Local and non-local tumour invasion models: Their mathematical analysis and computational simulations

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Abstract: In the present paper we investigate local and non-local type of mathematical models of tumour invasion with proliferation in order to understand the mechanism of the non-local tumour invasion. We consider the non-local tumour invasion model proposed by Gerisch and Chaplain and an approximation model by expanding the non-local term into Taylor series, which is closely related to Chaplain and Lolas model describing the local tumour invasion. We prove the global existence in time and asymptotic profile of the solution to the initial boundary value problem for the approximation model in one spacial dimension, by applying known mathematical results of the local tumour invasion model. Finally we show by computer simulations of the approximation model, which are verified by our mathematical analysis, the time dependent change of the non-local tumour invasion process and observe the relationship between the value of Taylor coefficients and the tumour cell density or so.

Key–Words: Non-local model, mathematical analysis, tumour invasion, Taylor expansion, computational simulation.

1 Introduction

The tissue invasion by tumour is one of the hallmarks of cancer. For the better understanding of this phenomena mathematical models of cancer invasion of tissue:local and non-local models are considered, and the effect of cell-cell and cell-matrix adhesion is investigated through the models by a number of authors([2][5]-[7], further references therein).

In [7] Gerisch and Chaplain proposed a mathematical model of non-local tumour invasion(cf. [6]):(CG)

$$\begin{cases} \dfrac{\partial n}{\partial t} = \nabla \cdot [D_1 \nabla n - n\mathcal{A}\{\underline{u}(t,\cdot)\}] + \mu_1 n(1-n-v), & (1) \\ \dfrac{\partial v}{\partial t} = -\gamma m v + \mu_2(1-n-v), & (2) \\ \dfrac{\partial m}{\partial t} = \nabla \cdot [D_3 \nabla m] + \alpha c - \lambda m. & (3) \end{cases}$$

where $n := n(x,t)$ is the density of tumour cells, $v := v(x,t)$ is the extra cellular matrix density (ECM density), $m := m(x,t)$ is degradation enzymes concentration (MDE concentration) , $D_1, D_3, \gamma, \alpha, \lambda, \mu_1$ and μ_2 are positive constants, $(x,t) \in \Omega \times (0,\infty)$, Ω is a bounded domain in R^n, with a smooth boundary $\partial\Omega$ and $\mathcal{A}\{\underline{u}(t,\cdot)\}$ is a non-local term. The model describes a complicated multiscale process cell-scale evolution of the tumour and the non-local term $\mathcal{A}\{\underline{u}(t,\cdot)\}(x)$ is referred as the adhesion velocity. In this paper we assume that for one spacial dimension and $\mu_2 = 0$ it takes the integral form for "sensing radius"$R > 0$, which detects the local environment of the cell,

$$\mathcal{A}\{\underline{u}(t,\cdot)\}(x) = \frac{1}{R}\int_{-R}^{R} \Omega(r) g(\underline{u}(t,x+r))dr$$

where $\Omega(r)$ is an odd function, for example,

$$\Omega(r) = \frac{1}{2R} \text{ for } r > 0, \Omega(r) = -\frac{1}{2R} \text{ for } r < 0.$$

We assume that $g(\underline{u}(t,x)) = k_1 n(x,t) + k_2 v(x,t)$ for nonnegative constants k_1, k_2. From section 2 to subsection 3.1 we deal with (GC) for $g(\underline{u}(t,x)) = v(x,t)$ for simplicity and $g(\underline{u}(t,x)) = k_1 n(x,t) + k_2 v(x,t)$ in subsection 3.2, which mean the effect of cell-cell adhesion and cell-matrix adhesion.

In [3][6][7] it is shown that as $R \to 0$ the non-local model converges to a localised tumour invasion model, which is the same type as Chaplain and Lolas model describing local tumour invasion with tumour cell proliferation. The following is the mathematical model proposed by Chaplain and Lolas ([5]) without

the chemotaxis term for one spacial dimension.

$$\text{(CL)}\begin{cases} \dfrac{\partial n}{\partial t} = d_n \dfrac{\partial^2 n}{\partial x^2} - \gamma \dfrac{\partial}{\partial x}\left(n \dfrac{\partial v}{\partial x}\right) + \mu_1 n(1-n-v) & (4) \\ \dfrac{\partial v}{\partial t} = -\eta m v + \mu_2 v(1-n-v) & (5) \\ \dfrac{\partial m}{\partial t} = d_m \dfrac{\partial^2 m}{\partial x^2} + \alpha n - \beta m & (6) \end{cases}$$

where d_n, γ, μ_1, η, μ_2, d_m, α and β are positive constants(cf.[4]). We have the global existence in time and the asymptotic behaviour of solutions to (CL) in [13]-[15],[18].

All through this paper we deal with a boundary value problem for all the problem in one spacial dimension satisfying initial data:
$n(x,0) = n_0(x), v(x,0) = v_0(x), m(x,0) = m_0(x)$, and zero-Neumann condition

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

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

Tumour invasion models without the non-local environment of the cell, for instance [2] [5], 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.

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. Hence 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 Gerisch and Chaplain in [7] proposed a non-local model of tumour invasion for a single cell population to describe a complicated multiscale process of cell-scale evolution of the tumour and the interaction between cell-cell and cell-matrix adhesion. They investigate and explorate the model by computational simulations.

Mathematical analysis of the model is given by Chaplain, Lachowicz, et al. [3]. However their result is not enough to justify the model because of the restriction of the regularity of the solution. In fact, since in [7] they justify the definition of the non-local term by using Taylor expansion of the non-local term and taking the limit of it as $R \to 0$, they need a sufficient regularity of the solution to realise it. Therefore in this paper according to their way to justify the model we consider an approximation model of (CG) by expanding the non-local term into Taylor series and obtain a desired sufficient regularity of the solution of it.

On the other hand, there are many mathematical models which can be found in the literature describing tumour angiogenesis, which is the early stage of tumour growth (cf. [1], [23], [24], [25]). In [23] 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 [1] 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. In [16, 17] a mathematical model of glioblastoma cell migration is considered, a mathematical understanding and computational simulation are obtained based on mathematical analysis of tumour angiogenesis.

Also mathematical approaches for tumour growth, invasion and migration models are known(see [3] [8]-[22][23][25] and [26]). Levine and Sleeman [23] 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. [8]-[22] show the time global solvability and asymptotic behavior of the solution to mathematical models considered in [1, 2][4]-[7][16, 17][23]-[25].

In this paper we deal with an approximation model of the non-local invasion model (CG), which is considered by using Taylor expansion of the non-local term. Then we obtain the existence and asymptotic behaviour of solutions of the approximation model by applying our known mathematical results of (CL) to the model, which enables us to gain the understanding of non-local tumour invasion and verify the computational simulation. By computational simulations we see how each of the Taylor expansion terms works by changing the value of Taylor coefficients appropriately. Actually by them visualizing the asymptotic behaviour of the solution of the model, we can observe the relationship and change between tumour

cells, ECM and MDE, depending on time.

2 Approximation model

In this section we deal (CG) for $g(\underline{u}(t,x)) = v(x,t)$.

2.1 Taylor expansion of the non-local term

Since the nonlocal term is in the integral form, that is, it is of an implicit form, it seems to be difficult to understand how the term relates to the tumour invasion phenomena. Thus by the Taylor expansion we reduce the integral form to a differential form and (1) is expressed by the regular form of partial differential equation.

In the non-local term we apply Taylor expansion of $g(\underline{u}(t,x+r))$ at x,

$$g(\underline{u}(t,x+r)) = \sum_{k=0}^{K} \frac{r^k}{k!}\frac{d^k}{dx^k} g(\underline{u}(t,x)) + \tilde{g}_K(r)$$

where $\tilde{g}_K(r)$ is a remainder term. Then we have

$$\mathcal{A}\{\underline{u}(t,\cdot)\}(x) = \sum_{k=0}^{K} \frac{d^k}{dx^k} g(\underline{u}) A_k(R) + \tilde{g}_K(r)$$

where $$A_k(R) := \frac{1}{R}\int_{-R}^{R} \frac{r^k}{k!}\Omega(r)dr.$$

When k is even number considering that $\Omega(r)$ is an odd function

$$A_k(R) = \frac{1}{R}\, p.v. \int_{-R}^{R} \frac{r^k}{k!}\Omega(r)dr = 0.$$

The terms of the derivatives of odd order are remained in the Taylor series of the non-local term. Therefore the non-local term is expanded into Taylor series as follows,

$$\mathcal{A}\{\underline{u}(t,\cdot)\} = \sum_{k=0}^{K} A_{2k+1}(R)\frac{d^{2k+1} g(\underline{u})}{dx^{2k+1}} + \tilde{g}_{2K+1}(r),$$

by $g(\underline{u}(t,x)) = v(x,t)$, then we have for $k = 0,1,2,\cdots$

$$A_{2k+1}\frac{\partial^{2k+1}}{\partial x^{2k+1}} g(\underline{u}(t,x)) = A_{2k+1}\frac{\partial^{2k+1}}{\partial x^{2k+1}} v(x,t).$$

Hence in case of $K = 0$ the model is same as the local tumour invasion model (CL) provided by Chaplain and Lolas ([5]).

In the next subsection we define an approximation model and in the next section show global existence in time and asymptotic behaviour of solutions of the initial boundary value problem for these models.

2.2 Approximation model of (CG)

By replacing the non-local term by Taylor series of it we consider an approximation equation of (1) and an approximation problem of (CG) by neglecting the remainder term of Taylor series.

$$\text{(CG)'} \begin{cases} \dfrac{\partial n}{\partial t} = \nabla\cdot[D_1\nabla n - n\mathcal{A}_K(v)] + \mu_1 n(1-n-v), \\ \dfrac{\partial v}{\partial t} = -\gamma m v + \mu_2(1-n-v), \\ \dfrac{\partial m}{\partial t} = \nabla\cdot[D_3\nabla m] + \alpha c - \lambda m. \end{cases} \tag{7}$$

where $\mathcal{A}_K(v) = \sum_{k=0}^{K} A_{2n+1}\dfrac{\partial^{2k+1}}{\partial x^{2k+1}} v$.

Since the non-local term $\mathcal{A}\{\underline{u}(t,\cdot)\}$ is in the integral form, it seems to be difficult to understand the interaction between the term and the invasion phenomena. However in (CG)', since $\mathcal{A}_K(v)$ is of the form of linear combination of derivatives of v, it enables us to investigate the the effect of the non-local term on the invasion phenomena more clearly.

Since for any integer $k \geq 1$

$$\frac{\partial n}{\partial t} = \nabla\cdot[D_1\nabla n - nA_k(v)] + \mu_1 n(1-n-v) \tag{8}$$

is of a regular form of partial differential equation, we can proceed the mathematical analysis of (CG)' by applying the known results of local tumour invasion models obtained already.

Also it is shown that as $R \to 0$ the non-local model (CG)' converges to a localised tumour invasion model, which is same type of Chaplain and Lolas [5] describing local tumour invasion(cf. [3][6][7]). In fact, it is easily seen that $A_3 \sim A_{2K+1} \to 0$ and $A_1 \to 1$ as $R \to 0$. In this sense (CL) is a local model of (CG), and (CG) is a generalized model of (CL).

3 Existence theorem

In the subsection 3.1 we deal with (CG)' for $g(\underline{u}(t,x)) = v(x,t)$ and in the subsection 3.2 $g(\underline{u}(t,x)) = k_1 n(x,t) + k_2 v(x,t)$.

3.1 $g(\underline{u}(t,x)) = v(x,t)$

In [13]-[15],[18] we show the global existence in time and the asymptotic behaviour of the solution to (CL).

Theorem 1 (Existence theorem of (CL)) *For sufficiently smooth initial data $\{n_0(x), v_0(x), m_0(x)\}$ and $m \geq [n/2]+3$, assume that $\|n_0 - 1\|^2_{m+1}$ is sufficiently small, then there are classical solutions of (CL)): $\{n(x,t), v(x,t), m(x,t)\}$ such that they satisfy the following asymptotic behaviour*

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

By applying Theorem 1 to (CG)' we obtain existence of solutions to (CG)'. In fact, first we consider the case of $K = 0$, i.e.,

$$\mathcal{A}_K(u) = A_1 \frac{\partial}{\partial x} v,$$

then we see that (CG)' coincides with (CL) for $\mu_2 = 0$. Hence by Theorem 1 we obtain the existence theorem of (CG)' for $K = 0$.
In the same way by applying Theorem 1 for (CG)' with $\mathcal{A}_i$ from $i = 1$ to $i = K$ we have the global existence in time and the asymptotic behaviour of the solution to (CG)' by taking $m \geq [n/2] + 3 + 2K$ in the statement of Theorem 1.

Theorem 2 (Existence theorem of (CG)') *For sufficiently smooth initial data $\{n_0(x), v_0(x), m_0(x)\}$ and $m \geq [n/2] + 3 + 2K$, assume that $\|n_0 - 1\|^2_{m+1}$ is sufficiently small, then there are classical solutions of (CG)': $\{n(x,t), v(x,t), m(x,t)\}$ such that they satisfy the following asymptotic behaviour*

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

3.2 $g(\underline{u}(t,x)) = k_1 n(x,t) + k_2 v(x,t)$

We further deal with the tumour invasion model additionally considering into the effect of cell-cell adhesion in (CL) as follows.

$$\text{(CL)'} \begin{cases} \dfrac{\partial n}{\partial t} = d_n \dfrac{\partial^2 n}{\partial x^2} - \gamma \dfrac{\partial}{\partial x}\left(n \dfrac{\partial v}{\partial x}\right) - a_1 \dfrac{\partial}{\partial x}\left(n \dfrac{\partial n}{\partial x}\right) \\ \quad +\mu_1 n(1-n-v) & (4)' \\ \dfrac{\partial v}{\partial t} = -\eta m v + \mu_2 v(1-n-v) & (5) \\ \dfrac{\partial m}{\partial t} = d_m \dfrac{\partial^2 m}{\partial x^2} + \alpha n - \beta m & (6) \end{cases}$$

where $a_1 \dfrac{\partial}{\partial x}\left(n \dfrac{\partial n}{\partial x}\right)$ is a cell-cell adhesion term and a_1 is a positive constant.
When we derive the energy estimate of (CL)' the diffusion term $-d_n n_{xx}$ is dominant to the cell-cell adhesion term $a_1 (n n_x)_x$ in the following sense. For the $L^2(\Omega)$ inner product of $-d_n \dfrac{\partial^2 n}{\partial x^2} + a_1 (n n_x)_x$ with n, we have

$$\left(-d_n \frac{\partial^2 n}{\partial x^2} + a_1 \frac{\partial}{\partial x}\left(n \frac{\partial n}{\partial x}\right), n\right)$$

$$= \left(d_n \frac{\partial n}{\partial x} - a_1 \left(n \frac{\partial n}{\partial x}\right), \frac{\partial n}{\partial x}\right)$$

if $|n| \sim 1$ and $d_n > a_1$

$$> C\|n_x\|^2$$

where $C > 0$. In fact, we see that $|n| \sim 1$ is satisfied by the asymptotic behaviour of u in Theorem 1. This inequality implies that we can derive the same type of the energy estimate of (CL)' as (CL), which gives the same type of existence theorem as Theorem 1 (see [13]-[15],[18]).

Theorem 3 (Existence theorem of (CL)') *Assume that $d_n > a_1$ in addition to the assumption of Theorem 1, then the same conclusion as obtained in Theorem1 holds.*

By the same argument as in the subsection 3.1 applying Theorem 3 to (CG)', we obtain the existence theorem of (CG)' for $g(\underline{u}) = \gamma v + a_1 u$, which is the same type of Theorem 2. Since we can take γ, a_1 arbitrary, we obtain the following result.

Theorem 4 (Existence theorem of (CG)') *Assume that $D_1 > k_1 \sum_{k=0}^{K} A_{2n+1}$ in addition to the assumption of Theorem 2, then the same conclusion as obtained in Theorem 2 holds.*

4 Computational simulations

Since we obtain the existence and asymptotic behaviour of the solution in Theorem 2 , it essentially verifies the following computational simulations. We show the computer simulations of the following problem.

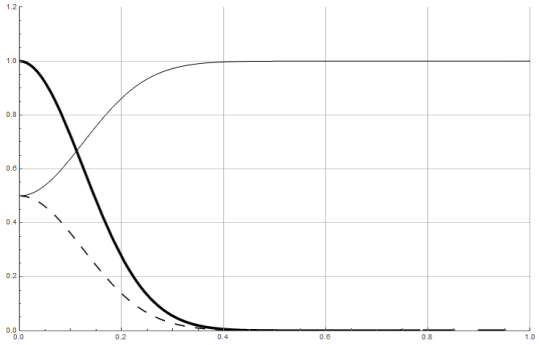
$$(CG)'_4 \begin{cases} \dfrac{\partial n}{\partial t} = D_1 \dfrac{\partial^2 n}{\partial x^2} - \dfrac{\partial}{\partial x}(n \mathcal{A}_4(v)) \\ \qquad\qquad +\mu_1 n(1-n-v), \\ \dfrac{\partial v}{\partial t} = -\gamma m v + \mu_2(1-n-v), \\ \dfrac{\partial m}{\partial t} = D_3 \dfrac{\partial^2 m}{\partial x^2} + \alpha c v - \lambda m. \end{cases}$$

In the following figures we show the computational simulations of (CG)'$_4$ for $\mathcal{A}_4(k_1 n + k_2 v)$, in case $k_2 = 0$ describes cell-cell adhesion and in case $k_1 = 0$ cell-matrix adhesion. We observe tumour cell proliferation, migration and interactions between the tumour and the surrounding tissue: tumour cell density (**thick line**), ECM density (**thin line**), and MDE concentration (**dotline**), taking A_1, A_3 from 0 to 10^{-1} and $A_5 = 8.33 \times 10^{-13}, A_7 = 1.98 \times 10^{-18}, A_9 = 2.76 \times 10^{-24}$ at $t =$ 0, 0.35, 0.7, 1.05 and 1.4.

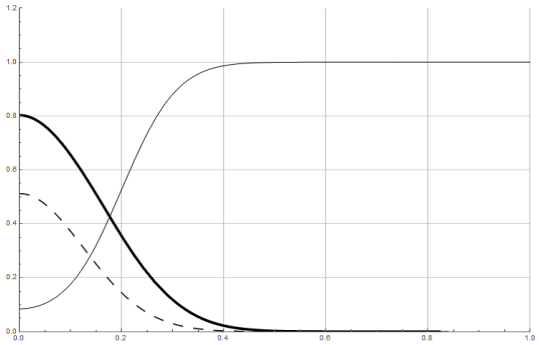
The parameter values of $D_1, \gamma, D_3, \mu_1, \mu_2, \alpha$ and λ are as follows in the simulation except for 4.1.2. $D_1 = 0.0085, \gamma = 10, D_3 = 0.0001, \mu_1 = 0.1, \mu_2 = 0.00001, \alpha = 0.1$, and $\lambda = 0.1$.

4.1 $g(\underline{u}(t,x)) = u + 2v$

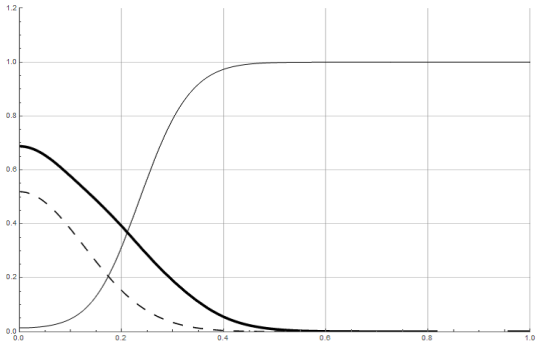
4.1.1 $D_1 = 0.0085$



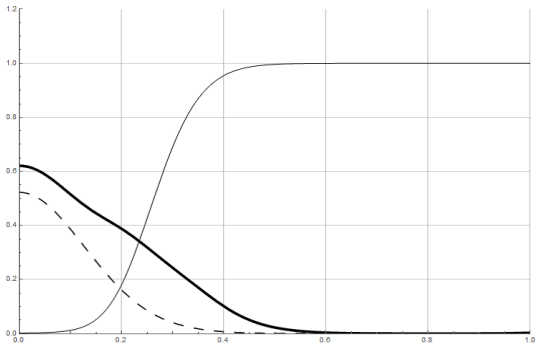
$t = 0$



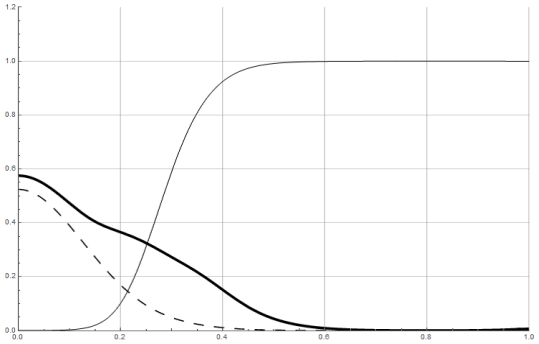
$t = 0.35$



$t = 0.7$

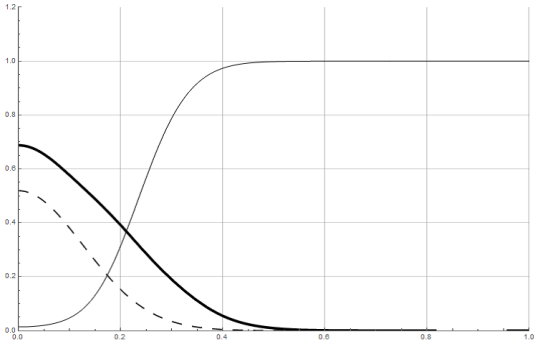


$t = 1.05$

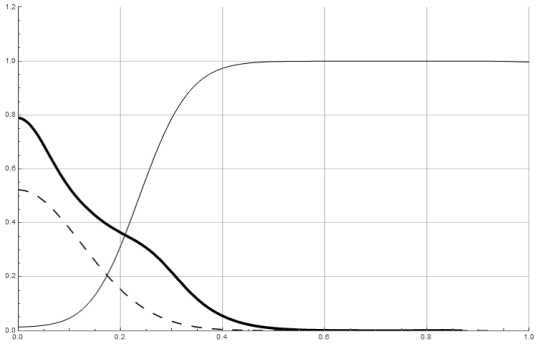


$t = 1.4$
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-5}$,
$A_5 = 8.33 \times 10^{-13}$,$A_7 = 1.98 \times 10^{-18}$, $A_9 = 2.76 \times 10^{-24}$

Fig.1: The three components are very stable in the time dependent simulation. Therefore in the below, based on the values of $A_1 \sim A_9$ taking as above, changing the values of A_1, A_3 appropriately we observe the relationship between tumour cell density and the value of $A_1 \sim A_9$ at $t = 0.7$.



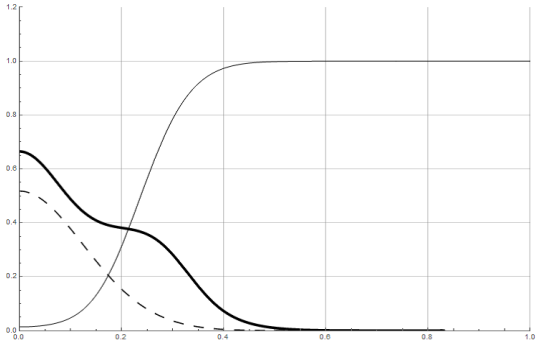
(1) $t = 0.7$,
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-5}$



(2) $t = 0.7$
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-7}$

Fig.2: We take $A_3 = 1.67 \times 10^{-5}$ in (1) two times the value in (2). Compared with the two figures, it is observed that the tumour cell density increases around

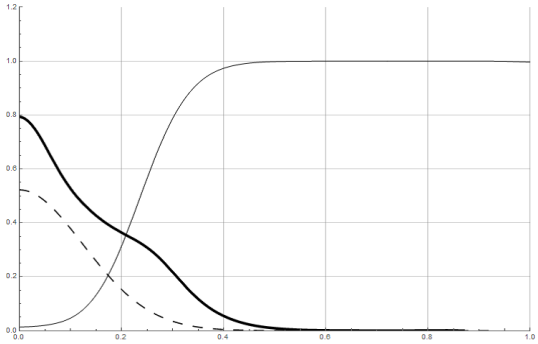
the boundary on ECM meeting the tumour cell as A_3 increases.



$t = 0.7$

$A_1 = 0.02$, other coefficients are same as in Fig.2-(1)

Fig.3: We take $A_1 = 0.02$ two times the value of A_1 in Figure 2-(1). Compared with two figures, it is observed that increase of A_1 forms a peak of tumour cell density inside ECM.



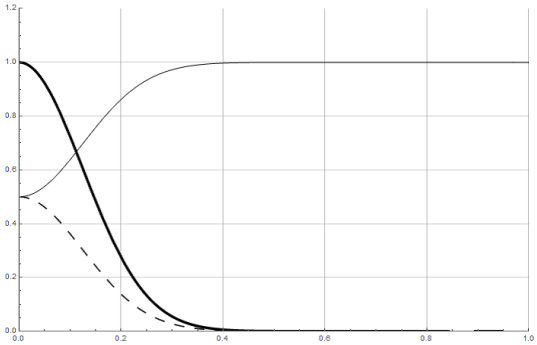
$t = 0.7$

$A_3 = 0$, other coefficients are same as in Fig.2-(1).

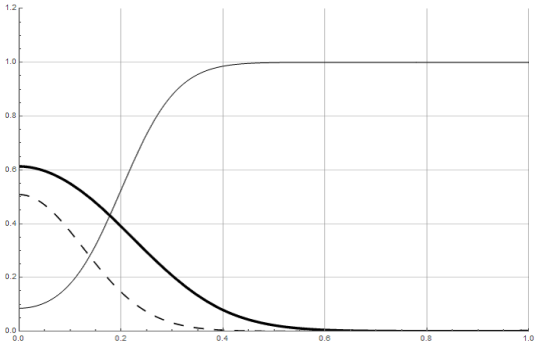
Fig.4: The above figure is almost same as Fig.2-(2). Compared to Figure 2-(1), it is observed that A_3 mainly makes the tumour cell density increase around the boundary on ECM meeting the tumour cell as they increase. Taking $A_5 \sim A_9$ larger appropriately, the simulation become more stable.

4.1.2 $D_1 = 0.03$

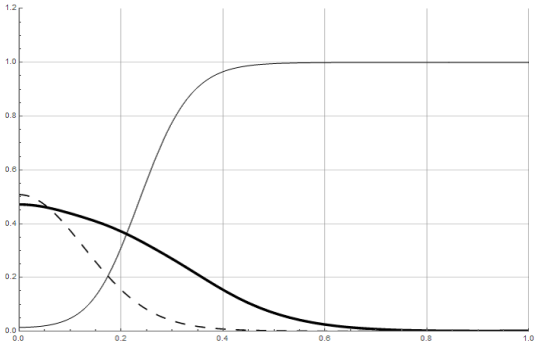
In this subsection we take $D_1 = 0.03$, and other parameters $\gamma, D_3, \mu_1, \mu_2, \alpha$, and λ same as 4.1.1. In this case $D_1 > \sum_{k=0}^{K} A_{2n+1}$ is satisfied. Hence Theorem 4 guarantees the existence of the time global solution of $(CG)'_4$.



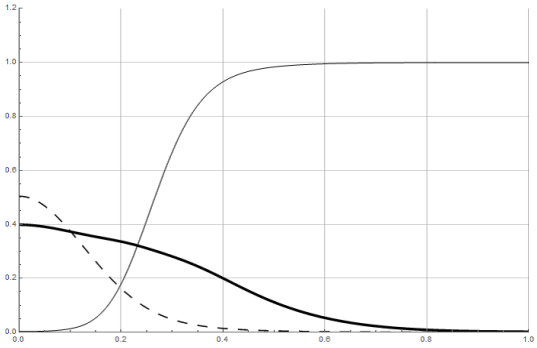
$t = 0$



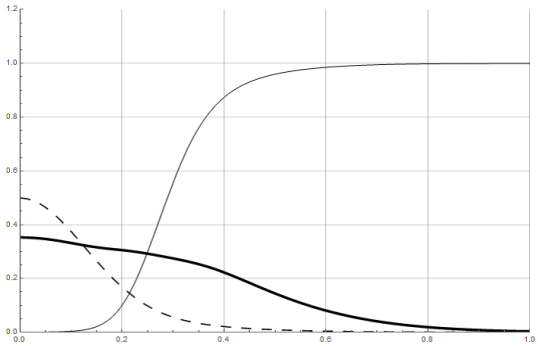
$t = 0.35$



$t = 0.7$

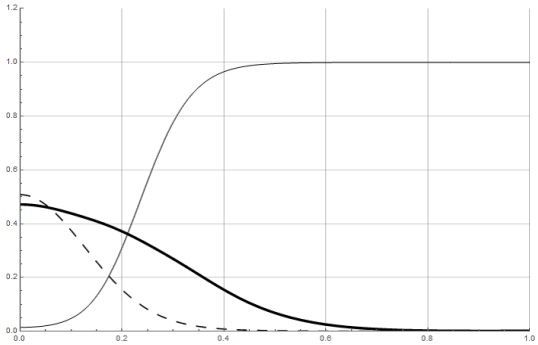


$t = 1.05$

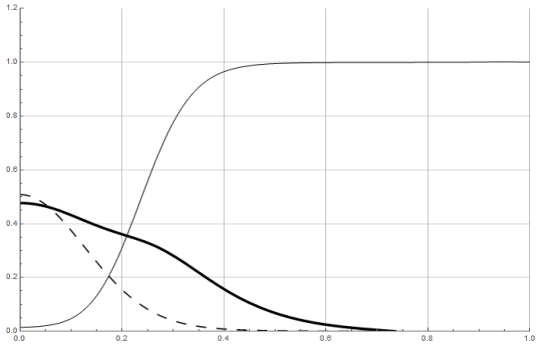


$t = 1.4$
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-5}$

Fig.1: Compared to Fig.1 of 4.1.1 we observe the curve of tumour cell population more diffusively and smoothly changes along the x-axis .

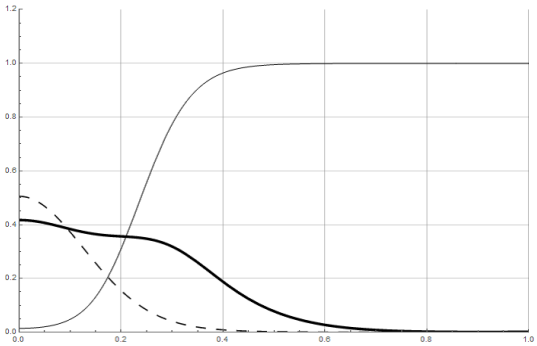


(1) $t = 0.7$,
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-5}$



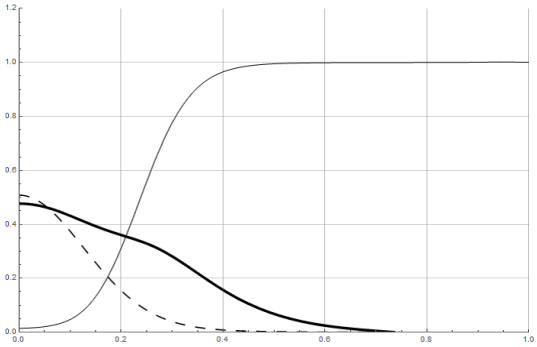
(2) $t = 0.7$
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-7}$

Fig.2: The same observation of the relationship between the figures (1), (2) and A_3 as in Fig.2 of 4.1.1 holds true.



$t = 0.7$
$A_1 = 0.02$, other coefficients are same as in Fig.2-(1)

Fig.3: The same observation as in Fig.3 of 4.1.1 holds.

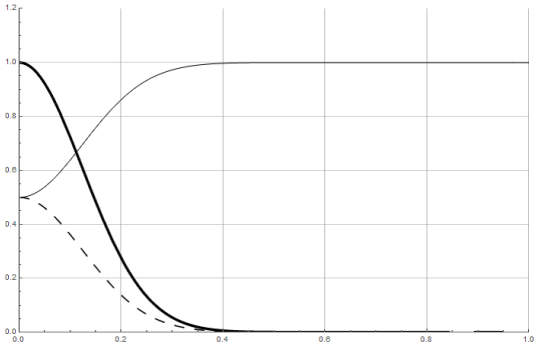


$t = 0.7$
$A_3 = 0$, other coefficients are same as in Fig.2-(1).

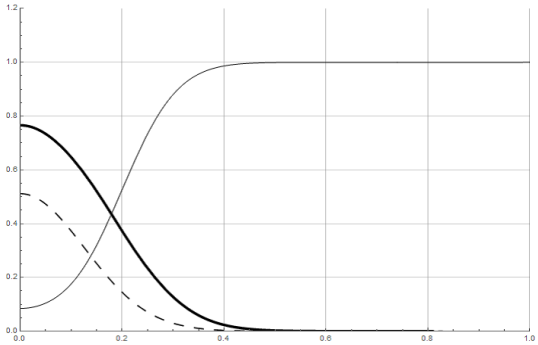
Fig.4: The same observation as in Fig.4 of 4.1.1 holds.

4.2 $g(\underline{u}) = 0.5u + 2v$

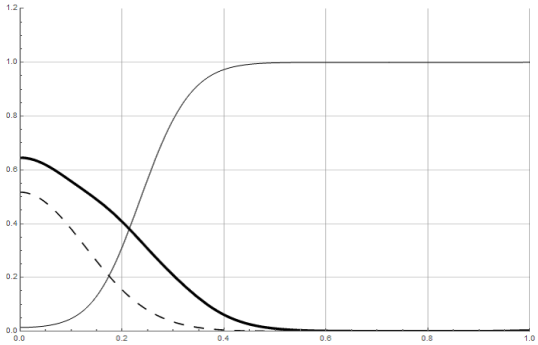
$D_1 > 0.5 \sum_{k=0}^{K} A_{2n+1}$ is satisfied. Hence Theorem 4 guarantees the existence of the time global solution of $(CG)'_4$.



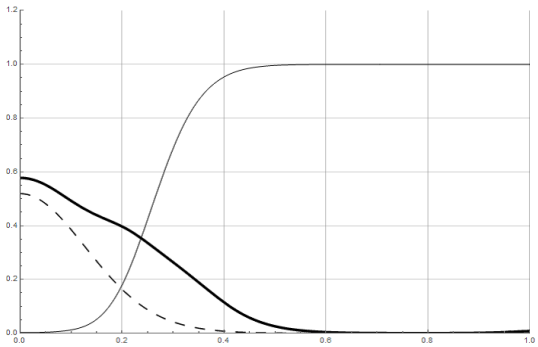
$t = 0$



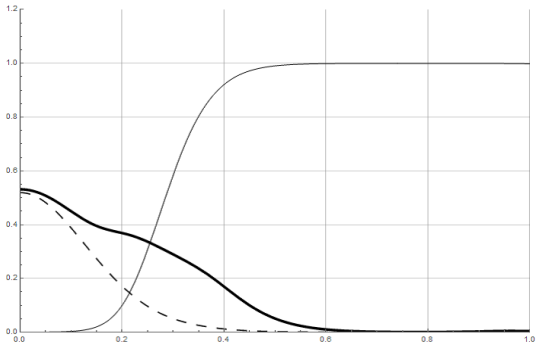
$t = 0.35$



$t = 0.7$

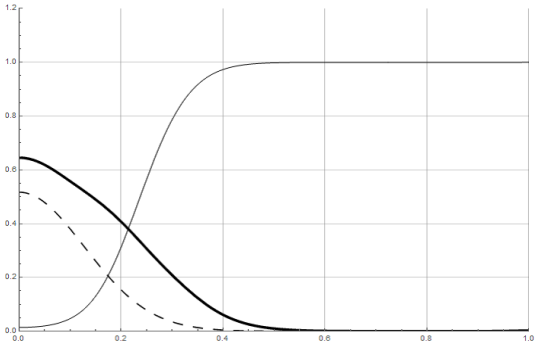


$t = 1.05$

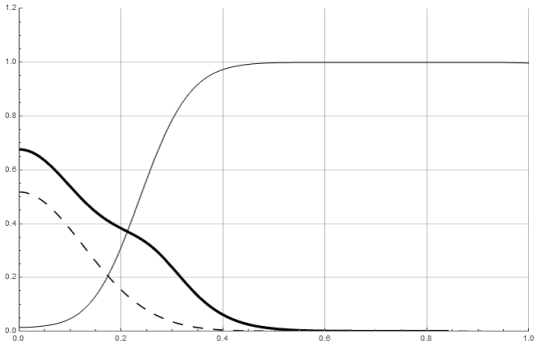


$t = 1.4$
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-5}$

Fig.1: The effect of cell-cell adhesion is one half of 4.1.1. As a result the slope of the tumour cell density decreases more slowly along the x-axis than Fig.1of 4.1.1.

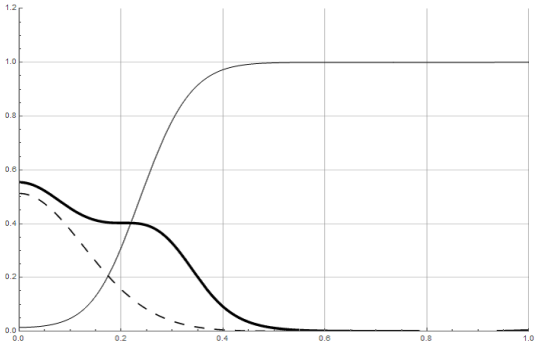


(1) $t = 0.7$,
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-5}$



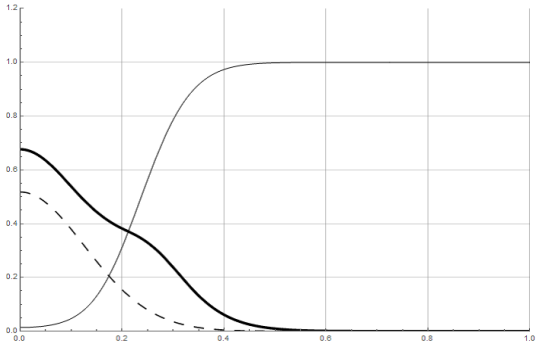
(2) $t = 0.7$
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-7}$

Fig.2: The same observation as in Fig.2 of 4.1.1 holds true.



$t = 0.7$
$A_1 = 0.02$, other coefficients are same as in Fig.2-(1)

Fig.3: We take $A_1 = 0.02$ two times the value of Fig.2-(1). A larger peak than Fig.3 of 4.1.1 appears.



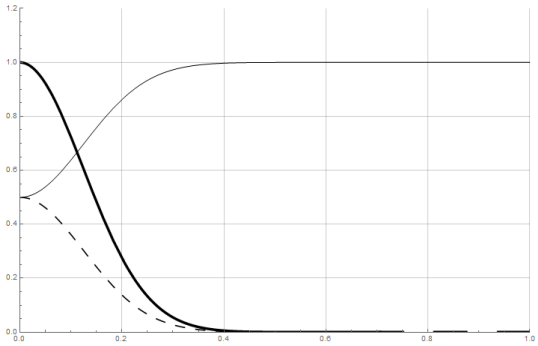
$t = 0.7$

$A_3 = 0$, other coefficients are same as in Fig.2-(1).

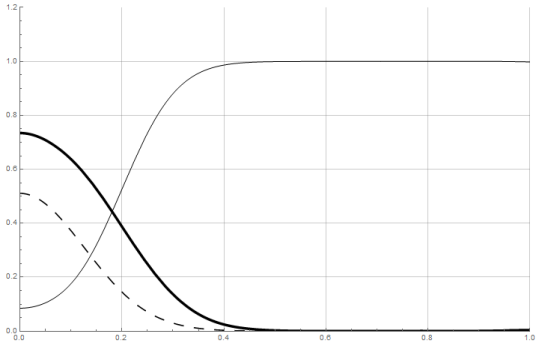
Fig.4: The same observation as in Fig.4 of 4.1.1 holds.

4.3 $g(\underline{u}(t,x)) = 2v$

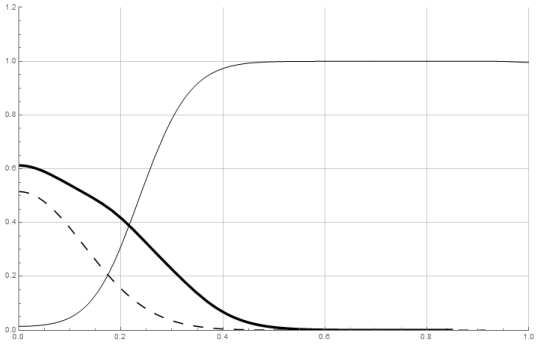
Theorem 2 guarantees the existence of the time global solution of $(CG)'_4$.



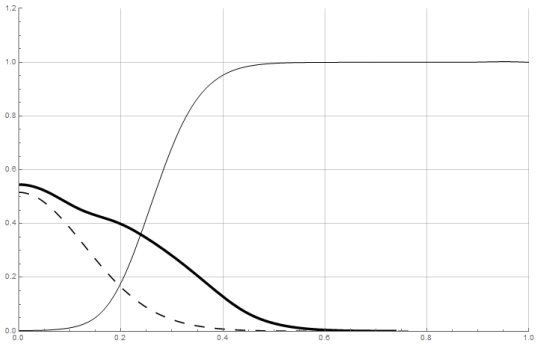
$t = 0$



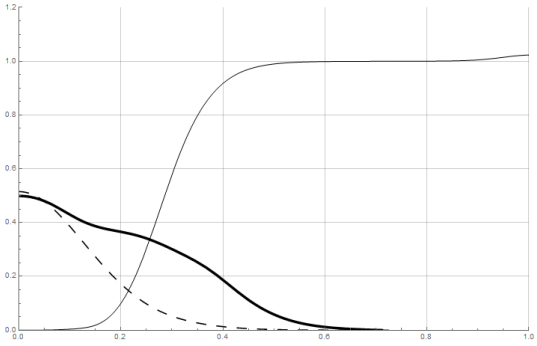
$t = 0.35$



$t = 0.7$



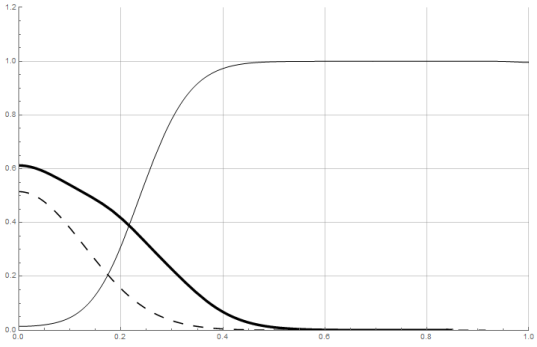
$t = 1.05$



$t = 1.4$

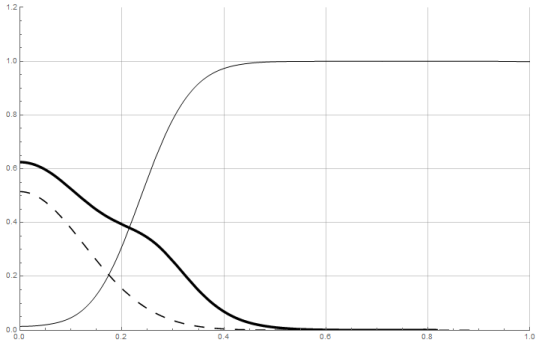
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-5}$

Fig.1: The slope of tumour cell density decreases more slowly than 4.1- 4.2.



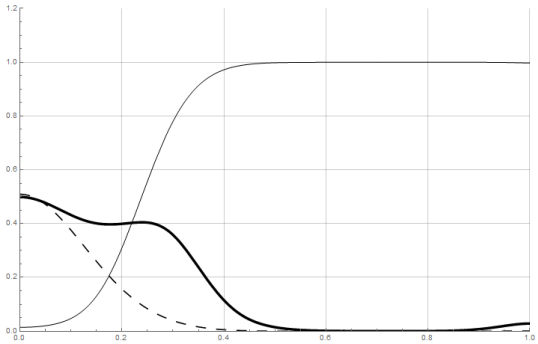
(1) $t = 0.7$,

$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-5}$



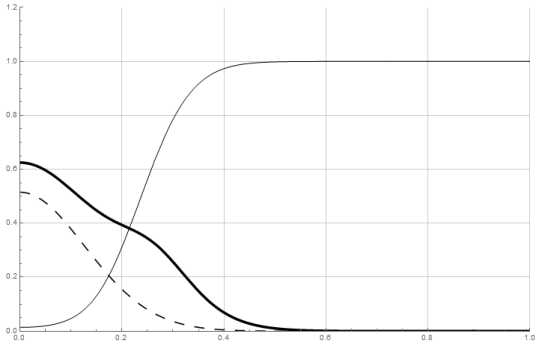
(2) $t = 0.7$
$A_1 = 0.01$, $A_3 = 1.67 \times 10^{-7}$

Fig.2: The same observation as in Fig.2 of 4.1.1 holds.



$t = 0.7$
$A_1 = 0.02$, other coefficients are same as in Fig.1-(1)

Fig.3: A larger peak than Fig.3 of 4.1-4.2 appears.



$t = 0.7$
$A_3 = 0$, other coefficients are same as in Fig.2-(1).

Fig.4: The same observation as in Fig.4 of 4.1.1 holds.

5 Conclusions

In the non-local model we gain the understanding of the multiscale process of tumour invasion and the interaction between cell-cell and cell-matrix adhesion, by the existence of the time global solution and its asymptotic behaviour of the model and computational simulations in section 4 in a certain region of parameter space. For this purpose first we show the existence of the solution and asymptotic behaviour of (CL)', which describes local cell-cell adhesion and cell-matrix adhesion. Expanding the non-local term into Taylor series we consider an approximation problem (CG)' of (CG) and applying our existence theorem of (CL)' we show rigorously the global existence in time and the asymptotic behavior of solutions of it. We obtain a mathematical understanding of (CG)' and it guarantees the validity of computational simulations of (CG)' that qualitatively replicate the complicated morphologies of non-local invasive tumour.

Numerical experiments in section 4 imply that as the value of some Taylor coefficients increases the density of tumour cell increases around the boundary of ECM intersecting tumour cell, which implies that the non-local term works as **dissipation** and **viscosity** in the tumour invasion phenomena. In Taylor coefficients of the non-local term A_1, A_3 have a crucial role of the stability and the behaviour of the tumour cell density in the simulation. Especially, in the computational simulation it is observed that the increase of A_1 makes the peak of tumour cells larger inside of ECM and if A_3 increases the tumour cell density around the intersection of ECM and tumour cells increases.

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