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Existence of solutions to a new model of biological pattern formation

M. Alber^{a,*}, H.G.E. Hentschel^b, B. Kazmierczak^{a,c}, S.A. Newman^d

^a *Department of Mathematics, University of Notre Dame, Notre Dame, IN 46556, USA*

^b *Department of Physics, Emory University, Atlanta, GA 30322, USA*

^c *Institute of Fundamental Technological Research, Swietokrzyska 21, 00-049 Warsaw, Poland*

^d *Department of Cell Biology and Anatomy, New York Medical College, Valhalla, NY 10595, USA*

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Abstract

In this paper we study the existence of classical solutions to a new model of skeletal development in the vertebrate limb. The model incorporates a general term describing adhesion interaction between cells and fibronectin, an extracellular matrix molecule secreted by the cells, as well as two secreted, diffusible regulators of fibronectin production, the positively-acting differentiation factor (“activator”) TGF- β , and a negatively-acting factor (“inhibitor”). Together, these terms constitute a pattern forming system of equations. We analyze the conditions guaranteeing that smooth solutions exist globally in time. We prove that these conditions can be significantly relaxed if we add a diffusion term to the equation describing the evolution of fibronectin.

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1. Introduction

Providing a mechanistic account of early development of multicellular organisms is one of the most challenging tasks in contemporary biology. One of the experimentally

* Corresponding author.

E-mail address: malber@nd.edu (M. Alber).

best-characterized examples of such development is vertebrate limb formation. The limb skeleton first forms as arrays of rods and nodules of cartilage, which are then replaced by bone in most species. The fundamental problem to be addressed by any mathematical model of limb development is the explanation of pattern formation during cartilage differentiation (chondrogenesis). To be more precise, we seek to explain how the cellular and molecular interactions occurring during the growth of the avian forelimb, for example, lead to spatiotemporal differentiation of cartilage, such that the number of bone primordia changes in time from one (*humerus*), to two (*radius* and *ulna*) and to three (*digits*).

The aim of this paper is to analyze some features of a new model introduced by Hentschel et al. [1]. The system of equations proposed in [1] has the following form:

$$\frac{\partial c}{\partial t} = D\nabla^2 c - kc + J(x, t), \quad (1.1)$$

$$\frac{\partial c_a}{\partial t} = D_a \nabla^2 c_a - k_a c_i c_a + J_a^1(c_a, c_i)R_1 + J_a(c_a, c_i)R_2, \quad (1.2)$$

$$\frac{\partial c_i}{\partial t} = D_i \nabla^2 c_i - k_a c_i c_a + k_f(c_a, c_i)R_2, \quad (1.3)$$

$$\frac{\partial R_1}{\partial t} = D_{\text{cell}} \nabla^2 R_1 - \text{div}(R_1 \chi \nabla \rho) + r R_1 (R_{\text{eq}} - R) + k_{21} R_2 - k_{12}(c, c_a)R_1, \quad (1.4)$$

$$\begin{aligned} \frac{\partial R_2}{\partial t} = D_{\text{cell}} \nabla^2 R_2 - \text{div}(R_2 \chi \nabla \rho) + r R_2 (R_{\text{eq}} - R) + k_{12}(c, c_a)R_1 \\ - k_{21} R_2 - k_{22} R_2, \end{aligned} \quad (1.5)$$

$$\frac{\partial R'_2}{\partial t} = D_{\text{cell}} \nabla^2 R'_2 - \text{div}(R'_2 \chi \nabla \rho) + r R'_2 (R_{\text{eq}} - R) + k_{22} R_2 - k_{23} R'_2, \quad (1.6)$$

$$\frac{\partial R_3}{\partial t} = r_3 R_3 (R_{3\text{eq}} - R_3) + k_{23} R'_2, \quad (1.7)$$

$$\frac{\partial \rho}{\partial t} = k_b (R_1 + R_2) + k'_b R'_2 - k_c \rho, \quad (1.8)$$

where $x \in \Omega$ and $t > 0$ and $R = R_1 + R_2 + R'_2$. The equations above involve four distinct cell types (R_1, R_2, R'_2, R_3) that have been identified during the early stages of skeletal development. These cells can be characterized by their respective receptors for the FGF family of growth factors. In the paper we use the notation $R_1(x, t)$ to describe the spatiotemporal distribution of R_1 cells, with similar notations for the other cell types. In addition we use the following notation: for the local concentration of the FGFs, $c(x, t)$; for the concentration of fibronectin, which controls the increase in cell density (condensation), a prerequisite for cartilage differentiation, $\rho(x, t)$; for the activator of fibronectin production, TGF- β , $c_a(x, t)$; and for the associated inhibitor, $c_i(x, t)$.

Although this paper is concerned with the mathematical analysis of this set of equations, it is important to amplify some of the key biological points involved, both to set the model in context, and to establish the importance of carrying out this analysis. A fuller account of the biological mechanisms involved can be found in [1], so we will only highlight a few key facts here. A schematic of this model is shown in Fig. 1. Results of some numerical calculations for a reduced version of system (1.1)–(1.8) derived by separation of time

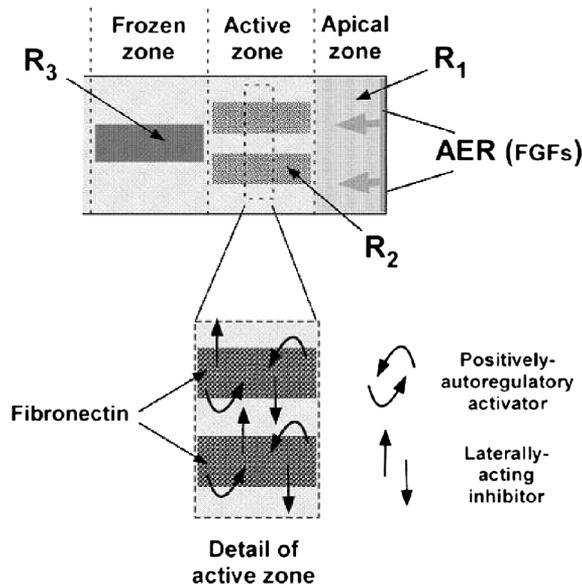
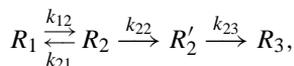


Fig. 1. Schematic representation of the biochemical-genetic circuitry underlying the pattern forming instability described in the model of Hentschel et al. [1], superimposed on a two-dimensional representation of a chicken limb bud midway through development. The “apical,” “active,” and “frozen” zones contain R_1 , $R_2 + R'_2$ and R_3 cells, respectively. In detail of active zone R'_2 cells are shown to produce, in response to the positively autoregulatory activator (TGF- β ; curved arrows), a laterally-acting inhibitor (straight arrows) of the activator. Cells also respond to activator by producing extracellular fibronectin, which promotes cell condensation. The thickness of the developing limb extending from the back to front surfaces (dorso-ventral dimension) is collapsed to zero in this simplified model. PD: proximo-distal; AP: antero-posterior. See [1] for additional details.

scales and gradient expansions are shown in [1]. Stability of different types of patterns is demonstrated in Alber et al. [2].

Spatiotemporal cellular differentiation leading to early skeletal development takes place in a domain (the “mesoblast”) consisting of loosely packed “mesenchymal” cells forming the interior of the embryonic limb. The mesoblast is ensheathed by a thin layer of embryonic skin, the “ectoderm,” which secretes growth factors of the FGF family. At the distal tip of the limb the ectoderm forms a raised ridge, the apical ectodermal ridge (AER), which produces high levels of FGFs and is required for proximo-distal (i.e., oriented away from the body) skeletal development. Just beneath the AER is the population of R_1 cells, which exist in a state prior to both overt cartilage differentiation and precartilage condensation. They are maintained in this state by the FGFs produced by the AER. Equation (1.1) thus allows us to find the FGF concentration c that together with the TGF- β concentration c_a is hypothesized to control the subsequent differentiation of R_1 cells into R_2 cells [3] (see Eqs. (1.4) and (1.5)). R_2 cells produce a lateral inhibitor of TGF- β activity and differentiate irreversibly into R'_2 cells, which produce fibronectin. The terminal cell type in this pattern-forming process, cartilage, results from the irreversible transformation of R'_2 cells into R_3 cells. Cartilage cells do not diffuse, and thus form steep density gradients. These

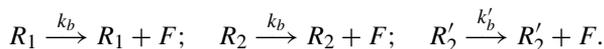
processes can be represented by the following graph:



where k_{21} , k_{22} and k_{23} are constants and $k_{12} = k_{12}(c, c_a)$. It is known [1] that $k_{12}(c, c_a)$ decreases with c and increases with c_a (see [1]). Beside to this, both the mobile (R_1 , R_2 and R'_2) cells and R_3 cells proliferate according to the logistic law. TGF- β , i.e., activator (A), is secreted by both R_1 and R_2 cells. The molecular identity of the inhibitor I is unknown, but on the basis of experimental evidence it is assumed to be produced only by R_2 cells [3]. Component I is assumed to inactivate component A by forming with it a complex P . Since P does not affect the considered process, it is not taken into account in the model. Thus the kinetics of A and I can be described schematically by the graphs



Finally fibronectin, F , is secreted by R_1 and R_2 cells at rate k_b and by R'_2 cells at rate k'_b , where $k_b \ll k'_b$ (see [1]):



Fibronectin decays at rate k_c . It is fibronectin which is the actual adhesive component causing mesenchymal cell condensation, and its spatiotemporal distribution provides a template for chondrogenic pattern formation [4–6]. Fibronectin is released by all mobile mesenchymal cell types into the extracellular matrix (ECM) creating adhesive gradients up which the cells can move. This velocity field effectively dragging the R_1 , R_2 and R'_2 cells into regions of high fibronectin concentration is modeled by the convective terms $\text{div}(R_1 \chi \nabla \rho)$, $\text{div}(R_2 \chi \nabla \rho)$, $\text{div}(R'_2 \chi \nabla \rho)$ in Eqs. (1.4)–(1.6). Here χ is the coefficient describing specific features of the cell-fibronectin interaction. Note that in Eq. (1.8) the fibronectin does not itself diffuse but remains localized in the ECM where it was deposited. This fact together with the presence of the above mentioned fibronectin haptotaxis terms is a source of serious mathematical difficulties (see below). By adding Eqs. (1.4)–(1.6) and neglecting the reaction terms, we obtain an equation for the density of mobile cells $R = R_1 + R_2 + R'_2$. Supposing additionally that $k_b = k'_b$ in Eq. (1.8) one can obtain a system of two equations (for R and ρ), which can be treated as a variant of a system describing chemotaxis. This fact suggests that solutions to our original system (1.1)–(1.8) may retain some properties peculiar to the solutions of the relevant chemotaxis systems. In particular starting from appropriate initial data they may lose smoothness and attain δ -singularities at some points of Ω within a finite time. (See [7,8] for analytical proofs and [9] for numerical evidence; see also [10] for the existence analysis of unbounded in time solutions. For results concerning blow-up in different variants of chemotaxis equations see, e.g., [11–16].)

System (1.1)–(1.8) exhibits Turing-type instabilities, consistent with an earlier suggestion that vertebrate limb development is governed by this class of mechanisms [6]. Recent experiments [17,18] have provided evidence that chondrogenic patterning in cultures of isolated limb cells self-organizes by a Turing-like process involving TGF- β and computational modeling has confirmed the plausibility of this mechanism [19]. In the system under

consideration the prepattern of activator concentration is transferred to the subsystem describing the dynamics of moving cells by using the coefficient $k_{12}(c, c_a)$ [1].

This paper is mainly concerned with the analysis of the conditions which guarantee global existence in time of classical (smooth) solutions to the system of Eqs. (1.1)–(1.8). For $\chi = \text{const}$ (Section 4), these conditions are shown to put strong restrictions either on the magnitude of some parameters (e.g., on the value of χ itself) or on the magnitude of the initial data. The situation changes if we add an arbitrarily small diffusion term $\varepsilon \nabla^2 \rho$ to Eq. (1.8) (Section 5) and allow χ to be a function of ρ . Then under one additional assumption (integrability of $\chi(\rho)$) we are able to prove the global existence of classical solutions. However, the norms of the derivatives of the solutions might tend to ∞ when $\varepsilon \searrow 0$. The proofs are based on a transformation of dependent variables used in the papers [20,21] and uses some of their results. The assumption of integrability of the coefficient $\chi(\rho)$ is in some sense similar to the modification of χ introduced in the papers [22,23].

2. Basic assumptions

In what follows we consider the initial boundary value problem for the system (1.1)–(1.8):

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

We assume that all the dependent variables except for R_3 and ρ satisfy so called no-flux conditions. Thus on the boundary $\partial\Omega$ the following conditions hold:

$$\frac{\partial c}{\partial n} = 0, \quad \frac{\partial c_a}{\partial n} = 0, \quad \frac{\partial c_i}{\partial n} = 0, \quad \frac{\partial R_1}{\partial n} = 0, \quad \frac{\partial R_2}{\partial n} = 0, \quad \frac{\partial R'_2}{\partial n} = 0, \quad (2.1)$$

where $n = n(x)$ is a unit outward normal to $\partial\Omega$ at x , whereas for $x \in \bar{\Omega}$ we have

$$\begin{aligned} c(x, 0) &= c_0(x), & c_a(x, 0) &= c_{a0}(x), & c_i(x, 0) &= c_{i0}(x), \\ R_1(x, 0) &= R_{10}(x), & R_2(x, 0) &= R_{20}(x), & R'_2(x, 0) &= R'_{20}(x), \\ R_3(x, 0) &= R_{30}(x), & \rho(x, 0) &= \rho_0(x). \end{aligned} \quad (2.2)$$

We also require that the consistency conditions are satisfied, namely that

$$\begin{aligned} \frac{\partial c_0(x)}{\partial n(x)} &= 0, & \frac{\partial c_{a0}(x)}{\partial n(x)} &= 0, & \frac{\partial c_{i0}(x)}{\partial n(x)} &= 0, \\ \frac{\partial R_{10}(x)}{\partial n(x)} &= 0, & \frac{\partial R_{20}(x)}{\partial n(x)} &= 0, & \frac{\partial R'_{20}(x)}{\partial n(x)} &= 0 \end{aligned} \quad (2.3)$$

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

We suppose that system (1.1)–(1.8) is written in a nondimensional form and that $D_{\text{cell}} = 1$. This can be achieved by a proper scaling of the spatial variables. Our analysis will be carried out under the following assumptions.

Assumption 1. $k, D, D_a, D_i, k_a, r, R_{\text{eq}}, r_3, R_{3\text{eq}}, k_b, k'_b, k_c$ and all k_{ij} except for k_{12} are positive constants.

Assumption 2. Let $J(x, t) : \bar{\Omega} \times [0, \infty) \rightarrow [0, C_J]$, $C_J > 0$, be such that its $C_{x,t}^{\beta, \beta/2}(\Omega \times (0, t))$ norm is bounded independently of $t > 0$. Let $k_{12}, J_a^1, J_a, k_f : \mathbb{R}^1 \times \mathbb{R}^1 \rightarrow [0, \infty)$ be bounded from above by the constants $\bar{k}_{12}, \bar{J}_{a1}, \bar{J}_a$ and \bar{k}_f , respectively, and such that their $C^{1+\beta}(K)$ norms, where $K \subset \mathbb{R}^1 \times \mathbb{R}^1$ is a compact set, are bounded from above by constants C_K .

Assumption 3. Suppose that:

- (1) The functions $c_0(x), c_{a0}, c_{i0}, R_{10}, R_{20}, R'_{20}, R_{30}$ and ρ_0 are of class $C^{2+\beta}(\bar{\Omega})$ and nonnegative in Ω .
- (2) $\partial\rho_0(x)/\partial n(x) = 0$ for $x \in \partial\Omega$.

Assumption 4. Let J_a^1, J_a be identically equal to 0 for $c_a > \tilde{C}_a > 0$ independently of c_i . Let $k_f(c_i, c_a)$ be identically equal to 0 for $c_i > \tilde{C}_i > 0$ independently of c_a .

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

For any $T > 0$ let us denote

$$\Omega_T := \Omega \times (0, T). \tag{2.4}$$

As we mentioned, we do not impose any boundary conditions for ρ (and R_3). However, due to the last assumption ρ preserves no-flux boundary conditions on the maximal interval of existence of the solution. The following lemma will be used in later sections.

Lemma 1. *Let Assumption 3 hold. Assume that for there exists a solution to system (1.1)–(1.8), (2.2), (2.1) bounded in $C_{x,t}^{1,1}(\Omega_T)$ norm. Then*

$$\frac{\partial\rho(x, t)}{\partial n(x)} = 0 \tag{2.5}$$

for $x \in \partial\Omega, t \in [0, T)$. In the same way $\partial R_3(x, t)/\partial n(x) = 0$, if $\partial R_{30}(x)/\partial n(x) = 0$.

Proof. According to the assumptions of the lemma the normal derivatives $\partial R_1(x, t)/\partial n(x), \partial R_2(x, t)/\partial n(x), \partial R'_2(x, t)/\partial n(x)$ are well defined and equal to 0 for all $t \in [0, T), x \in \partial\Omega$, due to conditions (2.1) and (2.3). Also $\partial\rho(x, 0)/\partial n(x)$ is well defined and equal to 0. Differentiating both sides of Eq. (1.8) along the normal $n(x)$ we obtain an ordinary differential equation

$$\frac{\partial}{\partial t} \left[\frac{\partial\rho}{\partial n} \right] = -k_c \frac{\partial\rho}{\partial n}.$$

At each point on the boundary this equation can be viewed as an ordinary differential equation for $\partial\rho(x, t)/\partial n(x)$ with the initial condition $\partial\rho(x, 0)/\partial n(x) = 0$. Using the Gronwall’s inequality we conclude the proof of the lemma. The proof for R_3 can be carried out in a similar way. \square

3. Main results

In what follows by a global solution we mean a solution defined for $t \in (0, \infty)$. In Section 4 we will analyze the case $\chi = \text{const} > 0$. Under Assumptions 1–4 we will prove existence of a unique global solution of system (1.1)–(1.8) satisfying conditions (2.1) and (2.2). This solution is nonnegative in every of its components. However, to obtain this result we have to assume that either χ or the numbers $(k_b + k'_b)/k_c$ and $\chi \|\rho_0\|_{C^0(\Omega)}$ are sufficiently small. This result is stated in Theorem 1 and in explanatory Remark 3.

In Appendix A we consider system (1.1)–(1.8) with Eq. (1.8) replaced by

$$\frac{\partial \rho}{\partial t} = \varepsilon \nabla^2 \rho + k_b(R_1 + R_2) + k'_b R'_2 - k_c \rho. \quad (3.1)$$

In this case Assumptions 1–4 and integrability of χ imply the existence of a unique solution globally in time. This result is stated in Theorem 4. Of course, as we mentioned in the Introduction the norms of the derivatives of the solutions may tend to ∞ when $\varepsilon \searrow 0$.

Methods of proof. As we mentioned above the main obstacle to applying the standard theory of systems of parabolic equations is the presence of the terms proportional to $\nabla^2 \rho$ in the equations for the moving cells. To eliminate these terms we apply a transformation of variables used in the papers [20] and [21]. The price we pay for it, namely additional non-differential terms appearing in the equations, is of much less importance than the advantage we gain. The next step consists in proving the existence of a solution for $t \in (0, T)$, with $T > 0$ sufficiently small, by using the contraction mapping theorem, as it is done in [20] or [21]. This solution is locally unique. It is crucial that the value of T , for which the contraction mapping theorem applies, depends only on appropriate Hölder space norms of the initial data (and the coefficients of the system). Thus, when we are able to obtain a priori estimates of these norms, we can apply the same procedure once more, treating the obtained solution as a new initial condition. In particular, if the a priori estimates do not depend on T , then repeating the process step by step, we can prove the existence of a global (in time) solution. In obtaining a priori C^0 bounds for the solutions, in several instances we employed theorems of invariant region type. This is an additional element in the proof, which in general follows the lines of the papers [20] and [21].

4. Existence theorem

In this section we assume that $\chi = \text{const} > 0$. The main result of the section is represented in the form of the following theorem.

Theorem 1. *Let Assumptions 1–4 be satisfied. Let $\chi = \text{const} > 0$. Suppose that one of the conditions holds:*

- (1⁰) χ is sufficiently small,
- (2⁰) $\chi \|\rho_0\|_{C^0(\Omega)} < 1$ and the number $(k_b + k'_b)/k_c$ is sufficiently small.

Then for all $t \in (0, T)$, $T \in (0, \infty)$, there exists a unique solution of system (1.1)–(1.8) satisfying conditions (2.1) and (2.2). This solution is nonnegative and every component except for R_3 has its $C_{x,t}^{2+\beta, 1+\beta/2}(\Omega_T)$ norm bounded by a constant independent of T , whereas R_3 has its $C_{x,t}^{0,1}(\Omega_T)$ norm bounded by a constant independent of T .

Before proving this theorem we establish several preliminary results.

The main difficulty in obtaining a priori bounds for the solutions of system (1.1)–(1.8) is the presence of the terms $\operatorname{div}(R_1 \chi \nabla \rho)$, $\operatorname{div}(R_2 \chi \nabla \rho)$ and $\operatorname{div}(R'_2 \chi \nabla \rho)$. To get rid of them we will apply a nonlinear transformation of R_1 , R_2 and R'_2 variables (see [20] and [21]).

Let

$$f(\rho) = \exp\left(\int_0^\rho \chi(s) ds\right). \quad (4.1)$$

For $\chi = \text{const}$ we have simply $f(\rho(x)) = \exp(\chi\rho(x))$. Let us introduce new variables S_1 , S_2 , S_4 and S by using the following formulae:

$$S_1 = \frac{R_1}{f(\rho)}, \quad S_2 = \frac{R_2}{f(\rho)}, \quad S_4 = \frac{R'_2}{f(\rho)}, \quad S = S_1 + S_2 + S_4. \quad (4.2)$$

After applying this transformation and setting $D_{\text{cell}} = 1$, the system of Eqs. (1.1)–(1.8) has the form

$$\frac{\partial c}{\partial t} - D \nabla^2 c = -kc + J(x, t), \quad (4.3)$$

$$\frac{\partial R_3}{\partial t} = r_3 R_3 (R_{3\text{eq}} - R_3) + k_{23} f(\rho) S_4, \quad (4.4)$$

$$\frac{\partial c_a}{\partial t} - D_a \nabla^2 c_a = -k_a c_i c_a + J_a^1(c_a, c_i) f(\rho) S_1 + J_a(c_a, c_i) f(\rho) S_2, \quad (4.5)$$

$$\frac{\partial c_i}{\partial t} - D_i \nabla^2 c_i = -k_a c_i c_a + k_f(c_a, c_i) f(\rho) S_2, \quad (4.6)$$

$$\begin{aligned} \frac{\partial S_1}{\partial t} - \nabla^2 S_1 &= \chi \nabla \rho \cdot \nabla S_1 + r S_1 (R_{\text{eq}} - f(\rho) S) + k_{21} S_2 \\ &\quad - k_{12}(c, c_a) S_1 - \chi S_1 g, \end{aligned} \quad (4.7)$$

$$\begin{aligned} \frac{\partial S_2}{\partial t} - \nabla^2 S_2 &= \chi \nabla \rho \cdot \nabla S_2 + r S_2 (R_{\text{eq}} - f(\rho) S) + k_{12}(c, c_a) S_1 \\ &\quad - k_{21} S_2 - k_{22} S_2 - \chi S_2 g, \end{aligned} \quad (4.8)$$

$$\frac{\partial S_4}{\partial t} - \nabla^2 S_4 = \chi \nabla \rho \cdot \nabla S_4 + r S_4 (R_{\text{eq}} - f(\rho) S) + k_{22} S_2 - k_{23} S_4 - \chi S_4 g, \quad (4.9)$$

$$\frac{\partial \rho}{\partial t} = g(S_1, S_2, S_4, \rho), \quad (4.10)$$

where $g = k_b f(\rho)(S_1 + S_2) + k'_b f(\rho) S_4 - k_c \rho$.

Notice that the solution of the first equation $c(x, t)$ (with $\partial c / \partial n = 0$ at the boundary) exists globally in $C^{2+\beta, 1+\beta/2}$ class and is nonnegative for nonnegative initial values $c(x, 0)$ as $J(x, t) \geq 0$. The second equation does not influence the rest of the system. Therefore,

we can confine ourselves to the system containing only the last six equations. Thus we consider the initial boundary value problem for the system (4.5)–(4.10). That is to say we assume that for $x \in \partial\Omega$ and all $t \geq 0$ in the interval of solution existence the following boundary conditions are satisfied:

$$\begin{aligned} \frac{\partial c_a(x, t)}{\partial n} &= 0, & \frac{\partial c_i(x, t)}{\partial n} &= 0, \\ \frac{\partial S_1(x, t)}{\partial n} &= 0, & \frac{\partial S_2(x, t)}{\partial n} &= 0, & \frac{\partial S_4(x, t)}{\partial n} &= 0. \end{aligned} \tag{4.11}$$

Simultaneously, we require that for $x \in \bar{\Omega}$,

$$\begin{aligned} c_a(x, 0) &= c_{a0}(x), & c_i(x, 0) &= c_{i0}(x), \\ S_1(x, 0) &= S_{10}(x), & S_2(x, 0) &= S_{20}(x), & S_4(x, 0) &= S_{40}(x), \\ \rho(x, 0) &= \rho_0(x) \end{aligned} \tag{4.12}$$

and that the consistency conditions are satisfied, i.e., for all $x \in \partial\Omega$,

$$\begin{aligned} \frac{\partial c_{a0}(x)}{\partial n(x)} &= 0, & \frac{\partial c_{i0}(x)}{\partial n(x)} &= 0, \\ \frac{\partial S_{10}(x)}{\partial n(x)} &= 0, & \frac{\partial S_{20}(x)}{\partial n(x)} &= 0, & \frac{\partial S_{40}(x)}{\partial n(x)} &= 0. \end{aligned} \tag{4.13}$$

Remark 1. The boundary conditions for S_i follow from the boundary conditions (2.1) for the initial problem, Assumption 3 and Lemma 1. Next, according to (4.2), we have

$$\begin{aligned} S_{10}(x)f(\rho_0(x)) &= R_{10}(x), & S_{20}(x)f(\rho_0(x)) &= R_{20}(x), \\ S_{10}(x)f(\rho_0(x)) &= R_{10}(x). \end{aligned}$$

Assumption 5. $\chi = \text{const} > 0$.

Let

$$U = (c_a, c_i, S_1, S_2, S_4, \rho). \tag{4.14}$$

Let the vector on the right and left-hand sides of the system of Eqs. (4.5)–(4.10) be denoted by

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

and

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

respectively. Given vector \tilde{U} , let $P(\tilde{U})$ be the solution of the system

$$L(U) = \Phi(\tilde{U}),$$

in the set $\Omega_T = \Omega \times (0, T)$ for some $T > 0$ subject to the initial and boundary conditions (4.12) and (4.11). Let us consider the mapping

$$U = P(\tilde{U}).$$

According to the Schauder estimates (see, e.g., [24,25]) for $T > 0$ sufficiently small P is a contractive mapping acting in the space $C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$. Thus from the contraction mapping principle we infer that 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 of the system

$$LU = \Phi(U).$$

One can prove that T depends only on the $C_x^{2+\beta}(\Omega)$ norm of the initial data. The proof may be carried out along the lines of [21, p. 1336]. It is based on the a priori estimates in $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ space (see Theorem IV.5.3 in [24]) and elementary theory of ordinary differential equations. For the convenience of the reader we have sketched the proof in Appendix A. It follows from 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 , that we can conclude, by applying the continuation method, that the solution exists globally.

The crucial condition for this analysis is provided by the following assumption.

Assumption 6. Suppose that for all $x \in \Omega$, $0 \leq c_{a0}(x) < C_a$ and $0 \leq c_{i0}(x) < C_i$ with $C_a > \bar{C}_a$ and $C_i > \bar{C}_i$. Suppose that there exists a positive solution $(\bar{S}_1, \bar{S}_2, \bar{S}_4, \bar{\rho})$ to the system of algebraic inequalities:

$$\begin{aligned} rS_1(R_{eq} - S_1) + k_{21}S_2 - \chi k_b S_1^2 + \chi k_c S_1 \rho &< 0, \\ rS_2(R_{eq} - S_2) + \bar{k}_{12}S_1 - \chi k_b S_2^2 + \chi k_c S_2 \rho &< 0, \\ rS_4(R_{eq} - S_4) + k_{22}S_2 - \chi k'_b S_4^2 + \chi k_c S_4 \rho &< 0, \\ k_b(S_1 + S_2) + k'_b S_4 - k_c \rho \exp(-\chi \rho) &< 0, \end{aligned} \tag{4.15}$$

such that for all $x \in \bar{\Omega}$,

$$0 \leq S_{10}(x) < \bar{S}_1, \quad 0 \leq S_{20}(x) < \bar{S}_2, \quad 0 \leq S_{40}(x) < \bar{S}_4, \quad 0 < \rho_0(x) \leq \bar{\rho}, \tag{4.16}$$

and $\bar{\rho} \leq \frac{1}{\chi}$.

Remark 2. Conditions (4.15) are closely related to the invariant region established by using sub- and supersolution method (see [26–28]). Namely, inequalities (4.15) and the inequalities

$$\begin{aligned} -k_a c_i C_a + J_a^1(C_a, c_i) f(\rho) S_1 + J_a(C_a, c_i) f(\rho) S_2 &\leq 0, \\ -k_a C_i c_a + k_f(C_i, c_a) f(\rho) S_2 &\leq 0, \end{aligned} \tag{4.17}$$

which, due to Assumption 4, hold for all $c_a \in [0, C_a]$, $c_i \in [0, C_i]$, $S_1 \in [0, \bar{S}_1]$, $S_2 \in [0, \bar{S}_2]$, $\rho \in [0, \bar{\rho}]$ provide a sufficient condition for inequalities (B.3) in Appendix B to hold for $Y = [C_a, C_i, \bar{S}_1, \bar{S}_2, \bar{S}_4, \bar{\rho}]$. Obviously, for $y = [0, 0, 0, 0, 0, 0]$ inequalities (B.2) are satisfied.

Remark 3. Notice that the set of parameters for which there exists a solution of (4.15) is not empty. Obviously, for $\chi = 0$ and any nonnegative data (4.15) always has a solution. Since the solution persists for sufficiently small $\chi > 0$, we can take $\bar{\rho} = (\sqrt{\chi})^{-1}$. Then $\bar{\rho} \exp(-\chi \bar{\rho}) = (\sqrt{\chi})^{-1} \exp(-\sqrt{\chi})$ can be made arbitrarily large, whereas $\chi \bar{\rho} = \sqrt{\chi}$ is arbitrarily small. If χ is not small some parameters can be still chosen to be small enough to guarantee the existence of a global solution. To be more specific, let $w = \|\rho_0\|_{C^0(\Omega)}$ and $w\chi < 1$. Let $\gamma \in (1, \infty)$. Consider the system of equations:

$$\begin{aligned} rS_1(R_{\text{eq}} - S_1) + k_{21}S_2 - \chi k_b S_1^2 + \gamma k_c S_1 &= 0, \\ rS_2(R_{\text{eq}} - S_2) + \bar{k}_{12}S_1 - \chi k_b S_2^2 + \gamma k_c S_2 &= 0, \\ rS_4(R_{\text{eq}} - S_4) + k_{22}S_2 - \chi k'_b S_4^2 + \gamma k_c S_4 &= 0. \end{aligned} \tag{4.18}$$

For fixed $S_4 = \zeta \geq 0$ the set of points with positive coordinates satisfying the first and the second equation can be written as $S_i = B(\gamma) + \sqrt{B^2(\gamma) + D_i S_{j(i)}}$, where $j(i) = 2$ for $i = 1$, $j(i) = 1$ for $i = 2$, $B(\gamma) > 0$, $D_i > 0$ and $B(\gamma)$ grows with γ . In the quarter $\{S_1 \geq 0, S_2 \geq 0\}$ these curves intersect at exactly one point $(\bar{S}_1(\gamma), \bar{S}_2(\gamma))$ with its coordinates growing with γ . The intersection of the set of points satisfying the third equation with the plane $\{S_4 = \zeta\}$ can be written in the form $k_{22}S_2 = -(rR_{\text{eq}} + \gamma k_c)\zeta + (r + \chi k'_b)\zeta^2$. By changing ζ one notes that there exists exactly one $\zeta = \bar{S}_4(\gamma) > 0$ for which the last straight line passes through the point $(\bar{S}_1(\gamma), \bar{S}_2(\gamma))$. Consequently this system has a unique positive solution $(\bar{S}_1(\gamma), \bar{S}_2(\gamma), \bar{S}_4(\gamma))$ growing (componentwise) with γ . We may choose γ so large that $\bar{S}_i > S_{i0}(x)$ for all $x \in \bar{\Omega}$, $i = 1, 2, 4$. Let $\bar{k}_b = \max\{k_b, k'_b\}$ and suppose that \bar{k}_b/k_c is so small that the expression $[k_b(\bar{S}_1 + \bar{S}_2) + k'_b \bar{S}_4] \exp(1)/k_c$ is smaller than χ^{-1} . Then for $\bar{\rho} = \chi^{-1}$, $(\bar{S}_1, \bar{S}_2, \bar{S}_4)$ satisfying (4.18), also satisfy (4.15) (with $\bar{\rho} = \chi^{-1}$). Thus, we have proven that if $\chi \|\rho_0\|_{C^0(\Omega)} < 1$ and \bar{k}_b/k_c is sufficiently small then Assumption 6 is satisfied.

The next lemma will be crucial in our analysis.

Lemma 2. Suppose that Assumptions 1–5 hold. Then for all possible $C^{2,1}_{x,t}(\Omega_T)$ solutions of system (4.5)–(4.10) we have

$$0 \leq (c_a, c_i, S_1, S_2, S_4, \rho)(x, t) < (C_a, C_i, \bar{S}_1, \bar{S}_2, \bar{S}_4, \bar{\rho}). \tag{4.19}$$

Proof. Given function $\rho(x, t)$ (together with $c(x, t)$) the system (4.5)–(4.9) becomes a system of five parabolic equations. According to Assumption 6 as long as $\rho(x, t) < \bar{\rho}$, the parallelepiped $0 \leq (c_a, c_i, S_1, S_2, S_4)(x, t) < (C_a, C_i, \bar{S}_1, \bar{S}_2, \bar{S}_4)$ (see Remark 2 following Assumption 6) is an invariant set. So solution (which is locally unique) must satisfy the nonnegativity condition $c_a(x, t) \geq 0$, $c_i(x, t) \geq 0$ and $S_i(x, t) \geq 0$, $i = 1, 2, 4$. This follows from Theorem B.1 described in Appendix B and which was taken from [26]. Notice that Theorem 1 from [28] cannot be applied directly to the system (4.5)–(4.9) because of specific conditions assumed in the case of zero-flux boundary conditions (see [28, p. 435]).

The right-hand side of the equation for S_1 is nonnegative for $S_1 = 0$, $0 \leq S_2 \leq \bar{S}_2$ and $0 \leq S_4 \leq \bar{S}_4$ independently of the value of ρ . Note also that when the function ρ is

treated as given and belongs at least to $C_x^{1+\beta}$, then we can obviously find a priori bounds for the functions ∇S_i , $i = 1, 2, 4$, as well as for $\nabla c_a, \nabla c_i$ by means of their C^0 norms (e.g., [24, Theorem V.7.2]). Now we can prove that $\rho(x, t) \geq 0$ in Ω_T . Suppose the contrary, namely that ρ attains the minimal value in Ω_{t_0} , $t_0 \leq T$, at a point (t_0, x_0) and that $\rho(t_0, x_0) < 0$. We should have then $(\partial/\partial t)\rho(t_0, x_0) \leq 0$. This leads to a contradiction since, as $S_i(t_0, x_0) \geq 0$ it follows from Eq. (4.10) that $(\partial/\partial t)\rho(t_0, x_0) > 0$. Now, suppose that $\rho(x, t)$ attains the maximal value in Ω_{t_0} at a point (t_0, x_0) which coincides with $\bar{\rho}$, whereas $S_i(t_0, x_0) \leq \bar{S}_i$. Again, this leads to a contradiction because it follows from Eq. (4.10) that $(\partial/\partial t)\rho(t_0, x_0) < 0$. \square

Now we can formulate the first existence theorem.

Theorem 2. *Let Assumptions 1–6 hold. Then for any $T > 0$ there exists a unique solution to the system (4.5)–(4.10) subject to the initial-boundary conditions (4.12) and (4.11) such that $C_{x,t}^{2+\beta, 1+\beta/2}(\Omega_T)$ norms of all the components are bounded by constants independent of T .*

Proof. According to the above remarks it is sufficient to prove a priori estimates for the solution which are independent of T . From Lemma 2 we know that if the $C_{x,t}^{2+\beta, 1+\beta/2}(\Omega_T)$ solution to the considered problem exists then all of its last four components are bounded in C^0 norm by constants independent of T . It follows that

$$f(\rho(x, t)) \geq 1, \quad \|f\|_{C^0(\Omega_T)} \leq C_0, \quad \|\tilde{\Phi}\|_{C^0(\Omega_T)} \leq C_0, \tag{4.20}$$

where $\tilde{\Phi} = (\Phi_3, \Phi_4, \Phi_5, \Phi_6)$ and C_0 is independent of T . Therefore, conditions (4.4) from [20] are satisfied. This results in following the estimates:

$$\|c_a\|_{C_{x,t}^{\beta, \beta/2}(\Omega_T)} \leq K, \quad \|c_i\|_{C_{x,t}^{\beta, \beta/2}(\Omega_T)} \leq K, \tag{4.21}$$

where K is independent of T . To proceed, we have to show that similar estimates hold for S_i :

$$\|S_i\|_{C_{x,t}^{\beta, \beta/2}(\Omega_T)} \leq K, \tag{4.22}$$

where K is also independent of T . This can be done by applying the arguments used in [20, p. 147] for each of the equations (4.7)–(4.9) separately.

The next step is to prove similar estimates for the function ρ and its derivative with respect to t . For given $x, y \in \Omega$ let

$$\rho_{(x,y)}^\beta(x, t) := \frac{\rho(x, t) - \rho(y, t)}{|x - y|^\beta}, \quad S_{i,(x,y)}^\beta(x, t) := \frac{S_i(x, t) - S_i(y, t)}{|x - y|^\beta}.$$

Then function $\rho_{(x,y)}^\beta$ satisfies the equation

$$\begin{aligned} & \frac{\partial}{\partial t} \rho_{(x,y)}^\beta(x, t) \\ &= \{ \chi f(\rho_\theta(x, y, t)) [k_b(S_1(y, t) + S_2(y, t)) + k'_b S_4(y, t)] - k_c \} \rho_{(x,y)}^\beta(x, t) \\ & \quad + \{ k_b(S_{1,(x,y)}^\beta + S_{2,(x,y)}^\beta) + k'_b S_{4,(x,y)}^\beta \} f(\rho(x, t)), \end{aligned} \tag{4.23}$$

which was obtained by using the identity $ab - a_0b_0 = a(b - b_0) + b_0(a - a_0)$ and notation

$$\rho_\theta(x, y, t) = \rho(x, t) + \theta(x, y, t)(\rho(y, t) - \rho(x, t)),$$

where $\theta(x, y, t) \in [0, 1]$. For fixed x and y the last equation has the following structure:

$$\zeta' = \xi(t)\zeta + \phi(t),$$

where, according to our previously obtained estimates, $\phi(t)$ is bounded for all $t \in [0, T]$. Thus, as long as $\xi(t) < 0$ for all $t \in [0, T)$ we have that

$$|\zeta(t)| \leq \max\{|\zeta(0)|, 1/\xi_{\min} \tilde{K}_1\}, \tag{4.24}$$

where \tilde{K}_1 depends only on C^0 norm of ρ and $C^{\beta, \beta/2}$ norms of S_i on Ω_T . Therefore, it is independent of T . Here ξ_{\min} is the minimal value of the function $|\xi|$ on the interval $[0, T)$. Let us analyze the condition $\xi(t) < 0$. After denoting $\rho_\theta(x, y, t) = \rho$ we see that the condition $\xi < 0$ for all $\rho \in [0, \bar{\rho}]$ is implied by the last condition from (4.15) if only

$$\bar{\rho} f(-\bar{\rho}) \chi f(\rho) \leq 1. \tag{4.25}$$

However, $\chi = \text{const}$ and $f(\rho)$ is an increasing function. Hence, condition (4.25) holds for $\rho \in [0, \bar{\rho}]$ if it holds for $\rho = \bar{\rho}$. But for $\rho = \bar{\rho}$ it is equivalent to the last condition in Assumption 6. Therefore, the fact that $\xi(t) < 0$ is independent of T . Since $\rho(x, t)$ is of C^1 class with respect to t then it is of $C^{\beta/2}$ class as well. Thus by using the inequality (4.24) we have that

$$\|\rho\|_{C^{\beta, \beta/2}_{x,t}(\Omega_T)} \leq K_1. \tag{4.26}$$

Now, let

$$\rho_{(t,\tau)}^{\beta/2}(x, t) := \frac{\rho(x, t) - \rho(x, \tau)}{|t - \tau|^{\beta/2}}, \quad S_{i,(t,\tau)}^{\beta/2}(x, t) := \frac{S_i(x, t) - S_i(x, \tau)}{|t - \tau|^{\beta/2}}$$

and

$$\rho_{t,(t,\tau)}^{\beta/2}(x, t) := \frac{\frac{\partial \rho}{\partial t}(x, t) - \frac{\partial \rho}{\partial t}(x, \tau)}{|t - \tau|^{\beta/2}}.$$

The function $\rho_{t,(t,\tau)}^{\beta/2}(x)$ can be expressed in terms of the constants k_b, k'_b and k_c and the functions $\rho_{(t,\tau)}^{\beta/2}(x)$ and $S_{i,(t,\tau)}^{\beta/2}(x)$ with absolute values bounded by constants independent of the points $(x, t), (x, \tau) \in \Omega_T$ and T itself (which follows from the previous estimates). Next, the right-hand side of Eq. (4.23) is in fact equal to $[\partial \rho(x, t)/\partial t - \partial \rho(y, t)/\partial t]/|x - y|^\beta$. We conclude from the estimates (4.26) and (4.22) that the absolute value of the last function is also bounded by constants independent of the points $(x, t), (x, \tau) \in \Omega_T$ and T . We have thus proved that

$$\left\| \frac{\partial \rho}{\partial t} \right\|_{C^{\beta, \beta/2}_{x,t}(\Omega_T)} \leq K_2. \tag{4.27}$$

By using (4.26) and (4.27) and method from Theorem 2.2 in [20] we can prove that S_i are bounded in the space $C^{1+\beta, \beta/2}$ by constants independent of T . Using the obtained estimates, similar calculations can be carried out for the components of the functions $\nabla \rho$

and $\partial/\partial t(\nabla\rho)$ resulting in demonstration of ρ being bounded in the norm of the space $C^{1+\beta, \beta/2}$. By applying the Schauder estimates to the system (4.7)–(4.9), and repeating the above procedure to Eq. (4.10) we conclude the proof of the theorem. \square

Remark 4. Theorem 2 implies that there exists a global smooth solution of the system (4.5)–(4.10). We also know that there exists a unique solution of Eq. (4.3). By using the functions $S_1(x, t)$, $S_2(x, t)$, $S_4(x, t)$ and ρ one can obtain the functions $R_1(x, t)$, $R_2(x, t)$ and $R'_2(x, t)$. The last function can be used for proving the existence of a unique solution of Eq. (1.7) defined for $(x, t) \in \bar{\Omega}_T$ and for any $T \in (0, \infty)$. Notice that $R_3(x, t) \geq 0$. (For sufficiently small $R_3 \geq 0$, $\partial R_3/\partial t \geq 0$ due to the nonnegativity of R'_2 .) Since R'_2 is globally bounded and there is a minus sign in front of the quadratic term $r_3 R_3^2$, $R_3(x, t)$ is bounded from above by a positive constant.

Proof of Theorem 1. The proof follows from the proof of Theorem 2 and Remarks 3 and 4. \square

5. Case of nonzero diffusion coefficient of fibronectin

The aim of this section is to study global existence in time of solutions of the system with the term $\varepsilon \nabla^2 \rho$ added to the last equation. In what follows we assume that χ , which now can depend on ρ , is an integrable decreasing function of its argument. In contrast to Section 4, we do not make any assumptions about the behavior of the coefficients of the system and the magnitude of the initial data. On the other hand, under these weaker conditions we cannot exclude in general case possibility of C^0 norms of the derivatives of the solutions tending to ∞ as $\varepsilon \searrow 0$.

Consider system (1.1)–(1.7) together with the equation

$$\frac{\partial \rho}{\partial t} = \varepsilon \nabla^2 \rho + k_b(R_1 + R_2) + k'_b R'_2 - k_c \rho \quad (5.1)$$

and initial-boundary conditions (2.2) and (2.1) and the boundary condition for ρ

$$\frac{\partial \rho(x, t)}{\partial n(x)} = 0, \quad x \in \partial \Omega. \quad (5.2)$$

As in Section 4, by using transformation (4.1)–(4.2) the analysis of the above system is reduced to analyzing system (4.5)–(4.10) subject to the initial-boundary conditions (4.12) and (4.11) with Eq. (4.10) replaced by the equation

$$\frac{\partial \rho}{\partial t} - \varepsilon \nabla^2 \rho = g(S_1, S_2, S_4, \rho), \quad (5.3)$$

where $g = k_b f(\rho)(S_1 + S_2) + k'_b f(\rho)S_4 - k_c \rho$.

Assumption 7. Let $C^2 \ni \chi : \mathbb{R}^1 \rightarrow [0, \infty)$ be a decreasing and integrable function with

$$\int_0^\infty \chi(s) ds = K.$$

Obviously, the last assumption implies that $\rho \chi(\rho) \rightarrow 0$ as $\rho \rightarrow \infty$.

As in Section 4 the global existence of bounded solutions is implied by the existence of solutions to an algebraic system of inequalities corresponding to the system (4.15) and (4.16). The crucial difference is the fact that now we do not require that a condition similar to the condition $\bar{\rho} \leq 1/\chi$ be satisfied. Namely, even without this condition we are able to find an estimate for the Hölder norm of the function ρ .

Lemma 3. *Assume that χ satisfies Assumption 7. Then the system*

$$\begin{aligned}
 rS_1(R_{\text{eq}} - S_1) + k_{21}S_2 + \sup_{\rho \in [0, \bar{\rho}]} [-\chi(\rho)k_bS_1^2 + \chi(\rho)S_1k_c\rho] &< 0, \\
 rS_2(R_{\text{eq}} - S_2) + \bar{k}_{12}S_1 + \sup_{\rho \in [0, \bar{\rho}]} [-\chi(\rho)k_bS_2^2 + \chi(\rho)S_2k_c\rho] &< 0, \\
 rS_4(R_{\text{eq}} - S_4) + k_{22}S_2 + \sup_{\rho \in [0, \bar{\rho}]} [-\chi(\rho)k_bS_4^2 + \chi(\rho)S_4k_c\rho] &< 0, \\
 k_b(S_1 + S_2) + k'_bS_4 - k_c\rho \exp\left(-\int_0^{\bar{\rho}} \chi(s) ds\right) &< 0
 \end{aligned} \tag{5.4}$$

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

$$0 \leq S_{10}(x) < \bar{S}_1, \quad 0 \leq S_{20}(x) < \bar{S}_2, \quad 0 \leq S_{40}(x) < \bar{S}_4, \quad 0 < \rho_0(x) \leq \bar{\rho}. \tag{5.5}$$

Proof. Let $\eta = \sup_{\rho \in [0, \infty]} \chi(\rho)\rho$. Then there exists a solution $\bar{S}_1, \bar{S}_2, \bar{S}_4$ of the system

$$\begin{aligned}
 rS_1(R_{\text{eq}} - S_1) + k_{21}S_2 + k_c\eta S_1 &< 0, \\
 rS_2(R_{\text{eq}} - S_2) + \bar{k}_{12}S_1 + k_c\eta S_2 &< 0, \\
 rS_4(R_{\text{eq}} - S_4) + k_{22}S_2 + k_c\eta S_4 &< 0,
 \end{aligned} \tag{5.6}$$

satisfying the first three of the conditions (5.5). Putting this solution into the fourth inequality in (5.4) results in the following condition:

$$k_b(\bar{S}_1 + \bar{S}_2) + k'_b\bar{S}_4 - k_c\bar{\rho} \exp\left(-\int_0^{\bar{\rho}} \chi(s) ds\right) < 0.$$

However, $\exp(-\int_0^{\bar{\rho}} \chi(s) ds) > \exp(-K)$ and thus there exists finite $\rho^* > 0$ such that for all $\bar{\rho} > \rho^*$ this condition is satisfied and also $\bar{\rho} \geq \rho_0(x)$ in Ω . But any such $\bar{\rho}$ satisfies also the first three inequalities of system (5.4) as $\bar{\rho}\chi(\bar{\rho}) \leq \eta$. \square

Now we can prove the following theorem.

Theorem 3. *Let Assumptions 1–4 and 7 hold. Then for any $T > 0$ there exists a unique solution of the system (4.5)–(4.9) and (5.1) subject to the initial-boundary conditions (4.12), (4.11) and (5.2), such that the $C_{x,t}^{2+\beta, 1+\beta/2}(\Omega_T)$ norms of all its components are bounded by constants independent of T and every component has its C^0 norm independent of ε*

and T . Moreover, for any $\gamma \in (0, 1)$ the $C_{x,t}^{1+\gamma,\gamma}(\Omega_T)$ norms of the functions c_a and c_i are independent of ε .

Proof. The proof is similar to the proof of the Theorem 2 and involves contraction mapping theorem in the space $C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$ for sufficiently small $T > 0$. The difference is that this time we can estimate the $C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$ norm of the function ρ (globally in time) by the Schauder estimates (see, e.g., [24,25]) only by using C^0 bounds for the functions c_a, c_i, S_1, S_2 and S_4 . Of course this norm may grow with $\varepsilon \searrow 0$. On the other hand, for any $\gamma \in (0, 1)$ the norms of the functions c_a and c_i depend only on the C^0 norms of the right-hand sides of Eqs. (4.5) and (4.6). These norms are independent of ε . \square

Theorem 3 and Remark 4 imply existence of the solution of the initial value problem.

Theorem 4. *Let Assumptions 1–4 be satisfied. Let χ be positive, decreasing and integrable function of ρ of C^2 class. Then for every $\varepsilon > 0$ there exists a unique classical solution of the system (1.1)–(1.7), (5.1) satisfying conditions (2.1), (5.2) and (2.2) defined for all $t \in (0, T)$, $T \in (0, \infty)$. This solution is nonnegative and has its C^0 norm bounded by a constant independent of ε and T . And every component except for R_3 has its $C_{x,t}^{2+\beta,1+\beta/2}(\Omega_T)$ norm bounded by a constant independent of $T \in (0, \infty)$. Moreover, for any $\gamma \in (0, 1)$, the $C_{x,t}^{1+\gamma,\gamma}(\Omega_T)$ norms of the functions c_a and c_i are independent of ε .*

6. Conclusions

In this paper we prove some existence theorems for the system (1.1)–(1.8). In particular, we prove that under certain conditions on the coefficients of the system or on the initial data a unique classical solution exists globally in time. The condition of sufficiently small initial value for ρ is biologically plausible, because the earliest cells in the developing limb (R_1 cells) secrete fibronectin only at relatively a small rate $k_b \ll k'_b$. The assumptions that the numbers χ or $\max\{k_b, k'_b\}/k_c$ are sufficiently small seem to be rather restrictive, however. At present there is a lack of precise experimental data to confirm their validity. We have not proved that the conditions from Theorem 1 are necessary for the global existence of smooth solutions. As we mentioned the possibility of blow-up of the solutions is suggested by [7] and [8], though the corresponding analysis would be much more complicated in the case of system (1.1)–(1.8).

We also show that by introducing arbitrarily small diffusion of fibronectin, we can reduce significantly the number of conditions necessary for the global existence of smooth solutions. Again while fibronectin diffusion in the ECM will certainly be slow because of its size and adhesive character, the assumption of a small finite diffusibility of fibronectin is by no means excluded by the biological evidence. For example, the domain of action of fibronectin spreads from its sites of initial deposition by conversion of its initially compact structure to a more extended structure [32]. Our dynamical analysis suggests that this important property of fibronectin matrix assembly may be a key aspect of developmental stability. The parabolic perturbation of Eq. (1.8) is thus a reasonable modification of the initial model.

Of course this is only the first step of the analysis. We do not examine large time asymptotics of the solutions, which in fact determines the final pattern in the considered model. Another important question concerns the region of validity of our model equations. It is clear that at high cellular densities, the use of PDEs to describe embryological development (which involves discrete multicellular processes) must break down. This breakdown will occur at scales of the order of a few cell diameters (i.e., on a linear scale of 10^2 microns), and to study events at this scale we will need to use discrete mathematical methods such as cellular automata (see [19]). Finally, in order to accurately describe the process of vertebrate limb formation one needs to take into account its growth, that is to say, one needs to consider a free boundary problem involving PDEs in a complex evolving domain whose growth and shape depend on the solution of these PDEs (cf., e.g., [29–31]).

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Appendix A. Properties of the operator P

P is a well-defined mapping from the space $\mathcal{M} = C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$ to itself. The norm $\|U\|_{\mathcal{M}}$ in this space is given by the sum of $C_{x,t}^{1+\beta,(1+\beta)/2}(\Omega_T)$ norms of U_i . Note that

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

(See Section I.1 in [24].) Let U_0 denote the vector of initial functions and consider a closed ball B in the considered space defined by $B = \{U \in \mathcal{M}: \|U - U_0\|_{\mathcal{M}} \leq 1\}$. Let $\tilde{U} \in B$. Then from the Schauder estimates (see Theorem IV.5.3 in [24]) and elementary theory of ordinary differential equations we know that as $t \rightarrow 0$,

$$\|U(\cdot, t) - U_0(\cdot)\|_{C_x^{1+\beta}(\Omega)} \rightarrow 0. \tag{A.2}$$

From the same estimates and the definition of the Hölder norms (Section I.1 in [24]) we know that

$$\begin{aligned} \left\| \frac{\partial U}{\partial t} \right\|_{C_{x,t}^{0,0}(\Omega_T)} < K_1, \quad \|D_x^2 U(x, \cdot)\|_{C_t^{\beta/2}((0,T))} < K_2, \\ \|\nabla U(x, \cdot)\|_{C_t^{(1+\beta)/2}((0,T))} < K_3, \end{aligned} \tag{A.3}$$

independently of $x \in \bar{\Omega}$. The constants K_i can be chosen independent of $\tilde{U} \in B$. From (A.2) and the first inequality in (A.3) we infer that the first term at the right-hand side of (A.1) tends to zero for $T \rightarrow 0$ as $T^{1/2-\beta/2}$. From (A.2) and the second inequality in (A.3) we infer that $\|U(\cdot, t) - U_0(\cdot)\|_{C_x^{1+\beta}(\Omega)}$ tends to zero for $T \rightarrow 0$ as $T^{\beta/2}$. Finally from (A.2) and the third inequality (A.3) we infer that $\|\nabla U(x, \cdot) - \nabla U_0(x)\|_{C_t^{\beta/2}((0,T))}$ tends

to zero for $T \rightarrow 0$ as $T^{1/2}$. Consequently, $\|U - U_0\|_{\mathcal{M}}$ behaves like $K_4 T^\delta$, $\delta > 0$, where the constant K_4 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 . Using the fact that Φ is of class $C^{1+\beta}$ and proceeding in the same way we can easily prove that $\|P(U_2) - P(U_1)\|_{\mathcal{M}} \leq T^\nu K_5 \|U_2 - U_1\|_{\mathcal{M}}$, for all $U_1, U_2 \in B$ with $\nu > 0$. Hence for $T > 0$ sufficiently small the mapping is a contraction from B to B .

Appendix B. Existence theorem via sub and super solution method

We consider a system of parabolic equations of the form

$$\begin{aligned} L_i(x, t)u_i &= f_i(x, t, u, \nabla u), & (x, t) \in \Omega_T, \quad T > 0, \\ \frac{\partial u_i}{\partial n} &= 0, & x \in \partial\Omega, \\ u_i(x, 0) &= u_{i0}(x), \end{aligned} \tag{B.1}$$

where $\Omega_T := \Omega \times (0, T)$, $i \in \{1, \dots, m \geq 1\}$, $\Omega \subset \mathbb{R}^n$ is an open bounded domain with $\partial\Omega$ of $C^{2+\beta}$ class, $\beta \in (0, 1)$, $n = n(x)$ is a unit outward normal to $\partial\Omega$ at x , and $u_{i0} \in C^{2+\beta}(\bar{\Omega})$ satisfies compatibility condition $\partial u_{i0} / \partial n = 0$ on $\partial\Omega$. The parabolic operators have the following form:

$$L_i = -\frac{\partial}{\partial t} + D_i(x, t)\nabla^2.$$

We assume that for all $i \in \{1, \dots, m\}$, all $(x, t) \in \bar{\pi}$, D_i is of class C^1 and

$$\infty > \nu \geq D_i(x, t) \geq \mu > 0$$

for all $(x, t) \in \bar{\pi}$. Above, for simplicity we denoted

$$\pi := \Omega_T.$$

We assume also that $f_i: \bar{\pi} \times \mathbb{R}^m \times \mathbb{R}^{mn} \rightarrow \mathbb{R}^m$ are locally Hölder continuous with exponents $\beta, \beta/2, \beta, \beta$, respectively.

Assumption B.1. For any $C^{2,1}$ solution to system (B.1) with its C^0 norm on $\bar{\pi}$ bounded by a constant $\eta < \infty$ we have an a priori estimate

$$\|\nabla u\| \leq W(\eta),$$

where $W: \mathbb{R}^1 \rightarrow \mathbb{R}^1$ is a continuous function depending on the coefficients of system (B.1) and Ω , but not depending on the solution u .

Now, let $y, Y: \bar{\pi} \rightarrow \mathbb{R}^m$, be given, with $y, Y \in C^{2,1}(\bar{\pi})$, $y = (y_1, \dots, y_m)$, $Y = (Y_1, \dots, Y_m)$. Assume that $y(x, t) < Y(x, t)$ componentwise on $\bar{\pi}$. Let $[y, Y] := \{u \in \mathbb{R}^m: y_i(x, t) \leq u_i \leq Y_i(x, t), (x, t) \in \bar{\pi}\}$. We have the following invariance principle.

Theorem B.1 (see [26]). Assume that for all $x \in \partial\Omega$, $i \in \{1, \dots, m\}$,

$$\frac{\partial y_i}{\partial n} \leq 0, \quad \frac{\partial Y_i}{\partial n} \geq 0$$

and that for all $(x, t) \in \bar{\pi}$, $y_j \leq u_j \leq Y_j$, $j \neq k$, $k = \{1, \dots, m\}$,

$$L_k(x, t)y_k - f_k(x, t, u_1, \dots, u_{k-1}, y_k, u_{k+1}, \dots, u_m, \nabla u_1, \dots, \nabla u_{k-1}, \nabla y_k, \nabla u_{k+1}, \dots, \nabla u_m) \geq 0, \quad (\text{B.2})$$

$$L_k(x, t)Y_k - f_k(x, t, u_1, \dots, u_{k-1}, Y_k, u_{k+1}, \dots, u_m, \nabla u_1, \dots, \nabla u_{k-1}, \nabla Y_k, \nabla u_{k+1}, \dots, \nabla u_m) \leq 0. \quad (\text{B.3})$$

Then system (B.1) has at least one solution $u: \bar{\pi} \rightarrow \mathbb{R}^m$ such that its $C_{x,t}^{2,1}(\pi)$ norm is bounded and its values are contained in $[y, Y]$ for all $t \in [0, T]$.

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