Mathematical analysis of some models of tumour growth and simulations

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Abstract: Our main interest is to characterize mathematical models of tumour growth by clarifying the equivalence and difference between them mathematically . We first discuss the solvability and the asymptotic profile of the solution to some parabolic ODE systems described tumour angiogenesis([12]-[15], [23], [24]) . These models are proposed independently, one arises from reinforced random walk, proposed by Othmer and Stevens and another from a number of researches in biology and biomedicine, proposed by Anderson and Chaplain. We show a rigorous relationship between them and give a mathematical framework of the solvability and asymptotic profiles of the solutions of them. Finally we study a mathematical model on generic solid tumour growth at the avascular stage, proposed by Anderson and Chaplain. The focus of their model is on an aspect of tissue invasion. Although it is the different phenomenon from angiogenesis, we can find a consistency in their mathematical structures. 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. On the other hand, we show some results of computer simulations of these models with the help of our mathematical analysis.

Key–Words: Tumour angiogenesis, Tumour invasion, Time global solution, Collapse, Simulations

1. Introduction

We begin with a brief explanation about tumour angiogenensis in Figure 1.

1.Tumour produces TAFs(some chemicals) as a trigger of tumour angiogenesis(Fig1-1). They diffuse and reach neighboring capillaries and other blood vessels(Fig1-2).

2. In response to TAFs(Fig1-3) EC(endothelial cells) surface begins to develop(Fig1-4,5) pseudopodia which penetrate the weakened basement membrane(Fig1-6).

3. Capillary sprouts continue to grow in length out of the parent vessels(Fig1-7) and form loops leading to micro circulation of blood(Fig1-8,9).

4. The resulting capillary network continues to progress and eventually invades the tumour colony(Fig1-10).

The above sequent procedure is called *tumour angiogenesis*, which permits the tumour to grow further.

In 1971 Folkman published a seminal paper [7] in the New England Journal of Medicine, proposing the hypothesis that all tumor growth is angiogenesis-dependent. The substance that is released by tumours and provides vascularization has been named TAF by him. This founded the field of angiogenesis research and opened a field of investigation now pursued by scientists in many fields worldwide(cf. [8]-[10]). Folkman's laboratory purified the first angiogenic protein from a tumor, discovered the first angiogenesis inhibitors and initiated clinical trials of antiangiogenic therapy. Such factor also has been proposed as useful for clinical treatment.

Recently, there are many mathematical models which can be found in the literature describing tumour angiogenesis(cf. [1]-[5], [19], [21]). In [19] Levine and Sleeman apply the diffusion equation provided by Othmer and Stevens [17] to obtain the understanding of tumour angiogenesis, which arises in the theory of reinforced random walk(see Davis [6]). 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

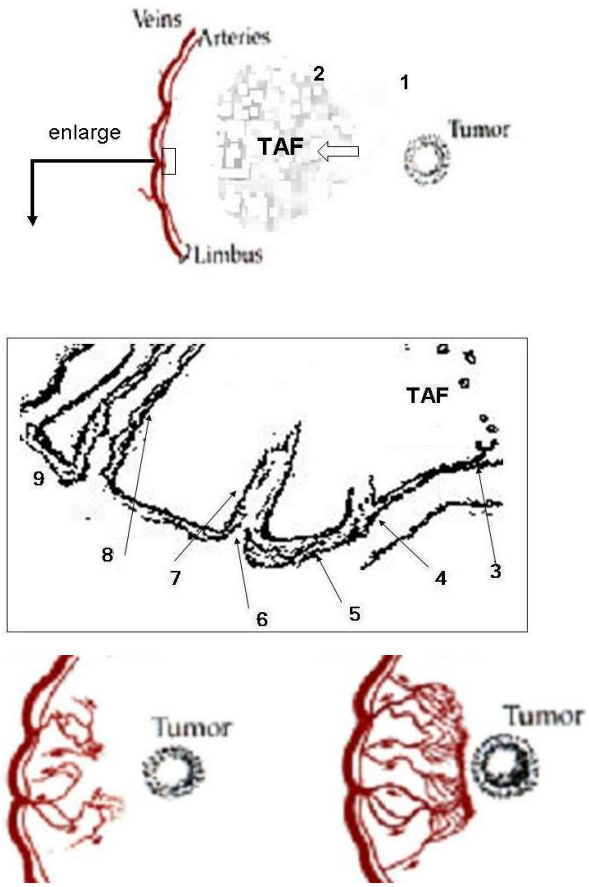

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Figure 1. Tumour angiogenesis

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 [12]-[16], [18] , [22], [23], [24]). Levine and Sleeman [16] and Yang, Chen and Liu [22] 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. [12]-[15] [23], [24] show the time global solvability and asymptotic behavior of the solution to the model without using such simplification. [13]-[15], [24] and Sleeman, Anderson and Chaplain [18] deal with the solvability of Anderson and Chaplain's model in [1] [2].

In [17] Othmer and Stevens derived a parabolic ODE system formulating the reinforced random walk model(cf.Davis [6]), where unknown functions $P = P(x,t)$ and $W = W(x,t)$ stand for the density of the particle and that of control species, respectively. That is,

$$P_t = D\nabla \cdot [P\nabla(\log \frac{P}{\Phi(W)})], \tag{1}$$

$$W_t = F(W,P), \qquad \text{in} \quad \Omega \times (0,\infty) \tag{2}$$

$$P\nabla[\log \frac{P}{\Phi(W)}] \cdot \nu = 0, \qquad \text{on } \partial\Omega \times (0,\infty) \tag{3}$$

(no-flux condition)

$$P(x,0) = P_0(x) \geq 0,\ W(x,0) = W_0(x) \geq 0, \tag{4}$$

where Ω is a bounded domain in $\boldsymbol{R}^n$ with smooth boundary $\partial\Omega$, $D > 0$ is a constant and ν denotes the outer unit normal vector. In fact, [17] provides the reinforced random walk on lattice points as in [6], takes the renormalized limit and gets the above system.

Classification of asymptotic properties of the solution

By the numerical computation Othmer and Stevens classified the solution according to its behaviour as $t \to +\infty$ in [17]:

1.(aggregation) $\|P(\cdot,t)\|_{L^\infty} < C$ for all t and

$$\liminf_{t\to\infty} \|P(\cdot,t)\|_{L^\infty} > \|P(\cdot,0)\|_{L^\infty}.$$

2.(blowup) $\|P(\cdot,t)\|_{L^\infty} \to \infty$ in finite time.
3.(collapse) $\limsup_{t\to\infty} \|P(\cdot,t)\|_{L^\infty} < \|P_0\|_{L^\infty}$.

In [16] Levine and Sleeman apply it to the understanding of tumour angiogenesis where P is the density of EC, W is TAFs(tumour angiogenic factors) concentration and the sensitivity function $\Phi(W)$ is of the form:

$$\Phi(W) = (\frac{W+\alpha}{W+\beta})^a, \tag{5}$$

where α, $\beta > 0$ and a is a constant. We first deal with (1)-(4), so called, Othmer-Stevens model(cf. [12]-[15], [23], [24]).

(1)-(4) with (5) for $a < 0$ and
$F(P,W) = WP$(exponential growth),

hereafter referred to as **[O-SE]**.

(1)-(4) with (5) for $a > 0$ and
$F(P,W) = -WP$(uptake),

is denoted by **[O-SU]** simply. We discuss [O-SU] in the same manner as used in [O-SE].

We explain briefly the existence of time global solution to a parabolic ODEs system modeling tumour angiogenesis considered by Anderson and Chaplain [1] [2], which is called Anderson-Chaplain model and

is denoted by **[A-C]** hereafter. We discuss a mathematical relationship between them and give a category of the solvability and asymptotic behaviour of the solution to these models. In the final section we study a mathematical model on generic solid tumour invasion at the avascular stage, proposed by Anderson and Chaplain. Then we will apply the approach used in above to the mathematical model and show the time global existence and the asymptotic profile of the solution of it.

2. Othmer-Stevens model

2.1. [O-SE]$(a < 0)$

Mathematical analysis of [O-SE] was done by Levine and Sleeman [16]. In fact, taking $\log W = \Psi$, we get $\Psi_t = P$ because of $W_t/W = P$ and it holds

$$Q_1[\Psi] = \Psi_{tt} - D\Delta\Psi_t + \nabla\cdot(\frac{aD(\beta-\alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)}\Psi_t\nabla\Psi)$$

$$= 0, \qquad \text{in} \quad \Omega\times(0,T) \tag{6}$$

from (1) and (2). Then our problem is reduced to the the following:

$$(TM)\begin{cases} Q_1[\Psi] = 0 & \text{in } \Omega\times(0,T) \\ \frac{\partial}{\partial\nu}\Psi|_{\partial\Omega} = 0 & \text{on } \partial\Omega\times(0,T) \\ \Psi_t(x,0) = P_0(x), \quad \Psi(x,0) = \log W_0(x). \end{cases}$$

In [16], Levine and Sleeman replaced the coefficient by a constant,

$$\frac{a(\beta-\alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)} = \frac{a(\beta-\alpha)W}{(W+\alpha)(W+\beta)}$$

$$\approx constant$$

under the agreement that

$$\alpha \ll W \ll \beta \text{ or } \beta \ll W \ll \alpha.$$

Their argument is verified in [16] if W is bounded for any $t > 0$. However, there is a case where $W = e^{\Psi}$ obtained in [16] is unbounded, here this simplification is not valid. Hence in this paper we do not consider the simplified case but it is easily seen that the same argument as discussed in this section holds for the simplified case, too.

On the other hand, the simplified case has been studied as a special case of the original problem. If $\alpha \ll W \ll \beta$, according to the above argument it is seen that $\Phi(W) \approx a\ constant \times W^a$. In this case (TM) is reduced to the following:

$$(CH)\begin{cases} \Psi_{tt} - D\Delta\Psi_t + aD\nabla\cdot(\Psi_t\nabla\Psi) = 0 \\ \frac{\partial}{\partial\nu}\Psi|_{\partial\Omega} = 0 \\ \Psi_t(x,0) = P_0(x), \quad \Psi(x,0) = \log W_0(x). \end{cases}$$

For (CH), Levine and Sleeman [16] constructed the solution when $n = 1,\ D = 1$ and $a = 1, -1$. They showed the existence of a collapse solution in the case of $n = 1$ and $a = -1$ and that of blow up solution in the case of $n = 1$ and $a = 1$. Yang, Chen and Liu [22] proved that both time global and blow up in finite time solutions exist dependent on their choice of initial data even if $n = 1$ and $a = 1$. Further they stated that one may obtain a collapse solution to (CH) for $a = -1$ and general spacial dimension in the same line.

In [12]- [15], [23], [24] we studied (TM) for $a < 0$ as follows. We put

$$\Psi(x,t) = \gamma t + u(x,t) \tag{7}$$

in (6) and derive the equation concerning $u = u(x,t)$:

$$Q_1[\gamma t + u(x,t)] = P_1[u] = u_{tt} - D\Delta u_t$$

$$-\nabla\cdot\left[\gamma A e^{-\gamma t-u}\nabla u\right] - \nabla\cdot\left[A e^{-\gamma t-u}u_t\nabla u\right] = 0 \tag{8}$$

where

$$A = A(t,u) = \frac{aD(\alpha-\beta)}{(1+\alpha e^{-\gamma t-u})(1+\beta e^{-\gamma t-u})}. \tag{9}$$

We assume the following assumption on α, β and a:

$$(\boldsymbol{A})_{-}\ \beta - \alpha > 0,\ a < 0,$$

$$(\boldsymbol{A})_{+}\ \beta - \alpha > 0,\ a > 0. \tag{10}$$

(TM) is reduced to

$$(TM)_t\begin{cases} P_1[u] = 0 & \text{in} \quad \Omega\times(0,\infty) \\ \frac{\partial u}{\partial\nu} = 0 & \text{on} \quad \partial\Omega\times(0,\infty) \\ u(x,0) = h_0(x), u_t(0,x) = h_1(x) & \text{in} \quad \Omega \\ \bar{u}_1 = \int_\Omega h_1 dx = 0. \end{cases}$$

Here, the additional assumption $\bar{u}_1 = 0$ leads to $\int_\Omega u_t dx = 0$ by the standard argument(see [12]). By deriving the energy estimate of $(TM)_t$, one can prove the existence of the time global solution of $(TM)_t$. The following results were obtained in [12]-[15], [23], [24].

Theorem 2.1. *Let the initial value (h_0, h_1) be sufficiently smooth, and the condition $(A)_-$ be satisfied. Then, if $\gamma > 0$ is large, we have a unique classical solution $u = u(t,x)$ to $(TM)_t$ and it holds that*

$$\lim_{t\to+\infty} \sup_{\Omega} |u_t| = 0. \tag{11}$$

In the proof of the above theorem the energy estimate plays an important role. The details of the proof is shown in Kubo-Suzuki [12].

From the above theorem, we get the solution (P, W) to [O-SE] with $(A)_-$ by putting

$$P(x,t) = \gamma + u_t(x,t), W(x,t) = e^{\gamma t + u(x,t)}.$$

Then, it follows that from (11) that

$$\lim_{t\to+\infty} \|P(\cdot,t) - \gamma\|_{L^\infty(\Omega)} = 0. \tag{12}$$

On the other hand, we have $P(x,0) = \gamma + h_1(x)$ and it is possible to take $h_1 = h_1(x)$ satisfying $\|P(\cdot,0)\|_{L^\infty} > \gamma$. Thus, we have the following.

Corollary 2.1. *If the same assumption as in Theorem 1.1 is satisfied, there is a collapse in [O-SE]. More precisely, (12) holds and consequently, it holds that*

$\lim_{t\to+\infty} \inf_\Omega W(\cdot,t) = +\infty$.

2.2. [O-SU]$(a > 0)$

In this subsection we deal with [O-SU] under the condition $(A)_+$, that is, (1) for $a > 0$, (2) with $F(W,P) = -PW$,(3) and (4). Putting for $\gamma > 0$

$$\Psi(x,t) = -\gamma t - u(x,t)$$

in (6) and setting

$$-Q_1[-\gamma t - u(x,t)] = P_2[u],$$

then we have

$$P_2[u] = u_{tt} - \nabla\cdot\big[\gamma A e^{-\gamma t-u}\nabla u\big] - \nabla\cdot\big[e^{-\gamma t-u} A u_t \nabla u\big]$$

$$-D\Delta u_t = 0$$

where

$$A = A(t,u) = \frac{aD(\beta-\alpha)}{(\alpha + e^{-\gamma t-u})(\beta + e^{-\gamma t-u})}.$$

Our problem is rewritten by

$$(TMU)_t \begin{cases} P_2[u] = 0 & \text{in} \quad \Omega\times(0,\infty) \\ \frac{\partial}{\partial\nu}u = 0 & \text{on} \quad \partial\Omega\times(0,\infty) \\ u(x,0) = h_0(x), u_t(0,x) = h_1(x). \end{cases}$$

Note that $P_2[u]$ for $(A)_+$ is the same type equation of (8) for $(A)_-$. Therefore, it implies that we can obtain the solution of $(TMU)_t$ for sufficiently large $\gamma > 0$ in the same way as in Theorem 2.1. Thus we obtain the following result.

Theorem 2.2. *Let the initial value (h_0, h_1) be sufficiently smooth and let the condition $(A)_+$ be satisfied. Then, if $\gamma > 0$ is large, there exists a time global smooth solution $u(x,t)$ to the problem $(TMU)_t$ such that (11) holds for $u_t(x,t)$.*

Putting

$$P(x,t) = \gamma + u_t(x,t),$$

$$W(x,t) = e^{-\gamma t - u},$$

it is seen that such $(P(x,t), W(x,t))$ is the solution of [O-SU] under the condition $(A)_+$(cf.[14]).

Corollary 2.2. *Under the same assumption as in Theorem 2.2, there is a collapse in $[O-SU]$. More precisely, (12) holds and consequently, it holds that* $\lim_{t\to+\infty} \sup_\Omega W(\cdot,t) = 0$.

Figure 2, Numerical experiments for simplified Othmer-Stevens model with a linear growth in $S^1 = R/Z$. In [14] N. Saito shows the plots of numerical solutions to $P(x,t)$ for $a = -1, -50$, and $\lambda = |||P_0|||_{L^1(S^1)} = 1, 100$ and $W_0 = 0$. It is observed that there are decaying traveling wavews when the effect of chemotaxis is stronger than that of diffusion.

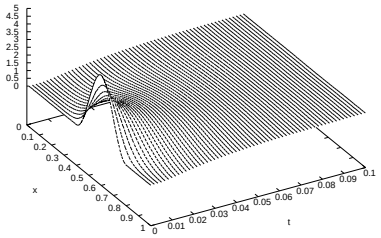
3. Anderson-Chaplain model

3.1. Global existence in time of the solution and asyptotic properties

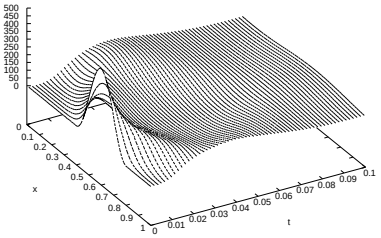
In [1][2], the equation describing EC migration is presented by, $(x,t) \in \Omega\times(0,\infty)$,

$$\frac{\partial n}{\partial t} = D\Delta n - \nabla\cdot(\chi(c)n\nabla c) - \rho_0\nabla\cdot(n\nabla f), \tag{13}$$

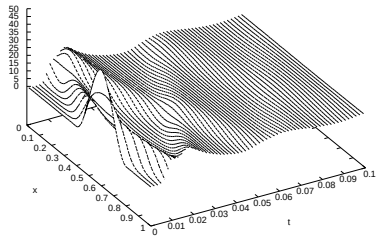
where $n = n(x,t)$ is the EC density, D is the cell random motility coefficient, $\chi(c) = \frac{\chi_0}{1+\alpha c}$ is the chemotactic function with respect to TAFs concentration $c = c(x,t)$, χ_0 and α are positive constants, $f = f(x,t)$



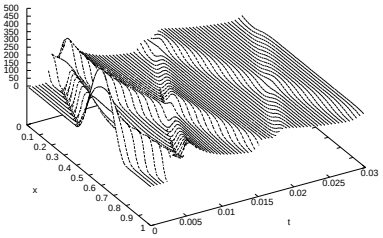
(i) $a = -1.0$, $\lambda = 1.0$, $T = 0.1$



(ii) $a = -1.0$, $\lambda = 100.0$, $T = 0.1$

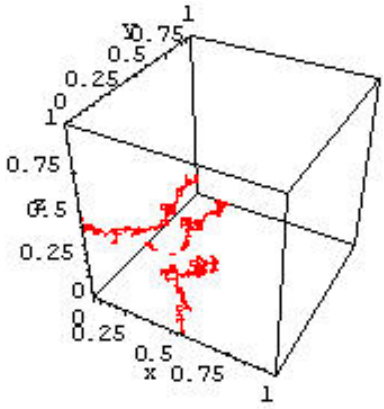


(iii) $a = -50.0$, $\lambda = 10.0$, $T = 0.1$

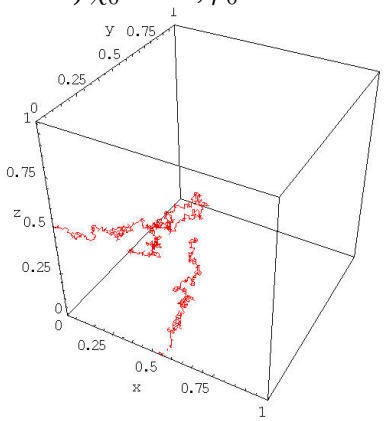


(iv) $a = -50.0$, $\lambda = 100.0$, $T = 0.03$

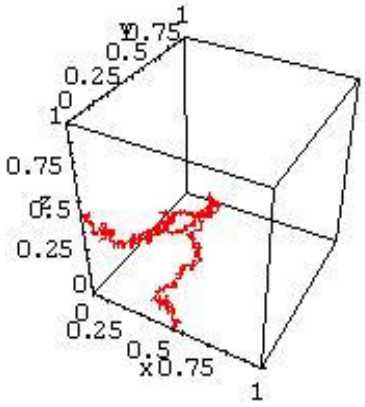
Figure 2. SImulation of simplified Othmer-Stevens model by N. Sito([14])



i) $\chi_0 = 0.4$, $\rho_0 = 0.1$.



ii) $\chi_0 = 0.5$, $\rho_0 = 0.1$.



iii) $\chi_0 = 0.8$, $\rho_0 = 0.1$.

Figure 3. Simulation of Anderson-Chaplain model in 3D by Y.Kida, M.Matsumoto and M.Kondo

is the concentration of an adhesive chemical such as fibronectin, ρ_0 is the (constant) haptotactic coefficient(see [1] [2]), They assume that c and f satisfy the following equations respectively: in $\Omega \times (0, \infty)$

$$\frac{\partial f}{\partial t} = \beta n - \gamma_0 n f, \ \frac{\partial c}{\partial t} = -\eta n c, \qquad (14)$$

where β, γ_0 and η are positive constants. We consider this model in the following form:(AC)

$$\begin{cases} \frac{\partial}{\partial t} n = D\Delta n - \nabla \cdot (\chi(c) n \nabla c) - \rho_0 \nabla \cdot (n \nabla f), \\ \frac{\partial}{\partial t} f = \beta n - \gamma_0 n f, \\ \frac{\partial}{\partial t} c = -\eta n c, \qquad \text{in} \quad \Omega \times (0, \infty) \\ \frac{\partial n}{\partial \nu}|_{\partial\Omega} = \frac{\partial c}{\partial \nu}|_{\partial\Omega} = \frac{\partial f}{\partial \nu}|_{\partial\Omega} = 0 \quad \text{on} \quad \partial\Omega \times (0, \infty) \\ n(x, 0) = n_0(x), \ f(x, 0) = f_0(x), \ c(x, 0) = c_0(x). \end{cases}$$

Sleeman, Anderson and Chaplain [18] constructed a solution of (AC) in case c and f depends on x only in 1 or 2 dimension.

Applying the reduction process used in subsection 2.2, we reduce (13)-(14) to the same type of a single equation P_2 under the condition $(A)_+$ and we can show the existence of the time global smooth solution (n, f, c) of (AC) and that n collapses. That is, Anderson-Chaplain model is essentially regarded as the same type of parabolic ODE system as [O-SU] with $(A)_+$ in this sense.

In fact, by (14) we have

$$\frac{\partial}{\partial t} \log |f - \frac{\beta}{\gamma_0}| = -\gamma_0 n, \ \frac{\partial}{\partial t} \log c = -\eta n.$$

Setting

$$\log c(x, t) = \Psi(x, t) \text{ and } n(x, t) = \eta^{-1} \Psi_t(x, t), \qquad (15)$$

then we have

$$f(x, t) = \beta\gamma_0^{-1} + e^{\eta^{-1}\gamma_0 \Psi(x,t)} (f_0(x) - \beta\gamma_0^{-1}) c_0(x)^{\frac{-\gamma_0}{\eta}}.$$

In terms of $\psi = \psi(x) = c_0(x)^{-\eta^{-1}\gamma_0}(f_0(x) - \beta\gamma_0^{-1})$, (13) and (14) are reduced to the following.

$$Q_2[\Psi] = \Psi_{tt} - D\Delta\Psi_t + \nabla \cdot (\frac{\chi_0 e^{\Psi}}{1 + \alpha e^{\Psi}} \Psi_t \nabla\Psi)$$

$$+\nabla \cdot (\rho_0 \Psi_t e^{\frac{\gamma_0}{\eta}\Psi} \nabla\psi + \nabla \cdot (\rho_0 \eta^{-1} \gamma_0 \Psi_t e^{\frac{\gamma_0}{\eta}\Psi} \psi \nabla\Psi) = 0.$$

If $\psi(x) > 0$, Q_2 with $(A)_+$ can be regarded as the same type equation of Q_1 with $(A)_-$. Therefore we can prove the time global existence of the solution of [A-C] in the same way as in Theorem 2.1. In fact, (AC) is reduced to the problem:

$$(AC)_t \begin{cases} P_3[u] = 0 & \text{in} \quad \Omega \times (0, \infty) \\ \frac{\partial}{\partial \nu} u = 0 & \text{on} \quad \partial\Omega \times (0, \infty) \\ u(x, 0) = h_0(x), u_t(0, x) = h_1(x). \end{cases}$$

where $P_3[u] = -Q_2[-\gamma t - u(x, t)]$. We can obtain the solution of $(AC)_t$ under the condition $(A)_+$ for sufficiently large $\gamma > 0$ in the same way as in Theorems 2.1 and 2.2. That is, for smooth initial data $(h_0(x), h_1(x))$, there exists the time global smooth solution $u(x, t)$ such that it satisfies

$$\lim_{t \to +\infty} \sup_{\Omega} |u_t| = 0.$$

Applying the reduction process used in subsection 2.2, we reduce (13)-(14) to the same type of a single equation as P_2 with $(A)_+$ and we can show the existence of the time global smooth solution (n, f, c) of (AC) and that n collapses.
Then we have the following result.

Theorem 3.1 *Let the initial value $(n_0(x), f_0(x), c_0(x))$ be sufficiently smooth and let $\psi(x) > 0$. There is a classical solution $(n(x, t), f(x, t), c(x, t))$ of (AC) such that*

$$\|n(x, t) - \bar{n}_0\|_{L^\infty(\Omega)} \to 0, \|c(x, t)\|_{L^\infty(\Omega)} \to 0,$$

$$\|f(x, t) - \frac{\beta}{\gamma_0}\|_{L^\infty(\Omega)} \to 0 \quad (t \to +\infty)$$

where $\bar{n}_0$ stands for the spatial average of $n_0(x)$.

Corollary 3. *Under the same assumption as in Theorem 3.1, there is a collapse in (AC).*

3.2. [O-SU] type of expression of [A-C] in the absence of fibronectin

We show a way linking [A-C] and [O-SU] with $(A)_+$ directly in the following. From (14) it follows that

$$\log |f - \beta\gamma_0^{-1}| = \frac{\gamma_0}{\eta} \log c.$$

Putting

$$f = c^{\frac{\gamma_0}{\eta}} + \beta\gamma_0^{-1}$$

and substituting f by the right hand side above in (13), we have

$$\frac{\partial}{\partial t}n = D\mathbf{\Delta}n - \nabla\cdot(\chi(c)n\nabla c) - \rho_0\nabla\cdot(n\nabla(c^{\frac{\gamma_0}{\eta}}))$$

$$= D\mathbf{\Delta}n - \nabla\cdot(n\nabla\{\log(1+\alpha c)^{\frac{\chi_0}{\alpha}}e^{\rho_0 c^{\frac{\gamma_0}{\eta}}}\})$$

$$= D\nabla\cdot(n\nabla\log\frac{n}{\{(1+\alpha c)^{\frac{\chi_0}{\alpha}}e^{\rho_0 c^{\frac{\gamma_0}{\eta}}}\}^{D^{-1}}})$$

Therefore we can say that the sensitivity function of the equation (13) is of the form:

$$(1+\alpha c)^{\frac{\chi_0}{D\alpha}}e^{\rho_0 D^{-1}c^{\frac{\gamma_0}{\eta}}}$$

which is corresponding to $\Phi(W)$ in Othmer-Stevens model. Hence we obtain the following result.

Theorem 3.2 *[A-C] is reduced to the same type of the parabolic ODE system as Othmer and Stevens model:*

$$n_t = D\nabla\cdot(n\nabla\log\frac{n}{(1+\alpha c)^{\frac{\chi_0}{D\alpha}}e^{\rho_0 D^{-1}c^{\frac{\gamma_0}{\eta}}}}),$$

$$c_t = -\eta cn, \qquad \textit{in} \quad \Omega\times(0,\infty)$$

$$n\nabla\log\frac{n}{(1+\alpha c)^{\frac{\chi_0}{D\alpha}}e^{\rho_0 D^{-1}c^{\frac{\gamma_0}{\eta}}}}\cdot\nu = 0, \quad \textit{on} \quad \partial\Omega\times(0,\infty)$$

which are just of the form of (1), (2) and (3) in [O-SU] with (A_+) respectively.

In Othmer-Stevens model the term $\Phi(W)$ is called sesitivity function which governs the motion of the cells in chemotaxis. Theorem 4 implies that in Anderson-Chaplain model the term

$$(1+\alpha c)^{\frac{\chi_0}{D\alpha}}e^{\rho_0 D^{-1}c^{\frac{\gamma_0}{\eta}}}$$

corresponds to the sensitivity function and all the arguments applicable to Othmer and Stevens model for uptake case can be applied to Anderson-Chaplain model too. Hence Theorem 4 is very useful to investigate Anderson-Chaplain model from the stand point of Othmer-Stevens model. In fact, making use of Theorem 4 the following result is obtained.

Figure 3, Reinforced random walk type of numerical simulation of Anderson-Chaplain model. Othmer and Stevens model arises from Reinforced random walk by Davis [6]), and hence Theorem 4 enables us to carry out a numerical computation based on the theory of reinforeced random walk. The numerical result is obtained according to Sleeman and Wallis's way in [20].

In Figures 3, we consider a full three dimensional configuration in which a tumour colony, idealised as a sphere of cells, is embedded in a cuboid domain. We consider the tumour colony taken to be a sphere of radius 0.1 situated at (0.5,0.5,0.5).

Figure 4, Categorical relationship of the models. Since in the above models $P_1[u], P_2[u]$ and $P_3[u]$ are in the same class of partial differential equation, that is, they are degenerate hyperbolic operators with strong dissipation, it seems that the models belong to the same framework of the solvability. Especially, further considering into the asymptotic profile of the solution, it is seen that [A-C] and [O-SU] with $(A)_+$ belong to the same family as the mathematical model.

Figure 5, Formal relationship between the models. We can reduce Othmer-Stevens model with exponential growth to Anderson-Chaplain model through Othmer-Stevens model with uptake and Othmer-Stevens model type of Anderdson-Chaplain model by formal calculations. Also by using it we can represent the solution of one of the models by the solution of other models.

4. Mathematical model of tumour invasion

Anderson and Chaplain [3] describe the process that solid tumour invade the surrounding tissues degradating extracellular matrix(cf. [4]).

$$\frac{\partial n}{\partial t} = d_n\nabla^2 n - \gamma\nabla\cdot(n\nabla f) \tag{16}$$

$$\frac{\partial f}{\partial t} = -\eta m f \tag{17}$$

$$\frac{\partial m}{\partial t} = d_m\nabla^2 m + \alpha n - \beta m \tag{18}$$

where $n := n(x,t)$ is the density of tumour cells, $m := m(x,t)$ MDE(Matrix degradative enzyme) concentration, $f := f(x,t)$ECM (extracelluer matrix) density. It is assumed that the tumour cells produce MDEs which degrade the ECM locally and that the ECM responds by producing endogenous inhibitors. 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 and which aid in tumour cell motility. We have therefore chosen 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.

From (17) it follows that $\frac{\partial}{\partial t}(\log f) = \frac{f_t}{t}$. Then we have by integrating over $(0,t)$

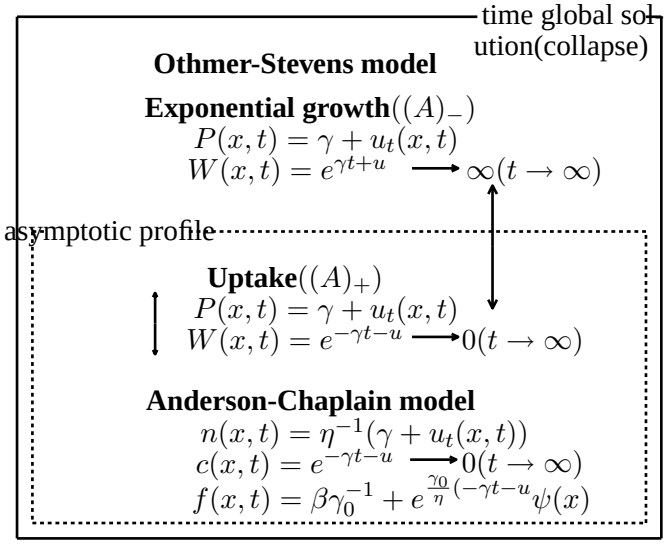


Figure 4. Categorical relationship of the models

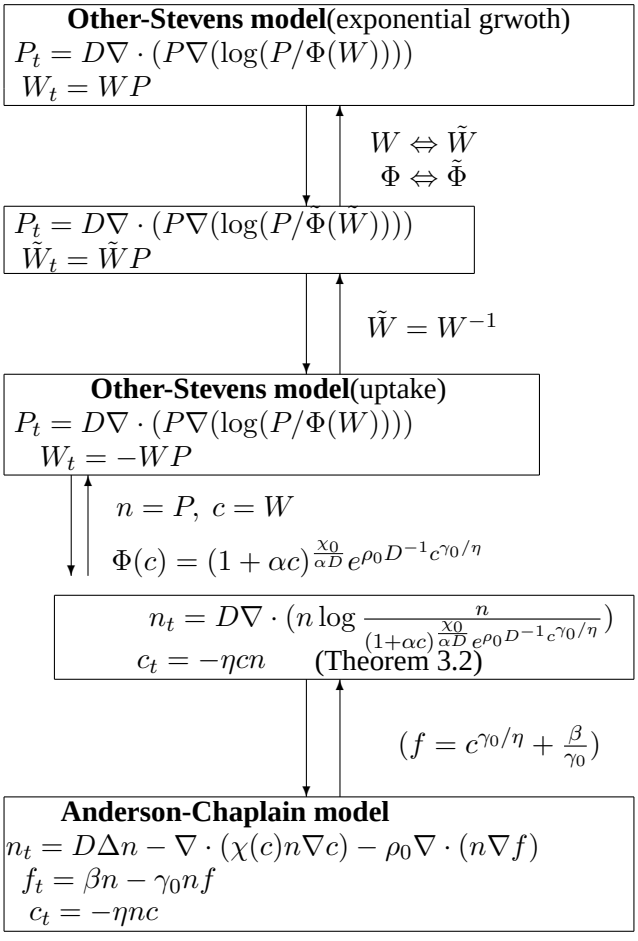


Figure 5. Formal relationship between the models

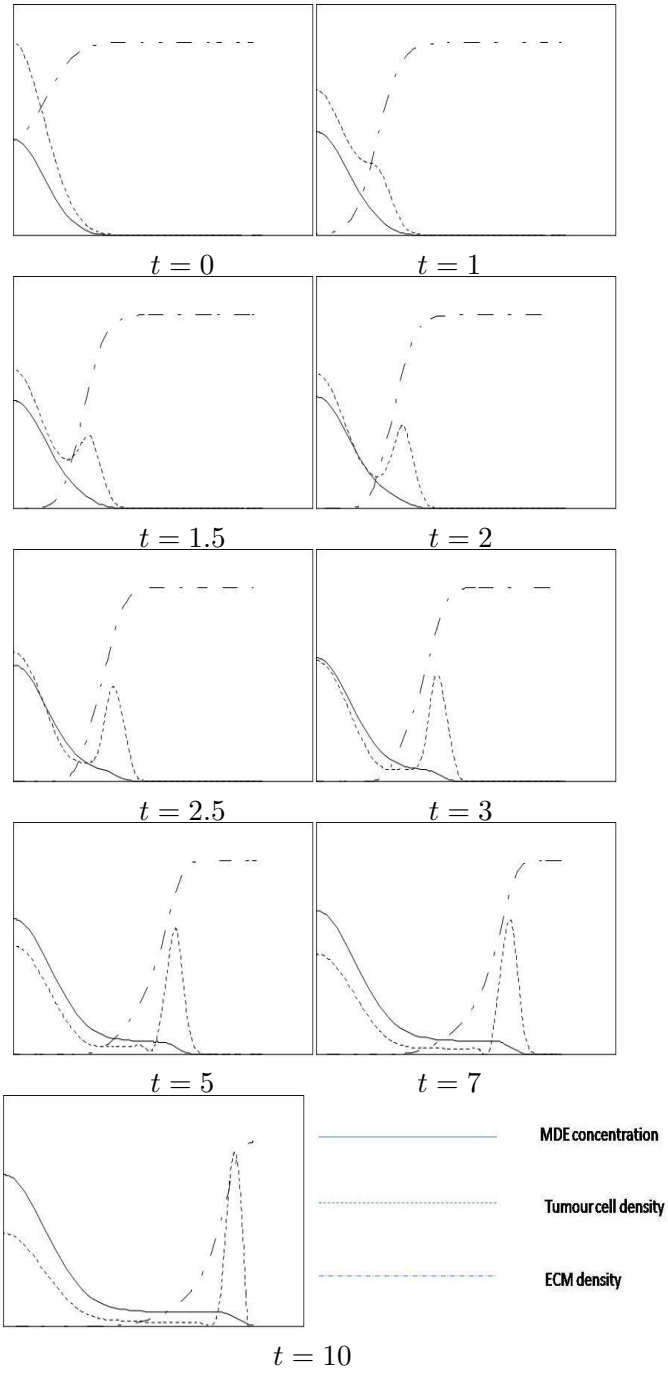


Figure 6. Simulation of Othmer-Stevens model in 1D by M.Matsumoto and M.Kondo

$$f(x,t) = f_0(x)e^{-\eta\int_0^t mds} \tag{19}$$

where $f_0(x)$ is the initial data of $f(x)$. Then (4.1) is rewritten by

$$\frac{\partial}{\partial t}n(x,t) = d_n\mathbf{\Delta}n - \gamma\nabla\cdot n(x,t)(\nabla\cdot e^{-\eta\int_0^t mds}) \tag{20}$$

where we put $f_0(x) \equiv 1$for the simplicity. Putting

$$\Psi(x,t) = \int_0^t n(x,s)ds, \Phi(x,t) = \int_0^t m(x,s)ds \tag{21}$$

The initial flux-zero boundary value problem of (16)-(18) is rewritten by

$$\begin{cases} \frac{\partial^2}{\partial t^2}\Psi(x,t) = d_n\Delta\Psi_t + \eta\gamma\nabla\cdot\Psi_t((\nabla\int_0^t mds)e^{-\eta\Phi}) \\ \frac{\partial^2}{\partial t^2}\Phi = d_m\Delta\Phi_t + \alpha\Psi_t - \beta \\ \Psi(x,0) = 0,\ \Psi_t(x,0) = n_0(x) \\ \Phi(x,0) = 0,\ \Phi_t(x,0) = m_0(x) \\ \frac{\partial}{\partial\nu}\Psi|_{\partial\Omega} = \frac{\partial}{\partial\nu}\Phi|_{\partial\Omega} = 0 \end{cases}$$

where $n_0(x)$ and $m_0(x)$ are initial data of $n(x)$and $m(x)$ respectively. Putting

$$\Psi(x,t) = \gamma_1 t + v(x,t), \Phi(x,t) = \gamma_2 t_T + w(x,t) \tag{22}$$

$$\text{(TMI)}\begin{cases} v_{tt} = d_n\Delta v_t + \eta\gamma\gamma_1\nabla\cdot(e^{-\eta(\gamma_2 t_T+w)}\nabla w) \\ \quad +\eta\gamma\nabla(\nabla w v_t e^{-\eta(\gamma_2 t_T+w)}) \\ w_{tt} = d_m\Delta w_t + \alpha(\gamma_1 + v_t) - \beta(\gamma_2 + w_t) \\ v(x,0) = v_0(x),\ v_t(x,0) = v_1(x) \\ w(x,0) = w_0(x),\ w_t(x,0) = w_1(x) \\ \frac{\partial v}{\partial\nu}|_{\partial\Omega} = \frac{\partial w}{\partial\nu}|_{\partial\Omega} = 0 \end{cases}$$

Then we obtain the following estimates of the first and second equation of (TMI) respectively by applying the energy method used in the previous sections.

$$E_k[v] + \int_0^t ||\nabla v_t||_k^2 dt \leqq CE_k[v](0) + C_T\int_0^t ||w_t||_{k+1}^2 dt, \tag{23}$$

$$||w_t||_k^2 + \int_0^t ||\nabla w_t||_k^2 dt \leqq CE_k[w](0) + C||v_t||_k^2. \tag{24}$$

where $k$is a positive integer and a constant $C_T$tends to zero as a parameter $T > 0$increases. For sufficiently large Twe derive the estimate of the above problem by combining the both sides of (23) and (24) respectively

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

$$\leqq CE_k[w](0) + CE_k[v](0). \tag{25}$$

By using (25) we can show the time global existence and asymptotic behaviour of the solution of the solution of (16)-(18). The following is the main theorem in this paper.

Theorem 4.1. For the initial flux-zero boundary value problem (16)-(18) satisfying flux-zero boundary condition and initial data $(n_0(x), f_0(x), m_0(x))$, there is a classical solution $(n(x,t), f(x,t), m(x,t))$assumed that initial data are sufficiently smooth.

Figure 6, Simulation of tissue invasion models in 1D. In the biginning we assume that tumour cells exist only near the origin. As t increases, Fig 6 shows that tumour cells are propagating as a traveling wave while MDE is degradating neighbouring ECM. The same type of numerical experiment has been shown by Anderson and Chaplain in [3].

5 Conclusion

It is shown that we can discuss the argument of the solvability of models arised in tumour angiogenesis in a same framework. Further we can apply such argument to mathematical understanding of tumour invasion proposed by Anderson and Chaplain. It is concluded that we can deal with tumour growth models, mathematical models of angiogenesis by Othmer-Stevens and Anderson-Chaplain and tumour invasion by Anderson-Chaplain, consistently by a reduction process to the same type of nonlinear evolution equtions. Also numerical experiments in this paper are allowed to verify by our mathematical analysis.

Acknowledgement: The research was partially supported by the Grant-in-Aide for Scientific Research (C) 16540176, 19540200 from Japan Society for the Promotion of Science. The author would like to express his gratitude to O. Umeda, Y. Kida, H. Katayama, M. Matsumoto, M. Kondo, K. Horiuchi and F. Nakanishi for their cooperation in numerical experiments and also to K. Ozaki, K. Bito and K. Kimura for their cooperation in mathematical analysis.

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