A toy model of fractal glioma development under RF electric field treatment

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A toy model for glioma treatment by a radio frequency electric field is suggested. This low-intensity, intermediate-frequency alternating electric field is known as the tumor-treating-field (TTF). In the framework of this model the efficiency of this TTF is estimated, and the interplay between the TTF and the migration-proliferation dichotomy of cancer cells is considered. The model is based on a modification of a comb model for cancer cells, where the migration-proliferation dichotomy becomes naturally apparent. Considering glioma cancer as a fractal dielectric composite of cancer cells and normal tissue cells, a new effective mechanism of glioma treatment is suggested in the form of a giant enhancement of the TTF. This leads to the irreversible electroporation that may be an effective non-invasive method of treating brain cancer.

PACS numbers: 05.40.FbRandom walks and Levy flights, 87.50.S-Radiofrequency/microwave fields effects , 87.17.EeGrowth and division

I. INTRODUCTION

Recent progress in treating glioma using an alternating, radio frequency electric field opens new questions about the migration-proliferation dichotomy of cancer cells extended to RF electric field. It was shown in in vitro and in vivo experiments that a low-intensity, intermediate-frequency (100-300 kHz), alternating electric field, known as the tumor-treating field (TTF), destroys cells that are undergoing division [1,2]. As explained, the modality of the TTF treatment is physical and related to dielectrophoresis (see e.g., [4]), when the non-uniformity of the TTF exerts a force, focusing at the narrow cytoplasmatic bridge between two daughter cells at fission. This leads to disruption of the cell proliferation, and, eventually, the cells are destroyed without the quiescent cells of normal tissues being affected [1,3].

One of the main features of malignant brain cancer is the ability of tumor cells to invade the normal tissue away from the multi-cell tumor core, and this motility is the most critical feature of brain cancer, causing treatment failure [3]. Clinical investigations of glioma show that the proliferation rate of migratory cells is essentially lower in the invasion region than in the tumor core [3,7]. This phenomenon is known as the migration-proliferation dichotomy, which is an inherent property of glioblastoma (glioma), making it a highly aggressive and invasive tumor. A question that may be of great importance for glioma treatment is whether the TTF is effective against invasive cells in the presence of the migration-proliferation dichotomy, when switching between migrating and proliferating phenotypes takes place. The switching process between these two phenotypes is still not well understood, and relevant models with different switching mechanisms are suggested. Comprehensive reviews of these sophisticated approaches can be found [8,12]. Therefore, for the medical treatment of cancers, dielectrophoresis of live cancer cells can be a new direction towards understanding this switching, since the polarization properties of migrating and dividing cells differ [14,15], and this great selectivity can be manipulated.

One of these experimental possibilities is dielectric spectroscopy, which is a powerful tool for investigating the dielectric properties of cells and the structural parts of cells, and can provide important knowledge about different cell structures, and resolve the different properties of normal and malignant cells [14,15].

Therefore, an essential question is how the TTF affects aggressive migrating cells in the outer-invasive region with a low-rate of proliferation, and what should be done to make the TTF an effective means of manipulating the cancer in this region. To shed light on this situation, we consider a simplified toy model, where a mathematical formulation of the migration-proliferation dichotomy can be performed in the framework of continuous-time random walks (CTRW) [16,17]. The simplest mathematical realization of the CTRW mechanism of the migration-proliferation dichotomy was introduced for a comb model [18], which is a toy model, where the migration-proliferation dichotomy is naturally apparent. The collective behavior of cells was considered and the primary focus was on the influence of cell fission on the transport properties of cells.

II. CELL KINETICS IN PRESENCE OF THE TTF

In the present study, we first consider the kinetic properties of cancer development in the presence of the TTF. These can be described by fractional kinetics in the framework of the comb model, where it is easier to draw an intelligible picture of interplay between high-motility aggressive cancer cells and the TTF in the outer-invasive region. Following toy model consideration [18], we restrict our model to one dimensional subdiffusion in the $x$ direction. In the comb model, this anomalous diffusion can be described by the 2D distribution function $P = P(x,y,t)$, and a special behavior is that the displacement in the $x$-direction is possible only along the structure axis ($x$-axis at $y = 0$). The Fokker-Planck
equation in some dimensionless variables reads
\[ \partial_t P = \delta(y)\partial_y^2 P + d\partial_y^2 P, \]
where \(d\) is an effective diffusion coefficient. Obviously, cell division is random in \(x\) and discontinuous, contrary to that in the tumor core. It can be reasonably considered as a fractal set \(F_T(x)\) with the fractal dimension \(\nu\), which is embedded in the 1D space, \(0 < \nu < 1\). Therefore, the effective diffusion coefficient becomes inhomogeneous \(d \rightarrow d(x)\), where \(d(x)\) is a characteristic function of the fractal, such that \(d(x) = 1\) for \(x \in F_T(x)\) and \(d(x) = 0\) for \(x \notin F_T(x)\). Now we take into account the influence of the TTF that affects (destroys) only the proliferation phenotype according to Refs. [1–3]. Mathematically, this process is expressed by diffusion in the \(y\) direction with decay:
\[ d\partial_y^2 P(x, y, t) \Rightarrow \chi(x)[d\partial_y^2 - C]P(x, y, t), \]
where coefficient \(C\) defines difference between the proliferation and the degradation rate. Taking this into account, one arrives at a model that makes it possible to understand the influence of the TTF on the cancer development.

First, we apply the Fourier transform to Eq. (1) with respect to the \(x\) coordinate. To apply this transformation to the last term in Eq. (1), we use the auxiliary identity \(\chi(x)f(x) = \partial_x \int_{-\infty}^\infty \chi(y)f(y)dy = -\partial_x \int_{-\infty}^\infty \chi(y)f(y)dy\) of the characteristic function can be carried out by means of a convolution [19–21]. To this end we will use the terminology and useful notations of fractional integration and differentiation [17,22,24]. Fractional integration of the order of \(\nu\) is defined by the operator (see also Appendix)

\[ -\infty I^\nu_x f(x) = \frac{1}{\Gamma(\nu)} \int_{-\infty}^x f(y)(x - y)^{\nu - 1}dy, \]

where \(0 < \nu < 1\) and \(\Gamma(\nu)\) is the Gamma function. The Weyl fractional derivative is
\[ W^{1-\nu}_x = \partial_x[-\infty I^\nu_x f(x)] = -\infty I^\nu_x[\partial_x f(x)]. \]

Using this notation, one introduces the coarse-graining integration with the characteristic function in the form of the Weyl fractional derivative [19]
\[ \chi(x)P(x, y, t) \Rightarrow W^{1-\nu}_x P(x, y, t). \]

The Fourier transform of the Weyl derivative yields
\[ \hat{\mathcal{F}}_x W^{1-\nu}_x P(x, y, t) = (ik)^{1-\nu} \hat{P}(k, y, t), \]
where \(\hat{\mathcal{F}}_x[P(x, y, t)] = \hat{P}(k, y, t)\). Presenting this Fourier transform in the symmetrical form, one obtains
\[ \partial_t \hat{P} = -k^2\delta(y)\hat{P} + |k|^{1-\nu}[d\partial_y^2 \hat{P} - C \hat{P}]. \]

The last term in the r.h.s. of Eq. (1) is eliminated by substituting \(\hat{P}(k, y, t) = e^{-C|k|^{1-\nu}}F(k, y, t)\). Then one carries out the Laplace transform in the time domain \(\hat{\mathcal{L}}[F(k, y, t)] = \hat{F}(k, y, s)\). Looking for the solution of the Laplace image in the form
\[ \hat{F}(k, y, s) = \exp[-|y|\sqrt{|k|^{\nu - 1}s/d}]f(k, s), \]
one arrives at the intermediate expression in the form of the Laplace and Fourier inversions
\[ P(x, y, t) = \int_{-\infty}^\infty e^{-C|x|^{1-\nu}t/2} \mathcal{L}^{-1} \left\{ \frac{2e^{-|y|\sqrt{|k|^{\nu - 1}s/d}}}{2\sqrt{sd|k|^{\nu - 1} + k^2}} \right\} dk. \]

One has to recognize that the \(y\) axis is the auxiliary coordinate, which determines the cell proliferating process (cell fission). Therefore to find the complete distribution of cancer cells in the \(x\) axis, integration over \(y\) is performed: \(\mathcal{P}(x, t) = \int_{-\infty}^\infty P(x, y, t)dy\). Both the integration over \(y\) and the inverse Laplace transform are carried out exactly. This, eventually, yields a solution in the convolution form

\[ \mathcal{P}(x, t) = \frac{1}{(Ct)^{\nu/2}} \int_{-\infty}^\infty \mathcal{R}_{x-x'}/(Ct)^{\nu/2} \mathcal{P}^\nu(x'/\sqrt{Ct}) \mathcal{E}_\alpha \left( -\frac{1}{2} \sqrt{|k|^{\nu - 1}t/d} \right) dk, \]

Here
\[ \mathcal{E}_\alpha(z) = \frac{1}{2\pi i} \int_{\gamma} \frac{u^{\alpha-1}e^u}{u^\alpha + z} \]

is the Mittag-Leffler function defined by the inverse Laplace transform with a corresponding deformation of the contour of the integration [27], while \(\mathcal{P}(z)\) is a solution for the untreated glioma with the scaling variable \(z = x/t^{\nu/2}\) and \(\mathcal{R}(z)\) is the kernel of the TTF treatment. For the small argument, which corresponds (for a short time) to a long-scale tail of the distribution, the Mittag-Leffler function decays exponentially \(\exp[\nu \sqrt{|k|^{3+\nu}t}]\) [17,27] with the generalized transport coefficient \(K_\nu = |2(3/2)\sqrt{d}|^{-1}\). This yields the solution for the untreated cancer in the form of the Fox functions [17]. Its large argument asymptotic solution yields the power law decay \(\mathcal{P}(z) \sim \sqrt{t/|x|^{5+\nu}}\) that is an indication of the non-localized diffusive cancer in the outer-invasive region [37].

Now we turn to the non-invasive treatment in Eqs. (7) and (8), described by the kernel
\[ \frac{1}{(Ct)^{\nu/2}} \mathcal{R}_{x-x'}/(Ct)^{\nu/2} = \hat{F}_{k} \left[ e^{-C|k|^{1-\nu}t} \right], \]

which is the Fox function. Therefore, the resulting solution in Eqs. (7) and (8) is the convolution of two Fox functions, which means that the TTF is a fairly inefficient treatment in the outer-invasive region. Our main
aim here is to understand the efficiency of the TTF. As seen from Eqs. (7) and (8), the crucial point is the fractal dimension \( \nu < 1 \). For \( \nu = 1 \) the solution is
\[
\mathcal{P}(x, t) = e^{-Ct} \mathcal{P}(x^2/t^2),
\]
where \( \mathcal{P}(z) \) is the stretched exponent. This means that the TTF is most efficient in the multi-cell tumor core and in the close vicinity of the core, where the proliferating cell distribution is continuous with the fractal dimension \( \nu = 1 \). Therefore, to increase the efficiency of the TTF in the outer-invasive region, the TTF must act on both the migrating and the proliferating cells.

III. ELECTROPORATION

In what follows we suggest a possible mechanism of such a treatment of the diffuse cancer using the TTF in the outer-invasive region. The idea is based on the differences between the dielectric properties of normal tissue cells and cancer cells that can lead to the local enhancement of the electric field and to electroporation of the cancer cells. Therefore, we consider the frequency-dependent permittivities of migrating cancer cells \( \varepsilon_m \) and the normal tissue cells \( \varepsilon_n \). Under certain frequency, the condition \( \varepsilon_m < \varepsilon_n \) can be fulfilled. This was found for dielectric properties of normal, and malignant lymphocytes [14]. Therefore, the outer-invasive region is a fractal composite of two dielectrics with permittivities \( \varepsilon_n \) and \( \varepsilon_m \), where \( \varepsilon_m = \varepsilon_m(\omega) \) corresponds to the host dielectric, while \( \varepsilon_m = \varepsilon_m(\omega) \) corresponds to the fractal cancer inclusion. We do not consider proliferating cancer cells, since the FFT destroys them effectively. Note also the wavelength of the TTF is much larger than any brain inhomogeneities, and therefore the quasi-electrostatic consideration is valid. The host volume of normal tissue cells is 3D, while the volume of cancer cells is fractal \( V \sim r^{D_{fr}} \) with fractal dimension \( D_{fr} < 3 \) due to their low concentration, which is much less than their concentration in a solid tumor. Therefore, the outer-invasive region can be considered as a random fractal cancer with an averaged fractal mass \( M(r) \sim r^{D_{fr}} \), as e.g., for low-grade astrocytomas. Note, in electrostatics, \( \rho(r) \) is considered as a fractal quenched disorder distribution.

Electrostatics in the frequency domain (when \( \mathbf{E} = \mathbf{E}(\omega, r) \)), in the random fractal dielectric composite is described by the Maxwell equation
\[
\nabla \cdot [\varepsilon(r) \mathbf{E}(r)] = 0,
\]
where the inhomogeneous permittivity is a function of the frequency of external TTF and coordinates: \( \varepsilon(r) = \varepsilon(\omega, r) \). The boundary conditions are determined by the external TTF. We work with dimensionless coordinates, which are scaled by the cell size. It is convenient to split the electric field inside the brain into two components \( \mathbf{E}(r) = \mathbf{E}_0(r) + \mathbf{E}_1(r) \), where \( \mathbf{E}_0 \) is the homogeneous electric field with the condition \( \nabla \cdot \mathbf{E}_0 = 0 \), while \( \mathbf{E}_1 \) is the electric field due to fractal cancer inhomogeneities. We take into account that the fractal mass \( M(r) \sim r^{D_{fr}} \) results from averaging over all the possible realizations of the random fractal. The averaged density distribution \( \rho(r) \) is isotropic and depends on the radius only (in complete agreement with the probabilistic sense of random fractals [28, 29]). This also supposes that the dielectric properties of the random fractal composite are isotropic, such that the space-dependent averaged polarization is a function of the radius only: \( \varepsilon(r) = \varepsilon(r) \). Therefore, it is reasonable to suppose that the response to the TTF due to the fractal inhomogeneities changes as a function of the radius \( E_0(\omega, r) = E_1(\omega, r) \), as well. Thus the divergence in the Maxwell equation for \( E_1 \) takes into account only the \( r \) component of the electric field. This yields \( \nabla \cdot E_1 = \nabla \cdot E_1(r) \), where \( E_1(r) \) is the \( r \) component of the electric field (the \( r \) index is omitted). The inhomogeneous permittivity of the composite we define by means of the fractal characteristic function \( \chi(r) = 1 \), if \( r \) belongs to cancer cells, and \( \chi(r) = 0 \), if \( r \) belongs to the normal tissues. Therefore \( \varepsilon(r) = \varepsilon_m \chi(r) + [1 - \chi(r)] \varepsilon_n \equiv \varepsilon_n [\chi(r) + 1] \), where we introduced dimensionless parameter \( \varepsilon = (\varepsilon_m - \varepsilon_n)/\varepsilon_n \). Substituting this in the Maxwell equation (9), one obtains
\[
[\varepsilon \chi(r) + 1] \nabla_r E_1 + E_1 \chi'(r) = -\bar{E}_r \chi'(r),
\]
where \( \chi'(r) = d\chi(r)/dr \), and we take into account that \( \nabla_r = \frac{1}{r^2} \partial_r r^2 \). We introduce a new function \( B(r) = r^2 E_1(r) \), and then the integration of Eq. (10) with the elementary volume \( dV = 4\pi r^2 dr \) reads
\[
\xi \int_0^r \chi(r) B'(dr) + B + \xi \int_0^r B \chi'(r) dr = -\xi \int_0^r \bar{E}_r(r) r^2 \chi'(r) dr,
\]
where \( B'(r) = dB/dr \).

Now we in a position to use fractional calculus for integration with the fractal characteristic function. By complete analogy with Eqs. (2) and (3), this integration corresponds to the convolution integral with the averaged density \( \rho(r) \) that yields [19]
\[
\int_0^r \chi(r) f(r) dr = \frac{1}{\Gamma(D_{fr}-2)} \int_0^r (r - r')^{D_{fr}-3} f(r') dr'
\equiv a I_F^{D_{fr}-2} f(r),
\]
where \( f(r) \) is arbitrary, in particular, \( f(r) = B'(r) \). The situation with polarization terms is more complicated, and one ought to take into account the electrostatic problem of polarization of dielectric balls by an external electric field [4]. All details of the inferring can be found in Refs. [19, 30], and the finite result reads
\[
\int_0^r \chi(r) B(r) dr = p a I_F^{D_{fr}-2} B(r),
\]
where $p = \frac{\xi^2}{\varepsilon_n}$ is a polarization parameter that is well known in the literature [4 31 32]. Using this expression and taking into account that in homogeneous media, when cancer is absent, $E = E_0/\varepsilon_n$, where $E_0 = E_0(\omega)$ is the amplitude of the TTF in the frequency domain, one easily calculates the term in the r.h.s. of Eq. (11):

$$pE_0 \xi_{D_h-2}^2 = \frac{2pE_0 \xi}{\varepsilon_n \Gamma(D_h + 1)} r^{-D_h}.$$ 

Now Eq. (11) can be rewritten in the form convenient for solving

$$\xi_0 I_{D_h-2}^{B'} + B + p_0 I_{D_h-2}^B = -\frac{2pE_0 \xi}{\varepsilon_n \Gamma(D_h + 1)} r^{-D_h}. \tag{12}$$

We consider a case with negative $\xi$ and $|\xi| \ll 1$, which is the most important for the electric response to the TTF. In this case one neglects the $p_0 I_{D_h-2}^B$ term. The Laplace transform method yields the solution in the form of the two-parameter Mittag-Leffler function [27]

$$E_{\alpha,\beta}(\xi) = \frac{r^{1-\beta}}{2\pi i} \int_\gamma \frac{\omega^{\alpha-\beta} e^{\omega r} d\omega}{\omega^{1-\beta/|\xi|}},$$

where, in our case, $\alpha = 3 - D_h$, $\beta = 4$. For small $|\xi|$, the large argument asymptotics of the Mittag-Leffler function is exponential [27]:

$$E_{\alpha,\beta}(z) \sim \frac{1}{\alpha} z^{-\beta} e^z, \text{ where } z = \frac{r^2}{|\xi|}.$$ 

This, finally, yields the solution for the electric field

$$E_1(r) \sim \frac{E_0}{\varepsilon_n} \left| \frac{\xi}{r^2} \right|^\frac{n-\alpha}{2} \exp \left( \frac{r}{|\xi|^{\frac{1}{2}}} \right), \quad \alpha = 3 - D_h. \tag{13}$$

Therefore, the respond electric field can be large enough to break the cell membrane. For example, for $|\xi| \sim 0.2$, $D_h = 2.5$, and $\varepsilon_n \sim 10^2$, the electric field response is $10^4 \pm 10^5$ V/cm, which exerts the irreversible electroporation $33$ due to the external TTF with amplitude $E_0 \sim 1$V/cm. This can be a mechanism for ablation of cancer cells, which effectively acts on migratory cancer cells. An important condition for this realization is $\varepsilon_m(\omega) < \varepsilon_n(\omega)$. These permittivities were observed in time domain dielectric spectroscopy in experimental studies of the static and dynamic dielectric properties of normal, transformed, and malignant B- and T-lymphocytes [14]. Such experimental studies of the glioma cells can not be overestimated.

IV. CONCLUSION

We presented two models of treating glioma by alternating, radio frequency electric field, which is the tumor treating field (TTF) in the presence of the migration-proliferation dichotomy of cancer cells. The first model considers the treating tumor development on a comb model. In the framework of this toy model of the migration-proliferation dichotomy, based on the fractional cell transport, it was possible to estimate the effectiveness of the TTF treatment in the outer-invasive region of the tumor development. We also show that while the TTF is highly effective in the multi-cell tumor core, its action is ineffective in the presence of the migration-proliferation dichotomy. The key reason is the fractal structure of the glioma cancer in the outer-invasive region. Therefore, another possible mechanism of the diffusive cancer treatment by the low-intensity alternating electric field has been suggested. The idea is based on the difference between the dielectric properties of normal tissue cells and cancer cells [14 15]. Since the cell permittivities are functions of the TTF frequency, it is supposed that there are conditions where the permittivity of normal cells is larger than that of cancer cells [14]. Therefore, considering the tumor invasion through normal tissue as a fractal dielectric composite in the presence of a high-frequency electric field, the electrostatic Maxwell equation in a fractal medium was considered. An analytical solution was obtained in the framework of fractional calculus, and an essential enhancement of the electric field was obtained. The result depends essentially on the cancer fractal dimension $D_h$ and the difference between the permittivities $|\xi| < 1$. In view of the toy model (11), this treatment leads to the solution $\mathcal{F}(x,t) \sim e^{-Ct} \mathcal{P}(x,t)$, where $C$ is electroporation, which is an effective treatment in the invasive region.

A key quantity of the cancer treatment is localization of the electroporation field $E_1(r)$ inside the cancer. There is a straightforward analogy with nanoplasmonics (see e.g., [34 35]), where the electric field enhancement is due to a so-called surface-plasmon resonance for a metal-dielectric composite, and localized surface plasmon oscillations are charge density oscillations confined to the conducting fractal nanostructure. The essential difference and similarity should be admitted: this biological, cell enhancement of the electric field is not resonant, but geometrical due to the fractal cancer structure [30]. In this connection, in vitro experiments can be important for further understanding the interplay between the TTF and the migration-proliferation dichotomy.

V. APPENDIX

Fractional integration of the order of $\alpha$ is defined by the operator

$$a \mathcal{I}_{x}^{\alpha} f(x) = \frac{1}{\Gamma(\alpha)} \int_{a}^{x} f(y)(x - y)^{\alpha - 1} dy,$$

where $\alpha > 0$, $x > a$ and $\Gamma(z)$ is the Gamma function. The fractional derivative is the inverse operator to $a \mathcal{I}_{x}^{\alpha}$ as $aD_{x}^{\alpha} f(x) = aI_{x}^{-\alpha}$ and $a \mathcal{I}_{x}^{\alpha} = aD_{x}^{-\alpha}$. Its explicit form is

$$aD_{x}^{-\alpha} = \frac{1}{\Gamma(-\alpha)} \int_{a}^{x} f(y)(x - y)^{-1-\alpha} dy.$$ 

For arbitrary $\alpha > 0$ this integral diverges, and as a result of a regularization procedure, there are two alternative definitions of $aD_{x}^{-\alpha}$. For an integer $n$ defined as $n -$
1 < \alpha < n, one obtains the Riemann-Liouville fractional derivative of the form
\[ aD_{RL}^\alpha f(x) = (d^n / x^n)_a I_x^{n-\alpha} f(x), \]
and fractional derivative in the Caputo form
\[ aD_C^\alpha f(x) = a I_x^{n-\alpha} f^{(n)}(x). \]

When \( a = -\infty \), the resulting Weyl derivative is
\[ W^\alpha = -\infty D_W^\alpha = -\infty D_{RL}^\alpha = -\infty D_C^\alpha. \]

One also has \( -\infty D_W e^x = e^x \) This property is convenient for the Fourier transform \( \hat{F}[W^\alpha f(x)] = (ik)^\alpha \hat{f}(k) \), where \( \hat{F}[f(x)] = \hat{f}(k) \).

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[35] M.I. Stockman, Physics Today 64(2), 39 (2011).
[36] Note, \( \int_{x}^{\infty} \lambda(y)f(y)dy = \sum_{x_j \in F_k} \int_{x_j}^{\infty} f(y)\delta(y-x_j)dy, \) where \( \sum_{x_j \in F_k} \delta(y-x_j) = \mu(x) \sim |x|^{\nu-1} \) is a fractal density, such that \( \int_{x}^{\infty} dp(y) \sim |x|^\nu \) corresponds to the fractal volume. Therefore, due to Theorem 3.1 in Ref. [21] we have \( \int_{\lambda(x)}^{\infty} f(y)dp(y) \approx \frac{1}{|x|^\nu} \int_{x}^{\infty} (x-y)^{\nu-1} f(y)dy. \)
[37] This is a mathematical expression of a statement that the surgical resection is ineffective since the cancer cells have already invaded into the surrounding brain tissue. This leads to recurrence of tumor and prognosis for patients suffering from malignant gliomas is very poor.