Mathematical Analysis of a Model of Tumour Invasion and Simulations

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Abstract—We study a parabolic ODE system modeling tumour invasion proposed by Anderson and Chaplain in 2003. Then we will apply the approach used in mathematical models of tumour angiogenesis to it and show the solvability and the asymptotic profile of the solution of it. Actually in use of the transformation of Levine and Sleeman, we reduce it to a system consist of evolution equations. Then, we show global existence in time of the solution in arbitrary space dimension by a priori estimate. Finally we show some results of computer simulations of the model with the help of our mathematical analysis.

Keywords—Tumour invasion, mathematical analysis, time global solution, Asymptotic property.

I. Introduction

THIS paper concerns mathematical analysis of a mathematical model of tumour invasion. Anderson and Chaplain [3] base the mathematical model on generic solid tumour growth, which for simplicity they assume is 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 initial model the following key variables are considered: tumour cell density (denoted by n),MDE concentration(denoted by m),ECM density(denoted by f),and endogenous inhibitor(e.g., tissue inhibiting metallo-proteases, TIMPs)concentration. Each of the variables (n, m and f)is a function of the spatial variable x and time *t*.

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 calls 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. They make a simplification by assuming that for an actively invading tumour, any negative effect of the endogeneous inhibitors has effectively been overcome by the MDEs. Therefore in this paper we do not consider the effect of the endogeneous inhibitors. Finally the following mathematical model is proposed of tumour tissue invasion.

$$\cdot \quad \frac{\partial n}{\partial t} = \overbrace{d_n \nabla^2 n}^{random\,motility} - \overbrace{\nabla \cdot (n \nabla f)}^{haptotaxis} \tag{1}$$

$$\cdot \quad \frac{\partial f}{\partial t} = - \overbrace{\eta m f}^{degradation} \tag{2}$$

$$\cdot \quad \frac{\partial m}{\partial t} = \overbrace{d_m \nabla^2 m}^{diffusion} + \overbrace{\alpha n}^{production} - \overbrace{\beta m}^{decay} \tag{3}$$

$n = n(x,t)$: density of tumour cells

$m = m(x,t)$: MDE concentration

$f = f(x,t)$: ECM concentration

d_n, d_m, α, β : positive constants

Initial condition is given by

(I) $n(x,0) = n_0(x)$, $m(x,0) = m_0(x)$, $f(x,0) = f_0(x)$

0-Neumann boundary condition is imposed

(B) $\frac{\partial}{\partial \nu} n = 0 \quad \frac{\partial}{\partial \nu} m = 0 \quad \frac{\partial}{\partial \nu} f = 0$ on $\partial\,\Omega \times (0,\infty)$

where ν is a unit outer normal vector and Ω is a bounded domain in R^n with a smooth boundary $\partial\,\Omega$.

Recently, there are many mathematical models which can be found in the literature describing tumour angiogenesis(cf.

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[1], [2], [11]). In [11] Levine and Sleeman apply the diffusion equation provided by Othmer and Stevens [12] to obtain the understanding of tumour angiogenesis, which arises in the theory of reinforced random walk(see [4]). Anderson and Chaplain [1], [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 angiogenesis have done(see [5]-[11] ,[15]-[18]). Levine and Sleeman [11] and Yang, Chen and Liu [15] 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. [5]-[10], [16]-[18] show the time global solvability and asymptotic behavior of the solution to the model without using such simplification. [5]-[10],[16]-[18] and Sleeman, Anderson and Chaplain [13] deal with the solvability of Anderson and Chaplain's model in [1], [2].

In [12] Othmer and Stevens derived a parabolic ODE system formulating the reinforced random walk model(cf.Davis [4]), where unknown functions P and W stand for the density of the particle and that of control species, respectively. That is,

$$\frac{\partial P}{\partial t} = D\nabla\cdot(P\nabla(\ln\frac{P}{\Phi(W)}))$$

$$\frac{\partial W}{\partial t} = F(P,W) \qquad \text{in } (x,t)\in\Omega\times(0,T)$$

$$P\nabla(\log\frac{P}{W^a})\cdot\nu = 0 \qquad \text{on } \partial\Omega\times(0,T)$$

(no-flux condition)

$$P(x,0) = P_0(x) > 0, \qquad W(x,0) = W_0(x) > 0$$

(initial data)

In [11] Levine and Sleeman apply it to the understanding of tumour angiogenesis where P is the density of EC(endothelial cells), W is TAFs(tumour angiogenic factors) concentration and the sensitivity function $\Phi(W)$ is of the form:

$$\Phi(W) = \left(\frac{W+\alpha}{W+\beta}\right)^a.$$

Mathematical analysis of Othmer and Stevens model was done by Levine and Sleeman [11]. In fact, in case

$$\frac{\partial W}{\partial t} = F(P,W) = WP \quad ,$$

taking

$$\log W = \Psi$$

we get $\Psi_t = P$ because of $\frac{W_t}{W} = P$ and Othmer and Stevens model is reduced to the a single equation with the initial condition and the boundary condition as follws.

$$\Psi_{tt} - D\Delta\Psi_t + \nabla\cdot(\frac{aD(\beta-\alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)}\Psi_t\nabla\Psi), \quad (4)$$

$$\frac{\partial}{\partial\nu}\Psi = 0, \quad \text{on } \partial\Omega\times(0,T)$$

$$\Psi_t(x,0) = P_0(x), \qquad \Psi(x,0) = \log W_0(x).$$

In [5]-[10], [16]-[18] a priori estimate was derived of the above reduced problem which plays an important role in the proof of the global existence in time of the solution of Othmer and Stevens model.

In this paper we will apply the approach used in above for mathematical models of tumour angiogenesis to it and show the solvability and the asymptotic profile of the solution of it.

II. Reduction Process

A. Substitution of fibronection concentration

According to the transformation used by Levine and Sleeman we reduced our problem to a system without ODE. From (2) it follows that

$$\frac{f_t}{f} = -\eta m$$

Integrating over $(0,t)$

$$\int_0^t \frac{\partial}{\partial t}(\log f)ds = -\eta\int_0^t m ds.$$

Therefore we have

$$f(x,t) = f_0(x)e^{-\eta\int_0^t m ds}. \quad (5)$$

Substituting $f(x,t)$ by the right hand side of (5) in (1), the problem (1)-(3) reduced to a system consist of two evolution equations with respect to m and n.

Actually by the substitution (5) it is seen that (1) is written by

$$\frac{\partial n}{\partial t} = d_n\Delta n - \gamma\nabla\cdot n(\nabla(f_0(x)e^{-\eta\int_0^t m ds}))$$

For our simplicity we assume $f_0(x)\equiv 1$. Putting

$$\Psi(x,t)=\int_0^t n(x,s)ds\,,$$

then we have

$$\frac{\partial^2}{\partial t^2}\Psi(x,t)=d_n\Delta\Psi_t-\gamma\nabla\cdot\Psi_t(\nabla e^{-\eta\int_0^t mds}). \qquad (6)$$

Next put

$$\Phi(x,t)=\int_0^t m(x,s)ds$$

then we have

$$\frac{\partial^2}{\partial t^2}\Phi=d_m\Delta\Phi_t+\alpha\Psi_t-\beta\Phi_t\,.$$

Remark. In (4) the nonlinear term can be estimated by some positive term from the below(see [5]-[10]). However in (6) it is difficult to deal with it in the same way because the nonlinear term of (6) contain not only Ψ but also Φ. The difficulty lies in this point when we derive a estimate of our problem.

Therefore our problem is reduced to the following system.

$$(RP1)\begin{cases}\dfrac{\partial^2}{\partial t^2}\Psi(x,t)=d_n\Delta\Psi_t+\eta\gamma\nabla\cdot\Psi_t((\nabla\int_0^t mds)e^{-\eta\Phi}) & (7)\\[2ex] \dfrac{\partial^2}{\partial t^2}\Phi=d_m\Delta\Phi_t+\alpha\Psi_t-\beta\Phi_t & (8)\\[2ex] \Psi(x,0)=0 \qquad \Psi_t(x,0)=n_0(x)\\[2ex] \Phi(x,0)=0 \qquad \Phi_t(x,0)=m_0(x)\\[2ex] \dfrac{\partial}{\partial\nu}\Psi\Big|_{\partial\Omega}=\dfrac{\partial}{\partial\nu}\Phi\Big|_{\partial\Omega}=0\end{cases}$$

B. Substitution of $\Psi(x,t)$ and $\Phi(x,t)$

For $\gamma_1,\gamma_2>0$ substituting $\Psi(x,t)$ and $\Phi(x,t)$ by

$$\gamma_1 t+v(x,t)\,,\ \gamma_2 t_T+w(x,t)\,,$$

respectively where $t_T=t+T,\quad T>0$. Then our problem finally is rewritten by the following problem.

$$(RP2)\begin{cases} v_{tt}=d_n\Delta v_t+\eta\gamma\gamma_1\nabla\cdot(e^{-\eta(\gamma_2 t_T+w)}\nabla w)\\ \qquad\qquad +\eta\gamma\nabla(\nabla w v_t e^{-\eta(\gamma_2 t_T+w)}) & (9)\\[2ex] w_{tt}=d_m\Delta w_t+\alpha(\gamma_1+v_t)-\beta(\gamma_2+w_t) & (10)\\[2ex] \dfrac{\partial v}{\partial\nu}\Big|_{\partial\Omega}=\dfrac{\partial w}{\partial\nu}\Big|_{\partial\Omega}=0\\[2ex] v(x,0)=0, \qquad v_t(x,0)=v_1(x)\\[2ex] w(x,0)=w_0(x), \qquad w_t(x,0)=w_1(x)\end{cases}$$

By this substitution we see that the term $e^{-\eta\int_0^t mds}$ involved in (9) and (10) behaves like e^{-ct} for a constant $c>0$ as $t\to\infty$ for sufficiently large $T>0$. This property plays a important role in deriving a priori estimate of the problem.

C. Iteration Scheme

For $i=0,1,2,\cdots$ we consider a simple interation scheme of (RP2).

$$(I)_i\begin{cases} v_{i+1tt}=d_n\Delta v_{i+1t}+\eta\gamma\gamma_1\nabla\cdot(e^{-\eta(\gamma_2 t_T+w_i)}\nabla w_i)\\ \qquad\qquad +\eta\gamma\nabla(v_{i+1t}e^{-\eta(\gamma_2 t_T+w_i)}\nabla w_i)\\[2ex] w_{i+1tt}=d_m\Delta w_{i+1t}+\alpha(v_{i+1t})-\beta(w_{i+1t})\end{cases}$$

where $w_0(x,t)=w_0(x)$.

D. A priori estimates

Let $\|\ \|_k$ be a norm of Sobolev space $H^k(\Omega)$ and denote $\|\ \|_0=\|\ \|$.

For sufficiently large $T>0$ we obtain the estimate of (9)

$$E_k[v]+\int_0^t \|\nabla v_t\|_k^2(\tau)d\tau \leqq CE_k[v](0) + C_T\int_0^t \|w_t\|_{k+1}^2(\tau)d\tau$$

where a constant $0<C_T$ monotonously decreases as $T>0$ increases, for any integer $k\geq 0$ we denote the energy by

$$E[u]=\|u_t\|^2+\|\partial^\alpha \nabla u\|^2$$

and $$E_k[u]=\sum_{|\alpha|\leq k}\|\partial^\alpha u_t\|^2+\|\partial^\alpha \nabla u\|^2.$$

Assuming that $\alpha\gamma_1=\beta\gamma_2$ we derive the estimate of (10)

$$\|w_t\|_k^2+\int_0^t \|\nabla w_t\|_k^2 dt \leqq CE_k[w](0)+C\|v_t\|_k^2$$

Combining above estimates we have for sufficiently large $T>0$

$$\|w_t\|_k^2+E_k[v]+\int_0^t \|\nabla v_t\|_k^2(\tau)d\tau+\int_0^t \|\nabla w_t\|_k^2 dt$$

$$\leq CE_k[w](0)+CE_k[v](0)$$

E. Convergence of the solutions

Put for $i=1,2,\cdots$

$$V_i=v_{i+1}-v_i,\quad W_i=w_{i+1}-w_i.$$

In the same way as derived in subsection *D* we obtain in $(I)_i$

$$\|W_{it}\|_k^2(t)+E_k[V_i](t) + \int_0^t \|\nabla v_{it}\|_k^2(\tau)d\tau+\int_0^t \|\nabla w_{it}\|_{k+1}^2 dt$$

$$\leq C_T\int_0^t \|\nabla w_{i-1t}\|_{k+1}^2 dt\cdots\cdots \leq {C_T}^{i-1}\int_0^t \|\nabla w_{1t}\|_{k+1}^2 dt$$

where

$$0<C_T \xrightarrow[i\to\infty]{} 0.$$

Taking T so large that $0<C_T<1$ holds it is concluded that

$${C_T}^{i-1}\int_0^t \|\nabla w_{1t}\|_{k+1}^2 dt\tau \xrightarrow[i\to\infty]{} 0.$$

Hence there are the solutions of the problem v,w such that

$$\lim_{i\to\infty} v_i = v,\quad \lim_{i\to\infty} w_i = w,$$

strongly in $C((0,\infty)\times H^k(\Omega))$.

III. Result

The following is a main result of the paper.

Theorem. For $\alpha,\beta,\gamma_1,\gamma_2$ satisfying $\alpha\gamma_1=\beta\gamma_2$ and sufficiently large T there is the classical solution of the problem (1)-(3) satisfying (I) and (B) such that the solution is in the form;

$$n(x,t)=\Psi_t=\gamma_1+v_t(x,t)$$
$$m(x,t)=\Phi_t(x,t)=\gamma_2+w_t(x,t)$$
$$f(x,t)=e^{-\eta\Phi(x,t)}=e^{-\eta(\gamma_2 t_T+w)}$$

of which asymptotic behavior is

$$\lim_{t\to\infty} n(x,t)=\gamma_1\quad \lim_{t\to\infty} m(x,t)=\gamma_2\quad \lim_{t\to\infty} f(x,t)=0.$$

IV. Discussion

It is easily seen that our way to derive the above result can be applied to the mathematical model of tumour angiogenesis proposed by Anderson and Chaplain [1] and [2](See [5]-[10],[16]-[18]):

(TA)

$$\begin{cases} \dfrac{\partial n}{\partial t} = \overbrace{D\nabla^2 n}^{\text{random motility}} - \overbrace{\nabla\cdot(\dfrac{\chi}{1+\sigma c}n\nabla c)}^{\text{chemotaxis}} - \overbrace{\nabla\cdot(\rho_0 n\nabla f)}^{\text{haptotaxis}} \\ \dfrac{\partial f}{\partial t} = \overbrace{\beta n}^{\text{production}} - \overbrace{\gamma_0 nf}^{\text{uptake}} \\ \dfrac{\partial c}{\partial t} = -\overbrace{\eta nc}^{\text{uptake}} \qquad in \quad \Omega\times(0,\infty) \\ n(x,0)=n_0(x)\quad f(x,0)=f_0(x)\quad c(x,0)=c_0(x) \\ \left.\dfrac{\partial n(x,t)}{\partial \nu}\right|_{\partial\Omega} = \left.\dfrac{\partial f(x,t)}{\partial \nu}\right|_{\partial\Omega} = \left.\dfrac{\partial c(x,t)}{\partial \nu}\right|_{\partial\Omega} = 0 \end{cases}$$

n(x,t) : ***endothelial-cell***

f(x,t) : ***the fibronectin concentration***

c (x,t) : ***TAF concentration***

The first equation describs EC migration

where $n = n(x,t)$ is the EC density, D is the cell random motility coefficient,

$$\chi(c) = \frac{\chi_0}{1+\alpha c}$$

is the chemotactic function with respect to TAFs concentration $c = c(x,t)$, χ and α are positive constants, $f = f(x,t)$ is the concentration of an adhesive chemical such as fibronectin, ρ_0 is the (constant) haptotactic coefficient. They assume that c and f satisfy the second and third equations (ODE system) where β, γ_0 and η are positive constants.

In [5]-[10] they obtain the classical solution in the form of the model. The form of the solution is as follows.

$$c(x,t) = e^{\gamma t+u},$$

$$f(x,t) = \kappa\tau^{-1} + \tau^{-1} e^{\frac{\tau}{\eta}(\gamma t+u)},$$

$$n(x,t) = \frac{-1}{\eta}(\gamma + u_t)$$

where a positive parameter γ is sufficiently large.

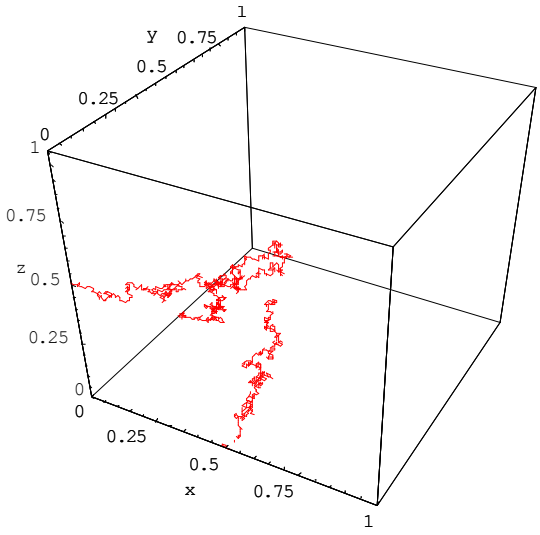


FIGURE 1. SIMULATION OF TUMOUR INDUCED ANGIOGENESIS

The above simulation of (TA) is carried out based on tumour induced angiogenesis as a reinforced random walk: modelling capillary network formation without endothelial cell proliferation.

The picture is idealised as a sphere cell, is embedded in the center of a cuboid domain. We assume no-flux boundary condition to hold on all the faces of the cube and that a priori steady state concentration profiles of TAF and fibronectin are given. To focus our attention on the behavior of EC, we do not consider the branching and anastomoses. It is seen that the capillary migarates and forcus rapidly towards the tumour colony.

In Theorem it is noticed that γ_1, γ_2 are any positive parameter satisfying

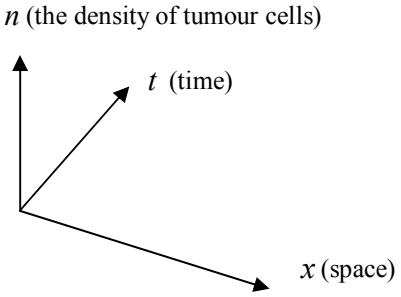
$$\alpha\gamma_1 = \beta\gamma_2.$$

Therefore it is seen that our result obtained in this paper can give an extended result of [5]-[10] in this sense. The more details of the proof of it and Theorem will be given in the forthcoming paper.

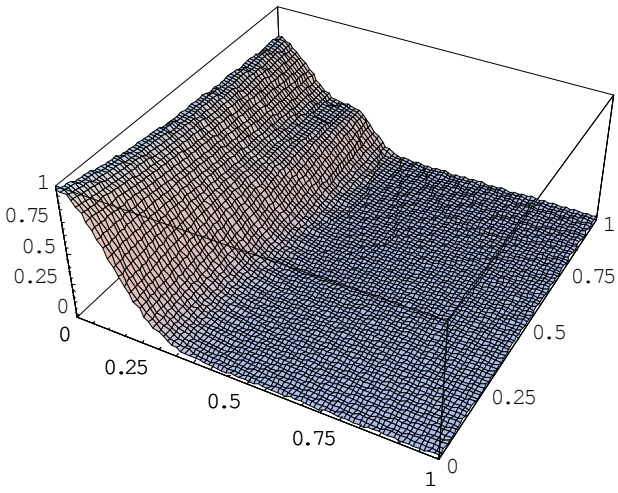
V. NUMERICAL EXPERIMENTS

Theorem implies the possibility of numerical experiments of (1)-(3) with (B) and (I) . The following numerical results are obtained using Mathemaica (4).

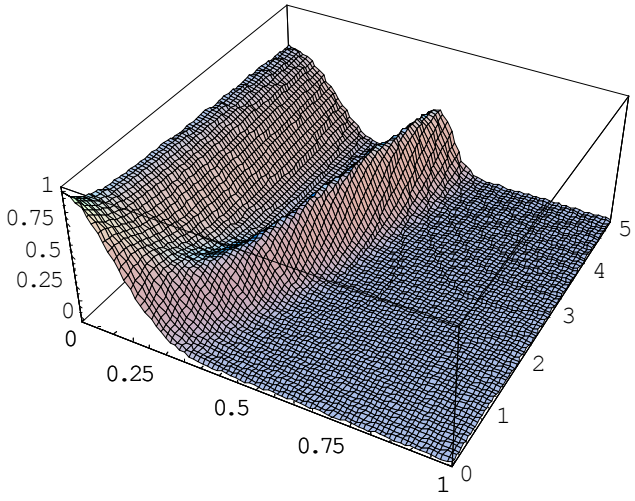
1. First, Figure 2 shows 3 numerical results in one spatial dimension and time of tumour cell density.

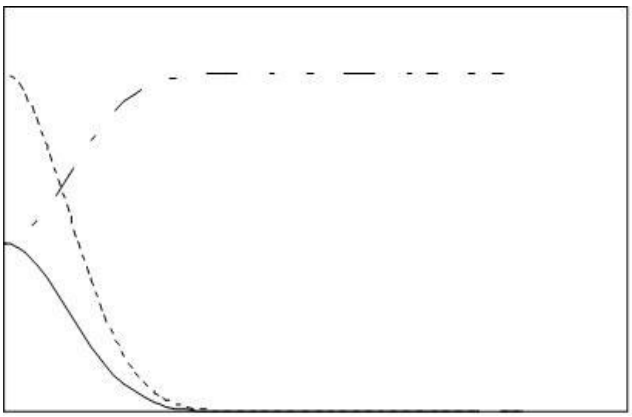


i) $0 \le t \le 1$



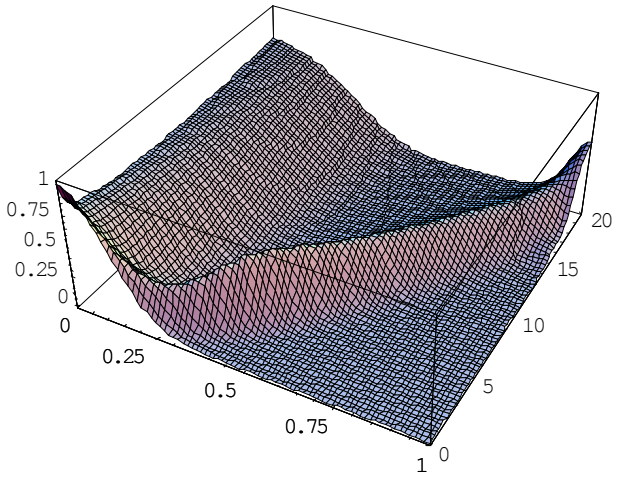
ii) $0 \le t \le 5$

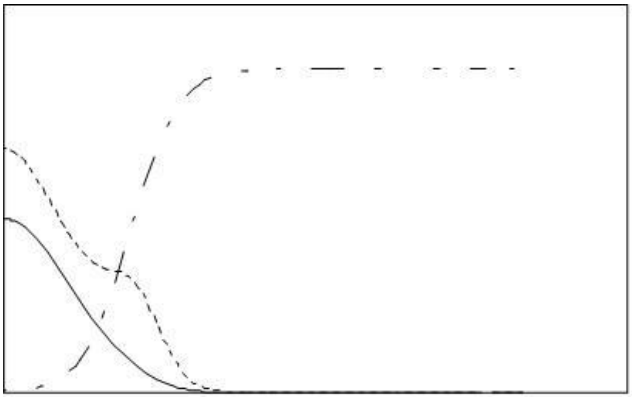




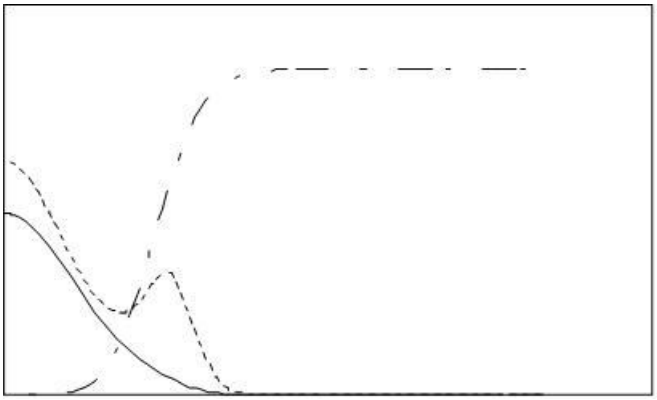
t=0

iii) $0 \le t \le 20$





t=1



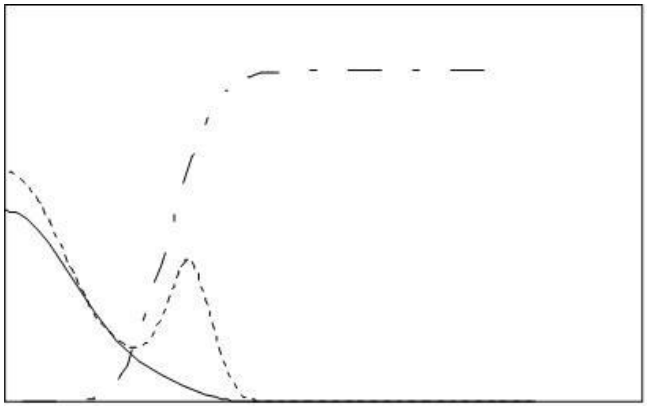
t=1.5

FIGURE 2. Simulation of tissue invasion models in 1D I.

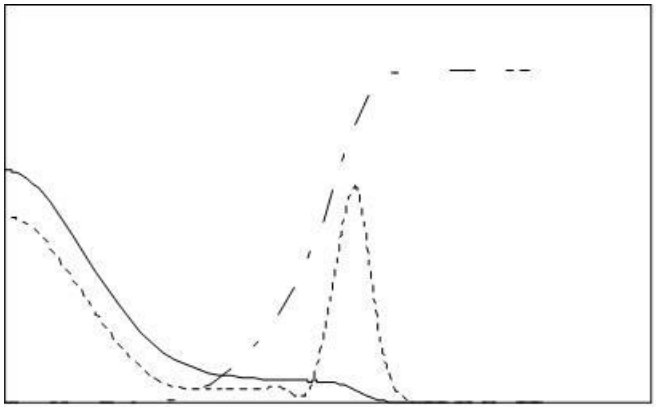
In Figure 2 we can observe that the tinitial unit of umour cells is separated into two clusters and the smaller one propagate as a TRAVELING WAVE.

2. Finally we intend to observe by numerical simulation of our problem the relationship in time between tumour cell density, ECM density and MDE concentration.

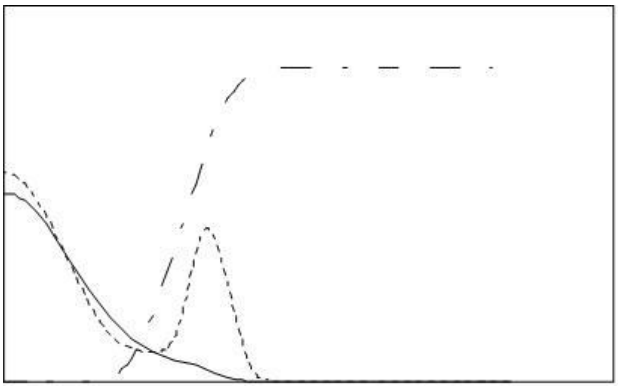
Figure 3 shows 9 snapshots in time of tumour cell density, ECM density and MDE concentration.



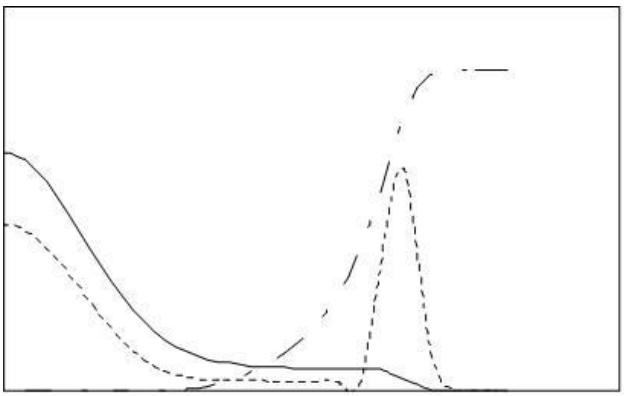
t=2



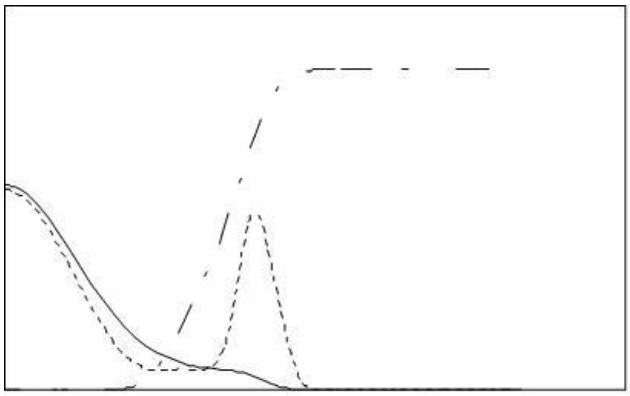
t=5



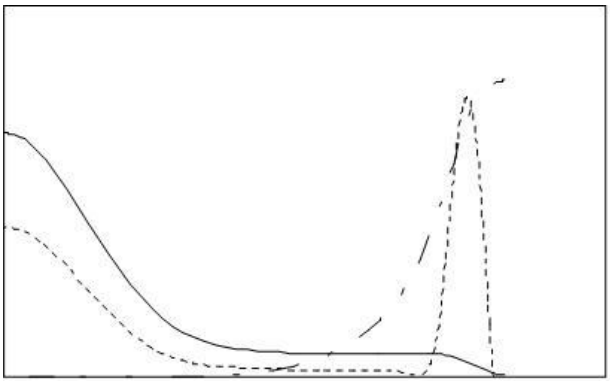
t=2.5



t=7



t=3



t=10

FIGURE 3, SIMULATION OF TISSUE INVASION MODELS IN 1D II.

We assume that the distribution tumour cells exist only near the origin(t=0).

The ECM profile shows clearly the degradation by the MDEs.

As time evolves, in Fig 1 from t=1 to 2.5 the tumour density distribution shows that a small cluster of cells has built up at the leading edge of the tumour due to haptotactic migration.

The initial cluster of tumour cells is broken into two separated clusters and a smaller one migrates further from the main body of the tumour and this cluster of tumour cells continues to invade the ECM, of which the profile looks like propagating as a kind of traveling wave while MDE is degradating neighbouring ECM(t=3, 5 and 7).

Hence if the main body of the tumour were to be surgically removed, the smaller cluster of cells that has invaded further into the ECM may go unnoticed by the surgeon and lead to a possible recurrence.

The similar type of numerical experiment has been already known in Anderson and Chaplain in [3] taking account of the effect of nonlinear diffusion on the invasion of the tumour cells.

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