Toy model of fractional transport of cancer cells due to self-entrapping

A. Iomin
Department of Physics, Technion, Haifa, 32000, Israel

(Received 8 September 2005; revised manuscript received 25 April 2006; published 26 June 2006)

A simple mathematical model is proposed to study the influence of cell fission on transport. The model describes fractional, in time, tumor development, which is a one-dimensional continuous-time random walk. The model is relevant for consideration of both solid and diffusive cancers.

DOI: 10.1103/PhysRevE.73.061918 PACS number(s): 87.15.Vv, 87.17.Ee, 87.18.Hf, 05.40.Fb

I. INTRODUCTION

Cancer is a complex disease which leads to the uncontrolled growth of abnormal cells, destruction of normal tissues, and invasion of vital organs. The malignant neoplasm cells spread through vascular or lymphatic vessels thus disseminating the disease with further lesion of vital organs. There are different stages of tumor development of varying duration, starting from genetic changes on the cell level and finishing with detachment of metastases and invasion. Tumor cell transport and proliferation are the main contributors to the malignant neoplasm dissemination (see, e.g., [1,2]). This evolution, related to collective or macroscopic behavior of cells, is described (in many cases) by kinetic cellular theory [3] (see also [1,2]). There are different approaches [1,2,4]. The most relevant for the present consideration of diffusive cancer is exemplified by brain tumor modeling [4], where an important factor is a dichotomy between migration and proliferation of cells, which is taken into account for numerical modeling of cancer development on a grid lattice. The existence of the dichotomy between these phenotypes of migration and proliferation was proposed in [5]; the molecular mechanism followed [6]; and then an active implementation for the brain tumor modeling, also related to fractional cancer topology, was established [4,7]. Independently of this approach, a mathematical formulation of the migration-proliferation dichotomy was performed in the framework of a continuous-time random walk (CTRW). A simple mathematical model of a CTRW by virtue of two time scales of tumor development was proposed [8,9]. The primary focus was on the influence of cell fission on transport properties of cells. It is worth mentioning that the mathematical apparatus of the fractional CTRW is well established for many applications in physics (see, e.g., [10–13]).

In the present paper we consider a collective behavior of cells, paying particular attention to an essential decrease in cell motility during the fission time, or self-entrapping, that is determined by the interaction of cells with their environment. The simplest realization of the model is a modification of the so-called comb structure [14–16]. It was shown, for this model, that tumor development corresponds to fractional transport [8,9]. Here we consider a different mechanism of proliferation. Solutions that are relevant for both solid tumors and metastases are obtained in the framework of the fractional Fokker-Planck equation, and an essential enhancement of anomalous transport due to proliferation is obtained as well.

II. FRACTIONAL MECHANISM OF TUMOR DEVELOPMENT

In this section we repeat the mathematical formulation of the migration-proliferation dichotomy in the framework of the CTRW. A simplified scheme of cell dissemination through the vessel network was considered by means of the following two steps [8,9]. 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 no transport (approximately). The duration of $\mathcal{T}_f$ can be arbitrarily large. During the second time $\mathcal{T}_t$, 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 that a cell travels during the time $\mathcal{T}_t X_t = V\mathcal{T}_t$. Hence, the cells form an initial packet of free-spreading particles, and the contribution of cell dissemination to the tumor development process consists of the following time sequence:

$$\mathcal{T}_f(1)\mathcal{T}_t(2)\mathcal{T}_f(3)\cdots . \tag{1}$$

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, one concludes that transport is characterized by random values $\mathcal{T}(i)$ which are the 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 [17]. It arises as a result of a sequence of independent identically distributed random waiting times $\mathcal{T}(i)$, each having the same probability distribution function (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 $\lambda(x)$ with a jump length variance σ^2. It is worth mentioning that a cell carries its own trap, by which it is set apart from transport. This process of self-entrapping differs from the standard CTRW, where traps are external with respect to the transporting particles. The crucial point of the fractional transport is the power law behavior of the waiting time PDF,

$$w(t) = \alpha\mathcal{T}(1 + t/\mathcal{T})^{1+\alpha}, \tag{2}$$

where $0<\alpha<1$ and $\mathcal{T}$ is a characteristic time. In this case $T=\infty$. A proper explanation of Eq. (2) can be the following

quotation from Ref. [12]: "A process with the long tailed pausing time distribution would suffer a very sporadic behavior—long intermittencies may exist, followed by bursts of events. The more probable pauses between events would be short but occasionally very long pauses would exist. Given a long pause, there is still a smaller but finite probability that an even longer one will occur. It is on this basis that one would not be able to measure a mean pausing time by examining data." Some justification of Eq. (2) for the fission times can be presented by proposing multiple time scales of self-entrapping. We can consider that self-entrapping for different generations of cells has different mean characteristic time scales. For example, we suppose that for the jth generation self-entrapping is the Poisson process $w_j(t)=\tau_j^{-1}\exp(-t/\tau_j)$ with the characteristic time scale $\tau_j=\tau^j$, where $\tau=\tau_1=\mathcal{T}$ is now the average time of cell divisions for the first generation. Therefore, following [12,18] and repeating the analysis of Ref. [18] (see [19]), one obtains that the PDF, which accounts for all exit events from proliferation occurring on all time scales, has the power law asymptotic of Eq. (2). However, it should be underlined that, contrary to the fractional electron transport in semiconductors [20,21], a mechanism of fractional cell transport is not yet developed. This approach needs separate consideration, e.g., in the framework of two component cell-nutrient reaction-diffusion equations. Nevertheless, Eq. (2) is valid, when cell transport is considered on a fractional subdiffusive structure such as a comb model.

III. COMBLIKE MODEL WITH PROLIFERATION

A. Comb model with proliferation

Fractional transport of cells, namely, subdiffusion, can be described in the framework of the comb model [14]. The comb model is an example of a subdiffusive one-dimensional medium where a CTRW takes place along the x structure axis. Diffusion in the y direction plays the role of traps with a PDF of delay times of the form $w(t)\sim 1/(1+t/\mathcal{T})^{3/2}$. A special behavior of diffusion on the comb structure is that displacement in the x direction is possible only along the structure axis (x axis at $y=0$). Thus, the diffusion coefficient in the x direction is $D_{xx}=D(x)\delta(y)$, while the diffusion coefficient in the transversal y direction is a constant $D_{yy}=D_0$. A random walk on the comb structure is described by the distribution function $P_1=P_1(x,y,t)$ and the current

$$\mathbf{j}=\left(-\delta(y)D(x)\frac{\partial P_1}{\partial x},-D_0\frac{\partial P_1}{\partial y}\right).$$

The continuity equation with proliferation $C(P_1)$ yields the following Fokker-Planck equation:

$$\frac{\partial P_1}{\partial t}+\delta(y)\mathcal{L}_{FP}(x)P_1-D_0\frac{\partial^2 P_1}{\partial y^2}=C(P_1), \tag{3}$$

with the Fokker-Planck operator $\mathcal{L}_{FP}=-\frac{\partial}{\partial x}D(x)\frac{\partial}{\partial x}$. The initial condition $P_1(x,y,0)=P_0(x)\delta(y)$ is an initial distribution on the x axis, and the boundary conditions are taken at infinities $P_1(t)=P_1'(t)=0$ for both the x and y coordinates. The primes denote spatial derivatives.

It is convenient to work with dimensionless variables and parameters. In the case of normal diffusion, when $D(x)=D_x=\text{const}$, the dimensionless time and coordinates are obtained by rescaling with relevant combinations of the comb parameters D_x and D_0. One obtains the dimensionless variables for time $(D_0^3/D_x^2)t\to t$ and for the coordinates $D_0x/D_x\to x$, $D_0y/D_x\to y$. In the case of inhomogeneous diffusion [we will consider $D(x)=vx^2$] the dimensionless time and coordinates, respectively, are $(v^2/D_0)t\to t$ and $vx/D_0\to x$, $vy/D_0\to y$.

We consider a possible mechanism of tumor cell proliferation. A different approach was developed in [9]. The term $C(P_1)$ in Eq. (3) determines the change in the total number of transporting cells due to proliferation at rate $\tilde{\mathcal{C}}$. This can be considered as a linear approximation of logistic population growth [22]

$$C(P_1)=\tilde{\mathcal{C}}P_1(1-P_1/K), \tag{4}$$

where K is the carrying capacity of the environment (see, e.g., [3]). It is worth stressing that linearization is important in the use of the powerful machinery of the Laplace transform. When $P_1/K\to P_1<1/2$ and $K\tilde{\mathcal{C}}=\mathcal{C}$, then the linearization $C(P_1)=\mathcal{C}P_1$ is valid [22]. In the opposite case, when $P_1>1/2$, the growth is approximated by $C(P_1)=\mathcal{C}\bar{P}_1$, where $\bar{P}_1=1-P_1$. According to the migration-proliferation dichotomy in the comb model, the transporting cells along the x axis do not proliferate. This means that cells proliferate only if they have a nonzero y coordinate. Therefore, $C(P_1)=\mathcal{C}[1-\delta(y)]P_1$, and Eq. (3) reads in the dimensionless form

$$\frac{\partial P_1}{\partial t}+\delta(y)\mathcal{L}_{FP}(x)P_1-\frac{\partial^2 P_1}{\partial y^2}=\mathcal{C}[1-\delta(y)]P_1. \tag{5}$$

When $\mathcal{C}>0$, Eq. (5) describes cell transport with proliferation, and the PDF P_1 corresponds to a low concentration of cells. In the opposite case, when $\mathcal{C}<0$, Eq. (5) describes fractional cell transport with degradation that corresponds to a high cell concentration, and P_1 is exchanged for $\bar{P}_1$.

The first term in the right-hand side of Eq. (5) is eliminated by substitution $P_1=e^{\mathcal{C}t}F_1$. Carrying out the Laplace transform $\tilde{F}_1(s,x,y)=\hat{L}[F_1(x,y,t)]$ and looking for the solution in the form $\tilde{F}_1=e^{-\sqrt{s}|y|}f(x,s)$, one obtains

$$F_1(x,y,t)=\hat{L}^{-1}[f(x,s)\exp(-\sqrt{s}|y|)]. \tag{6}$$

Integrating Eq. (5) with respect to the variable y and introducing the PDF

$$P(x,t)=\int_{-\infty}^{\infty}P_1(x,y,t)dy, \tag{7}$$

one obtains the following equation for $F=e^{-\mathcal{C}t}P$ in the Laplace space $\tilde{F}(s)=\hat{L}[F(t)]$:

$$s\tilde{F} + \hat{\mathcal{L}}_{FP} f = P_0(x) - \mathcal{C}f. \tag{8}$$

Integrating Eq. (6) over y, we obtain a relation between the PDFs of the total number of cells F and transporting number of cells f in the Laplace space

$$f \equiv \tilde{F}_1(x, y=0, s) = (1/2)\sqrt{s}\tilde{F}(x,s).$$

Substitution of this relation in Eq. (8) yields, after Laplace inversion, the Fokker-Planck equation for the distribution F. To this end, Eq. (8) is multiplied by $\sqrt{s}$ and then by virtue of Eq. (A6) the inverse Laplace transform yields the following equation for F:

$$2D_C^{1/2} F + \hat{\mathcal{L}}_{FP} F = -\mathcal{C}F, \tag{9}$$

where D_C^α is the fractional derivative in the Caputo form [23] (see the Appendix). This equation describes fractional transport of cells with fission when $\mathcal{C}>0$ and degradation when $\mathcal{C}<0$, where the sign of $\mathcal{C}$ depends on whether $P=e^{\mathcal{C}t}F < 1/2$ or $P>1/2$ [24].

IV. FRACTIONAL DYNAMICS OF UNTREATED CANCER

As shown, cell fission is the source of the fractional time derivatives. This equation can be extended for an arbitrary fractional exponent $0<\alpha<1$: $1/2 \to \alpha$. Therefore, this generalization of Eq. (9) yields

$$D_C^\alpha F + \alpha \hat{\mathcal{L}}_{FP} F = -\alpha \mathcal{C} F. \tag{10}$$

Taking into account that D_C^α can be expressed by the Riemann-Liouville fractional derivatives D_{RL}^α (see the Appendix) $D_C^\alpha = D_{RL}^{\alpha-1} D_{RL}^1$ and $D_{RL}^{1-\alpha} D_{RL}^{\alpha-1} = 1$, we obtain another, standard, form for the fractional Fokker-Planck equation (FFPE) with proliferation, or degradation,

$$\alpha \frac{\partial F}{\partial t} + \alpha D_{RL}^{1-\alpha} \hat{\mathcal{L}}_{FP} F = -\alpha \mathcal{C} D_{RL}^{1-\alpha} F. \tag{11}$$

To solve Eq. (11), we use separation of variables [11]. First, we consider homogeneous diffusion $\mathcal{L}_{FP} = -\frac{\partial^2}{\partial x^2}$ and $C = K\tilde{C} D_x^2 / D_0^3$.

A. Homogeneous diffusion: $D(x)=1$

We consider an analytical solution for $P<1/2$ using the following substitution:

$$F(x,t) = \sum_n F_n = \sum_n T_n(t)\phi_n(x). \tag{12}$$

Therefore, a solution that corresponds to the initial condition $P_0(x)$ is determined by the Green's function $W(x,t|x',0)$:

$$F(x,t) = \int_{-\infty}^{\infty} dx' W(x,t|x',0) P_0(x')$$

$$= \int_{-\infty}^{\infty} dx' \int dk\, T_k(t)\phi_k(x)\phi_k^*(x') P_0(x'). \tag{13}$$

Here $\phi_k(x)$ is a solution of the eigenvalue problem $-\partial^2 \phi_k / \partial x^2 = \lambda(k)\phi_k$, where $\lambda(k)=k^2$ is the continuous spectrum with eigenfunctions

$$\phi_k(x) = \exp[\pm kx]. \tag{14}$$

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

$$\dot{T}_k(t) + \alpha \lambda_{\mathcal{C}}(k) D_{RL}^{1-\alpha} T_k(t) = 0, \tag{15}$$

where $\lambda_{\mathcal{C}}(k) = (k^2 + \mathcal{C})$. The solution is described by the Mittag-Leffler function $E_\alpha(z) \equiv E_{\alpha,1}(z)$ [11] (see the Appendix)

$$T_k(t) = E_\alpha[\alpha \lambda_{\mathcal{C}}(k) t^\alpha], \tag{16}$$

where $T_k(0)=1$, and $E_\alpha(z)$ has the initial stretched exponential behavior

$$T_k(t) \sim \exp\left[-[\alpha \lambda_{\mathcal{C}}(k) t^\alpha]/\Gamma(1+\alpha)\right] \tag{17}$$

which turns over to the power law long-time asymptotics

$$T_k(t) \sim [\Gamma(1-\alpha)\alpha \lambda_{\mathcal{C}}(k) t^\alpha]^{-1}. \tag{18}$$

Using these properties of $E_\alpha(z)$, the fractional spreading of cancer cells can be evaluated analytically for both initial and long-time behaviors. Substitution of Eqs. (14) and (17) in Eq. (13) yields the following initial-time solution:

$$P(x,t) \propto \sqrt{\frac{\pi \Gamma(1+\alpha)}{\alpha t^\alpha}} \exp[\mathcal{C}t - \alpha \mathcal{C} t^\alpha / \Gamma(1+\alpha)]$$

$$\times \exp[-\Gamma(1+\alpha) x^2 / 4\alpha t^\alpha]. \tag{19}$$

Analogously, the long-time solution is

$$P(x,t) \propto \frac{1}{\alpha t^\alpha \Gamma(1-\alpha)} \exp(\mathcal{C}t - \sqrt{\mathcal{C}}|x|), \tag{20}$$

where we take, for clarity, $P_0 = \delta(x)$ for both the short- and long-time solutions. The most interesting is Eq. (20), since it describes long-time dynamics. When the index in the exponential function is zero, it corresponds to a front of cell invasion with the equation $x \sim l_0 = \sqrt{\mathcal{C}}t$. This is the so-called linear model, which describes a solid tumor growth. In the region $x<l_0$ exponential growth $e^{\mathcal{C}t}$ is dominant. Thus, when $P>1/2$ (and $\mathcal{C}<0$) the solution of Eq. (20) contains an imaging exponent $P \sim 1 - \exp(-\mathcal{C}t \pm i\sqrt{|\mathcal{C}|}x)$. This expression does not contradict to boundary conditions, since this high-concentration solution is valid in the restricted region $|x| < l_0$ only. Equation (20) corresponds to the long-time solution with $\mathcal{C}t \gg 1$, and $P = 1 - \bar{P} \approx 1$. Therefore, the solid tumor consists of a core of size $\sim l_0$ with an almost constant concentration $P \sim 1$. For a two-component model this high-concentration part corresponds to a necrotic core [1]. The situation changes dramatically when the diffusion operator $\hat{\mathcal{L}}_{FP}$ corresponds to inhomogeneous diffusion.

B. Inhomogeneous diffusion: $D(x)=vx^2$

When $D(x)=vx^2$, the dimensionless proliferation rate is $\mathcal{C} = K(D_0/v^2)\tilde{\mathcal{C}}$. The FFPE is now

$$\frac{\partial}{\partial t}F - \alpha D^{1-\alpha}\frac{\partial}{\partial x}x^2\frac{\partial}{\partial x}F = -\alpha \mathcal{C} D^{1-\alpha}F. \tag{21}$$

The solution differs essentially from the one obtained in the previous section. The short-time solution is obtained in the form of the log-normal distribution

$$P(x,t) \propto \exp\left(\mathcal{C}t - \frac{\Gamma(1+\alpha)}{4\alpha t^{\alpha}}\ln^2|x|\right). \tag{22}$$

In this case, even for the short-time scale, cancer cells spread exponentially fast, and the front of invasion is due to the stretched exponential $l_0=|x|\sim\exp[2\sqrt{\alpha\mathcal{C}/\Gamma(1+\alpha)}t^{(1+\alpha)/2}]$. This dynamics is the initial stage of metastasis, which is determined by the long-time dynamics, namely, Lévy flights,

$$P(x,t) \propto \frac{\exp(\mathcal{C}t)}{(|x|^{1/2+\mathcal{C}}t^{\alpha})}, \tag{23}$$

where the front of invasion is an exponential function $l_0 \sim\exp[2\mathcal{C}t/(1+2\mathcal{C})]$. We consider here $D(x)=vx^2$, since this case is analytically tractable. As shown in [8,15,16], inhomogeneous convection with velocity $\sim x^s$ leads to superdiffusion for $0<s\leqslant 1$. For $s>1$ an asymptotic analysis for $x \gg 1$ yields Lévy flights. Therefore, an asymptotic solution of Eq. (11) can be obtained, by analogy with Refs. [8,15,16], for the comb model in the presence of inhomogeneous convection with x^s, where $s>0$ and is arbitrary, but $D(x)$ is a constant value. This case can be relevant, e.g., for cancer cell transport modeling in a vascular or lymphatic vessel network (see [8]).

V. CONCLUSION

The present study focuses on the influence of cell proliferation on transport properties. The mathematical formulation of this proliferation-migration dichotomy is based on two main stages: cell fission with the self-entrapping time $\mathcal{T}_f$ and cell transport with duration $\mathcal{T}_t$. By virtue of these two time scales the description of tumor development is reduced to a CTRW process. A toy model of cancer development is suggested by using heuristic arguments on the relation between tumor development and the CTRW. In this case fractional tumor development becomes a well-defined problem since the mathematical apparatus of CTRW is well established (see, e.g., [10–13,25]). The constructed model is a modification of the so-called comb structure [14–16]. An important feature of this consideration of cell transport in the framework of the comb model is an essential enhancement of anomalous transport due to proliferation. Moreover, we obtained that the distribution function of the fractional transport depends on only two parameters, namely, the scaled proliferation rate $\mathcal{C}$ and the fractional exponent α, where $\alpha=1/2$ for the comb model. Another important result is the homogeneity property of the diffusion coefficient $D=D(x)$. When the Fokker-Planck operator describes normal diffusion, the fractional tumor transport is relevant to solid tumor development. When the Fokker-Planck operator corresponds to inhomogeneous, or turbulent, diffusion, the fractional transport corresponds to superdiffusion, which is relevant to metastasis.

ACKNOWLEDGMENT

This research was supported by the Israel Science Foundation.

APPENDIX: FRACTIONAL INTEGRO-DIFFERENTIATION

A basic introduction to the fractional calculus can be found, e.g., in Ref. [25]. Fractional integration of the order of α is defined by the operator

$$I_a^{\alpha}f(t) = \frac{1}{\Gamma(\alpha)}\int_a^t f(\tau)(t-\tau)^{\alpha-1}d\tau \quad (\alpha>0). \tag{A1}$$

There is no constraint on the limit a. In our consideration, $a=0$ since this is a natural limit for the time. The fractional derivative is defined as the inverse operator to $I^{\alpha}\equiv I_0^{\alpha}$:

$$\frac{d^{\alpha}}{dt^{\alpha}} = I^{-\alpha} = D^{\alpha}, \quad I^{\alpha} = \frac{d^{-\alpha}}{dt^{-\alpha}} = D^{-\alpha}.$$

Its explicit form is the convolution

$$D^{\alpha}f(t) = \frac{1}{\Gamma(-\alpha)}\int_0^t \frac{f(\tau)}{(t-\tau)^{\alpha+1}}d\tau. \tag{A2}$$

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 [23]:

$$D_{RL}^{\alpha}f(t) = D^n I^{n-\alpha}f(t) = \frac{1}{\Gamma(n-\alpha)}\frac{d^n}{dt^n}\int_0^t \frac{f(\tau)}{(t-\tau)^{\alpha+1-n}}d\tau, \tag{A3}$$

$$D_C^{\alpha}f(t) = I^{n-\alpha}D^n f(t) = \frac{1}{\Gamma(n-\alpha)}\int_0^t \frac{f^{(n)}(\tau)}{(t-\tau)^{\alpha+1-n}}d\tau, \tag{A4}$$

where $n-1<\alpha<n$, $n=1,2,\ldots$. Equation (A3) is the Riemann-Liouville derivative, while Eq. (A4) is the fractional derivative in the Caputo form [23,25]. Performing integration by parts in Eq. (A3) and then applying Leibnitz's rule for the derivative of an integral and repeating this procedure n times, we obtain

$$D_{RL}^{\alpha}f(t) = D_C^{\alpha}f(t) + \sum_{k=0}^{n-1} f^{(k)}(0^+)\frac{t^{k-\alpha}}{\Gamma(k-\alpha+1)}. \tag{A5}$$

The Laplace transform can be obtained for Eq. (A4). If $\hat{L}f(t)=\tilde{f}(s)$ is the Laplace transform of $f(t)$, then

$$\hat{L}[D_C^{\alpha}f(t)] = s^{\alpha}\tilde{f}(s) - \sum_{k=0}^{n-1} f^{(k)}(0^+)s^{\alpha-1-k}. \tag{A6}$$

We also note that

$$D_{RL}^{\alpha}[1] = \frac{t^{-\alpha}}{\Gamma(1-\alpha)}, \quad D_C^{\alpha}[1] = 0. \tag{A7}$$

The fractional derivative of a power function is

$$D_{RL}^{\alpha} t^{\beta} = \frac{t^{\beta-\alpha}\Gamma(\beta+1)}{\Gamma(\beta+1-\alpha)}, \tag{A8}$$

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., [25]):

$$E_{\gamma,\delta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\gamma k + \delta)}. \tag{A9}$$

Therefore, from Eqs. (A8) and (A9) we have the expression

$$D_{RL}^{\alpha} e^{\lambda t} = t^{\alpha} E_{1,1-\alpha}(\lambda t). \tag{A10}$$

[1] N. Bellomo and L. Preziosi, Math. Comput. Modell. **32**, 413 (2000).
[2] K. R. Swanson, S. Bridge, J. D. Murray and E. S. Alvord, Jr., J. Neurol. Sci. **216**, 1 (2003).
[3] J. D. Murray, *Mathematical Biology* (Springer, Heidelberg, 1993).
[4] Y. Mansury and T. Deisboeck, Physica A **331**, 219 (2004); Physica D **196**, 193 (2004).
[5] A. Giese *et al.*, Int. J. Cancer **67**, 275 (1996).
[6] A. Wells, Int. J. Biochem. Cell Biol. **31**, 637 (1999).
[7] C. A. Athale, Y. Mansury, and T. S. Deisboeck, J. Theor. Biol. **233**, 469 (2005).
[8] A. Iomin, J. Phys.: Conf. Ser. **7**, 57 (2005).
[9] A. Iomin, WSEAS Trans. Biol. Biomed. **2**, 82 (2005).
[10] *Fractional Calculus in Physics*, edited by R. Hilfer (World Scientific, Singapore, 2000).
[11] R. Metzler and J. Klafter, Phys. Rep. **339**, 1 (2000).
[12] E. W. Montroll and M. F. Shlesinger, in *Studies in Statistical Mechanics* (North-Holland, Amsterdam, 1984), Vol. 11.
[13] R. Gorenflo and F. Mainardi, *Processes with Long Range Correlations* (Springer Verlag, Berlin, 2003).
[14] G. H. Weiss and S. Havlin, Physica A **134**, 474 (1984).
[15] E. Baskin and A. Iomin, Phys. Rev. Lett. **93**, 120603 (2004).
[16] A. Iomin and E. Baskin, Phys. Rev. E **71**, 061101 (2005).
[17] E. W. Montroll and G. H. Weiss, J. Math. Phys. **6**, 167 (1965).
[18] A. Blumen, J. Klafter, and G. Zumofen, in *Fractals in Physics*, edited by L. Pietronero and E. Tosatti (North-Holland, Amsterdam, 1986), p. 399.
[19] Repeating exactly the analysis of Ref. [18], we obtain, by taking into account events occurring on all time scales, the following distribution: $w(t)=[(1-b)/b]\Sigma_{j=1}^{\infty} b^j \tau^{-j} \exp(-t/\tau^j)$, where $b<1$ is a normalization constant. Therefore, the last expression is a normalized sum and $w(t/\tau)=\tau w(t)/b-(1-b)\exp(-t/\tau)/b$. Using the conditions $t \gg \tau > 1/b$, one obtains that at longer times $w(t/\tau)=\tau w(t)/b$. The last expression is equivalent to $w(t) \sim 1/t^{1+\alpha}$, where $\alpha=\ln(b)/\ln(1/\tau)$.
[20] M. F. Shlesinger, J. Stat. Phys. **10**, 421 (1974).
[21] M. Pollak, Philos. Mag. **36**, 1157 (1977).
[22] S. V. Petrovskii and B.-L. Li, *Exactly Solvable Models of Biological Invasion* (Chapman & Hall, Boca Raton, FL, 2005).
[23] F. Mainardi, Chaos, Solitons Fractals **7**, 1461 (1996).
[24] Since $\partial \bar{P}_1 = -\partial P_1$, Eq. (5) for P_1 (when $P_1 < 1/2$) just coincides with that for $\bar{P}_1 = 1 - P_1$ (when $P_1 > 1/2$). The only difference is when $P_1 < 1/2$, $\mathcal{C} > 0$, while for $P_1 > 1/2$ one has $\mathcal{C} < 0$.
[25] I. Podlubny, *Fractional Differential Equations* (Academic Press, San Diego, 1999).