ARTICLE IN PRESS

Applied Mathematics Letters ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Applied Mathematics Letters

journal homepage: www.elsevier.com/locate/aml

Existence of global solutions of a macroscopic model of cellular motion in a chemotactic field

Mark Alber[a,*], Richard Gejji[a], Bogdan Kazmierczak[b]

[a] *Department of Mathematics, University of Notre Dame, Notre Dame, 46656, USA*
[b] *Institute of Fundamental Technological Research, PAS, 00-049 Warszawa, Poland*

ARTICLE INFO

Article history:
Received 21 February 2009
Received in revised form 13 May 2009
Accepted 20 May 2009

Keywords:
Reaction–diffusion systems
Nonlinear diffusion
Global existence
Continuous limit
Cellular motion
Chemotaxis

ABSTRACT

Existence of global classical solutions of a class of reaction–diffusion systems with chemotactic terms is demonstrated. This class contains a system of equations derived recently as a continuous limit of the stochastic discrete cellular Potts model. This provides mathematical justification for using numerical solutions of this system for modeling cellular motion in a chemotactic field.

1. Introduction

Continuous limits of microscopic models of biological systems based on point-wise cell representations were extensively studied over the past 30 years. In particular, classical Keller–Segel PDE model has been derived from a discrete model with point-wise cells undergoing random walk in chemotactic field. This model was studied among others in [1,2]. It is known that in this model, under certain conditions, a blow up of a solution may occur in finite time [3,4]. To avoid this, various modifications of the Keller–Segel model have been introduced (see, e.g. [5–7] and the references therein). A new system of macroscopic nonlinear reaction–diffusion equations has been derived recently in [8] from the stochastic discrete cellular Potts model (CPM) with extended cell representation. This system can be written in the form:

$$\partial_t u = \nabla \cdot [\Gamma(u)\nabla u] - \chi_0 \nabla [u \nabla v] \tag{1}$$

$$\partial_t v = d\nabla^2 v + au - \gamma v. \tag{2}$$

Here u is the fraction of volume occupied by cells and v denotes the concentration of the chemical, whereas

$$\Gamma(u) = \frac{1+u}{1-u+u\log(u)}. \tag{3}$$

The constants χ_0, d, a and γ have the obvious physical interpretation. This system is considered in a bounded domain $\Omega \subset \mathbb{R}^2$ with $\partial\Omega \in C^{2+\eta}$, $\eta \in (0, 1)$, subject to the initial and boundary conditions

$$(u(0,x), v(0,x)) = (u_0(x), v_0(x)), \;\; x \in \Omega, \qquad \frac{\partial u}{\partial \nu}(x) = \frac{\partial v}{\partial \nu}(x) = 0, \quad x \in \partial\Omega \tag{4}$$

---

[*] Corresponding address: Department of Mathematics, University of Notre Dame, 255 Hurley Building, Notre Dame, 46556-4618, IN, USA. Tel.: +1 574 631 8371.
E-mail address: malber@nd.edu (M. Alber).

0893-9659/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.aml.2009.05.013

Please cite this article in press as: M. Alber, et al., Existence of global solutions of a macroscopic model of cellular motion in a chemotactic field, Appl. Math. Lett. (2009), doi:10.1016/j.aml.2009.05.013

where $\nu = \nu(x)$ denotes the outward unit normal to $\partial\Omega$. Let us note that the coefficient $\Gamma(u) \nearrow \infty$ as $u \nearrow 1$. We will show that this prevents the blow up of solutions. A very good agreement was shown in [8] between Monte Carlo simulations of the microscopic CPM and numerical solutions of Eqs. (1)–(2). Combination of microscopic and macroscopic models like system (1)–(2) can be used to simulate growth of structures similar to early vascular networks [8]. In this paper we show the global in time existence of classical solutions to a generalization of system (1)–(2). This provides a mathematical justification for using numerical solutions of system (1)–(2) for biological modeling. The proof is based (modulo slight modifications) on the method described in [9].

2. Global existence of solutions

In this section we show the existence of a global in time solution for the following system

$$\partial_t u = \nabla \cdot [\Gamma(u)\nabla u] - \nabla[\chi(u,v)\nabla v] + g(u,v) \tag{5}$$

$$\partial_t v = \nabla \cdot [d(v)\nabla v] + f(u,v) \tag{6}$$

in $\Omega \times [0,T)$, where Ω is a bounded domain in $\mathbb{R}^n$, with the initial–boundary conditions

$$(u(0,x), v(0,x)) = (u_0(x), v_0(x)), \quad x \in \Omega, \qquad \frac{\partial u}{\partial \nu}(x) = \frac{\partial v}{\partial \nu}(x) = 0, \quad x \in \partial\Omega. \tag{7}$$

H0 $n \ge 1$. $\partial\Omega$ is of $C^{2+\eta}$ class, $\eta \in (0,1)$
H1 Let $\mathcal{D} := [0,1] \times [0,\infty)$. Let $\chi : \mathcal{D} \to [0,\infty)$ be of C^2 class, and $\chi(0,v) = 0$ for $v \ge 0$
H2 $g : \mathcal{D} \to \mathbb{R}$ is of C^2 class. $g(u,v) \le M_g(1-u)$, $g(0,v) \ge 0$ for all $(u,v) \in \mathcal{D}$, $M_g \ge 0$;
  $f : \mathcal{D} \to \mathbb{R}$ is of C^2 class. $f(u,v) < 0$ for all $v \ge V > 0$, $f(u,0) \ge 0$ for all $u \in [0,1]$;
  $d : [0,\infty) \to [d_1, d_2)$ is of C^2 class, $0 < d_1 < d_2 < \infty$
H3 $u_0, v_0 \in C^{2+\eta}(\overline{\Omega})$, $0 \le u_0(x) < 1$, $0 \le v_0(x)$ for $x \in \overline{\Omega}$ and $\frac{\partial u_0}{\partial \nu}(x) = 0$, $\frac{\partial v_0}{\partial \nu}(x) = 0$ for $x \in \partial\Omega$
H4 $\Gamma : [0,1) \to (0,\infty)$ is of C^2 class. There exist positive numbers $\varepsilon_1 > 0$, $\varepsilon_2 > 0$ and $\varepsilon_3 > 0$ such that $\Gamma(u) > \varepsilon_1$ for all $u \in [0,1]$ and $\Gamma(u) \ge \varepsilon_2(1-u)^{-\alpha}$ for $u \in [1-\varepsilon_3, 1)$ and $\alpha \ge 2$.

As one can see from assumptions H1–H4, system (5)–(6) is more general than the system considered in the paper [9]. Among others, it includes a nonlinear term $g(u,v)$ describing cell proliferation.

Lemma 1. *Assume* H4. *Then there exists a constant* $K > 0$ *such that, for all* $u \in [0,1)$, $\Gamma(u) \ge K\frac{1}{(1-u)^\alpha}$.

Proof. Let $\varepsilon_4 = \inf_{u \in (0,1-\varepsilon_3)} \Gamma(u)(1-u)^\alpha$. If $K = \min\{\varepsilon_4, \varepsilon_2\}$ then the thesis of the lemma holds. □

Lemma 2 (*See Lemma 3.1 in [9]*). *Let hypotheses* H0–H4 *hold. Then*

1. *There exists a positive constant* T_0 *depending on initial data* (u_0, v_0) *such that system* (5)–(6) *with initial–boundary conditions* (7) *has a unique maximal solution* (u,v) *in the space* $C^{1+\eta/2,2+\eta}([0,T_0) \times \bar{\Omega}; \mathbb{R}^2)$ *with* $u(t,x) \ge 0$ *and* $v(t,x) \ge 0$.
2. *If* u *is bounded away from* 1 *for each finite time* $t > 0$, *then* $T_0 = \infty$, *namely, the solution is a global classical solution of system* (5)–(6), (7).

Proof. Let $\omega = (u,v)$. Then system (5)–(6), (7) can be written as

$$\begin{aligned} &\partial_t \omega = \nabla \cdot (A(\omega)\nabla\omega) + \mathcal{F}(\omega), \quad \omega(0,\cdot) = (u_0, v_0) \quad \text{in } \Omega, \\ &[\Gamma(u)\nabla u - \chi(u,v)\nabla v] \cdot \nu = 0, \quad [d(v)\nabla v] \cdot \nu = 0 \quad \text{on } \partial\Omega \end{aligned} \tag{8}$$

where $A \equiv A_{ij}, i,j = 1,2, A_{11} = \Gamma(u), A_{12} = -\chi(u,v), A_{21} = 0, A_{22} = d(v), \mathcal{F} = (g(u,v), f(u,v))^T$. We can extend all the considered functions to the set $\mathcal{G} = \{(u,v) \in (-\delta,1) \times (-\delta,\infty)\}$, $\delta > 0$, in C^2 class in such a way that $\Gamma(u) > \Gamma_0 > 0$ and $d(v) > d_0 > 0$ for all $(u,v) \in \mathcal{G}$. Thus the local existence and conditions for the global existence of solutions to this system follow e.g. from Theorem 7.3 and Corollary 9.3 in [10], Theorem 5.2 in [11] or Theorem 14.6 in [12]. The solution exists globally, if $(u(t,x), v(t,x))$, $x \in \overline{\Omega}$, does not reach the boundary of $\mathcal{G}$ for any finite $t > 0$. According to H1–H3 we can prove that, as long as the solution exists, $u(t,x) \ge 0$ and $v(t,x) \ge 0$ for all $x \in \overline{\Omega}$. To do this, we can either use the comparison principle for diagonal parabolic systems (if we treat the function v in the equation for u as given, due to the fact that $\chi_{,v}(0,v) = 0$) or use Theorem 15.1 of [12] as in [7]. Moreover, according to H2, $v(t,x)$ is bounded from above, as long as $\|u\|_{L^\infty} \le 1$, by a constant $c_v = \max\{\sup_{x\in\Omega} v_0(x), V\}$. Thus the sufficient condition for the existence of the global classical solution is that u is bounded away from 1. □

Theorem 1. *Let the conditions* H0 *to* H4 *hold. Then there exists a unique global solution* (u,v) *to system* (5)- (6), (7) *such that* u *and* v *are in* $C^{1+\eta/2,2+\eta}([0,\infty) \times \overline{\Omega})$. *Moreover, there exists a constant* $c_v \ge 0$ *such that* $0 \le v(t,x) \le c_v$ *and* $0 \le u(t,x) < 1$ *for all* $x \in \overline{\Omega}$ *and all* $t > 0$.

Please cite this article in press as: M. Alber, et al., Existence of global solutions of a macroscopic model of cellular motion in a chemotactic field, Appl. Math. Lett. (2009), doi:10.1016/j.aml.2009.05.013

Proof. It is easy to note that by appropriate scaling we can obtain a system in a region Ω satisfying $|\Omega| = 1$ and such that $\Gamma(u) \geq (1-u)^{-\alpha}$ for $u \in [0, 1)$. The proof of the theorem is based on the proof of Theorem 1.1 from [9]. Let us consider the auxiliary scalar equation

$$\begin{aligned}&\partial_t u = \nabla \cdot [\Gamma(u)\nabla u] - \nabla \cdot b(t, x) + G(u, t, x), \quad (t, x) \in [0, T) \times \Omega\\ &u(0, x) = u_0(x), \quad x \in \Omega, \quad \frac{\partial u}{\partial \nu}(x) = 0 \quad x \in \partial\Omega\end{aligned} \tag{9}$$

where $b \in L^{\infty}((0, \infty) \times \Omega)$ is a given function. Below, we will use the following lemma. □

Lemma 3 (*See Theorem 1.1 in [9]*). *Let* $0 \leq u_0(x) < 1$ *for* $x \in \overline{\Omega}$. *Let* $\|b\|_{L^{\infty}((0,\infty)\times\Omega)} = M_b$ *and* $\|G(u, \cdot, \cdot)\|_{L^{\infty}((0,\infty)\times\Omega)} \leq M_g(1-u)$ *for* $u \in [0, 1]$. *Let us assume that u is a classical solution to Eq.* (9) *and* $0 \leq u(t, x) < 1$ *for* $(t, x) \in Q_T = [0, T) \times \overline{\Omega}$. *Then, for any* $T > 0$, *there exists a constant* $\delta_T > 0$ *such that* $u(t, x) < 1 - \delta_T$ *for all* $(t, x) \in Q_T$. *The constant* δ_T *depends only on* M_b, $\delta = \|1 - u_0\|_{L^{\infty}(\Omega)}$ *and* T.

So suppose to the contrary that the classical solution does not exist globally. According to Lemma 2, it follows that there exists finite $T_0 > 0$ such that $\|u(t, \cdot)\|_{L^{\infty}(\Omega)} \to 1$ as $t \to T_0$ and $\|u(t, \cdot)\|_{L^{\infty}(\Omega)} < 1$ for any $t < T_0$. However, as $v(t, x) \leq c_v$, due to Theorem 6.49 in [13], $\|v\|_{C^{(1+\eta)/2,1+\eta}(\Omega_{T_0})} \leq W_{T_0}(\|v_0\|_{C^{1+\eta}(\overline{\Omega})} + 1)$. Then, $b = [\chi(u, v)\nabla v]$ is bounded on $[0, T_0] \times \overline{\Omega}$, so according to Lemma 3, for any $t < T_0$, we would have $u(t, x) < 1 - \delta_t$, where δ_t does not tend to 0 as $t \to T_0$. We thus arrive at a contradiction as the solution could be prolonged for $t > T_0$. This concludes the proof of Theorem 1. □

Proof of Lemma 3. Multiplying both sides by $p(1-u)^{-p-1}$ and integrating we obtain

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\int_{\Omega}(1-u)^{-p}\mathrm{d}x &= p\int_{\Omega}(1-u)^{-p-1}u_t\mathrm{d}x\\ &= p\int_{\Omega}(1-u)^{-p-1}\nabla \cdot [\Gamma(u)\nabla u - b]\mathrm{d}x + p\int_{\Omega}(1-u)^{-p-1}G(u, t, x)\mathrm{d}x\\ &= -p(1+p)\int_{\Omega}\left\{\Gamma(u)(1-u)^{-(p+2)}|\nabla u|^2 - \frac{\nabla u \cdot b}{(1-u)^{p+2}}\right\}\mathrm{d}x + \int_{\Omega} p\frac{G(u, t, x)}{(1-u)^{p+1}}\mathrm{d}x\\ &\leq -p(1+p)\int_{\Omega}\left\{\frac{|\nabla u|^2}{(1-u)^{-(\alpha+p+2)}} - \frac{\nabla u \cdot b}{(1-u)^{p+2}}\right\}\mathrm{d}x + p\int_{\Omega} M_g(1-u)^{-p}\mathrm{d}x\end{aligned} \tag{10}$$

where the last inequality follows from the fact that $\Gamma(u) \geq (1-u)^{-\alpha}$ and the assumption concerning the function G. Let $w_p = (1-u)^{-\frac{\alpha+p}{2}}$. Then, we can proceed, as in [9] to obtain

$$\begin{aligned}&\frac{\mathrm{d}}{\mathrm{d}t}\int_{\Omega}(1-u)^{-p}\mathrm{d}x - p\int_{\Omega} M_g(1-u)^{-p}\mathrm{d}x \leq \frac{p(1+p)}{\alpha+p}\left(-\frac{4}{\alpha+p}\int_{\Omega}|\nabla w_p|^2\mathrm{d}x + 2\int_{\Omega}\frac{\nabla w_p \cdot b}{(1-u)^{(p+2-\alpha)/2}}\mathrm{d}x\right)\\ &\leq \frac{p(1+p)}{\alpha+p}\left(-\frac{4}{\alpha+p}\int_{\Omega}|\nabla w_p|^2\mathrm{d}x + 2M_b\int_{\Omega}\frac{|\nabla w_p|}{(1-u)^{(p+2-\alpha)/2}}\mathrm{d}x\right)\\ &\leq \frac{p(1+p)}{\alpha+p}\left(-\frac{2}{\alpha+p}\int_{\Omega}|\nabla w_p|^2\mathrm{d}x + \frac{M_b^2(\alpha+p)}{2}\int_{\Omega}\frac{1}{(1-u)^{(p+2-\alpha)}}\mathrm{d}x\right)\end{aligned} \tag{11}$$

where we have used Young's inequality. According to the assumptions of the lemma, $0 \leq u(t, x) < 1$ and $\alpha \geq 2$, we obtain the inequality

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_{\Omega}(1-u)^{-p}\mathrm{d}x \leq \frac{p(1+p)}{\alpha+p}\left(-\frac{2}{\alpha+p}\int_{\Omega}|\nabla w_p|^2\mathrm{d}x + \frac{M^2(\alpha+p)}{2}\int_{\Omega}\frac{1}{(1-u)^p}\mathrm{d}x\right) \tag{12}$$

where $M^2 = M_b^2 + M_g$. The rest of the proof of the lemma can be carried out exactly as the proof of Lemma 2.4 in [9]. This is due to the fact that the concrete form of the coefficient Γ is not used in the subsequent considerations. □

Theorem 2. *Let* $u_0, v_0 \in C^{2+\eta}$ *be non-negative. Then there exists a unique global solution* (u, v) *to the system* (1) – (2) *and* (4) *such that* $(u, v) \in C^{1+\eta/2,2+\eta}([0, \infty) \times \overline{\Omega}; \mathbb{R}^2)$. *Moreover, there exists a constant* c_v *such that* $0 \leq v(t, x) \leq c_v$ *and* $0 \leq u(t, x) < 1$ *for all* $x \in \overline{\Omega}$ *and all* $t > 0$.

Proof. Due to Theorem 1, one has only to show that H4 is satisfied, i.e. $\Gamma(u) \geq 1/(1-u)^2$. This can be easily done. □

3. Conclusions

We proved the existence of global in time classical solutions of the system (5)–(6), generalization of both system (1)–(2) and system considered in [9]. This demonstrates that these systems cannot have a blow up of solutions in finite time and justifies the usage of numerical solutions of the macroscopic model of early vascularization suggested in [8].

Please cite this article in press as: M. Alber, et al., Existence of global solutions of a macroscopic model of cellular motion in a chemotactic field, Appl. Math. Lett. (2009), doi:10.1016/j.aml.2009.05.013

Acknowledgements

We would like to thank Zhian Wang for a very helpful discussion. Mark Alber and Richard Gejji were partially supported by the NSF grant DMS 0719895, Bogdan Kazmierczak by MNSW grant N N501 132936.

References

[1] W. Alt, Biased random walk models for chemotaxis and related diffusion approximations, J. Math. Biol. 9 (1980) 147.

[2] H.G. Othmer, A. Stevens, Aggregation, blowup, and collapse: The ABC's of taxis in reinforced random walks, SIAM J. Appl. Math 57 (4) (1997) 1044.

[3] M.A. Herrero, J.J.L Velázquez, Singularity patterns in chemotaxis model, Math. Ann. 306 (1996) 583.

[4] M.P. Brenner, P. Constantin, L.P. Kadanoff, A. Shenkel, S.C. Venkataramani, Diffusion, attraction and collapse, Nonlinearity 12 (1999) 1071.

[5] K. Painter, T. Hillen, Volume-filling and quorum-sensing in models for chemosensitive movement, Canadian Appl. Math. Quart. 10 (2002) 501–543.

[6] D. Wrzosek, Model of chemotaxis with threshold density and singular diffusion (in preparation).

[7] Z.A. Wang, T. Hillen, Classical solutions and pattern formation for a volume filling chemotaxis model, Chaos 17 (2007) 037108.

[8] P.M. Lushnikov, N. Chen, M. Alber, Macroscopic dynamics of biological cells interacting via chemotaxis and direct contact, Phys. Rev. E. 78 (2008) 061904.

[9] Y.S. Choi, Z.A. Wang, Prevention of blow up in chemotaxis by fast diffusion, J. Differential Equations (submitted for publication).

[10] H. Amann, Dynamic theory of quasilinear parabolic equations II: Reaction–diffusion systems, Differential and Integral Equations 3 (1990) 3–75.

[11] H. Amann, Dynamic theory of quasilinear parabolic equations III: Global existence, Math. Z. 202 (1989) 219–250.

[12] H. Amann, Nonhomogeneous linear and quasilinear elliptic and parabolic boundary value problems, in: H.J. Schmeisser, H. Triebel (Eds.), Function Spaces, Differential Operators and Nonlinear Analysis, 1993, pp. 9–126.

[13] G.M. Lieberman, Second Order Parabolic Differential Equations, World Scientific, Singapore, 1996.

Please cite this article in press as: M. Alber, et al., Existence of global solutions of a macroscopic model of cellular motion in a chemotactic field, Appl. Math. Lett. (2009), doi:10.1016/j.aml.2009.05.013