Exact traveling wave solutions of 1D model of cancer invasion

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Abstract

In this paper we consider the continuous mathematical model of tumour growth and invasion based on the model introduced by Anderson, Chaplain et al. [1], for the case of one space dimension. The model consists of a system of three coupled nonlinear reaction-diffusion-taxis partial differential equations describing the interactions between cancer cells, the matrix degrading enzyme and the tissue. For this model under certain conditions on the model parameters we obtain the exact analytical solutions in terms of traveling wave variables. These solutions are smooth positive definite functions whose profiles agree with those obtained from numerical computations [4] for not very large time intervals.

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I. INTRODUCTION

The creation of mathematical models for the description of dynamic biological processes has a long history. Since its inception, mathematical models in oncology have been actively developing. The phenomenon of the onset and development of cancerous tumours is very complicated, it includes many interrelated processes at many spatial and temporal scales. Describing schematically, a solid tumour grows through two distinct phases: the initial phase is the avascular phase, and then the vascular phase. During the avascular growth phase the size of the solid tumour is restricted and the tumour remains localised. The transition from avascular growth to vascular one depends on the formation of blood vessels from a pre-existing vasculature, or angiogenesis. During the growth of a solid tumour the capillary sprout network is formed in response to chemical stimuli (tumour angiogenic factors) secreted by the cells of this tumour \[2, 3\]. This stimulates neighboring capillary blood vessels to grow and penetrate the tumour, repeatedly supplying this tumour with a vital nutrient. With the vascular growth phase the process of cancer invasion of peritumoral tissue can and does take place \[4\]. Invasion of tissue plays a key role in the growth and spread of cancer and the formation of metastases. The process of invasion is the following: the cancer cells secrete various matrix degrading enzymes, which destroy the surrounding tissue or extracellular matrix (ECM), and then the cancer cells actively spread into the surrounding tissue through migration and proliferation. Thus, the primary tumour locally invades the surrounding tissue and spreads to distant sites of the body to form secondary tumours \[6\]. These are secondary tumours (metastases) which are the main cause of death from cancer.

The exhaustive exposition of the biological and medical aspects underlying the construction of mathematical models can be found in the cited literature. The study of the various phases of solid tumour growth by mathematical modeling methods has been going on for several decades. A comprehensive review of this area is given in the works \[7\]-\[11\] and references therein. Mathematical modeling of cancer invasion is also presented in the research literature. One of the first models of cancer cells invasion, described by the system of partial differential equations, were developed in \[12\] and in \[13, 1\]; in the last two works the continuous mathematical models are described by the systems of reaction-diffusion-taxis partial differential equations, where the process of haptotaxis, or directed cells movement in response to chemical concentration gradient (gradient of extracellular matrix density or of
adhesive molecules in the extracellular matrix) plays a key role in the tumour cell migration. The model introduced in Anderson, Chaplain et al. [1] consists of three partial differential equations and describes the space-time evolution and interaction of cancer cells, the matrix degrading enzyme (the urokinase-type plasminogen activator, uPA) and the host tissue. It should be noted that it is on this model that the model considered in our paper is based. Further modifications and development of this model was obtained by Anderson [14], Enderling et al. [15]; Chaplain and Lolas [5, 4] and Andasari, Gerisch, Lolas et al. [16] focus their attention on the role of a generic matrix degrading enzyme (MDEs) such as uPA and metalloproteinases. Gerisch and Chaplain [17] formulate a continuum model incorporating the cell-cell and cell-matrix adhesion using non-local terms; different aspects of cell invasion are also considered in [18–21]; Enderling and Chaplain [6] describe fundamentals of mathematical modeling of tumour growth and summarize most prominent approaches. Currently, the invasion models continue to actively develop; in [22] a new two-scale moving boundary model of cancer invasion is presented; in [23] the authors establish a general spatio-temporal-structural framework that allows to describe the interaction of cell population dynamics with molecular binding processes; a nonlocal mathematical model describing cancer cell invasion as a result of integrin-controlled cell-cell adhesion and cell-matrix adhesion is developed in [24], [25]; in [26] the authors present two mathematical models related to different aspects and scales of cancer growth.

The existence of traveling wave solutions for a different models of tumour invasion with haptotaxis term was established in the numerical computations results [4], as well as in [27–30] where a detailed study of traveling wave behavior is performed. However, as far as we know, the model considered in this paper and the solutions presented here are new.

II. THE MODEL UNDER CONSIDERATION

As mentioned above, the model considered here is based on the continuous mathematical model of generic solid tumour growth and invasion introduced in Anderson, Chaplain et al. [1]. In [4] Chaplain and Lolas initially develop and modify this model focusing solely on the interactions between the cancer cells and the surrounding tissue, and study a system of three coupled nonlinear partial differential equations (PDEs) describing the space-time behavior of tumour cells, ECM density and uPA protease concentration.
First it is assumed that the cell number density \( c(t, \vec{r}) \) changes because of dispersion arising from the random locomotion. The choice of the cell random motility coefficient \( D_c \) to be constant does not affect the general framework of the process since the contribution of the chemokinetic term is always the smallest in the locomotion of cancer cells \[4\]. Further the cell density is assumed to be also changed due to directed migratory response of tumour cells to gradients of diffusible (uPA) and non-diffusible (ECM) macromolecules, or chemotaxis and haptotaxis respectively, see \[4\] and ref.therein. In \[4\] the proliferation of cancer cells is also considered.

The ECM \( v(t, \vec{r}) \) is not assumed to move and it changes solely due to its degradation by uPA protease upon contact and to its remodelling by cancer and other cells.

The behavior and the evolution of uPA protease concentration \( u(t, \vec{r}) \) is governed by diffusion, protease production and protease decay. uPA is produced by the tumour cells, diffuses throughout the extracellular matrix with constant diffusion coefficient \( D_u \) and undergoes decay.

It seems that this model can not be solved analytically. In this paper we consider the model that, it seems to us, is as close as possible to the model in \[1\], \[4\] and which allows an exact solution. So, we examine the above model in one space dimension (1D) with logarithmic chemotactical and haptotactical sensitivity functions, without proliferation and reestablishment terms and with slightly modified equation for ECM. For certain values of the model parameters we obtain exact analytical solutions in terms of traveling wave variable for the velocity depending on these parameters. The aim of this paper is to present these solutions and to verify that they are consistent with the numerical solutions obtained in \[4\]. As will be seen from the following the profiles of traveling wave solutions are similar to those in \[4\], Fig.10. for not very large time intervals.

So, the general form of the considered model is:

\[
\begin{align*}
\frac{c_t}{c} &= D_c \frac{c_{xx}}{c} - \chi_c \left( \frac{c u_x}{u} \right)_x - \xi_c \left( \frac{c v_x}{v} \right)_x \\
\frac{v_t}{v} &= -\delta u v^\rho \\
\frac{u_t}{u} &= D_u \frac{u_{xx}}{u} + \alpha c - \beta u
\end{align*}
\]

where the constant positive parameters of the model are: \( D_c \) and \( D_u \) are cells and uPA diffusion coefficients respectively, \( \chi_c \) and \( \xi_c \) are chemotaxis and haptotaxis coefficients; \( \delta \) is the rate of ECM degradation by uPA; \( \alpha \) and \( \beta \) are the rates of uPA production and decay.
The second equation in (1) differs from [1], [4] by the presence of the power \( p \) of \( v \) and we consider \( 0 < p < 1 \). For \( p = 1 \) we did not obtain biologically acceptable solutions, however, as we shall see below, \( p \) can be made close to 1, for example \( p = 0.95 \). Further, in order that the presented results can be compared with the numerical results of the authors cited we consider this system under the assumption that it is dimensionless. The transformation of the variables and parameters in equations (1) into dimensionless quantities is the same as in the cited works except \( \delta, \chi_c \) and \( \xi_c \). Thus

\[
t \rightarrow \frac{t}{\tau}, \quad x \rightarrow \frac{x}{L}, \quad c \rightarrow \frac{c}{c_0}, \quad v \rightarrow \frac{v}{v_0}, \quad u \rightarrow \frac{u}{u_0};
\]

\[
D_c \rightarrow \frac{D_c}{D}, \quad D_u \rightarrow \frac{D_u}{D}, \quad \alpha \rightarrow \alpha \tau \frac{c_0}{u_0}, \quad \beta \rightarrow \beta \tau, \quad \delta \rightarrow \delta \tau u_0 v_0^{p-1},
\]

where \( c_0, v_0 \) and \( u_0 \) are appropriate reference tumour cell density, extracellular matrix density and reference uPA concentration respectively; \( \tau = \frac{L^2}{D} \), \( L = 0.1 \text{ cm} \) and \( D = 10^{-6} \text{ cm}^2 \text{ s}^{-1} \) [4]. We denote the new parameters by the same symbols. Consequently the values of parameters are: \( D_c \sim 10^{-5} - 10^{-3}, \quad D_u \sim 10^{-3} - 1, \quad \delta \sim 10^{-5(p-1)} - 20 \times 10^{-6(p-1)}, \quad \alpha \sim 0.05 - 1 \) and \( \beta \sim 0.13 - 0.95 \). As for \( \chi_c \) and \( \xi_c \) we take the dimensionless values as in [4] i.e \( \chi_c \sim \xi_c \sim 10^{-3} - 1 \).

In terms of traveling wave variable \( y = x - \nu t, \nu = \text{const} \) this system has the form:

\[
\begin{align*}
\nu c + D_c c_y - \chi_c c (\ln u)_y - \xi_c c (\ln v)_y &= \lambda \\
\nu v_y - \delta u v^p &= 0 \\
\nu u_y + D_u u_{yy} + \alpha c - \beta u &= 0,
\end{align*}
\]

(1*)

where \( c = c(y), \quad v = v(y), \quad u = u(y) \) and \( \lambda \) is an integration constant. Further we put \( \lambda = 0 \).

If we introduce the function

\[
F = \frac{v^{1-p}}{1-p},
\]

(2)

the first two equations in (1*) give

\[
\begin{align*}
c &= C_c (e^{-\nu y} v^{\xi_c} u^{\chi_c})^{\frac{1}{1-p}} \\
u &= \frac{\nu}{\delta} F_y.
\end{align*}
\]

(3)

\( C_c > 0 \) is a constant. Substituting (2) and (3) into the third equation of system (1*) we obtain:

\[
D_u F_{yyy} + \nu F_{yy} - \beta F_y + C_1 e^{-\frac{\chi_c}{D_c} y} F \frac{\xi_c}{D_c} F \frac{\alpha}{D_c} F \frac{F}{F^{1-p}} = 0,
\]

(4)
where \( C_1 = C_c \alpha \left( \frac{\xi_c}{\nu} \right)^{\frac{\nu}{\nu_c}} \frac{\xi_c}{\nu_c(1-p)} D_c \), and further we will investigate this equation.

It seems to us that for arbitrary values of the system parameters it is impossible to obtain an exact solution in explicit form. Therefore, we impose a number of restrictions on these parameters. So, let

\[
\frac{\chi_c}{D_c} = 1
\]

that is, we are considering \( \chi_c = D_c \sim 10^{-3} \). Then there is a ‘chosen’ value of the speed of the traveling waves for which we obtain two classes of different solutions. Let

\[
\nu^2 = \frac{\beta D_c^2}{D_u - D_c}
\]

It is possible to do this because \( D_u \geq D_c \) and we do not consider the case \( D_u = D_c \). Then it can be shown that equation (4) can be reduced to the form:

\[
F_{yy} - \nu(D_u - D_c) \frac{D_y}{D_u} F_y + \frac{C_1 D_c(1-p)}{D_u(\xi_c + D_c(1-p))} e^{-\frac{\nu}{D_c} y} F \frac{\xi_c}{D_c (1-p)} + 1 = 0
\]

(with a constant of integration equal to zero). To integrate this equation we use the Lie group method of infinitesimal transformations \([31]\). We find a group invariant of a second prolongation of one–parameter symmetry group vector of (7) and with its help we transform equation (7) into an equation of the first order. It turns out that there are two nontrivial symmetry groups depending on the ratio of the parameters that give two different types of solutions. Let us consider the first of them.

III. EXACT SOLUTIONS

1. First type of exact solutions

The possibility to reduce equation (7) to a first order equation and solve it requires the following condition:

\[
1 - p = \frac{\xi_c(D_u - D_c)}{2D_u D_c}.
\]

If we introduce the new variable \( z \) and the new function \( w \):

\[
\begin{align*}
 z &= F e^{-\frac{y}{\xi_c}} \\
 w &= -\frac{D_c}{\nu} \frac{F_y e^{-\frac{y}{\xi_c}}}{\xi_c} 
\end{align*}
\]
then after elementary integration equation (7) turns into a quadratic equation on $w(z)$:

$$w^2 + \frac{2(1-p)D_c}{\xi_c} z w + C_2 z^{\frac{\xi_c}{D_c(1-p)}} = 0,$$

(10)

where the constant of integration is equal to zero and $C_2 = \frac{2C_c D_c^4(1-p)z^{\frac{\xi_c}{D_c(1-p)}}}{\nu^2(\xi_c + D_c(1-p))(\xi_c + 2D_c(1-p))}$. Returning to the initial function $F$ and variable $y$ and integrating (10) we obtain a solution for $F$:

$$F = C_3 \left(e^{-\frac{\nu}{D_c} y + C_F} \right) \left(\frac{2D_c(1-p)}{\xi_c}\right),$$

(11)

where $C_F$ is a positive constant and $C_3 = (C_F \frac{2\nu^2D_c(\xi_c + D_c(1-p))(\xi_c + 2D_c(1-p))(1-p)}{C_c \alpha D_c^2 \xi_c}) \frac{D_c(1-p)}{\xi_c}$. Substituting this into (2) and (3) we obtain the first type of solution $s$ of system (1) in the form:

$$c(y) = C_C e^{-\frac{\nu}{D_c} y} \left(e^{-\frac{\nu}{D_c} y + C_F} \right)^{-\frac{D_u(\xi_c + 2D_c(1-p))}{\xi_c}} - 2$$

$$v(y) = C_v \left(e^{-\frac{\nu}{D_c} y + C_F} \right)^{-\frac{2D_c}{\xi_c}}$$

$$u(y) = C_u e^{-\frac{\nu}{D_c} y} \left(e^{-\frac{\nu}{D_c} y + C_F} \right)^{-\frac{D_u(\xi_c + 2D_c(1-p))}{\xi_c}} ,$$

(12)

where the constants are

$$C_v = \left(\frac{C_F}{C_c} \frac{\beta(\xi_c + D_c(1-p))(\xi_c + 2D_c(1-p))}{\alpha D_c \xi_c (1-p)} \right) \frac{D_c}{\xi_c}$$

$$C_u = C_u \frac{\nu}{D_c} \frac{\beta D_c}{\delta D_u (1-p)}$$

$$C_C = C_c C_u C_v \frac{\xi_c}{D_c}.$$

As can be seen from (12) these solutions are the positive functions defined for all values of $y$. Despite the fact that because of the biological context we are interested in solutions in a restricted space-time domain, it is easy to see that for $D_u > D_c$ the tumour cell density $c(y)$ and the uPA concentration $u(y)$ vanish at $y \to \pm \infty$; the extracellular matrix density $v(y) \to C_v C_F^{2\nu y}$ at $\nu y \to +\infty$ and $v(y) \to 0$ at $\nu y \to -\infty$. It can also be seen that $c(y)$ and $u(y)$ have a single maximum; its values, as well as the asymptotic value of $v(y)$ at $\nu y \to +\infty$ depend on the chosen parameters. These functions are presented in Fig.1–Fig.2. for different values of parameters and for $\nu > 0$.

In Fig.3 we show the sequence of profiles of travelling waves which propagate into the tissue. A thick line shows the curves at the time $t = 0$. 

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Let us return to equation (7) and consider the relation similar to (8):

$$1 - p = \frac{\xi_c (D_u - D_c)}{D_c (2D_c - D_u)}.$$  \hfill (14)

It should be noted that (8) and (14) can not be equal because of $D_u > D_c$. Further, as can be seen from (14) the restriction on $D_u$ and $D_c$ becomes more strict: $D_c < D_u < 2D_c$. Similarly to the case of the first class of solutions we introduce the new variable $z$ and the new function $w$:

$$z = F e^{-\frac{\nu(D_u-D_c)}{D_uD_c} y}$$  \hfill (15)

$$w = F - \frac{D_u D_c}{\nu(D_u-D_c) F_y}$$

and equation (7) turns into a quadratic equation on $w(z)$:

$$w^2 + C_4 z \frac{D_u}{D_u-D_c} - C_w = 0,$$  \hfill (16)
where $C_w > 0$ is the constant of integration, $C_4 = \frac{2C_w \alpha (D_u - D_c) (1 - p) \tau C_2}{\beta D_c}$. 

Then we find solutions of equation (16) in parametric form with a parameter $\tau$: 

$$\tau^2 + 1 = \frac{C_w}{C_4} z^{-\frac{D_u}{D_u - D_c}}.$$ 

(17)

The analysis of solutions asymptotic forms at $\pm \infty$ and the requirement of positivity of functions $c(y)$, $v(y)$ and $u(y)$ determine one of the constants of integration. The formulas obtained are rather complicated, for this reason we introduce the notation: 

$$\Theta(\tau) = -\tau^2 F_1(\frac{1}{2} : \frac{3}{2} - \frac{D_u}{D_u} : \frac{3}{2} : -\tau^2) + \frac{\sqrt{\pi} \Gamma(1 - \frac{D_u}{D_u})}{2 \Gamma(\frac{3}{2} - \frac{D_u}{D_u})},$$ 

(18)

and express our solutions in terms of $\Theta(\tau)$. We also give the solutions for $\nu > 0$. This yields the following expressions for the second type of solutions:

$$y(\tau) = - \frac{D_u}{\sqrt{\beta(D_u - D_c)}} \ln \left( \frac{C_w \frac{1}{2} - \frac{D_u}{D_u} \frac{2(D_u - D_c)}{D_u}}{C_4 \frac{1}{1 - \frac{D_u}{D_u}}} \frac{2(D_u - D_c)}{D_u} \Theta(\tau) \right).$$ 

(19)

$$v(\tau) = \left( \frac{C_w \frac{1}{2} D_u (1 - p)}{2(D_u - D_c)} \right)^{\frac{1}{1 - p}} (\tau^2 + 1)^{-\frac{D_u}{D_u - D_c} - p} \Theta(\tau)^{-\frac{1}{1 - p}}$$

(20)

$$u(\tau) = - \frac{C_w \frac{1}{2} \beta D_c}{\delta D_u} \tau (\tau^2 + 1)^{2 - \frac{D_u}{D_u}} 2 F_1(\frac{1}{2} : \frac{3}{2} - \frac{D_u}{D_u} : \frac{3}{2} : -\tau^2) -$$

$$- \tau^2 (1 - \frac{2D_u}{3D_u}) 2 F_1(\frac{3}{2} : \frac{5}{2} - \frac{D_u}{D_u} : \frac{5}{2} : -\tau^2) \left( (\tau^2 + 1)^{-\frac{D_u}{D_u - D_c}} \Theta(\tau) \right)^{-1}$$

and since (3) the expression for the tumour cells density $c(\tau)$ has the form:

$$c(\tau) = \frac{2 \beta D_c (D_u - D_c)}{\alpha D_u^2} (\tau^2 + 1)^{1 - \frac{D_u}{D_u}} \Theta(\tau)^2 u(\tau).$$ 

(21)

Here $2 F_1$ is the hypergeometric Gauss function, $\Gamma$ is the Gamma-function. We can see from (18), (20)-(21) that the functions $v(\tau)$, $u(\tau)$ and $c(\tau)$ are smooth positive definite functions. The tumour cell density $c(\tau) \to 0$ at $\tau \to \pm \infty$, the uPA concentration $u(\tau) \to u_0$ at $\tau \to -\infty$ and $u(\tau)$ vanish at $\tau \to +\infty$; the extracellular matrix density $v(\tau) \to 0$ at $\tau \to -\infty$ and $v(\tau) \to v_0$ at $\tau \to +\infty$ where the values of $u_0$ and $v_0$ can be obtained from (20). However as can be seen from (18)-(19) $y \to y_0$ at $\tau \to -\infty$, where $y_0$ is a finite value that can be made $< 0$ (or $\geq 0$) by choosing constants of integration. This leads to the fact that the solutions
obtained as functions of $y$ can be considered only in a limited time interval. In other words since $x \in [0; 1]$ and $t \geq 0$ formally $y \in [-\nu t; 1 - \nu t]$ (for $\nu > 0$). But since $y$ is bounded from the left by $y_0$, then for each $y_0$ there exists a value of time $t_0$ after which no solutions are defined. This, in turn, leads to the fact that the solutions obtained, being smooth functions on the whole axis, simply break off from the left at point $y_0$. The graphs of these solutions are presented in Fig.4.

Fig.4: $p = 0.9; D_c = \chi_c = 8 \times 10^{-3}; D_u = 10^{-2}; \xi_c = 2.4 \times 10^{-3}; \alpha = 0.5; \beta = 0.4; \delta = 4; C_w = 100; C_c = 1$

IV. CONCLUSION

We investigate the continuous mathematical model of tumour growth and invasion based on the model introduced by Anderson, Chaplain et al. [1] in one space dimension. The model consists of a system of three coupled nonlinear reaction-diffusion-taxis partial differential equations describing the interactions between tumour cells, the uPA protease concentration and the ECM density. To obtain the exact analytical solutions we consider the model with logarithmic chemotactical and haptotactical sensitivity functions, without proliferation and reestablishment terms and with slightly modified equation for ECM density. This allowed us under certain conditions on the model parameters to obtain two types of solutions in terms of traveling wave variables. The first type describes smooth positive functions defined for any values of $y$. Despite the changes made to the model [1] the graphs of these functions are very close to those obtained in [4] from numerical computations. The solutions of the second type also have the similar graphs, but they have a disadvantage: the functions obtained are
defined only on restricted time intervals.

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