MATHEMATICAL METHODS IN THE APPLIED SCIENCES
Math. Meth. Appl. Sci. (2008)
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/mma.1034
MOS subject classification: 35 B 35; 35 K 57; 35 K 55

Existence of global solutions to a model of chondrogenesis

B. Kazmierczak*,†

Institute for Fundamental Technological Research, PAS, Warsaw, Poland

Communicated by J. Banasiak

SUMMARY

The paper considers conditions sufficient for the existence of classical $C_{x,t}^{2+\beta,1+\beta/2}$ solutions to a new model of chondrogenesis during the vertebrate limb formation. We assume that the diffusion coefficient of the fibronectin is positive and that the function describing the interaction between the fibronectin and cells satisfies some additional properties. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS: bone pattern formation; chemotaxis; invariant region method

1. INTRODUCTION

Understanding of chondrogenesis (process of bone formation during the vertebrate limb growth) is one of the main aims of morphogenesis models. The objective of every mathematical model of chondrogenesis is to explain how the various interactions inside the growing limb can lead to spatio-temporal differentiation of cartilage, such that the number of bones changes in time from one (*humerus*), to two (*radius* and *ulna*) and to three, four or five *digits* (depending on the species) [1]. This paper is a continuation of the analysis of the new model of the chondrogenesis process during the development of vertebrate limb formation [2]. The first part of this analysis can be found in [1].

In this paper we will consider the following generalized version of the system proposed in [2]:

$$\partial c/\partial t = D_c \nabla^2 c - k_c c + J(x,t) \tag{1}$$

$$\partial R_3/\partial t = r_3 R_3 (R_{3\mathrm{eq}} - R_3) + k_{23} R_4 \tag{2}$$

$$\partial c_a/\partial t = D_a \nabla^2 c_a - k_a c_{\mathrm{inh}} c_a + J_a^1(c_a, c_{\mathrm{inh}}) R_1 + J_a(c_a, c_{\mathrm{inh}}) R_2 \tag{3}$$

*Correspondence to: B. Kazmierczak, Institute for Fundamental Technological Research, PAS, Warsaw, Poland.
†E-mail: bkazmier@ippt.gov.pl

Contract/grant sponsor: Polish Ministry of Science and Higher Education; contract/grant number: 1P03A01230
Contract/grant sponsor: NSF; contract/grant number: IBN-034467

Received 2 October 2007

$$\partial c_{\text{inh}}/\partial t = D_{\text{inh}}\nabla^2 c_{\text{inh}} - k_a c_{\text{inh}} c_a + k_f(c_a, c_{\text{inh}})R_2 \tag{4}$$

$$\partial R_1/\partial t = \text{div}(D_1(\rho)\nabla R_1) - \text{div}(R_1\chi_1\nabla\rho) + rR_1(R_{\text{eq}} - R) + k_{21}R_2 - k_{12}(c, c_a)R_1 \tag{5}$$

$$\partial R_2/\partial t = \text{div}(D_2(\rho)\nabla R_2) - \text{div}(R_2\chi_2\nabla\rho) + rR_2(R_{\text{eq}} - R) + k_{12}(c, c_a)R_1 - k_{21}R_2 - k_{22}R_2 \tag{6}$$

$$\partial R_4/\partial t = \text{div}(D_4(\rho)\nabla R_4) - \text{div}(R_4\chi_4\nabla\rho) + rR_4(R_{\text{eq}} - R) + k_{22}R_2 - k_{23}R_4 \tag{7}$$

$$\partial\rho/\partial t = \varepsilon\nabla^2\rho + k_1R_1 + k_2R_2 + k_4R_4 - k\rho \tag{8}$$

where $x \in \Omega$ and $t > 0$. Obviously, Ω models the limb region and the effect of its growth should be taken into account, but this process is neglected in this paper. In the above system of equations c denotes the density of the FGF-factor, which suppresses the differentiation of R_1 cells into R_2 cells, c_a denotes the density of the factor TGF, a diffusible activator of chondrogenesis, c_{inh} is the density of the inhibitor, R_1, R_2, R_4, R_3 are the densities of different kinds of cells and ρ is the density of fibronectin. The quantity

$$R = R_1 + R_2 + R_4$$

denotes the density of the mobile cells and χ_j, $j = 1, 2, 4$, are the coefficients describing specific features of cells–fibronectin interactions [1].

The mechanisms incorporated into this model take into account classical dynamics of morphogens and its coupling with the process of cell differentiation. Moreover, the model also incorporates direct adhesive interactions between cells via cell adhesion molecules and between cells and secreted substrate adhesion molecules (fibronectin). The cells–fibronectin interaction generates a specific velocity field for the moving cells, effectively dragging them into regions of high fibronectin density. This phenomenon is described by the convective terms $\text{div}(R_1\chi_1\nabla\rho)$, $\text{div}(R_2\chi_2\nabla\rho)$ and $\text{div}(R_4\chi_4\nabla\rho)$ in Equations (5)–(7). Such a mechanism may provide a possible explanation of high cell concentration centers, resulting in the pattern formation of chondrogenesis. For more detailed biological analysis of the model, see [1, 2].

A simple but very probable scenario leading to a pattern formation in a growing chicken limb, which can be described by system (1)–(8), consists of a sequence of processes initiated by a Turing instability of the activator–inhibitor subsystem (3)–(4) (see, e.g. [3]). It is assumed that c_a (activator) and c_{inh} (inhibitor) molecules are secreted by R_1 cells (i.e. cells bearing the R_1 receptor for FGF) at a small rate and, if the density of the activator is not small, by R_2 cells (i.e. cells bearing R_2 receptor for FGF) at a higher rate. The prepattern of activator concentration may be then transferred to the subsystem describing the dynamics of moving cells by the coefficient $k_{12}(c, c_a)$. It is known that, below a certain threshold of c_a, k_{12} is an increasing function of the activator density c_a with $k_{12\max}/k_{21} \cong 4$ (see [2]). Moreover, R_2 cells differentiate irreversibly into R_4 cells. The fibronectin slows down the diffusive motion of the moving cells; hence, R_2 and R_4 cells tend to concentrate in the regions of larger activator density of the chemical prepattern. Finally, R_4 cells differentiate irreversibly into R_3 cells, which are differentiated cartilage cells. These cells practically do not diffuse and thus their density can form steep density gradients enhancing the final pattern of chondrogenesis [1].

DOI: 10.1002/mma

2. MAIN RESULTS

Paper [1] was mainly devoted to the analysis of the case $\varepsilon = 0$ (non-diffusing fibronectin). To be more precise, in [1] we found conditions, which guarantee global in time existence of classical (smooth) solutions in the case $\varepsilon = 0$, whereas the case $\varepsilon \neq 0$ was considered only marginally (without precise proofs). This paper concentrates on the case of non-zero diffusion coefficient of fibronectin. As it was remarked in [1], the assumption of a small diffusivity of fibronectin cannot be by no means excluded by the biological evidence. For example, as it is noted in [4], the domain of action of fibronectin spreads from its sites of initial deposition by conversion of its initially compact structure to a more extended one, which may be interpreted as a result of non-zero diffusion. The possibility of non-zero diffusivity of the fibronectin is also mentioned in [5, pp. 819, 820]. With respect to the system considered in [1] system (1)–(8) is more general. Thus, in this paper the diffusion coefficients of the moving cells may depend on the density of the fibronectin, i.e. $D_i = D_i(\rho)$, $i = 1, 2, 4$. Moreover, we assign different functions χ_i describing cells–fibronectin interactions to different moving cells, whereas in [1] all these functions were equal.

Our knowledge about the cells–fibronectin interaction is only qualitative. In this paper we find several specific cases in which there exists a global in time solution to system (1)–(8). The results are stated in Theorems 2–5. In Theorems 2 and 3 the conditions imposed on the chemotaxis coefficients χ_i, $i = 1, 2, 4$, assume that they vanish sufficiently fast as a function of ρ. In Theorem 4, this condition is replaced by the demand that k_i depend on R_i and the quantities $k_i(R_i)R_i$ are uniformly bounded for all $R_i \in [0, \infty)$. We are forced to impose these kinds of conditions, to ensure the existence of global in time solutions, which are bounded in $C^{2+\beta, 1+\beta/2}_{x,t}$ spaces.

The main problem in using the standard theory of systems of parabolic equations is the effective presence of the terms proportional to $\nabla^2 \rho$ in the equations for the moving cells R_i, $i = 1, 2, 4$. To eliminate these terms we apply a generalization of the transformation of variables used in [1, 6, 7]. However, this transformation, when applied to the case of non-vanishing diffusion coefficient of the fibronectin, generates certain new terms which demand additional treatment. This analysis is the main mathematical task of this paper. We are concentrated on the case when the diffusion coefficient is small. To be more precise, it must be smaller than the diffusion coefficient of the mobile cells. This condition is present in point 1. of Assumptions 5 and 6.

3. BASIC ASSUMPTIONS

In what follows we consider the initial boundary value problem for system (1)–(8) in a bounded domain Ω

$$\Omega \subset \mathbb{R}^m, \quad m \geqslant 1, \quad \partial\Omega \in C^{2+\beta}, \quad \beta \in (0, 1)$$

We assume that all the dependent variables, except R_3, satisfy the no-flux conditions on the boundary $\partial\Omega$; that is to say that the following conditions hold:

$$\frac{\partial c}{\partial n} = 0, \quad \frac{\partial c_a}{\partial n} = 0, \quad \frac{\partial c_{\text{inh}}}{\partial n} = 0, \quad \frac{\partial R_1}{\partial n} = 0, \quad \frac{\partial R_2}{\partial n} = 0, \quad \frac{\partial R_4}{\partial n} = 0, \quad \frac{\partial \rho}{\partial n} = 0 \tag{9}$$

DOI: 10.1002/mma

where $n = n(x)$ is the unit outward normal to $\partial\Omega$ at x. The initial conditions are of the form:

$$\begin{aligned} c(x,0) = c_0(x), \quad c_a(x,0) = c_{a0}(x), \quad c_{\mathrm{inh}}(x,0) = c_{\mathrm{inh}0}(x), \quad R_1(x,0) = R_{10}(x) \\ R_2(x,0) = R_{20}(x), \quad R_4(x,0) = R_{40}(x), \quad R_3(x,0) = R_{30}(x), \quad \rho(x,0) = \rho_0(x) \end{aligned} \tag{10}$$

where $x \in \overline{\Omega}$. We demand that the compatibility conditions are satisfied, namely

$$\frac{\partial c_0}{\partial n} = 0, \quad \frac{\partial c_{a_0}}{\partial n} = 0, \quad \frac{\partial c_{\mathrm{inh}0}}{\partial n} = 0, \quad \frac{\partial R_{10}}{\partial n} = 0, \quad \frac{\partial R_{20}}{\partial n} = 0, \quad \frac{\partial R_{40}}{\partial n} = 0, \quad \frac{\partial \rho_0}{\partial n} = 0 \tag{11}$$

for all $x \in \partial\Omega$.

Assumption 1
$k_c, D_c, D_a, D_{\mathrm{inh}}, k_a, r, R_{\mathrm{eq}}, r_3, R_{3\mathrm{eq}}, k_1, k_2, k_4, k$ and all k_{ij} except for k_{12} are positive constants.

Assumption 2
$J(x,t) : \overline{\Omega} \times [0,\infty) \to [0, C_J]$, $C_J > 0$, is such that its $C^{\beta,\beta/2}_{x,t}(\overline{\Omega} \times [0,t])$ norm is bounded independently of $t > 0$. The functions $k_{12}, J_a^1, J_a, k_f : \mathbb{R}^1 \times \mathbb{R}^1 \to [0,\infty)$ are bounded from above by the constants $\overline{k}_{12}, \overline{J}_{a1}, \overline{J}_a$ and $\overline{k}_f$, respectively, and such that their $C^\beta(K)$ norms, $\mathbb{R}^1 \times \mathbb{R}^1 \supset K$ compact, are bounded from above by a constant C independent of K.

Assumption 3
Suppose that

1. The functions $c_0(x), c_{a0}, c_{i0}, R_{10}, R_{20}, R_{40}, R_{30}$ and ρ_0 are of class $C^{2+\beta}(\overline{\Omega})$ and non-negative in Ω.
2. $\partial R_{30}(x)/\partial n(x) = 0$ for $x \in \partial\Omega$.

Assumption 4
Let J_a^1, J_a be identically equal to 0 for $c_a > \widetilde{C}_a > 0$ independently of c_{inh}. Let $k_f(c_{\mathrm{inh}}, c_a)$ be identically equal to 0 for $c_{\mathrm{inh}} > \widetilde{C}_{\mathrm{inh}} > 0$ independently of c_a.

Biologically the last condition means that the production of secreted molecules stops after their density attains certain threshold values.

As mentioned, we do not impose any boundary condition for R_3. However, due to point 2. of Assumption 3, R_3 preserves the no-flux boundary conditions on the maximal interval of existence of the solution. In fact, differentiating both sides of Equation (2) at a point $x \in \partial\Omega$ along the normal $n(x)$ and using the boundary conditions $\partial R_4/\partial x = 0$, $\partial\rho/\partial x = 0$ we obtain the equation

$$\frac{\partial}{\partial t}\left[\frac{\partial R_3}{\partial n}\right] = r_3(R_{3\mathrm{eq}} - 2R_3)\frac{\partial R_3}{\partial n}$$

At each point of the boundary this equation may be viewed as an ordinary differential equation for $\partial R_3(x,t)/\partial n(x)$ with the initial condition $\partial R_3(0,x)/\partial n(x) = 0$. Hence, by the use of the Gronwall inequality we obtain our claim.

For any $T > 0$ let us denote

$$\Omega_T := \Omega \times (0,T) \tag{12}$$

In [1] we analyzed the case $\varepsilon=0$, $\chi_i=\chi=\text{const}>0$ and $D_i=1$, $i=1,2,4$. Let us remind the main result of [1]. It is contained in the following theorem.

Theorem 1
Let Assumptions 1–4 be satisfied. Let $\varepsilon=0$, $\chi_i(\rho)=\chi=\text{const}>0$, $D_i(\rho)=1$, $i=1,2,4$. Suppose that χ or the numbers $(k_b+k_b')/k$ and $\chi\|\rho_0\|_{C_x^0(\Omega)}$ are sufficiently small. Then there exists a unique global solution to system (1)–(8) satisfying (9) and (10). This solution is non-negative and each of the components $c, c_a, c_{\text{inh}}, R_1, R_2, R_4$ and ρ has its $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ norm bounded by a constant independent of $T\in(0,\infty)$, whereas R_3 has its $C_{x,t}^{0,1}(\Omega_T)$ norm bounded by a constant independent of T.

The proof of this theorem is facilitated by the following change of variables [6]:

$$S_i=\frac{R_i}{f(\rho)} \tag{13}$$

where

$$f(\rho(x))=\exp(\chi\rho(x)) \tag{14}$$

In [1] constructive conditions on the smallness of χ, which ensure that the global existence of solutions are given. It is worth wile to note that a system bearing some similarities with the one considered here and in [1] is analyzed in [8].

4. EXISTENCE RESULTS FOR NON-ZERO DIFFUSIVITY OF FIBRONECTIN

As mentioned above the main objective of this paper is to show that for a large class of the coefficients the classical solution to system (1)–(8) with $\varepsilon\neq 0$ exists globally in time.

As in the case of constant χ, we will introduce the transformation of the dependent variables, which is a generalization of transformation (13) and (14). First, let

$$f_i(\rho)=\exp\left\{\int_0^{\rho}\frac{\chi_i(s)}{[D_i(s)-\varepsilon]}\,\mathrm{d}s\right\},\quad i=1,2,4 \tag{15}$$

Then, let

$$S_1=\frac{R_1}{f_1(\rho)},\quad S_2=\frac{R_2}{f_2(\rho)},\quad S_4=\frac{R_4}{f_4(\rho)},\quad S=S_1+S_2+S_4 \tag{16}$$

It is easy to check that by means of the above transformations system (1)–(8) can be expressed in the form

$$\partial c/\partial t-D\nabla^2 c=-k_c c+J(x,t) \tag{17}$$

$$\partial R_3/\partial t=r_3R_3(R_{3\text{eq}}-R_3)+k_{23}f_4(\rho)S_4 \tag{18}$$

$$\partial c_a/\partial t-D_a\nabla^2 c_a=-k_a c_{\text{inh}}c_a+J_a^1(c_a,c_{\text{inh}})f_1(\rho)S_1+J_a(c_a,c_{\text{inh}})f_2(\rho)S_2 \tag{19}$$

$$\partial c_{\text{inh}}/\partial t-D_{\text{inh}}\nabla^2 c_{\text{inh}}=-k_a c_{\text{inh}}c_a+k_f(c_a,c_{\text{inh}})f_2(\rho)S_2 \tag{20}$$

DOI: 10.1002/mma

$$\partial S_1/\partial t - D_1\nabla^2 S_1 = \left[D_{1,\rho} + \chi_1 \frac{D_1+\varepsilon}{D_1-\varepsilon}\right]\nabla S_1\cdot\nabla\rho + S_1\Psi_1(\rho)(\nabla\rho)^2 + rS_1(R_{\mathrm{eq}}-S_f)$$
$$+k_{21}S_2 f_2(\rho) f_1(\rho)^{-1} - k_{12}(c(x,t),c_a)S_1 - \frac{\chi_1}{D_1-\varepsilon}S_1 g \qquad (21)$$

$$\partial S_2/\partial t - D_2(\rho)\nabla^2 S_2 = \left[D_{2,\rho} + \chi_2 \frac{D_2+\varepsilon}{D_2-\varepsilon}\right]\nabla S_2\cdot\nabla\rho + S_2\Psi_2(\rho)(\nabla\rho)^2$$
$$+rS_2(R_{\mathrm{eq}}-S_f) + k_{12}(c(x,t),c_a)S_1 f_1(\rho) f_2(\rho)^{-1}$$
$$-k_{21}S_2 - k_{22}S_2 - \frac{\chi_2}{D_2-\varepsilon}S_2 g \qquad (22)$$

$$\partial S_4/\partial t - D_4(\rho)\nabla^2 S_4 = \left[D_{4,\rho} + \chi_4 \frac{D_4+\varepsilon}{D_4-\varepsilon}\right]\nabla S_4\cdot\nabla\rho + S_4\Psi_4(\rho)(\nabla\rho)^2$$
$$+rS_4(R_{\mathrm{eq}}-S_f) + k_{22}S_2 f_2(\rho) f_4(\rho)^{-1} - k_{23}S_4 - \frac{\chi_4}{D_4-\varepsilon}S_4 g \qquad (23)$$

$$\partial\rho/\partial t - \varepsilon\nabla^2\rho = g(S_1,S_2,S_4,\rho) \qquad (24)$$

where

$$g = k_1 S_1 f_1 + k_2 S_2 f_2 + k_4 S_4 f_4 - k\rho \qquad (25)$$

$$S_f = f_1 S_1 + f_2 S_2 + f_4 S_4 \qquad (26)$$

and for $i = 1, 2, 4$,

$$\Psi_i(\rho) = \frac{\varepsilon}{f_i(\rho)}\left[f_i(\rho)\frac{\chi_i(\rho)}{(D_i(\rho)-\varepsilon)}\right]' \qquad (27)$$

Conditions (9), Assumption 3 and the remarks preceding Equation (12) imply the conditions:

$$\frac{\partial c}{\partial n}=0,\quad \frac{\partial c_a}{\partial n}=0,\quad \frac{\partial c_{\mathrm{inh}}}{\partial n}=0,\quad \frac{\partial S_1}{\partial n}=0,\quad \frac{\partial S_2}{\partial n}=0,\quad \frac{\partial S_4}{\partial n}=0,\quad \frac{\partial \rho}{\partial n}=0,\quad \frac{\partial R_3}{\partial n}=0 \qquad (28)$$

and the initial conditions corresponding to (10)

$$\begin{aligned} &c(x,0) = c_0(x), \quad c_a(x,0) = c_{a0}(x), \quad c_{\mathrm{inh}}(x,0) = c_{i0}(x)\\ &\rho(x,0) = \rho_0(x), \quad R_3(x,0) = R_{30}(x)\\ &S_1(x,0) = S_{10}(x) = R_1(x)/f_1(\rho_0(x)), \quad S_2(x,0) = S_{20}(x)/f_2(\rho_0(x))\\ &S_4(x,0) = S_{40}(x)/f_4(\rho_0(x)) \end{aligned} \qquad (29)$$

It is also obvious that the consistency conditions analogous to those in (11) are satisfied by the functions S_1, S_2, S_4.

DOI: 10.1002/mma

Assumption 5
For $i=1,2,4$:

1. $\varepsilon=\text{const}>0$, $C^2 \ni D_i:\mathbb{R}^1 \to [\mathscr{D}_i,\infty)$ and $\mathscr{D}_i-\varepsilon>a_i>0$.
2. $C^2 \ni \chi_i:\mathbb{R}^1 \to [0,h_i]$, $h_i=\text{const}\geqslant 0$.
3. $\Psi_i(\rho)\leqslant 0$ for all $\rho\in[0,\infty]$.
4. χ_i, D_i and ε are such that $f_i(\rho)=o(\rho)$ as $\rho\to\infty$ and for all $\rho\in[0,\infty)$ and some positive constants F_{12}, F_{21}, F_{42}, $f_2(\rho)f_1(\rho)^{-2}<F_{12}$, $f_1(\rho)f_2(\rho)^{-2}<F_{21}$, $f_2(\rho)f_4(\rho)^{-2}<F_{42}$.

Remark
The analysis of the inequality from point 3. of Assumption 5.
For $i=1,2,4$, let

$$\zeta_i(\rho):=\chi_i(\rho)(D_i(\rho)-\varepsilon)^{-1} \tag{30}$$

Then, after performing differentiation in (27), we obtain $\Psi_i(\rho)=\varepsilon(\zeta_i^2(\rho)+\zeta_i'(\rho))$; therefore, point 3. of Assumption 5 is equivalent to the demand

$$\zeta_i^2(\rho)+\zeta_i'(\rho)\leqslant 0, \quad \rho\in[0,\infty) \tag{31}$$

Let us note that $\zeta_i^2(\rho)+\zeta_i'(\rho)\leqslant 0$, e.g. for the class of functions of the form $\zeta_i(\rho)=C_1/(C_2\rho+1)^{1+\kappa}$, $C_1, C_2\geqslant 0$, $C_2(1+\kappa)\geqslant C_1$, $\kappa\geqslant 0$. In particular for given $C_1>0$, $C_2>0$ the last condition can be satisfied for κ sufficiently large. For example, the function

$$\zeta(\rho)=\zeta_0[\rho/(1+C\rho)]'=\zeta_0/(1+C\rho)^2$$

satisfies inequality (31) for $C\geqslant\zeta_0/2$.

We can give more precise characterization of functions $\zeta(\cdot)$ satisfying inequality (31).

Lemma 1
Suppose that $0<\zeta(0)=C$ and that for all $\rho\in[0,\infty)$

$$\zeta'(\rho)+\zeta^2(\rho)\leqslant 0 \tag{32}$$

Then ζ must satisfy the condition

$$\zeta(\rho)\leqslant\frac{C}{C\rho+1}:=\widetilde{\zeta}(C;\rho) \tag{33}$$

Moreover, either $\zeta(\rho)=\widetilde{\zeta}(C;\rho)$ for all $\rho\in[0,\infty)$ or there exist $\rho^*>0$ and $C^*<C$ such that $\zeta(\rho)\leqslant\widetilde{\zeta}(C^*;\rho)$ for all $\rho>\rho^*$.

Proof
First, let us note that the function $\widetilde{\zeta}$ determined in (33) satisfies the equation $\widetilde{\zeta}'+\widetilde{\zeta}^2=0$, $\widetilde{\zeta}(0)=C$, $C>0$. Therefore, the graph of the function $\zeta:[0,\infty)\to\mathbb{R}^1$ satisfying inequality (32) and such that $\zeta(0)=C$ cannot get above the graph of the function $\widetilde{\zeta}(\rho)$. To prove it, suppose to the contrary that for some $\rho=\rho_*$ we have $\zeta(\rho_*)>\widetilde{\zeta}(\rho_*)$. It follows that $\zeta'(\rho_*)<\widetilde{\zeta}'(\rho_*)$. This would imply that $\zeta(\rho)>\widetilde{\zeta}(\rho)$ for all $\rho\in[0,\rho_*)$, hence the initial condition $\zeta(0)=C$ cannot be satisfied. Hence, (33) is proved. Now, the quarter $\{(\rho,\zeta):\rho\geqslant 0,\zeta\geqslant 0\}$ can be covered by a family of curves $\zeta=K/(K\rho+1)$ with $K\in[0,\infty)$. These curves do not intersect. Suppose that $\zeta(\cdot)\neq\widetilde{\zeta}(C;\cdot)$. Then

DOI: 10.1002/mma

according to (33) there must exist $\rho^*>0$ such that $\zeta(\rho^*)=\tilde{\zeta}(C^*,\rho^*)$ with some $C^*\in[0,C)$. Now, similarly as in the proof of Lemma 1, we can show that $\zeta(\rho)\leqslant\tilde{\zeta}(\rho)$ for all $\rho\geqslant\rho^*$. Thus, the lemma is proved. □

Lemma 2
Suppose that $\zeta_i(\rho)\leqslant C_1/(C_2\rho+1)^{1+\kappa}$, where $C_1, C_2\geqslant 0, C_2(1+\kappa)\geqslant C_1$ for $\kappa>0$ and $C_2>C_1$ for $\kappa=0$. Then $f_i(\rho)=o(\rho)$ as $\rho\to\infty$.

Proof
If $\kappa>0$ then ζ_i is integrable; hence, the lemma is true. Suppose that $\kappa=0$ and $C_1<C_2$. We have $\int_0^\rho \zeta_i(s)\,\mathrm{d}s=\ln|(C_2\rho+1)^{C1/C_2}|$. Thus, $f_i(\rho)=(C_2\rho+1)^{C_1/C_2}=o(\rho)$ for $\rho\to\infty$. □

Remark
As it is seen from the proof of Lemma 2, condition 3. of Assumption 5 does not always imply condition 4. One of the exceptions is realized by the class of functions $\zeta=C_1/(C_1\rho+1)$.

We will start our considerations by an auxiliary lemma, which will be useful in the proof of the estimate of the upper C^0-bounds of the functions ρ and S_i, $i=1,2,4$ satisfying system (17)–(24).

Lemma 3
Assume that Assumption 5 is satisfied. Then the system

$$
\begin{aligned}
&\sup_{\rho\in[0,\overline{\rho}]}\{rS_1(R_{\mathrm{eq}}f_1(\rho)^{-1}-S_1)+k_{21}S_2f_2(\rho)f_1(\rho)^{-2}+f_1(\rho)^{-1}\zeta_1(\rho)[-f_1(\rho)k_1S_1^2+S_1k\rho]\}<0\\
&\sup_{\rho\in[0,\overline{\rho}]}\{rS_2(R_{\mathrm{eq}}f_2(\rho)^{-1}-S_2)+\overline{k}_{12}S_1f_1(\rho)f_2(\rho)^{-2}+f_2(\rho)^{-1}\zeta_2(\rho)[-f_2(\rho)k_2S_2^2+S_2k\rho]\}<0\\
&\sup_{\rho\in[0,\overline{\rho}]}\{rS_4(R_{\mathrm{eq}}f_4(\rho)^{-1}-S_4)+k_{22}S_2f_2(\rho)f_4(\rho)^{-2}+f_4(\rho)^{-1}\zeta_4(\rho)[-f_4(\rho)k_4S_4^2+S_4k\rho]\}<0\\
&\qquad k_1S_1f_1(\rho)+k_2S_2f_2(\rho)+k_4S_4f_4(\rho)-k\rho<0
\end{aligned}
\tag{34}
$$

where $\overline{k}_{12}$ is defined in Assumption 2 and

$$\zeta_i(\rho)=\chi_i(\rho)/(D_i(\rho)-\varepsilon) \tag{35}$$

possesses a positive solution $(\overline{S}_1,\overline{S}_2,\overline{S}_4,\overline{\rho})$ such that for all $x\in\overline{\Omega}$

$$
\begin{aligned}
0\leqslant S_{10}(x)<\overline{S}_1,\quad 0\leqslant S_{20}(x)<\overline{S}_2\\
0\leqslant S_{40}(x)<\overline{S}_4,\quad 0\leqslant\rho_0(x)<\overline{\rho}
\end{aligned}
\tag{36}
$$

Proof
Note that, according to the Remark after Assumption 5 and Lemma 1, $\zeta_i(\rho)=\chi_i(\rho)/(D_i(\rho)-\varepsilon)$ behaves like $O(\rho^{-1})$ as $\rho\to\infty$. Thus, the numbers

$$\mathscr{I}_i=\sup_{\rho\in(0,\infty)}\rho\chi_i(\rho)/(D_i(\rho)-\varepsilon) \tag{37}$$

DOI: 10.1002/mma

are finite. Hence, due to point 4. of Assumption 5, we note that, independently of the value of ρ, there exists a solution $\overline{S}_1, \overline{S}_2, \overline{S}_4$ to the system of the first three inequalities of (34) satisfying the condition $\overline{S}_i > S_{i0}(x)$ for all $x \in \overline{\Omega}$. By putting this solution to the last inequality of this system, we obtain the condition

$$k_1 \overline{S}_1 f_1(\rho) + k_2 \overline{S}_2 f_2(\rho) + k_4 \overline{S}_4 f_4(\rho) - k\rho < 0$$

But, due to Lemma 2 and Assumption 5, $f_i(\rho) = o(\rho)$ as $\rho \to \infty$; hence, obviously we can find a solution $\overline{\rho}$ to the above equation such that $\overline{\rho} > \rho_0(x)$ in Ω. □

Below, we will need the following auxiliary lemma.

Lemma 4
Assume that u is a solution to the problem

$$u_t - L_0 u = f(x,t), \quad (x,t) \in \Omega \times (0,T)$$

$$\frac{\partial u}{\partial n} = 0, \quad (x,t) \in \partial\Omega \times (0,T), \quad u(x,0) = \phi(x), \quad x \in \overline{\Omega}, \quad \frac{\partial \phi}{\partial n} = 0, \quad x \in \partial\Omega$$

where L_0 is a uniformly elliptic operator of the form

$$L_0 u = \sum_{i,j=1,\dots,m} a_{ij}(x,t) \frac{\partial^2}{\partial x_j \partial x_j} u + \sum_{i=1,\dots,m} B_i(x,t) \frac{\partial}{\partial x_i} u + A(x,t) u$$

Suppose that $\phi \in C_x^{1+\beta}(\Omega)$ and that for all $i, j = 1, \dots, m$ the coefficients of the operator L_0 satisfy the following conditions:

$$\|a_{ij}\|_{C_t^{\beta/2}(\Omega\times(0,\infty))} + \|a_{ij}\|_{C_x^1(\Omega\times(0,\infty))} \leqslant M_a, \quad \|B_i\|_{L^\infty(\Omega\times(0,\infty))} \leqslant C_B, \quad \|A\|_{L^\infty(\Omega\times(0,\infty))} \leqslant C_A \tag{38}$$

where M_a, C_B and C_A are constants. Fix, any $\widetilde{T} > 0$. Then for $T \in (0, 2\widetilde{T})$

$$\|u\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega\times(0,T))} \leqslant W_1(T)[\|f\|_{C^0(\Omega\times(0,T))} + \|\phi\|_{C_x^{1+\beta}(\Omega)}] \tag{39}$$

whereas for every $T > t_0 \geqslant \max\{\widetilde{T}, T - \widetilde{T}\}$ the following estimation holds:

$$\|u\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega\times(t_0,T))} \leqslant C^*[\|f\|_{C^0(\Omega\times(t_0 - \widetilde{T}/2,T))} + \|u\|_{C^0(\Omega\times(t_0-\widetilde{T}/2,T))}] \tag{40}$$

where the constant C^* can be chosen to be independent of T.

Proof
According to Theorem 6.49 of section VI in [9], for every $T > 0$ the following estimation holds:

$$\|u\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega\times(0,T))} \leqslant W[\|f\|_{L^\infty(\Omega\times(0,T))} + \|\phi\|_{C_x^{1+\beta}(\Omega)}] \tag{41}$$

(Note that $f \in L^\infty(\Omega \times (0,T))$ belongs also to the Morrey space $M_{1,1+m+\beta}$ and that L_0 can be written in the quasi-divergence form defined implicitly by (6.2) in [9].) The constant W in the above estimation depends on the constants M_a, C_B, C_A and in principle it may depend also on T.

DOI: 10.1002/mma

To prove that W may be chosen independent of T, assume that the considered solution (existing for $t\in(0,T)$) has its C^0 norm bounded uniformly in t and let us denote $\widetilde{T}=2K$. For $t\in(0,\widetilde{T})$ we can use estimation (39). Suppose that we are interested in the estimation of $\|u\|_{C^{1+\beta,(1+\beta)/2}_{x,t}}$ in $\Omega\times(t_0,T)$. Let $\eta(t)$ be a C^∞ cutting-off function, such that $\eta:\mathbb{R}^1\to[0,1]$, $\eta(t)\equiv 0$ for $t\leqslant t_0-K$ and $\eta(t)\equiv 1$ for $t\geqslant t_0$. The function $w=\eta u$ satisfies the equation

$$w_t-L_0 w=\eta f(x,t)+\eta'(t)u(x,t),\quad (x,t)\in\Omega\times(t_0-K,T)$$

with the no-flux boundary conditions and zero initial conditions at $t=t_0-K$. Thus, by means of inequality (41) we have the estimation

$$\|w\|_{C^{1+\beta,(1+\beta)/2}_{x,t}(\Omega\times(t_0-K,T))}\leqslant C[\|f\|_{L^\infty(\Omega\times(t_0-K,T))}+E\|u\|_{C^0(\Omega\times(t_0-K,T))}] \tag{42}$$

where $E=\sup_t \eta'(t)$, from which follows the $C^{1+\beta,(1+\beta)/2}_{x,t}$ estimation of u on the set $\Omega\times(t_0,T)$. Hence, there exists a constant C_* such that for all $t\in(t_0,T)$

$$\|u\|_{C^{1+\beta,(1+\beta)/2}_{x,t}(\Omega\times(t_0,T))}\leqslant C_*[\|f\|_{C^0(\Omega\times((t_0-\widetilde{T}/2,T))}+E\|u\|_{C^0(\Omega\times(t_0-\widetilde{T}/2,T))}] \tag{43}$$

which is equivalent to (40). □

Remark
An inequality similar to inequality (41) can also be deduced from Theorems IV.9.1 and IV.10.1 in [10].

Theorem 2
Let Assumptions 1–5 hold. Then for any $T>0$ there exists a unique solution to system (19)–(24) which satisfies the boundary–initial conditions (28)–(29) and such that the $C^{2+\beta,1+\beta/2}_{x,t}(\Omega_T)$ norms of the functions $c_a, c_{\text{inh}}, S_1, S_2, S_4$ and ρ are bounded by constants independent of T.

Proof of Theorem 2
Let

$$U=(c_a,c_{\text{inh}},S_1,S_2,S_4,\rho) \tag{44}$$

Let the vector of the right-hand sides of Equations (19)–(24) be denoted by

$$\Phi(U)=(\Phi_1(U),\Phi_2(U),\Phi_3(U),\Phi_4(U),\Phi_5(U),\Phi_6(U))$$

and the vector of left-hand side operators by

$$L=(L_1,L_2,L_3,L_4,L_5,L_6)$$

Given the vector $\widetilde{U}$, let $U=P(\widetilde{U})$ be the solution to the system

$$L(\widetilde{\rho})U=\Phi(\widetilde{U}) \tag{45}$$

in the set $\Omega_T=\Omega\times(0,T)$ for some $T>0$ subject to the initial and boundary conditions (29) and (28). Above, by writing $L(\widetilde{\rho})$ we mean that in the left-hand side operators we take $D_i(\widetilde{\rho})$, $i=1,2,4$. Let us consider the mapping

$$U=P(\widetilde{U})$$

DOI: 10.1002/mma

We will prove below using the Schauder estimates (see, e.g. Theorem IV.5.3 in [9, 10]) that for $T>0$ sufficiently small P is a contractive mapping acting from the space $\mathscr{M}=C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$ to itself. The norm $\|U\|_{\mathscr{M}}$ is given by the sum of $C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$ norms of U_i. According to the definition of the Hölder norms (see Section I.1 in [10]) for $h\in C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$ we have

$$\|h\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)}=\sup_{x\in\Omega}\|h(x,\cdot)\|_{C_t^{(1+\beta)/2}((0,T))}+\|\nabla h\|_{C_{x,t}^{\beta,\beta/2}(\Omega_T)} \tag{46}$$

Let U_0 denote the vector of initial functions and consider a closed ball B in the considered space defined by $B=\{U\in\mathscr{M}:\|U-U_0\|_{\mathscr{M}}\leqslant 1\}$, that is to say

$$\|U-U_0\|_{\mathscr{M}}=\sum_{i=1}^{6}\|U_i-U_{0i}\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)}$$

and due to (46)

$$\begin{aligned}\|U_i-U_{0i}\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)} &=\sup_{x\in\Omega}\|U_i(x,\cdot)-U_{0i}(x)\|_{C_t^{(1+\beta)/2}((0,T))}\\ &\quad+\sup_{x\in\Omega}\|\nabla U_i(x,\cdot)-\nabla U_{0i}(x,\cdot)\|_{C_t^{\beta/2}(0,T)}\\ &\quad+\sup_{t\in(0,T)}\|\nabla U_i(\cdot,t)-\nabla U_{0i}(\cdot,t)\|_{C_x^{\beta}(\Omega)}\end{aligned} \tag{47}$$

Let $\widetilde{U}\in B$. Then every $U_i\in C_{x,t}^{2+\beta,1+\beta/2}$ and from the Schauder estimates for the function U_i-U_{0i} (see Theorem IV.5.3 in [10]) we know that as $t\to 0$

$$\|U_i(\cdot,t)-U_{0i}(\cdot)\|_{C_x^2(\Omega)}\to 0 \tag{48}$$

To be more precise, it follows from inequality (5.11) of section IV in [10] that (U_i-U_{0i}) and its first and second derivatives with respect to x belong to the class $C_t^{\beta/2}((0,T))$. Hence, the third term in (47) vanishes as $T^{\beta/2}$ for $T\to 0$. From the same inequality we infer that for all $i=1,\ldots,6$

$$\|\partial U_i/\partial t\|_{C^0(\Omega_T)}<K_1,\quad \|\nabla U_i(x,\cdot)-\nabla U_{0i}(x,\cdot)\|_{C_t^{(1+\beta)/2}((0,T))}<K_2 \tag{49}$$

independent of $x\in\overline{\Omega}$. The constants K_1,K_2 can be chosen independent of $\widetilde{U}\in B$. From (48) and the first inequality in (49) we infer that the first term at the right-hand side of (47) tends to zero for $T\to 0$ as $T^{1/2-\beta/2}$. Finally, from the second inequality in (49) we infer that $\|\nabla U_i(x,\cdot)-\nabla U_{0i}(x)\|_{C_t^{\beta/2}((0,T))}$ tends to zero for $T\to 0$ as $T^{1/2}$. Consequently, $\|U-U_0\|_{\mathscr{M}}$ behaves like K_3T^{δ}, $\delta>0$, where the constant K_3 depends on the $C^{2+\beta,1+\beta/2}$ norms of U_0 and the region Ω. It follows that for $T>0$ sufficiently small P acts from B to B. Proceeding in the same manner we can easily prove that

$$\|P(\widetilde{U}_2)-P(\widetilde{U}_1)\|_{\mathscr{M}}\leqslant T^{\nu}K_4\|\widetilde{U}_2-\widetilde{U}_1\|_{\mathscr{M}} \tag{50}$$

for all $\widetilde{U}_1,\widetilde{U}_2\in B$ with $\nu>0$. To be more precise, let us note that the equation for U_1-U_2 can be obtained by subtracting the equations for U_1 and U_2 and moving the terms $[D_i(\widetilde{\rho}_1)-D_i(\widetilde{\rho}_2)]\Delta S_{2i}=(\widetilde{\rho}_2-\widetilde{\rho}_1)D_i'(\widetilde{\rho}_1+\theta(\widetilde{\rho}_2-\widetilde{\rho}_1))\Delta S_{2i}$ in the equation for S_{2i}, $i=1,2,4$ to the right-hand side. U_1-U_2 satisfies zero initial and no-flux boundary conditions. Moreover, every component of U_1-U_2

DOI: 10.1002/mma

satisfies an equation, the right-hand side of which can be estimated as a sum of the absolute value of components of $U_1 - U_2$ and $(\nabla U_1 - \nabla U_2)$. Thus, according to Lemma 4, inequality (50) is satisfied. Hence, for $T>0$ sufficiently small mapping is a contraction from B to B.

Thus, from the contraction mapping principle we infer that for $T>0$ sufficiently small P has a unique fixed point in the same space. Moreover, this fixed point is of class

$$C^{2+\beta,1+\beta/2}_{x,t}(\Omega_T)$$

and in fact is a solution to the system

$$LU = \Phi(U)$$

It is clear that T depends only on the $C^{2+\beta}_x(\Omega)$ norm of the initial data [7, 9, 10]. It follows that being able to prove *a priori* that the $C^{2+\beta,1+\beta/2}_{x,t}(\Omega_T)$ norm of all the components of U is bounded by a common constant C, which is independent of T, we can conclude, applying the continuation method (by successive changing of the initial conditions), that the solution exists globally.

We start our estimations by establishing the C^0-bounds of the functions c_a, c_{inh}, ρ and S_i, $i=1,2,4$.

Lemma 5

Suppose that Assumptions 1–5 are satisfied. Let $\overline{S}_1, \overline{S}_2, \overline{S}_4$ and $\overline{\rho}$ be as in Lemma 3. Let $C_a > \widetilde{C}_a$, $C_{\text{inh}} > \widetilde{C}_{\text{inh}}$ with $\widetilde{C}_a$ and $\widetilde{C}_{\text{inh}}$ determined in Assumption 4 be such that $0 \leqslant c_{a0}(x) \leqslant C_a$, $0 \leqslant c_{\text{inh}0}(x) < C_{\text{inh}}$. Suppose that for $t \in (0,T)$, $T>0$, there exists a unique $C^{2,1}_{x,t}(\Omega_T)$ solution to system (17), (19)–(24). Then

$$0 \leqslant c(x,t) < C_c, \quad 0 \leqslant c_a(x,t) < C_a, \quad 0 \leqslant c_{\text{inh}}(x,t) < C_{\text{inh}} \tag{51}$$

and

$$0 \leqslant S_1(x,t) < \overline{S}_1, \quad 0 \leqslant S_2(x,t) < \overline{S}_2, \quad 0 \leqslant S_4(x,t) < \overline{S}_4, \quad 0 \leqslant \rho_0(x) < \overline{\rho} \tag{52}$$

Proof

Obviously, due to Assumption 2, $c(x,t) \in C^{2,1}_{x,t}(\Omega_T)$ and by the maximum principle (Theorem 3.4.7 in [11]), we conclude that there exists a positive constant C_c such that $0 \leqslant c(x,t) < C_c$. Now, we will prove the validity of inequalities (52). To this end we will consider the following modification of system (21)–(24) with the Lipschitz continuous source functions:

$$\begin{aligned}\partial S_1/\partial t - D_1(\rho)\nabla^2 S_1 = {} & \left[D_{1,\rho} + \chi_1 \frac{D_1+\varepsilon}{D_1-\varepsilon}\right] \nabla S_1 \cdot \nabla\rho + S_1^+ \Psi_1(\rho)(\nabla\rho)^2 \\ & + r|S_1|R_{\text{eq}} - r S_1^+ S_f + k_{21}|S_2| f_2(\rho) f_1(\rho)^{-1} \\ & - k_{12}(c(x,t), c_a) S_1 - \frac{\chi_1}{D_1-\varepsilon} S_1^+ g \end{aligned} \tag{53}$$

$$\begin{aligned}\partial S_2/\partial t - D_2(\rho)\nabla^2 S_2 = {} & \left[D_{2,\rho} + \chi_2 \frac{D_2+\varepsilon}{D_2-\varepsilon}\right] \nabla S_2 \cdot \nabla\rho + S_2^+ \Psi_2(\rho)(\nabla\rho)^2 \\ & + r|S_2|R_{\text{eq}} - r S_2^+ S_f + k_{12}(c(x,t), c_a)|S_1| f_1(\rho) f_2(\rho)^{-1} \\ & - k_{21} S_2 - k_{22} S_2 - \frac{\chi_2}{D_2-\varepsilon} S_2^+ g \end{aligned} \tag{54}$$

DOI: 10.1002/mma

$$\begin{aligned}\partial S_4/\partial t - D_4(\rho)\nabla^2 S_4 = &\left[D_{4,\rho} + \chi_4 \frac{D_4+\varepsilon}{D_4-\varepsilon}\right]\nabla S_4\cdot\nabla\rho + S_4^+\Psi_4(\rho)(\nabla\rho)^2 \\ &+ r|S_4|R_{\mathrm{eq}} - rS_4^+S_f + k_{22}|S_2|f_2(\rho)f_4(\rho)^{-1} \\ &- k_{23}S_4 - \frac{\chi_4}{D_4-\varepsilon}S_4^+ g \end{aligned} \tag{55}$$

$$\partial\rho/\partial t - \varepsilon\nabla^2\rho = |k_1 S_1| f_1 + |k_2 S_2| f_2 + |k_4 S_4| f_4 - k\rho \tag{56}$$

Here $S_i^+ := \max\{0, S_i\}$, $i=1,2,4$. (Note that according to Assumptions 2 and 5, the functions k_{12}, D_i and χ_i are defined also for negative values of their arguments.) It is obvious that for the modified system consisting of Equations (17), (19)–(20) and (53)–(56), we can apply the above considerations, which ensure the existence of a unique local in time solution as the source functions are Lipschitz continuous. (Note that $||a|-|b||\leqslant|a-b|$ and $|a^+-b^+|\leqslant|a-b|$.) First, suppose that there exists a time $t_0>0$ in the interval of existence such that $\rho(\cdot,t_0)$, attains a negative minimum equal to $(-\eta)<0$ at a point $x_0\in\overline{\Omega}$. We can take $\eta>0$ arbitrarily small and assume that the time derivative of ρ at the point (x_0,t_0) is non-positive. Suppose that $x_0\in\Omega$. Then $\Delta\rho(x_0,t_0)\geqslant 0$. Hence, we arrive at a contradiction as the right-hand side of Equation (56) is positive at (x_0,t_0). As η can be taken arbitrarily small we conclude that ρ is non-negative on the maximal interval of the solution existence. If $x_0\in\partial\Omega$ and $\rho(x,t_0)>-\eta$ for $x\in\Omega$, then using the maximum principle (see, e.g. Theorem 2.3.7 in [11]) stating that $\partial\rho/\partial n\,(x_0,t_0)<0$ we arrive at a contradiction as ρ satisfies zero Neumann boundary conditions. Having proved the non-negativity of $\rho(x,t)$, we can use the same arguments to show that the functions S_1, S_2, S_4 are non-negative on the maximal interval of the solution existence. First, suppose that at $t=t_0$, the function S_i attains a negative minimum equal to $(-\eta)<0$ at a point $x_0\in\Omega$ and that its time derivative is non-positive. Then $\nabla S_i(x_0,t_0)=0$, whereas $\Delta S_i(x_0,t_0)\geqslant 0$. We thus arrive at a contradiction as the source term in the equation for S_i is strictly positive for $\eta>0$. If $x_0\in\partial\Omega$ and $S_i(x,t_0)>-\eta$ for $x\in\Omega$, then by means of the maximum principle (e.g. Theorem 2.3.7 in [11]) we would have $\partial S_i/\partial n\,(x_0,t_0)<0$; hence, we arrive at a contradiction as S_i satisfies zero Neumann boundary conditions. As the source functions have been changed only for negative values of S_1, S_2, S_4 and ρ, we have proved that the unique solution to the problem satisfies the non-negativity bounds. The proof that $S_i(t,x)<\overline{S}_i$, $\rho(x,t)<\overline{\rho}$ for all $x\in\overline{\Omega}$ and $t>0$ in the maximal interval of existence can be carried out in the same manner. In this case, we use Lemma 3 and the fact that the terms $\overline{S}_i\Psi_i(\rho)$ are non-positive. Having proved estimations (52), we can use Theorem 8.9.3 in [12] to claim that there exists a unique classical solution (c_a, c_{inh}) to system (19), (20), which satisfies the bounds $c_a(x,t)\in[0,C_a)$, $c_{\mathrm{inh}}(x,t)\in[0,C_{\mathrm{inh}})$. In consequence, in view of the uniqueness of the solution to the initial boundary value problem we obtain the claim of the lemma as the solution to system (53)–(56) is in fact the solution to system (21)–(24). □

Having the C^0-bounds of the functions $c, c_a, c_{\mathrm{inh}}, S_1 S_2, S_4$ and ρ we can obtain further estimations.

Lemma 6

Suppose that for $t\in(0,T)$, $T>0$, there exists a unique solution to system (17)–(24) satisfying the conditions of Lemma 5. Then there exists a constant M depending only on $C_c, C_a, C_{\mathrm{inh}}, \overline{\rho}, \overline{S}_1, \overline{S}_2$

DOI: 10.1002/mma

and $\overline{S}_4$ such that

$$|\rho(x,t)|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)} \leqslant M$$

Similarly

$$|c_a(x,t)|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)} \leqslant M, \quad |c_{\mathrm{inh}}(x,t)|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)} \leqslant M$$

Proof
The proof follows from Lemma 4. Here we treat $k_1 S_1 f_1(\rho) + k_2 S_2 f_2(\rho) + k_4 S_4 f_4(\rho)$ as well as the right-hand sides of Equations (19) and (20) as free terms. □

Equation (17) separates from the rest of the system. According to Assumptions 1–2, the unique solution to Equation (17) is non-negative and $\|c\|_{C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)} \leqslant K_c$ with K_c independent of T.

Next, we can estimate the $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ norms of the solution. This can be done in three steps. In the first we use the Hölder estimates for c_a, c_{inh}, ρ and Lemma 4 (by treating S_j, $j \neq i$, in the equation for S_i as C_0 bounded functions) to obtain the Hölder continuity of S_i. In the second, we use the Schauder estimates (e.g. Theorem IV.5.3 in [9, 10]) to estimate the $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ norms of c_a, c_{inh} and ρ. Finally, we can obtain the boundedness of $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ norms of S_i, $i = 1, 2, 4$. The theorem is proved. Equation (18) is solvable knowing the functions S_4 and ρ. Theorem 2 is proved. □

According to Remarks after Assumption 5 and Lemma 2 we can formulate a more specific theorem.

Theorem 3
Let Assumptions 1–4 hold. Let points 1. and 2. of Assumption 5 hold. Suppose that, for $i = 1, 2, 4$, $\zeta_i(\rho)$ defined by Equation (35), satisfy the equality $\zeta_i(\rho) = C_{1i}/(C_{2i}\rho + 1)^{1+\kappa}$ where $C_{1i}, C_{2i} \geqslant 0, C_{2i}(1+\kappa) \geqslant C_{1i}$ for $\kappa > 0$ and $C_{2i} > C_{1i}$ for $\kappa = 0$. Then for any $T > 0$ there exists a unique solution to system (19)–(24) subject to the boundary–initial conditions (28)–(29) such that the $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ norm of the functions $c_a, c_{\mathrm{inh}}, S_1, S_2, S_4$ and ρ is bounded by constants independent of T.

Remark
In particular, we can suppose that for each $i = 1, 2, 4$, either

$$\zeta_i(\rho) = C_{1i}/(C_{2i}\rho + 1), \quad C_{2i} > C_{1i}$$

or

$$\zeta_i(\rho) = C_{1i}/(C_{2i}\rho + 1)^2, \quad C_{2i} \geqslant C_{1i}/2$$

The first case is called the logarithmic sensitivity case, the second one is called the receptor's kinetics case (see [13, p. 13]).

Now, we will consider the case, when $k_i = k_i(R_i)$. To be more precise we assume that the products $k_i(R_i)R_i$, $i = 1, 2, 4$, are bounded uniformly for all $R_i \geqslant 0$. This time we may discard points 3. and 4. of Assumption 5. Biologically, this assumption means that the speed of the fibronectin production is finite, independent on the local densities of the mobile cells.

DOI: 10.1002/mma

Assumption 6
For $i=1,2,4$, let

1. $C^2 \ni D_i : \mathbb{R}^1 \to [\mathscr{D}_i, \infty)$, $\varepsilon = \text{const} > 0$ and $\mathscr{D}_i - \varepsilon > a_i > 0$.
2. $C^2 \ni \chi_i : \mathbb{R}^1 \to [0, h_i]$, $h_i = \text{const} \geqslant 0$.
3. $k_i \in C^2(\mathbb{R}^1)$, $k_i(R_i)R_i < \mathscr{C}_i$, $i=1,2,4$.

Remark
Point 3. of Assumption 6 implies, according to transformation (16), that for all $S_i \in [0,\infty)$, $\rho \in [0,\infty)$

$$\hat{k}_i(S_i,\rho)S_i f_i(\rho) = k_i(S_i f_i(\rho))S_i f_i(\rho) < \mathscr{C}_i$$

Theorem 4
Let Assumptions 2, 3, 4 and 6 hold. Let Assumption 1 hold except for k_i, $i=1,2,4$, which satisfy point 3. of Assumption 6. Then for any $T>0$ there exists a unique solution to system (19)–(24) subject to the boundary–initial conditions (28)–(29) such that the $C^{2+\beta,1+\beta/2}_{x,t}(\Omega_T)$ norm of the functions $c_a, c_{\text{inh}}, S_1, S_2, S_4$ and ρ is bounded by constants independent of T.

Proof
The proof will be a modification of the proof of Theorem 3. First, we can choose $\rho = \overline{\rho}$, sufficiently large, so that the fourth inequality (36) is satisfied. To be more precise, $\rho = \overline{\rho}$ may be taken so large that

$$\sum_{i=1,2,4} \mathscr{C}_i - k\overline{\rho} < 0$$

and the last of the inequalities in (36) is satisfied. Now, treating $\sum \hat{k}_i(S_i,\rho)S_i f_i(\rho)$ in Equation (24) as a free term (bounded in C^0 norm by $\sum_{i=1,2,4}\mathscr{C}_i$), we can use Lemma 4 to estimate the norm of the spatial derivatives of the function ρ. Hence, the terms $\nabla^2\rho$ can be *a priori* estimated by a constant p, that is to say $\sup_{(x,t)\in\Omega_T} \nabla^2\rho(x,t) < p$, where p depends only on the numbers $\mathscr{C}_i$. Consequently, we can find $\overline{S}_i$ such that for $S_i = \overline{S}_i$, $i=1,2,4$, $\rho \in [0,\overline{\rho}]$, the system

$$\begin{aligned}
&rS_1(R_{\text{eq}} - S_1 f_1(\rho)) + k_{21}S_2 f_2(\rho) f_1(\rho)^{-1} + \zeta_1(\rho)S_1[-f_1(\rho)\hat{k}_1(S_1,\rho)S_1 + k\rho] + S_1 p\overline{\Psi}_1 < 0\\
&rS_2(R_{\text{eq}} - S_2 f_2(\rho)) + \overline{k}_{12}S_1 f_1(\rho) f_2(\rho)^{-1} + \zeta_2(\rho)S_2[-f_2(\rho)\hat{k}_2(S_2,\rho)S_2 + k\rho] + S_2 p\overline{\Psi}_2 < 0\\
&rS_4(R_{\text{eq}} - S_4 f_4(\rho)) + k_{22}S_2 f_2(\rho) f_4(\rho)^{-1} + \zeta_4(\rho)S_4[-f_4(\rho)\hat{k}_4(S_4,\rho)S_4 + k\rho] + S_4 p\overline{\Psi}_4 < 0
\end{aligned} \quad (57)$$

being a modification of system (34) by the terms $S_i p\overline{\Psi}_i$, where $\overline{\Psi}_i = \sup_{\rho\in[0,\overline{\rho}]} \Psi_i(\rho)$, is satisfied. This is due to the fact that p depends only on $\mathscr{C}_1, \mathscr{C}_2, \mathscr{C}_4$ (and not on $\overline{S}_i$) and that the coefficient r by the quadratic terms S_i^2 in each of the equations is negative. It is easy to note that the solvability of this system implies the existence of a global solution to system (19)–(24). □

Remark
Let us note that this time we do not assume any additional conditions concerning the coefficients D_i and χ_i. Theorem 4 holds even if the quantities $\zeta_i(\rho) = \chi_i(\rho)/(D_i(\rho) - \varepsilon)$ are not tending to zero or even growing to infinity for $\rho \to \infty$.

DOI: 10.1002/mma

Obviously, having the functions $\rho(\cdot,\cdot)$, $S_1(\cdot,\cdot)$, $S_2(\cdot,\cdot)$ and $S_4(\cdot,\cdot)$ we can invert the transformation (16) to obtain the functions $R_1(\cdot,\cdot)$, $R_2(\cdot,\cdot)$ and $R_4(\cdot,\cdot)$.

Theorem 5
Let the assumptions of one of Theorems 2–4 be satisfied. Then there exists a unique global classical solution to system (1)–(8) satisfying conditions (10) and (9). This solution is non-negative. The functions $c, c_a, c_{\text{inh}}, R_1, R_2, R_4$ and ρ have their $C^{2+\beta,1+\beta/2}_{x,t}(\Omega_T)$ norms bounded by constants independent of $T\in(0,\infty)$. The function $R_3(x,t)$ has its $C^{0,0}_{x,t}$ norm bounded by a constant independent of T.

Proof
We have to show only the last statement. Since R_2 is globally bounded and there is a minus sign in front of the quadratic term $r_3R_3^2$, the function $R_3(x,t)<C$ for $(x,t)\in\overline{\Omega}_T$. □

5. CASE OF FAST EQUILIBRATING FIBRONECTIN

In this section we will assume that the evolution of the fibronectin is fast. To be more precise, we will approximate the equation describing the evolution of fibronectin by the stationary one

$$0=\varepsilon\nabla^2\rho+k_1R_1+k_2R_2+k_4R_4-k\rho \tag{58}$$

This time we will not apply the change of variables $R_i\to S_i$, $i=1,2,4$. However, using Equation (58), we can replace the terms $(-R_i\chi_i(\rho)\nabla^2\rho)$ simply by the non-differential terms $R_i\chi_i(\rho)\varepsilon^{-1}(k_1R_1+k_2R_2+k_4R_4-k\rho)$. Hence, we obtain the following system:

$$\partial c/\partial t-D\nabla^2c=-k_cc+J(x,t) \tag{59}$$

$$\partial R_3/\partial t=r_3R_3(R_{3\text{eq}}-R_3)+k_{23}R_4 \tag{60}$$

$$\partial c_a/\partial t-D_a\nabla^2c_a=-k_ac_{\text{inh}}c_a+J_a^1(c_a,c_{\text{inh}})R_1+J_a(c_a,c_{\text{inh}})R_2 \tag{61}$$

$$\partial c_{\text{inh}}/\partial t-D_{\text{inh}}\nabla^2c_{\text{inh}}=-k_ac_{\text{inh}}c_a+k_f(c_a,c_{\text{inh}})R_2 \tag{62}$$

$$\begin{aligned}\partial R_1/\partial t-D_1(\rho)\nabla^2R_1&=[D_1'(\rho)-\chi_1(\rho)]\nabla R_1\cdot\nabla\rho-R_1\chi_1'(\rho)(\nabla\rho)^2\\&\quad+\chi_1(\rho)\varepsilon^{-1}R_1(k_1R_1+k_2R_2+k_4R_4-k\rho)\\&\quad+rR_1(R_{\text{eq}}-R)+k_{21}R_2-k_{12}(c,c_a)R_1\end{aligned} \tag{63}$$

$$\begin{aligned}\partial R_2/\partial t-D_2(\rho)\nabla^2R_2&=[D_2'(\rho)-\chi_2(\rho)]\nabla R_2\cdot\nabla\rho-R_2\chi_2'(\rho)(\nabla\rho)^2\\&\quad+\chi_2(\rho)\varepsilon^{-1}R_2(k_1R_1+k_2R_2+k_4R_4-k\rho)\\&\quad+rR_2(R_{\text{eq}}-R)+k_{12}(c,c_a)R_1-k_{21}R_2-k_{22}R_2\end{aligned} \tag{64}$$

DOI: 10.1002/mma

$$\partial R_4/\partial t - D_4(\rho)\nabla^2 R_4 = [D_4'(\rho)-\chi_4(\rho)]\nabla R_4\cdot\nabla\rho - R_4\chi_4'(\rho)(\nabla\rho)^2 + \chi_4(\rho)\varepsilon^{-1}R_4(k_1R_1+k_2R_2+k_4R_4-k\rho) + rR_4(R_{\text{eq}}-R)+k_{22}R_2-k_{23}R_4 \tag{65}$$

$$0=\varepsilon\nabla^2\rho+k_1R_1+k_2R_2+k_4R_4-k\rho \tag{66}$$

It follows from the considerations of the last section that in order to use the invariant region method, due to the sign by the terms $k\rho$, it suffices to consider the existence of a triple $(\overline{R}_1,\overline{R}_2,\overline{R}_3)$ such that for $(R_1,R_2,R_3)=(\overline{R}_1,\overline{R}_2,\overline{R}_3)$ and all the considered values of ρ the following system of inequalities is satisfied:

$$\begin{aligned}\chi_1(\rho)\varepsilon^{-1}R_1(k_1R_1+k_2R_2+k_4R_4)+rR_1(R_{\text{eq}}-R)+k_{21}R_2-k_{12}(c,c_a)R_1&<0\\ \chi_2(\rho)\varepsilon^{-1}R_2(k_1R_1+k_2R_2+k_4R_4)+rR_2(R_{\text{eq}}-R)+k_{12}(c,c_a)R_1-k_{21}R_2-k_{22}R_2&<0\\ \chi_4(\rho)\varepsilon^{-1}R_4(k_1R_1+k_2R_2+k_4R_4)+rR_4(R_{\text{eq}}-R)+k_{22}R_2-k_{23}R_4&<0\end{aligned} \tag{67}$$

and such that for $x\in\overline{\Omega}$:

$$0\leqslant R_{10}(x)<\overline{R}_1,\quad 0\leqslant R_{20}(x)<\overline{R}_2,\quad 0\leqslant R_{40}(x)<\overline{R}_4 \tag{68}$$

Assumption 7
For $i=1,2,4$ suppose that χ_i satisfies point 2. of Assumption 5 and that $\chi_i'(\rho)\geqslant 0$ for all $\rho\in[0,\overline{\rho}]$.

Note that χ_i satisfying the above assumption is bounded ($\chi_i(\rho)\leqslant h_i$) and may behave qualitatively as $C(1-c_1\exp[-c_2\rho])$ for some non-negative constants C, c_1, c_2.

Assumption 8
Suppose that system (67) possesses a solution $\overline{R}_1,\overline{R}_2,\overline{R}_4$ satisfying conditions (68).

Remark
The last assumption is satisfied, for example, if the constant r multiplying the mitotic terms is sufficiently large in comparison with the constants $\sup_{\rho\in(0,\infty)}\chi_i(\rho)\varepsilon^{-1}(k_1+k_2+k_4)$. The solvability of system (67) can be also ensured, if we replace the constant r in the equations for R_i, $i=1,2,4$, by the functions $r_i(R_i)$ such that $r_i(R_i)\to\infty$ as $R_i\to\infty$.

Obviously, these inequalities have solutions for $\overline{R}_1,\overline{R}_2,\overline{R}_4$ satisfying the above conditions. Having the values of $\overline{R}_1,\overline{R}_2,\overline{R}_4$ we can in turn find the value of $\overline{\rho}$ satisfying the inequalities

$$k_1\overline{R}_1+k_2\overline{R}_2+k_4\overline{R}_4-k\overline{\rho}<0,\quad 0\leqslant\rho_0(x)<\overline{\rho},\quad x\in\overline{\Omega}$$

Lemma 7
Suppose that the functions $R_i,\hat{R}_i\in C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$, $i=1,2,4$, are given and $0\leqslant R_i(x,t),\hat{R}_i(x,t)\leqslant\overline{R}_i$ in Ω_T. Then there exists a unique solution $\rho(\cdot)$ to Equation (66) with its values in the interval $[0,\overline{\rho}]$ and positive constants P, P_i, Q_i, $i=1,2,4$, such that

$$\sup_{t\in(0,T)}\|\rho(\cdot,t)\|_{C^{1+\beta}(\Omega)}\leqslant P\sum_{i=1,2,4}k_i\overline{R}_i \tag{69}$$

$$\|\rho\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)}\leqslant\sum_{i=1,2,4}P_i\|R_i\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)} \tag{70}$$

DOI: 10.1002/mma

and

$$\|\rho(R_1, R_2, R_4) - \rho(\hat{R}_1, \hat{R}_2, \hat{R}_4)\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)} \leqslant \sum_{i=1,2,4} Q_i \|R_i - \hat{R}_i\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)} \tag{71}$$

Proof
The existence of a unique solution $\rho(\cdot)$ of Equation (66) with its values in $[0, \overline{\rho}]$ follows, e.g. from the results of Section 3.2 in [12]. Estimation (69) is proved by means of Lemmas 3.1.1 and 3.1.2 in [12] (where p is taken sufficiently large). To find the properties of the function ρ with respect to t, let us consider the equation for the difference quotient $\rho_\tau^\alpha(x,t) = [\rho(x, t+\tau) - \rho(x,t)]/|\tau|^\alpha$, $|\tau| \in (0, \tau_0)$ with $\tau_0 > 0$ sufficiently small, and τ such that $t+\tau \in (0, T)$. Then ρ_τ^α satisfies the equation

$$0 = \varepsilon \nabla^2 \rho_\tau^\alpha(x,t) + \sum_{i=1,2,4} k_i R_{i\tau}^\alpha(x,t) - k\rho_\tau^\alpha(x,t) \tag{72}$$

where $R_{i\tau}^\alpha(x,t) = [R_i(x, t+\tau) - R_i(x,t)]/|\tau|^\alpha$. For any $|\tau| \in (0, \tau_0)$ the function ρ_τ^α satisfies the no-flux boundary conditions at $\partial\Omega$. Take $\alpha = (1+\beta)/2$. As $\|R_i\|_{C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)} \leqslant C_R$, by the maximum principle, we infer, by taking the suprema over the set $(x,t) \in \Omega_T$, $|\tau| \in (0, \tau_0)$, that $\langle\rho\rangle_t^{((1+\beta)/2)} \leqslant \sum_{i=1,2,4} C_{i0} < R_{i,t}^{((1+\beta)/2)} >$ in the denotation used in (I.1.12) of [10]. Moreover, for fixed t and τ we may use Lemmas 3.1.1 and 3.1.2 in [12] (where p is taken sufficiently large) to conclude that

$$\sup |\nabla \rho_\tau^{(1+\beta)/2}| \leqslant \sum_{i=1,2,4} C_{i1} \sup |R_{i\tau}^{(1+\beta)/2}|$$

with the suprema over the set $(x,t) \in \Omega_T$, $|\tau| \in (0, \tau_0)$, $t+\tau \in (0, T)$. Using estimation (69) we thus conclude that (70) is valid. In the similar manner we can obtain estimation (71). □

Theorem 6
Let Assumptions 1–4, point 1. of Assumption 5, Assumptions 7 and 8 hold. Then for any $T > 0$ there exists a unique solution to system (59)–(66) satisfying the boundary–initial conditions (9)–(10) and such that the $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ norm of the functions $c_a, c_{\text{inh}}, R_1, R_2, R_4$ and ρ is bounded by constants independent of T.

Proof
Let

$$U = (c_a, c_{\text{inh}}, R_1, R_2, R_4) \tag{73}$$

Let the vector of the right-hand sides of Equations (61)–(65) be denoted by

$$\Phi(U, \rho(U)) = (\Phi_1(U, \rho(U)), \Phi_2(U, \rho(U)), \Phi_3(U, \rho(U)), \Phi_4(U, \rho(U)), \Phi_5(U, \rho(U)))$$

where $\rho(U)$ is the unique solution to Equation (66) characterized in Lemma 7 given the functions $R_1 = U_3$, $R_2 = U_4$ and $R_4 = U_5$. Let us denote the vector of left-hand side operators by

$$L = (L_1, L_2, L_3, L_4, L_5)$$

Given the vector $\widetilde{U}$, let $P(\widetilde{U})$ be the solution to the system

$$L[\rho(\widetilde{U})]U = \Phi(\widetilde{U}) \tag{74}$$

DOI: 10.1002/mma

in the set $\Omega_T = \Omega \times (0, T)$ for some $T > 0$ subject to the initial and boundary conditions (10) and (9). As in the case of Theorem 2, we can prove that, for $T > 0$ sufficiently small, the operator $\widetilde{U} \to P(\widetilde{U}) = U$, where U is the unique solution to system (74), is a contraction mapping in the space $\mathscr{M}$, where $\mathscr{M}$ contains the elements $U = (U_1, U_2, U_3, U_4, U_5)$ and $U_i \in C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$, $i = 1, 2, 3, 4, 5$. The rest of the proof can be carried out, by taking advantage of Lemma 7 along the lines of the proof of Theorem 2. □

6. CONCLUSIONS

In this paper we prove some existence results for system (1)–(8) under the assumption that the coefficient of diffusion of fibronectin is positive. We demonstrate that under some conditions on the other coefficients of the system a unique classical solution exists globally in time. Moreover, we have not imposed any conditions on the initial conditions. It seems that the conditions demanding the non-positivity of the functions Ψ_i (Assumption 5) are technical and arise as a consequence of using transformation (15), (16). Hopefully, working with solutions in the Sobolev spaces would allow us to avoid this restricting conditions.

The mathematical problems encountered while analyzing the considered system of equations differ from those which appear in the classical chemotaxis systems (see, e.g. [14–21]). The difference comes from the fact that the mitotic terms, which behave like $(-r R_i^2)$ for large values of the concentrations R_i are present in the equations for the densities of the mobile cells R_i, $i = 1, 2, 4$. Thus, these terms that are absent in classical chemotaxis equations may effectively counteract the possible blow-up of solutions in finite time.

To describe the process of vertebrate limb formation one needs to take into account its growth, that is to say, consider a free boundary problem. This task will be undertaken in a future paper.

ACKNOWLEDGEMENTS

This paper was partially supported by the Polish Ministry of Science and Higher Education Grant No. 1P03A01230. The author also wishes to express his gratitude to Mark Alber for the possibility to visit the Notre Dame University under the NSF Grant No. IBN-034467.

REFERENCES

1. Alber M, Hentschel HGE, Kazmierczak B, Newman S. Existence of solutions to a new model of biological pattern formation. *Journal of Mathematical Analysis and Applications* 2005; **308**:175–194.
2. Hentschel HGE, Glimm T, Newman SA, Glazier JA. Dynamical mechanisms for skeletal pattern formation in the avian limb. *Proceedings of the Royal Society of London*, *Series B*, *Biological Sciences* 2004; **271**:1713–1722.
3. Murray JD. *Mathematical Biology* (2nd edn). Springer: Berlin, 1993.
4. Wierzbicka-Patynowski I, Schwarzbauer JE. The ins and outs of fibronectin matrix assembly. *Journal of Cell Science* 2003; **116**:3269–3276.
5. Levine HA, Pamuk S, Sleeman BD, Nilsen-Hamilton M. Mathematical modeling of capillary formation and development in tumor angiogenesis: penetration into the stroma. *Bulletin of Mathematical Biology* 2001; **63**: 801–863.
6. Friedman A, Tello JI. Stability of solutions of chemotaxis equations in reinforced random walks. *Journal of Mathematical Analysis and Applications* 2002; **272**:138–163.
7. Fontelos MA, Friedman A, Hu B. Mathematical analysis of a model for the initiation of angiogenesis. *SIAM Journal on Mathematical Analysis* 2002; **33**:1330–1355.

DOI: 10.1002/mma

8. Ignacio Tello J. Mathematical analysis and stability of a chemotaxis model with logistic term. *Mathematical Methods in the Applied Sciences* 2004; **27**:1865–1880.
9. Lieberman GM. *Second Order Parabolic Differential Equations*. World Scientific: Singapore, 1996.
10. Ladyženskaja DA, Solonnikov VA, Uraltseva NN. *Linear and Quasilinear Equations of Parabolic Type*. Translations of the American Mathematical Society. American Mathematical Society: Providence, RI, 1968.
11. Protter MH, Weinberger HF. *Maximum Principle in Differential Equations*. Prentice-Hall: Englewood Cliffs, NJ, 1967.
12. Pao CV. *Nonlinear Parabolic and Elliptic Equations*. Plenum Press: New York, 1992.
13. Post K. A system of nonlinear partial differential equations modelling chemotaxis with sensitivity functions. *Doctoral Dissertation*, Humboldt University, Berlin, 1999.
14. Keller EF, Segel LA. A model for chemotaxis. *Journal of Theoretical Biology* 1971; **30**:225–234.
15. Gajewsky H, Zacharias K. Global behaviour of a reaction–diffusion system modeling chemotaxis. *Mathematische Nachrichten* 1998; **195**:177–194.
16. Herrero MA, Velazquez JJL. A blow-up mechanism for a chemotaxis model. *Annali della Scuola Normale Superiore di Pisa Classe di Scienze* 1997; **4**:633–683.
17. Jager W, Luckhaus S. On explosion of solutions to a system of partial differential equations modeling chemotaxis. *Transactions of the American Mathematical Society* 1992; **329**:819–824.
18. Nagai T. Blow-up of radially symmetric solutions to a chemotaxis system. *Advances in Mathematical Sciences and Applications* 1995; **5**:581–601.
19. Stevens A. A stochastic cellular automaton modeling gliding and aggregation of myxobacteria. *SIAM Journal on Applied Mathematics* 2000; **61**:172–182.
20. Othmer HG, Stevens A. Aggregation, blowup and collapse: the ABC's of taxis in reinforced random walks. *SIAM Journal on Applied Mathematics* 1997; **57**:1044–1081.
21. Wrzosek D. Long-time behaviour of solutions to a chemotaxis model with volume-filling effect. *Proceedings of the Royal Society of Edinburgh*, *Section A* 2006; **136**:431–444.