Existence of global solutions to a model of chondrogenesis

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SUMMARY

The paper considers conditions sufficient for the existence of classical $C^{2 + \beta, 1 + \beta / 2}_{x,t}$ 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.

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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]:

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

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

$$\frac{\partial c_a}{\partial t} = D_a \nabla^2 c_a - k_a c_{inh} c_a + J_1^a (c_a, c_{inh}) R_1 + J_a (c_a, c_{inh}) R_2$$ (3)

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\[ \frac{\partial c_{\text{inh}}}{\partial t} = D_{\text{inh}} \nabla^2 c_{\text{inh}} - k_c c_{\text{inh}} c_a + k_f (c_a, c_{\text{inh}}) R_2 \]  
\[ \frac{\partial R_1}{\partial t} = \text{div}(D_1(\rho) \nabla R_1) - \text{div}(R_1 \chi_1 \nabla \rho) + r R_1 (R_{\text{eq}} - R) + k_{21} R_2 - k_{12}(c, c_a) R_1 \]  
\[ \frac{\partial R_2}{\partial t} = \text{div}(D_2(\rho) \nabla R_2) - \text{div}(R_2 \chi_2 \nabla \rho) + r R_2 (R_{\text{eq}} - R) + k_{12}(c, c_a) R_1 - k_{23} R_2 \]  
\[ \frac{\partial R_4}{\partial t} = \text{div}(D_4(\rho) \nabla R_4) - \text{div}(R_4 \chi_4 \nabla \rho) + r R_4 (R_{\text{eq}} - R) + k_{22} R_2 - k_{23} R_4 \]  
\[ \frac{\partial \rho}{\partial t} = \varepsilon \nabla^2 \rho + k_1 R_1 + k_2 R_2 + k_4 R_4 - k \rho \]  

where \( x \in \Omega \) and \( t > 0 \). Obviously, \( \Omega \) 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, \( c_{\text{inh}} \) is the density of the inhibitor, \( R_1, R_2, R_4, R_3 \) are the densities of different kinds of cells and \( \rho \) is the density of fibronectin. The quantity

\[ R = R_1 + R_2 + R_4 \]

denotes the density of the mobile cells and \( \chi_j, j = 1, 2, 4 \), 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 \( c_{\text{inh}} \) (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 \( k_{12\text{max}}/k_{21} \approx 4 \) (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].
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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 \( \chi_i \) 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 \( \chi_i, i = 1, 2, 4 \), assume that they vanish sufficiently fast as a function of \( \rho \). 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 \( C_{x,t}^{2+\beta,1+\beta/2} \) 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 \( \Omega \)

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

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:

\[
\frac{\partial c}{\partial n} = 0, \quad \frac{\partial c_a}{\partial n} = 0, \quad \frac{\partial c_{inh}}{\partial n} = 0, \quad \frac{\partial R_1}{\partial n} = 0, \quad \frac{\partial R_2}{\partial n} = 0, \quad \frac{\partial R_4}{\partial n} = 0, \quad \frac{\partial \rho}{\partial n} = 0 \quad (9)
\]
Assumption 1
$k_c, D_c, D_{inh}, k_a, r, R_{eq}, r_3, R_{3eq}, k_1, k_2, k_4, k$ and all $k_{ij}$ except for $k_{12}$ are positive constants.

Assumption 2

$J(x, t): \Omega \times [0, \infty) \rightarrow [0, C_1], C_1 > 0$, is such that its $C^\beta_{x,t}(\Omega \times [0, t])$ norm is bounded independently of $t > 0$. The functions $k_{12}, J_1, J_2, k_f: \mathbb{R}^1 \times \mathbb{R}^1 \rightarrow [0, \infty)$ are bounded from above by the constants $k_{12}, J_{a1}, J_{a2}$ and $k_f$, respectively, and such that their $C^\beta(K)$ norms, $\mathbb{R}^1 \times \mathbb{R}^1 \subseteq K$ 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 $\rho_0$ are of class $C^{2+\beta}(\Omega)$ and non-negative in $\Omega$.
2. $\partial R_{30}(x)/\partial n(x) = 0$ for $x \in \partial \Omega$.

Assumption 4

Let $J_1, J_2$ be identically equal to 0 for $c_a > \tilde{C}_a > 0$ independently of $c_{inh}$. Let $k_f(c_{inh}, c_a)$ be identically equal to 0 for $c_{inh} > \tilde{C}_{inh} > 0$ 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 $\partial R_4/\partial n = 0$, $\partial \rho/\partial n = 0$ we obtain the equation

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

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

$$\Omega_T := \Omega \times (0, T)$$

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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 \( \chi \) or the numbers \((k_b + k'_p)/k\) and \( \|\rho_0\|C^0_\Omega \) 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 \( c, c_a, c_{inh}, R_1, R_2, R_4 \) and \( \rho \) has its \( C^{2+\beta,1+\beta/2}_{x,i}(\Omega_T) \) norm bounded by a constant independent of \( T \in (0, \infty) \), whereas \( R_3 \) has its \( C^{0,1}_{x,i}(\Omega_T) \) norm bounded by a constant independent of \( T \).

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

\[
S_i = \frac{R_i}{f(\rho)}
\]

where

\[
f(\rho(x)) = \exp(\chi \rho(x))
\]

In [1] constructive conditions on the smallness of \( \chi \), 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 \( \chi \), we will introduce the transformation of the dependent variables, which is a generalization of transformation (13) and (14). First, let

\[
f_i(\rho) = \exp\left\{ \int_0^\rho \frac{f_i(s)}{[D_i(s) - \varepsilon]} \, ds \right\}, \quad i = 1, 2, 4
\]

Then, let

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

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

\[
\partial c/\partial t - D \nabla^2 c = -k_c c + J(x, t)
\]

\[
\partial R_3/\partial t = r_3 R_3 (R_{3eq} - R_3) + k_{23} f_4(\rho) S_4
\]

\[
\partial c_a/\partial t - D_a \nabla^2 c_a = -k_a c_{inh} c_a + J_{a1}(c_a, c_{inh}) f_1(\rho) S_1 + J_{a2}(c_a, c_{inh}) f_2(\rho) S_2
\]

\[
\partial c_{inh}/\partial t - D_{inh} \nabla^2 c_{inh} = -k_a c_{inh} c_a + k_f (c_a, c_{inh}) f_2(\rho) S_2
\]
\[ \frac{\partial S_1}{\partial t} - D_1 \nabla^2 S_1 = \left[ D_{1, \rho} + \frac{D_1 + \epsilon}{D_1 - \epsilon} \right] \nabla S_1 \cdot \nabla \rho + S_1 \Psi_1(\rho)(\nabla \rho)^2 + r S_1 (R_{eq} - S_f) + k_{21} S_2 f_2(\rho) f_1(\rho)^{-1} - k_{12} (c(x, t), c_a) S_1 - \frac{\chi_1}{D_1 - \epsilon} S_1 g \] (21)

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

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

\[ \frac{\partial \rho}{\partial t} - \epsilon \nabla^2 \rho = g(S_1, S_2, S_3, \rho) \] (24)

where

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

\[ S_f = f_1 S_1 + f_2 S_2 + f_4 S_4 \] (26)

and for \( i = 1, 2, 4 \),

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

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

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

and the initial conditions corresponding to (10)

\[ c(x, 0) = c_0(x), \quad c_a(x, 0) = c_{a0}(x), \quad c_{inh}(x, 0) = c_{i0}(x) \]
\[ \rho(x, 0) = \rho_0(x), \quad R_3(x, 0) = R_{30}(x) \]
\[ S_1(x, 0) = S_{10}(x) = R_1(x)/f_1(\rho_0(x)), \quad S_2(x, 0) = S_{20}(x)/f_2(\rho_0(x)) \]
\[ S_4(x, 0) = S_{40}(x)/f_4(\rho_0(x)) \] (29)

It is also obvious that the consistency conditions analogous to those in (11) are satisfied by the functions \( S_1, S_2, S_4 \).
Assumption 5
For $i = 1, 2, 4$:

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

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

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

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

$$\zeta_i^2(\rho) + \zeta_i'(\rho) \leq 0, \quad \rho \in [0, \infty) \quad (31)$$

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

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

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

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 $\rho \in [0, \infty)$

$$\zeta'(\rho) + \zeta^2(\rho) \leq 0 \quad (32)$$

Then $\zeta$ must satisfy the condition

$$\zeta(\rho) \leq \frac{C}{C\rho + 1} := \tilde{\zeta}(C; \rho) \quad (33)$$

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

Proof
First, let us note that the function $\tilde{\zeta}$ determined in (33) satisfies the equation $\tilde{\zeta}' + \tilde{\zeta}^2 = 0$, $\tilde{\zeta}(0) = C$, $C > 0$. Therefore, the graph of the function $\tilde{\zeta} : [0, \infty) \rightarrow \mathbb{R}^1$ satisfying inequality (32) and such that $\zeta(0) = C$ cannot get above the graph of the function $\tilde{\zeta}(\rho)$. To prove it, suppose to the contrary that for some $\rho = \rho_*$ we have $\tilde{\zeta}(\rho_*) > \tilde{\zeta}(\rho_*)$. It follows that $\zeta'(\rho_*) < \zeta'(\rho_*)$. This would imply that $\zeta(\rho) > \tilde{\zeta}(\rho)$ for all $\rho \in [0, \rho_*)$, hence the initial condition $\zeta(0) = C$ cannot be satisfied. Hence, (33) is proved. Now, the quarter $\{(\rho, \zeta) : \rho > 0, \zeta \geq 0\}$ 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 $\zeta(\cdot) \neq \tilde{\zeta}(C; \cdot)$. Then
according to (33) there must exist $\rho^* > 0$ such that $\zeta(\rho^*) = \tilde{\gamma}(C^*, \rho^*)$ with some $C^* \in [0, C)$. Now, similarly as in the proof of Lemma 1, we can show that $\zeta(\rho) \leq \tilde{\gamma}(\rho)$ for all $\rho \geq \rho^*$. Thus, the lemma is proved.

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

Proof
If $\kappa > 0$ then $\zeta_i$ is integrable; hence, the lemma is true. Suppose that $\kappa = 0$ and $C_1 < C_2$. We have $\int_0^\rho \zeta_i(s) \, ds = \ln |(C_2 \rho + 1)^{C_1/C_2}|$. 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 $\rho$ and $S_i$, $i = 1, 2, 4$ satisfying system (17)–(24).

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

$$
\begin{align*}
\sup_{\rho \in [0, \overline{\rho}]} \{ rS_1(R_{eq}f_1(\rho)^{-1} - S_1) + k_{21}S_2f_2(\rho) f_1(\rho)^{-2} + f_1(\rho)^{-1} \zeta_1(\rho) [-f_1(\rho)k_1S_1^2 + S_1k\rho] \} &< 0 \\
\sup_{\rho \in [0, \overline{\rho}]} \{ rS_2(R_{eq}f_2(\rho)^{-1} - S_2) + k_{12}S_1f_1(\rho) f_2(\rho)^{-2} + f_2(\rho)^{-1} \zeta_2(\rho) [-f_2(\rho)k_2S_2^2 + S_2k\rho] \} &< 0 \\
\sup_{\rho \in [0, \overline{\rho}]} \{ rS_4(R_{eq}f_4(\rho)^{-1} - S_4) + k_{42}S_2f_2(\rho) f_4(\rho)^{-2} + f_4(\rho)^{-1} \zeta_4(\rho) [-f_4(\rho)k_4S_4^2 + S_4k\rho] \} &< 0 \\
&\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad k_1S_1f_1(\rho) + k_2S_2f_2(\rho) + k_4S_4f_4(\rho) - k\rho < 0
\end{align*}
$$

(34)

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

$$
\zeta_i(\rho) = \chi_i(\rho)/(D_i(\rho) - \varepsilon)
$$

(35)

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

$$
0 \leq S_{10}(x) < \overline{S}_1, \quad 0 \leq S_{20}(x) < \overline{S}_2
$$

$$
0 \leq S_{40}(x) < \overline{S}_4, \quad 0 \leq \rho_0(x) < \overline{\rho}
$$

(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

$$
\mathcal{J}_i = \sup_{\rho \in (0, \infty)} \rho \chi_i(\rho)/(D_i(\rho) - \varepsilon)
$$

(37)
are finite. Hence, due to point 4. of Assumption 5, we note that, independently of the value of $\rho$, there exists a solution $\overline{S}_1, \overline{S}_2, \overline{S}_3$ to the system of the first three inequalities of (34) satisfying the condition $\overline{S}_i > \overline{S}_i(0)$ 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 $\Omega$. \hfill \Box

Below, we will need the following auxiliary lemma.

**Lemma 4**

Assume that $u$ is a solution to the problem

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

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

where $L_0$ is a uniformly elliptic operator of the form

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

Suppose that $\phi \in C^{1+\beta/2}_{\kappa}(\Omega)$ and that for all $i, j = 1, \ldots, m$ the coefficients of the operator $L_0$ satisfy the following conditions:

$$\|a_{ij}\|_{C^{\beta/2}_{\kappa}(\Omega \times (0, \infty))} + \|B_i\|_{L^\infty(\Omega \times (0, \infty))} \leq C_M, \quad \|B_i\|_{L^\infty(\Omega \times (0, \infty))} \leq C_B, \quad \|A\|_{L^\infty(\Omega \times (0, \infty))} \leq C_A$$

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

$$\|u\|_{C^{1+\beta/2}_{\kappa}(\Omega \times (0, T))} \leq W_1(T) \|f\|_{C^{0}(\Omega \times (0, T))} + \|\phi\|_{C^{1+\beta}_{\kappa}(\Omega)}$$

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

$$\|u\|_{C^{1+\beta/2}_{\kappa}(\Omega \times (0, T))} \leq C^* \|f\|_{C^{0}(\Omega \times (0, T))} + \|u\|_{C^{0}(\Omega \times (0, T))}$$

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:

$$\|u\|_{C^{1+\beta/2}_{\kappa}(\Omega \times (0, T))} \leq W(\|f\|_{L^\infty(\Omega \times (0, T))} + \|\phi\|_{C^{1+\beta}_{\kappa}(\Omega)})$$

(Note that $f \in L^\infty(\Omega \times (0, T))$ belongs also to the Morrey space $M^{1+\beta/2}_{1, \kappa}$ 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 $T$.  

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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 \( \tilde{T} = 2K \). For \( t \in (0, \tilde{T}) \) we can use estimation (39). Suppose that we are interested in the estimation of \( \|u\|_{C_{x,t}^{1+\beta,(1+\beta)/2}} \) in \( \Omega \times (t_0, T) \). Let \( \eta(t) \) be a \( C^\infty \) cutting-off function, such that \( \eta: \mathbb{R}^1 \to [0, 1] \), \( \eta(t) \equiv 0 \) for \( t < t_0 - K \) and \( \eta(t) \equiv 1 \) for \( t \geq t_0 \). 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

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

(42)

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

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

(43)

which is equivalent to (40).

\[\square\]

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 \( C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T) \) norms of the functions \( c_a, c_{inh}, S_1, S_2, S_4 \) and \( \rho \) are bounded by constants independent of \( T \).

Proof of Theorem 2

Let

\[
U = (c_a, c_{inh}, S_1, S_2, S_4, \rho)
\]

(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 \( \tilde{U} \), let \( U = P(\tilde{U}) \) be the solution to the system

\[
L(\tilde{\rho}) U = \Phi(\tilde{U})
\]

(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 \( L(\tilde{\rho}) \) we mean that in the left-hand side operators we take \( D_i(\tilde{\rho}), i = 1, 2, 4. \)

Let us consider the mapping

\[
U = P(\tilde{U})
\]
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 \( \mathcal{C} = C^{1+\beta, (1+\beta)/2}_{x,t}(\Omega_T) \) to itself. The norm \( \|U\|_\mathcal{C} \) is given by the sum of \( C^{1+\beta, (1+\beta)/2}_{x,t}(\Omega_T) \) norms of \( U_i \). According to the definition of the Hölder norms (see Section I.1 in [10]) for \( h \in C^{1+\beta, (1+\beta)/2}_{x,t}(\Omega_T) \) we have

\[
\|h\|_{C^{1+\beta, (1+\beta)/2}_{x,t}(\Omega_T)} = \sup_{x \in \Omega} \|h(x, \cdot)\|_{C^{(1+\beta)/2}_{t}(0,T)} + \|\nabla h\|_{C^\beta_{x,t}(\Omega_T)}
\]

(46)

Let \( U_0 \) denote the vector of initial functions and consider a closed ball \( B \) in the considered space defined by \( B = \{U \in \mathcal{C}: \|U - U_0\|_\mathcal{C} \leq 1\} \), that is to say

\[
\|U - U_0\|_\mathcal{C} = \sum_{i=1}^{6} \|U_i - U_{0i}\|_{C^{1+\beta, (1+\beta)/2}_{x,t}(\Omega_T)}
\]

and due to (46)

\[
\|U_i - U_{0i}\|_{C^{1+\beta, (1+\beta)/2}_{x,t}(\Omega_T)} = \sup_{x \in \Omega} \|U_i(x, \cdot) - U_{0i}(x)\|_{C^{(1+\beta)/2}_{t}(0,T)} + \sup_{x \in \Omega} \|\nabla U_i(x, \cdot) - \nabla U_{0i}(x, \cdot)\|_{C^{\beta/2}_{t}(0,T)} + \sup_{t \in (0,T)} \|\nabla U_i(\cdot, t) - \nabla U_{0i}(\cdot, t)\|_{C^\beta_{x}(\Omega)}
\]

(47)

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

\[
\|U_i(\cdot, t) - U_{0i}(\cdot)\|_{C^2_{x}(\Omega)} \to 0
\]

(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 \( C^{\beta/2}_{t}(0,T) \). Hence, the third term in (47) vanishes as \( T^{\beta/2} \) for \( T \to 0 \). From the same inequality we infer that for all \( i = 1, \ldots, 6 \)

\[
\|\partial_t U_i/\partial t\|_{C^0_{\mathcal{C}_T}(\Omega)} < K_1, \quad \|\nabla U_i(x, \cdot) - \nabla U_{0i}(x, \cdot)\|_{C^{(1+\beta)/2}_{t}(0,T)} < K_2
\]

(49)

independent of \( x \in \overline{\Omega} \). The constants \( K_1, K_2 \) can be chosen independent of \( \tilde{U} \in B \). 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 \( \|\nabla U_i(x, \cdot) - \nabla U_{0i}(x, \cdot)\|_{C^{1+\beta/2}_{t}(0,T)} \) tends to zero for \( T \to 0 \) as \( T^{1/2} \). Consequently, \( \|U - U_0\|_\mathcal{C} \) behaves like \( K_3 T^\delta \), \( \delta > 0 \), where the constant \( K_3 \) depends on the \( C^{2+\beta, 1+\beta/2}_{x,t} \) norms of \( U_0 \) and the region \( \Omega \). It follows that for \( T \to 0 \) sufficiently small \( P \) acts from \( B \) to \( \overline{B} \). Proceeding in the same manner we can easily prove that

\[
\|P(\tilde{U}_2) - P(\tilde{U}_1)\|_\mathcal{C} \leq T^\nu K_4 \|\tilde{U}_2 - \tilde{U}_1\|_\mathcal{C}
\]

(50)

for all \( \tilde{U}_1, \tilde{U}_2 \in B \) 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 \( |D_i(\tilde{P}_i) - D_i(\tilde{P}_2)|\Delta S_{2i} = (\tilde{P}_2 - \tilde{P}_1) D_i'(\tilde{P}_1 + \theta(\tilde{P}_2 - \tilde{P}_1)) \Delta S_{2i} \) in the equation for \( \Delta S_{2i}, i = 1, 2, 4 \) to the right-hand side. \( U_1 - U_2 \) satisfies zero initial and no-flux boundary conditions. Moreover, every component of \( U_1 - U_2 \)
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

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

and in fact is a solution to the system

$$LU = \Phi(U)$$

It is clear that $T$ depends only on the $C_{x}^{2+\beta}(\Omega)$ norm of the initial data [7, 9, 10]. It follows that being able to prove a priori that the $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ 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 $c_a$, $c_{inh}$, $\rho$ 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 $\overline{p}$ be as in Lemma 3. Let $C_a > \overline{C}_a$, $C_{inh} > \overline{C}_{inh}$ with $\overline{C}_a$ and $\overline{C}_{inh}$ determined in Assumption 4 be such that $0 < c_{a0}(x) \leq C_a$, $0 < c_{inh0}(x) < C_{inh}$. Suppose that for $t \in (0, T)$, $T > 0$, there exists a unique $C_{x,t}^{2,1}(\Omega_T)$ solution to system (17), (19)–(24). Then

$$0 \leq c(x, t) < C_c, \quad 0 \leq c_a(x, t) < C_a, \quad 0 \leq c_{inh}(x, t) < C_{inh}$$

and

$$0 \leq S_1(x, t) < \overline{S}_1, \quad 0 \leq S_2(x, t) < \overline{S}_2, \quad 0 \leq S_4(x, t) < \overline{S}_4, \quad 0 \leq \rho_0(x) < \overline{p}$$

**Proof**

Obviously, due to Assumption 2, $c(x, t) \in C_{x,t}^{2,1}(\Omega_T)$ and by the maximum principle (Theorem 3.4.7 in [11]), we conclude that there exists a positive constant $C_c$ such that $0 < c(x, t) < C_c$. 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:

$$\frac{\partial S_1}{\partial t} - D_1(\rho)\nabla^2 S_1 = \left[ D_{1,\rho} + \frac{D_1(\rho)}{D_1(\rho)} \right] \nabla S_1 \cdot \nabla \rho + S_1^+ \Psi_1(\rho)(\nabla \rho)^2 + r|S_1| |R_{eq} - r S_1^+ S_f + k_{21}|S_2| f_2(\rho) f_1(\rho)|^{-1} - k_{12}(c(x, t), c_a) S_1 - \frac{\lambda_1}{D_1(\rho)} S_1^+ g$$

and

$$\frac{\partial S_2}{\partial t} - D_2(\rho)\nabla^2 S_2 = \left[ D_{2,\rho} + \frac{D_2(\rho)}{D_2(\rho)} \right] \nabla S_2 \cdot \nabla \rho + S_2^+ \Psi_2(\rho)(\nabla \rho)^2 + r|S_2| |R_{eq} - r S_2^+ S_f + k_{12}(c(x, t), c_a) |S_1| f_1(\rho) f_2(\rho)|^{-1} - k_{21} S_2 - k_{22} S_2 - \frac{\lambda_2}{D_2(\rho)} S_2^+ g$$
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\[
\partial_t S^4 - D_4(\rho)\nabla^2 S^4 = \left[ D_{4,\rho} + \mathcal{J}_4 \frac{D_4 + \varepsilon}{D_4 - \varepsilon} \right] \nabla S^4 \cdot \nabla \rho + S^4_+ \Psi_4(\rho)(\nabla \rho)^2 + r |S_4| R_{eq} - r S^4_+ S_f + k_{22} |S_2| f_2(\rho)f_4(\rho)^{-1} - k_{23} S_4 - \frac{\mathcal{J}_4}{D_4 - \varepsilon} S^+_4 g
\]

(55)

\[
\partial_t \rho - \varepsilon \nabla^2 \rho = |k_1 S_1 f_1 + k_2 S_2 f_2 + k_4 S_4 f_4 - k \rho
\]

(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 \( \mathcal{J}_i \) 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 \(|a| - |b| \leq |a - b|\) and \(|a^+ - b^+| \leq |a - b|\).) 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 \( x_0 \in \Omega \). We can take \( \eta > 0 \) arbitrarily small and assume that the time derivative of \( \rho \) at the point \((x_0, t_0)\) is non-positive. Suppose that \( x_0 \in \Omega \). Then \( \Delta \rho(x_0, t_0) > 0 \). Hence, we arrive at a contradiction as the right-hand side of Equation (56) is positive at \((x_0, t_0)\). As \( \eta \) can be taken arbitrarily small we conclude that \( \rho \) is non-negative on the maximal interval of the solution existence. If \( x_0 \notin \Omega \) and \( \rho(x, t_0) > -\eta \) for \( x \in \Omega \), then by means of the maximum principle (see, e.g. Theorem 2.3.7 in [11]) stating that \( \partial \rho/\partial t(x_0, t_0) < 0 \) we arrive at a contradiction as \( \rho \) 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 \( \Delta S_i(x_0, t_0) > 0 \). We thus arrive at a contradiction as the source term in the equation for \( S_i \) is strictly positive for \( \eta > 0 \). If \( x_0 \notin \Omega \) 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 \( \partial S_i/\partial t(x_0, t_0) < 0 \); 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 \( \rho \), we have proved that the unique solution to the problem satisfies the non-negativity bounds. The proof that \( S_i(t, x) \leq S_i^\infty \), \( \rho(x, t) \leq \rho^\infty \) for all \( x \in \Omega \) 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-negative. Having proved estimations (52), we can use Theorem 8.9.3 in [12] to claim that there exists a unique classical solution \( (c_a, c^\text{inh}) \) to system (19), (20), which satisfies the bounds \( c_a(x, t) \in [0, C_a), c^\text{inh}(x, t) \in [0, C^\text{inh}) \). 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 \( c, c_a, c^\text{inh}, S_1, S_2, S_4 \) and \( \rho \) 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 \( C_c, C_a, C^\text{inh}, \rho, S_1, S_2 \).
and \( S_4 \) such that
\[
|\rho(x, t)|_{C^{1+\beta, 1+\beta/2}_{x,t}(\Omega_T)} \leq M
\]
Similarly
\[
|c_a(x, t)|_{C^{1+\beta, 1+\beta/2}_{x,t}(\Omega_T)} \leq M, \quad |c_{inh}(x, t)|_{C^{1+\beta, 1+\beta/2}_{x,t}(\Omega_T)} \leq M
\]

**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 system (19)–(24) subject to the boundary–initial conditions (28)–(29) such that the \( \rho \) is bounded by constants \( K_c \) with \( K_c \) independent of \( T \).

Next, we can estimate the \( C^{2+\beta, 1+\beta/2}_{x,t}(\Omega_T) \) norms of the solution. This can be done in three steps. In the first we use the Hölder estimates for \( c_a, c_{inh}, \rho \) 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 \( C^{2+\beta, 1+\beta/2}_{x,t}(\Omega_T) \) norms of \( c_a, c_{inh} \) and \( \rho \). Finally, we can obtain the boundedness of \( C^{2+\beta, 1+\beta/2}_{x,t}(\Omega_T) \) norms of \( S_i, i = 1, 2, 4 \). The theorem is proved. Equation (18) is solvable knowing the functions \( S_4 \) and \( \rho \). 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 \( C_{1i}, C_{2i} \geq 0 \), \( C_{2i}(1+\kappa) \geq C_{1i} \) 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 \( C^{2+\beta, 1+\beta/2}_{x,t}(\Omega_T) \) norm of the functions \( c_a, c_{inh}, S_1, S_2, S_4 \) and \( \rho \) 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
\[
\zeta_i(\rho) = C_{1i}/(C_{2i}\rho + 1)^2, \quad C_{2i} \geq C_{1i}/2
\]
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 \( R_i \geq 0 \). 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.
Assumption 6
For \( i = 1, 2, 4, \) let
1. \( C^2 \ni D_i : \mathbb{R}^1 \to [\mathcal{D}_i, \infty), \varepsilon = \text{const} > 0 \) and \( \mathcal{D}_i - \varepsilon > a_i > 0. \)
2. \( C^2 \ni \mathcal{K}_i : \mathbb{R}^1 \to [0, h_i], h_i = \text{const} \geq 0. \)
3. \( k_i \in C^2(\mathbb{R}^1), k_i(R_i)R_i < \mathcal{G}_i, i = 1, 2, 4. \)

Remark
Point 3. of Assumption 6 implies, according to transformation (16), that for all \( S_i \in [0, \infty) , \rho \in [0, \infty) \)
\[
\hat{k}_i(S_i, \rho)S_i f_i(\rho) = k_i(S_i f_i(\rho))S_i f_i(\rho) < \mathcal{G}_i.
\]

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 \( \rho \) 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
\[
\sum_{i=1,2,4} \mathcal{G}_i - k_i \overline{\rho} < 0
\]
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 \( \sum_{i=1,2,4} \mathcal{G}_i \)), we can use Lemma 4 to estimate the norm of the spatial derivatives of the function \( \rho. \) Hence, the terms \( \nabla^2 \rho \) can be \text{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 \( \mathcal{G}_i. \)
Consequently, we can find \( \overline{\mathcal{S}}_i \) such that for \( S_i = \overline{\mathcal{S}}_i, i = 1, 2, 4, \rho \in [0, \overline{\rho}], \) the system
\[
\begin{align*}
 r S_1(R_{\text{eq}} - S_1 f_1(\rho)) + k_{21} S_2 f_2(\rho) f_1(\rho)^{-1} + \zeta_1(\rho) S_1[-f_1(\rho) \hat{k}_1(S_1, \rho) S_1 + k \rho] + S_1 \rho \overline{\mathcal{S}}_1 &< 0 \\
 r S_2(R_{\text{eq}} - S_2 f_2(\rho)) + k_{12} S_1 f_1(\rho) f_2(\rho)^{-1} + \zeta_2(\rho) S_2[-f_2(\rho) \hat{k}_2(S_2, \rho) S_2 + k \rho] + S_2 \rho \overline{\mathcal{S}}_2 &< 0 \\
 r S_4(R_{\text{eq}} - S_4 f_4(\rho)) + k_{22} S_2 f_2(\rho) f_4(\rho)^{-1} + \zeta_4(\rho) S_4[-f_4(\rho) \hat{k}_4(S_4, \rho) S_4 + k \rho] + S_4 \rho \overline{\mathcal{S}}_4 &< 0
\end{align*}
\]
being a modification of system (34) by the terms \( S_i p \overline{\mathcal{S}}_i, \) where \( \overline{\mathcal{S}}_i = \sup_{\rho \in [0, \overline{\rho}]} \Psi_i(\rho), \) is satisfied. This is due to the fact that \( p \) depends only on \( \mathcal{G}_1, \mathcal{G}_2, \mathcal{G}_4 \) (and not on \( \overline{\mathcal{S}}_i ) \) 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 \( \mathcal{K}_i. \) Theorem 4 holds even if the quantities \( \zeta_i(\rho) = \mathcal{K}_i(\rho)/(D_i(\rho) - \varepsilon) \) are not tending to zero or even growing to infinity for \( \rho \to \infty. \)
In this section we will assume that the evolution of the fibronectin is fast. To be more precise, we can replace the terms \( T_{\text{independent of }} \) in front of the quadratic term \( r_3 R_3 \), the function \( R_3(x, t) \) has its \( C_{x,t}^{0,0} \) 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 \( r_3 R_3 \), the function \( R_3(x, t) \) for \( (x, t) \in \Omega_T \).

\[ \Box \]

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

\[ 0 = \epsilon \nabla^2 \rho + k_1 R_1 + k_2 R_2 + k_4 R_4 - k \rho \]  

This time we will not apply the change of variables \( R_i \rightarrow S_i, \ i = 1, 2, 4 \). However, using Equation (58), we can replace the terms \( (-R_i \chi_i(\rho) \nabla^2 \rho) \) simply by the non-differential terms \( R_i \chi_i(\rho) \epsilon^{-1}(k_1 R_1 + k_2 R_2 + k_4 R_4 - k \rho) \). Hence, we obtain the following system:

\[ \frac{\partial c}{\partial t} - D \nabla^2 c = -k_c c + J(x, t) \]  

\[ \frac{\partial R_3}{\partial t} = r_3 R_3(R_{3eq} - R_3) + k_{23} R_4 \]  

\[ \frac{\partial c_a}{\partial t} - D_a \nabla^2 c_a = -k_a c_{\text{inh}} c_a + J_a^1(c_a, c_{\text{inh}}) R_1 + J_a(c_a, c_{\text{inh}}) R_2 \]  

\[ \frac{\partial c_{\text{inh}}}{\partial t} - D_{\text{inh}} \nabla^2 c_{\text{inh}} = -k_a c_{\text{inh}} c_a + k_f(c_a, c_{\text{inh}}) R_2 \]  

\[ \frac{\partial R_1}{\partial t} - D_1(\rho) \nabla^2 R_1 = [D_1'(\rho) - \chi_1(\rho)] \nabla R_1 \cdot \nabla \rho - R_1 \chi_1'(\rho) (\nabla \rho)^2 + \chi_1(\rho) \epsilon^{-1} R_1(k_1 R_1 + k_2 R_2 + k_4 R_4 - k \rho) + r R_1(R_{eq} - R) + k_{21} R_2 - k_{12}(c, c_a) R_1 \]  

\[ \frac{\partial R_2}{\partial t} - D_2(\rho) \nabla^2 R_2 = [D_2'(\rho) - \chi_2(\rho)] \nabla R_2 \cdot \nabla \rho - R_2 \chi_2'(\rho) (\nabla \rho)^2 + \chi_2(\rho) \epsilon^{-1} R_2(k_1 R_1 + k_2 R_2 + k_4 R_4 - k \rho) + r R_2(R_{eq} - R) + k_{21} R_2 - k_{22} R_2 \]
\[
\hat{c}_4 r_4/\hat{c}_4 t - D_4(\rho) \nabla^2 r_4 = \left[ D'_4(\rho) - \chi_4(\rho) \right] \nabla r_4 \cdot \nabla \rho - r_4 \chi'_4(\rho)(\nabla \rho)^2
+ \chi_4(\rho) e^{-1} r_4 (k_1 r_1 + k_2 r_2 + k_4 r_4 - k \rho)
+ r_4 (r_{eq} - R) + k_{22} r_2 - k_{23} r_4
\]

\[0 = \epsilon \nabla^2 \rho + k_1 r_1 + k_2 r_2 + k_4 r_4 - k \rho\]

(65)

(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 \((R_1, R_2, R_3)\) such that for \((R_1, R_2, R_3) = (\overline{R}_1, \overline{R}_2, \overline{R}_3)\) and all the considered values of \(\rho\) the following system of inequalities is satisfied:

\[
\chi_1(\rho) e^{-1} r_1 (k_1 r_1 + k_2 r_2 + k_4 r_4 + r r_1 (r_{eq} - R) + k_{21} r_2 - k_{12} (r, c, a) R_1 < 0
\]

\[
\chi_2(\rho) e^{-1} r_1 (k_1 r_1 + k_2 r_2 + k_4 r_4 + r r_2 (r_{eq} - R) + k_{22} r_2 - k_{22} R_2 < 0
\]

\[
\chi_4(\rho) e^{-1} r_1 (k_1 r_1 + k_2 r_2 + k_4 r_4 + r r_4 (r_{eq} - R) + k_{22} r_2 - k_{23} R_4 < 0
\]

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

\[
0 \leq R_{10}(x) < \overline{R}_1,
0 \leq R_{20}(x) < \overline{R}_2,
0 \leq R_{40}(x) < \overline{R}_4
\]

(68)

Assumption 7

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

Note that \(\chi_i\) satisfying the above assumption is bounded \((\chi_i(\rho) \leq h_i)\) 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 \(\sup_{\rho \in (0, \infty)} \chi_i(\rho) e^{-1} (k_1 + k_2 + k_4)\). 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

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

Lemma 7

Suppose that the functions \(R_i, \tilde{R}_i \in C_{x,t}^{1, \beta, (1 + \beta)/2}(\Omega_T), i = 1, 2, 4\), are given and \(0 \leq R_i(x, t) \leq \overline{R}_i\) in \(\Omega_T\). 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

\[
\sup_{t \in (0, T)} \|\rho(\cdot, t)\|_{C_{x,t}^{1, \beta, (1 + \beta)/2}(\Omega_T)} \leq P \sum_{i=1,2,4} k_i \overline{R}_i
\]

(69)

\[
\|\rho\|_{C_{x,t}^{1, \beta, (1 + \beta)/2}(\Omega_T)} \leq \sum_{i=1,2,4} P_i \|R_i\|_{C_{x,t}^{1, \beta, (1 + \beta)/2}(\Omega_T)}
\]

(70)
and
\[
\|\rho(R_1, R_2, R_4) - \rho(\hat{R}_1, \hat{R}_2, \hat{R}_4)\|_{C^{1+\beta,(1+\beta)/2}_{\infty,T}} \leq \sum_{i=1,2,4} Q_i \|R_i - \hat{R}_i\|_{C^{1+\beta,(1+\beta)/2}_{\infty,T}} \tag{71}
\]

Proof
The existence of a unique solution \(\rho(\cdot)\) of Equation (66) with its values in \([0, T]\) 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 \(\rho\) with respect to \(t\), let us consider the equation for the difference quotient \(\rho_t^2(x, t) = [\rho(x, t + \tau) - \rho(x, t)]/|\tau|^2\), \(|\tau| \in (0, \tau_0)\) with \(\tau_0 > 0\) sufficiently small, and \(\tau\) such that \(t + \tau \in (0, T)\). Then \(\rho_t^2\) satisfies the equation
\[
0 = \varepsilon \nabla^2 \rho_t^2(x, t) + \sum_{i=1,2,4} k_i R_{1i}^2(x, t) - k \rho_t^2(x, t) \tag{72}
\]
where \(R_{1i}^2(x, t) = [R_i(x, t + \tau) - R_i(x, t)]/|\tau|^2\). For any \(|\tau| \in (0, \tau_0)\) the function \(\rho_t^2\) satisfies the no-flux boundary conditions at \(\partial \Omega\). Take \(\varepsilon = (1 + \beta)/2\). As \(\|R_i\|_{C^{1+\beta,(1+\beta)/2}_{\infty,T}} \leq C_R\), by the maximum principle, we infer, by taking the suprema over the set \((x, t) \in \Omega_T, |\tau| \in (0, \tau_0)\), that \(\langle \rho_t \rangle^{(1+\beta)/2} \leq \sum_{i=1,2,4} C_i 0 < R_{1i}^{(1+\beta)/2}\) in the denotation used in (1.1.12) of [10]. Moreover, for fixed \(t\) and \(\tau\) we may use Lemmas 3.1.1 and 3.1.2 in [12] (where \(p\) is taken sufficiently large) to conclude that
\[
\sup_{(x, t) \in \Omega_T} |\nabla \rho_t^{(1+\beta)/2}| \leq \sum_{i=1,2,4} C_i \sup_{(x, t) \in \Omega_T} |R_{1i}^{(1+\beta)/2}| \]
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). \(\square\)

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 \(C^{2+\beta,1+\beta/2}_{\infty,T}\) norm of the functions \(c_a, c_{inh}, R_1, R_2, R_4\) and \(\rho\) is bounded by constants independent of \(T\).

Proof
Let
\[
U = (c_a, c_{inh}, R_1, R_2, R_4) \tag{73}
\]
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 \(\tilde{U}\), let \(P(\tilde{U})\) be the solution to the system
\[
L[\rho(\tilde{U})]U = \Phi(\tilde{U}) \tag{74}
\]
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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 \( U \rightarrow P(U) = U \), where \( U \) is the unique solution to system (74), is a contraction mapping in the space \( \mathcal{H} \), where \( \mathcal{H} \) contains the elements \( U = (U_1, U_2, U_3, U_4, U_5) \) and \( U_i \in C^{1+\beta, (1+\beta)/2}_{x,t} (\Omega_T) \), \( i = 1, 2, 3, 4, 5 \). The rest of the proof can be carried out, by taking advantage of Lemma 7 along the lines of the proof of Theorem 2.

\( \Box \)

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 \( \Psi_i \) (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 \((-r R^2_i)\) 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.

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