Mathematical Analysis of a chemotaxis type of model and applications to Biomedicine

Będlewo, 12-17 Sep, 2010

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Outline

- Analysis of Mathematical models of tumour angiogenesis

  - Othmer-Stevens (1997)
    Parabolic ODE

  - Anderson-Chaplain(1998)
    Parabolic ODEs system

  Existence, Asymptotic behavior of the solution
  Mathematical structure

Top down Model

Othmer and Stevens

(Mathematical Analysis)

Bottom up model

Anderson and Chaplain

Parabolic ODE system
(Othmer and Stevens)

$$P_t = D\nabla \cdot [P\nabla \log(\frac{P}{\Phi(W)})], \quad \text{in} \quad \Omega \times (0,\infty) \tag{1.1}$$

$$= D\Delta P - D\nabla \cdot [\frac{\Phi'(W)}{\Phi(W)}\nabla W],$$

$$W_t = F(P,W) \tag{1.2}$$

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

No-flux condition

$$P(x,0) = P_0(x) \geq 0, \quad W(x,0) = W_0(x) > 0 \tag{1.4}$$

Initial data

- $P(x,t)$: the density of particle

  $W(x,t)$: control spices

- ν is the outer unit normal vector.

- Ω is a bounded domain in R^n with a smooth boundary $\partial\Omega$.

- $\Phi(W) = (\frac{W+\alpha}{W+\beta})^a, \quad D > 0, \alpha, \beta \geq 0.$

⇨ Tumour angiogenesis by Levine and Sleeman

$$W_t = F(P, W)$$

$$W_t = \lambda P \text{ (linear growth)}$$

$$W_t = \lambda PW \text{ (exponential growth)}$$

$$F(P, W) = -\lambda PW(\underline{uptake})$$

Reduction process (Levine and Sleeman)

i) Put $\log W = \Psi (\Leftrightarrow \Psi_t = P)$, $(1.1)(1.2)(EG) \Rightarrow$

$$\Psi_{tt} = D\Delta\Psi_t - \nabla\cdot(\frac{aD(\beta-\alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)}\Psi_t\nabla\Psi) \qquad (1.5)$$

ii) Put $\Psi = \gamma t + u(x,t)$ for $\gamma > 0$,

$$Q[u] = u_{tt} - \nabla\cdot(\gamma A e^{-\gamma t - v}\nabla u) - D\Delta u_t$$
$$-\nabla\cdot(A e^{-\gamma t - v} u_t \nabla v) = 0, \qquad (1.6)$$
$$where\ A := A(t,u) = \frac{-aD(\beta-\alpha)}{(1+\alpha e^{-\gamma t}e^{-u})(1+\beta e^{-\gamma t}e^{-u})}$$

Explicite solution for a simplified equation, 1 space dimension

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

$\mathrm{Q[u]}$: Hyperbolic

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

$\mathrm{Q[u]}$: Elliptic

Exponential growth ((A)_, K-S[4-6])

- sufficiently large γ

$$\begin{cases} P_t = D\Delta P - \nabla \cdot (P\nabla \log(P/\Phi(W))), (A)_- \\ W_t = W P \qquad\qquad in \quad \Omega \times (0,\infty) \end{cases}$$

$$\Psi_{tt} + \nabla \cdot (\frac{aD(\beta-\alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)}\Psi_t \nabla \Psi) = D\Delta\Psi_t, \qquad \Psi = \gamma t + u(x,t)$$

- $P(x,t) = \gamma + u_t(x,t),\ W(x,t) = e^{\gamma t + u(x,t)}$
- Classical, Collapse, n－demension

Up take $((A)_+)$

- sufficiently large γ

$$\begin{cases} P_t = D\Delta P - \nabla \cdot (P \nabla \log(P/\Phi(W))), \ (A)_+ \\ W_t = -WP(up\ take) \quad in \quad \Omega \times (0,\infty) \end{cases}$$

$$\Psi_{tt} + \nabla \cdot \left(\frac{aD(\beta-\alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)} \Psi_t \nabla \Psi\right) = D\Delta \Psi_t, \quad \Psi = -\gamma t - u(x,t)$$

- $P(x,t) = \gamma + u_t(x,t)$ and $W(x,t) = e^{-\gamma t - u(x,t)}$
- Classical, Collapse, n－dimension

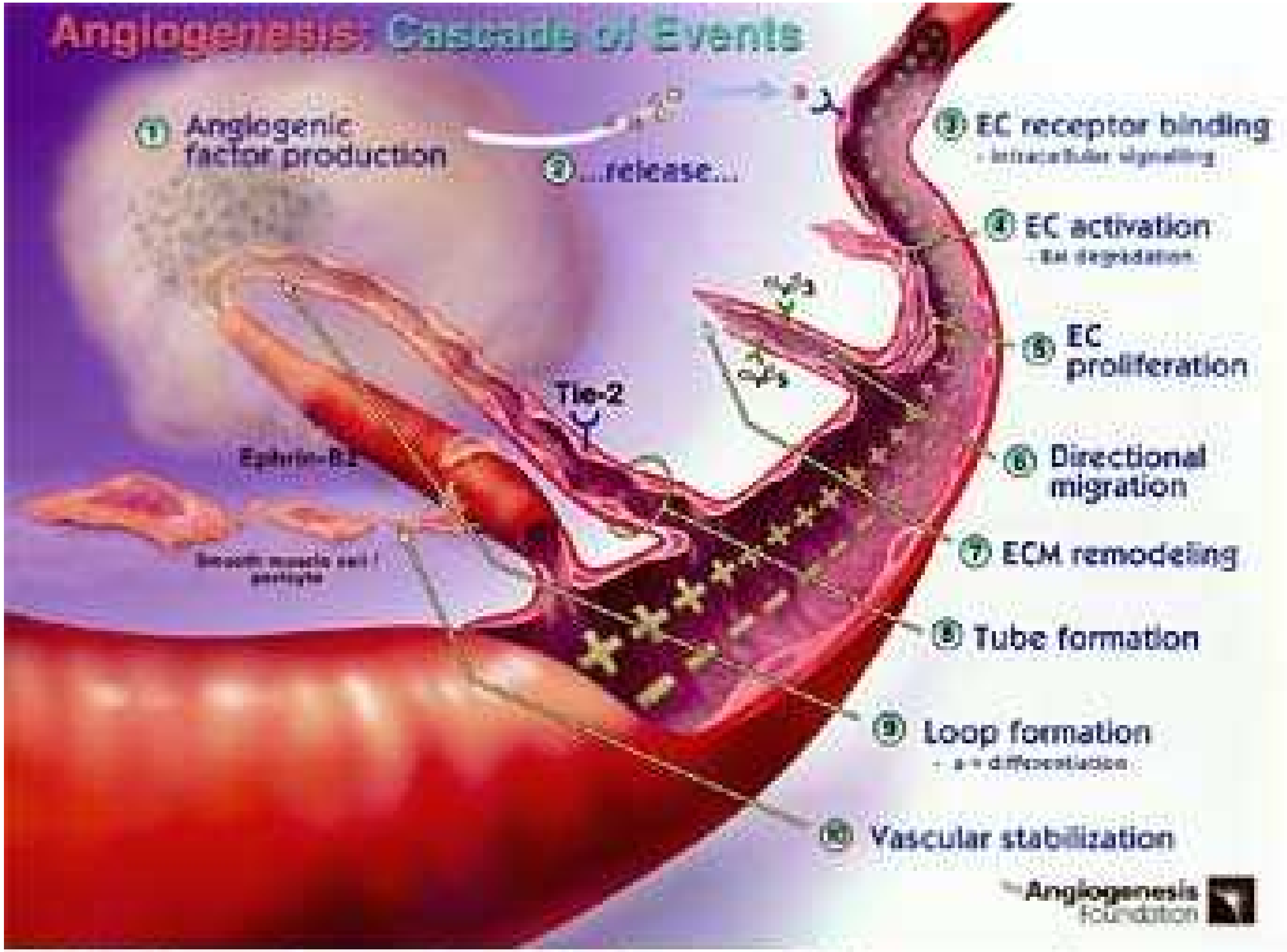
Anderson and Chaplain Model
of tumour induced angiogenesis

$$
(AC)\begin{cases}
\dfrac{\partial n}{\partial t} = D\nabla^2 n - \nabla\cdot\left(\dfrac{\chi}{1+\sigma c} n\nabla c\right) - \nabla\cdot(\rho_0 n\nabla f) \\[2ex]
\dfrac{\partial f}{\partial t} = \beta n - \gamma_0 nf \\[2ex]
\dfrac{\partial c}{\partial t} = -\eta nc \qquad \text{in} \qquad \Omega\times(0,\infty) \\[2ex]
n(x,0) = n_0(x) \quad f(x,0) = f_0(x) \quad c(x,0) = c_0(x) \\[2ex]
\left.\dfrac{\partial n(x,t)}{\partial \nu}\right|_{\partial\Omega} = \left.\dfrac{\partial f(x,t)}{\partial \nu}\right|_{\partial\Omega} = \left.\dfrac{\partial c(x,t)}{\partial \nu}\right|_{\partial\Omega} = 0
\end{cases}
$$

$n(x,t)$: endothelial-cell density

$f(x,t)$: the fibronectin concentration

$c\ (x,t)$: TAF concentration


Angiogenesis: Cascade of Events
1 Angiogenic factor production
2 ...release...
3 EC receptor binding
4 EC activation
5 EC proliferation
6 Directional migration
7 ECM remodeling
8 Tube formation
9 Loop formation
10 Vascular stabilization
Tie-2
Ephrin-B2
The Angiogenesis Foundation

Our approach

- Anderson- Chaplain model

$$\Psi_{tt} + \nabla \cdot (\frac{\chi e^{\Psi}}{1+\sigma e^{\Psi}} \Psi_t \nabla \Psi) + \nabla \cdot (\frac{\rho\tau}{\eta} e^{(\frac{\tau}{\eta}\Psi)} \Psi_t \nabla \Psi) - D \Delta \Psi_t = 0$$

$$c(\Leftrightarrow W) = e^{\Psi} = e^{-\gamma t - u}$$

$$n(\Leftrightarrow P) = \frac{1}{\eta}(\gamma + u_t)$$

$$c(x,t) = e^{\Psi},$$

$$f(x,t) = \kappa\tau^{-1} + \tau^{-1} e^{(\frac{\tau}{\eta}\Psi)},$$

$$n(x,t) = \frac{-1}{\eta}\Psi_t$$

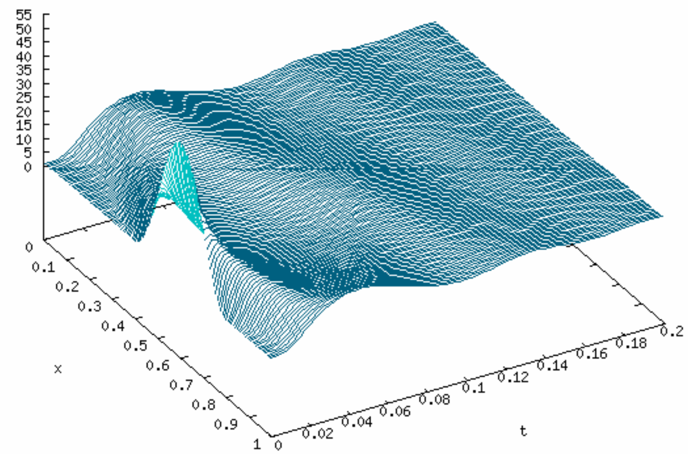
- Othmer-Stevens model

$$F(P,W) = -\lambda PW (\underline{uptake})$$

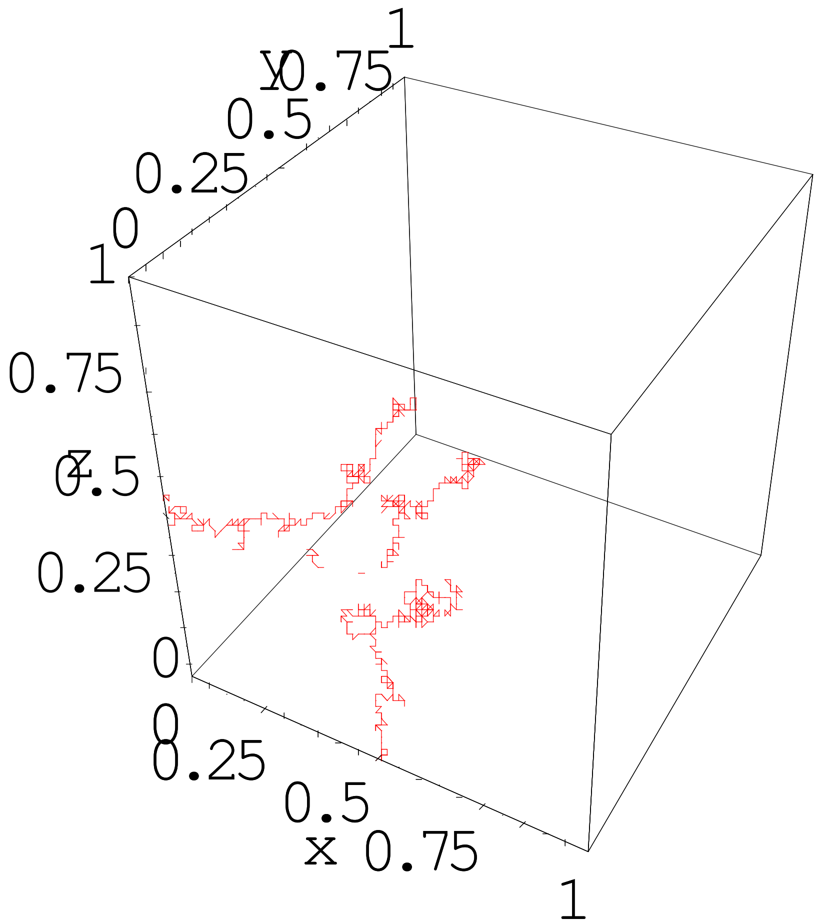
$$\Psi_{tt} + \nabla \cdot (\frac{aD(\beta - \alpha)e^{\Psi}}{(e^{\Psi}+\alpha)(e^{\Psi}+\beta)} \Psi_t \nabla \Psi) - D \Delta \Psi_t = 0$$

$$W = e^{\Psi} = e^{-\gamma t - u}$$

$$P = -\frac{W_t}{W} = \gamma + u_t$$



Othmer and Stevens model(uptake)



y
0
0.25
0.5
0.75
1
z
0
0.25
0.5
0.75
1
x
0
0.25
0.5
0.75
1

Mathematical Analysis

$$\begin{cases} u_{tt} = D\nabla^2 u_t + \nabla \cdot (\chi(u_t, e^{-u}) e^{-u} \nabla u) \\ \dfrac{\partial}{\partial \nu} u \,\big|_{\partial\Omega} = 0 \\ u(x,0) = u_0(x), \quad u_t(x,0) = u_1(x) \end{cases}$$

$$u(x,t) = a + bt + v(x,t)$$

$(u(x,t) = 0 + \gamma t + v(x,t))$:the previous result

$$\begin{cases} Q[v] = v_{tt} - D\nabla^2 v_t + \nabla \cdot (\chi_{a,b}(v) e^{-a-bt-v} \nabla v) = 0 \\ \dfrac{\partial}{\partial \nu} v \,|_{\partial\Omega} = 0 \\ v(x,0) = v_0(x), \quad v_t(x,0) = v_1(x) \end{cases}$$

$$\chi_{a,b} = \chi(v_t + b,\ e^{-a-bt-v})$$

$$0 < v_t + b = u_t$$

$$(A) \qquad 0 < \chi(v_t + b,\ e^{-a-bt-v}) \in C^m(R \times R_+),$$

(a) $$\| v_t \|^2 (t) + \int_0^t 2D \| \nabla v_\tau \|^2 d\tau + \left\| \sqrt{\chi_{a,b}(v) e^{-a-bt-v}} \nabla v \right\|^2 (t)$$

$$+ \int_0^t ((b - \delta_r)\chi_{a,b}(v) e^{-a-b\tau-v} \nabla v, \nabla v) d\tau$$

$$\leq CE[v](0) + (b + C_r) e^{-a} \sup_t \|\nabla v\|^2 (t).$$

(b) $$D \|\nabla v\|^2 (t) + \int_0^t 2 \left\| \sqrt{\chi_{a,b}(w)} \nabla v \right\|^2 d\tau \leq$$

$$C(\int_0^t \|v_\tau\|^2 d\tau + \kappa^{-1} \|v_t\|^2 + E[v](0)).$$

$$\mathrm{E_k[u]} = \sum_{|\alpha| \leq \mathrm{k}} \left\| \partial^\alpha \mathrm{u_t} \right\|^2 + \left\| \partial^\alpha \nabla \mathrm{u} \right\|^2$$

(a)+(b)

$$\int_0^t \left\|\sqrt{\chi_{a,b}(w)}\nabla v\right\|^2 d\tau + \int_0^t \|\nabla v_\tau\|^2 d\tau + E[v](t) \le CE[v](0).$$

$$\mathrm{E_k[u]} = \sum_{|\alpha| \le \mathrm{k}} \left\|\partial^\alpha \mathrm{u_t}\right\|^2 + \left\|\partial^\alpha \nabla \mathrm{u}\right\|^2$$

$$\sum_{j=1}^{k+1}(||\nabla^{j-1}v_t||^2(t) + \int_0^t 2D\,||\nabla^j v_\tau||^2 d\tau + \left\|\sqrt{\chi_{a,b}(v)e^{-a-bt-v}}\nabla^j v\right\|^2(t)$$

$$+\int_0^t ((b-\delta_r)\chi_{a,b}(v)e^{-a-b\tau-v}\nabla^j v, \nabla^j v)d\tau) \le CE_{k-1}[v](0)$$

$w_i = u_{i+1} - u_i.$

$$E_{i,M}[w_i](t) + D\int_0^t |\nabla w_{it}|_M^2 \, dt$$

$$\leq C_{M,a} E_{i,M}[w_{i-1}] \leq \cdots\cdots \leq C_{M,\alpha}{}^{i-1} \int_0^t \|w_{1t}\|_{k+1}^2 d\tau \qquad (*)$$

$$(*) \xrightarrow[i\to\infty]{} 0$$

$$\lim_{i\to\infty} u_i = u \qquad \text{in} \qquad C((0,\infty)\times H^k(\Omega))$$

Mathematical result

Assume that (A) holds and for any integer $m \geq [n/2] + 3$

$$(h_0(x), h_1(x)) \in W^{m+1}(\Omega) \times W^m(\Omega)$$

for $h_0(x) = u_0(x) - a$ and $h_1(x) = u_1(x) - b$. For sufficiently large a and b satisfying $b > \delta_0$ there is a classical solution $u(x,t)$ such that

$$\lim_{t\to\infty} \|u_t(x,t) - \overline{u}_1\|_{m-2} = 0$$

where $\overline{u}_1 = |\Omega|^{-1} \int_\Omega u_1(x)dx$.

Thank you very much