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Partial Differential Equations

A chemotaxis model motivated by angiogenesis

Un modèle de chimiotactisme motivé par l'angiogénèse

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Abstract

We consider a simple model arising in modeling angiogenesis and more specifically the development of capillary blood vessels due to an exogenous chemo-attractive signal (solid tumors for instance). It is given as coupled system of parabolic equations through a nonlinear transport term. We show that, by opposition to some classical chemotaxis model, this system admits a positive energy. This allows us to develop an existence theory for weak solutions. We also show that, in two dimensions, this system admits a family of self-similar waves. ***To cite this article: L. Corrias et al., C. R. Acad. Sci. Paris, Ser. I 336 (2003).***

Résumé

Nous considérons un modèle simplifié intervenant dans la modélisation de l'angiogénèse et plus précisément le développement de vaisseaux sanguins capillaires sous l'effet d'un signal chemo-attractif exogène (tumeurs solides par exemple). Il s'agit d'un système parabolique couplé par un terme de transport non linéaire. Nous montrons que, contrairement au cas d'autres modèles de chimiotactisme, ce système admet une énergie positive. Ceci nous permet de développer une théorie d'existence de solutions faibles. Nous montrons aussi que, en deux dimensions, ce système admet une famille de solutions autosimilaires. ***Pour citer cet article : L. Corrias et al., C. R. Acad. Sci. Paris, Ser. I 336 (2003).***

Version française abrégée

L'angiogénèse concerne la formation de vaisseaux sanguins capillaires et joue un rôle fondamental dans le développement de tumeurs solides qui sécrètent une substance chimique favorisant la migration de cellules endothéliales vers la tumeur elle-même (Anderson et Chaplain [1], Sleeman et al. [18], Davidson et al. [8], Levine

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et al. [14,15], Chaplain [6]). La modélisation complète du système tumeur, angiogénèse et système immunitaire conduit à des équations complexes (Bellomo et Preziosi [2], Chaplain et Preziosi [7], De Angelis et Jabin [9]).

On peut toutefois isoler un système de base [7] utilisé pour les simulations numériques, qui prend la forme

$$\begin{cases} \frac{\partial}{\partial t} n - \kappa \Delta n + \operatorname{div}\big[n\chi(c)\nabla c\big] = 0, \quad t > 0,\ x \in \Omega, \\ \frac{\partial}{\partial t} c = -cn. \end{cases}$$

Ici n est la densité de cellules endothéliales, c la concentration du signal chimique exogène émis et $\Omega = \mathbb{R}^d$ ou Ω est un ouvert borné (on complète alors l'équation avec des conditions de flux nul sur n). Ce système se comporte de façon très différente du système de chimiotactisme pour lequel l'explosion en temps finie est établie (Herrero et al. [13], Betterton et Brenner [3], Brenner et al. [4,5]). En effet, nous démontrons qu'il existe toujours une solution faible vérifiant $n \geqslant 0$, $0 \leqslant c \leqslant \|c(t=0)\|_{L^\infty}$ et l'inégalité d'énergie

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_\Omega \left[\frac{1}{2} \big|\nabla \Phi(c)\big|^2 + n \ln(n) \right] \leqslant 0,$$

avec $\Phi'(c) = \sqrt{\chi(c)/c}$.

En dimension 2, ce modèle admet également des solutions autosimilaires qui sont présentées ci-dessous (Section 4). Elles mettent en évidence le comportement qualitatif attendu de la modélisation : la densité d'organisme n, initialement une masse de Dirac, est transportée de façon radiale vers les plus grandes valeurs de c.

1. Biological model

Angiogenesis refers to the formation of a capillary network of blood vessels (see Anderson and Chaplain [1], Sleeman et al. [18], Davidson et al. [8], Levine et al. [14,15], Chaplain [6]). It is essential for the growth and development of solid tumors. In order to facilitate angiogenesis, the tumor secretes some chemical substances whose concentration is denoted by $c(x,t)$ below. This chemical induces neighboring endothelial cells to migrate towards the tumor through a chemotaxis phenomena (see Levine et al. [15] and the references therein). Full modeling of the complete tumor, angiogenesis and immune system leads of course to complex mathematical models (see Bellomo and Preziosi [2], Chaplain and Preziosi [7], De Angelis and Jabin [9]). Here we consider a simple model related to this theory.

Denoting by $n(x,t)$ the concentration of the endothelial cells, then the following parabolic system ($\kappa > 0$) set in a domain Ω which is either $\mathbb{R}^d$ or a bounded region of $\mathbb{R}^d$ is a basic mathematical model for angiogenesis, used at least for numerical simulations (see [7]):

$$\begin{cases} \frac{\partial}{\partial t} n - \kappa \Delta n + \operatorname{div}\big[n\chi(c)\nabla c\big] = 0, \quad t > 0,\ x \in \Omega, \\ \frac{\partial}{\partial t} c = -cn. \end{cases} \tag{1}$$

Initial data for this problem is given by:

$$\begin{cases} n(t=0,x) = n^0(x) \geqslant 0, \quad n^0 \in L^1(\Omega),\ n^0 \ln(n^0) \in L^1(\Omega), \\ 0 \leqslant c(t=0,x) = c^0(x) \leqslant K. \end{cases} \tag{2}$$

When Ω is a bounded domain, we also consider the no flux boundary condition:

$$\kappa \frac{\partial n}{\partial \nu} - n\chi(c) \frac{\partial c}{\partial \nu} = 0 \quad \text{on } \partial\Omega. \tag{3}$$

The function χ is the chemotactic sensitivity. It is a given C^1 function on $\mathbb{R}_+$ and we assume

$$\chi(c) > 0, \quad \inf_{c \geqslant 0} \frac{c\chi'(c)}{\chi(c)} > -1, \tag{4}$$

and we set

$$\Phi'(c) = \sqrt{\frac{\chi(c)}{c}}, \qquad \mu = \frac{1}{2}\left[1 + \inf \frac{c\chi'(c)}{\chi}\right] > 0.$$

These assumptions hold in the case $\chi = Cst$, and we find $\Phi(c) = 2\sqrt{c}$, and $\mu = 1/2$.

This model differs somewhat from another chemotaxis mechanism where the chemical substance is emitted by the bacteria themselves and thus leads to equation

$$-\Delta c = n,$$

even though many variants exists (see Brenner et al. [5]). This leads to the collapse of the system in finite time in dimensions larger than 3 or in dimension 2 for large mass, see Jäger and Luckhaus [11], Herrero et al. [13] and for numerical simulations Brenner et al. [4], Marrocco [12]. On the other hand, existence of smooth solutions to an angiogenesis model similar to (1) was proved in one dimension by Rascle [16] and some blow-up cases (singular nonlinearities) were also analysed in Rascle and Ziti [17]. A general class of systems, Lyapunov functionals and results is also studied in Horstmann [10] but does not cover our model neither our analysis.

Our purpose is to show that the case of the angiogenesis model (1) leads to global existence of weak solutions without blow-up, to study the time asymptotic behavior and to exhibit self-similar solutions. The analysis that we carry out relies on the following a priori and energy estimates which follow from the above assumption (4)

$$\begin{cases} \int_\Omega n(t,x)\,\mathrm{d}x = \int_\Omega n^0\,\mathrm{d}x := m_0 \quad \text{(mass conservation)}, \\ 0 \leqslant c(t,x) \leqslant K, \quad 0 \leqslant n(t,x) \quad \text{(maximum principle)}, \\ \frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \left[\frac{1}{2}|\nabla\Phi(c)|^2 + n\ln(n)\right] \leqslant -\int_\Omega n\left[\kappa|\nabla\ln(n)|^2 + \mu|\nabla\Phi(c)|^2\right] \leqslant 0 \quad \text{(energy)}. \end{cases} \tag{5}$$

We do not prove these relations and just point out that the energy inequality relies on the following computations

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega n\ln(n)\,\mathrm{d}x = -\kappa\int_\Omega \frac{|\nabla n|^2}{n} + \int_\Omega \chi(c)\nabla n\cdot\nabla c,$$

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \left|\nabla\Phi(c)\right|^2 = -\int_\Omega cn\left|\nabla\Phi(c)\right|^2\frac{\Phi''}{\Phi'} - \int_\Omega \Phi'^2(c)\left[c\nabla n\cdot\nabla c + n|\nabla c|^2\right].$$

Then the two terms with scalar products cancel thanks to the choice of Φ which gives $c(\Phi')^2(c) = \chi(c)$. Moreover, $c\Phi''/\Phi' = \frac{1}{2}[c\chi'(c)/\chi(c) - 1]$ and thanks to assumption (4), we conclude the energy relation.

The problem in the use of this energy inequality comes from the sign of the term $n\ln(n)$. We will try to solve that in the next sections. We distinguish the case of a bounded domain and of the full space.

2. Case of a bounded domain

Theorem 2.1 (Bounded domain). *With the assumption* (4)*, there is a weak solution to* (1)–(3)*,* $n \in C(\mathbb{R}^+; L^1(\Omega))$*,* $c \in L^\infty(\mathbb{R}^+ \times \Omega)$*. Moreover, relations* (5) *hold and* $\nabla\sqrt{n}$*,* $\sqrt{n}\nabla\Phi(c)$ *belong to* $L^2((0,\infty)\times\mathbb{R}^d)$*. As* $t \to \infty$

$$n(t) \to \frac{1}{|\Omega|}\int_\Omega n^0(x)\,\mathrm{d}x \quad \text{in } w - L^1(\Omega), \qquad c(t) \to 0 \quad \text{in } L^p(\Omega),\ p < \infty.$$

Remark 1. Notice that the drift term is also written $\mathrm{div}[n\sqrt{c\chi(c)}\nabla\Phi(c)]$. It is well defined, in distributional sense, with the properties stated in Theorem 2.1.

Proof. *First step: Existence.* To prove existence we introduce a regularized problem (we call $(n_\varepsilon, c_\varepsilon)$ the solution), where the c equation is replaced by

$$\frac{\partial}{\partial t}c_\varepsilon = -c_\varepsilon n_\varepsilon^{(1+\varepsilon)}.$$

This model admits a regularized energy

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \left[\frac{1}{2}\left|\nabla\Phi(c_\varepsilon)\right|^2 + \frac{1}{\varepsilon}n_\varepsilon^{(1+\varepsilon)}\right] \leqslant -\int_\Omega n_\varepsilon^{1+\varepsilon}\left[\kappa(1+\varepsilon)\left|\nabla\ln(n_\varepsilon)\right|^2 + \mu\left|\nabla\Phi(c_\varepsilon)\right|^2\right] \leqslant 0.$$

Now this equation can be solved by a fixed point theorem with standard arguments. It remains to pass to the limits as $\varepsilon \to 0$ and we obtain the existence result.

Second step: Asymptotic behaviour. We define $n_k = n(t+k)$, $c_k = c(t+k)$. From the a priori bounds, we can extract a subsequence such that, for all $T > 0$

$$n_k \rightharpoonup \bar{n} \quad \text{in } w - L^1\big((0,T)\times\mathbb{R}^d\big), \qquad c_k \downarrow \bar{c}. \tag{6}$$

Also, integrating (5), we have

$$\int_0^\infty\int_\Omega \left|\nabla\sqrt{n}\,\right|^2 \mathrm{d}x\,\mathrm{d}t \leqslant Cst,$$

therefore, as $k \to \infty$,

$$\int_0^\infty\int_\Omega \left|\nabla\sqrt{n_k}\,\right|^2 \mathrm{d}x\,\mathrm{d}t = \int_k^\infty\int_\Omega |\nabla\sqrt{n}|^2\,\mathrm{d}x\,\mathrm{d}t \to 0.$$

As a consequence $\bar{n}$ is constant and by mass conservation it is $m_0/|\Omega|$. The same argument, using $\Phi(c)$ shows that $\bar{c}$ is also constant, and passing to the weak-strong limit in the equation for c_k, we deduce that $\bar{c}\bar{n} = 0$, and thus we have $\bar{c} = 0$.

3. Case of the full space

In the case of the full space, the difficulty of small values of n in the term $n\ln(n)$ is more stringent and requires an additional control. Our result is

Theorem 3.1 (Unbounded domain). *With the assumptions of Theorem* 2.1 *and* $n^0\ln(1+|x|^{d+1}) \in L^1(\mathbb{R}^d)$, *there exist a weak solution to* (1)–(2), *such that* $n \in C(\mathbb{R}^+; L^1(\Omega))$, $c \in L^\infty(\mathbb{R}^+\times\Omega)$ *and*

$$\int_{\mathbb{R}^d}\left|\nabla\Phi(c)\right|^2 \leqslant C(1+t), \qquad \int_{\mathbb{R}^d} n\left|\ln\big(n\big(1+|x|^{d+1}\big)\big)\right| \leqslant C(1+t).$$

Proof. Here, we modify the energy in order to control the zone $0 < n \leqslant 1$. Let f be a function such that $f(x) \geqslant 1$ over $\mathbb{R}^d$, $f^{-1} \in L^1(\mathbb{R}^d)$ and $|\nabla\ln(f)| \in L^\infty(\mathbb{R}^d)$. The choice $f(x) = (1+|x|^{d+1})$ is possible for instance and leads to the statement of Theorem 3.1.

The idea is to add in the energy inequality another term. We compute

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_{\mathbb{R}^d} n\ln\bigl(f(x)\bigr) = \int_{\mathbb{R}^d} \frac{1}{f}\bigl[-\kappa\nabla f\cdot\nabla n + n\chi(c)\nabla f\cdot\nabla c\bigr]$$
$$\leqslant \frac{1}{2}\int_{\mathbb{R}^d} n\bigl[\kappa\bigl|\nabla\ln(n)\bigr|^2 + \mu\bigl|\nabla\Phi(c)\bigr|^2\bigr] + \frac{1}{2}\int_{\mathbb{R}^d} n\left[\kappa + \frac{c\chi(c)}{\mu}\right]\bigl|\nabla\ln(f)\bigr|^2, \tag{7}$$

and thus we obtain, thanks to (5),

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_{\mathbb{R}^d}\left[\frac{1}{2}\bigl|\nabla\Phi(c)\bigr|^2 + n\ln(nf)\right] \leqslant -\frac{1}{2}\int_{\mathbb{R}^d} n\bigl[\kappa\bigl|\nabla\ln(n)\bigr|^2 + \mu\bigl|\nabla\Phi(c)\bigr|^2\bigr] + C_1, \tag{8}$$

with $C_1 = \frac{1}{2}m^0[\kappa + \mu^{-1}\sup_{0\leqslant c\leqslant K}(c\chi(c))]\|\nabla\ln(f)\|^2_{L^\infty(\mathbb{R}^d)}$.

Next, let $v = nf$ and $C_2 = \|f^{-1}\|_{L^1(\mathbb{R}^d)}$. Then

$$n\ln(nf) = f^{-1}v\ln(v) \geqslant -f^{-1}v^{1/2}$$

and

$$-\int_{\mathbb{R}^d} n\bigl(\ln(nf)\bigr) \leqslant \int_{\mathbb{R}^d} f^{-1}v^{1/2} = \int_{\mathbb{R}^d} n^{1/2}f^{-1/2} \leqslant m_0^{1/2}\left(\int_{\mathbb{R}^d} f^{-1}\right)^{1/2}$$

so that,

$$\int_{\mathbb{R}^d}\left[n\ln(nf) + \left(\frac{C_2}{m_0}\right)^{1/2} n\right] \geqslant 0. \tag{9}$$

Combining this with (8), we arrive separately at controls

$$\int_{\mathbb{R}^d}\bigl|\nabla\Phi(c)\bigr|^2 \leqslant C(1+t), \quad \int_{\mathbb{R}^d} n\bigl|\ln(nf)\bigr| \leqslant C(1+t), \tag{10}$$

as announced. With these estimates, the end of the proof is similar to the case of a bounded domain.

4. Self-similar solutions

In this section, we consider the space dimension $d = 2$ and the case when the chemotactic function χ is constant ($\chi = 1$). We also take $\kappa = 1$. We show the existence of radially symmetric self-similar solutions to system (1) of the form

$$n(t,x) = \frac{1}{t}\bar{n}\left(\frac{|x|}{\sqrt{t}}\right) \quad \text{and} \quad c(t,x) = \bar{c}\left(\frac{|x|}{\sqrt{t}}\right). \tag{11}$$

To do so we first notice that $(n = 1/t\bar{n}(x/\sqrt{t}), c = \bar{c}(x/\sqrt{t}))$ is a solution of (1) if and only if the profiles $\bar{n}$ and $\bar{c}$ are solution of

$$\begin{cases} \nabla_z\cdot\bigl[\bar{n}\bigl(-\frac{1}{2}z - \nabla_z\ln(\bar{n}) + \nabla_z\bar{c}\bigr)\bigr] = 0, \\ z\cdot\nabla_z\bar{c} = 2\bar{c}\bar{n}, \end{cases} \tag{12}$$

where $z = x/\sqrt{t}$. Finally, we obtain radially symmetric self-similar solutions to (1) considering any radial solution of

$$\begin{cases} -\frac{1}{2}z - \nabla_z\ln(\bar{n}) + \nabla_z\bar{c} = 0, \\ z\cdot\nabla_z\bar{c} = 2\bar{c}\bar{n}. \end{cases} \tag{13}$$

Theorem 4.1 (Self-similar solutions in 2D). *There is a two-parameter family of radial solutions* $(\bar{n}, \bar{c})$ *to* (13) *with the properties*

$$0 \leqslant \bar{c} \leqslant K, \quad \bar{c}(0) = 0, \quad \bar{c}' \geqslant 0,$$
$$0 < \bar{n}(r) \in L^1\big(r^q \,\mathrm{d}r\big), \quad \forall q > 0.$$

In particular, these solutions are in accordance with the intuition behind the model. The initial Dirac mass for n is smoothed out and the endothelial cells move outwards, where the signal is higher.

Proof. Let $\bar{n}(z) = \mathrm{e}^{-\lambda(|z|^2/2)}$ and $\bar{c}(z) = g(|z|^2/2)$. Then, system (13) gives $\lambda(u) + g(u) = \frac{1}{2}u + \alpha$, $\alpha \in \mathbb{R}$, and $g'/(g\,\mathrm{e}^g) = \frac{1}{2}\,\mathrm{e}^{-\alpha}/(\frac{u}{2}\,\mathrm{e}^{u/2})$, i.e.,

$$\psi\big(g(u)\big) = \mathrm{e}^{-\alpha}\psi\left(\frac{u}{2}\right) + \beta, \quad \beta \in \mathbb{R}, \tag{14}$$

where ψ is a primitive of $1/(u\,\mathrm{e}^u)$. Since ψ is a strictly increasing function on $\mathbb{R}_+$, from $-\infty$ to some finite limit $\psi(\infty)$ it is invertible as long as we choose $\beta < \psi(\infty)(1 - \mathrm{e}^{-\alpha})$. The function g is then increasing from $g(0) = 0$ to some limit $\psi(g(\infty)) < \psi(\infty)$.

This gives us the profile $\bar{c}$. We deduce the properties of the profile $\bar{n}$ from the properties of λ from its definition and the properties of g. Especially $\lambda(u) \approx \frac{1}{2}u + \alpha - g(\infty)$ for large values of u.

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