Superdiffusion of cancer on a comb structure

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Abstract. The influence of cell fission on transport properties of the vessel network is studied. A simple mathematical model is proposed by virtue of heuristic arguments on tumor development. The constructed model is a modification of a so-called comb structure. In the framework of this model we are able to show that the tumor development corresponds to fractional transport of cells. A possible answer to the question how the malignant neoplasm cells appear at an arbitrary distance from the primary tumor is proposed. The model could also be a possible mechanism for diffusive cancers.

1. Introduction
Mathematical modeling of tumor development is an important and new application of mathematical physics in biology and medicine. Although it is mainly aimed at diagnostics and treatments of cancers, the importance of tumor modeling for the understanding of cancer cell transport cannot be overestimated. Recent surveys describe different aspects of the modeling of tumors including solid tumors [1, 2, 3] interacting with the immune system [1], diffusive models related e.g. to brain tumors [4], process of tumor induced vascularization [5, 6], and fractal geometry of pathological architecture of tumor [7], as well as chemotherapy strategies [1, 2, 3, 4, 6]. Tumor development consists of complicated processes with different stages (see e.g. [1]) where the tumor’s cell transport and their proliferation are the main contributors to the malignant neoplasm dissemination. Interplay between these two main processes of cell proliferation and transport leads to the essential complication of the mathematical modeling of the tumor growth [1, 5].

In the present study, we focus primarily on the influence of the cell proliferation (fission) on transport properties through vessel network 1. Our primary interest is concerned with the main stages of tumor development, which are cell fission and transport. A simple mathematical model is proposed, using heuristic arguments on tumor development due to these two main stages. The constructed model is a modification of a so-called comb structure [8, 9, 10]. By virtue of this model we are able to show that the tumor development corresponds to fractional transport whose mathematical apparatus is well established (see e.g. [11, 12, 13, 14]). Using this simplified approach of fractional transport, a possible answer to the question how the neoplasm cells appear arbitrarily far from the main (primary) tumor in the case of solid tumor [3] is proposed. The model can be considered as a possible mechanism for diffusive cancers [4] as well.

1 It could be either vascular or lymphatic net. Since we do not specify a kind of tumor, we do not specify a kind of vessels.
The article describes an application of some of our results on superdiffusion on a comb structure \[10, 15\] to fractional transport of cancer cells through vessels network \[16, 17\]. The paper is organized as follows. The main assumptions concerning the two time scales which determine a tumor’s growth are proposed in Section 2. We show here that the kinetics of cancer cells is fractional and could be described in the framework of so-called continuous time random walk. Some familiar examples of the continuous time random walk adapted to cancer cells transport are presented in section 3. Section 4 is devoted to a specific realization of fractional kinetics in the framework of the comb model. Inhomogeneous properties of cancer cell transport through the vessel network are studied in Section 5, where we consider a weak inhomogeneous convection. The influence of the proliferation of cancer cells on transport is studied in Section 6. A case of strong inhomogeneous convection through the net is considered in Section 7. Transport in this case corresponds to the Lévy flights, and mathematical justification of the approximations used to obtain this result is presented in Section 8. The results are summarized in Section 9.

2. Main assumptions: Models of fractional kinetics

First, we consider a simplified scheme of cell dissemination through the vessel network. We consider this process by means of the following two steps. The first step is the biological process of cell fission. The duration of this stage is \(T_f\). The second process is cell transport itself having a duration \(T_t\). Therefore the cell dissemination is approximately characterized by the fission time \(T_f\) and the transport time \(T_t\). During the time scale \(T_f\) the cells interact strongly \[18\], motility of the cells is weak, and there is no transport (approximately). The duration of \(T_f\) could be arbitrarily large, and it reaches \(10^7 \div 10^8\) sec \[19\]. During the second time \(T_t\) interaction between the cells is weak and motility of the cells is determined by the velocity \(V\) of either vascular or lymphatic flow through the vessel network. It is convenient to introduce a “jump” length \(X_t\) as the distance which a cell travels during the time \(T_t\)

\[
X_t = V T_t. 
\]

Hence, the cells form an initial packet of free spreading particles and the tumor development process consists of the following time consequences

\[
T_f(1)T_t(2)T_f(3)\ldots .
\]

There are different realizations of this chain of times, due to different duration of \(T_f(i)\) and \(T_t(i)\), where \(i = 1, 2, \ldots \). Therefore one comes to the conclusion that transport is characterized by random values \(T(i)\) which are waiting times between any two successive jumps of random length \(X(i)\). This phenomenon is known as a continuous time random walk (CTRW) \[11, 12, 13, 20\]. It arises as a result of a sequence of independent identically distributed random waiting times \(T(i)\), each having the same probability density function (PDF) \(w(t)\), \(t > 0\) with a mean waiting time

\[
\langle t \rangle = \int_0^\infty tw(t)dt,
\]

and a sequence of independent identically distributed random jumps, \(x = X(i)\), each having the same PDF \(\lambda(x)\) with the jump length variance

\[
\sigma^2 \equiv \langle x^2 \rangle = \int_{-\infty}^{\infty} x^2 \lambda(x)dx.
\]

Now we introduce the PDF \(P(x,t)\) of the particle to be in point \(x\) at the time \(t\). Due to the probabilistic description that defines an appropriate relation between these three PDFs, \(P(x,t), w(t), \lambda(x)\) (see e.g. \[11, 13\]), one obtains the following integral equation for \(P(x,t)\):

\[
P(x,t) = \delta(x) \int_t^\infty w(t')dt' + \int_0^\infty w(t-t') \int_{-\infty}^{\infty} \lambda(x-x')P(x',t')dt'dx'
\]
with the initial condition $P(x, 0) = \delta(x)$. It is worth stressing that the Fourier and Laplace
$(F - L)$ transforms play an important role in the CTRW, since a simple form relation between
$P(x, t)$ and $w(t), \lambda(x)$ takes place in the Fourier-Laplace space [11, 12, 13, 20]. Suppose that
$P(x, t), w(t), \lambda(x)$ are well behaved functions, such that the Fourier-Laplace transforms could be
applied
\[ \tilde{w}(p) = \hat{L}[w(t)]; \quad \tilde{\lambda}(k) = \hat{F}[\lambda(x)]; \quad \tilde{P}(k, p) = \hat{F}\hat{L}[P(x, t)]. \] (4)

Then we deduce the integral equation (3) to the Montroll-Weiss equation [11, 13]:
\[ \tilde{P}(k, p) = \frac{1 - \tilde{w}(p)}{p} \cdot \frac{1}{1 - \tilde{w}(p)\lambda(k)}. \] (5)

This is the main result in which we were able to establish a link between the tumor
development and the CTRW process which is described by equation (5). In later sections we
consider some examples of the CTRW dynamics that could be applied for different realization
of tumor cell transport. First, we present familiar examples of fractional transport used for a
variety of realizations in physics, chemistry, biology and so on (see e.g. recent surveys [11, 14]).
These examples are also relevant to the tumor development.

3. CTRW examples

(a) First we consider normal diffusion where $\sigma^2$ and $T$ are finite and correspond to the
distributions
\[ w(t) = \frac{1}{T} e^{-t/T}, \quad \lambda(x) = \frac{1}{[4\pi \sigma^2]^{1/2}} e^{-x^2/4\sigma^2}. \] (6)
Asymptotic solutions when $(k, p) \to (0, 0)$ for the Fourier-Laplace transforms are $\tilde{w}(p) \sim 1 -Tp$
and $\tilde{\lambda}(k) \sim 1 - \sigma^2 k^2$. Then one obtains from (5)
\[ \tilde{P}(k, p) = 1/(p + Dk^2), \] (7)
where $D = \sigma^2/T$ is a coefficient of normal diffusion in the real $(x, t)$ space, and the mean squared
displacement (MSD) is $\langle x^2(t) \rangle = Dt$.

(b) The situation, when $\lambda(x)$ is the same as in Eq. (6), but $T$ diverges is described by a
long–tailed waiting time PDF with an asymptotic behavior $w(t) \sim A_\alpha (T/t)\alpha$, $0 < \alpha < 1$. The
Laplace transform is $\tilde{w}(p) \sim 1 - (pT)^\alpha$. Therefore, Eq. (5) reads
\[ \tilde{P}(k, p) = 1/(p + D_\alpha p^{1-\alpha} k^2), \] (8)
where the generalized diffusion constant is now $D_\alpha = \sigma^2/T^\alpha$. The MSD is calculated from (8)
via the following relation
\[ \langle x^2(t) \rangle = L^{-1} \lim_{k \to 0} \{-\langle d^2/dk^2 \rangle \tilde{P}(k, p)\}, \]
where $L^{-1}$ means the Laplace inversion. It results in
\[ \langle x^2(t) \rangle = 2D_\alpha t^\alpha / \Gamma(1 + \alpha), \] (9)
where $\Gamma(z)$ is a gamma function [21]. Since $\alpha < 1$, this is subdiffusion.

(c) The opposite case is superdiffusion when $T$ is a finite value and $w(t)$ is the same as in Eq.
(6), while $\sigma^2$ is infinite with asymptotic behavior of the PDF $\lambda(x) \sim A_\mu \sigma^{-\mu} |x|^{-1-\mu}$, $1 < \mu < 2$.
This gives for the Laplace transform $\tilde{\lambda}(k) = 1 - \sigma^\mu |k|^\mu$, and Eq. (5) has the following solution
\[ \tilde{P}(k, p) = 1/(p + K_\mu |k|^\mu), \] (10)
where the generalized diffusion constant is $K_\mu = \sigma_\mu/T$. The characteristic function $\tilde{P}(k,t) = \hat{L}^{-1}[\tilde{P}(k,p)] = \exp[-K_\mu t|k|^\mu]$ is the stationary Lévy distribution [11, 12]. This process is known as Lévy flights, with the MSD equaling infinity.

These examples are also relevant to tumor development with different rates of cell dissemination through the fractional net of vessels embedded in the three-dimensional (3d) space. Cases (a) and (b) are relevant, e.g., for description of both a diffusive cancer and a primary solid tumor, while (c) is more relevant to metastasis.

4. Comb model
Fractional transport of cells, namely subdiffusion, could be described in the framework of a so-called comb model (or CTRW structure) [8]. The comb model shown in Fig. 1 is an example of subdiffusive 1d media where CTRW takes place along the $x$ structure axis. Diffusion in the $y$ direction plays the role of traps with the PDF of delay times of the form $u(t) \sim 1/(1 + t/T)^{3/2}$. A special behavior of diffusion on the comb structure is that the displacement in the $x$-direction is possible only along the structure axis ($x$-axis at $y = 0$). Therefore, cell motility is highly inhomogeneous in the $y$-direction, while diffusion coefficient in the $y$-direction along the teeth is a constant $D_{yy} = D$. In the present consideration we consider anomalous convection in the $x$ direction with a velocity $v(x,y) = vx^s\delta(y)$, where the inhomogeneity is chosen to be weak $|s| \ll 1$. The Liouville equation

$$\frac{\partial P}{\partial t} + \text{div} j = 0 \quad (11)$$

describes a random walk on this structure with the distribution function $P = P(t,x,y)$, and the current $j = (-v(x,y)P, -D\frac{\partial P}{\partial y})$. It yields the following Fokker–Planck equation

$$\frac{\partial P}{\partial t} - v(x)\delta(y)\frac{\partial x^s P}{\partial x} - D\frac{\partial^2 P}{\partial y^2} = 0 \quad (12)$$

with the initial conditions $P(0,x,y) = \delta(x)\delta(y)$ and the boundary conditions on the infinities $P(t,\pm\infty,\pm\infty) = P'(t,\pm\infty,\pm\infty) = 0$. Let us introduce an external forcing in the form of the inhomogeneous convection along the structure $x$-axis with the convection velocity $v_x = v(x)\delta(y) = vx^s\delta(y)$. Note that the dimension of $v(x)$ is $D$. First, let us consider a transport problem on the comb structure due to the constant convection velocity $v_x = v_0\delta(y)$. Then, we have

$$\frac{\partial P}{\partial t} + v_0\delta(y)\frac{\partial P}{\partial x} - D\frac{\partial^2 P}{\partial y^2} = 0. \quad (13)$$

Here and in further description the primes mean the spatial derivatives.
Now applying the Laplace and Fourier transforms, this equation is solved exactly with the solution

\[ P(t, x, 0) = \frac{D^{1/2}x}{v_0^2 \sqrt{\pi t^3}} \exp(-Dx^2/v_0^2 t), \]  

(14)

and \( P = 0 \) for \( x < 0 \), since the distribution function must be positive. This solution describes diffusion of cells in the convection media with traps. It corresponds to the normal diffusion with the second moment

\[ \langle x^2(t) \rangle = \frac{v_0^2}{D} t, \]  

(15)

but the effective diffusion coefficient \( \frac{v_0^2}{D} \) is determined by the external convective forcing \( v_0 \). It is worth stressing that it is a nontrivial result, and therefore one should anticipate superdiffusion due to the inhomogeneous convection of the form \( vx^s \) with \( s > 0 \), and, correspondingly, subdiffusion when \( s < 0 \).

5. Inhomogeneous convection

For a realization of an inhomogeneous current in the \( x \)-direction, we consider the following two-dimensional current with convection in the \( x \) component

\[ j = (vx^s P(t, x, y)\delta(y), -D\partial P(t, x, y)/\partial y). \]  

(16)

A substitution of Eq. (16) in the Liouville equation (11) gives a modification of Eq. (13) in the form

\[ \frac{\partial P}{\partial t} + \hat{L}_{FP}(x)P\delta(y) - D\frac{\partial^2 P}{\partial y^2} = 0, \]  

(17)

where

\[ \hat{L}_{FP}(x)P = vx^s \frac{\partial P}{\partial x} + svx^{s-1} P. \]  

(18)

After the Laplace transform with respect to time, one obtains the following solution

\[ \tilde{P}(p, x, y) = f(p, x) \exp \left[ -(p/D)^{1/2}|y| \right]. \]  

(19)

We used that

\[ \frac{\partial^2}{\partial y^2} \exp \left[ -\sqrt{\frac{p}{D}}|y| \right] = \left[ \frac{p}{D} - 2\sqrt{\frac{p}{D}} \delta(y) \right] \exp \left[ -\sqrt{\frac{p}{D}}|y| \right]. \]

Substituting Eq. (19) in Eq. (17), we obtain the following equation for \( f \equiv f(p, x) \)

\[ vx^sf' + svx^{s-1}f + 2[pD]^{1/2}f = \delta(x) \]  

(20)

with the following boundary conditions on the infinity \( f(p, \infty) = 0 \) and \( f(p, x) = 0 \) for \( x < 0 \).

5.1. superdiffusion: \( s > 0 \)

For \( 0 < s < 1 \), the solution of Eq. (20) has the following form

\[ f = \frac{\delta(x)}{2v_0^2 \sqrt{pD}} + \frac{1}{vx^s} \exp \left[ -2(Dp)^{1/2}x^{1-s} \right], \]  

(21)

\[ \text{When } s \geq 1 \text{ the Laplace inversion of Eq. (21) does not exist for } v > 0. \]
where $x^s \delta(x) = 0$. This solution corresponds to the Lévy walk with superdiffusion along the structure axis, where all moments are determined by the following distribution function for $x \geq 0$ [10]

$$
P(t, x, 0) = \frac{\delta(x)}{2\sqrt{\pi Dt}} + \frac{D_2^2 x^{1-2s}}{v^2 (1-s) \sqrt{\pi t^3}} \exp \left[ -\frac{D x^{2-2s}}{v^2 (1-s) t} \right],$$

while $P(t, x, 0) = 0$ for $x < 0$. From (22) we obtain the mean squared displacement in the form [10]:

$$
\langle x^2(t) \rangle = \Gamma \left( 2 - \frac{s}{1-s} \right) \cdot \left[ \frac{v^2 (1-s)^2}{D} \right]^\mu \cdot t^\mu,
$$

where $\Gamma(z)$ is a gamma function [21]. The transport exponent $\mu = 1/(1-s)$ corresponds to superdiffusion and is $\mu \approx 1 + s$ for $s \ll 1$; in the general case it could be arbitrarily large $1 < \mu < \infty$. Nevertheless, as can clearly be seen from Eq. (22), all moments are finite. Therefore it is the Lévy walk [10]. When $s = 0$, Eq. (22) coincides with Eq. (14) for $x > 0$.

5.2. Subdiffusion: $s < 0$

For $s < 0$ the solution of Eq. (20) is

$$
f(x) = \Theta(x) \frac{x^{-s}}{v} \exp \left[ -\frac{x^{1-s} (pD)^{1/2}}{v(1-s)} \right],
$$

where $\frac{d}{dx} \Theta(x) = \delta(x)$ and $\delta(x)e^{bx} \equiv \delta(x)$ for any $b$ and $x$. The transport exponent for the mean squared displacement in this case is $\mu \approx 1 - |s| < 1$ which corresponds to subdiffusion.

Since the diffusion term is not taken into account in equations (21), (22), and (24), these solutions are relevant for the large scale asymptotic $x \gg 1$.

6. Proliferation of cells

In this section we consider a possible mechanism of tumor cell proliferation in the framework of the comb model. The total number of the transporting cells,

$$
N(t) = \int \int dx dy P(t, x, y),
$$

described by the Fokker–Planck equation (12) is conserved. Nevertheless, the process of proliferation should be taken into account not only by counting the waiting time PDF but also due to the fact that number of cells is not conserved $dN/dt > 0$. Since, according the CTRW model, the transporting cells along the $x$ axis do not proliferate, we introduce the proliferation rate as a change of the total number of cells with time $dN/dt = g(t)$, where $g(t)$ is taken from empirical (clinical) data. It is convenient to present $g(t)$ as an integration over entire configuration space $(x, y)$. Then we have

$$
\frac{dN}{dt} = g(t) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} dx dy G(x, y, t),
$$

4 Asymptotic behavior for $s > 1$ is considered in Sects. 7 and 8.
where \( G(x, y, t) \) is an arbitrary function which satisfies (26). For example, one could present it in the following convenient form
\[
G(x, y, t) = \frac{1}{4\pi D} \exp \left[ -\frac{(x^2 + y^2)}{4Dt} \right].
\] (27)

Substituting Eqs. (26) and (27) in Eq. (12) one obtains
\[
\frac{\partial P}{\partial t} + \delta(y) \hat{L}_{FP} P - D \frac{\partial^2 P}{\partial y^2} = G(x, y, t),
\] (28)

where the boundary conditions remain the same, but the initial condition is
\[
P(t = 0, x, y) = 0.
\]
This condition means that the population of cells in the system is just due to the proliferation. For the sake of clarity and simplicity we take here that \( g(t) = bt \), while \( \hat{L}_{FP}(x) = -\hat{D} \frac{\partial^2}{\partial x^2} \), which corresponds to the standard comb model \([8, 9, 10]\). Performing the Laplace transform, we obtain the solution in the following form:
\[
\tilde{P}(p, x, y) = f(p, x) \exp \left[ -\left| y \right| \sqrt{p/D} \right].
\] (29)

Then integrating both the sides of the equation over \( y \); \( \int_{-\infty}^{\infty} dy \), we arrive at the equation for \( f \equiv f(p, x) \)
\[
\hat{D} \tilde{f}''(p, k) + 2\sqrt{pD} \tilde{f}(p, k) = -\frac{b}{2D^{1/2}} \frac{d}{dp} \frac{e^{-|x|\sqrt{p/D}}}{\sqrt{p}}.
\] (30)

Performing the Fourier transform of Eq. (30), one has
\[
k^2 \hat{D} \tilde{f}(p, k) + 2\sqrt{pD} \tilde{f}(p, k) = \frac{2b}{\sqrt{\pi}} \frac{1}{(p + Dk^2)^2}.
\] (31)

Eventually, the solution in the Fourier–Laplace domain reads
\[
\tilde{f}(p, k) = \frac{2b}{\sqrt{\pi}(p + Dk^2)^2} \cdot \frac{1}{Dk^2 + 2\sqrt{Dp}}.
\] (32)

Since solution (32) is the product of two functions \( \tilde{f}(p, k) = \tilde{f}_1(p, k) \tilde{f}_2(p, k) \), where \( \tilde{f}_1(2) = \hat{L} \tilde{f}\left[ f_{1(2)}(t, x) \right] \), one can use the properties of the Fourier and Laplace transforms for the convolutions. Therefore we obtain for the Laplace inversion
\[
P(t, k, 0) = \hat{L}^{-1} \left[ \tilde{f}(p, k) \right] = \int_0^t f_1(t - \tau, k) f_2(\tau, k) d\tau.
\] (33)

Here the functions \( f_{1(2)} \) are
\[
f_1(t, k) = t \exp[\hat{D}tk^2],
\] (34)
\[
f_2(t, k) = \left[ \frac{1}{\sqrt{4\pi Dt}} - \frac{\hat{D}k^2}{4D} \exp \left[ \frac{\hat{D}k^2t}{4D} \right] \right] \text{erfc} \left( \frac{\hat{D}k^2}{\sqrt{4Dt}} \right),
\] (35)

where \( \text{erfc}(z) \) is the error function \([21]\). To perform the Fourier inverse transform, we consider two limits of (35). The first limit is the large scale asymptotic, when \( k \to 0 \) and \( k^2t \ll 1 \), \( \forall t \). In this case, only the first term in (35) should be taken into consideration. The Fourier inversion is carried out exactly. One arrives at the following expression:
\[
P(t, x, 0) = \int_0^t d\tau \sqrt{\frac{t - \tau}{DDt}} \exp \left[ -\frac{x^2}{4D(t - \tau)} \right] \propto \frac{t^2}{x^2} \exp \left[ -\frac{x^2}{4Dt} \right].
\] (36)
This result is valid for $x > \tilde{D}/D$. As follows from Eq. (36), the rate of the cells dissemination on this large scale asymptotic is of the order of $\langle x^2(t) \rangle \sim t^{5/2}$. The second limit is $k^4t \gg 1$.

In this case Eq. (35) reads $f_2(t, k) \approx \frac{\sqrt{D}t^{7/2}}{\sqrt{2\pi x^4}} \exp \left[ -\frac{x^2}{4\tilde{D}t} \right]$.

Finally, we obtain for $x < \tilde{D}/D$

$$P(t, x, 0) = \int_0^t d\tau \frac{\sqrt{32D^3D(t-\tau)^{9/2}}}{t^{3/2}x^4} \exp \left[ -\frac{x^2}{4D(t-\tau)} \right] \propto \frac{t^5}{x^6} \exp \left[ -\frac{x^2}{4\tilde{D}t} \right].$$

(37)

Since $\langle x^2(t) \rangle \sim \infty$, hence in this short range, $x < \tilde{D}/D$, the cells spread due to proliferation and tumor size is determined by transport on the size scale larger than $\tilde{D}/D$.

7. Lévy flights for $s > 1$

7.1. Lévy flights

In the case of strong inhomogeneity, when $s > 1$, the situation changes and leads to a new effect. Indeed, for $s > 1$, the necessary condition to perform the inverse Laplace transform in (21) is negative velocity, $v < 0$. Hence, the solution is

$$P(x, 0, t) = D^{1/2}|x|^{1-2s} \exp \left[ -\frac{Dx^{2-2s}}{v^2(s-1)\sqrt{\pi t^3}} \right].$$

(38)

To define an asymptotic behavior, it is convenient to deal with dimensionless variables $x, t$. Let us introduce dimensionless variables with the relevant combination of the comb parameters $\tilde{D}$ and $D$ [15]. One obtains the following new variables:

$$\frac{D^3t}{D^2} \rightarrow t, \quad \frac{D}{D} \rightarrow \tilde{D}/D \rightarrow v.$$ 

(39)

When $|x| \gg 1$ and $t$ is large enough, the exponential in (38) is equal to unity. This results in the power law form for the distribution which corresponds to superdiffusion of particles

$$g(t, x) \propto \frac{1}{|x|^{2s-1}\sqrt{\pi t^3}}.$$ 

(40)

All moments of $x$ higher than $2s - 2$ are equal to infinity. This means that for the large scale asymptotic, when $x^{2(s-1)t} \gg 1$, there is superdiffusion which is analogous to Lévy flights. It should be emphasized that the flux on the infinities is vanishing. An important feature of this superdiffusion is that it occurs in the direction opposite to the inhomogeneous convection current.

This new phenomenon is related to the relaxation process with diffusion, where the Kolmogorov conditions (see [22]) are necessary infer the Fokker–Plank equation (FPE). This means that in the absence of the convection the solution of the FPE gives that at any moment $t > 0$ the particles are spread over the whole $x$–axis from minus infinity to plus infinity, with exponentially small tails. Therefore, there is a finite concentration of the contaminant at any moment and at any point. This solution was obtained in [15] and has been named the negative superdiffusion (NS).
7.2. Fractional equation

Following [15] we infer the fractional Fokker–Plank equation when a total number of transporting cells is preserved. The total number of transporting particles on the structure axis decreases with time due to the comb structure: [9, 10]

\[ \langle P \rangle = \int_{-\infty}^{\infty} P(t, x, 0)dx = 1/2\sqrt{\pi}t. \] (41)

The formulation of the NS problem with conservation of the total number of particles is equivalent to the case with a continuous distribution of the delay times [12], where the total number of particles is described by the function \( P_1(t, x) = \int_{-\infty}^{\infty} P(t, x, y)dy \). This is the CTRW approach. It is easy to see from Eq. (17) that

\[ P(t, x, y) = \hat{L}^{-1} \left[ f(p, x)e^{-\sqrt{fp}y} \right]. \] (42)

Taking this into account, one obtains the equation for \( P_1 \) by integrating Eq. (19) with respect to the variable \( y \). It reads in the Laplace space for \( f_1(p, x) = \hat{L}[P_1(t, x)] \):

\[ pf_1(p, x) + \hat{L}_{FP}(x)f(p, x) = \delta(x), \] (43)

where the Fokker–Planck operator is now a combination of diffusion and inhomogeneous convection

\[ \hat{L}_{FP}(x) = -\hat{D} \frac{\partial^2}{\partial x^2} + vxs \frac{\partial}{\partial x} + svx^{s-1}. \] (44)

It is easy to see by carrying out the Laplace transform of Eq. (17) that

\[ \hat{L}_{FP}(x)f(p, x) = \delta(x) - 2\sqrt{Dp}P(p, x). \]

Substitution of this expression in Eq. (43) yields

\[ f(p, x) = \frac{1}{2} \sqrt{p}f_1(p, x). \] (45)

Again, after substitution of this relation in Eq. (43), the CTRW equation in the Laplace space is

\[ pf_1 + \frac{1}{2} p^{1/2} \hat{L}_{FP}(x)f_1 = \delta(x). \] (46)

We introduced here the Riemann–Liouville fractional derivatives (see, for example, [11, 24]) \( \frac{\partial^\alpha}{\partial t^\alpha} f(t) \) by means of the Laplace transform \((0 < \alpha < 1)\):

\[ \hat{L}[\frac{\partial^\alpha}{\partial t^\alpha} f(t)] = p^\alpha \hat{f}(p) - p^{1-\alpha} f(0^+), \] (47)

where \( \hat{L}[f(t)] = \hat{f}(p) \), and it also implies \( \partial^\alpha[1]/\partial t^\alpha = 0 \) [24]. Using this definition, we write the CTRW equation, which corresponds to the comb model described by Eq. (17), in the following form

\[ \frac{\partial P_1}{\partial t} + \frac{1}{2} \frac{\partial^{1/2}}{\partial t^{1/2}} \hat{L}_{FP}(x)P_1 = 0. \] (48)

Here the initial condition is \( P_1(0, x) = \delta(x) \). For the asymptotically large scale \( x \gg 1 \) (or \( x \ll -1 \)), we neglect the inhomogeneous term together with the second derivatives with respect to \( x \) in Eq. (46) and obtain a solution determined by Eqs. (21) and (45). This is the NS related to the CTRW by the following result

\[ f_1(p, x) = \frac{2}{vxs^{1/2}} \exp \left[ \frac{2p^{1/2}x^{1-s}}{v(s-1)} \right]. \] (49)
8. Liouville–Green approximation, $s > 1$
In this section we infer the NS in the framework of the Liouville–Green (LG) asymptotic solution for linear differential equations [23]. We show that the large scale approximation performed above due to the condition $x \gg 1$ is sufficiently good and corresponds to the Liouville–Green approximation also called the WKB approximation.\footnote{This approximation was used independently by Liouville and Green. In quantum mechanics this approximation considered near turning points is known as the Wentzel–Kramers–Brillouin (WKB) approximation.} The CTRW equation (48) in the generalized form reads
\[ \partial P_1 / \partial t + \alpha \partial P_1 / \partial t - \alpha \partial x \partial P_1 = 0, \tag{50} \]
where $0 < \alpha < 1$. Hence, for $x \gg 1$, we obtain the homogeneous part (lhs) of Eq. (46), where the item $p^{1/2}$ is substituted by $p^\alpha$. It reads
\[ p_1 f_1 + \alpha p^{1-\alpha} [-f_1'' + v x^s f_1' + sv x^{s-1} f_1] = 0. \tag{51} \]
The term in the first derivative is removed from the equation by the substitution
\[ f_1 = p^\alpha - 1 \exp \left[ -\int R(x)^{1/2} dx \right] = B \left[ \exp \left( -\frac{v x^{s+1}}{2(s+1)} \right) + \frac{p^\alpha x^{1-s}}{\alpha v (s-1)} \right], \tag{53} \]
where $B$ is a constant. Analogously, we obtain the LG solution for the negative $x \ll -1$. Therefore, taking $B = (2/v)^{3/2}$ and $\alpha = 1/2$, we obtain that Eq. (52) coincides exactly with the solution (49). This means that the removing of the second derivatives from the Fokker–Plank operator $\hat{L}_{FP}(x)$ or the term $k^2$ in the Fourier space in the limit $k \to 0$ corresponds to the Liouville–Green approximation for the Fokker–Planck equation with inhomogeneous (superdiffusive) convection. This asymptotic solution is the superdiffusive transport of particles in the direction opposite to the convection current, namely the NS.

9. Conclusion
The main focus of the present study has been the influence of cell proliferation on transport properties through vessel’s network (either vascular or lymphatic). Two main stages have been highlighted: cell fission and transport with durations $T_f$ and $T_t$, correspondingly. Using these time scales, we were able to deduce a description of the tumor development to a CTRW process. A simple mathematical model is constructed, using heuristic arguments on the relation of tumor development and the CTRW whose mathematical apparatus is well established (see e.g. [11, 12, 13, 14]. The constructed model is a modification of a so–called comb structure [8, 9, 10]. Using this simplified approach to the fractional transport of tumor cells, we can answer the question how the malignant neoplasm cells appear arbitrarily far from the main (primary) tumor in the case of solid tumor. The model could also be considered as a possible mechanism for diffusive cancers. We presented analytical solutions of the problem. To this end
we consider one dimensional (1d) transport. A generalization of the analytical consideration on the 3d case is straightforward when an interaction between the degrees of freedom is absent.

Two important features are considered in the framework of the CTRW model. The first one is inhomogeneous properties of vessel network which are taken into account by virtue of the inhomogeneous convection. We have considered superdiffusion or even enhanced superdiffusion on the subdiffusive medium where the inhomogeneous convection is the mechanism of this anomalous transport. In our consideration the mean squared displacement as well as all other moments are finite and defined rigorously. The transport exponent is an arbitrary value (it could be arbitrarily large) and is unambiguously determined by the power law behavior of the inhomogeneous convection as a function of coordinates. The second feature is the influence of the cell proliferation on transport. We found an essential enhancing of anomalous transport due to proliferation. Moreover in some cases it could be dominant.

A possible classification of tumor growth as anomalous transport on a subdiffusive substrate could be made due to the inhomogeneous convection as well. As shown here, it depends on the external forcing according to the power rate of the inhomogeneous convection in the net flow which is modeled by the following current $j_{x}(x,t) = vx^{s} \delta(y)P(t,x,0)$. When $s < 0$, the solution (24) corresponds to subdiffusion. When $s > 0$ it is superdiffusion (see Eqs. (22),(23)), where all moments are finite. It is the Lévy–like process. The homogeneous convection with $s = 0$ corresponds formally to the normal diffusion as in Eq. (15), but the effective diffusion coefficient $v_{0}^{2}/D$ is determined by the external forcing $v_{0}$. When $s > 1$, it corresponds to superdiffusion (38),(40) with Lévy flights, as well.

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