse along the gradient, leading to enhanced accumulation in specific regions of the lattice. This comparison demonstrates that while subdiffusion alone yields slow but uniform spreading, the presence of chemotaxis significantly alters the invasion pattern, producing anisotropic diffusion more consistent with observed tumor invasion dynamics in heterogeneous biological environments.

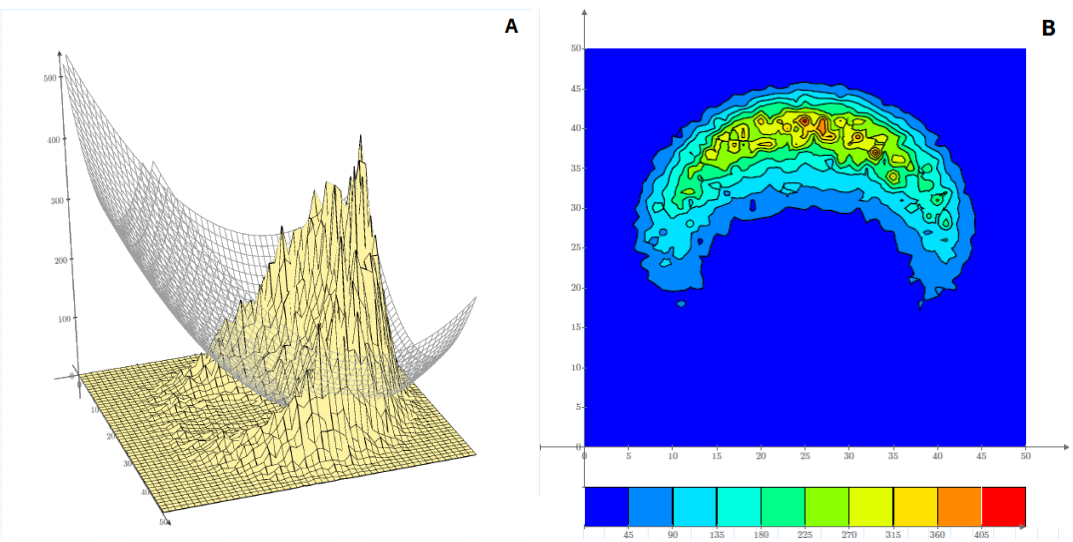

Figure 3: The distribution of particles with chemical reaction $S(x,y) = (x-25)^2 + (y-25)^2$ (gray mesh) affecting the diffusion, with chemotaxis coefficient $\chi = 2.76 \times 10^{-4}$[20].

4. Conclusions

This study introduced a nonlinear non-Markovian subdiffusion model of tumor invasion, incorporating density effects and chemotactic gradients. Monte Carlo simulations showed that in the absence of chemotaxis, particle spreading remains isotropic and anomalously slow, consistent with subdiffusive scaling $\langle r^2(t)\rangle \sim t^\mu (0 < \mu < 1)$. When a chemotactic gradient is present, the invasion pattern becomes anisotropic, with directional bias and preferential accumulation along the gradient. These findings indicate that while subdiffusion explains the slowed, heterogeneous nature of tumor spread, chemotaxis provides the directional drive observed in glioma invasion. Extending this framework to higher dimensions and integrating additional biological processes will further enhance its applicability to experimental and clinical contexts.

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