Characterization of Mathematical Models of Tumour Angiogenesis

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Abstract: We deal with well known two kinds of mathematical models of tumour angiogenesis. We first study the solvability and the asymptotic profile of the solution to a parabolic ODE system proposed by Othmer and Stevens. Next we deal with the model of tumour induced angiogenesis by Anderson and Chaplain in the same line. Finally we discuss how the models link to each other and provide some frameworks of the solvability and the asymptotic profile of the solution to them for which our method is applicable.

Key–Words: Tumour angiogenesis, Othmer and Stevens model, Exponential growth, Uptake, Anderson and Chapalin model, Collapse, Solvability, Asmptotic profile .

1 Introduction

We begin with a brief explanation about tumour angiogensis.
1.Tumour produces TAFs(some chemicals) as a trigger of tumour angiogenesis. They diffuse and reach neighboring capillaries and other blood vessels.
2. In response to TAFs EC(endothelial cells) surface begins to develop pseudopodia which penetrate the weakened basement membrane.
3. Capillary sprouts continue to grow in length out of the parent vessels and form loops leading to micro circulation of blood.
4. The resulting capillary network continues to progress and eventually invades the tumour colony.

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

In [8] Othmer and Stevens derived a parabolic ODE system formulating the reinforced random walk model(cf.Davis[3]), 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,

$$P_t = D\nabla\cdot[P\nabla(\log(P/\Phi(W)))], \quad (1.1)$$

$$W_t = F(W,P), \qquad \text{in} \quad \Omega\times(0,\infty) \quad (1.2)$$

$$P\nabla(\log(P/\Phi(W)))\cdot\nu = 0, \quad \text{on } \partial\Omega\times(0,T) \quad (1.3)$$

(no-flux condition)

$$P(x,0) = P_0(x) \geq 0,\ W(x,0) = W_0(x) \geq 0, \quad (1.4)$$

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, [8] provides the reinforced random walk on lattice points as in Davis [3], takes the renormalized limit and gets the above system. By the numerical computation [8] classified the solution according to its behaviour as $t \to +\infty$:

1.(aggregation) $\|P(\cdot,t)\|_{L^\infty} < C$ for all t, $\liminf_{t\to\infty}\|P(\cdot,t)\|_{L^\infty} > \|P(\cdot,0)\|_{L^\infty}$.
2.(blowup)$\|P(\cdot,t)\|_{L^\infty}$ becomes unbounded in finite time.
3.(collapse)$\limsup_{t\to\infty}\|P(\cdot,t)\|_{L^\infty} < \|P(\cdot,0)\|_{L^\infty}$.

Levine and Sleeman[7] apply it to the understanding of tumour angiogenesis where P is the density of EC, W is TAFs concentration and the sensitivity function $\Phi(W)$ is of the form:

$$\Phi(W) = (\frac{W+\alpha}{W+\beta})^a, \quad (1.5)$$

where α, $\beta > 0$ and a is a constant. In this paper, we first review (1.1)-(1.4), so called, Othmer-Stevens model(cf.[4]-[6]). We deal with the existence of time global solution to (1.1)-(1.4) with (1.5) for $a > 0$ and $F(P,W) = WP$(exponential growth), hereafter referred to as [O-SE]. We introduce the problem (1.1)-(1.4) with (1.5) for $a > 0$ and $F(P,W) = -WP$(uptake) , which is written by [O-SU] simply hereafter.

In the same line, we show the existence of time global solution to a parabolic ODEs system modeling tumour angiogenesis by Anderson and Chaplain[1][2], which is called Anderson-Chaplain model and is sometimes denoted by [A-C] hereafter. [A-C] has been provided based on physiological and morphological observations and experiments independently of Othmer-Stevens model.We finally discuss a connection between these models and find a generic framework of the solvability and the asymptotic profile of the solution to them.

2 Othmer-Stevens model

2.1. Exponential growth case for $a < 0$

In this subsection we consider the problem (1.1)-(1.4) for $a < 0$ and $F(W,P) = WP$, that is, [O-SE]. Mathematical analysis of this model was done by Levine and Sleeman [7]. In fact, taking $\log W = \Psi$, we get $\Psi_t = P$ because of $W_t/W = P$ and it holds

$$Q_1[\Psi] = \Psi_{tt} - D\Delta\Psi_t + \nabla\cdot\left(\frac{aD(\beta-\alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)}\Psi_t\nabla\Psi\right) = 0, \qquad \text{in} \quad \Omega\times(0,T) \tag{2.1}$$

from (1.1) and (1.2). 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 [7], Levine and Sleeman replaced the coefficient by a constant,

$$\frac{a(\beta-\alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)} = \frac{a(\beta-\alpha)W}{(W+\alpha)(W+\beta)} = constant \tag{2.2}$$

under the agreement that $\alpha \ll W \ll \beta$ or $\beta \ll W \ll \alpha$. Their argument is verified in [7] if W is bounded for any $t > 0$. However, there is a case that $W = e^{\Psi}$ obtained in [7] is unbounded, where this simplification is not valid. Hence in this paper we do not consider the simplified case but the argument discussed in this section holds in 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:

$$(CH)\begin{cases} \Psi_{tt} - D\Delta\Psi_t + aD\nabla\cdot(\Psi_t\nabla\Psi) = 0 & (2.3) \\ \frac{\partial}{\partial\nu}\Psi|_{\partial\Omega} = 0 \\ \Psi_t(x,0) = P_0(x), \quad \Psi(x,0) = \log W_0(x) \end{cases}$$

For (CH), Levine and Sleeman [7] 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 [10] 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 [4]-[6], we studied (TM) for $a < 0$. We put $\Psi(x,t) = \gamma t + u(x,t)$ in (2.1) and derive the equation concerning $u = u(x,t)$:

$$Q_1[\gamma t + u(x,t)] = P_1[u] = u_{tt} - D\Delta u_t - \nabla\cdot\left[\gamma A(t,u)e^{-\gamma t-u}\nabla u\right] - \nabla\cdot\left[A(t,u)e^{-\gamma t-u}u_t\nabla u\right] = 0 \tag{2.4}$$

where

$$A = A(t,u) = \frac{aD(\alpha-\beta)}{(1+\alpha e^{-\gamma t-u})(1+\beta e^{-\gamma t-u})}. \tag{2.5}$$

If $\beta > \alpha$, $a < 0$, the second order terms of (2.4) is a hyperbolic operator, that is, (2.4) is hyperbolic with the strong dissipation. In this paper we deal with only parabolic ODE system of which can be reduced to this type of the equation.
Hence we assume the following assumption:

$$\boldsymbol{(A)}_{-}\ \beta-\alpha > 0,\ a < 0 \ \left(\boldsymbol{(A)}_{+}\ \beta-\alpha > 0,\ a > 0\right) \tag{2.6}$$

(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 Kubo and Suzuki[4]).

Theorem 2.1.([6;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*

$$\lim_{t\to+\infty}\ \sup_\Omega |u_t| = 0. \tag{2.7}$$

From the above theorem, we get the solution (P, W) to [O-SE] by putting $P(x,t) = \gamma + u_t(x,t)$ and $W(x,t) = e^{\gamma t + u(x,t)}$. Then, it follows that from (2.7) that

$$\lim_{t\to+\infty} \|P(\cdot,t) - \gamma\|_{L^\infty(\Omega)} = 0. \qquad (2.8)$$

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.([6;Corollary 2.1]). *If the same assumption as in Theorem 1.1 is satisfied, there is a collapse in [O-SE]. More precisely,* (2.7) *holds and consequently, it holds that*

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

2.2. Uptake case for $a > 0$

In this subsection we deal with [O-SU] for $(A)_+$, that is, (1.1) for $a > 0$, (1.2) for $F(W,P) = -PW$,(1.3),(1.4). Putting $\Psi(x,t) = -\gamma t - u(x,t)$ for $\gamma > 0$, (2.1) is reduced to the following:

$$-Q_1[-\gamma t - u(x,t)] = P_2[u] = u_{tt} - \nabla\cdot\left[\gamma A e^{-\gamma t - u}\nabla u\right]$$

$$-\nabla\cdot\left[e^{-\gamma t-u} A u_t \nabla u\right] - D\Delta u_t = 0 \qquad (2.9)$$

where $A = A(t,u) = \frac{aD(\beta-\alpha)}{(\alpha+e^{-\gamma t-u})(\beta+e^{-\gamma t-u})}$. Our problem is rewritten by

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

Under $(A)_+$ $P_2[u]$ is the same type equation of (2.4) for $(A)_-$, that is, it implies that we can obtain the solution of $(TMU)_t$ in the case of $(A)_+$ for sufficiently large $\gamma > 0$ in the same way as in Theorem 2.1. In fact, for smooth initial data $(h_0(x), h_1(x))$, there exists the smooth solution $u(x,t)$ such that it satisfies

$$\lim_{t\to\infty} u_t(x,t) = 0. \qquad (2.10)$$

Putting $P(x,t) = \gamma + u_t(x,t)$, $W(x,t) = e^{-\gamma t - u}$, it is seen that $(P(x,t), W(x,t))$ is the solution of [O-SU] with $(A)_+$(cf.[6]).

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* $(TMU)_t$.

Taking account of (2.10), we have the following asymptotic property of the solution.

Corollary 2.2. *Under the same assumption as in Theorem 2.2, there is a collapse in* $[O-SU]$.

(Remark) the relationship between exponential growth and uptake. In [O-SE] with $(A)_-$, we have $W(x,t) = e^{\gamma t+u(x,t)}$ and in [O-SU] with $(A)_+$, we have $W(x,t) = e^{-\gamma t - u(x,t)}$. Hence in [O-SU] with $(A)_+$(1.1) and (1.2) can be reduced to the following for $\tilde{W}(x,t) = W^{-1}(x,t)$ and $\tilde{\Phi}(W) = \left(\frac{\beta W+1}{\alpha W+1}\right)^a$, $a > 0$:

$$P_t = D\Delta P - D\nabla\cdot(P\nabla \log\tilde{\Phi}(\tilde{W})), \;\; \tilde{W}_t = \tilde{W}P,$$

which is of the form of [O-SE].

3 Anderson-Chaplain model

In this section we deal with a parabolic ODEs system modeling tumour induced angiogenesis provided by Anderson and Chaplain [1][2]. The equation describing EC(endothelial cells) migration is presented by,

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

$$\text{in} \quad \Omega\times(0,\infty) \qquad (3.1)$$

where $n = n(x,t)$ is the EC density, which is corresponding to $P(x,t)$ in Othmer-Stevens model, D is the cell random motility coefficient, $\chi(c)$ is the chemotactic function with respect to TAF(tumour angiogenesis factors) concentration $c = c(x,t)$, which is corresponding to $W(x,t)$ in Othmer-Stevens model, $f = f(x,t)$ is the concentration of an adhesive chemical such as fibronectin, ρ_0 is the (constant) haptotactic coefficient(see [1],[2]). It is assumed that $\chi(c)$ takes the form

$$\chi(c) = \frac{\chi_0}{1+\alpha c},$$

where χ_0 represents the maximum chemotactic response and α is a measure of the severity of desensitisation of EC receptors to TAF. They assume that c and f satisfy the following equations respectively:

$$\frac{\partial f}{\partial t} = \beta n - \gamma_0 n f, \qquad \text{in} \quad \Omega\times(0,\infty) \qquad (3.2)$$

$$\frac{\partial c}{\partial t} = -\eta n c, \qquad \text{in} \quad \Omega\times(0,\infty) \qquad (3.3)$$

where β, γ_0 and η are positive constants. The equations are normally posed in a bounded domain Ω with no-flux boundary conditions on $\partial\Omega$. In this section we consider this model in the following form:(AC)

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

Sleeman, Anderson and Chaplain [9] constructed a solution of (AC) in case c and f depend on x only in 1 or 2 dimension. In this section we find how the models link to each other in the continuous form. Improving the reduction process used in section 2, we reduce (3.1)-(3.3) to the same type of a single equation as (2.9) for $(A)_+$. That is, Anderson-Chaplain model is essentially regarded as the same type of parabolic ODE system as [O-SU] for $(A)_+$ in this sense. According to the way used in subsection 2.2, we can show the existence of the time global smooth solution (n,f,c) of (AC), of which n collapses. In fact, by (3.2) and (3.3) we have

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

In subsection 2.2 the procedure from (2.1) to $(TMU)_t$ play the most important role to obtain the solution of [O-SU] for $(A)_+$. Since (2.1) is derived in exponential growth case, in order to deal with (3.1)-(3.3) in the same procedure, instead of (3.2)-(3.3) it should start with the following:

$$\frac{\partial}{\partial t}\log|f-\beta\gamma_0^{-1}| = \gamma_0 n, \qquad \frac{\partial}{\partial t}\log c = \eta n. \quad (3.4)$$

Setting $\log c(x,t) = \Psi(x,t)$, $n(x,t) = \eta^{-1}\Psi_t(x,t)$, 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 $\psi = \psi(x) = c_0(x)^{-\eta^{-1}\gamma_0}(f_0(x) - \beta\gamma_0^{-1})$, (3.1) and (3.4) are reduced to the following.

$$Q_2[\Psi] = \Psi_{tt} - D\Delta\Psi_t + \nabla\cdot(\frac{\chi_0 e^{\Psi}}{1+\alpha e^{\Psi}}\Psi_t\nabla\Psi)$$
$$+\nabla\cdot(\rho_0\Psi_t e^{\frac{\gamma_0}{\eta}\Psi}\nabla\psi + \nabla\cdot(\rho_0\eta^{-1}\gamma_0\Psi_t e^{\frac{\gamma_0}{\eta}\Psi}\psi\nabla\Psi)$$
$$= 0. \qquad (3.5)$$

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(cf.[6]).

$$(AC)_t \begin{cases} -Q_2[-\gamma t - u(x,t)] = P_3[u] = 0 \\ \qquad\qquad \text{in} \quad \Omega\times(0,\infty) \\ \frac{\partial}{\partial\nu}u = 0 \qquad \text{on} \quad \partial\Omega\times(0,\infty) \\ u(x,0) = h_0(x), u_t(0,x) = h_1(x). \end{cases}$$

In fact, we can obtain the solution of $(AC)_t$ in the case of $(A)_+$ for sufficiently large $\gamma > 0$ in the same way as in Theorems 2.1 and 2.2. In fact, for smooth initial data $(h_0(x), h_1(x))$, there exists the smooth solution $u(x,t)$ such that it satisfies

$$\lim_{t\to\infty} u_t(x,t) = 0.$$

Theorem 3. *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*

$$n(x,t) = \eta^{-1}(\gamma + u_t(x,t)),\ c(x,t) = e^{-\gamma t - u(x,t)}$$

$$f(x,t) = \beta\gamma_0^{-1} + e^{\frac{\gamma_0}{\eta}(-\gamma t - u(x,t))}\psi(x)$$

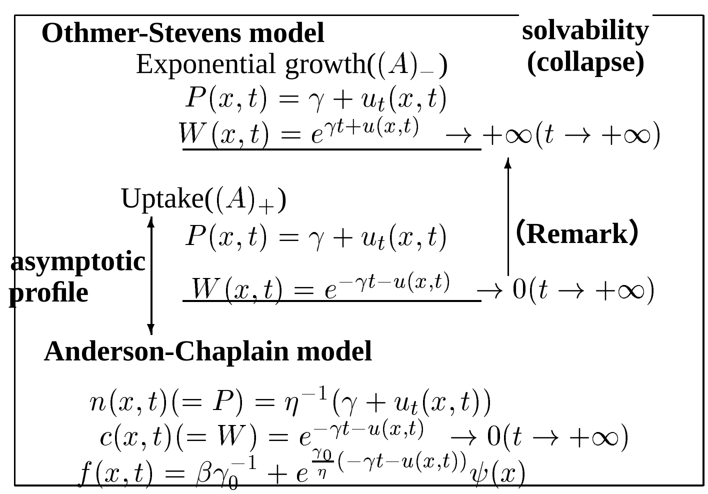
and that it holds

$$\|n(x,t) - \bar{n}_0\|_{L^\infty(\Omega)} \to 0,\ \|c(x,t)\|_{L^\infty(\Omega)} \to 0,$$
$$\|f(x,t) - \frac{\beta}{\gamma_0}\|_{L^\infty(\Omega)} \to 0 \quad (t\to+\infty)$$

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).*

4 Conclusion



Since in above models $P_1[u], P_2[u]$ and $P_3[u]$ are in the same class of partial differential equation, 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. In fact, the approachs used for obtaining the solution of [A-C] and [O-SU] are quite same as shown in subsection 2.2 and section 3.

Finally, we show the way of linking [A-C] and [O-SU] explicitely in the following. From (3.4) it follows that

$$\log |f - \beta\gamma_0^{-1}| = \frac{\gamma_0}{\eta} \log c. \tag{4.1}$$

Putting

$$f = c^{\frac{\gamma_0}{\eta}} + \beta\gamma_0^{-1} \tag{4.2}$$

and substituting f by (4.2) in (3.1), we have

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

$$= D\nabla \cdot (n \nabla \log \frac{n}{\{(1+\alpha c)^{\frac{\chi_0}{\alpha}} e^{\rho_0 c^{\frac{\gamma_0}{\eta}}}\}^{D^{-1}}}) \tag{4.3}$$

Therefore it is seen that the transition rate of the master equation (3.1) is of the form:

$$\{(1+\alpha c)^{\frac{\chi_0}{\alpha}} e^{\rho_0 c^{\frac{\gamma_0}{\eta}}}\}^{D^{-1}} \tag{4.4}$$

which is corresponding to $\Phi(W)$ in Othmer-Stevens model. The following result implies that (A-C) and [O-SU] with $(A)_+$ are essentially the same type of the parabolic ODE system.

Theorem 4. *[A-C] is reduced to the same type of the parabolic ODE system as Othmer and Stevens model:*

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

$$c_t = -\eta c n,$$

which are of the form of (1.1) and (1.2) in [O-SU] with (A_+) *respectively.*

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