

# Non-Markovian models for migration-proliferation dichotomy of cancer cells: Anomalous switching and spreading rate

Sergei Fedotov,<sup>1</sup> Alexander Iomin,<sup>2</sup> and Lev Ryashko<sup>3</sup><sup>1</sup>*School of Mathematics, The University of Manchester, Manchester M60 1QD, United Kingdom*<sup>2</sup>*Department of Physics, Technion, Haifa 32000, Israel*<sup>3</sup>*Department of Mathematical Physics, Ural Federal University, Ekaterinburg, Russia*

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Proliferation and migration dichotomy of the tumor cell invasion is examined within two non-Markovian models. We consider the tumor spheroid, which consists of the tumor core with a high density of cells and the outer invasive zone. We distinguish two different regions of the outer invasive zone and develop models for both zones. In model I we analyze the near-core-outer region, where biased migration away from the tumor spheroid core takes place. We suggest non-Markovian switching between the migrating and proliferating phenotypes of tumor cells. Nonlinear master equations for mean densities of cancer cells of both phenotypes are derived. In *anomalous switching* case we estimate the average size of the near-core-outer region that corresponds to sublinear growth  $\langle r(t) \rangle \sim t^\mu$  for  $0 < \mu < 1$ . In model II we consider the outer zone, where the density of cancer cells is very low. We suggest an integrodifferential equation for the total density of cancer cells. For proliferation rate we use the classical logistic growth, while the migration of cells is subdiffusive. The exact formulas for the overall spreading rate of cancer cells are obtained by a hyperbolic scaling and Hamilton-Jacobi techniques.

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## I. INTRODUCTION

Clinical investigations of a glioma cancer show that the proliferation rate of migratory cells is essentially lower in the invasion region than in the tumor core [1,2]. This phenomenon is known as the *migration-proliferation dichotomy*. Proliferation and migration of cells are mutually exclusive: the high motility suppresses cell proliferation and vice versa. This finding triggered extensive theoretical studies that resulted in several phenomenological models [3–14]. A switching process between two phenotypes still is not well understood, and a lot of efforts are taken to develop relevant models with different mechanisms of switching of the glioma cells. It was suggested by Khain *et al.* [3,4] that the motility of cancer cells is a function of their density. Multiparametric modeling of the phenotype switching was considered in Ref. [5]. The agent-based approach to simulate multiscale glioma growth and invasion was used in Refs. [6,7]. Subdiffusive cancer development on a comb was studied in Ref. [8]. A stochastic approach for the proliferation-migration switching involving only two parameters was proposed in Refs. [9,10] where the transport of cancer cells was formulated in terms of a continuous time random walk (CTRW). A “go or grow” mechanism was proposed in Ref. [11], where the transition to invasive tumor phenotypes can be explained on the basis of the oxygen shortage in the environment of a growing tumor. Phenotypic switching due to density effect was also suggested in Refs. [12,13]. Both numerical and analytical approaches were developed in Ref. [14] to study the glioma propagation in the framework of reaction-diffusion equations, where the phenotype switching depends on oxygen in a threshold manner. Collective behavior of brain tumor cells under the hypoxia condition was studied in Ref. [15]. We should also mention the cellular automaton modeling for tumor invasion [16]. The multiscale approaches for modeling of tumor growth was reviewed in Ref. [17].

One of the main features of malignant brain cancer is the ability of tumor cells to invade the normal tissue away from the multicell tumor core, and the motility is the most critical feature of brain cancer, causing treatment failure [18]. The main problem in glioma treatment is how to distinguish the genuine boundaries of the invaded area. There is a need for a proper description of cancer cell motility. As shown in Refs. [19,20], and then verified in Refs. [9,10], the standard diffusion approximation for the transport together with a logistic growth yields an overestimation of the overall propagation rate. The main reason for employing the CTRW models [21–23], beyond the standard diffusion approximation, is to give the mesoscopic description of cell motility by taking into account memory effects [24] and anomalous dynamics of cell migration [25–27].

To describe a migration-proliferation dichotomy, one can use the standard phenomenological model involving reaction-diffusion equations. In this model one assumes that the cancer cells can be in two states: mobile state (migratory phenotype) and immobile state (proliferating phenotype). If we introduce the density of the cells of migrating phenotype,  $n_1(t, \mathbf{x})$ , and the density of the cells of proliferating phenotype,  $n_2(t, \mathbf{x})$ , then the system of equations can be written as

$$\frac{\partial n_1}{\partial t} + \nabla \cdot (vn_1) = \nabla \cdot (D\nabla n_1) - \beta_1 n_1 + \beta_2 n_2, \quad (1)$$

$$\frac{\partial n_2}{\partial t} = f(n)n_2 + \beta_1 n_1 - \beta_2 n_2, \quad (2)$$

where  $v$  is the advective velocity,  $D$  is the diffusion coefficient. The switching between two phenotypes is determined by the switching rates  $\beta_1$  and  $\beta_2$ . The nonlinear function  $f(n)$  is the proliferation rate, where  $n = n_1 + n_2$ . For example, the logistic growth rate corresponds to

$$f(n) = U \left[ 1 - \frac{n}{K} \right], \quad (3)$$

where  $U$  is the cell proliferation rate and  $K$  is the carrying capacity. It should be noted that the reaction-diffusion equations are standard and very effective tools for the analysis of cancer cell invasion involving diffusion and directed response of the cancer cells to extracellular matrix gradients (haptotaxis) and chemoattractants gradient (chemotaxis) [28–32]. In particular, we mention the “acid-mediated tumor invasion” models [33–35] in which tumor cells create an acidic environment leading to normal cell death and subsequent tumor invasion.

In our recent papers [9,10] we suggested a model for tumor cell invasion involving non-Markovian anomalous transport and Markovian phenotype switching. The main idea was to use a mesoscopic approach for the cell transport involving the CTRW. We have taken into account the subdiffusive behavior of cell transport, which leads to an essential decrease in cell mobility. The resulting master equations for cell densities are nonlocal in time and space,

$$\frac{\partial n_1}{\partial t} = \int_0^t \int_{R^d} \alpha(t-t') [n_1(t', \mathbf{x} - \mathbf{z}) - n_1(t', \mathbf{x})] \times \rho(\mathbf{z}) d\mathbf{z} dt' - \beta_1 n_1 + \beta_2 n_2, \quad (4)$$

$$\frac{\partial n_2}{\partial t} = f(n) n_2 + \beta_1 n_1 - \beta_2 n_2. \quad (5)$$

The memory kernel  $\alpha(t)$  is defined in terms of its Laplace transform:

$$\tilde{\alpha}(s) = \frac{(s + \beta_1) \tilde{\psi}(s + \beta_1)}{1 - \tilde{\psi}(s + \beta_1)}, \quad (6)$$

and establishes the relationship between the transport memory kernel  $\alpha(t)$  and the waiting-time probability distribution function (PDF)  $\psi(t)$  for jumps in terms of their Laplace transforms. The jump lengths are described by the PDF  $\rho(\mathbf{z})$ . The phenotype switching process in Eqs. (4) and (5) is continuous time Markov chain with rates  $\beta_1$  and  $\beta_2$ .

The purpose of this paper is to develop two alternative models of the migration-proliferation dichotomy. In the first model (in the sequel model I) we take into account the *anomalous switching* between two phenotypes of cancer cells in a closed vicinity of the tumor core. This anomalous switching was neglected in our previous models [9,10]. The second model (model II) describes front propagation of glioma cells on the boundary edge of the tumor development. In this case, one concerns with the reduction of the system of equations (4) and (5) to a single equation for a total density  $n = n_1 + n_2$ . The advantage of this reduction is the possibility to find the exact expression for the rate of glioma invasion.

## II. MODEL I: NON-MARKOVIAN PROLIFERATION-MIGRATION SWITCHING

In this section we consider the growing tumor spheroid, which consists of the tumor core with a high density of cells and the outer invasive zone where the cell density is smaller than in the tumor spheroid core. The mobile cells are biased to migrate away from the tumor spheroid core. The main reasons for this radial motility are the nonuniform nutrient, oxygen concentration and the gradient of cell adhesion sites. In the general case the advection term in Eq. (1) involves a position and time dependent velocity field. In what follows,

we assume for simplicity that the cells migrate with a constant velocity  $v$ . To validate this assumption, one can consider the case when the density of the proliferating cancer cells is very low in the outer region and the nutrition process can be considered as a time independent process with a constant gradient. It should be also noted that simplicity does not mean triviality. Indeed, the velocity of cell migration is assumed to be constant due to the following reasons. In general, chemotaxis, haptotaxis, and fluctuations in the nutrition transport are extremely complicated processes that take place simultaneously. Therefore for long-time window averaging it is physically reasonable to take into account only the average constant advection velocity. This simplification makes it possible to analyze the system analytically without missing the main details of the anomalous transport.

Unlike in our previous works [9,10], in model I we will focus on the *non-Markovian* switching process (proliferation and migration). The Markovian assumption has previously been made for mathematical convenience. Here our intention is to develop a more realistic theory for the phenotype switching. We adopt the following stochastic model for migration-proliferation dichotomy. The individual cell moves with the speed  $v$  along the radial direction during random time  $T_1$  before switching to the proliferating state. A cell spends a random time  $T_2$  in the proliferating state before switching to the migrating state again. We denote the “migrating” time PDF by  $\psi_1(\tau)$  and the residence time PDF for the proliferating state by  $\psi_2(\tau)$ .

The Markovian model with switching rates  $\beta_1$  and  $\beta_2$  corresponds to the exponential time PDF’s  $\psi_k(\tau) = \beta_k \exp(-\beta_k \tau)$ ,  $k = 1, 2$ . The balance equations for the mean densities  $n_1(t, r)$  and  $n_2(t, r)$  are

$$\begin{aligned} \frac{\partial n_1}{\partial t} + v \frac{\partial n_1}{\partial r} &= -\beta_1 n_1 + \beta_2 n_2, \\ \frac{\partial n_2}{\partial t} &= f(n) n_2 + \beta_1 n_1 - \beta_2 n_2, \end{aligned}$$

where  $r$  is the radial distance from a point to the origin (the center of tumor core).

In what follows we consider arbitrary time PDF’s  $\psi_k(\tau)$  including power law distributions. In this non-Markovian case the balance equations for the densities can be written as a system of integrodifferential equations,

$$\frac{\partial n_1}{\partial t} + v \frac{\partial n_1}{\partial r} = -i_1(t, r) + i_2(t, r), \quad (7)$$

$$\frac{\partial n_2}{\partial t} = f(n) n_2 - i_2(t, r) + i_1(t, r), \quad (8)$$

where  $i_1(t, r)$  and  $i_2(t, r)$  describe the phenotype switching rates between migrating and proliferating populations:

$$i_1(t, r) = \int_0^t I_1(t-t') n_1(t', r - v(t-t')) dt', \quad (9)$$

$$i_2(t, r) = \int_0^t I_2(t-t') n_2(t', r) e^{\int_{t'}^t f(n(s, r)) ds} dt'. \quad (10)$$

Derivation of integrodifferential equations (7)–(10) is presented in the next subsection. Note that this non-Markovian motility model can be used for the analysis of experimental time series for trajectories of cells that have the memory [24].

It should be noted that the diffusion term  $D\partial^2 n_1/\partial r^2$  can be also taken into account by modifying Eqs. (7) and (9). The memory kernel  $I_i(t)$  is defined by the following ratio:

$$\tilde{I}_k(s) = \frac{\tilde{\psi}_k(s)}{\tilde{\Phi}_k(s)}, \quad k = 1, 2. \quad (11)$$

Here  $\tilde{\psi}_k(s)$  and  $\tilde{\Phi}_k(s)$  are the Laplace transforms of residence time PDF's  $\psi_k(\tau)$  and survival probability  $\Phi_k(t) = \int_t^\infty \psi_k(\tau) d\tau$  correspondingly. The switching rate  $i_1(t, r)$  describes the average flux of cells from migrating state to proliferating state. The characteristic feature of the flux of cells from proliferating state to migrating state  $i_2(t, r)$  is that it depends on proliferating rate  $f(n)$  [36,37]. This phenomenon does not exist in the Markovian case for which  $\psi_k(\tau) = \beta_k \exp(-\beta_k \tau)$  and the memory kernel is the  $\delta$  function,

$$I_k(t) = \beta_k \delta(t). \quad (12)$$

In this case, it follows from Eqs. (9), (10), and (12) that

$$i_k(t, r) = \beta_k n_k(t, r), \quad k = 1, 2. \quad (13)$$

#### A. Markovian model with structured densities

The purpose of this subsection is to formulate the Markovian model for the transport and reactions of cancer cells and derive non-Markovian master equations (7) and (8) with Eqs. (9) and (10). One can introduce transition probabilities  $\beta_1(\tau)$  and  $\beta_2(\tau)$  that depend on the residence time  $\tau$  in the migrating and proliferating states correspondingly [38]. It is also convenient to introduce the structured densities of cancer cells that depend on  $\tau$  [39]. Let  $\xi_1(t, \tau, r)$  be the density of migrating cells at time  $t$  at point  $r$  whose residence time in the migrating state lies in the interval  $(\tau, \tau + d\tau)$ . The corresponding density of cells in proliferating state  $\xi_2(t, \tau, r)$ . The obvious purpose of introduction of additional variable  $\tau$  is to set up the Markovian model for densities  $\xi_k(t, \tau, r)$ . We assume that initial conditions are

$$\xi_k(0, \tau, r) = n_k^0(r) \delta(\tau), \quad k = 1, 2, \quad (14)$$

where  $n_k^0(x)$  is the initial densities of cancer cells, so

$$0 \leq \tau \leq t.$$

Integration of structured densities  $\xi_k(t, \tau, r)$  over residence time variable  $\tau$  gives the mean densities [39]

$$n_k(t, r) = \int_0^t \xi_k(t, \tau, r) d\tau, \quad k = 1, 2. \quad (15)$$

Phenotype switching rates  $i_1(t, r)$  and  $i_2(t, r)$  in Eq. (7), (8) can be defined as

$$i_k(t, r) = \int_0^t \beta_k(\tau) \xi_k(t, \tau, r) d\tau, \quad k = 1, 2. \quad (16)$$

The meaning of Eq. (16) is that the product  $\beta_k(\tau) \xi_k(t, \tau, r)$  is the rate corresponding to a particular residence time  $\tau$ . To get the total rate  $i_k(t, r)$  we need to integrate  $\beta_k \xi_k$  over variable  $\tau$  from 0 to  $t$ . It follows from Eqs. (15) and (16) that for  $\beta_k = \text{const}$ , we have  $i_k(t, r) = \beta_k n_k(t, r)$ . The purpose now is to express  $i_1$  and  $i_2$  in terms of the mean densities  $n_1$  and  $n_2$ , when  $\beta_k(\tau)$

depends on  $\tau$ . We note that the boundary conditions at  $\tau = 0$  are

$$i_1(t, r) = \xi_2(t, 0, r), \quad i_2(t, r) = \xi_1(t, 0, r). \quad (17)$$

Let us formulate Markovian balance equations for structured densities  $\xi_1(t, \tau, r)$  and  $\xi_2(t, \tau, r)$ :

*For a migrating state*

$$\frac{\partial \xi_1}{\partial t} + \frac{\partial \xi_1}{\partial \tau} + v \frac{\partial \xi_1}{\partial r} = -\beta_1(\tau) \xi_1, \quad (18)$$

*For a proliferating state*

$$\frac{\partial \xi_2}{\partial t} + \frac{\partial \xi_2}{\partial \tau} = -\beta_2(\tau) \xi_2 + f(n) \xi_2. \quad (19)$$

Using the method of characteristics, we obtain the solutions to Eqs. (18) and (19):

*For a migrating state* ( $0 \leq \tau < t$ )

$$\xi_1(t, \tau, r) = \xi_1(t - \tau, 0, r - v\tau) e^{-\int_0^\tau \beta_1(s) ds}. \quad (20)$$

*For a proliferating state* ( $0 \leq \tau < t$ )

$$\xi_2(t, \tau, r) = \xi_2(t - \tau, 0, r) e^{-\int_0^\tau \beta_2(s) ds + \int_{t-\tau}^t f(n(s, r)) ds}. \quad (21)$$

Both solutions (20) and (21) involve a common exponential factor that can be interpreted as the survival function  $\Psi_k(\tau)$ :

$$\Psi_k(\tau) = e^{-\int_0^\tau \beta_k(s) ds}, \quad k = 1, 2. \quad (22)$$

Taking into account the boundary conditions (17) and (22) we can write

$$\xi_1(t, \tau, r) = i_2(t - \tau, r - v\tau) \Psi_1(\tau), \quad (23)$$

and

$$\xi_2(t, \tau, r) = i_1(t - \tau, r) \Psi_2(\tau) e^{\int_{t-\tau}^t f(n(s, r)) ds}. \quad (24)$$

Note that the residence time PDF  $\psi_k(\tau) = \dot{\Psi}_k(\tau)$  can be written in terms of the transition rate  $\beta_k(\tau)$  as follows [38]:

$$\psi_k(\tau) = \beta_k(\tau) e^{-\int_0^\tau \beta_k(s) ds}, \quad k = 1, 2. \quad (25)$$

The next step is the derivation of integral equations for  $i_k(t, r)$  and  $n_k(t, r)$  (similar equations were postulated in Ref. [40]) from which the explicit expressions for  $i_k(t, r)$ ,  $k = 1, 2$ , Eqs. (9) and (10), can be found (see the Appendix).

#### B. Anomalous switching and sub-ballistic motion

In this subsection we determine an average position of a migrating cancer cell ( $r(t)$ ). Since the cancer cell proliferation depends on many various conditions, we assume that a characteristic proliferating residence time scale is absent. Therefore the residence time PDF  $\psi_2(\tau)$  for proliferating state behaves like a power law,

$$\psi_2(\tau) \sim \left(\frac{\tau_2}{\tau}\right)^{1+\mu}, \quad 0 < \mu < 1, \quad (26)$$

as  $\tau \rightarrow \infty$ . Here  $\tau_2$  is a parameter with units of time. Contrary to the proliferating process, an average transport time is finite. Therefore we assume that the residence time PDF  $\psi_1(\tau)$  is exponential:

$$\psi_1(\tau) = \beta_1 e^{-\beta_1 \tau},$$

where  $\beta_1$  is constant. The Laplace transform of  $\psi_1(\tau)$  is

$$\tilde{\psi}_1(s) = \frac{\beta_1}{\beta_1 + s}. \quad (27)$$

The purpose now is to show that if the mobile cells move with a constant velocity  $v$  along the radial direction, then the mean cell position  $\langle r(t) \rangle$  increases as  $t^\mu$  for  $0 < \mu < 1$  (anomalous advection or sub-ballistic motion). Note that experimental data [25,26] show anomalous sub-ballistic superdiffusive dynamics of cell migration.

The Laplace transform  $\tilde{\psi}_2(s)$  corresponding to Eq. (26) can be approximated by

$$\tilde{\psi}_2(s) \sim 1 - (\tau_2 s)^\mu, \quad 0 < \mu < 1 \quad (28)$$

for small  $s$ . The mean waiting time  $\langle \tau \rangle = \int_0^\infty \tau \psi_2(\tau) d\tau$  is infinite in this case.

To find the average position  $\langle r(t) \rangle$  of cancer cells for large time asymptotic  $t \rightarrow \infty$ , we use the following idea. For a small proliferation rate  $f(n)$ , the average position  $\langle r(t) \rangle$  can be found as the product of the average number of jumps  $\langle N(t) \rangle$  from proliferating state to migrating state and the distance  $v\langle T \rangle$ , where  $\langle T \rangle = \beta_1^{-1}$  is the average time spent in a migrating state. Then

$$\langle r(t) \rangle = \frac{v\langle N(t) \rangle}{\beta_1}.$$

It is well known from the renewal theory, e.g., [38,41], that the Laplace transform of  $P(n, t) = \text{Pr}[N(t) = n]$  is

$$\tilde{P}(n, s) = \frac{\tilde{\psi}_2^n(s)[1 - \tilde{\psi}_2(s)]}{s}. \quad (29)$$

The Laplace transform of the average number of jumps from proliferating state  $\langle N(t) \rangle$  is

$$\langle \tilde{N}(s) \rangle = \sum_{n=0}^{\infty} n \tilde{P}(n, s) = \frac{\tilde{\psi}_2(s)}{s[1 - \tilde{\psi}_2(s)]}.$$

It follows from Eq. (28) that  $\langle \tilde{N}(s) \rangle \sim \tau_2^{-\mu} s^{-(1+\mu)}$  as  $s \rightarrow 0$  and

$$\langle N(t) \rangle \sim \frac{t^\mu}{\Gamma(1 + \mu)\tau_2^\mu}.$$

Finally, in the limit  $t \rightarrow \infty$  the average position of cancer cell is

$$\langle r(t) \rangle \sim \frac{vt^\mu}{\Gamma(1 + \mu)\beta_1\tau_2^\mu}, \quad 0 < \mu < 1, \quad (30)$$

which is sublinear. One can show that  $\langle r^2(t) \rangle \sim t^{2\mu}$ . This is due to *anomalous switching* [42] described by proliferating residence time PDF (26) with infinite mean residence time. Note that these results can be obtained directly from the non-Markovian balance equations (7)–(10). Our interpretation of Eq. (30) is that the average size of the near-core-outer region grows as  $t^\mu$ . This anomalous advection reflects the memory effect corresponding to cell trapping in the proliferating state. Of course,  $\mu = 1$  corresponds to the ballistic motion of cancer cells. Another specific property of the anomalous advection is superdiffusion of cancer cells for  $1/2 < \mu < 1$ , when the mean squared displacement (MSD)  $\langle r^2(t) \rangle \sim t^{2\mu}$ . Subballistic superdiffusive behavior of the MSD in time was observed in

experiments on wild-type and mutated epithelial cells [25] and cancer cells [26]. It should be noted that these anomalous properties of cell transport have been previously explained by the fractional Klein-Kramers equation for the PDF of the velocity and position of a particle [25]. This equation assumes a power-law decaying autocorrelation function  $\langle v(t)v(0) \rangle$  for a velocity  $v(t)$ , which implies the superdiffusive behavior of the mean squared displacement. It follows from the standard equation  $d\langle r^2(t) \rangle/dt = 2 \int_0^t \langle v(t)v(0) \rangle dt$ . Note that sublinear dependence of the first moment  $\langle r(t) \rangle$  and superdiffusive behavior of the second moment  $\langle r^2(t) \rangle$  can be also obtained by using the Galilei variant fractional diffusion-advection equation (FDAE) (see details on pp. 33–35 of Ref. [22] and see Ref. [27]). In this paper we offer an alternative explanation of sub-ballistic superdiffusive transport based on the two-state model with anomalous switching with the exponent  $\mu$  in the interval  $1/2 < \mu < 1$ . It would be also interesting to consider the phenomenon when the MSD undergoes a transition from subdiffusive to superdiffusive behavior with time [43].

### III. MODEL II: NON-MARKOVIAN TRANSPORT WITH MEMORY

In this section we are concerned with the problem of cancer cells spreading in the outer invasive zone of the growing tumor spheroid where the density of cells is very low. For the logistic growth rate (3), this outer zone determines the rate at which total population of cancer cells spreads. In this region we can neglect the biased movement of cancer cells and consider only transport along the radial direction in diffusion approximation. By assuming the general form of waiting time PDF  $\psi(t)$  for jumps, we deal with non-Markovian transport. The curvature effects can be also neglected. Effectively we consider the plane front propagation. Here we adopt the idea of the local equilibrium of the switching process. The densities  $n_1(t, r)$  and  $n_2(t, r)$  can be written in terms of the total density  $n(t, r) = n_1(t, r) + n_2(t, r)$  as follows:

$$n_1(t, r) = p_1 n(t, r), \quad n_2(t, r) = p_2 n(t, r), \quad (31)$$

where  $p_1 + p_2 = 1$ . The governing equation for  $n$  is

$$\frac{\partial n}{\partial t} = \frac{p_1 \sigma^2}{2d} \frac{\partial^2}{\partial r^2} \int_0^t K_n(t, t') n(t', r) dt' + p_2 U n \left( 1 - \frac{n}{K} \right), \quad (32)$$

where  $\sigma^2$  is the variance of jumps PDF  $\rho(\mathbf{r})$  and  $d$  is the dimension. This equation tells us that the rate of change of the total density  $n$  depends on transport and proliferating terms with corresponding weights  $p_1$  and  $p_2$ . It follows from the general theory [44–48] that the transport kernel  $K_n(t, t')$  depends on the proliferation term and can be written in two different forms:

$$K_n(t, t') = K_0(t - t') e^{p_2 U \int_{t'}^t (1 - n(s, r)/K) ds} \quad (33)$$

and

$$K_n(t, t') = K_0(t - t') e^{-(p_2 U/K) \int_{t'}^t n(s, r) ds}, \quad (34)$$

where  $K_0(t)$  is defined in terms of its Laplace transform,

$$\tilde{K}_0(H) = \int_0^\infty K_0(t)e^{-Ht} dt = \frac{H\tilde{\psi}(H)}{1 - \tilde{\psi}(H)}.$$

The last formula establishes the relationship between  $K_0(t)$  and  $\psi(t)$  [22]. The reason why we use the notation  $H$  for the Laplace variable instead of the standard notation  $s$  will be explained in the next subsection.

The first kernel (33) corresponds to the case when the “new-born” cancer cells have the same waiting time PDF as their “parents.” In the second case (34), when a new cancer cell is produced, it is given a new waiting time for a jump (see details in Ref. [23]). Non-Markovian reaction-transport equation (32) can be considered as phenomenological integrodifferential equation that takes into account transport memory effects. Equation (32) can be also derived from Eqs. (4) and (5) together with Eqs. (3) and (31) under diffusion approximation.

As an example, consider subdiffusive transport for which the waiting time pdf  $\psi(t)$  has a power-law tail:  $\psi(t) \sim (\tau_0/t)^{1+\alpha}$  with  $0 < \alpha < 1$  as  $t \rightarrow \infty$  [22]. One can use the following expression for the survival probability  $\Psi(t) = \int_t^\infty \psi(t)dt$  :

$$\Psi(t) = E_\alpha \left[ - \left( \frac{t}{\tau_0} \right)^\alpha \right], \quad 0 < \alpha < 1, \quad (35)$$

where  $E_\alpha[x] = \sum_0^\infty x^n / \Gamma(\alpha n + 1)$  is the Mittag-Leffler function. The Laplace transform of  $\psi(t)$  is

$$\tilde{\psi}(H) = \int_0^\infty \psi(t)e^{-Ht} dt = \frac{1}{1 + (\tau_0 H)^\alpha} \quad (36)$$

and therefore the Laplace transform of the memory kernel is

$$\tilde{K}_0(H) = \frac{H^{1-\alpha}}{\tau_0^\alpha}. \quad (37)$$

Equation (32) with the kernel (33) takes the form of fractional equation

$$\frac{\partial n}{\partial t} = p_1 D_\alpha \frac{\partial^2}{\partial r^2} \left\{ e^{p_2 U \int_0^t (1-n(s,r)/K) ds} D_t^{1-\alpha} [n(t,r)] \times e^{-U \int_0^t (1-n(s,r)/K) ds} \right\} + p_2 U n(1 - n/K), \quad (38)$$

where  $D_\alpha = \sigma^2/2d\tau_0^\alpha$  is the anomalous diffusivity and  $D_t^{1-\alpha}$  is the Riemann-Liouville fractional derivative defined as

$$D_t^{1-\alpha} n(t,r) = \frac{1}{\Gamma(1-\alpha)} \frac{\partial}{\partial t} \int_0^t \frac{n(\tau,r) d\tau}{(t-\tau)^\alpha}.$$

### A. Cancer spreading rate

Equations (32) and (38) allow us to find the exact formula for the overall rate  $u$  at which cancer cells spread. For the classical Fisher equation with frontlike initial condition, the propagation rate is  $u = 2\sqrt{DU}$ , where  $D$  is the diffusion coefficient and  $U$  is the proliferation rate [49]. The speed of this front is determined by the leading edge of the cells profile where the density is very small. The main aim of this subsection is to find the dependence of this propagation rate on the second moment for random jumps  $\sigma^2$  and memory kernel (33). We find the rate  $u$  without resolving the shape of the traveling waves [23]. Here we use a standard technique of

hyperbolic scaling  $r \rightarrow r/\varepsilon, t \rightarrow t/\varepsilon$ . The density  $n^\varepsilon(t,r) = n(t/\varepsilon, r/\varepsilon)$  can be written in the exponential form

$$n^\varepsilon(t,r) = A_0 \exp \left( - \frac{G^\varepsilon(t,r)}{\varepsilon} \right), \quad (39)$$

where  $A_0$  is a constant. The non-negative function  $G^\varepsilon(t,r)$  determines the position of the front in the limit  $\varepsilon \rightarrow 0$ . It follows from Eq. (39) that the equation

$$\lim_{\varepsilon \rightarrow 0} G^\varepsilon(t,r(t)) = 0 \quad (40)$$

gives us the spreading front position  $r(t)$  in the long-time and large-distance limit [23]. Substitution of the exponential transformation (39) into Eq. (32) with kernel (33) yields the integrodifferential equation for  $G(t,r) = \lim_{\varepsilon \rightarrow 0} G^\varepsilon(t,r)$ ,

$$\frac{\partial G}{\partial t} + \frac{p_1 \sigma^2}{6} \left( \frac{\partial G}{\partial r} \right)^2 \int_0^\infty K(s) \exp \left( s \left[ \frac{\partial G}{\partial t} + p_2 U \right] \right) ds + p_2 U = 0. \quad (41)$$

We interpret  $G(t,r)$  as the action function such that

$$H = - \frac{\partial G}{\partial t}, \quad p = \frac{\partial G}{\partial r} \quad (42)$$

are the Hamiltonian and the generalized momentum. It should be noted that the Hamiltonian  $H$  plays the role of the Laplace variable. Equation (41) is the Hamilton-Jacobi equation, which can be rewritten as

$$\frac{\partial G}{\partial t} + H \left( \frac{\partial G}{\partial r} \right) = 0, \quad (43)$$

where

$$H(p) = \frac{p_1 \sigma^2}{6} p^2 \tilde{K}_0(H - p_2 U) + p_2 U. \quad (44)$$

For the memory kernel (34) we find that the Hamiltonian is

$$H(p) = \frac{p_1 \sigma^2}{6} p^2 \tilde{K}_0(H) + p_2 U. \quad (45)$$

The overall propagation rate  $u$  can be found from Ref. [23]

$$u = \frac{\partial H}{\partial p} = \frac{H}{p}. \quad (46)$$

### 1. Markovian case

For the Markovian case when the waiting time PDF is exponential,

$$\psi(t) = \lambda \exp(-\lambda t), \quad (47)$$

we obtain  $\tilde{\psi}(H) = \lambda/(\lambda + H)$ . Therefore the Laplace transform of memory kernel is constant, that is  $\tilde{K}_0(H) = \lambda = \text{const}$ . In this case the Hamiltonian in Eq. (44) is

$$H = p_1 D p^2 + p_2 U \quad (48)$$

with the diffusion coefficient  $D = \lambda \sigma^2/6$ . We find from Eq. (46) that

$$p = \sqrt{\frac{p_2 U}{p_1 D}}, \quad H = 2p_2 U. \quad (49)$$

The overall front propagation rate is

$$u = 2\sqrt{p_1 p_2 U D}. \quad (50)$$

For  $p_1 = p_2 = 1/2$ , this result yields a half of the classical Fisher–Kolmogorov–Petrovskii–Piskunov (FKPP) formula [23].

## 2. Non-Markovian anomalous case

Now we consider the power-law distribution for the waiting time PDF,

$$\psi(t) \sim (t/\tau_0)^{-1-\alpha}, \quad 0 < \alpha < 1, \quad (51)$$

as  $t \rightarrow \infty$ . Using Eqs. (37) and (44), one can obtain the Hamiltonian in subdiffusive case:

$$H(p) = p_1 D_\alpha (H - p_2 U)^{1-\alpha} p^2 + p_2 U, \quad (52)$$

where  $D_\alpha = \sigma^2/6\tau_0^\alpha$  is a generalized diffusion coefficient. First we find from Eq. (52) the momentum  $p$  as the function of the Hamiltonian  $H$ ,

$$p(H) = \sqrt{\frac{H - p_2 U}{p_1 D_\alpha (H - p_2 U)^{1-\alpha}}}. \quad (53)$$

This expression together with Eq. (46) gives us the equation for  $H$ ,

$$H \frac{d \ln p(H)}{dH} = 1. \quad (54)$$

We obtain

$$p = \sqrt{\frac{(\alpha p_2 U)^\alpha}{(2-\alpha)^\alpha p_1 D}}, \quad H = \frac{2p_2 U}{2-\alpha}. \quad (55)$$

So the cancer spreading rate  $u = H/p$  is

$$u = 2\sqrt{\frac{(p_2 U)^{2-\alpha} p_1 D_\alpha}{(2-\alpha)^{2-\alpha} \alpha^\alpha}}. \quad (56)$$

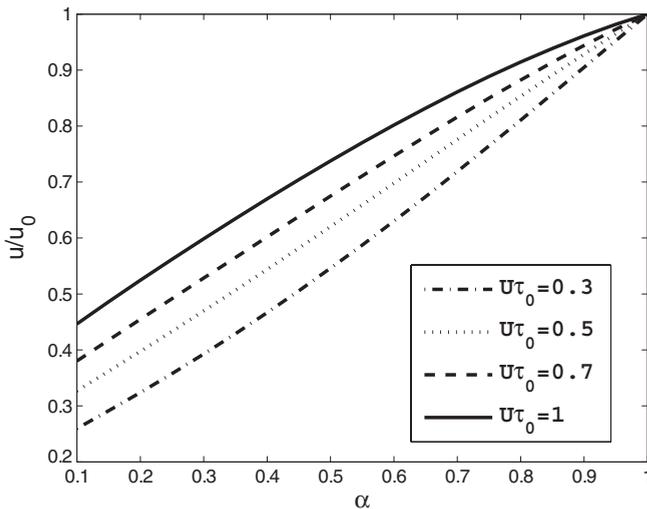


FIG. 1. The ratio of anomalous spreading rate  $u$  given by Eq. (56) and classical diffusion propagation rate  $u_0 = 2\sqrt{p_1 p_2 U D}$  vs anomalous exponent  $\alpha$  for  $p_1 = 0.5$ ,  $\lambda\tau_0 = 1$ , and  $U\tau_0 = [0.3, 0.5, 0.7, 1]$ .

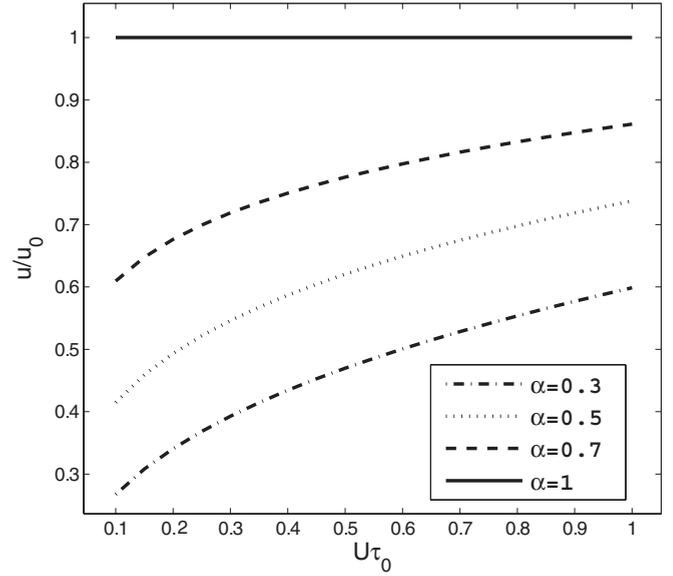


FIG. 2. The ratio of anomalous spreading rate  $u$  given by Eq. (56) and classical diffusion propagation rate  $u_0 = 2\sqrt{p_1 p_2 U D}$  vs dimensionless cell proliferation rate  $U\tau_0$  for  $p_1 = 0.5$ ,  $\lambda\tau_0 = 1$ , and  $\alpha = [0.3, 0.5, 0.7, 1]$ .

For the kernel (34) the Hamiltonian is  $H(p) = p_1 D_\alpha H^{1-\alpha} p^2 + p_2 U$ . One can find the following propagation rate:

$$u = \sqrt{\frac{(p_2 U)^{2-\alpha} p_1 D_\alpha (3-\alpha)^{3-\alpha}}{(2-\alpha)^{2-\alpha}}}, \quad (57)$$

which is slightly different from Eq. (56). For  $\alpha = 1$  and  $\lambda\tau_0 = 1$  both formulas coincide with Eq. (50). It is convenient to rescale anomalous propagation rate  $u$  by the rate of the standard front propagation  $u_0 = 2\sqrt{p_1 p_2 U D}$ . Figure 1 shows the ratio  $u/u_0$  as the function of anomalous parameter  $\alpha$ . It is clear that the subdiffusion decreases the effective propagation rate compared to the classical diffusion. For small  $\alpha \sim 0.2$ , the reduction of propagation rate is more than 50%. An interesting feature of both formulas is the dependence of the propagation rate  $u$  on the proliferation rate  $U$  and anomalous exponent  $\alpha$ :  $u \sim U^{(2-\alpha)/2}$ . Figure 2 demonstrates the dependence of the rescaled front propagation rate on the dimensionless cell proliferation rate  $U\tau_0$ . One can see from Eq. (56) and Fig. 2 that the front propagation rate is a monotonically increasing function of the proliferation rate  $U$  and is strongly affected by the subdiffusion parameter  $\alpha$ . It should be noted that the propagation rate for some subdiffusion-reaction systems can be zero for subdiffusive transport [50–52]. The discussion of this issue can be found in Ref. [53].

## IV. CONCLUSIONS

We have developed two non-Markovian models for a *migration-proliferation dichotomy* in the spreading of tumor cells in the invasive zone. In the migratory state the cells move without proliferation, while in the proliferating state the cancer cells do not migrate. We have considered the growing tumor spheroid, which consists of the tumor core

with a high density of cells and the outer invasive zone. We have distinguished two different regions of the outer invasive zone and suggested two corresponding models: model I and model II.

In model I we have considered the near-core-outer region, where biased migration away from the tumor spheroid core takes place. Previous works by the authors [9,10] have neglected non-Markovian switching between migrating and proliferating phenotypes of cancer cells. In the present model we have taken into account anomalous switching and derived corresponding nonlinear master equations for mean densities of cells of both phenotypes. This non-Markovian motility model can be used for the analysis of experimental time series for trajectories of cells with memory [24]. We have been able to estimate the average size of the near-core-outer region that corresponds to sublinear growth in time:  $\langle r(t) \rangle \sim t^\mu$  for  $0 < \mu < 1$ . Straightforward measurements of  $r(t)$  *in vitro* experiments, probably, make it possible to estimate parameters of switching between the two phenotypes. It should be noted that superdiffusive behavior of cell transport has been previously explained by the fractional Klein-Kramers equation [25] or the Galilei variant fractional diffusion-advection equation (FDAE) [22]. In this paper we suggest an alternative explanation of superdiffusive subballistic movement of cancer cells based on the two-state model with anomalous switching for which the mean squared displacement (MSD)  $\langle r^2(t) \rangle \sim t^{2\mu}$  for  $1/2 < \mu < 1$ .

The second model, model II, corresponds to the outer zone, where the density of cancer cells is very low. For proliferation rate we used the classical logistic growth, while the migration of cells was subdiffusive. Unlike our previous works [9,10], we have managed to derive the exact formulas for the minimal spreading rate of cancer cells. We have shown that the subdiffusive transport of cancer cells leads to a nontrivial dependence of spreading rate  $u$  on the proliferation rate  $U$ :  $u \sim U^{(2-\alpha)/2}$ , where  $\alpha$  is the anomalous exponent ( $0 < \alpha \leq 1$ ). It follows from Eq. (56) that in the subdiffusive case we observe a stronger dependence of propagation speed on proliferation rate  $U$  compared to the classical Fisher equation:  $u \sim U^{1/2}$ .

We should mention the fact that our reaction-transport models (model I and model II) are pretty universal and have possible applications in physics of random media, ecology, population theory, and cellular biology. Both models belong to a widely used class of transport models with a so-called resting phase. Examples of quiescent states are porous media with immobilized particles, hunting spots for predators, reproduction sites, nerve cells, and microbes at rest, etc. Transport theory with resting phases is well developed only for Markov switching processes [54,55]. Model I provides the general theory for the reaction-transport systems with the non-Markovian and anomalous switching between moving phase and quiescent phase.

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**APPENDIX**

The purpose of this Appendix is to present the derivation of (i) integral equations for  $i_k(t,r)$  and  $n_k(t,r)$ , (ii) explicit expression for  $i_k(t,r)$  in terms of  $n_k(t,r)$  [see Eqs. (9) and (10)]. To derive the balance equations for  $i_1(t,r)$  and  $i_2(t,r)$ , we substitute Eqs. (23) and (24) into Eq. (16) and take into account the initial conditions (14) and formula (25):

$$i_1(t,r) = \int_0^t \psi_1(\tau) i_2(t-\tau, r - v\tau) d\tau + n_1^0(r - vt) \psi_1(t), \tag{A1}$$

$$i_2(t,r) = \int_0^t \psi_2(\tau) i_1(t-\tau, r) e^{\int_{t-\tau}^t f(n(s,r)) ds} d\tau + n_2^0(r) \psi_2(t) e^{\int_0^t f(n(s,r)) ds}. \tag{A2}$$

To find the integral equations for  $n_1(t,r)$  and  $n_2(t,r)$ , we substitute Eqs. (23) and (24) into Eq. (15) and take into account the conditions (14),

$$n_1(t,r) = \int_0^t i_2(t-\tau, r - v\tau) \Psi_1(\tau) d\tau + n_1^0(r - vt) \Psi_1(t), \tag{A3}$$

$$n_2(t,r) = \int_0^t i_1(t-\tau, r) \Psi_2(\tau) e^{\int_{t-\tau}^t f(n(s,r)) ds} d\tau + n_2^0(r) \Psi_2(t) e^{\int_0^t f(n(s,r)) ds}. \tag{A4}$$

One way to obtain the nonlinear Master equations for  $n_1(t,r)$  and  $n_2(t,r)$  is to differentiate the densities given by Eqs. (A3) and (A4) with respect to time  $t$ . It turns out that it is sufficient to find  $i_1(t,r)$  and  $i_2(t,r)$  in terms of  $n_1(t,r)$  and  $n_2(t,r)$  and substitute them into Eqs. (7) and (8).

Multiplying Eqs. (A2) and (A4) by  $e^{-\int_0^t f(n(s,r)) ds}$  and taking the Laplace transform  $\mathcal{L}\{f\}$ , we obtain

$$\begin{aligned} \mathcal{L}\{i_2(t,r) e^{-\int_0^t f(n(s,r)) ds}\} \\ = [n_2^0(r) + \mathcal{L}\{i_1(t,r) e^{-\int_0^t f(n(s,r)) ds}\}] \tilde{\psi}_2(s), \end{aligned}$$

$$\begin{aligned} \mathcal{L}\{n_2(t,r) e^{-\int_0^t f(n(s,r)) ds}\} \\ = [n_2^0(r) + \mathcal{L}\{i_1(t,r) e^{-\int_0^t f(n(s,r)) ds}\}] \tilde{\Psi}_2(s). \end{aligned}$$

Then

$$\mathcal{L}\{i_2(t,r) e^{-\int_0^t f(n(s,r)) ds}\} = \mathcal{L}\{n_2(t,r) e^{-\int_0^t f(n(s,r)) ds}\} \frac{\tilde{\psi}_2(s)}{\tilde{\Psi}_2(s)}. \tag{A5}$$

Using inverse Laplace transform we obtain

$$i_2(t,r) e^{-\int_0^t f(n(s,r)) ds} = \int_0^t I_2(t-t') n_2(t', r) e^{-\int_0^{t'} f(n(s,r)) ds} dt', \tag{A6}$$

where  $K_2(t)$  is the memory kernel defined by

$$\tilde{I}_2(s) = \frac{\tilde{\psi}_2(s)}{\tilde{\Psi}_2(s)}.$$

From Eq. (A6), we get Eq. (10).

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