Fractional Transport of Tumor Cells

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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.

Key–Words: - Tumor, fractional transport, cell fission, comb model

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 fission on transport properties through vessel network. 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. Our primary interest is concerned with the main stages of tumor development, which are cell fission and transport. A simple mathematical model of a continuous time random walk (CTRW) [8] 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 [9,10,11,12]. 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.* [13,14,15,16,17]). 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.

2 Main Assumptions for the CTRW

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

$$X_t = VT_t. \quad (1)$$

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

$$T_f(1)T_t(2)T_f(3)\ldots. \quad (2)$$

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) [8,13,14,15]. 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

$$T \equiv \langle t \rangle = \int_0^\infty t w(t) dt,$$

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.* [13,15]), one obtains the following integral equation for $P(x,t)$:

$$P(x,t) = \delta(x) \int_t^\infty w(t')dt' + \int_0^\infty w(t-t') \int_{-\infty}^{\infty} \lambda(x-x') P(x',t') dt' dx' \quad (3)$$

with the initial condition $P(x,0) = \delta(x)$. It is worth stressing that the Fourier and Laplace ($\hat{F} - \hat{L}$) 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 [8,13,14,15]. Suppose that $P(x,t), w(t), \lambda(x)$ are well behaved functions, such that the Fourier-Laplace transforms could be applied

$$\tilde{w}(p) = \hat{L}[w(t)];\ \tilde{\lambda}(k) = \hat{F}[\lambda(x)];$$
$$\tilde{P}(k,p) = \hat{F}\hat{L}[P(x,t)]. \quad (4)$$

Then we deduce the integral equation (3) to the Montroll-Weiss equation [13,15]:

$$\tilde{P}(k,p) = \frac{1-\tilde{w}(p)}{p} \cdot \frac{1}{1-\tilde{w}(p)\tilde{\lambda}(k)}. \quad (5)$$

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 sequel we consider some examples of the CTRW dynamics that could be applied for different realization of tumor cell transport.

3 CTRW Equation

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 [13,17]). These examples are also relevant to the tumor development.

We consider a situation when σ^2 is finite and corresponds to the following distribution

$$\lambda(x) = \frac{1}{[4\pi\sigma^2]^{1/2}} e^{-x^2/4\sigma^2}, \quad (6)$$

while T diverges and 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

$$\tilde{P}(k,p) = 1/(p + D_\alpha p^{1-\alpha} k^2), \quad (7)$$

where the generalized diffusion constant is now $D_\alpha = \sigma^2/T^\alpha$. The MSD is calculated from (7) via the following relation

$$\langle x^2(t) \rangle = \hat{L}^{-1} \lim_{k \to 0} [-(d^2/dk^2)\tilde{P}(k,p)],$$

where $\hat{L}^{-1}$ means the Laplace inversion. It results in

$$\langle x^2(t) \rangle = 2D_\alpha t^\alpha / \Gamma(1+\alpha), \quad (8)$$

where $\Gamma(z)$ is a gamma function [20]. Since $\alpha < 1$, this is subdiffusion.

This is an example for tumor development with different rates of cell dissemination through the fractional net of vessels embedded in the three–dimensional (3d) space. This is relevant, *e.g.*, for

description of both a diffusive cancer and a primary solid tumor.

3.1 Fractional Equation

To obtain the fractional or CTRW equation which produces the solution (7), we introduced here the Riemann–Liouville fractional derivatives (see, for example, [13,16]) $\frac{\partial^\alpha}{\partial t^\alpha} f(t)$ by means of the Laplace transform ($0 < \alpha < 1$):

$$\hat{L}[\frac{\partial^\alpha}{\partial t^\alpha} f(t)] = p^\alpha \tilde{f}(p) - p^{1-\alpha} f(0^+), \quad (9)$$

where $\hat{L}[f(t)] = \tilde{f}(p)$, and it also implies $\partial^\alpha [1]/\partial t^\alpha = 0$ [16]. Using this definition, we write the CTRW equation in the following form

$$\frac{\partial P}{\partial t} + \alpha \frac{\partial^{1-\alpha}}{\partial t^{1-\alpha}} \hat{L}_{FP}(x) P = 0, \quad (10)$$

where the Fokker–Planck operator is diffusion

$$\hat{L}_{FP}(x) = -\tilde{D} \frac{\partial^2}{\partial x^2}. \quad (11)$$

For $\alpha = 1/2$ the situation is the most simple, and the traps can be modeled by normal diffusion in the additional y direction. Therefore the fraction equation (10) corresponds to a so–called comb model.

3.2 Comb Model

Fractional transport of cells, namely subdiffusion, could be described in the framework of the comb model (or CTRW structure) [9]. 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 $w(t) \sim 1/(1 + t/T)^{3/2}$. 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 $D_{yy} = D$.

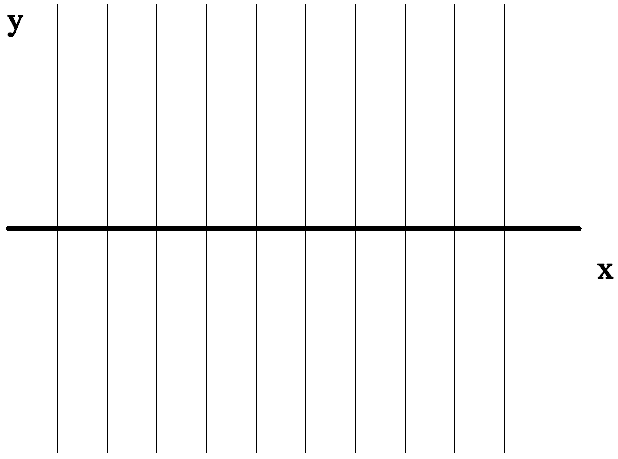

Figure 1. A comb structure

In this section we consider homogeneous convection in the x direction with a velocity $v(y) = V\delta(y)$ instead of diffusion. A random walk on the comb structure is described by the distribution function $P_1 = P_1(t, x, y)$ and the current

$$\mathbf{j} = (-v(y)P_1, -D\frac{\partial P_1}{\partial y}),$$

where

$$P(t, x) = \int_{-\infty}^{\infty} P_1(t, x, y)dy, \quad (12)$$

The Liouville equation

$$\frac{\partial P_1}{\partial t} + \operatorname{div} \mathbf{j} = 0 \quad (13)$$

yields the following Fokker–Planck equation

$$\frac{\partial P_1}{\partial t} - V\delta(y)\frac{\partial P_1}{\partial x} - D\frac{\partial^2 P_1}{\partial y^2} = 0 \quad (14)$$

with the initial conditions $P_1(0, x, y) = \delta(x)\delta(y)$ and the boundary conditions on the infinities $P_1(t, \pm\infty, \pm\infty) = P_1'(t, \pm\infty, \pm\infty) = 0$.

Here and in sequel the primes mean the spatial derivatives. Applying the Laplace and Fourier transforms, this equation is solved exactly with the solution

$$P_1(t, x, 0) = \frac{D^{1/2} x}{v_0^2 \sqrt{\pi t^3}} \exp(-Dx^2/V^2 t), \quad (15)$$

and $P_1 = 0$ 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

$$\langle x^2(t)\rangle = \frac{V^2}{D}t, \qquad (16)$$

but the effective diffusion coefficient V^2/D is determined by the external convective forcing V which is defined *e.g.* in (1). It is worth stressing that it is a nontrivial result, and therefore one should anticipate superdiffusion due to the inhomogeneous convection of the form $V \to vx^s$ with $s > 0$, and, correspondingly, subdiffusion when $s < 0$ [11,12].

4 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,

$$N(t) = \int_{-\infty}^{\infty} dx P(t,x), \qquad (17)$$

described by the Fokker–Planck equation (14) 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

$$\frac{dN}{dt} = g(t) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} dxdy G(x,y,t), \qquad (18)$$

where $G(x,y,t)$ is an arbitrary function which satisfies (18). For example, one could present it in the following convenient form

$$G(x,y,t) = \frac{1}{4\pi D}\exp\left[-(x^2+y^2)/4Dg(t)\right]. \qquad (19)$$

Substituting Eqs. (18) and (19) in Eq. (14) one obtains

$$\frac{\partial P_1}{\partial t} + \delta(y)\hat{L}_{FP}P_1 - D\frac{\partial^2 P_1}{\partial y^2} = G(x,y,t), \qquad (20)$$

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 $\hat{L}_{FP}(x) = -\tilde{D}\frac{\partial^2}{\partial x^2}$, which corresponds to the standard comb model [9,10,11]. Performing the Laplace transform, we obtain the solution in the following form:

$$P_1(p,x,y) = f(p,x)\exp[-|y|\sqrt{p/D}]. \qquad (21)$$

Then integrating both the sides of the equation over y; $\int_{-\infty}^{\infty} dy$, we arrive at the equation for $f \equiv f(p,x)$

$$\tilde{D}f'' + 2\sqrt{pD}f = -\frac{b}{2D^{1/2}}\frac{d}{dp}\frac{e^{-|x|\sqrt{p/D}}}{\sqrt{p}}. \qquad (22)$$

Performing the Fourier transform of Eq. (22), we obtain, eventually, the solution in the Fourier–Laplace domain

$$\tilde{f}(p,k) = \frac{2b}{\sqrt{\pi}\,(p+Dk^2)^2}\cdot\frac{1}{\tilde{D}k^2 + 2\sqrt{Dp}}. \qquad (23)$$

Since solution (23) is the product of two functions $\tilde{f}(p,k) = \tilde{f}_1(p,k)\tilde{f}_2(p,k)$, where $\tilde{f}_{1(2)} = \hat{L}\hat{F}\left[f_{1(2)}(t,x)\right]$, one can use the properties of the Fourier and Laplace transforms for the convolutions. Therefore we obtain for the Laplace inversion

$$\tilde{P}_1(t,k,0) = \hat{L}^{-1}\left[\tilde{f}(p,k)\right] = \int_0^t f_1(t-\tau,k)f_2(\tau,k)d\tau\,. \qquad (24)$$

Here the functions $f_{1(2)}$ are

$$f_1(t,k) = t\exp[\tilde{D}tk^2], \qquad (25)$$

$$f_2(t,k) = \left[\frac{1}{\sqrt{4\pi Dt}} - \frac{\tilde{D}k^2}{4D}\exp\left[\frac{\tilde{D}^2k^4t}{4D}\right]\mathrm{erfc}\left(\frac{\tilde{D}k^2t^{1/2}}{2D^{1/2}}\right)\right], \qquad (26)$$

where $\mathrm{erfc}(z)$ is the error function [20]. To perform the Fourier inverse transform, we consider two limits of (26). 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 (26) should be taken into consideration. The Fourier inversion is carried out exactly. One arrives at the following expression:

$$P_1(t,x,0) = \int_0^t d\tau\sqrt{\frac{t-\tau}{D\tilde{D}t}}\exp\left[-\frac{x^2}{4\tilde{D}(t-\tau)}\right] \propto \frac{t^2}{x^2}\exp\left[-\frac{x^2}{4\tilde{D}t}\right]. \qquad (27)$$

This result is valid for $x \gg \tilde{D}/D$. As follows from Eq. (27), 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 $k^4 t \gg 1$. In this case Eq. (26) reads $f_2(t,k) \approx \frac{\sqrt{4D}}{4\tilde{D}^2 k^4 t^{3/2}}$. The Fourier inversion is carried out by the stationary phase approximation that gives

$$\int_{-\infty}^{\infty} \frac{1}{k^4} e^{-ikx} e^{-\tilde{D}tk^2} dk \approx \frac{16\tilde{D}^{7/2}t^{7/2}}{\sqrt{2}x^4} \exp[-\frac{x^2}{4\tilde{D}t}]. \quad (28)$$

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

$$P(t,x,0) = \int_0^t d\tau \frac{\sqrt{32\tilde{D}^3 D}(t-\tau)^{9/2}}{t^{3/2}x^4} \times \exp\left[-\frac{x^2}{4\tilde{D}(t-\tau)}\right] \propto \frac{t^5}{x^6} \exp\left[-\frac{x^2}{4\tilde{D}t}\right]. \quad (29)$$

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 $\tilde{D}/D$.

5 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.* [13,14,15,17]. The constructed model is a modification of a so–called comb structure [9,10,11,12]. Using this simplified approach to the fractional transport of tumor cells, we can answer the question how the malignant neoplasm cells spread for both solid tumors and 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.

An important feature considered in the framework of the CTRW model is an essential enhancing of anomalous transport due to proliferation. Moreover in some cases it could be dominant.

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