Mathematical analysis of tumour invasion model with proliferation and re-establishment

AKISATO KUBO
Fujita Health University
Department of Mathematics, School of Health Sciences
1-98, Toyoake, Aichi 470-1192
JAPAN
akikubo@fujita-hu.ac.jp

Abstract: We study the global existence in time and asymptotic profile of solutions of a mathematical model of tumour invasion proposed by Chaplain and Lolas. We consider related nonlinear evolution equations with strong dissipation, proliferation and an initial Neumann-boundary value problem. We show global existence in time of solutions to the initial boundary value problem in arbitrary space dimension by using the method of energy. Applying the result of existence and asymptotic behaviour of solutions to our problem we discuss the property of the solution to the tumour invasion model. Further we discuss a more general form of the nonlinear evolution equation, which could give the same type of existence theorem for a more general form of the tumour invasion model.

Key–Words: Nonlinear evolution equation, mathematical analysis, tumour invasion, cell proliferation, re-establishment of MDE.

1 Introduction

In this paper we consider the mathematical model by Chaplain and Lolas [3] described tumour invasion with tumour cell proliferation and re-establishment of ECM in $\Omega \times (0, T)$: (C-L)

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

where Ω is a bounded domain in R^n, $n := n(x, t)$ is the density of tumour cells, $m := m(x, t)$ is degradation enzymes concentration (MDE concentration) and $f := f(x, t)$ is the extra cellular matrix density (ECM concentration) and d_n, γ, μ_1, η, μ_2, d_m, α and β are positive constants.

In this model , we neglect the chemotaxis term because compared with the hapotaxis term, the second term of (1), the effect of it is known to be quite small. Actually even if the chemotaxis term is considered into, we can deal with the problem involving the chemotaxis term with sufficiently small coefficient in the same way as follows in this paper.

In the previous paper [5] we consider only the case of $\mu_2 = 0$ for our convenience. In this paper we consider the case of $\mu_2 > 0$ as well as $\mu_1 > 0$. Then (C-L) describes tumour invasion phenomena with tumour cells cell proliferation and re-establishment of ECM. We deal with a initial boundary value problem for (C-L) satisfying:

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

$n(x, 0) = n_0(x), f(x, 0) = f_0(x), m(x, 0) = m_0(x)$ where $\partial\Omega$ is a smooth boundary of Ω and ν is the outer unit normal vector.

Chaplain and Anderson [2], which is corresponding to the case of $\mu_1 = \mu_2 = 0$ in (C-L), base on 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 model the following key variables are considered: tumour cell density: n, MDE concentration: m, ECM density concentration: f.

MDEs are important at many stages of tumour growth, invasion, and metastasis, and the manner in which they interact with endogeneous inhibitors, growth factor, and tumour cells is very complex. In the model they assume that the tumour cells produce

MDEs which degrade the ECM locally and that the ECM responds by producing endogeneous inhibitors (e.g., TIMPs). The ECM degradation, as well as making space into which tumour cells may move by simple diffusion, results in the production of molecules which are actively attractive to tumour cells (e.g., fibronectin) and which then aid in tumour cell motility. They refer to the movement of tumour cells at a gradient of such molecules as haptotaxis and then consider tumour cell motion to be driven mainly by random motility and haptotaxis in response to adhesive or attractive gradients created by degradation of the matrix.

Recently, there are many mathematical models which can be found in the literature describing tumour angiogenesis(cf. [1], [13]- [15]). In [13] Levine and Sleeman apply the diffusion equation provided by Othmer and Stevens [15] 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.

On the other hand, mathematical approaches for models of tumour growth have done(see [5]-[15]). Levine and Sleeman [12] 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]-[11] show the time global solvability and asymptotic behavior of the solution to the model proposed by [1][2][12]-[14].

2 Reduced problem

2.1 Simplification of the system

Following to Levine and Sleeman [13] we reduce our problem to a simpler system(see [5]-[12]).

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

$$\frac{\partial}{\partial t}(\log f) = -\eta m + \mu_2(1-n-f) \qquad (4)$$

Integrating (4) over $(0,t)$ for $f(x,0)=f_0(x)$

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

Put $n = l(t) + \tilde{n}$ and $m = b + \tilde{m}$, then for a constant $b > 0$,

$$f(x,t) = f_0(x)\cdot e^{-a-bt-\eta\int_0^t \tilde{m}ds - \mu_2\int_0^t (l(t)-1+\tilde{n}+f)ds}$$

denoting $\int_0^t \tilde{n}ds = u$ and $\int_0^t \tilde{m}ds = v$

$$= f_0(x)\cdot e^{a-bt-\eta v-\mu_2((\int_0^t (l(s)-1)ds+u+\int_0^t fds)}$$

Substituting $f(x,t)$ by the right hand side of (4), from (1) and (3) it follows that

$$\frac{\partial^2}{\partial t^2}u = d_n\triangle u_t$$

$$-\gamma\nabla\cdot u_t(\nabla f_0\cdot e^{-a-bt-\eta v-\mu_2(\int_0^t (l(s)-1)ds+u+\int_0^t fds))}$$

$$+\mu_1 u_t(1-2l(t)-u_t-f_0\cdot e^{-a-bt-\eta v-\mu_2(\int_0^t (l(s)-1)ds+u+\int_0^t fds)})$$

$$-\mu_1 l(t)e^{-a-bt-\eta v-\mu_2(\int_0^t (l(s)-1)ds+u+\int_0^t fds)} \qquad (5)$$

and

$$v_{tt} = d_m\partial_x^2 v_t + \alpha u_t - \beta v_t. \qquad (6)$$

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

2.2 Related nonlinear evolution equations

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

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

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

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

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

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

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

where β is a multi-index for $\beta=(\beta_1,\cdots,\beta_{\ n})$.
The eigenvalues of $-\Delta$ with the homogeneous Neumann boundary conditions are denoted by

$$\{\lambda_i|i=0,1,2,\cdots\},0=\lambda_0<\lambda_1\le\cdots\to+\infty,$$

and $\varphi_i = \varphi_i(x)$ indicates the L^2 normalized eigenfunction corresponding to λ_i. For a non-negative integer l, we set $W^l(\Omega)$ as a closure of $\{\varphi_1,\varphi_2,\cdots\varphi_n,\cdots\}$ in the function space $H^l(\Omega)$. It is noticed that we have $\int_\Omega h(x)=0$ for $h(x)\in W^l(\Omega)$, which enables us to use Poincare's Inequality.

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

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

where

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

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

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

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

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

3 Existence theorem of (NE)

By deriving the energy estimate of (RP)(see [6]-[8]) and considering the iteration scheme we obtain existence of solutions to (RP) by the standard argument to show the convergence of solutions of the iteration scheme.

In the same way as used in [6]-[8] we have the following estimate of (RP) (cf. Dionne[4]).

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

$$\sum_{j=1}^{M+1}(||\nabla^{j-1}v_t||^2(t)+\int_0^t D||\nabla^j v_t||^2(\tau)d\tau)$$
$$\le CE_M[v](0)$$

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

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

We consider the iteration scheme of (RP):

$$(i+1)\begin{cases} Q_i[v_{i+1}]=v_{i+1tt}-D\nabla^2 v_{i+1t} \\ +\nabla\cdot(\chi_{a,1}(v_i)e^{-L_a(t)-v_i}\nabla v_{i+1}) \\ -\mu_1 v_{i+1t}(-1+2l(t)+v_{it})\ =0 \\ \dfrac{\partial}{\partial\nu}v_{i+1}|_{\partial\Omega}=0, \\ v_{i+1}(x,0)=v_0(x),\ v_{i+1t}(x,0)=v_1(x), \end{cases}$$

where $v_i=\sum_{j=1}^\infty f_{ij}(t)\varphi_j(x)$, $v_0(x)=\sum_{j=1}^\infty h_j\varphi_j(x)$, $v_1(x)=\sum_{j=1}^\infty h'_j\varphi_j(x)$.
The energy estimate Lemma 1 guarantees the uniform estimate of each $(i+1)$ for $i=1,2,\cdots$. We determine $f_{ij}(t)$ by the solution of the following system of ordinary equations with initial data. For $j=1,2,\cdots$

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

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

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

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

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

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

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

4 Main result

The equations (5) and (6) are essentially regarded as the same type of equation as (7). The energy estimates of u and v follow and combining these estimates we obtain the desired estimate.

Lemma 3 (Energy estimate) *We obtain the energy inequality of the reduced problem (RP) for $m > M \geq [n/2] + 1$ and sufficiently large a*

$$\|u_t\|_M^2 + d_n \int_0^t \|u_s\|_{M+1}^2 ds + \|v_t\|_M^2 + d_m \int_0^t \|v_s\|_{M+1}^2 ds$$
$$+ \|f\|_M^2 + \int_0^t \|f\|_{M+1}^2 ds \leq C(E_{a,M}[u](0) + E_{a,M}[v](0) + E_{a,M}[f](0)) + C_a \quad (4.10)$$

where $C_a \to 0$ as $a \to \infty$.

Then applying the same argument as used for Theorem 2 to the above mathematical model, we have existence and asymptotic behaviour of the solutions to our mathematical model.

Our main result is as follows.

Theorem 4 *For smooth initial data $\{\ n_0(x), f_0(x), m_0(x)\ \}$ there are classical solutions of (C-L)): $\{\ n(x,t), f(x,t), m(x,t)\ \}$ such that they satisfy the following asymptotic behaviour.*

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

5 Conclusion

In order to obtain the global existence in time and asymptotic profile of solutions of a mathematical model of tumour invasion by Chaplain and Lolas, we investigate related nonlinear evolution equations with strong dissipation and proliferation to our mathematical models as an initial Neumann-boundary value problem. We could show the global existence in time of solutions to the initial boundary value problem in arbitrary space dimension by the method of energy. Applying the result to our model we show the property of the solution to the model.

Also in the same way as above we can show as a further study the existence of solutions to (NE) for the following equation instead of (7):

$u_{tt} = D\Delta u_t + \nabla \cdot (\chi(u_t, e^{-u})\chi_1(u, \nabla u)e^{-u}\nabla u)$
$+\mu p(u_t)$

where $\chi_1(s_3, s_4) \in \text{ß}^m(R^2)$ for $(s_3, s_4) \in R^2$,
$p(b + v_t) = v_t\tilde{p}(b + v_t)$ for $u_t = b + v_t, b > 0, \tilde{p} < 0$

and $p(s_1) \in \text{ß}^m(I_r)$. Note that the above equation is of a generalised form of (7). Finally it is possible that based on our mathematical result we can show the result of computer simulations of (C-L).

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