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PHYSICS

MALIGNANT INVASION MODEL WITH A SMALL AMOUNT OF DIFFUSION IN THE FRAMEWORK OF THE NON-STANDARD SCALE RELATIVITY THEORY. Part I – EVOLUTION EQUATIONS

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Abstract. A particular model of tumor progression (extended Perumpanani's model), assuming that the invasive cells, the connective tissue and the proteases are moving through a non-differential medium governed by the Non-Standard Scale Relativity Theory (Scale Relativity Theory with arbitrary constant fractal dimension) is analyzed. In such context an action-reaction type law acting on the complex system formed by the extracellular matrix and the non-differential medium is considered. As a result, artificial cancer cell proliferation satisfies a logistic law accounting for the competition for space with the non-differential medium. Moreover, the connective tissues concentration increases proportionally to the real fractal velocity, squared. Over small distances, it results that even in avascular stages, malignant tumors might propagate and invade healthy tissues.

Key words: malignant invasion model, chemotaxis, chemokinesis, haptotaxis, necrotaxis, Non-Standard Scale Relativity Theory, fractality.

1. INTRODUCTION

In [1] Abbey Perumpanani, John Norbury, Jonathan A. Sherratt and Helen Byrne developed a mathematical model to analyze the interaction between cell movement and the breakdown of the extracellular matrix of surrounding tissue. This model is described by a coupled system of partial differential equations, in which the invading cells create a gradient of extracellular matrix around them, with more extracellular matrix ahead of the cells (in the direction of invasion) and less behind. The cells tend to move up gradients of extracellular matrix ("haptotaxis"), and thus invade the surrounding tissue.

In the biological systems the fractal structure of space (in which cells interact and differentiate) is essential for their self-organization and emergence of the hierarchical network of multiple cross-interacting cells, sensitive to external and internal conditions. Thus, the biological phenomena take place in the fractionary dimensions space. In particular, malignant tumors [2–5] and neuronal cells [6, 7] grow in a fractal space. To be more explicit, it was proved that the analytical formulae describing the time-dependence of the temporal fractal dimension and scaling factor reproduce the growth of the Flexner–Jobling rat's tumor in particular and growth of other rat's tumors. The results of some test calculations indicated that the formulae derived for the time-dependent temporal fractal dimension and the scaling factor satisfactory describe the experimental data obtained by Schrek for the Brown-Pearce rabbit's tumor growth in the fractal space-time

[2–5]. Moreover, the hypothesis that tumorigenesis has a lot in common with the neuronal differentiation and synapse formation comes from the fact that they are qualitatively described by the same Gompertz function of growth and take place in the fractal space-time whose mean temporal fractal dimension is lost during progression [6, 7].

The aim of this paper is to study the Perumpanani's malignant invasion model with a small amount of diffusion in the framework of Non-Standard Scale Relativity Theory (NSRT) [8–10]. Evolution equation of the model and the effects induced by these are obtained.

2. PERUMPANANI'S MALIGNANT INVASION MODEL REVISITED

The malignant invasion model [1] depends both on the spatial coordinate x and time t. This model operates with the following variables: $n(x, t)$ is the concentration of invasive cells, $c(x, t)$ is the concentration of connective tissue (which is made of extracellular matrix elements) and $p(x, t)$ is the concentration of proteases. All these concentrations are measured per unit volume at position x and time t. More explicitely, this model analyses the averaged behaviour of cells which vary in the direction of invasion only (the variations in the plane perpendicular to the axis of invasion it is ignored).

In the general case we note that there are several forms of locomotion at cellular level, each of them responsible for migration of cells in biological systems. Chemotaxis is the directional movement of cells due to a chemoattractant in a fluid phase (Fig. 1). Chemokinesis takes place in a liquid phase of the environment, it has no directional components, it is a random migration of cells between two points due to a chemical gradient (Fig. 2). In haptotaxis the chemoattractant is bound on a surface, and the most haptotactic surface in biological systems is the extracellular matrix, inducing transendothelial migration and angiogenesis (Fig. 3). Necrotaxis is the migration of cells due to a chemoattractant released by necrotic or apoptotic cells (Fig. 4).

Fig. 1 – Chemotaxis is the directed cell locomotion in concentration gradients of soluble extracellular agents.

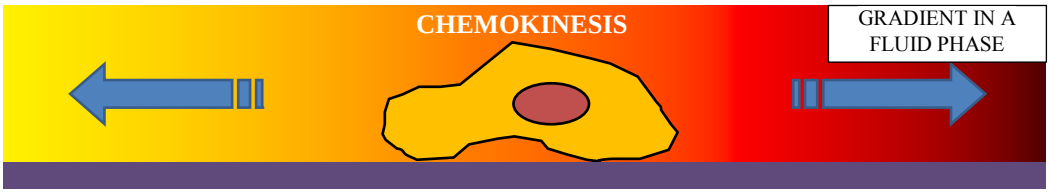

Fig. 2 – Chemokinesis is random cell movement, a non-vectorial, random taxis. Amplitude of movement and frequency of motion have no directional components, even though a certain gradient is present.

Fig. 3 – Haptotaxis is the directional motility of cells. This process is governed by gradients of cellular adhesion sites or substrate-bound chemoattractants. These gradients are naturally present in the extracellular matrix (ECM) of the body during processes such as angiogenesis or artificially present in biomaterials where gradients are established by altering the concentration of adhesion sites on a polymer substrate.

Fig. 4 – Necrotaxis is a special type of cell movement when the chemoattractants are released by necrotic or apoptotic cells.

The major motility mechanism (which governs the behavior of the malignant cells) is haptotaxis (Fig. 3) up the gradient of connective tissue. This is given by an invasive flux proportional to $n\partial c/\partial x$ and thus an invasive velocity will be proportional to $\partial c/\partial x$. Also in reference [1] the logistic proliferation of the malignant cells via the non-dimensionalized term $n(1-n)$ is included. With non-connective tissue gradient present (*i.e.* $\partial c/\partial x \equiv 0$), the malignant cells will grow from small densities to the non-dimensionalized steady-state carrying capacity scaled to be unitate. This capacity is a result of inhibition of the division of cells by their neighbours, by means of mechanisms generically referred to as contact inhibition.

Upon contact with connective tissue the invasive cells produce proteases of density $p(x, t)$ at a rate proportional to nc. Proteases dissolves the connective tissue at a rate proportional to cp. The proteases itself undergo natural decay proportional to their own concentration.

Let us follow the non-dimensionalization in which is removed all but one of the parameter values. Then the equations of the model have the form [1]:

$$\frac{\partial n}{\partial t} = n(1-n) - \frac{\partial}{\partial x}\left(n\frac{\partial c}{\partial x}\right) \tag{1}$$

$$\frac{\partial c}{\partial t} = -pc \tag{2}$$

$$\frac{\partial p}{\partial t} = \frac{1}{\varepsilon}(nc - p). \tag{3}$$

In equation (3) ε is a positive constant representing the relative time scale of the protease dynamics to that of the cell growth dynamics. In the above equations t is scaled so that n grows on the O(1) time scale to the n scaled carrying capacity of unity, x is scaled so that the rate of haptotaxis is of the same order, p is scaled so that c dissolves on the same time scale and c is scaled so that p and nc are of the same order in equation (3). This leaves the p time scale relatively much faster, so that ε is small.

Authors of reference [1] approximated the equations (1)–(3) by a two-equations system in [11]. Exploiting the small parameter ε they approximated the protease dynamics (3) by

$$p = nc + O(\varepsilon)$$

This is appropriate provided that $\partial p/\partial t$ is bounded. By setting $p = nc$ the three-variable problem could be reduced to the two-variable problem

$$\frac{\partial n}{\partial t} = n(1-n) - \frac{\partial}{\partial x}\left(n\frac{\partial c}{\partial x}\right) \tag{4}$$

$$\frac{\partial c}{\partial t} = -nc^2. \tag{5}$$

Numerical evidence suggests that stable travelling wave solutions of (1)–(3) may only evolve from semi-compact $n(x, t = 0)$ initial data if a small amount of diffusion is added to the model. This is biologically realistic, since (1)–(3) is merely an approximation to the invasive situation in which diffusion has been neglected. Assuming that this diffusion is linear, we can consider the equations system from [12]

$$\frac{\partial n}{\partial t} = n(1-n) - \frac{\partial}{\partial x}\left(n\frac{\partial c}{\partial x}\right) + D_n \frac{\partial^2 n}{\partial x^2} \tag{6}$$

$$\frac{\partial c}{\partial t} = -pc + D_c \frac{\partial^2 c}{\partial x^2} \tag{7}$$

$$\frac{\partial p}{\partial t} = \frac{1}{\varepsilon}(nc - p) + D_p \frac{\partial^2 p}{\partial x^2}, \tag{8}$$

where D_n, D_c and D_p are diffusion coefficients.

We investigate a leading-order asymptotic approximation to (1)-(3) when a small amount of diffusion of the invading cells is included in the system. We assume that $D_n = O(\varepsilon)$ and $D_c = D_p = 0$. This is realistic for some invasive situations. Indeed, the connective tissue is a large immobile matrix so it is reasonable to suppose that $D_c = 0$. Tsuboi and Rifkin [13] stated that uPA, a protease produced by HT1080 cells, is bound to the extracellular matrix. Therefore the diffusion is null so we can take $D_p = 0$. Aznavoorian et al [14] found that HT1080 melanoma cells had a haptotactic response more than 50 times greater than the random response, offering a justification for a small value of D_n. In these conditions the equations system (6)-(8) become [12]:

$$\frac{\partial n}{\partial t} = n(1-n) - \frac{\partial}{\partial x}\left(n\frac{\partial c}{\partial x}\right) + D_n \frac{\partial^2 n}{\partial x^2} \tag{9}$$

$$\frac{\partial c}{\partial t} = -nc^2. \tag{10}$$

These equations define the Perumpanani's malignant invasion model with a small amount of diffusion.

3. PERUMPANANI'S MALIGNANT INVASION MODEL IN NON-STANDARD SCALE RELATIVITY THEORY

Let us assume the invasive cells, the connective tissue (which is made of extracellular matrix elements) and the proteases are moving through the **non-differential medium** governed by NSRT. Mathematically, we can express this by replacing the usual time derivative, $\hat{\partial}/\partial t$ in Perumpanani's system of equations (9)–(10), by the complex time-derivative operator of NSRT for fractal curves movements with arbitrary fractal dimension D_F in the one-dimensional case, $\hat{\partial}/\partial t$ [8–10]:

$$\frac{\hat{\partial}}{\partial t} = \frac{\partial}{\partial t} + V_x \frac{\partial}{\partial x} - iD(\mathrm{d}t)^{\left(2/D_F\right)-1} \frac{\partial^2}{\partial x^2}, \tag{11}$$

where

$$V_x = v_x - iu_x \tag{12}$$

is the complex velocity field, v_x is differentiable and independent scale resolution velocity field, u_x is the non-differentiable and dependent scale resolution velocity field, D is the diffusion coefficient associated to fractal – non-fractal transition, dt is the temporal scale resolution and D_F is the fractal dimension.

If we separate the real and imaginary parts, we get for the real part (*i.e.* at differentiable scale resolution)

$$\frac{\partial n}{\partial t} = n\left(1 - n - \frac{\partial^2 c}{\partial x^2}\right) - \left(v_x + \frac{\partial c}{\partial x}\right)\frac{\partial n}{\partial x} + D_n \frac{\partial^2 n}{\partial x^2}$$
$$\frac{\partial c}{\partial t} = -nc^2 - v_x \frac{\partial c}{\partial x} \qquad (13\ \text{a,b})$$

and for the imaginary one (*i.e.* at fractal scale resolution)

$$u_x \frac{\partial n}{\partial x} + \bar{D}\frac{\partial^2 n}{\partial x^2} = 0,\ u_x \frac{\partial c}{\partial x} + \bar{D}\frac{\partial^2 c}{\partial x^2} = 0,\ \bar{D} = D\left(\mathrm{d}t\right)^{(2/D_F)-1}. \qquad (14\ \text{a–c})$$

Let us take in (13 a,b). It is like an action-reaction type law acting on the system formed by the extracellular matrix and the non-differential medium. Any increase in the gradient of the extracellular matrix produces a counter-reaction in the fractal space, i.e. an increase of the real velocity v_x is equal in module and inverse in sense to the direction of haptotaxis (ECM gradient increase). Consequently, (13 a,b) become:

$$\frac{\partial n}{\partial t} = n\left(1 - n + \frac{\partial v_x}{\partial x}\right) + D_n \frac{\partial^2 n}{\partial x^2},\ \ \frac{\partial c}{\partial t} = -nc^2 + v_x^2. \qquad (15\ \text{a,b})$$

Some interesting aspects occur: cancer cell proliferation satisfies a logistic law accounting for the competition for space with the non-differential medium (characterized by the term $\partial v_x/\partial x$) and the time evolution of the concentration of the connective tissue increases proportional to the real fractal velocity, squared v_x^2. For details see also [15].

Now, let us take the set of equations (14a,b). If we use again the action-reaction type law above, we get

$$u_x \frac{\partial n}{\partial x} = -\bar{D}\frac{\partial^2 n}{\partial x^2},\ \ u_x v_x + \bar{D}\frac{\partial v_x}{\partial x} = 0. \qquad (16\ \text{a,b})$$

Furthermore, we are able to make more assumptions, based on the results from [16]

$$v_x = 2DA_x,\ \ \frac{\partial A_x}{\partial x} = 0, \qquad (17\ \text{a,b})$$

where D is the same parameter as above, characterizing the fractal behavior of trajectories, and A_x is the vector potential. The first relation is nothing but the condition for a zero momentum of the superconducting pair, and is the London equation (for details see [16]). The second relation is the one-dimensional London gauge. In other words, equations (17a, b) are nothing but the London equations, which naturally result from the time dependent Ginzburg-Landau equation system completed with the hydrodynamic formulation of NSRT [16]. Using (17 a,b) in (16b) we arrive at the fact that either v_x, or u_x is zero. If u_x would be zero, the fractal potential [8–10] characterizing the non-differential medium would be zero (see again [17, 18]), which is opposite to the situation assumed in this paper, that the invasive cells, the connective tissue and the proteases are moving through a non-differential medium governed by the NSRT. Accordingly, we consider $v_x = 0,\ \partial v_x/\partial x = 0$ and (15a,b) finally become:

$$\frac{\partial n}{\partial t} = n\left(1 - n\right) + D_n \frac{\partial^2 n}{\partial x^2},\ \ \frac{\partial c}{\partial t} = -nc^2. \qquad (18\ \text{a,b})$$

Equation (16a) may be thought as in [18]. If we compare it with Navier-Stokes equation, from fluid mechanics [19]

$$\frac{D\boldsymbol{v}}{Dt} = \frac{\partial \boldsymbol{v}}{\partial t} + \boldsymbol{v}\cdot\nabla\boldsymbol{v} = \nu\nabla^2\boldsymbol{v} \qquad (19)$$

we can see the left side of (16a) gives the rate at which n (the concentration of invasive cells) is transported through a 'fluid' by means of the motion of 'fluid' particles with the velocity $\boldsymbol{u}$; the right hand side gives the

diffusion of n, $\overline{D}$ which is the amplitude of the fractal fluctuations, plays here the role of the 'kinematic viscosity' of the 'fluid'). One can notice, in those regions in which the right hand side of (17) is negligible, $D\boldsymbol{v}/Dt = 0$. This means that in inviscid flows, for instance, $\boldsymbol{v}$ is frozen into the 'particles of the fluid'. Physically this is because in an inviscid 'fluid' shear stresses are zero, so that there is no mechanism by which $\boldsymbol{v}$ can be transferred from one 'fluid' particle to another. This may be the case for the transport of n by $\boldsymbol{u}$ in (16a) (for more details see [18]). In other words, we find that, considering the space (-time) where tumor cells move, changes from classical to non-differentiable, a second diffusion phenomena, over the Newtonian fluid, described by eq. (16a) and characterized by $\overline{D}$ the 'kinematic viscosity' (or ''amplitude'' of the fractal fluctuations), over much smaller distances of the order $L_c(\mathrm{d}t)^{(2/D_F)-1}$occurs – leading to a very important feature of malignant tumors, that even in avascular stages they might propagate and invade healthy tissues (for more details see [20–23]).

4. DISCUSSIONS AND CONCLUSIONS

In this paper, we study a particular model of tumor progression, *i.e.* Perumpanani's malignant invasion model extended.

We first acknowledge that a transition from classical (differentiable) mechanics to the scale relativistic framework is implemented by passing to a fluid-like description, considering the velocity field a fractal function explicitly depending on a scale variable and defining two fractal velocity fields which are fractal functions of the scale variable dt. Accordingly, the operator $\hat{\partial}/\partial t$ plays the role of a 'covariant derivative operator' and it is used to write the fundamental equation of dynamics under the same form it has in the classical and differentiable case.

Then, we consider the original Perumpanani's malignant invasion model which depends upon one space direction x and time t and has three generic variables, namely $n(x, t)$ the concentration of invasive cells, $c(x, t)$ the concentration of connective tissue (which is made of extracellular matrix elements) and $p(x, t)$ the concentration of proteases. Numerical evidence suggests that stable travelling wave solutions of (1)–(3) may only evolve from semi-compact $n(x, t = 0)$ initial data if a small amount of diffusion is added to the model. A leading-order asymptotic approximation to (6)–(8) when a small amount of diffusion of the invading cells is included in the system, is investigated. The system (6)–(8) under particular considerations and exploiting the small parameter ε, may be written in a two-variable form (9), (10) and is called Perumpanani's malignant invasion model with a small amount of diffusion.

The main assumption of this work is the invasive cells, the connective tissue (which is made of extracellular matrix elements) and the proteases are moving through a non-differential medium governed by the NSRT, as defined above.

Furthermore, we consider an action-reaction law acting on the system formed by the extracellular matrix and the non-differential medium. Any increase in the gradient of the extracellular matrix produces a counter-reaction in the fractal space (-time), *i.e.* an increase of the real velocity v_x is equal in module and inverse in sense with the haptotaxis (ECM gradient increase).

As a result, some interesting aspects occur:

– cancer cell proliferation satisfies a logistic law accounting for the competition for space with the non-differential medium (characterized by the term $\partial v_x/\partial x$,

– the time evolution of the concentration of the connective tissue increases proportional to the real fractal velocity squared v_x^2.

The time dependent Ginzburg-Landau equation system completed with the hydrodynamic formulation of NSRT (London gauge and London equation) forced us to simplify the problem and consider $v_x = 0$, $\partial v_x/\partial x = 0$ and to get Perumpanani's malignant invasion model extended.

Here again, we find an intriguing feature of malignant tumors invasion in the framework of NSRT that reads: over small distances, even in avascular stages, they might propagate and invade healthy tissues.

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