THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

PROCEEDINGS OF THE ROMANIAN ACADEMY, Series A,
Volume 17, Number 4/2016, pp. 293–299

NOTE ON THE WELL-POSEDNESS OF A NONLINEAR HYPERBOLIC-PARABOLIC SYSTEM FOR CELL GROWTH

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Abstract. We study a system of nonlinear hyperbolic equations, with nonlocal boundary conditions, arising in the modeling of cell growth. The basic model introduced in [7] is completed with a parabolic equation simulating the effect of a treatment introduced in the cell system. The mechanism described is based on experimental evidence for tumoral cells. The aim of the paper is to prove the well-posedness of the system under certain conditions on the parameters.

Key words: nonlinear hyperbolic-parabolic system, nonlocal boundary conditions, cell growth, dynamics of the treatment.

1. PRESENTATION OF THE PROBLEM

The model we consider describes the cell growth in a tissue viewed as an aggregate of different cells which are arranged in multiple layers and undergoes a continuous renewal process. Many mathematical models have been proposed for cell aggregates, including age structure (see [2, 5, 9, 10]), but few models have been devoted to the spatial organization of stratified epithelia (see [1]). A model describing in a more rigorous way the epidermis formation as a system with age and space structure was introduced in [6] where conditions for the existence of a steady state were investigated. Paper [7] was devoted to prove existence and uniqueness of a solution to the evolution problem and of the related moving boundary representing the external surface of the epidermis. In [8] a numerical scheme for the computation of the cell densities was proposed, its convergence was studied and numerical simulations were provided.

In this paper, we complete the basic model [7] with a parabolic equation simulating the effect of a treatment introduced in the cell system. Thus, we shall analyze the following nonlinear hyperbolic-parabolic system in the domain age-space $(a,x)\in(0,a_i^+)\times(0,L)$, $i=1,2,3,$ for the time $t\in(0,T)$ with a_i^+, L and T finite

$$\begin{aligned}
&\frac{\partial p_1}{\partial t}+\frac{\partial p_1}{\partial a}+\frac{\partial}{\partial x}\big(U(t,x;p)\,p_1\big)+\mu_1(t,a,x)\,p_1=-\lambda_{13}(\sigma)\,p_1+\lambda_{31}(\sigma)\,p_3,\\
&p_1(t,0,x)=0,\\
&p_1(t,a,0)=P_1(t,a),\\
&p_1(0,a,x)=p_{10}(a,x),
\end{aligned}\tag{1}$$

$$\begin{aligned}
&\frac{\partial p_2}{\partial t}+\frac{\partial p_2}{\partial a}+\frac{\partial}{\partial x}\big(U(t,x;p)\,p_2\big)+\mu_2(t,a,x)\,p_2=0,\\
&p_2(t,0,x)=r(t,x)\int_0^{a_1^+}\beta_1(a)\,M_1(a)\,p_1(t,a,x)\,\mathrm{d}a,\\
&p_2(t,a,0)=P_2(t,a),\\
&p_2(0,a,x)=p_{20}(a,x),
\end{aligned}\tag{2}$$

$$\frac{\partial p_3}{\partial t}+\frac{\partial p_3}{\partial a}+\frac{\partial}{\partial x}\big(U(t,x;p)\,p_3\big)+\mu_3(t,a,x)\,p_3=\lambda_{13}(\sigma)\,p_1-\lambda_{31}(\sigma)\,p_3,$$
$$p_3(t,0,x)=0,$$
$$p_3(t,a,0)=0, \tag{3}$$
$$p_3(0,a,x)=p_{30}(a,x),$$

$$\frac{\partial\sigma}{\partial t}-\Delta\sigma=-\sum_{i=1}^{3}d_i(t,x)\int_0^{a_i^+}p_i(t,a,x)\,\mathrm{d}a+f(t,x),$$
$$\frac{\partial\sigma}{\partial\nu}(t,L)=0, \tag{4}$$
$$\sigma(t,0)=\sigma^0(t),$$
$$\sigma(0,x)=\sigma_0(x),$$

where U has the representation (see [7])

$$U(t,x;p)=u_0(t)+\frac{1}{\Phi^*}\sum_{i=1}^{3}\int_0^x\int_0^{a_i^+}\tilde{k}_i(t,a,\xi)\,p_i(t,a,\xi)\,\mathrm{d}a\mathrm{d}\xi. \tag{5}$$

In this model, p_1 and p_2 are two types of cells, e.g., proliferating cells (initiating the tissue formation) and differentiate cells (forming the tissue), U is the velocity of the tissue growth, depending on $t\in(0,T)$, $x\in(0,L)$ and on all system $p=(p_1,p_2,p_3)$. The functions μ_1, μ_2, μ_3, β_1, M_1, r are the vital rates representing the mortality (μ_i) of the cells p_i, fertility of p_1 (β_1,M_1) and the average number (r) of cells obtained by the division of p_1, respectively. At $x=0$ the system is supplied with p_1 and p_2 cells by the known fluxes P_1 and P_2. Finally, $u_0(t)$ is given, Φ^* is a constant and $\tilde{k}_i$ include the variations of the cell volumes and of the other parameters with respect to a and x.

In the model of this paper we introduced another type of cells, denoted p_3, which is a population formed from p_1 under the action of a medicine σ. More exactly, cells from the population p_1, under the action of σ, can cease to proliferate and become inactive cells p_3. They are removed from the population p_1 with the rate λ_{13} depending on σ. At the same time they enter into the population p_3 with the same rate. This transition can be temporary and the process can revert, that is p_3 can go back into p_1 with the rate λ_{31} depending on σ. This mechanism was described e.g., in [3] for tumoral cells.

Equation (4) represents the dynamics of the treatment, supplied by the source f. The first term on the right-hand side in (4) shows the consumption of σ by all types of cells with the nonnegative rates d_i. The boundary condition on $\{x=0\}$ indicates another possibility of introducing the treatment in the tissue by a supply σ^0, while the boundary condition on $\{x=L\}$ shows that there is no medicine flux through this boundary. The conditions on the boundaries can be reverted.

If $\lambda_{13}=\lambda_{31}=0$ we retrieve the model proposed in [7], for less types of cells, without the influence of σ.

The aim of this paper is to prove the well-posedness of the system (1)-(4) under certain conditions on the parameters.

2. MAIN RESULTS

We shall prove the solution existence by a fixed point theorem.

Hypotheses:

$$
\begin{aligned}
& p_{i0} \in C\left(\left[0,a_i^+\right];C^1\left[0,L\right]\right),\ P_i \in C^1\left(\left[0,T\right]\times\left[0,a_i^+\right]\right),\\
& \mu_i \in C\left(\left[0,T\right];C\left(\left[0,a_i^+\right];C^1\left[0,L\right]\right)\right),\ \tilde{k}_i \in C\left(\left[0,T\right];L^1\left(0,a_i^+;C^1\left[0,L\right]\right)\right),\\
& r \in C^1\left(\left[0,T\right]\times\left[0,L\right]\right),\\
& u_0\left(t\right)>0,\ \mu_i\left(t,a,x\right)\geq 0,\ r\left(t,x\right)\in\left[0,2\right],
\end{aligned}
\tag{6}
$$

$$
\begin{aligned}
& \left|\lambda_{13}\left(r\right)-\lambda_{13}\left(\overline{r}\right)\right|\leq L_{13}\left|r-\overline{r}\right|,\ r,\overline{r}\in\mathbb{R},\\
& \left|\lambda_{31}\left(r\right)-\lambda_{31}\left(\overline{r}\right)\right|\leq L_{31}\left|r-\overline{r}\right|,\ r,\overline{r}\in\mathbb{R},\\
& \lambda_{13},\ \lambda_{31}\geq 0,
\end{aligned}
\tag{7}
$$

$$
f\in C^1\left(\left[0,T\right]\times\left[0,L\right]\right),\ d_i\in C^1\left(\left[0,T\right]\times\left[0,L\right]\right),\ 0\leq d_i\left(t,x\right)\leq d_M, \tag{8}
$$

$$
\sigma_0\in H^4\left(\Omega\right),\ \left(\Delta\sigma_0\right)\left(0\right)=0,\ \sigma^0\in C^2\left(\left[0,T\right]\right),\ \sigma_0\left(0\right)=\sigma^0\left(0\right). \tag{9}
$$

Let us denote by C_α, C_d two positive constants depending on the norms of $\tilde{k}_i$, μ_i, p_{i0}, P_i, f, d_i.

THEOREM 2.1. *Let* $R_1>0,\ R_2>0$ *be fixed and assume that* C_α, C_d *and* T *are such that the following inequalities*

$$
\begin{aligned}
& C_d e^{3TC_\alpha R_1}\leq R_1,\\
& R_1\left(1+C_\alpha R_1+TC_\alpha\left(R_1+R_2\right)\right)\leq R_2
\end{aligned}
\tag{10}
$$

hold. Then, system (1–4) under the hypotheses (6–9) has a unique solution

$$
p_i\in C\left(\left[0,T\right]\times\left[0,a_i^+\right]\times\left[0,L\right]\right). \tag{11}
$$

Proof. Let us consider the spaces

$$
Y=\prod_{i=1}^{3}C\left(\left[0,a_i^+\right]\times\left[0,L\right]\right),\ X=C\left(\left[0,T\right];Y\right),
$$

respectively endowed with the norms

$$
\begin{aligned}
& \left\|h\right\|_Y=\sum_{i=1}^{3}\left|h_i\right|_\infty,\ h=\left(h_1,h_2,h_3\right)\in Y,\\
& \left\|z\right\|_X=\sup_{t\in\left[0,T\right]}\left\|z\left(t\right)\right\|_Y,\ \text{for } z\in X,
\end{aligned}
$$

where $\left|\cdot\right|_\infty$ denotes the L^∞-norm. We define the subsets of X,

$$
\begin{aligned}
M_0=\Big\{ & z=\left(z_1,z_2,z_3\right)\in X;\ z_i\in C\left(\left[0,T\right];C\left(\left[0,a_i^+\right];C^1\left[0,L\right]\right)\right),\\
& \left|z_i\right|_\infty\leq R_1,\ z_i\left(t,a,0\right)=P_i\left(t,a\right),\ \left|z_{ix}\right|_\infty\leq R_2\Big\}
\end{aligned}
\tag{12}
$$

and

$$
\begin{aligned}
M=\Big\{ & z=\left(z_1,z_2,z_3\right)\in X;\ z_i\in C\left(\left[0,T\right];C\left(\left[0,a_i^+\right];W^{1,\infty}\left(0,L\right)\right)\right),\\
& \left|z_i\right|_\infty\leq R_1,\ z_i\left(t,a,0\right)=P_i\left(t,a\right),\ \left|z_{ix}\right|_{L^\infty}\leq R_2\Big\}
\end{aligned}
\tag{13}
$$

and we observe that M is closed and $M = \overline{M_0}$.

Let $z \in X$ and fix $p = z$ in the expression of $U(t,x;p)$ and in some terms (which will be see below) on the right-hand sides of (1–4). So, we are led to the following problem with the solution denoted $Z_i(t)$ and σ^z which depend on $z = (z_1, z_2, z_3)$,

$$\begin{aligned}
&\frac{\partial Z_1}{\partial t} + \frac{\partial Z_1}{\partial a} + \frac{\partial}{\partial x}\left(\alpha(t,x) Z_1\right) + \mu_1(t,a,x) Z_1 = -\lambda_{13}(\sigma^z) Z_1 + \lambda_{31}(\sigma^z) z_3,\\
&Z_1(t,0,x) = 0,\\
&Z_1(t,a,0) = P_1(t,a),\\
&Z_1(0,a,x) = p_{10}(a,x),
\end{aligned} \tag{14}$$

$$\begin{aligned}
&\frac{\partial Z_2}{\partial t} + \frac{\partial Z_2}{\partial a} + \frac{\partial}{\partial x}\left(\alpha(t,x) Z_2\right) + \mu_2(t,a,x) Z_2 = 0,\\
&Z_2(t,0,x) = r(t,x)\int_0^{a_1^+} \beta_1(a) M_1(a) Z_1(t,a,x)\,\mathrm{d}a,\\
&Z_2(t,a,0) = P_2(t,a),\\
&Z_2(0,a,x) = p_{20}(a,x),
\end{aligned} \tag{15}$$

$$\begin{aligned}
&\frac{\partial Z_3}{\partial t} + \frac{\partial Z_3}{\partial a} + \frac{\partial}{\partial x}\left(\alpha(t,x) Z_3\right) + \mu_3(t,a,x) Z_3 = \lambda_{13}(\sigma^z) z_1 - \lambda_{31}(\sigma^z) Z_3,\\
&Z_3(t,0,x) = 0,\\
&Z_3(t,a,0) = 0,\\
&Z_3(0,a,x) = p_{30}(a,x),
\end{aligned} \tag{16}$$

$$\begin{aligned}
&\frac{\partial \sigma^z}{\partial t} - \Delta\sigma^z = -\sum_{i=1}^{3} d_i(t,x)\int_0^{a_i^+} z_i(t,a,x)\,\mathrm{d}a + f(t,x),\\
&\frac{\partial \sigma^z}{\partial \nu}(t,L) = 0,\\
&\sigma^z(t,0) = \sigma^0(t),\\
&\sigma^z(0,x) = \sigma_0(x),
\end{aligned} \tag{17}$$

where

$$\alpha(t,x) := U(t,x;z) = u_0(t) + \frac{1}{\Phi^*}\sum_{i=1}^{3}\int_0^x\int_0^{a_i^+} \tilde{k}_i(t,a,\xi) z_i(t,a,\xi)\,\mathrm{d}a\mathrm{d}\xi \tag{18}$$

with $\alpha(t,0) = u_0(t)$.

First, we treat system (17), where we make the transformation

$$w^z(t,x) = \sigma^z(t,x) - \sigma^0(t).$$

This relationship replaced into (17) gives

$$\begin{aligned}
&\frac{\partial w^z}{\partial t} - \Delta w^z = F(t,x),\\
&\frac{\partial w^z}{\partial \nu}(t,L) = 0,\ w^z(t,0) = 0,\ w^z(0,x) = w_0(x) = \sigma_0(x) - \sigma^0(0),
\end{aligned} \tag{19}$$

where

$$F(t) = -\sum_{i=1}^{3} d_i(t,x)\int_0^{a_i^+} z_i(t,a,x)\,\mathrm{d}a + f(t,x) + \frac{\partial \sigma^0}{\partial t}(t).$$

Let us denote $\Omega = (0,L)$ and $V = \{y \in H^1(\Omega); y(0) = 0\}$ endowed with the scalar product of $H_0^1(\Omega)$. Let $A: D(A) \subset L^2(\Omega) \to L^2(\Omega)$ be the operator $Aw = -\Delta w$ with

$$D(A) = \left\{ y \in H^2(\Omega) \cap H_0^1(\Omega); y(0) = 0,\ \frac{\partial y}{\partial \nu}(L) = 0 \right\}.$$

Here, $F \in C^1([0,T]\times[0,L])$ and $w^z(0) \in D(A^2)$. Then, (19) can be written

$$\begin{aligned} &\frac{\mathrm{d}w^z}{\mathrm{d}t} + Aw^z(t) = F(t) \text{ a.e. } t \in (0,T), \\ &w^z(0) = w_0, \end{aligned} \tag{20}$$

where by the hypotheses (8–9) and the choice of $z \in M_0$, we note that $F \in C^1([0,T]\times C^1[0,L])$ and $w_0 \in D(A^2) = \{w \in D(A); Aw \in D(A)\}$. Then, (20) has a unique solution

$$w^z \in C^1([0,T];D(A)) \cap C([0,T];D(A^2)),$$

that is $w^z \in C^1([0,T]\times[0,L])$, – [4, p. 191]. Reverting to (17) we get that it has a unique solution

$$\sigma^z \in C^1([0,T]\times[0,L]). \tag{21}$$

Moreover, by taking two data z and $\overline{z}$ in M_0 with the corresponding solutions σ^z and $\sigma^{\overline{z}}$ we compute the estimate

$$\left\|\left(\sigma^z - \sigma^{\overline{z}}\right)(t)\right\|_{L^2(\Omega)}^2 \le C\int_0^t \left\|(z-\overline{z})(s)\right\|_{L^2(\Omega)}^2 \mathrm{d}s, \tag{22}$$

with C a constant depending on d_i. Then, the solution σ^z is introduced in (14–16) and lead on the right-hand sides to regular coefficients $f_{13}(t,x) = \lambda_{13}(\sigma^z(t,x)), f_{31}(t,x) = \lambda_{31}(\sigma^z(t,x))$, where $f_{13}, f_{31} \in C^1([0,T]\times[0,L])$.

Now, we define a mapping $\Psi : X \to X$, $\Psi(z) = Z$ for the solution (Z_1, Z_2, Z_3) to (14–16) and we intend to apply the Banach fixed point theorem on M. However, this cannot be done directly, so that we apply it first on M_0 and then deduce the result by density, relying on the fact that $M = \overline{M_0}$. For the last result we need to prove also that:

(i) $\Psi(M_0) \subset M_0$,

(ii) Ψ is continuous on X.

The last step is to show that Ψ is a contraction on M_0.

Equation (14) becomes

$$\begin{aligned} &\frac{\partial Z_1}{\partial t} + \frac{\partial Z_1}{\partial a} + \frac{\partial}{\partial x}\left(\alpha(t,x)Z_1\right) + \left(\mu_1(t,a,x) + g_1(t,x)\right)Z_1 = f_{13}(t,a,x), \\ &Z_1(t,0,x) = 0, \\ &Z_1(t,a,0) = P_1(t,a), \\ &Z_1(0,a,x) = p_{10}(a,x). \end{aligned} \tag{23}$$

According to Proposition 2.2 in [7], Eq. (23) has a unique solution $Z_1 \in C^1([0,T]\times[0,a_1^+]\times[0,L])$. This solution is introduced in (15) and implies that $Z_2(t,0,x) = F_2(t,x) := r(t,x)\int_0^{a_1^+} \beta_1(a)M_1(a)Z_1(t,a,x)\mathrm{d}a$, where $F_2 \in C^1([0,T];C^1[0,L])$. So, by the same result in [7], it follows that (15) has a unique solution $Z_2 \in C^1([0,T]\times[0,a_2^+]\times[0,L])$. Proceeding further in the same way we get that (16) has the unique solution $Z_3 \in C^1([0,T]\times[0,a_3^+]\times[0,L])$. By some straightforward computations based on the estimates given by Proposition 2.2 in [7] and by taking into account (12) it follows that all solutions satisfy

$$|Z_i|_\infty \le C_d e^{3TC_\alpha R_1},\ |Z_{ix}|_\infty \le C_d e^{2TC_\alpha R_1}\left(1 + C_\alpha R_1 + TC_\alpha(R_1+R_2)\right), \tag{24}$$

where C_d and C_α depend on the data as specified before. This explains the choice of the space M, because the estimates we can obtain for Z_i are in $C\left([0,T];C\left([0,a_i^+];W^{1,\infty}(0,L)\right)\right)$ and not in $C\left([0,T];C\left([0,a_i^+];C^1[0,L]\right)\right)$ as in M_0. But, since we need a better regularity for z_i in order to apply Proposition 2.2 in [7] we are obliged to work first on M_0.

Now, we come back to show the properties of Ψ. Let $z_n \in X$, $z_n \to z$ strongly in X, as $n\to\infty$. Then, it is readily seen that $U(t,x;z_n)\to U(t,x;z)$ strongly in $C([0,T]\times[0,L])$ and by using the continuity property of the characteristics associated to $U(t,x;z_n)$ it follows that $\Psi(z_n)\to\Psi(z)$ strongly in X, as $n\to\infty$. In order to prove (ii) we use (24) and see that it is sufficient to impose

$$\begin{aligned}&|Z_i|_\infty \le C_d e^{3TC_\alpha R_1} \le R_1,\\ &|Z_{ix}|_\infty \le R_1\left(1+C_\alpha R_1 + TC_\alpha(R_1+R_2)\right)\le R_2,\end{aligned}$$

for appropriate choices of the parameters, as specified in (10). This proves (i).

Moreover, we write (14–17) for two functions z and $\overline{z}$ in M_0 with the solutions $Z=\Psi(z)$ and $\overline{Z}=\Psi(\overline{z})$, make the difference of each corresponding equations i, multiply it by $\Psi(z(t))-\Psi(\overline{z}(t))$ and then integrate over Ω and $(0,t)$. By a straightforward computation and using (22) we arrive to

$$\left\|\Psi(z(t))-\Psi(\overline{z}(t))\right\|_Y^2 \le C(R_1,R_2)\int_0^t \left\|z(s)-\overline{z}(s)\right\|_Y^2 \mathrm{d}s,\ \forall z,\overline{z}\in M_0 \tag{25}$$

with a constant $C(R_1,R_2)$. Introducing the norm $\|w\|_B = \sup_{t\in[0,T]}\left\{e^{-\gamma t}\|w(t)\|_Y\right\}$ for any $w\in X$, which is equivalent with the norm on X, we can rewrite the previous estimate by applying this new norm. We have

$$\begin{aligned}&e^{-2\gamma t}\left\|\Psi(z(t))-\Psi(\overline{z}(t))\right\|_Y^2 \le C(R_1,R_2)e^{-2\gamma t}\int_0^t e^{2\gamma s}e^{-2\gamma s}\left\|z(s)-\overline{z}(s)\right\|_Y^2\mathrm{d}s\\ &\le C(R_1,R_2)e^{-2\gamma t}\int_0^t e^{2\gamma s}\|z-\overline{z}\|_B^2\mathrm{d}s \le \frac{C(R_1,R_2)}{2\gamma}\left(1-e^{-2\gamma t}\right)\|z-\overline{z}\|_B^2.\end{aligned}$$

Hence

$$e^{-2\gamma t}\left\|\Psi(z(t))-\Psi(\overline{z}(t))\right\|_Y^2 \le \frac{C(R_1,R_2)}{2\gamma}\|z-\overline{z}\|_B^2$$

and taking the supremum with respect to t we obtain

$$\left\|\Psi\left(z(t)\right)-\Psi\left(\overline{z}(t)\right)\right\|_B^2 \le \frac{C\left(R_1,R_2\right)}{2\gamma}\left\|z-\overline{z}\right\|_B^2, \text{ for } z,\overline{z}\in M_0.$$

Now, choosing γ such that $2\gamma > C\left(R_1,R_2\right)$, we obtain that Ψ is a contraction on M_0.

By continuity and (i) it follows that $\Psi\left(M\right)\subset M$, while (25) implies that Ψ is a contraction on X, for any $z,\overline{z}\in M$, too. Hence, Ψ has a fixed point $\Psi\left(z\right)=Z$ which means that (1–4) has a unique solution $p_i \in C\left(\left[0,T\right]\times\left[0,a_i^+\right]\times\left[0,L\right]\right)$ for $i=1,2,3$.

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Received February 15, 2016