# Mathematical analysis of tumour invasion with proliferation model and simulations

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*Abstract:* In this paper it is shown that the global existence in time and asymptotic profile of the solution of a mathematical model of tumour invasion with proliferation proposed by Chaplain et al. For this purpose we consider a related nonlinear evolution equation with strong dissipation and proliferation corresponding to our mathematical model and the initial Neumann-boundary value problem for the evolution equation. We prove the global existence in time of solutions to the problem for the nonlinear evolution equation in arbitrary space dimension by the method of energy. In this paper our main mathematical approach is heavily based on energy estimates. Applying our mathematical result of the problem to the tumour invasion model we will discuss the existence and property of solutions to the model which gives us a rigorous mathematical understanding of the model. Finally we will show the time depending relationship and interaction between tumour cells, the tissue and degradation enzymes by computer simulations of the model. It is seen that our mathematical result of the existence and asymptotic behaviour of solutions guarantees the validity of computer simulations and implies the pattern figure of each component of the model respectively.

*Key–Words:* Nonlinear evolution equation, mathematical analysis, tumour invasion, cells proliferation, simulation.

## 1 Introduction

In the last several decades, a number of mathematical models describing the procedure of tumourigenesis and tumour growth have been the remarkable subject of research (cf. [1]-[5], [7]-[9], [20]-[25]). Especially our main concern of this paper is specific mathematical models of avascular tumour growth proposed by Chaplain et al. ([3][4]). They are considered mainly by three variables in the process of tumour invasion, tumour cells, ECM and MDEs without the effect of proliferation. Anderson and Chaplain [3] has been developed by Chaplain and Lolas [4] additionally considering into chemotaxis, proliferation of tumour cells and reestablishment of the ECM.

Their mathematical approach to above models is usually numerical analysis and computer simulations. On the other hand, rigorous mathematical results have been almost unknown for such models.

Our main goal is to give a rigorous mathematical understanding to tumour invasion models. While by computer simulations of our model (the usage of Mathematica 4 in section 5) we can easily observe morphologies of complicated procedure of tumour invasion and the relationship to our mathematical result. Identifying our rigorous result and computer simulations we will arrive at a better understanding of the mechanism of tumour invasion.

Now we consider a mathematical model based on Chaplain and Lolas [4] described tumour invasion with tumour cell proliferation in the following form: (CAL)

$$\begin{cases} \dfrac{\partial n}{\partial t} = d_n \dfrac{\partial^2 n}{\partial x^2} - \gamma \dfrac{\partial}{\partial x}\left(n \dfrac{\partial f}{\partial x}\right) + \mu_1 n(1-n-f) & (1) \\ \dfrac{\partial f}{\partial t} = -\eta m f + \mu_2 f(1-n-f) & (2) \\ \dfrac{\partial m}{\partial t} = d_m \dfrac{\partial^2 m}{\partial x^2} + \alpha n - \beta m & (3) \end{cases}$$

where $n := n(x,t)$ is the density of tumour cells, $m := m(x,t)$ is degradation enzymes concentration (MDE concentration) and $f := f(x,t)$ is the extra cellular matrix density (ECM density) and $d_n, \gamma, \mu_1, \eta, \mu_2, d_m, \alpha$ and $\beta$ are positive constants,

$(x,t) \in \Omega \times (0,\infty)$ and $\Omega$ is a bounded domain in $R^n$ with a smooth boundary $\partial\Omega$.

In the below we consider only the case of $\mu_2 = 0$ for our convenience. (CAL) describes tumour invasion phenomena with tumour cell proliferation. We deal with a boundary value problem for (CAL) satisfying initial condition:
$n(x,0) = n_0(x), f(x,0) = f_0(x), m(x,0) = m_0(x)$
and zero-Neumann condition:

$$\frac{\partial}{\partial\nu}n(x,t) = \frac{\partial}{\partial\nu}f(x,t) = \frac{\partial}{\partial\nu}m(x,t) = 0$$

on $\partial\Omega \times (0,\infty)$ where $\nu$ is a outer unit normal vector.

Chaplain and Anderson [3], corresponding to the case of $\mu_1 = \mu_2 = 0$ in (CAL), base the mathematical model on generic solid tumour growth, which for simplicity they assume at the avascular stage. While most tumours are asymptomatic at this stage, it is still possible for cells to escape and migrate to the lymph nodes and for the more aggressive tumours to invade. In the model the following key variables are considered: tumour cell density, MDE concentration, ECM density.

MDEs are important at many stages of tumour growth, invasion, and metastasis, and the manner in which they interact with endogeneous inhibitors, growth factor, and tumour cells is very complex. In the model they assume that the tumour cells produce MDEs which degrade the ECM locally and that the ECM responds by producing endogeneous inhibitors (e.g., TIMPs). The ECM degradation, as well as making space into which tumour cells may move by simple diffusion, results in the production of molecules which are actively attractive to tumour cells (e.g., fibronectin) and which then aid in tumour cell motility. They refer to the movement of tumour cells up a gradient of such molecules as haptotaxis and then choose to consider tumour cell motion to be driven only by random motility and haptotaxis in response to adhesive or attractive gradients created by degradation of the matrix.

Recently, there are many mathematical models which can be found in the literature describing tumour angiogenesis (cf.[2], [20], [24], [25]). In [20] Levine and Sleeman apply the diffusion equation provided by Othmer and Stevens [24] to obtain the understanding of tumour angiogenesis, which arises in the theory of reinforced random walk. Anderson and Chaplain [2] proposed a model for angiogenesis considered into endothelial tip-cell migration, i.e., the model considered the motion of the cells located at the tips of the growing sprouts. The model has cell migration governed by three factors: diffusion, chemotaxis and haptotaxis.

On the other hand, mathematical approaches for models of tumour growth have done (see [10]-[20][25][26]). Levine and Sleeman [20] and Yang, Chen and Liu [26] studied the existence of the time global solution and blow up solutions to a simplified case of Othmer and Stevens type of the model. Kubo et al. [10]-[19] show the time global solvability and asymptotic behaviour of the solution to the model proposed in [2][3][20][24][25].

In this paper we deal with a reduced nonlinear evolution equation from the model (CAL) and obtain the existence and asymptotic behaviour of solutions. Applying our mathematical results to the model we gain a understanding of a mechanism of tumour invasion. By computer simulations we see the effect of proliferation in the tumour invasion model as $\mu_1$ increases. Actually visualizing the asymptotic behaviour of solutions of the model, we can observe clearly the time depending relationship and interaction between tumour cells, ECM and MDE.

# 2 Reduced problem

## 2.1 Reduction process

Following to Levine and Sleeman [20] we reduce our problem to more simplified one (see [10]-[19]).

It is easily seen in (2) that $f(x,t)$ is written by

$$f(x,t) = f_0(x) \cdot e^{-\eta\int_0^t m ds} \tag{4}$$

Substituting $f(x,t)$ by the right hand side of (4) and putting

$$\Psi = \int_0^t n ds \text{ and } \Phi = \int_0^t m ds,$$

from (1) and (3) it following that

$$\Psi_{tt} = d_n\partial_x^2\Psi_t + \gamma\eta\partial_x(f_0(x)\Psi_t\Phi_x e^{-\eta\Phi})$$
$$-\gamma\partial_x(f_{0x}(x)\Psi_t e^{-\eta\Phi}) + \mu_1\Psi_t(1-\Psi_t - f_0(x)e^{-\eta\Phi}) \tag{5}$$

and

$$\Phi_{tt} = d_m\partial_x^2\Phi_t + \alpha\Psi_t - \beta\Phi_t. \tag{6}$$

In the next subsection we propose a class of nonlinear evolution equations covering (5) and (6) and show global existence in time and asymptotic behaviour of solutions of the initial boundary value problem for such equations.

### 2.2 Related nonlinear evolution equations

In this subsection we consider the initial Neumann-boundary value problem of nonlinear evolution equations related to (CAL): (NE)

$$\begin{cases} u_{tt} = D\nabla^2 u_t + \nabla\cdot(\chi(u_t, e^{-u})e^{-u}\nabla u) \\ \qquad\qquad +\mu(1-u_t)u_t \qquad \text{in } \Omega\times(0,T) \ (7) \\ \dfrac{\partial}{\partial\nu}u|_{\partial\Omega} = 0 \qquad\qquad \text{on } \partial\Omega\times(0,T) \ (8) \\ u(x,0) = u_0(x),\ u_t(x,0) = u_1(x) \qquad \text{in } \Omega \ (9) \end{cases}$$

$$\frac{\partial}{\partial t} = \partial_t, \frac{\partial}{\partial x_i} = \partial x_i, i = 1,\cdots,n, \nabla u = (\partial_{x_1}u, \cdots \partial_{x_n}u)$$

$$\nabla^2 u = \nabla\cdot\nabla u = \triangle u = \partial_{x_1}^2 u + \cdots + \partial_{x_n}^2 u$$

where $D$ is a positive constant, $\Omega$ is a bounded domain in $R^n$ and $\partial\Omega$ is a smooth boundary of $\Omega$ and $\nu$ is the outer unit normal vector.

Let us introduce function spaces used in this paper. First, $H^l(\Omega)$ denotes the usual Sobolev space $W^{l,2}(\Omega)$ of order $l$ on $\Omega$. For functions $h(x,t)$ and $k(x,t)$ defined in $\Omega\times[0,\infty)$, we put

$$(h,k)(t) = \int_\Omega h(x,t)k(x,t)dx,$$

$$||h||_l^2(t) = \sum_{|\beta|\le l} |\partial_x^\beta h(\cdot,t)|^2_{L^2(\mathbf{\Omega})}(t)$$

and sometimes we write $||h||_0(t)$ by $||h||(t)$ for simplicity where $\beta$ is a multi-index for $\beta = (\beta_1,\cdots,\beta_n)$.

Putting $u(x,t) = L_a(t) + v(x,t)$ we have in (7)

$$v_{tt} = D\nabla^2 v_t$$
$$+\nabla\cdot(\chi(l(t)+v_t, e^{-L_a(t)-v})e^{-L_a(t)-v}\cdot\nabla v)$$
$$+\mu v_t(t)(1-2l(t)-v_t)$$

where

$$L_a(t) = \int_0^t l(\tau)d\tau + a,$$

$a$ is a positive parameter and $l(t)$ satisfies the initial problem for the logistic equation:

$$l_t(t) = \mu l(t)(1-l(t)),\ \ l(0) = l_0 > 0$$

then (NE) is rewritten by the following problem: (RP)

$$\begin{cases} Q[v] = v_{tt} - D\nabla^2 v_t \\ \qquad -\nabla\cdot(\chi(l(t)+v_t,\ e^{-L_a(t)-v})e^{-L_a(t)-v}\cdot\nabla v) \\ \qquad -\mu v_t(t)(1-2l(t)-v_t) \ = 0, \\ \dfrac{\partial}{\partial\nu}v|_{\partial\Omega} = 0, \\ v(x,0) = v_0(x),\ \ v_t(x,0) = v_1(x). \end{cases}$$

## 3 Existence theorem of (NE)

By deriving the energy estimate of (RP) (see [15]) and considering the iteration scheme we obtain existence of solutions to (RP) by the standard argument to show the convergence of the solution of iteration scheme.

In the same way as used in [10]-[19] we have the following estimate of (RP) (cf. Dionne [6]).

**Lemma 1** *Assume that $\chi(s_1,s_2)$ for $(s_1,s_2)\in R^2_+$ satisfies appropriate regularity condition. We have the energy estimate of (RP) for $M\ge[n/2]+3$*

$$\sum_{j=1}^{M+1}(||\nabla^{j-1}v_t||^2(t) + \int_0^t D||\nabla^j v_t||^2(\tau)d\tau)$$

$$\le CE_M[v](0)$$

*where we denote for any non-negative integer $k\le M\le m$,*

$$E_k[v](t) = E[\nabla^k v],\quad E[v] = ||v_t||^2 + ||\nabla v||^2.$$

We consider the iteration scheme of (RP):

$$(i{+}1)\begin{cases} Q_i[v_{i+1}] = \partial_t^2 v_{i+1} - \partial_t\Delta v_{i+1} \\ -\nabla\cdot(e^{-a-bt}\chi(u_{it}, e^{-u_i})e^{-v_i}\nabla v_{i+1}) = 0, \\ \dfrac{\partial}{\partial\nu}v_{i+1}|_{\partial\Omega} = 0, \\ v_{i+1}(x,0) = v_0(x),\ v_{i+1t}(x,0) = v_1(x), \end{cases}$$

where $v_i = \sum_{j=1}^{\infty} f_{ij}(t)\varphi_j(x), v_0(x) = \sum_{j=1}^{\infty} h_j\varphi_j(x)$, $v_1(x) = \sum_{j=1}^{\infty} h'_j\varphi_j(x)$.

The energy estimate lemma 1 guarantees the uniform estimate of each $(i+1)$ for $i = 1, 2, \cdots$. We determine $f_{ij}(t)$ by the solution of the following system of ordinary equations with initial data. For $j = 1, 2, \cdots$

$$\begin{cases} (Q_i[v_{i+1}], \varphi_j) = 0, \\ f_{i+1j}(0) = h_{i+1},\ f_{i+1jt}(0) = h'_{i+1}. \end{cases}$$

It is not difficult to assure the local existence in time of $f_{ij}(t)$ by the theory of ordinary differential equations. Therefore, deriving the energy estimates, the global existence in time of the solution $\{u_i\}$ satisfying the regularity required to derive the energy inequality in section 2 and justification of the limiting process are assured in the usual way. The energy estimate enables us to get the solution by considering $Q_i[v_{i+1}] - Q_{i-1}[v_i]$ and the standard argument of convergence for $v_{i+1} - v_i = w_i$.

Then we obtain the following result of (NE) via (RP).

**Theorem 2** *Assume that $\chi(s_1, s_2)$ satisfies appropriate smooth regularity condition with respect to $(s_1, s_2) \in R^2_+$ and initial data $(v_0(x), v_1(x))$ are sufficiently smooth for $v_0(x) = u_0(x) - a, v_1(x) = u_1(x) - l_0$. For sufficiently large $a$, there is a solution for $m \geq [n/2] + 3$*

$$u(x,t) = L_a(t) + v(x,t) \in \bigcap_{i=0}^{1} C^i([0,\infty); H^{m-i}(\Omega))$$

*to (NE) such that it satisfies the following asymptotic behaviour*

$$\lim_{t\to\infty} ||u_t(x,t) - l(t)||_{m-1} = 0.$$

# 4 Existence theorem of (CAL)

The equations (5) and (6) are essentially regarded as the same type of equation as (9). The energy estimates of $\Psi$ and $\Phi$ follow and combining these estimates we obtain the desired estimate. Hence applying the same argument as used for theorem 2 to our mathematical model, in the same way as in [18][19] we have existence and asymptotic behaviour of the solutions to our mathematical model.

Our main result is as follows.

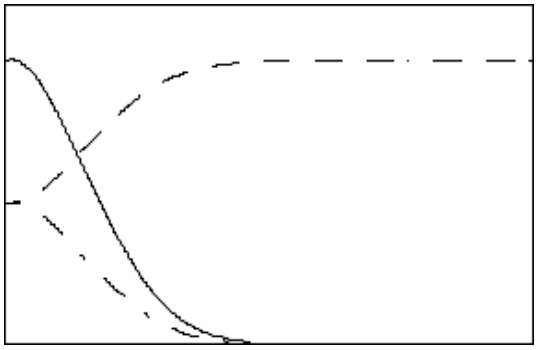
**Theorem 3** *For smooth initial data $\{n_0(x), f_0(x), m_0(x)\}$ there are classical solutions of (CAL): $\{n(x,t), f(x,t), m(x,t)\}$ such that they satisfy the following asymptotic behaviour.*

$$\lim_{t\to\infty} n(x,t) = 1, \quad \lim_{t\to\infty} f(x,t) = 0.$$

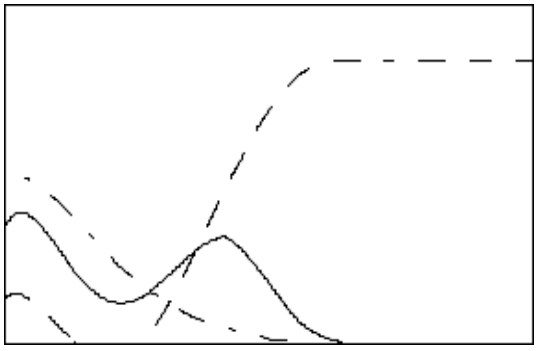
# 5 Computer simulations

In Figures 1-5 illustrated below we show snapshots in time of the computer simulations of the model taking $\mu_1$ from 0 to 10 at $t$ = 0,2,4 and 6.5 by Mathematica 4. We use other parameter values $d_n = 0.001, d_m = 0.001, \gamma = 0.02, \eta = 10, \mu_1 = 0, \mu_2 = 0, \alpha = 0.1$, and $\beta = 0$ , specified in the captions of the figures.

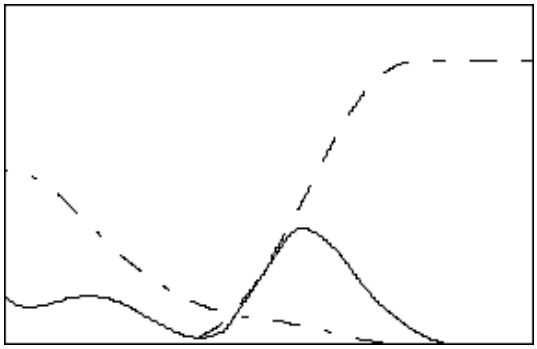
We will see the time dependent relationship and interaction between tumour cells (solid), the tissue (dashed) and degradation enzymes (dashdot). In the following graph a coordinate axis of the horizontal direction indicates the position and the vertical direction indicates the density of each component of the model.



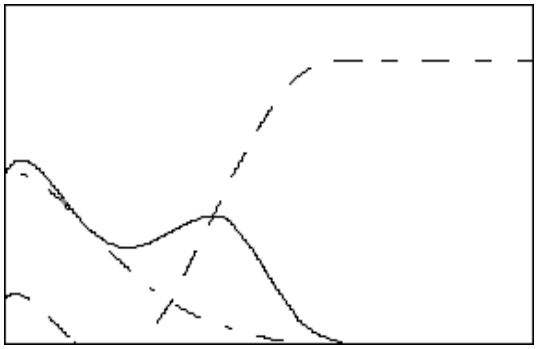
$t = 0$



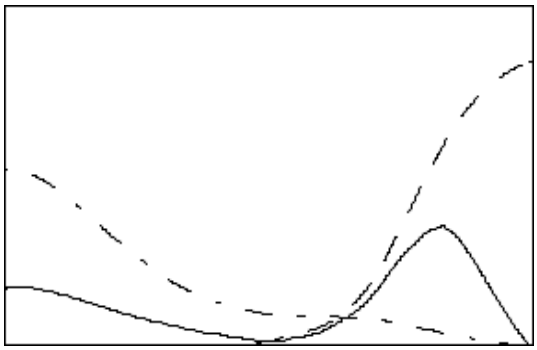
$t = 2.0$



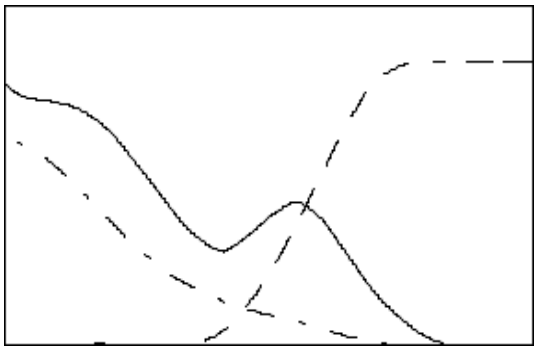
$t = 4.0$



$t = 2.0$

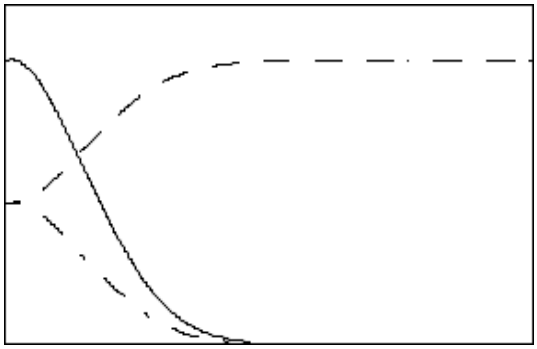


$t = 6.5$

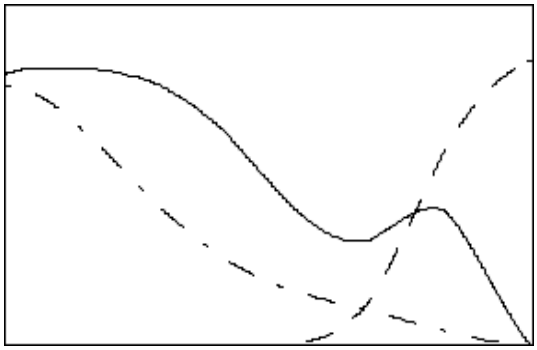


$t = 4.0$

Figure 1: Tumour cell proliferation, migration, ECM re-establishment, and interactions between the tumour and the surrounding tissue: tumour cell density (solid), ECM density (dashed), and MDE concentration (dashdot). Solutions to (1)-(3) with the parameter values $d_n = 0.001, d_m = 0.001, \gamma = 0.02, \eta = 10, \mu_1 = 0, \mu_2 = 0, \alpha = 0.1$, and $\beta = 0$.

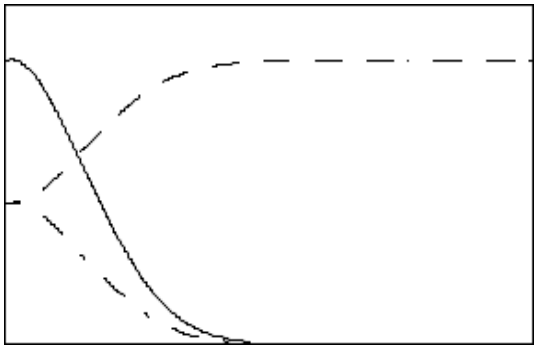


$t = 0$

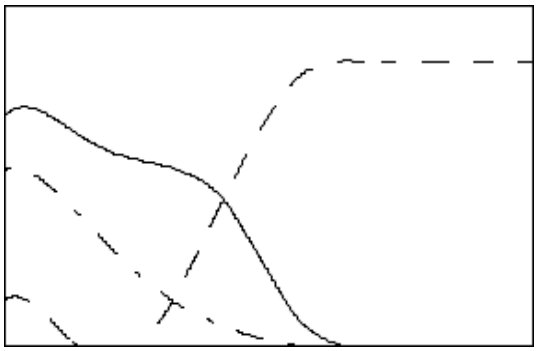


$t = 6.5$

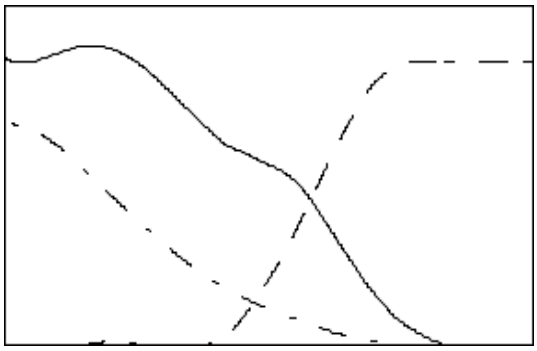
Figure 2: Tumour cell proliferation, migration, ECM re-establishment, and interactions between the tumour and the surrounding tissue: tumour cell density (solid), ECM density (dashed), and MDE concentration (dashdot). Solutions to (1)-(3) with the parameter values $d_n = 0.001, d_m = 0.001, \gamma = 0.02, \eta = 10, \mu_1 = 1.0, \mu_2 = 0, \alpha = 0.1$, and $\beta = 0$.



$t = 0$



$t = 2.0$



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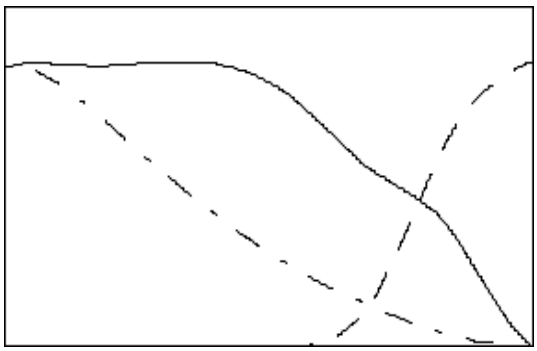
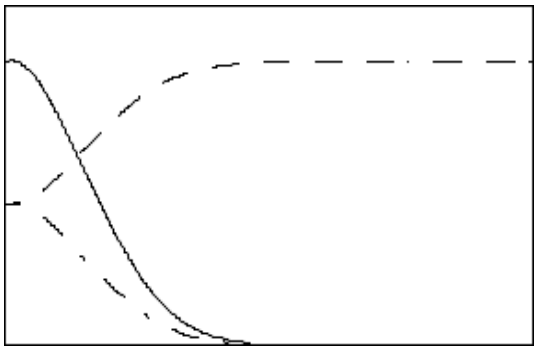
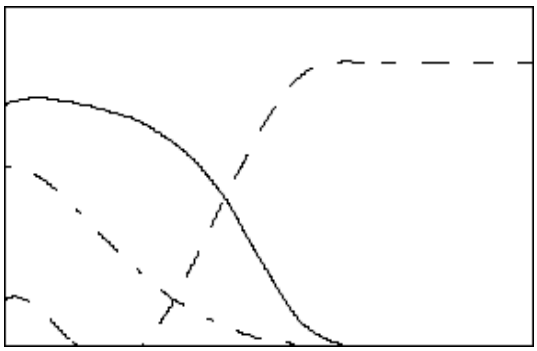


$t = 6.5$

Figure 3: Tumour cell proliferation, migration, ECM re-establishment, and interactions between the tumour and the surrounding tissue: tumour cell density (solid), ECM density (dashed), and MDE concentration (dashdot). Solutions to (1)-(3) with the parameter values $d_n = 0.001, d_m = 0.001, \gamma = 0.02, \eta = 10, \mu_1 = 3.0, \mu_2 = 0, \alpha = 0.1$, and $\beta = 0$.



$t = 0$



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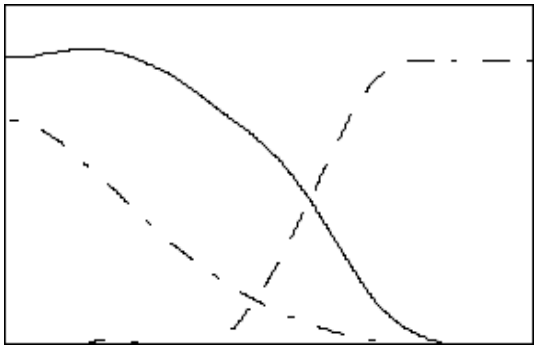
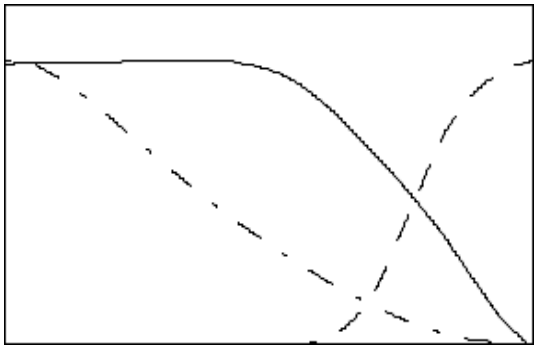
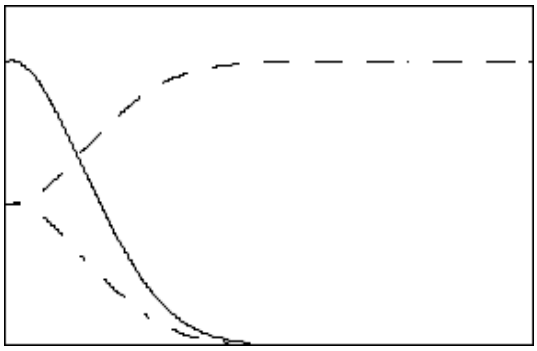


$t = 4.0$

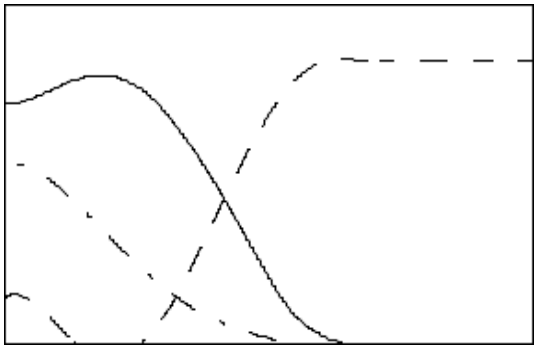


$t = 6.5$

Figure 4: Tumour cell proliferation, migration, ECM re-establishment, and interactions between the tumour and the surrounding tissue: tumour cell density (solid), ECM density (dashed), and MDE concentration (dashdot). Solutions to (1)-(3) with the parameter values $d_n = 0.001, d_m = 0.001, \gamma = 0.02, \eta = 10, \mu_1 = 5.0, \mu_2 = 0, \alpha = 0.1$, and $\beta = 0$.



$t = 0$



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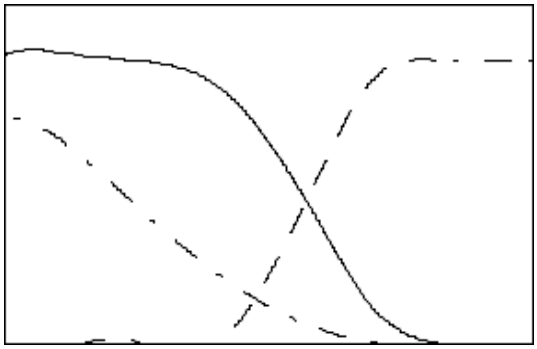

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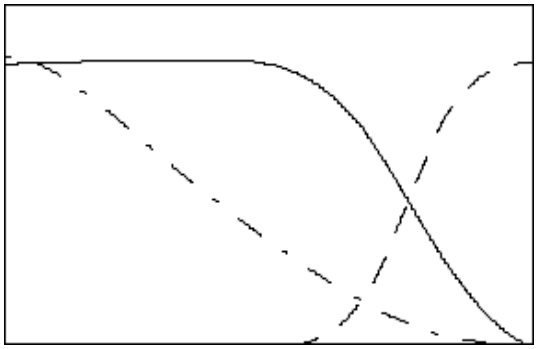

$t = 6.5$

Figure 5: Tumour cell proliferation, migration, ECM re-establishment, and interactions between the tumour and the surrounding tissue: tumour cell density (solid), ECM density (dashed), and MDE concentration (dashdot). Solutions to (1)-(3) with the parameter values $d_n = 0.001, d_m = 0.001, \gamma = 0.02, \eta = 10, \mu_1 = 10, \mu_2 = 0, \alpha = 0.1$, and $\beta = 0$.

In Figures 1-5 it is shown that MDE degradates ECM and tumour cells migrate to a degradated space in the tissue, that is, tumour invades the nearby tissue.

In the case of $\mu_1 = 0$ invasive tumour cells form a peak in the nearby tissue and continues to invade (Figure 1). In Figure 2 for $\mu_1 > 0$ the front of invasive tumour cells still form a peak and tumour cell density increases outside of ECM. When $\mu_1$ is taken large enough (Figure 4-5), it is observed that tumour cells proliferation and form the traveling wave and continue to propagate forward.

# 6 Conclusions

The model shows that tumour invasion into healthy tissue, as showed in computer simulations in section 5 followed in certain regions of parameter space. Considering into global existence in time and the asymptotic behaviour of solutions of the initial boundary

value problem (NE) for the nonlinear evolution equation reduced from the model, we can show the rigorous result of existence and asymptotic properties of solutions of (CAL).

Our main purpose is focused on a rigorous mathematical understanding of the model rather than application dominated and it guarantees the validity of computer simulations that qualitatively replicate the complicated morphologies invasive tumour. Actually, the asymptotic behaviour of $n(x,t)$ and $f(x,t)$ stated in theorem 3 imply the pattern figures of tumour cells density and ECM density respectively as $t$ is large enough in the computer simulations, in Figures 4-5.

Identifying our mathematical results and computer simulations we seems to arrive at a better understanding of tumour invasion.

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