Maximum therapeutic effect of glioma treatment by radio-frequency electric field

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Abstract

The influence of a radio-frequency electric field on glioma brain cancer development is considered. Specifically, the effectiveness of this medical technology against invasive cells with a high motility, when switching between migrating and proliferating phenotypes takes place, is addressed. It is shown that glioma development under the external field treatment can be modelled in the framework of the continuous time random walk, where the segregation of proliferating from not proliferating cells by the external electric field is naturally accounted for. The constructed reaction-transport equation is based on the fact that cytokinesis affects the cell dynamics strongly, and the cell kinetics is non-Markovian, which is reflected in both the transport and reaction properties of cells. As a result of the interplay between cell proliferation and cell degradation, migrating cancer cells spread freely without being influenced by the details of the degradation of the proliferating cells, which leads to a decrease in the effectiveness of the treatment.

Keywords: Glioma brain cancer, Tumor treating field, Fractional kinetics, Continuous time random walks

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1. Introduction

A new therapeutic method suggested in [1, 2, 3] for non-invasive treatment of glioma brain cancer by a radio-frequency electric field also opens new directions of understanding of glioma development. A specific question that emerges is the effectiveness of this new medical technology against invasive cells with high motility, when switching between migrating and proliferating phenotypes takes place. As is well known, one of the main features of malignant brain cancer is the ability of tumor cells originating in the glioma to invade normal tissue at a distance from the multi-cell tumor core. This abnormal motility constitutes the metastasis feature of brain cancer, causing treatment failure [4]. This problem relates to modelling of the dynamics of cancer glial cells in heterogeneous media (as brain cancer is) in the presence of a radio-frequency electric field, which acts as a tumor treating field (TTField) [1, 2, 3]. As reported, this transcranial treatment by a low-intensity (1-3 V/cm), intermediate-frequency (100-200 kHz) alternating electric field, produced by electrode arrays applied to the scalp, destroys cancer cells that are undergoing division, while normal tissue cells are relatively unaffected. An important result of this new treatment technology is that the survival period is increased twofold.

Glioma is one of the most recalcitrant brain diseases, with a standard treatment survival period of 7-12 months [3, 5]. One of the main mechanisms of this devastating manifestation is the migration-proliferation dichotomy of cancer cells. This phenomenon was first observed in clinical investigations [6, 7], where it was shown that cancer cells in the outer invasive zone of glioma possess the high motility property, while the proliferation rate of these migratory cells is essentially lower than those in the tumor core. This anti-correlation between proliferation and migration of cancer cells, also known as the Go or Grow hypothesis (see discussions in [8, 9]), suggests that cell division and cell migration are temporally exclusive phenotypes [6]. The phenomenon that tumor cells defer proliferation for cell migration was also experimentally demonstrated in
The switching process between these two phenotypes is still not well understood. Moreover, it should be mentioned that conflicting data appear in the literature concerning the Go or Grow hypothesis; details of discussions on this can be found in [9, 8].

Extensive theoretical modelling followed these findings, and much effort is being invested in developing relevant models with relevant switching mechanisms of the glioma cells to understand this dichotomy, when the high motility suppresses cell proliferation in the outer invasive region, while the immobile cancer cells have a high proliferation rate like the cells in the cancer core. There are different approaches that have resulted in several phenomenological models, which have supplied also experimental in vitro confirmation data [14, 15]. Comprehensive discussions of these models appear in [14, 16, 17, 18, 19].

The main subject of the paper is the fractional kinetics of the new therapeutic technology [1, 2, 3], where the TTField acts against invasive proliferating cancer cells. The TTField segregates proliferating cells (either transporting or not) from transporting cells out of cytokinesis. As stated in Ref. [8], on the individual cell level, the processes of migration and proliferation are separated in time. The TTField “fills” this dichotomy of a single cell. These facts are important for a continuous time random walk (CTRW) description, since it is based on the dynamics of a single particle (e.g., see review [20]). Therefore, we follow the CTRW consideration presented in [21], where a mechanism for entrapping transporting cells by fission was suggested, and the migration-proliferation dichotomy appears naturally. Therefore, the efficiency of the TTField action can be evaluated in the framework of the fractional kinetics of glioma development under the TTField treatment. The first study of this kinetics in the framework of a fractional comb model [22] showed that the TTField efficiency is restricted by its space dispersion. In particular, it depends on the fractal mass dimension of the cancer cells. In the present research, we propose a general,

\[ \text{This kind of migration-proliferation dichotomy was also found at metastatic behavior of breast cancer [1].} \]
probabilistic consideration of cancer cell kinetics and obtain a solution for an arbitrary distribution of proliferating cells, which can change in time and space. In the framework of the constructed model, we show that the glioma development corresponds to the compensated cancer development, when the TTField compensates cell proliferation, and we consider this solution as the maximum therapeutic effect of glioma treatment due to the TTField.

2. Time multi-scaling of the CTRW modelling of cell transport

2.1. Fission and motility times

A simplified scheme of the migration-proliferation dichotomy of cancer cells can be considered by virtue of two time scales of tumor development. The first corresponds to the biological process of cell fission with random duration $T_f$. The second process is cell transport with random duration $T_t$. During the time scale $T_f$, the cells interact strongly with the environment, and the motility of the cells is vanishingly small. During the second time $T_t$, interaction between the cells is weak and the motility of the cells leads to cell invasion, which is a very complex process controlled by matrix adhesion. It involves several steps, including receptor-mediated adhesion of cells to the extracellular matrix (ECM), matrix degradation by tumor-secreted proteases (proteolysis), detachment from ECM adhesion sites, and active invasion into the intercellular space created by protease degradation. It is convenient to introduce a “jump” length, $X_t$, of these detachments as the distance that a cell travels during the time $T_t$. 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 sequences: $T_f(1)T_t(2)T_f(3)$. There are different realizations of this chain of times, due to different durations of $T_f(i)$ and $T_t(i)$, where $i = 1, 2, \ldots$. Therefore, one concludes that transport is characterized by random values $T(i)$, 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). It arises as a result of a sequence
of independent identically distributed random waiting times $T(i)$, each having the same pdf $\psi(t)$, $t > 0$ with a mean characteristic time $T$, and a sequence of independent identically distributed random jumps, $x = X(i)$, each having the same pdf $p(x)$ with a jump length variance $\sigma^2$, equal to the square averaged intercellular/cellular space $\sigma \sim 10^{-3}$ cm. It is worth mentioning that a cell “carries” its own trap, by which it is set apart from the transport process. This process of self-entrapping differs from the standard CTRW, where traps are external with respect to the transporting particles. The probability to “escape from $i$-th trap” of fission is locally determined by the Poisson distribution $e^{-t/\tau_i}$ with different time scales, or even random scales.

2.2. Example of power law: a toy model

This absence of a unique time scale leads to the power law distribution of fission times. For example, one can suppose that self-entrapping for different generations of cells has different mean characteristic time scales. We consider that the $j$-th generation of self-entrapping is the Poisson process

$$w_j(t) = \tau_j^{-1} \exp\left(-t/\tau_j\right)$$

with the characteristic time scale $\tau_j = \tau^j$, where $\tau_1 = \tau$ is now an average cell division time for the first generation. Therefore, following [26, 27] and repeating exactly the analysis of Ref. [27], we obtain, by taking into account events occurring on all time scales, the distribution

$$\psi(t) = \frac{1}{b} \sum_{j=1}^{\infty} b^j \tau_j^{-j} \exp\left(-t/\tau_j\right),$$

where $b < 1$ is a normalization constant. Therefore, the last expression is a normalized sum and

$$\psi(t/\tau) = \tau \psi(t)/b - (1 - b) \exp(-t/\tau)/b.$$

Using conditions $t \gg \tau > 1/b$, one obtains that at longer times $\psi(t/\tau) = \tau \psi(t)/b$. The last expression is equivalent to

$$\psi(t) \sim 1/t^{1+\alpha},$$

(1)
where $\alpha = \ln(b) / \ln(1/\tau)$.

### 2.3. Power law distribution of fission times

As shown in the above example, one obtains that the pdf accounts for all exit events from the proliferation process occurring on all time scales, and has the power law asymptotic solution \([1]\), where $0 < \alpha < 1$ and $\tau$ is a characteristic time. Taking into account the normalization condition, one obtains

$$\psi(t) = \frac{\alpha \tau^\alpha}{(\tau + t)^{1+\alpha}}$$

(2)

In this case, the averaged time is infinite. A clear explanation of Eq. (2) can be the following quotation from Ref. \([28]\): “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.”

Following statistical arguments, one should bear in mind that the absence of a scale (or existence of a random fission scale) follows from the variety of fluctuations of the cell environment with which cancer cells interact \([29]\). As stated in \([8]\), the competition of proliferation and migration for the finite free energy resources supports the mutual exclusiveness of these cellular processes. Therefore, for the fixed cell energy, there is a degeneracy property of many cell states that leads to the cell state entropy $S$. As a result of this interaction with the environment and the energy competition, as well as of the environmental fluctuations, the escape probability from the “fission traps” is described by Boltzmann’s distribution $\exp(S)$. This value is proportional to the inverse waiting time $t^{-1} \sim \exp(S)$ \([31]\). Obviously, $S$ depends on a variety of external

\(^2\)Note that the entropy is negative. For the entropy role in carcinogenesis and tumor growth see paper by Gatenby and Frieden \([30]\).
(environmental) characteristics and can be considered as a random value with
the Poisson distribution (for the local time and space) $P(S) = \langle S \rangle \exp(S/\langle S \rangle)$,
where a normalization constant $\langle S \rangle$ is the absolute value of the mean entropy.
The probability to find the waiting time in the interval $(t,t+dt)$ is equal to
the probability to find the entropy (as a trapping potential) in the interval
$(S,S+d(-S))$, namely, $\psi(t)dt = P(S)d(-S)$. Taking into account these probabilistic arguments, one obtains $\psi(t) \sim \frac{dt}{\langle S \rangle}$. This leads to the normalized distribution of Eq. (2), where the transport exponent $\alpha$, as a rate of the escape, is determined as the inverse mean entropy
\[ \alpha = \frac{1}{\langle S \rangle}. \] (3)

3. Kinetic equation of cell CTRW

Since the pdfs of waiting times $\psi(t)$ and jump length $p(r)$ are specified
in Sec. 2 we can construct a kinetic equation of cells, following the CTRW
approach [25] and paraphrasing it from [20, 31]. First, we consider a process of
jumps. Let $P_j(r)$ be the pdf of being at $r$ after $j$ jumps. As described in Sec. 2
the cell jumps are independent and obey the Markov property
\[ P_{j+1}(x) = \int P_j(r')p(r-r')d^3r', \] (4)
where $P_0(r)$ is the initial condition.

Now, let us consider the pdf $\psi(t)$ taking into account the dynamics of the
jumps. As mentioned in Sec. 2 waiting times for different jumps are statistically
independent. Therefore, indexing the waiting time pdf by the jump number,
we define that $\psi_j(t)$ is the probability density that the $j$th jump occurs at time $t$ (see e.g., [31], p.42). Because of the reasonable assumption that jumps are
independent transitions, we also introduce the Markov property for $\psi_j(t)$, which reads
\[ \psi_{j+1}(t) = \int_0^\infty \psi_j(t')\psi(t-t')dt', \] (5)
where $\psi_1(t) \equiv \psi(t)$. Now, we introduce the pdf $P(r,t) = \sum_j P_j(r)\psi_j(t)$ of
arriving at coordinate $r$ at time $t$. From Eqs. (4) and (5), we introduce the
which relates the pdf $P(r, t)$ of just having arrived at position $r$ at time $t$ to the pdf $P(r', t')$ of just arriving at $r'$ at time $t'$. The last term in Eq. (6) is the initial condition. Thus, the pdf $n(r, t)$ of being at position $r$ at time $t$ is given by arrival at $r$ at time $t'$ and not moving after this event, namely

$$n(r, t) = \int_0^t P(r, t') \Psi(t - t') dt',$$  \hspace{1cm} (7)

where $\Psi(t) = 1 - \int_0^t \psi(t') dt'$ denotes the probability of no jump during the time interval $(0, t)$. Performing the Fourier transform $\hat{p}(k) = \mathcal{F} p(x)$ and the Laplace transform $\hat{\psi}(s) = \mathcal{L} \psi(t)$, we obtain the Montroll-Weiss equation

$$\hat{n}(k, s) = \hat{F} \hat{\mathcal{L}} n = 1 - \frac{\hat{\psi}(s)}{s} \hat{\hat{n}}_0(k) \frac{1}{1 - \hat{p}(k) \hat{\psi}(s)}.$$  \hspace{1cm} (8)

Eq. (8) can be simplified for the long time $s \ll 1$ and the large scale $k \ll 1$ asymptotics, which corresponds to the diffusion limit $(k, s) \to (0, 0)$. For the intermediate asymptotic times, restricted from above, $t < T_{\text{max}}$, we consider the large scale limit $k \ll 1$ only. Here $k = |k|$. Taking into account the Fourier $\hat{p}(k)$ image in Eq. (8), where

$$p(r) = \frac{1}{\sqrt{4\pi\sigma_x^2}} e^{-\frac{x^2}{2\sigma_x^2}} \frac{1}{\sqrt{4\pi\sigma_y^2}} e^{-\frac{y^2}{2\sigma_y^2}} \frac{1}{\sqrt{4\pi\sigma_z^2}} e^{-\frac{z^2}{2\sigma_z^2}},$$

one obtains

$$\hat{p}(k) \approx 1 - \frac{\sigma^2}{6} (k_x^2 + k_y^2 + k_z^2).$$  \hspace{1cm} (9)

Here, the factor $\frac{1}{6}$ is responsible for the equal probability to jump in either direction. Substituting Eq. (9) in the Montroll-Weiss equation (8), one obtains a kinetic equation in the Fourier-Laplace space. Performing the Fourier and the Laplace inversion, one obtains the kinetic equation of cancer cells without proliferation.

$$\partial_t n(r, t) = \frac{\sigma^2}{6} \Delta \int_0^t K(t - t') n(r, t') dt'.$$  \hspace{1cm} (10)
Here, $\Delta = \partial^2_x + \partial^2_y + \partial^2_z$ and the kinetic kernel of the transition probability $K(t)\frac{s\psi(s)}{1-\psi(s)}$ is determined from Eq. (5). In the next section, we consider a general scheme of cancer cells transport provided with the antimitotic treatment of proliferating cancer cells.

4. CTRW analysis with antimitotic treatment

We are concerned with the problem of the glial cancer cell spreading in the outer invasive region as a growing tumor spheroid, where the density of cells is $n(r, t)$ and $r = (x, y, z)$. Following a standard CTRW scheme for the description of a non-Markovian transport, suggested in Secs. 2 and 3, we introduce a power law waiting time probability distribution function (waiting time pdf) $\psi(t) \sim \tau/t^{1+\alpha}$ between any two successive cell moves/jumps, where $0 < \alpha < 1$ and $\tau$ is a characteristic time scale; for example, it can be the average time of the cell’s division. This function has a general impact on both the transition probability kernel and the proliferation kernel, which govern the total density of cancer cells $n(r, t)$ in the framework of the master equation

$$\partial_t n(r, t) = \frac{\sigma^2}{6} \Delta n(r, t) + \int_0^t K(t-t')n(r, t')dt' + \int_{-\infty}^{t} d^3r' \int_0^t C(r-r', t-t')n(r', t')dt'. \quad (11)$$

The kinetic part of the equation is inferred in the previous section, see Eq. (10).

Here, the kinetic kernel of the transition probability $K(t)$ reflects non-Markovian cell transport and it relates to the waiting time pdf $\psi(t)$ in the Laplace space of the Montroll-Weiss equation $25$

$$\hat{K}(s) = \hat{L}[K(t)] = \frac{s\hat{\psi}(s)}{1-\hat{\psi}(s)}, \quad \hat{\psi}(s) = \hat{L}[\psi(t)]. \quad (12)$$

Like any chronic antimitotic treatment, the proliferation-treating kernel, or the TTField kernel $C(r, t)$ describes an effect of the TTField action on the pro-

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3In the Markov case, when $\psi(t) = \frac{1}{\tau}e^{-t/\tau}$ and $\mathcal{K}(t-t') = \frac{1}{\tau}\delta(t-t')$, the kinetic part reduces to the standard Fokker-Planck equation $\partial_t n(r, t) = K\Delta n(r, t)$, where $K = \frac{\sigma^2}{6\tau}$. 

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liferating cells. In the general case, it is a random in space and time operator. Another important property of the cell proliferation in the outer invasive region is that this process takes place in some fraction of the invasive volume with some fractal dimension $D_{fr}$. Here, the TTField action will be considered as an averaged result of the competition between proliferation and degradation (due to the TTField) of cells with the maximum therapeutic effect. In this case, the dispersion of the TTField kernel is described in the Fourier space $C(k, t) = \hat{F}[C(r, t)]$.

We take this dependence in the multiplicative form, where the TTField kernel is proportional to the dispersion of the proliferation cell density $C_0(k)$ and its probability $\Psi(t)$ to stay in the proliferation phenotype until time $t$:

$$C(k, t) = C_0(k)\Psi(t) = C_0(k) \int_t^\infty \psi(t')dt' ,$$

and $\hat{C}(k, s) = \hat{L}[C(t)] = C_0(k)(1 - \hat{\psi}(s))/s$. Here, the dispersion $C_0(k) > 0$ is also a compensation rate between a cell’s degradation and proliferation, which depends on the density of proliferating cancer cells. At this point, we do not specify explicitly the details of this dispersion. Note only that in a dispersionless case, $C_0 = \text{const}$, and integration over the space in Eq. (11) disappears. Equation (11) in the Fourier-Laplace space reads

$$s\hat{n} = -\frac{\sigma^2}{6}k^2\hat{K}(s)\hat{n} - C_0(k)\frac{1 - \hat{\psi}(s)}{s}\hat{n} + \hat{n}_0(k),$$

where $\hat{n} = \hat{n}(k, s) = \hat{F}[n(r, t)]$ is the Fourier-Laplace image of the pdf and $k^2 = |k|^2$. Here, $\hat{n}_0(k) = \hat{F}[n(r, t = 0)]$ is the Fourier image of the initial conditions. For simplicity, we take it in the form of a constant value $n_0$. In this case, the pdf $n(r, t)$ coincides with Green’s function. Therefore, the cell

\footnote{Contrary to the drug anti-mitotic action, the modality of the TTField action is physical and related to dielectrophoresis (see, e.g., [32]), when the non-uniformity of the TTField exerts a force, focusing at the narrow cytoplasmatic bridge between two daughter cells at fission. This leads to disruption of the cytokinesis stage of the cell proliferation; eventually, the cells are destroyed without the quiescent cells of normal tissues being affected [1, 2, 3].}
dynamics is described by the Fourier and the Laplace inversions

\[ n(r, t) = \hat{F}^{-1} \hat{L}^{-1} \left[ \frac{\tilde{n}_0}{s + \frac{\sigma^2}{6} \hat{K}(s) k^2 + C_0 \frac{1 - \tilde{\psi}(s)}{s}} \right]. \tag{15} \]

Here and in the following, we use \( C_0 \equiv C_0(k) \). In the Fourier space, solution (15) can be expressed by the Mittag-Leffler function \[33\]. For the non-Markovian dynamics, the Laplace image of the waiting time pdf is \( \tilde{\psi}(s) = \frac{1}{1 + (\tau s)^\alpha} \). Therefore, the transition probability kernel (12) is \( \hat{K}(s) = s^{1-\alpha}/\tau^\alpha \), and the TTField term is

\[ C_0 \frac{1 - \tilde{\psi}(s)}{s} = \frac{C_0 \tau^\alpha s^{\alpha-1}}{1 + (\tau s)^\alpha} \approx C_\alpha s^{\alpha-1}, \tag{16} \]

where \( C_\alpha = C_0 \tau^\alpha \). We use \( \tau s \ll 1 \), which corresponds to the consideration of the cell dynamics at the time scale \( t \gg \tau \). Substituting these expressions in Eq. (15), one expands the latter over the TTField term, defined in Eq. (16). This yields

\[ n(r, t) = n_0 \hat{F}^{-1} \hat{L}^{-1} \left[ \sum_{l=0}^{\infty} \frac{(-C_\alpha)^l (s^{\alpha-1})^{2l+1}}{(s^\alpha + K_\alpha k^2)^{l+1}} \right]. \tag{17} \]

Here, \( K_\alpha = \frac{\sigma^2}{6 \tau^\alpha} \) is a generalized diffusion coefficient.

5. The TTField kernel

Equation (17) can be presented in the form of the convolution between the first term and the rest of the expansion. The first term of the expansion corresponds to the compensated cancer solution, when \( C_0 = 0 \). As presented in the previous section, the kernel \( C(k, t) \) in Eq. (13) results from the competition between proliferation and the antimitotic TTField action. Therefore, when \( C_0 = 0 \), the TTField compensates the proliferation of cancer cells. We call this cancer development by “compensated cancer development”. Evidently, this expression makes sense only for the cancer development in the presence of the TTField, when \( C_0 = 0 \), and only the first term remains in expansion (17). In the Fourier space, this solution can be expressed by the Mittag-Leffler function.
One obtains from Eq. (17)

\[ n_c(r, t) = \hat{\mathcal{F}}^{-1} \hat{\mathcal{L}}^{-1} \left[ \frac{n_0 s^{\alpha - 1}}{s^\alpha + K_\alpha k^2} \right] , \]  

(18)

where the inverse Laplace transform is nothing but the definition of the Mittag-Leffler function \[ E_\alpha(-K_\alpha k^2 t^\alpha) = \int_{-i\infty}^{i\infty} e^{st} s^{\alpha - 1} ds \]

Note that the pdf \( n_c(r, t) \) is the radial function, where \( r = |r| \). Therefore, the cancer development with proliferation compensated by the TTField is expressed by the Fourier image of the Mittag-Leffler function

\[ n_c(r, t) = n_0 \hat{\mathcal{F}}^{-1} [E_\alpha(-K_\alpha k^2 t^\alpha)] . \]  

(19)

One obtains from Eqs. (17), (18) and (19)

\[ n(r, t) = n_c(r, t) + n_0 \hat{\mathcal{F}}^{-1} \left[ E_\alpha(-K_\alpha k^2 t^\alpha) * \mathcal{R}(kt) \right] , \]  

(20)

where the Fourier inversion is the convolution integral with the TTField kernel

\[ \mathcal{R}(k, t) = \hat{\mathcal{L}}^{-1} \left[ \sum_{l=1}^{\infty} \frac{(-C_\alpha s^{2\alpha - 2})^l}{(s^\alpha + K_\alpha k^2)^l} \right] . \]  

(21)

Symbol * in Eq. (20) denotes the time convolution integral.

Now, we estimate \( \mathcal{R}(k, t) \). To this end, the denominator of the expansion should be simplified in the limit \( s^\alpha \gg K_\alpha k^2 \), which is valid in the outer invasive zone. Performing this simplification, one obtains

\[ \left[ \frac{1}{(s^\alpha + K_\alpha k^2)^l} \right] \approx \frac{1}{s^{\alpha l}} \left[ 1 - l K_\alpha k^2 / s^\alpha \right] . \]  

(22)

The Laplace inversion determines a generalization of the Mittag-Leffler function

\[ E_{\alpha,\beta}(z) = \sum_{l=0}^{\infty} \Gamma(\alpha l + \beta) \frac{z^l}{\Gamma(\alpha l + \beta + 1)} , \]  

where \( \Gamma(\alpha l + \beta) \) (see Eq. (A.9) in Appendix A); one obtains

\[ \mathcal{R}(k, t) = -C_\alpha t^{1-\alpha} E_{2-\alpha, 2-\alpha}(-C_\alpha t^{2-\alpha}) + \]  

\[ + K_\alpha k^2 C_\alpha t \sum_{l=0}^{\infty} \frac{(l+1)(-1)^l C_\alpha t^{l(2-\alpha)}}{(l(2-\alpha)+2)} \equiv \mathcal{R}_1 + \mathcal{R}_2 . \]  

(23)
Let us first treat the first term in Eq. (23). The argument of the Mittag-Leffler functions is large, which yields the power-law behavior \[ E_{\alpha,\beta}(z) \sim -\frac{1}{\Gamma(\beta - \alpha)z} \].

In this case, the TTField kernel needs to be treated in the framework of the generalized functions (distributions) \[ R_1 = \delta(t) \] for the kernel in the convolution integral. This contribution to the distribution function in the Fourier space is the inversion of the Mittag-Leffler function, which compensates \( n_c(r,t) \) exactly:

\[
n_c(r,t) - n_0 \hat{f}^{-1} \left[ E_{\alpha}\left( -K_\alpha k^2 t^\alpha \right) \right] = 0. \tag{25}
\]

Therefore, the solution in Eq. (20) is determined by the convolution with the second term \( R_2 \) of the TTField kernel in Eq. (23). To obtain the analytical expression, some simplification of the gamma function should be performed. This reads

\[
\frac{l + 1}{\Gamma[(2 - \alpha)l + 2]} = \frac{l + 1}{(2 - \alpha)l + 2\Gamma[(2 - \alpha)l + 1]} \approx \frac{1}{2\Gamma[(2 - \alpha)l + 1]}. \tag{26}
\]

Again, we arrive at the two-parameter Mittag-Leffler function, whose asymptotic behavior \[ E_{\alpha,1+\alpha}(z) \sim \exp[-K_\alpha k^2 t^\alpha] \] yields the kernel \( R_2 = \frac{\alpha K_\alpha k^2}{2\Gamma(\alpha)} t^{\alpha-1} \). Therefore, one obtains the fractional integration of the Mittag-Leffler function with the TT kernel

\[
n(r,t) = \frac{n_0 \alpha K_\alpha}{2} \hat{f}^{-1} \left[ \frac{k^2}{\Gamma(\alpha)} \int_0^t (t-t')^{\alpha-1} E_{\alpha}\left( -K_\alpha k^2 t'^\alpha \right) dt' \right]. \tag{27}
\]

Note that \( n(r,t) \) is the radial function. The integration over the time is well defined and yields (see e.g., \[ \text{Eq. (1.100)} \])

\[
n(r,t) = \frac{n_0 \alpha K_\alpha}{2} \hat{f}^{-1} \left[ t^{\alpha} k^2 \cdot E_{\alpha,1+\alpha}\left( -K_\alpha k^2 t^\alpha \right) \right]. \tag{28}
\]

In the outer invasive zone for the initial time scenario, when \( K_\alpha k^2 t^\alpha < 1 \) is valid, the Mittag-Leffler function constitutes the stretched exponential behavior

\[
E_{\alpha,1+\alpha}\left( -K_\alpha k^2 t^\alpha \right) \sim \exp[-\lambda K_\alpha k^2 t^\alpha],
\]
where $\lambda = \Gamma(1 + \alpha)$. Note also that we work with the three-dimensional Fourier transform. Therefore, since $k^2 = k_x^2 + k_y^2 + k_z^2$, differentiating over $\lambda$ reduces the problem to the simple Fourier inversion of the Gaussian packets, which yields

$$n(r, t) = -\frac{\partial}{\partial \lambda} \frac{n_0 \alpha}{2 \sqrt{4 \pi \lambda K_{\alpha} t^\alpha}} \exp \left[ -\frac{r^2}{4 \lambda K_{\alpha} t^\alpha} \right]$$

$$\propto r^2 (K_{\alpha} t)^{-\frac{3}{2}} \exp \left( -\frac{r^2}{K_{\alpha} t^\alpha} \right). \quad (29)$$

This solution (29) exhibits the result of the TTField action on the glioma development that leads to subdiffusion, or the stretched exponential restriction of the cancer cells spreading. An important fact here is that expression (29) is independent of $C_0 = C_0(k)$ and, correspondingly, is independent of any dispersive properties of the tissues interacting with the TTField.

As observed, the TTField cannot stop the cancer spreading as the averaged radius of the outer invasive zone increases subdiffusively $\langle r^2(t) \rangle \sim t^\alpha$. An example of compensated cancer invasion with time is shown in Fig. 1. This weakening of the TTField action is due to the migration-proliferation dichotomy, and is reflected in the convolution treatment term with the power-law time delay kernel $C(t) = C_0(k) \Psi(t)$ in Eq. (11). The final result in Eq. (29) is independent of the treatment rate as well.

6. Untreated cancer development

The TTField action, as any other antimitotic treatment, is important and leads to an increase in the survival period as a result of the essential decrease in the cancer spread rate. To understand this phenomenon, one needs to compare the spread of cancer cells with and without the TTFields. For example, let us consider the overall velocity of the constant concentration front propagation in the case of treated and untreated cancer. It follows from Eq. (29) that the front of constant concentration corresponds, approximately, to the solution $r^2 \sim \frac{1}{2} K_{\alpha} t^\alpha \ln t$. Therefore, for $C_0 = 0$, the spread rate of the treated cancer decreases with time $v_0 = \dot{r} \sim K_{\alpha} t^{\frac{\alpha}{2} - 1}$ and vanishes at the asymptotics $t \to \infty$. The situation changes dramatically for untreated cancer. In the present analysis,
Figure 1: Increasing concentration of cancer cells with time for the dimensionless radius $r$ and time, according to Eq. (29). Different plots correspond to different times: from bottom to top $t = 10, 25, 50, 75$. Here, $K_\alpha = 1$ and $\alpha = 1/3$. In the vicinity of $r = 6$, the condition of the outer invasive zone $K_\alpha t^\alpha / r^2 \ll 1$ is fulfilled.
it corresponds to $C_0 < 0$, where in the absence of the TTField $|C_0|$ is now the rate of proliferation of cancer cells. Cell proliferation contributes strongly to the transport, since the density of cancer cells $n(r,t)$ increases with time. It is well known that this process leads to the nonzero velocity of the front propagation, which has the form $v_C \sim \sqrt{C_0 K}$. Therefore, the TTField leads to the failure of the asymptotic front propagation of the cancer spread, while the front of untreated cancer spreads with a constant velocity.

Another important property is the mean squared displacements (MSD) $\langle r^2(t) \rangle$, which can be calculated for both treated and untreated cancers. There are various scenarios of the cancer spread and some approaches have been presented in [14, 16, 17, 18, 19]. Here, it is instructive to consider the cancer spread in the presence of the migration-proliferation dichotomy as a renewal process (see e.g. [38, 39]), following [19]. The switching between migrating and proliferating phenotypes for untreated cancer leads to the superdiffusive/sub-ballistic spread of cancer cells, when the transport exponent is larger than 1.

From the compensated cancer solution (29), one obtains that the MSD for the treated cancer reads

$$\langle r^2(t) \rangle \sim K_\alpha t^\alpha,$$

which corresponds to subdiffusion. For untreated cancers, a reversible process of switching between migration and proliferation phenotypes leads to the increase in the cancer cell population. Therefore, to apply the renewal theory with the constant cell population, we consider the dynamics of cells with the migration-proliferation switching that are simultaneously moving together with the front with the constant velocity $v_C$. This yields the following scheme. The random cell transport is considered for the constant number of cancer cells, while proliferation contributes to advection with the constant velocity of the cancer cells $v_C$ along the radial direction.

Now we take into account the process of migration-proliferation switching. The residence time pdf for the cell proliferation, described by Eqs. (1) and (2), is $\psi(t) \sim (\tau/t)^{1+\alpha}$ with the infinite averaged residence time. Contrary to the
proliferation time, the averaged transport time \( \langle t \rangle = \bar{t} \) is finite. During this time, cancer cells move the distance \( r(\bar{t}) = v_c \bar{t} \). To find the MSD \( \langle r^2(t) \rangle \) for the asymptotically large time, we consider that the displacement of a cell at time \( t \) is proportional to the number of migration-proliferation switchings \( N(t) \), such that \( r(t) \sim v_C \bar{t} N(t) \). Therefore, one obtains for the MSD \( \langle r^2(t) \rangle \geq \langle r(t) \rangle^2 \sim [v_C \bar{t}]^2 \langle N(t) \rangle^2 \).

Note that the number of cells is constant, and therefore, the distribution function \( n(r, t) \) of cancer cells to be at the position \( r(t) \) at time \( t \) can be considered a function of the number of switchings \( n(r, t) \equiv p(N, t) = \Pr[N(t) = N] \). Using a well known result from the renewal theory (see e.g. \[38, 39\]), one obtains that the Laplace transform of \( p(N, t) \) is determined by \( \tilde{\psi}(s) \)

\[
\tilde{p}(N, s) = \frac{\tilde{N}^N [1 - \tilde{\psi}]}{s}.
\]  \( (31) \)

One obtains the second moment \( \langle N^2(t) \rangle = \sum_{N=0}^{\infty} N^2 p(N, t) \), which reads in the Laplace space

\[
\langle \tilde{N}^2(s) \rangle = \sum_{N=0}^{\infty} N^2 \tilde{p}(N, s) = \frac{1 - \tilde{\psi}}{s} \sum_{N=0}^{\infty} N^2 \tilde{\psi}^N.
\]  \( (32) \)

Taking into account that for the large time asymptotic \( \tilde{\psi}(s) \approx 1 - (st)^\alpha \), one obtains after the Laplace inversion that \( \langle N^2(t) \rangle \sim \frac{(t/\tau)^{2\alpha}}{\Gamma(1 + 2\alpha)} \). Finally, one obtains that the MSD reads

\[
\langle r^2(t) \rangle \sim \left[ \frac{v_c \bar{t}}{\Gamma(1 + 2\alpha)} \left( \frac{t}{\tau} \right)^{2\alpha} \right].
\]  \( (33) \)

As follows from Eqs. \[30\] and \[33\], the main benefit of any antimitotic treatment, including the TTField, is decreasing the transport exponent of the cancer spread twofold. Moreover, the changes can be more dramatic, when \( \frac{1}{2} < \alpha < 1 \). In this case the difference between treated and untreated cancer corresponds to the difference between a subdiffusive cancer spread and a superdiffusive one.

7. Conclusion

Understanding of glioma cancer kinetics in the presence of the tumor treating field (TTField) can be important for the further development of the TTField’s
efficiency for medical treatment. It should be stressed that the TTField technology is already an officially accepted method for cancer treatment. We have shown that glioma development under the TTField treatment can be modelled in the framework of the continuous time random walk, where the TTField segregation of proliferating from not proliferating cells is naturally accounted. The constructed reaction-transport equation is based on the fact that the cytokinesis affects the cell dynamics strongly, and the cell kinetics is non-Markovian, which is reflected in both the transport and reaction terms of Eq. As was stated in Ref. “As a matter of fact, in one single cell, cytokinesis and migration are separated temporally; but on the level of a cell population - and this is the case of tumors - cell migration and proliferation occurs simultaneously.” Obviously, for the CTRW consideration, which accounts for the dynamics of the entire population at the individual particle level, the dynamics of one single cell with the migration-proliferation dichotomy is the most important.

The TTField technology, eventually, fails to stop glioma cancer development. This conclusion also correlates with the recent empirical (clinical) data, observed in, where the effect of the field strength on glioblastoma multiforme response was studied in patients treated with the TTField. The authors observed that cancer cells respond to the TTFields in such a way that they avoid the field affect. To some extent, this is indirect clinical evidence that supports the hypothesis that the main reason for the treatment failure is the migration-proliferation dichotomy, which is completely independent of the field. It should be noted that TTFields belong to a wide class of therapies that are effective against the abnormal proliferation of transformed cells. However, as compared to chemotherapy regimens, the treatment modality is completely different, being of a physical nature, and accompanied by minimal local side effect and no systemic side effects. Therefore, therapy efficiency can be improved by combining chemotherapy with the TTField, as was stated in.

The kernel $C(r, t)$ describes the competition between proliferation and degra-

\footnote{See \url{http://www.novocure.com/}}
dation due to the TTField action. This complicated function is random in space and time, and the result depends essentially on its sign. When it is negative, which means that the treatment is sufficient, or is absent, the kernel \( \text{kernel} \) \( \text{is no longer the TTField kernel, and corresponds to proliferation. Since the argument in the Mittag-Leffler function is positive, this leads to the exponential growth of the density of cancer cells} \sim \exp(C_\alpha t). \) In this case, the nonlinear mechanism becomes important in that it restricts the unlimited growth of cell numbers, see e.g. \[36, 37\].

First, an analytical attempt to understand the TTField’s influence on glioma development has been suggested by virtue of the geometrical construction of both the anomalous cell transport and the inhomogeneous distribution of proliferating cells in the framework of a fractional comb model for the 1D \[22\] and the 3D \[41\] analysis. It has been shown there that the efficiency of the medical treatment depends essentially on the mass fractal dimension of the cancer in the outer invasive zone. In the present research, a generalization of these geometrical constructions of the TTField action was suggested. The solution for the cell density of the developing glioma \( n(r,t) \) was obtained for any arbitrary distribution of proliferating cells. Moreover, the obtained final result in Eq. \[29\] corresponds to the compensated cancer solution with \( C(r,t) = 0 \). In this case, any inhomogeneities do not affect subdiffusion of cancer cells that leads to subdiffusion of free particles. This result is valid for any arbitrary \( C(r,t) \). To some extent, one can anticipate this property of the intermediate asymptotic result \[29\], that all proliferating cells disappear, and correspondingly, the TTField becomes ineffective. As a result, a clone of migrating cancer cells spreads freely according to Eq. \[29\] without the details of the degradation rate of proliferating cells due to the TTField having an influence. In this case, the TTField plays the role of an experimental/technological separation mechanism for the surviving migrating cells only. Probably, this process can be important for understanding the mechanism of the migration-proliferation dichotomy.

One should recognize that the obtained results correspond to the intermediate asymptotic solution according to Eq. \[22\], when time is restricted from
above $t < T_{\text{max}} \sim \left( \frac{r_{\text{max}}^2}{K_\alpha} \right)^{\frac{1}{\alpha}} = \left( \frac{r_{\text{max}}^2}{\sigma^2} \right)^{\frac{1}{\alpha}} \tau$, where $T_{\text{max}}/\tau \gg 1$. Taking $T_{\text{max}}$ as the maximum survival time of the order of $10^3$ days [3] and $1/\tau \sim (\text{day})^{-1}$ as the averaged proliferation rate [8], one obtains $T_{\text{max}}/\tau \sim 10^3$, which corresponds to the intermediate asymptotics approximation, performed in Eq. [22]. Therefore, the main conditions for the performed approximations that are valid for the intermediate asymptotic times $t$ in the outer-invasive region $r$ are $1 \gg (\tau/t)^{\alpha} \gg \sigma^2/r^2$. Taking into account that the outer-invasive region is of the order of $r \sim 1$ cm and $\sigma \sim 10^{-3}$ cm, one obtains that these inequalities are valid and verify the obtained result.

Finally, it is tempting to find what happens if a patient has a possibility to survive beyond the time $T_{\text{max}}$, when $t \to \infty$. In this case, when $s \to 0$, the Tauberian theorem [35], applied to Eq. [21], gives $R(k, t) \sim \delta(t)$, which yields $n(r, t \to \infty) \equiv 0$. Again, one anticipates this result at the infinite time scale, when all migrating cells have a possibility to be converted into proliferating cells with further degradation due to the TTField. Therefore, one has to consider a stationary value problem (for $t \to \infty$) with a constant flux of cancer cells from the boundary of the tumor core, and the result with $n(r, t \to \infty) \equiv 0$ is no longer valid. Moreover, since the initial value problem of Eq. [11] is described by the fractional Fokker-Planck equation, the problem of a stationary solution should be revised carefully. This problem will be the subject of future studies.

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Appendix A. Fractional integro–differentiation

The consideration of a non-Markovian process in the framework of kinetic equations leads to the study of the so-called fractional Fokker-Planck equation, where time processes are not local [20]. In this case, time derivations are substituted by time integration with the power law kernels. One arrives at so-called fractional integro–differentiation.

A basic introduction to fractional calculus can be found, e.g., in Ref. [35, 42].
Fractional integration of the order of $\alpha$ is defined by the operator

$$a I_t^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_a^t f(\tau)(t - \tau)^{\alpha - 1} d\tau, \quad (\alpha > 0), \quad (A. 1)$$

where $\Gamma(\alpha)$ is a gamma function. 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 $a I_t^\alpha \equiv I_t^{-\alpha}$ as $\frac{d}{dt} I_t^{-\alpha} = D_t^\alpha$; correspondingly $I_t^\alpha = \frac{d}{dt}^{-\alpha} = D_t^{-\alpha}$. Its explicit form is convolution

$$D_t^\alpha = \frac{1}{\Gamma(-\alpha)} \int_0^t \frac{f(\tau)}{(t - \tau)^{\alpha + 1}} d\tau. \quad (A. 2)$$

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

$$RLD_{(0,1)}^\alpha f(t) \equiv D_{RL}^\alpha f(t) = D^n \Gamma(1 - \alpha) \frac{d^n}{dt^n} \int_0^t \frac{f(\tau)d\tau}{(t - \tau)^{\alpha + 1 - n}}, \quad \text{Eq. (A. 3)}$$

$$D_C^\alpha f(t) = I_{-\alpha}^n D^n f(t) \frac{1}{\Gamma(n - \alpha)} \int_0^t \frac{f(\tau)d\tau}{(t - \tau)^{\alpha + 1 - n}}, \quad \text{Eq. (A. 4)}$$

where $n - 1 < \alpha < n, \quad n = 1, 2, \ldots$. Eq. (A. 3) is the Riemann–Liouville derivative, while Eq. (A. 4) is the fractional derivative in the Caputo form. Performing integration by part in Eq. (A. 3) and then applying Leibniz’s rule for the derivative of an integral and repeating this procedure $n$ times, we obtain

$$D_{RL}^\alpha f(t) = D_C^\alpha f(t) + \sum_{k=0}^{n-1} f^{(k)}(0^+) \frac{t^{k-\alpha}}{\Gamma(k - \alpha + 1)}. \quad (A. 5)$$

The Laplace transform can be obtained for Eq. (A. 4). If $\hat{L}[f(t)] = \hat{f}(s)$, then

$$\hat{L}[D_C^\alpha f(t)] = s^\alpha \hat{f}(s) - \sum_{k=0}^{n-1} f^{(k)}(0^+) s^{\alpha-1-k}. \quad (A. 6)$$

The following fractional derivatives are helpful for the present analysis

$$D_{RL}^\alpha [1] = \frac{t^{-\alpha}}{\Gamma(1 - \alpha)}, \quad D_C^\alpha [1] = 0. \quad (A. 7)$$

We also note that

$$D_{RL}^\alpha t^\beta = \frac{t^{\beta - \alpha} \Gamma(\beta + 1)}{\Gamma(\beta + 1 - \alpha)}, \quad (A. 8)$$
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., [35, 33]):

$$E_{\gamma, \delta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\gamma k + \delta)}.$$  \hspace{1cm} (A. 9)

Therefore, we have the following expression

$$D_{RL}^\alpha e^{\lambda t} = t^{-\alpha} E_{1, 1-\alpha}(\lambda t).$$  \hspace{1cm} (A. 10)

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