Fractional development under periodic forcing

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Abstract: Fractional tumor development is considered in the framework of one dimensional continuous time random walk (CTRW) in the presence of a periodic potential. Chemotherapy influence on the CTRW is studied by observations of both stationary solutions due to proliferation and fractional evolution in time.

Key–Words: tumor development, migration–proliferation dichotomy, fractional transport

1 Introduction

Mathematical modeling of tumor development is mainly aimed at diagnostics and treatments of cancers, since it may lead to the reduction of expensive experiments *in vivo*. Recent reviews describe different aspects of the modeling of growth patterns [1]. There are different stages of tumor development of varying duration, starting from genetic changes on the cell level and finishing with detachment of metastasis and invasion. Tumor cell transport and their proliferation are the main contributors to the malignant neoplasm dissemination (see *e.g.* [2, 3]), and interplay between these two main processes leads to an essential complication in the mathematical modeling of tumor growth [2, 4]. This evolution, related to the collective or macroscopic behavior of cells, is described (in many cases) by kinetic cellular theory [5] (see also *e.g.* [2, 3]).

The migration–proliferation dichotomy of cancer cells, proposed in [6], has been considered in the framework of a continuous time random walk (CTRW) by virtue of two time scales of tumor development [7]. The collective behavior of cells was studied, paying particular attention to the influence of tumor cell fission on transport. This influence leads to an essential decrease in cell motility during fission time or self–entrapping that is determined by the interaction of cells with their environment. An important feature of the CTRW of cells is the essential enhancement of anomalous transport due to proliferation. Moreover, it is a dominant process which could be eliminated by chemotherapy. Chemotherapy changes tumor development and leads to a decrease in the number of tumor cells and, correspondingly, eliminates tumor development. In reality, a cancer cell is unstable and can mutate, developing a clone which resists chemotherapeutical influence (see *e.g.*, Ref. [3] and references therein). Therefore, mathematical modeling of chemotherapy optimization is an important component of cancer modeling [2, 3].

In this study we identified a condition when chemotherapy negates cell proliferation and leads to either fractional transport with the conservation of a number of cells or a stationary solution which describes time independent localization of cancer development. A specific feature of the analysis is cell diffusion in a periodic potential. This can model, *e.g.*, metastasis cell transport along the spinal column, where vertebrae form a periodic potential.

1.1 Fractional mechanism of tumor development

A simplified scheme of migration–proliferation dichotomy, which is responsible for cell dissemination through the vessel network, was considered by means of the following two steps [7]. The first step is the biological process of cell fission. The duration of this stage is $\mathcal{T}_f$. The second process is cell transport itself with duration $\mathcal{T}_t$. Therefore, the cell dissemination is approximately characterized by the fission time $\mathcal{T}_f$ and the transport time $\mathcal{T}_t$. During the time scale $\mathcal{T}_f$, the cells interact strongly and motility of the cells is small, and we suppose that there is (almost) no transport. During the second time $\mathcal{T}_t$, interaction between the cells is weak and motility of the cells is determined by the velocity V, and a "jump" length X_t as the distance which a cell travels during the time $\mathcal{T}_t$ $X_t = V\mathcal{T}_t$. Hence, the contribution of cell dissemination to the tumor development process consists of the time consequences $\mathcal{T}_f(1)\mathcal{T}_t(2)\mathcal{T}_f(3)\ldots$.

There are different realizations of this chain of times, due to different durations of $\mathcal{T}_f(i)$ and $\mathcal{T}_t(i)$, where $i = 1, 2, \ldots$. Therefore, transport is characterized by random values $\mathcal{T}(i)$ which are waiting (or self–entrapping) times between any two successive jumps of random length $X(i)$. This phenomenon is known as a continuous time random walk (CTRW) [8, 9]. It arises as a result of a sequence of independent identically distributed random waiting times $\mathcal{T}(i)$, each having the same PDF $w(t),\ t > 0$ with a mean characteristic time T and a sequence of independent identically distributed random jumps, $x = X(i)$, each having the same PDF with jump length variance σ^2. It is worth mentioning that a cell carries its own trap, by which it is set apart from transport. The crucial point of the fractional transport is the power law behavior of the waiting time PDF

$$w(t) = \alpha\bar{T}/(1 + t/\bar{T})^{1+\alpha} \tag{1}$$

where $0 < \alpha < 1$ and $\bar{T}$ is a characteristic time. In this case $T = \infty$.

1.2 Fractional integro–differentiation

A basic introduction to fractional calculus can be found, *e.g.*, in Ref. [10]. Fractional integration of the order of α is defined by the operator

$$I_a^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_a^t f(\tau)(t-\tau)^{\alpha-1} d\tau, \ \ (\alpha > 0)\,. \tag{2}$$

There is no constraint on the limit a. In our consideration, $a = 0$ since this is a natural limit for the time. A fractional derivative is defined as an inverse operator to $I^\alpha \equiv I_0^\alpha$ as $\frac{d^\alpha}{dt^\alpha} = I^{-\alpha} = D^\alpha$, $I^\alpha = \frac{d^{-\alpha}}{dt^{-\alpha}} = D^{-\alpha}$. Its explicit form is convolution

$$D^\alpha = \frac{1}{\Gamma(-\alpha)} \int_0^t \frac{f(\tau)}{(t-\tau)^{\alpha+1}} d\tau\,. \tag{3}$$

For arbitrary $\alpha > 0$ this integral is, in general, divergent. As a regularization of the divergent integral, the following two alternative definitions for D^α exist

$$D_{RL}^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_0^t \frac{f(\tau)}{(t-\tau)^{\alpha+1-n}} d\tau\,, \tag{4}$$

$$D_C^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{f^{(n)}(\tau)}{(t-\tau)^{\alpha+1-n}} d\tau\,, \tag{5}$$

where $n - 1 < \alpha < n, \ \ n = 1, 2, \ldots$. Eq. (4) is the Riemann–Liouville derivative, while Eq. (5) is the fractional derivative in the Caputo form [10]. Performing integration by part in Eq. (4) and then applying Leibniz's rule for the derivative of an integral and repeating this procedure n times, we obtain

$$D_{RL}^\alpha f(t) = D_C^\alpha f(t) + \sum_{k=0}^{n-1} f^{(k)}(0^+) \frac{t^{k-\alpha}}{\Gamma(k-\alpha+1)}\,. \tag{6}$$

The Laplace transform can be obtained for Eq. (5). If $\hat{L} f(t) = \tilde{f}(s)$, then

$$\hat{L}[D_C^\alpha f(t)] = s^\alpha \tilde{f}(s) - \sum_{k=0}^{n-1} f^{(k)}(0^+) s^{\alpha-1-k}\,. \tag{7}$$

We also note that $D_{RL}^\alpha[1] = \frac{t^{-\alpha}}{\Gamma(1-\alpha)}$, $D_C^\alpha[1] = 0$. where $\beta > -1$ and $\alpha > 0$. The fractional derivative from an exponential function can be simply calculated as well by virtue of the Mittag–Leffler function (see *e.g.*, [10]):

$$E_{\gamma,\delta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\gamma k + \delta)}\,. \tag{8}$$

Therefore, we have the following expression

$$D_{RL}^\alpha e^{\lambda t} = t^\alpha E_{1,1-\alpha}(\lambda t)\,. \tag{9}$$

2 Fractional Fokker–Planck equation with proliferation

Fractional transport of cells, namely, subdiffusion, with proliferation can be described by the fractional Fokker–Planck equation (FFPE) obtained in Ref. [11]. A random walk of cancer cells described by the distribution function $P = P(x,t)$ and exponential proliferation $\mathcal{C}P$ with a proliferation rate $\mathcal{C}$ corresponds to the FFPE with proliferation

$$\alpha^{-1} D_C^\alpha P e^{-\mathcal{C}t} + \hat{\mathcal{L}}_{FP} P e^{-\mathcal{C}t} = -\mathcal{C} P e^{-\mathcal{C}t}\,, \tag{10}$$

where D_C^α is the fractional derivative in the Caputo form and the Fokker–Planck operator is $\mathcal{L}_{FP} = -\partial_x D(x) \partial_x$ with the diffusion coefficient $D(x)$.

For the present purpose we modify Eq. (10) in the form

$$\alpha^{-1} e^{\mathcal{C}t} D_C^\alpha e^{-\mathcal{C}t} P + \hat{\mathcal{L}}_{FP} P = -C(P) - G(P)\,, \tag{11}$$

where proliferation is a logistic law, such that $C(P) = \mathcal{C}P(1-P)$, and $G(P)$ is an action of chemotherapy. The Fokker–Planck operator is chosen in the following, standard, form

$$\mathcal{L}_{FP} = -\partial_x \left[(\partial_x U) + d\partial_x \right]\,, \tag{12}$$

that corresponds to the Langevin equation $\dot{x} = -\partial_x U + \eta(t)$ with $\eta(t)$ being a Gaussian white noise

with mean value $\langle \eta(t) \rangle = 0$ and a correlation function $\langle \eta(t)\eta(t') \rangle = 2d\delta(t-t')$. Expression (11) is the main equation in question. We present it without inferring, which is not a simple task and deserved a separate consideration [13]. It is worth mentioning that this equation reflects migration–proliferation dichotomy, where cell fission is the source of the fractional time derivatives. This process is modeled by the power law of the self–entrapping time PDF $w(t)$ in Eq. (1). When $\alpha = 1$, Eq. (11) reduces to an example of brain tumor modeling [3] with $w(t)$ being the exponential function with the finite time scale T.

In the rest of the paper we study the influence of chemotherapy on possible solutions of Eq. (11). The following two possible scenarios related to stationary solutions and the fractional dynamics are considered.

2.1 Stationary solution due to chemotherapy

Let the chemotherapy influence lead to the compensation of tumor development including cell fission due to the following condition

$$e^{\mathcal{C}t} D_C^\alpha e^{-\mathcal{C}t} P = -\alpha G(P) \,. \tag{13}$$

Thus, Eqs. (11) and (13) describe a stationary process, where $P_{st} = P_{st}(x)$ is a time independent function

$$e^{\mathcal{C}t} D_C^\alpha e^{-\mathcal{C}t} P_{st} = -\alpha g_1(t) P_{st} \,, \tag{14}$$

where $e^{\mathcal{C}t} D_C^\alpha e^{-\mathcal{C}t} = -g_1(t)$. We can also change the convection term by the following chemotherapeutical procedure $U' \partial_x P_{st} = (U')^2 P_{st} + g_2(x) P_{st}$. Therefore,

$$G(P) = g_1(t) P_{st}(x) + g_2(x) P_s t(x) \,. \tag{15}$$

One should bear in mind that $G(P)$ is a function of the external control which can always be adjusted to these forms. Taking this into account, we obtain the following equation for the stationary distribution $P = P_{st}$

$$-d\partial_x^2 P + U'' P + (U')^2 P = -\mathcal{C} P(1-P) \,. \tag{16}$$

Let $U' = -\tan\left(\sqrt{d}x\right)$ be a periodic convection. Thus, Eq. (16) corresponds to a nonlinear system with a Hamiltonian $H(u,v) = u^2/2 + V(v)$ (which is the first integral of equations, *e.g.*, for $v > 0$)

$$v' = u = \partial_u H \,, \;\; u' = -qv + rv^2 = -\partial_v V \,, \tag{17}$$

where $q = (\mathcal{C} - d)/d$ and $r = \mathcal{C}/d$. A solution can be expressed in terms of the elliptic functions. One should bear in mind that P is a positive function. Therefore, the cubic potential $V(P) = V(|v|)$ is symmetrical in v and possesses two maxima for $|v_m| = q/r$. An important property of this dynamical system is a separatrix which separates confined motion with $|v| < |v_m|$ from extended one, where $|v| \geq |v_m|$. The first kind of the solution corresponds to a solid tumor, while the second one corresponds to metastasis. The size of the solid tumor is determined by the period of the confined solution which is the complete elliptic integral of the first kind [12]

$$\Delta x = \oint \frac{dv}{4u} = K(H) \,, \tag{18}$$

where the energy H plays a role of the modulus of the elliptic functions. When $H = q^3/6r^2$, the size of the solid tumor approaches to infinity $\Delta x = \infty$ on the separatrix. Therefore, when the cell concentration reaches the critical point $P = |v_m| = (\mathcal{C} - d)/\mathcal{C}$ a transition from the solid tumor to metastasis takes place. When $d \geq \mathcal{C}$ (in the dimensional units) the condition for the confined solution is violated, and dynamics corresponds to a so–called diffusive cancer.. In this case the chemotherapy scenario is not effective for the cancer treatment. In the opposite case, the chemotherapy leads to the cancer localization with a well defined finite size.

3 Fractional dynamics

Taking into account that D_C^α can be expressed by the Riemann–Liouville fractional derivatives D_{RL}^α as $D_C^\alpha = D_{RL}^{\alpha-1} D_{RL}^1$ and $D_{RL}^{1-\alpha} D_{RL}^{\alpha-1} = 1$, we rewrite FFPE with proliferation, and chemotherapy (11) in the form

$$\partial_t F + \alpha D_{RL}^{1-\alpha} \hat{\mathcal{L}}_{FP} F = \alpha D_{RL}^{1-\alpha} \left[C(F) - G(F) \right] \,, \tag{19}$$

where $F = e^{-\mathcal{C}t} P$. Let chemotherapy compensates proliferation. Therefore, one obtains from Eq. (19

$$\partial_t F + \alpha D_{RL}^{1-\alpha} \hat{\mathcal{L}}_{FP} F = 0 \,. \tag{20}$$

Using the variable separation analogously to [14], one has the following expression for the solution

$$F(x,t) = \sum_n F_n = \sum_n T_n(t) \psi_n(x) \,, \tag{21}$$

where $psi_n(x)$ is a solution of the eigenvalue problem

$$\mathcal{L}_{FP} \psi = \lambda \psi \,. \tag{22}$$

The temporal eigenfunction $T_n(t)$ is governed by the fractional equation

$$\dot{T}_n(t) + \alpha \lambda_n D_{RL}^{1-\alpha} T_n(t) = 0 \,. \tag{23}$$

The solution is described by the Mittag–Leffler function [14] $T_n(t) = E_n\left[\alpha\lambda_n t^\alpha\right]$, where $T_n(0) = 1$, and $E_\alpha(z)$ has the initial stretched exponent behavior

$$T_n(t) \sim \exp\left[-\alpha\lambda_n t^\alpha/\Gamma(1+\alpha)\right] \qquad (24)$$

which turns over to the power law long–time asymptotics

$$T_n(t) \sim \left[\Gamma(1-\alpha)\alpha\lambda_n t^\alpha\right]^{-1} . \qquad (25)$$

Now we return to the eigenvalue problem of Eq. (22), taking into account the explicit form the Fokker–Planck operator and carrying out the following transformation $\psi(x) = \exp\left[-U(x)/2d\right]\Psi(x)$, one obtains the eigenvalue problem in the Hamiltonian form

$$\hat{H}\Psi_n = \lambda_n\Psi_n\,, \qquad (26)$$

$$\hat{H} = -d\left[\partial_x^2 + W(x) - W'(x)\right] , \qquad (27)$$

where $W(x) = U'(x)/2d$ is a so called superpotential [15]. For simplicity, we take the periodic potential in the following form $W(x) = \tan(x)$. This choice immediately yields a solution of the eigenvalue equation (26)

$$\Psi_k = A\exp(kx), \qquad (28)$$

with the eigenvalues $\lambda_k = d(k^2-1)$. Since additional constraints, such as normalization, are absent, we take the constant A to be independent of k. For $k < 1$, the spectrum corresponds to a bounded system. For $k > 1$, the spectrum is unbounded (continuous). Substitution of Eqs. (28) and (24) in Eq. (21) yields for the short time asymptotic solution

$$P(x,t \sim \sqrt{\frac{\pi\Gamma(\alpha+1)}{\alpha t^\alpha}}|\cos(x)|$$
$$\times\exp\left[\mathcal{C}t + \frac{\alpha t^\alpha}{\Gamma(1+\alpha)} - \frac{x^2\Gamma(1+\alpha}{4t^\alpha}\right] . \qquad (29)$$

Therefore, the initial rate of the cell spreading is $\dot{x} \approx \mathcal{C}(1+\alpha)t^{\alpha-1/2}/\Gamma(1+\alpha)$.

4 Conclusion

A toy model of fractional transport of tumor cells in a periodic potential is considered. Influence of chemotherapy leads to a variety of possible scenarios of tumor development. The main characteristics studied here are conditions of tumor localization and rate of invasion of cells. We considered two scenarios, namely the stationary solution due to chemotherapy in the presence of a periodic forcing and fractional dynamics of cancer development. The main result obtained for the first scenario is a transition from a solid tumor to metastasis due the concentration density of cancer cells. The second scenario corresponds to a fractional development of a solid tumor in the initial stage. We obtained that for $\alpha < 0.5$ chemotherapy can be an effective treatment of the initial stage of solid tumor development only. For the long–time asymptotics the solution corresponds to metastasis and should be considered in the framework of another chemotherapy scenario.

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