Mathematical analysis of non-local tumour invasion model and simulations

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Abstract: In this paper we investigate a mathematical model of non-local tumour invasion with proliferation proposed by Grisch and Chaplain in 2008. For the better understanding of the model we consider an approximation model expanding the non-local term into Taylor series. We prove the global existence in time and asymptotic profile of the solution to the initial boundary value problem for the approximation model in 1 spacial dimension. Applying known mathematical results of usual(local) tumour invasion models, which are corresponding to the same type problem of Chaplain and Lolas model, we discuss the existence and property of solutions to the problem. Finally we show the time dependent change of the non-local tumour invasion process by computational simulations of the approximation model.

Key–Words: Non-local model, mathematical analysis, tumour invasion, Taylor expansion, 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, the effect of cell-cell and cell-matrix adhesion is investigated through the models by a number of authors([2][4]-[6], further references therein).

In [6] Gerisch and Chaplain proposed a non-local model of tumour invasion(cf. [5]):(CG)

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

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_n,D_m, γ, α, λ, μ_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 $\partial\Omega$. 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 for 1 spacial dimension and $\mu_2 = 0$ it takes the form for "sensing rudius"$R > 0$, 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,

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

In addition we assume that $g(\underline{u}(t,x+r)) = v(x,t)$ for our convenience.

In [3][5][6] it is shown that as $R \to 0$ the non-local model converges to a localised tumour invasion model same type of Chaplain and Lolas [4], which described local tumour invasion with tumour cell proliferation. The following is the mathematical model proposed by Chaplain and Lolas without the chemotaxis term in 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. We have the global existence in time and the asymptotic behaviour of solutions to (CL) in [12]-[15].

In 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 considering the non-local environment of the cell, for instance [2] [4], 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 degrades 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 [6] proposed a non-local model of tumour incasion 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 applicable to our case because of the restriction of the regularity of the solution. Since in [6] they verify the form of the non-local term by using Taylor expansion of the non-local term, in this paper according to their way we consider an approximation model of (CG) by expanding the non-local term into Taylor series and computational simulations of it.

On the other hand, there are many related mathematical models which can be found in the literature describing tumour angiogenesis(cf. [1], [20], [21], [22]). In [20] Levine and Sleeman apply the diffusion equation provided by Othmer and Stevens [21] 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. The model has cell migration governed by three factors: diffusion, chemotaxis and haptotaxis.

Also mathematical approaches for tumour growth models are known(see [3] [7]-[19][20][22] and [23]). Levine and Sleeman [20] and Yang, Chen and Liu [23]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. [7]-[19] show the time global solvability and asymptotic behavior of the solution to tumour growth models considered in [1][2][4]-[6][20]-[22].

In this paper we deal with an approximation model of nonlocal invasion model (CG), which is considered by using Taylor expansion of the non-local term, and obtain the existence and asymptotic behaviour of solutions of the problem by applying our mathematical results of (CL) to the model and we obtain the understanding of non-local tumour invasion and computational simulations. By computational simulations we see the effect of the Taylor expansion terms on the model as the amplitude of Taylor coefficients changes. Actually visualizing the asymptotic behaviour of solutions of the model, we can observe easily the relationship and change between tumour cells, ECM and MDE, depending on time.

2 Approximation model

2.1 Taylor expansion of the non-local term

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

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

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

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

Only the term with 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,

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

Since $g(\underline{u}(t,x+r)) = v(x,t)$, then we have

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

Hence in case of $K = 0$ the model is same as the local tumour invasion model provided by Chaplain and Lolas [4].

In the next subsection we consider 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 such models.

2.2 Approximation model of (CG)

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

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

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

Since the original 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 in the form of a sum of derivatives of v, it enables us to investigate the the effect of the non-local term on the invasion phenomena more clearly.

3 Existence theorem

In [12]-[15] we obtain 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, a is large enough, 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 the existence theorem of (CL) 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)'.

In the same way by applying Theorem 1 for $\mathcal{A}_i$ 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.

Our main result is as follows.

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, a is large enough, then there are classical solutions of (CG)': $\{n(x,t), v(x,t), m(x,t)\}$ such that they satisfy the following asymptotic behaviour.*

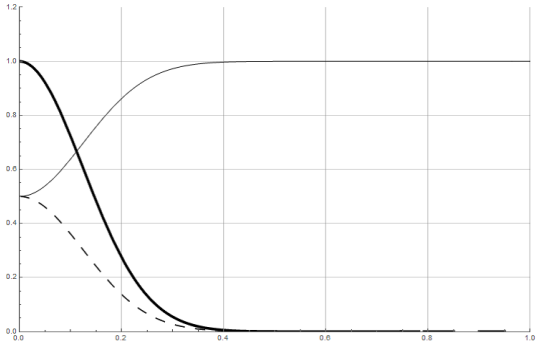
$$\lim_{t\to\infty} n(x,t) = 1,\quad \lim_{t\to\infty} v(x,t) = 0.$$

4 Computational simulations

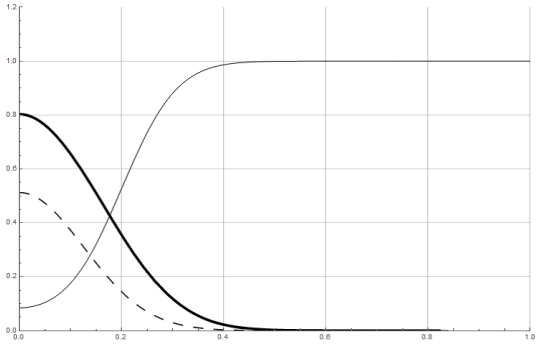
Since we obtain the existence and asymptotic behaviour of the solution in Theorem 2 , it essentially justifies the following numerical experiments by computational simulations. We show the computational simulations of the following problem.

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

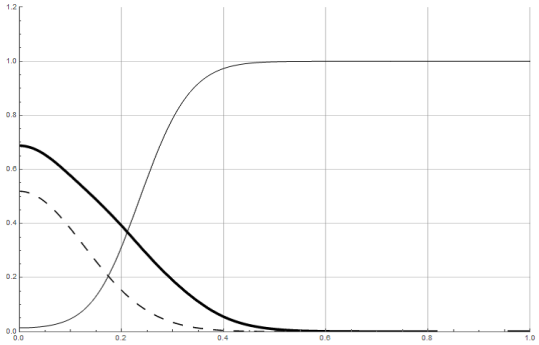
In Figure $1 \sim 5$ we show the computational simulations of (CG)'$_4$ for $\mathcal{A}_4(u+2v)$ instead of $\mathcal{A}_4(v)$, since the result is similar to the case of $\mathcal{A}_4(v)$ but much more stable than it. We observe tumour cell proliferation, migration and interactions between the tumour and the surrounding tissue: tumour cell density (thick line), ECM density (thin line), and MDE concentration (dotline), taking $A_3 \sim A_9$ from 0 to 10^{-1} at $t =$ 0, 0.35, 0.7, 1.05 and 1.4.



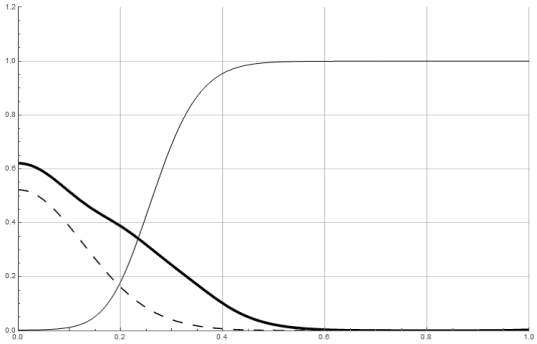
$t = 0$



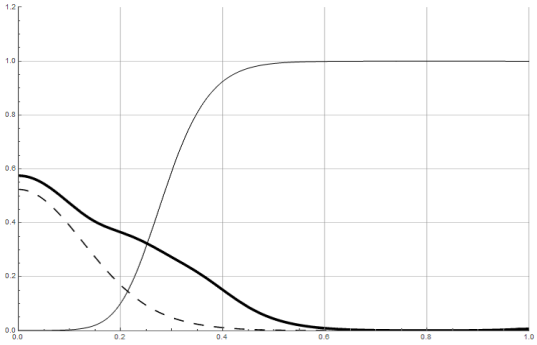
$t = 0.35$



$t = 0.7$



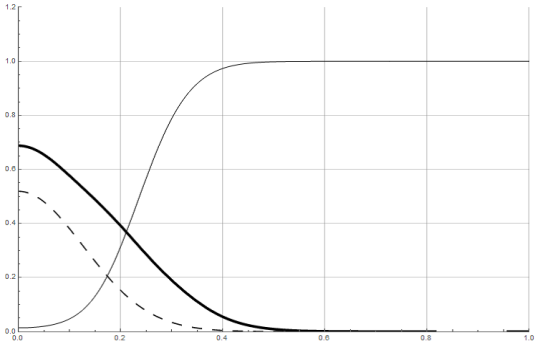
$t = 1.05$



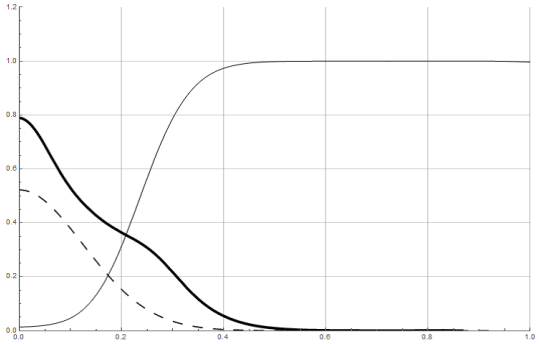
$t = 1.4$

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

Figure 1: Three components are very stable in the time dependent simulation. Therefore based on the amplitude of $A_1 \sim A_9$ as above, in the below changing the value of $A_1 \sim A_9$ appropriately we observe the change of the relationship between tumour cell density and the value of $A_1 \sim A_9$.

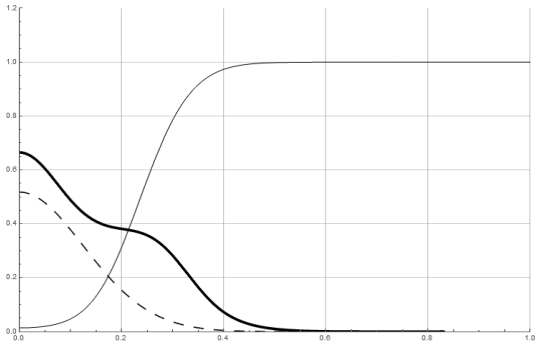


(1) $t = 0.7$,
$A_1 = 0.01$ $A_3 = 1.67 \times 10^{-5}$ $A_5 = 8.33 \times 10^{-13}$,
$A_7 = 1.98 \times 10^{-18}$, $A_9 = 2.76 \times 10^{-24}$



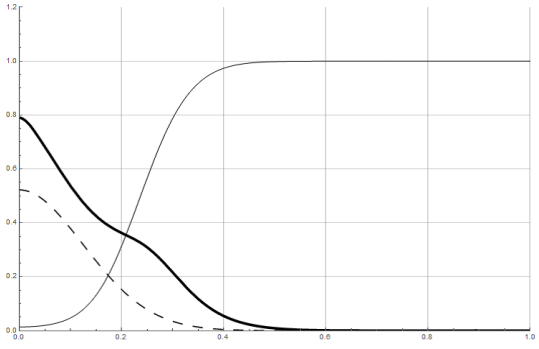
(2) $t = 0.7$
$A_1 = 0.01$ $A_3 = 1.67 \times 10^{-7} A_5 = 8.33 \times 10^{-13}$,
$A_7 = 1.98 \times 10^{-18}, A_9 = 2.76 \times 10^{-24}$

Figure 2: We take $A_3 = 1.67 \times 10^{-5}$ in (1) and 1.67×10^{-7} in (2). Compared with two figures, it is observed that the amplitude of A_3 makes the tumour cell density increase around the boundary of ECM intersecting tumour cell as it increases.



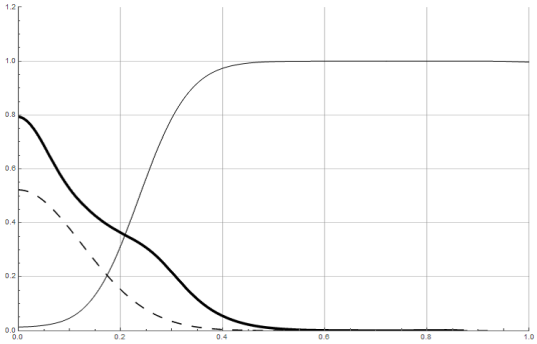
$t = 0.7$
$A_1 = 0.02$ other coefficients are same as in Figure 1-(1)

Figure 3: We take $A_1 = 0.02$ which is more than in Figure 1-(1). Compared with two figures, it is observed that the amplitude of A_1 makes the tumour cell density increase around the boundary of ECM intersecting tumour cell as it increases.



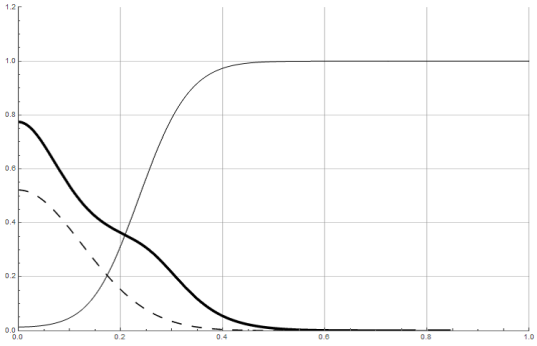
$t = 0.7$
$A_1 = 0.01$ other coefficients are 0

Figure 4: We take $A_1 = 0,01$ which is same as in Figure 1-(1) again. In this case our model is same as (CL). Compared to Figure 1-(1), it is observed that the amplitude of $A_3 \sim A_9$ makes the tumour cell density increase around the boundary of ECM intersecting tumour cell as they increase.



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

Figure 5: After $t = 0.7$ the simulation becomes unstable soon. Instead taking the coefficients $A_5 \sim A_9$ larger as below, the simulation becomes stable again.



$t = 0.7$
$A_1 = 0.01$, $A_3 = 0$,$A_5 = 8.33 \times 10^{-10}$, $A_7 = 1.98 \times 10^{-12}$, $A_9 = 2.76 \times 10^{-16}$

5 Conclusions

The non-local model shows that the multiscale proces of tumour invasion into tissue and the complicated interaction between cell-cell and cell-matrix adhesion, as showed in computational simulations in section 4 in a certain region of parameter space. Expanding the non-local term into Taylor series we consider an approximation problem of (CG) and show rigorously the global existence in time and the asymptotic behavior of solutions of it. Our main aim is focused on a better mathematical understanding of the model and it gu-

rantees the validity of computational simulations that qualitively replicate the complicated morphologies of non-local invasive tumour. Numerical experiments in section 4 imply that as the amplitude of Taylor coefficients increases the density of tumour cell increases around the boundary of ECM intersecting tumour cell, which means that Taylor series of the non-local term work as **dissipation** and **viscosity**. Hence we might respect the non-local term as dissipation term in the tumour invsion. In Taylor coefficients of the non-local term A_1, A_2 are crucial for the stability and the behaviour of the tumour cell density in the simulation.

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