Characterization of an integral operator arised in non-local tumour invasion model and its mathematical analysis

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Abstract: In this paper we investigate a mathematical model of non-local tumour invasion with proliferation proposed by Gerisch and Chaplain. We show the global existence in time and asymptotic profile of the solution to the initial boundary value problem for the model. For this purpose we deal with the problem applying the argument of the singular integral operator to the non-local term, and we finally arrive at our desired result. In order to show computer simulations of the model we consider an approximation problem of the model, and we can discuss the time dependent change of the non-local tumour invasion process by computer simulations.

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

1 Introduction

Tumour invasion models in local or non-local environment of the cell([1][3]-[5], further references therein), base on the generic solid tumour growth, which for simplicity they assume is at the avascular stage. For the better understanding of this phenomena mathematical models of cancer invasion of tissue in local or non-local case, the effect of cell-cell and cell-matrix adhesion is investigated.

In [5] Gerisch and Chaplain proposed a non-local model of tumour invasion(cf. [4]):(CG)

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

where $n := n(x,t)$ is the density of tumour cells, $f := f(x,t)$ is the extra cellular matrix density (ECM density), $m := m(x,t)$is degradation enzymes concentration (MDE concentration) , $D_1, D_3, \gamma, \alpha, \lambda$, 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 one spacial dimension it takes the 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,

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

$g(\underline{u}(t,x))$ will be specified later.

In [2][4][5] it is shown that as $R \to 0$ the non-local model converges to a usual(local) tumour invasion model same type of Chaplain and Lolas [3], 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.

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

where d_n, γ, μ_1, η, μ_2, d_m, α and β are positive constants. We have the global existence in time of solutions to (CL) ([6]-[9]).

In this paper we deal with the initial-boundary value problem for all the problem in one spacial dimension satisfying

$$n(x,0) = n_0(x), f(x,0) = f_0(x), m(x,0) = m_0(x), \quad (7)$$

and zero-Neumann condition

$$\frac{\partial}{\partial \nu} n(x,t) = \frac{\partial}{\partial \nu} f(x,t) = \frac{\partial}{\partial \nu} m(x,t) = 0 \quad (8)$$

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

It is supposed in our models that the tumour cells produce MDEs which degrade the ECM locally and that the ECM responds by producing endogeneous inhibitors. The ECM degradation, as well as making space into which tumour cells can move by simple diffusion, results in the production of molecules which are actively attractive to tumour cells and which then aid in tumour cell motility.

Recently Gerisch and Chaplain [5] proposed a nonlocal 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. [2].

However in their result the regularity of the solution is limited and further, though in [5] they verify the special form of the non-local term by using Taylor expansion and the principal value of the non-local term, they deal with the model without the structure of the principal value in [5]. In this paper taking account of such mathematical structure, we consider the nonlocal term as a singular integral operator and show the energy estimate. By using the estimate in the same way as used in our previous papers we obtain the existence and asymptotic behaviour of solutions of the problem and we gain the understanding of non-local tumour invasion and computer simulations.

In the previous paper [8] instead of (CG) we consider an approximation problem of (CG) by using Taylor expansion of the nonlocal term. However in this paper we can directly deal with (CG) applying the argument of the singular integral operator to the nonlocal term, finally arrive at the our desired result in the same way as used in (CL) or so. Replicating 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 Existence and asymptotic profile

2.1 Singular integral operator

Following to Domschke, Trucu, Gerisch and Chaplain [4] we consider the non-local term in the form.

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

$$= \frac{1}{R}\int_{-R}^{R} \Omega(r)\tilde{g}(n,f)(t,x+r)((a_n n + a_f f)(t,x+r)dr \quad (9)$$

where $\tilde{g}(n,f)(t,y)$ is a zero-extension for $x \notin \Omega$ and a_n, a_f are constants. Samely we can consider a zero-extention functions $\tilde{n}, \tilde{f}$ of n,f in $[0,T] \times$ R so that they satisfy (see Mizohata[Th.3.13;14])

$$\|\tilde{n}\|_m \le C\|n\|_{m,\Omega}, \|\tilde{f}\|_m \le C\|f\|_{m,\Omega}. \quad (10)$$

where $\|\cdot\|_{m,\Omega}$ is the Sobolev norm of order m defined in Ω and it is written by $\|\cdot\|_m$ when $\Omega =$ R. We also denote $\|\cdot\|_0$ and $\|\cdot\|_{0,\Omega}$ by $\|\cdot\|$ and $\|\cdot\|_\Omega$ respectively. Putting $x+r = y$, the non-local term can be expressed by the form:

$$\frac{1}{R}\int_{-\infty}^{\infty} \Omega(y-x)\tilde{g}(c,v)(t,y)(a_n\tilde{n} + a_f\tilde{f})(t,y)dy$$

taking account of the principal value of the non-local term as used in [5] for the justification of the form of it,

$$:= \frac{1}{R}\lim_{\epsilon\to 0}\int_{|y-x|\ge\epsilon} \Omega(y-x)\tilde{g}(c,v)(t,y)(a_n\tilde{n}+a_f\tilde{f})(t,y)dy.$$

which can be regarded as a singular integral operator.

2.2 The estimate of the nonlocal term

In the below we put $a_n = 0$ for the sake of simplicity. Considering $\Omega(r)$ is homogeneous of order 0, due to

$$|\Omega(r)| = \frac{1}{2R}\frac{1}{r}\cdot r$$

then we obtain by the well known L^2 estimate of the singular integral operators(see Mizohata[Chap.6;14])

$$\|\mathcal{A}\{\underline{u}(t,\cdot)\}(\underline{x})\|_\Omega^2 \le C\|f\|_\Omega^2 \quad (11)$$

Then in (2) we have by the reduction process as used in [6]-[12]

$$\frac{\partial}{\partial t}(\log f) = -\gamma m + \mu_2(1-n-f).$$

integrating the both sides of the above over $(0,t)$

$$f(x,t) = f_0(x)\cdot e^{-\gamma\int_0^t m ds + \mu_2\int_0^t (1-n-f)ds}.$$

Substituting $f(x,t)$ by the right hand side of the above in (1) we have

$$(RP)\begin{cases} \frac{\partial^2}{\partial t^2}u = D_1\triangle u_t - \nabla\cdot u_t\mathcal{A}\{\tilde{g}(u_t, f_0(x)\Theta)\} \\ \qquad -\mu_1 u_t(1+u_t+f_0(x)\Theta) - \mu_1 f_0(x)\Theta \\ \frac{\partial^2}{\partial t^2}v = D_3\triangle v_t + \alpha u_t - \lambda v_t \end{cases}$$

where $f = f_0\Theta$ and $\Theta = e^{-a-bt-\gamma v-\mu_2(u+\int_0^t fds)}$ for positive parameter a, b and $n = 1+u_t$, $m = b+v_t$. By using the estimate of the non-local term (11) we have the following estimate.

Lemma 1 *For sufficiently smooth u, v satisfying (RP) we have*

$$\|\mathcal{A}\{\tilde{g}(u_t, f_0(x)\Theta)\|_\Omega^2 \le C\|u_t\|_\Omega^2 \qquad (12)$$

By using this Lemma we obtain the following estimate of (RP).

Theorem 2 (Estimate of (RP)) *For the smooth solution of our problem $u(x,t)$ and $v(x,t)$ of (RP) satisfying $|u_t| < 1$ it holds that for $m \ge [\frac{n}{2}]+1$*

$$\|\partial_t^m u_t\|_\Omega^2 + \int_0^t \|\partial_t^m \nabla u_t\|_{m,\Omega}^2 d\tau \le C(\|u_t\|_{m,\Omega}^2(0) + e^{-2a}\|\nabla u\|_{m,\Omega}^2(0))$$

for sufficiently large a.

Remark 3 *It is very crucial to consider the principal value in the non-local term because they use it for the verification of the special form of the term. Therefore any argument and result concerning the non-local term without the principal value seems to be not essential. But in[4], not considering it they derive the estimate and the existence theorem of (CG).*

2.3 Existence theorem

In the same way as used in [6]-[12] using Theorem 2 we obtain the global existence in time of solutions and asymptotic behaviour.

Theorem 4 (Existence theorem of (CG)) *For sufficiently smooth initial data $\{n_0(x), f_0(x), m_0(x)\}$ and $m \ge [n/2]+3$, assume that $\|n_0-1\|_{m+1}^2$ is sufficiently small, a is large enough, then there are classical solutions of (CG)): $\{n(x,t), f(x,t), m(x,t)\}$ such that they satisfy the following asymptotic behaviour*

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

Remark 5 *We can take the regularity of the solution higher as required according to the smoothness of the initial data. However in [4] they can not increase the regularity of the solution as required even for any smooth initial data.*
Since A_1 is of the special form of $A_1 = R$, therefore taking A_1 larger is to take the sensing radius R larger, which plays a very important role in the non-local properties of the model.

3 Computational simulations

3.1 Approximation model

In the section in order to obtain the simulation of (CG) we consider an approximation problem of (CG) same as used in [4]. Since the non-local term $\mathcal{A}\{\underline{u}(t,\cdot)\}$ is in the integral form, it seems to be difficult to realize the simulation and understand the interaction between the term and the phenomena by computational simulation. Hence we consider an approximation model by using Taylor expansion of $g(\underline{u}(t,x+r)) = v(x+r,t)$ at $r=0$ in the non-local term,

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

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

Our approximation problem of (CG) is as follows by neglecting the remainder term $\tilde{g}_K(r)$ of Taylor series.

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

where $\mathcal{A}_K(f) = \sum_{k=0}^{K} A_{2k+1}\frac{\partial^{2k+1}}{\partial x^{2k+1}}f$. It is noticed that $A_{2k} = 0, k = 0,1,2,\cdots$ because $\Omega(r)$ is an odd function. (see [5][8]).

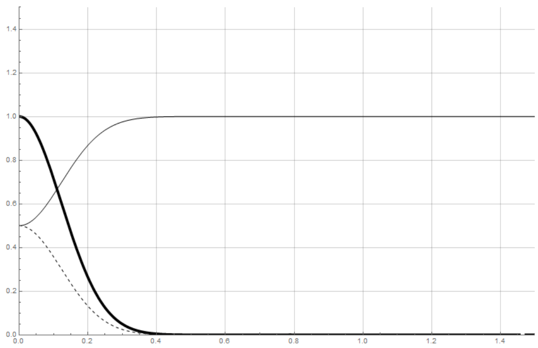
Remark 6 *In case of $K = 0$ the model is same as the local tumour invasion model proposed by Chaplain and Lolas [3]. We obtain the existence theorem of (CG)' in the previous paper(see [8]), which verifies our simulations. Especially the Taylor coefficient A_1 is crucial because A_1 is equal to the sensing radius R and it mainly governs the non-local phenomena of the model.*

3.2 Computational simulations

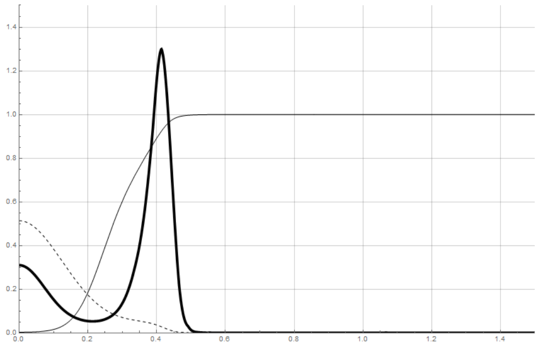
Since we obtain the existence and asymptotic behaviour of the solution in Theorem 2 , it essentially justifies the following numerical experiments. We show the computer simulations of (CG)', approximating (CG).

We can improve the simulations by Mathematica 11 so that it is more stable for enough time and we can take some parameters larger and realize the peak of tumour cell density becomes much higher in ECM remarkably.

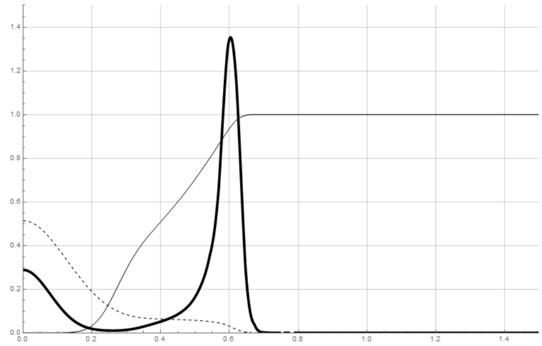
In the following Figures, first we show the computer simulations of (CL), then (CG)' to observe tumour cell proliferation, migration, ECM re-establishment, and interactions between the tumour and the surrounding tissue: tumour cell density (thick line), ECM density (thin line), and MDE concentration (dashdot).



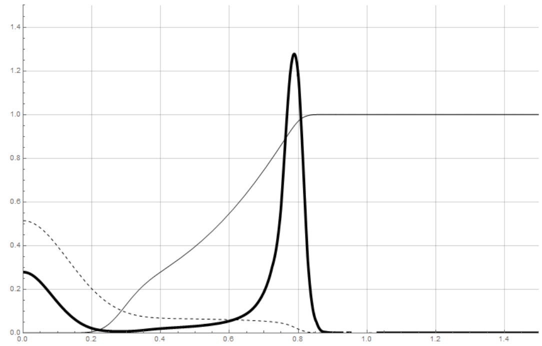
$t = 0$



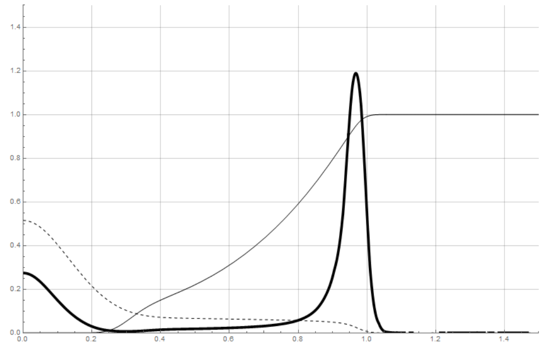
$t = 1$



$t = 2$

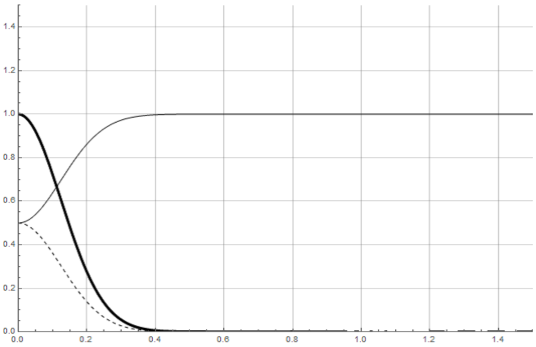


$t = 3$

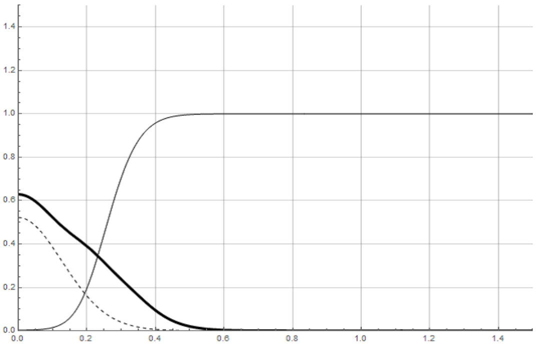


$t = 4$

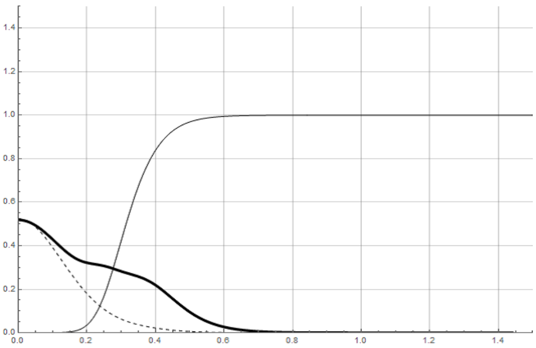
Figure 1: Solutions of (CL) with the parameter values $d_n = 0.002, d_m = 0.001, x_n = 0.007, \gamma = 0.1, \eta = 10, \mu_1 = 0.1\mu_2 = 0.1, \alpha = 0.1$, and $\beta = 0$. The three components are very stable in the time dependent simulation result and the peak of the tumour cell density much higher than in the previous results ([6]-[9]) remarkably.



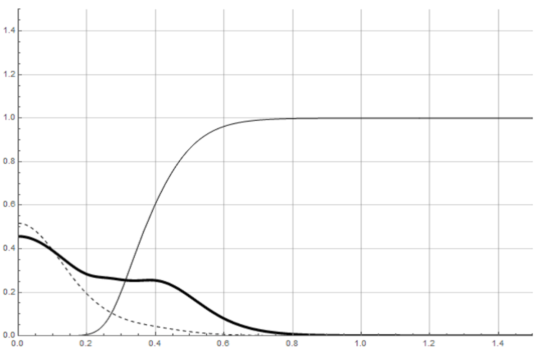
$t = 0$



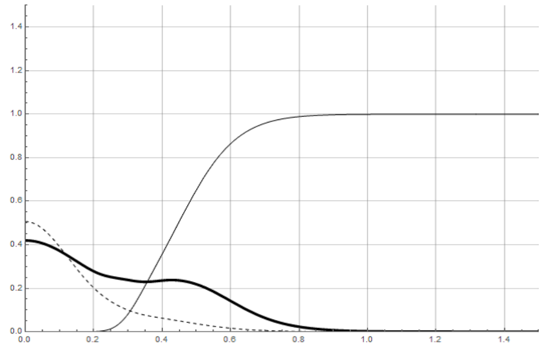
$t = 1$



$t = 2$



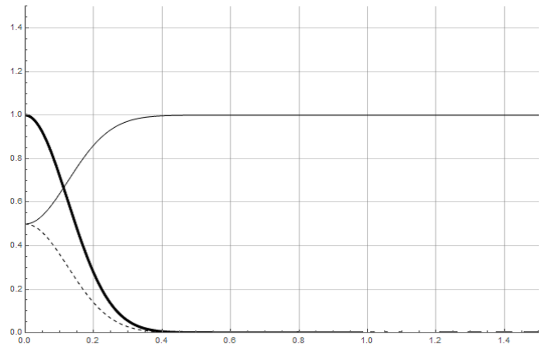
$t = 3$



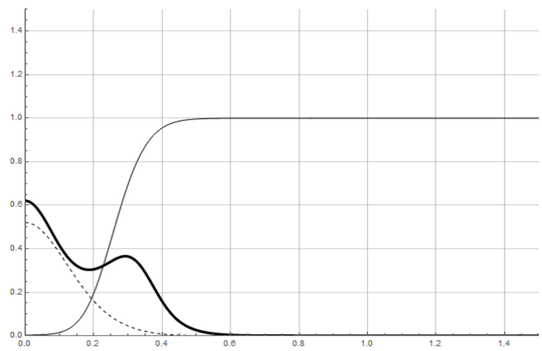
$t = 4$

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

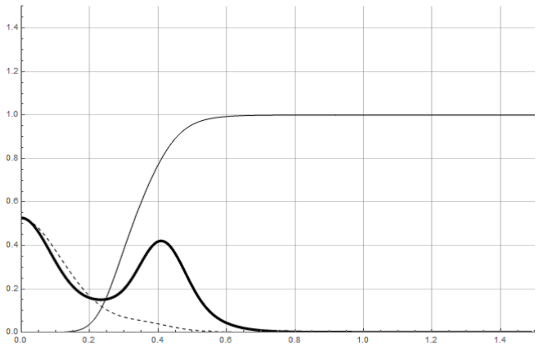
Figure 2: The above simulation result is already obtained in [8]. Here since it is very difficult to take A_1 higher than 0.01, we put $A_1 = 0.01$. However in this paper we can improve the simulation method so that A_1 can be taken more than 0.01 and the result is shown in the next figure.



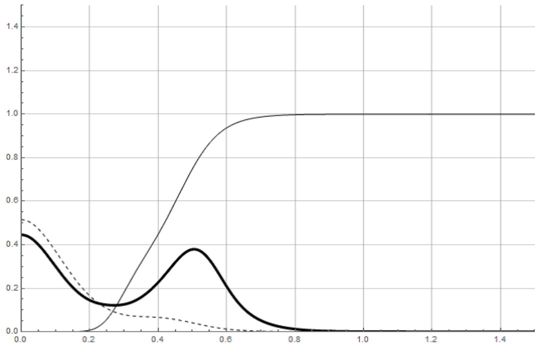
$t = 0$



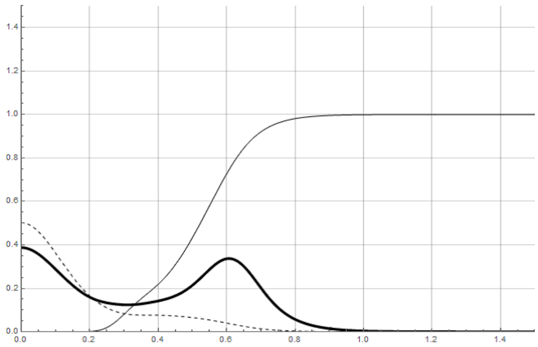
$t = 1$



$t = 2$



$t = 3$



$t = 4$

$A_1 = 0.02, A_3 = 1.67 \times 10^{-5}, A_5 = 8.33 \times 10^{-13}, A_7 = 1.98 \times 10^{-18}, A_9 = 2.76 \times 10^{-24}$
Figure 3: Compared with Figure 2 the peak of the tumour cell density is clearly appear, while compared with Figure 1 the height of the peak become much lower. In this paper our improvement of numerical experiments enables us to realize the simulations by taking $A_1 \geq 0.2$, though in [8] it is impossible to take A_1 more than 0.01.

4 Conclusions

In this paper we show the global existence in time and asymptotic profile of the solution to the initial boundary value problem (CG). From the stand point of view of [4], the non-local term can be considered as a singular integral operator by using appropriate zero-extensions of the nonlocal term and the unknown functions and derive the energy estimates of (CG). By using it we can arrive at the desired result by the standard argument.

The model shows the multiscale process of tumour invasion and the complicated interaction between cell-cell and cell-matrix adhesion, as in computer simulations in section 3, in a certain region of parameter space. For this purpose expanding the non-local term into Taylor series we consider an approximation problem of (CG) , of which the global existence in time and the asymptotic behavior of solutions of it is shown already in our previous paper [8]. We can gain a better mathematical understanding of the model and it guarantees the validity of computer simulations.

Numerical experiments are much more improved by the usage of Mathematica ver. 11 than in the previous paper [8]. In [8] we should take $A_1 = R = 0.01$ only and it is very difficult to take it more but in this paper our device make it possible. The Taylor coefficient A_1 are very crucial for the stability, the behaviour of the tumour cell density and the no-local property in the simulations because of $A_1 = R$ for the sensing radius R, which mainly governs the non-local properties of the model. The larger we take R, the more the non-local property seems to appear clearly. Especially taking it more than 0.01 it is observed the tumour cell density makes a small peak in ECM, which is much lower than in (CL). Hence it is concluded that the non-local term seems to work on the tumour invasion as **dissipation** and **viscosity**.

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