ROMANIAN ACADEMY
” SIMION STOILOW” INSTITUTE OF MATHEMATICS

DOCTORAL THESIS

ABSTRACT

VARIATIONAL METHODS FOR REACTION-DUFFUSION PROBLEMS AND APPLICATIONS

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BUCHAREST
2016

This thesis deals with the study of a system of nonlinear hyperbolic equations that analyses the evolution of the system of cells of a normal epidermis and the influence of some medicinal treatments administred in certain purposes. The hyperbolic system is coupled with a nonlinear parabolic problem that describes the interaction between the epidermis and the treatment.

The structure of the thesis is the following: in the first chapter we briefly present the model with age and space structure of a normal epidermis proposed in [27], model that describes the structure of a normal epidermis that is formed of four types of cells. In the second chapter we start from this model and we adapt it for the study of an epidermis that has been administred a medication with the purpose of adjusting the processes of divizion and differentiation of cells. Thus we obtain the mathematical model for the suprabasal layer that represents the main problem we deal with. In order to determine the entrances in the system that represents the model for the suprabasal layer, we present in this chapter the model in the basal layer and we obtain its solution. This chapter also contains the calculation of the velocity of the cells in the suprabasal layer and the condition for determining the boundary surface.

In the third chapter we demonstrate the existance of the strict solution of an intermediate generic problem that appears in the demonstration of the existance of the solution of the system of equations from the forth chapter. We use here the theory of semigroups of linear operators (Hille-Yosida).

In the forth chapter we present the properties of function U that represents the velocity of the cells and we demonstrate the existance and unicity of the solution of the problem we deal with. Here we use a fixed point procedure that is essentially based on the Schauder's fixed point theorem.

In the last chapter of this paper we propose a numerical solution for the problem. The numerical scheme proposed is based on a finite difference scheme that uses the approximation of the characteristics of the nonlocal boundary value problems that compose the mathematical model. The final part of the chapter contains the expressions of the model parameters, the error computation, numerical results and their interpretation.

The models of populations structured depending on age, size and spatial structure have many applications in biology. Thus in [27], [28], [29], are presented and analyzed models that describe the structure and the evolution of the cells that compose the epidermis. The epidermis is formed of multiple layers of epitelial cells that undergo a continuous process of renewal. In [27] the authors propose a stationary model for the evolution of a normal, unperturbed epidermis, this model having age and space structure. In normal skin the proliferation of the cells takes place almost exclusively in the basal layer where the stem cells generate proliferant cells that after some rounds of proliferation cease to divide, thus producing non-proliferant (quiescent), differentiated cells. The model proposed in [27] for the domains $\left(0, a_i^+\right) \times (0, L)$, $i = \overline{1,4}$ includes four types of cells (*proliferating -1, differentiated -2, corneous -3 şi apoptotic -4).*

In what follows we refer to the model with age and space structure of the cells for the evolution of the suprabasal epidermis presented in [27]. We consider a one-dimensional geometry so that the Cartesian coordinate x is perpendicular to the epidermis plane. The variable x varies from $x = 0$ (the suprabasal layerl) to $x = L$ (the end of the stratum corneum).

In normal epidermis the proliferation of cells occurs in the basal layer where stem cells generate proliferant cells. After four-five rounds of proliferation these cells cease to divide, thus producing non-proliferating (quiescent), differentiated cells. The differentiated cells are pushed to the suprabasal layer and are transformed into corneous cells by a process of keratinization. The model includes four types of cells: *proliferating* cells, *differentiated* cells, *corneous* cells and *apoptotic* cells. The apoptotic cells are dead cells that result from the phenomenon of pathological mitosis and from the death of proliferatint and differentiated cells due to external causes. Those types of cells are indexed by $i = 1, ..., 4$. We denote by $n_i(a, x)$ the density with regerd to age $a \in \left[0, a_i^+\right]$ of the number of cells i per unit volume, at position x. We assume that all cells move towards the surface of the epidermis with the same positive velocity $u(x)$.

The innovation of the model proposed in this tesis is that the model is more complex because we take into account a medicinal treatment administred to the system of cells, with the purpose of influencing on the proliferation of proliferating cells into themselves in the suprabasal layer. As a result of this treatment, the cells $n_1(a, x)$ stop proliferating for a life period, remaining inactive and forming the population named $n_5(a, x)$. If the treatment ceases or is not enough, the cells $n_5(a, x)$ may begin to proliferate at a certain age, turning back into the population $n_1(a, x)$. Another situation consists in accelerating the proliferation of proliferating cells if this situation is desired. We denote by σ the concentration of the medicine and by λ_1, λ_5 the rates of transfer corresponding to the transformation of the cells of types 1 and 5 respectively, as a result of the treatment.

2. The mathematical model

2.1. The mathematical model for the suprabasal layer

In the conditions above, the model that describes the structure of the epidermis in the domains $\left(0, a_i^+\right) \times (0, L)$, $i = \overline{1,5}$ is the following:

$$\begin{cases} \frac{\partial n_1}{\partial a} + \frac{\partial}{\partial x}\left(un_1\right) + \beta_1\left(a\right)n_1 + \mu_1\left(a,x\right)n_1 + \lambda_1\left(\sigma\right)n_1 - \lambda_5\left(\sigma\right)n_5 = 0, \\ n_1\left(0,x\right) = \chi\left(x\right)\int_0^{a_1^+}\beta_P\left(a\right)n_1\left(a,x\right)da, \\ u\left(0\right)n_1\left(a,0\right) = S_1\left(a\right), \end{cases} \tag{1}$$

$$\begin{cases} \frac{\partial n_2}{\partial a} + \frac{\partial}{\partial x}\left(un_2\right) + \beta_2\left(a\right)n_2 + \mu_2\left(a,x\right)n_2 = 0, \\ n_2\left(0,x\right) = r\left(x\right)\int_0^{a_1^+}\beta_1\left(a\right)n_1\left(a,x\right)da, \\ u\left(0\right)n_2\left(a,0\right) = S_2\left(a\right), \end{cases} \tag{2}$$

$$\begin{cases} \frac{\partial n_3}{\partial a} + \frac{\partial}{\partial x}\left(un_3\right) + \beta_3\left(a\right)n_3 = 0, \\ n_3\left(0,x\right) = \int_0^{a_2^+}\beta_2\left(a\right)n_2\left(a,x\right)da, \\ u\left(0\right)n_3\left(a,0\right) = 0, \end{cases} \tag{3}$$

$$\begin{cases} \frac{\partial n_4}{\partial a_4} + \frac{\partial}{\partial x}\left(un_4\right) + \beta_4\left(a_4\right)n_4 = 0, \\ n_4\left(0,x\right) = \sum\limits_{i=1}^{2}\int_0^{a_i^+}\mu_i\left(a,x\right)n_i\left(a,x\right)da_i, \\ +\left(2 - r\left(x\right)\right)\int_0^{a_1^+}\beta_1\left(a\right)n_1\left(a,x\right)da, \\ u\left(0\right)n_4\left(a,0\right) = 0, \end{cases} \tag{4}$$

$$\begin{cases} \frac{\partial n_5}{\partial a} + \frac{\partial}{\partial x}\left(un_5\right) + \mu_5\left(a,x\right)n_5 + \lambda_5\left(\sigma\right)n_5 - \lambda_1\left(\sigma\right)n_1 + \beta_5\left(a\right)n_5 = 0, \\ n_5\left(0,x\right) = 0, \\ n_5\left(a,0\right) = 0, \end{cases} \tag{5}$$

$$\begin{cases} -\frac{d^2\sigma}{dx^2} = d_1\left(\sigma\right)\int_0^{a_1^+}n_1\left(a\right)v_1\left(a\right)da \\ +d_2\left(\sigma\right)\int_0^{a_2^+}n_2\left(a\right)v_2\left(a\right)da \\ +d_5\left(\sigma\right)\int_0^{a_5^+}n_5\left(a\right)v_5\left(a\right)da + f(x), \\ \sigma\left(0\right) = \sigma_0, \frac{d\sigma}{dx}\left(L\right) + \widetilde{\alpha}\sigma\left(L\right) = \sigma_L. \end{cases} \tag{6}$$

Equation (6) describes the action of the treatment. We consider the treatment to be administred by a flux type relation or by a Dirichlet condition.

In the problem (1)-(6) we made the following notations:

β_p represents the rate of proliferation (fertility) of the cells of type 1 that are transformed in cells of type 1;

β_1 represents the rate of transfer of proliferating cells into differentiated cells;

β_2 represents the rate of tranzition of differentiated cells into corneous cells;

β_3 represents the rate of degradation of corneous cells;

β_4 represents the rate of degradation of the apoptotic cells into liquid waste;

β_5 represents the rate of degradation of the cells n_5;

σ represents the concentration of the treatment;

d_i represents the absorption rate of the medication by the cells of type i, $i \in \{1, 2, 5\}$;

λ_i represents the rate of transformation of the cells of type i as a result of the medicinal treatment, $i \in \{1, 5\}$.

The function r represents the medium number of viable cells that result from the process of division of the proliferating cells. In normal conditions $r \equiv 2$. In pathological conditions, $r \in [0, 2)$. The function χ represents the number of proliferating cells that are obtained from a division of the proliferating cells into themselves. If $r = 2$ then $\chi = 0$ and if $r = 0$ then $\chi = 1$ or $\chi = 2$.

The functions μ_1, μ_2 represent the rates of mortality of the proliferating cells and differentiated cells, respectively, due to external causes. The functions $S_1(a), S_2(a)$ represent the flux of proliferating and differentiated cells,respectively, from the basal layer, generated by the stem cells. We suppose that in the basal layer we do not have entries of cells of types 3 and 4, and so we consider $S_3(a) = S_4(a) = 0$.

We consider the rates β_i, β_p to depend on the age of the cells and to blow-up on $a = a_i^+$, $i = \overline{1,5}$ so that

$$\int_0^{a_i^+} \beta_i(a)\, da = +\infty, i = \overline{1,5}, \tag{7}$$

$$\int_0^{a_1^+} \beta_p(a)\, da = +\infty. \tag{8}$$

Thus, the age of the cells n_i is limited by a finite value $a_i^+, i = \overline{1,5}$ and the density of the cells n_i is annuled at $a = a_i^+$. We consider $a_1^+ = a_5^+$.

2.4. The model in the basal layer

In what follows we will complete the model (1)-(6) with a model that describes the activity of the cells in the basal layer. The purpose of this model is to obtain the analytic expressions for the functions $S_1, S_2, S_3, S_{4,}S_5$.

These functions represent the entries to the system (1)-(6) and modelate the activity of producing the cells in the basal layer.

The functions $S_1(a)$, $S_2(a)$ represent the flux of proliferating and differentiated cells, respectively, from the basal layer and represent the entries into the system. We consider that we do not have a flux of corneous cells from the basal layer, so $S_3(a) = 0$.

Leaving aside the spacial structure of the basal layer and following the ideas from [38] we can describe the population of cells by the age densities of the number of cells per unit volume. Let m be the number of rounds of division of the proliferating cells, $\nu_i(a)$ the age density of the cells into the i-th round of division, $\nu_D(a)$ the age density of the differentiated cells and $\nu_A(a)$ the age density of the apoptotic cells. We can write the following system of equations:

$$\begin{cases} \frac{\partial \nu_1}{\partial a} = -\left(\beta_1(a) + \mu_{1_0}(a)\right)\nu_1(a), \\ \nu_1(0) = s, \end{cases} \tag{9}$$

$$\begin{cases} \frac{\partial \nu_2}{\partial a} = -\left(\beta_1(a) + \mu_{1_0}(a)\right)\nu_2(a), \\ \nu_2(0) = r_0 \int_0^{a_1^+} \beta_1(a)\,\nu_1(a)\,da, \end{cases} \tag{10}$$

$$\vdots$$

$$\begin{cases} \frac{\partial \nu_{m-1}}{\partial a} = -\left(\beta_1(a) + \mu_{1_0}(a,t)\right)\nu_{m-1}(a), \\ \nu_{m-1}(0) = r_0 \int_0^{a_1^+} \beta_1(a)\,\nu_{m-2}(a)\,da, \end{cases} \tag{11}$$

$$\begin{cases} \frac{\partial \nu_m}{\partial a} = -\left(\beta_1(a) + \eta_1(a) + \mu_{1_0}(a)\right)\nu_m(a), \\ \nu_m(0) = r_0 \int_0^{a_1^+} \beta_1(a)\,\nu_{m-1}(a)\,da, \end{cases} \tag{12}$$

$$\begin{cases} \frac{\partial \nu_D}{\partial a} = -\left(\eta_2(a) + \mu_{2_0}(a)\right)\nu_D(a), \\ \nu_D(0) = r_0(t) \int_0^{a_1^+} \beta_1(a)\,\nu_m(a)\,da, \end{cases} \tag{13}$$

$$\begin{cases} \frac{\partial \nu_A}{\partial a} = -\left(\beta_4(a) + \eta_4(a)\right)\nu_A(a), \\ \nu_A(0) = \sum_{i=1}^{m} \int_0^{a_1^+} \left(\mu_{1_0}(a) + (2 - r_0)\,\beta_1(a)\right)\nu_i(a)\,da \\ \qquad + \int_0^{a_2^+} \mu_{2_0}(a)\,\nu_D(a)\,da. \end{cases} \tag{14}$$

In the formulas above, s characterizes the input of proliferating cells that are generated by stem cells, $\beta_1(a)$ represents the rate of transfer of the proliferating cells, μ_{1_0}, μ_{2_0} represent the distructive action of the external agents,

η_1, η_2 represent the rate of detachment of the cells in the m-th round of division and of the differentiated cells, respectively. The function $\eta_4(a)$ represents the rate of detachment of the apoptotic cells from the basal layer.

Under these circumstances, the flows $S_1(a)$ and $S_2(a)$ are given by the formulas:

$$S_1(a) = \eta_1(a)\,\nu_m(a), \tag{15}$$

$$S_2(a) = \eta_2(a)\,\nu_D(a), \tag{16}$$

$$S_4(a) = \eta_4(a)\,\nu_A(a). \tag{17}$$

We will consider that the flow of the corneous cells in the suprabasal layer is equal to zero, i.e. $S_3(a) = 0$.

2.5. The transformed model in the suprabasal layer

We introduce the survival probability functions :

$$M_i(a_i) = \exp\left(-\int_0^{a_i} \beta_i(\xi)\,d\xi\right), i = \overline{1,5}, \tag{18}$$

and instead of the state variables $n_i(a,x)$ (the density of the i-th cells) we introduce the normalized densities:

$$p_i(a,x) = \frac{n_i(a,x)}{M_i(a)}, i = \overline{1,5}. \tag{19}$$

The velocity of the cells was determined in paragraph 2.3. Since u depends on p_i, we adopt the following notation for the velocity of the cells

$$U(x,p) = u_0 + \frac{1}{\Phi^*}\sum_{i=1}^{5}\int_0^x\int_0^{a_i^+} k_i(a,\xi)\,M_i(a)\,p_i(a,\xi)\,da d\xi, \tag{20}$$

where $u_0 > 0$ is

$$u_0 = \frac{1}{\Phi^*}\sum_{i=1}^{5}\int_0^{a_i^+} v_i(a)\,S_i(a), \tag{21}$$

and $p = (p_1, p_2, p_3, p_4, p_5)$.

If we use now (19) the problem (1)-(6) becomes:

$$\left\{\begin{array}{c} \frac{\partial p_1}{\partial a} + \frac{\partial}{\partial x}(U(x,p)\,p_1) + (\mu_1(a,x) + \lambda_1(\sigma))\,p_1 - \lambda_5(\sigma)\,p_5\frac{M_5(a)}{M_1(a)} = 0, \\ p_1(0,x) = \chi(x)\int_0^{a_1^+}\beta_p(a)\,p_1(a,x)\,M_1(a)\,da, \\ p_1(a,0) = \widetilde{N}_1(a), \end{array}\right. \tag{22}$$

$$\begin{cases} \frac{\partial p_2}{\partial a} + \frac{\partial}{\partial x}\left(U\left(x,p\right)p_2\right) + \mu_2\left(a,x\right)p_2 = 0, \\ p_2\left(0,x\right) = r\left(x\right)\int_0^{a_1^+} \beta_1\left(a\right)p_1\left(a,x\right)M_1\left(a\right)da, \\ p_2\left(a,0\right) = \widetilde{N}_2\left(a\right), \end{cases} \tag{23}$$

$$\begin{cases} \frac{\partial p_3}{\partial a_3} + \frac{\partial}{\partial x}\left(U\left(x,p\right)p_3\right) = 0, \\ p_3\left(0,x\right) = \int_0^{a_2^+} \beta_2\left(a\right)p_2\left(a,x\right)M_2\left(a\right)da, \\ p_3\left(a,0\right) = 0, \end{cases} \tag{24}$$

$$\begin{cases} \frac{\partial p_4}{\partial a_4} + \frac{\partial}{\partial x}\left(U\left(x,p\right)p_4\right) = 0, \\ p_4\left(0,x\right) = \sum_{i=1}^{2}\int_0^{a_i^+} \mu_i\left(a\right)p_i\left(a,x\right)M_i\left(a\right)da \\ \quad + \left(2 - r\left(x\right)\right)\int_0^{a_1^+} \beta_1\left(a\right)M_1\left(a\right)p_1\left(a,x\right)da, \\ p_4\left(a,0\right) = 0, \end{cases} \tag{25}$$

$$\begin{cases} \frac{\partial p_5}{\partial a} + \frac{\partial}{\partial x}\left(U\left(x,p\right)p_5\right) + \left(\mu_5\left(a,x\right) + \lambda_5\left(\sigma\right)\right)p_5 - \lambda_1\left(\sigma\right)p_1 = 0, \\ p_5\left(0,x\right) = 0, \\ p_5\left(a,0\right) = 0, \end{cases} \tag{26}$$

$$\begin{cases} -\frac{d^2\sigma}{dx^2} = d_1\left(\sigma\right)\int_0^{a_1^+} M_1\left(a\right)v_1\left(a\right)p_1\left(a,x\right)da \\ \quad +d_2\left(\sigma\right)\int_0^{a_2^+} M_2\left(a\right)v_2\left(a\right)p_2\left(a,x\right)da \\ +d_5\left(\sigma\right)\int_0^{a_5^+} M_5\left(a\right)v_5\left(a\right)p_5\left(a,x\right)da + f(x), \\ \sigma\left(0\right) = \sigma_0, \frac{d\sigma}{dx}\left(L\right) + \widetilde{\alpha}\sigma\left(L\right) = \sigma_L. \end{cases} \tag{27}$$

In the problem above $a_i^+, L > 0$ and $\mu_i, \beta_i, M_i, \widetilde{N}_i, \lambda_i$ are known functions.

Hypotheses:

i) $\mu_i \in C^2\left(\left[0,a^+\right] \times \left[0,L\right]\right); \mu_i \geq 0;$

ii) $\beta_i \in L^1_{loc}\left(0,a_i^+\right); \int_0^{a_i^+} \beta_i\left(a\right)da = +\infty, \beta_i \geq 0, i = \overline{1,5},$

$\beta_1 = \beta_5 + \delta\left(a\right),\ \left|\delta\left(a\right)\right| \leq \overline{\delta}; \delta \in L^\infty\left(0,a_1^+\right).$

iii) $r \in C^1\left(\left[0,L\right]\right), 0 \leq r\left(x\right) \leq 2, x \in \left[0,L\right].$

iv) $\widetilde{N}_i \in C^2\left(\left[0,a_i^+\right]\right), \widetilde{N}_i \geq 0, a_i \in \left[0,a_i^+\right]$, unde

$$\widetilde{N}_i\left(a\right) = \frac{N_i\left(a\right)}{M_i\left(a\right)} = \frac{S_i\left(a\right)}{u_0 M_i\left(a\right)}, a_i \in \left[0,a_i^+\right], i = 1,2, \tag{28}$$

v) $\chi \in C[0,L]$;

vi) $M_i(a) = \exp\left(-\int_0^a \beta_i(\xi)\,d\xi\right), i = \overline{1,5}$;

vii) $\lambda_1, \lambda_5 \in Lip(\mathbb{R}) \cap L^\infty(\mathbb{R})$;

viii) $v_i \in C^1\left[0, a_i^+\right], i = \overline{1,5}$;

ix) $\beta_p \in L^1_{loc}\left(0, a_1^+\right), \int_0^{a_1^+} \beta_p(a)\,da = +\infty, \beta_p \geq 0, \left|\beta_p - \beta_1\right| < \delta_p, \delta_p > 0$;

x) $d_1, d_2, d_5 \in Lip(\mathbb{R}) \cap L^\infty(\mathbb{R})$

3. Preliminary results

In the following theoretical results we assume L to be fixed, and its determination will be done numerically. The system (22)-(27) will be solved by fixed point theorems. We chose the vector $(p_1, p_2, p_3, p_4, p_5)$ from a certain space of functions, we fix $p_1,\ p_2,\ p_3,\ p_4, p_5$ in the nonlinear terms from the equations (22)-(27) and in certain linear terms. Thus, each of the systems (22)-(26) has the following generic form:

$$\left\{ \begin{array}{c} \varphi_a + (g(x)\varphi)_x + h(a,x)\varphi = f,\ \ (a,x) \in (0,a^+) \times (0,L), \\ \varphi(a,0) = G(a),\ \ a \in (0,a^+), \\ \varphi(0,x) = F(x),\ \ x \in (0,L), \end{array} \right. \tag{29}$$

We make the following hypotheses:

$$g \in H^2(0,L),\ \ g > 0 \text{ for } x \in (0,L), \tag{30}$$

$$G \in C^2\left[0,a^+\right],\ \ F \in H^1(0,L),\ \ F(0) = G(0), \tag{31}$$

$$h \in C^2\left(\left[0,a^+\right] \times [0,L]\right), \quad f \in C^1\left(\left[0,a^+\right]; H^1[0,L]\right). \tag{32}$$

The system (29) is linear, with local boundary conditions and with free boundary.

Definition 3.1. We call a strict solution of the problem (29) a function

$$\varphi \in C^1\left(\left[0,a^+\right]; L^2(0,L)\right) \cap C\left(\left[0,a^+\right]; H^1(0,L)\right) \tag{33}$$

that satisfies (29).

Let

$$h_+ = \|h\|_{C^1([0,a^+]\times[0,L])} \tag{34}$$

$$\varpi = \frac{3}{2} \|g_x\|_\infty + \|g_{xx}\| \sqrt{L} + h_+ (L+1) + \frac{1}{2}. \tag{35}$$

In what follows, we will denote the norm of a function $u \in L^2(0, L)$ by $\|u\|$.

The central result of the following developments is given by Theorem 3.1 .

Theorem 3.1. We assume that the hypotheses (30), (31), (32) hold. Then, the problem (29) has an unique strict solution which satisfies the inequality

$$\|\varphi\|_{C([0,a^+];H^1(0,L))} \leq e^{\varpi a^+} \{\|F\|_{H^1(0,L)} + \sqrt{a^+}\sqrt{g(0)}\, \|G\|_{C[0,a^+]}$$
$$+\sqrt{a^+}\, \|f\|_{C([0,a^+];H^1(0,L))}\}. \tag{36}$$

If in addition

$$F(x) \geq 0 \text{ for } x \in [0, L],\ G(a) \geq 0 \text{ for } a \in \left[0, a^+\right],\ f = 0, \tag{37}$$

then the solution of the problem (29) satisfies the property

$$\varphi(a, x) \geq 0,\ (\forall)\ \ (a, x) \in \left[0, a^+\right] \times [0, L]. \tag{38}$$

4. Results of existence and unicity for the complete model

Our purpose in this chapter is to demonstrate the existence and unicity of the solution of the problem (22)-(27).

We will consider the spaces

$$V_i = C\left(\left[0, a_i^+\right]; H^1(0, L)\right) \text{ and } H_i = C\left(\left[0, a_i^+\right]; L^2(0, L)\right) \tag{39}$$

$$\|\psi\|_{V_i} = \max_{a \in \left[0, a_i^+\right]} \|\psi(a)\|_{H^1(0,L)},\ \ \|\psi\|_{H_i} = \max_{a \in \left[0, a_i^+\right]} \|\psi(a)\|_{L^2(0,L)}.$$

$$Y = \prod_{i=1}^{5} C\left(\left[0, a_i^+\right]; L^2(0, L)\right), \tag{40}$$

$$\|z\|_Y = \left(\sum_{i=1}^{5} \|z_i\|_{H_i}^2\right)^{\frac{1}{2}}, z = (z_1, z_2, z_3, z_4, z_5) \in Y. \tag{41}$$

Let $R > 0$. We consider the set

$$\mathcal{M} = \left\{z \in Y; z_i \in V_i, \|z_i\|_{V_i} \leq R, z_i(a, x) \geq 0, z_i(a, 0) = \widetilde{N}_i(a), i = \overline{1, 5}\right\}, \tag{42}$$

$$R < \frac{u_0}{\sqrt{L}C_\alpha}. \tag{43}$$

In order to assure the positivity of the function U we will search for solutions of the problems (22)-(26) that satisfy the property

$$\|p_i\|_{C\left(\left[0.a_i^+\right];H^1(0,L)\right)} < \frac{u_0}{\sqrt{L}C_\alpha}, \tag{44}$$

$$C_\alpha = \frac{1}{\Phi^*}\sum_{i=1}^{5}\left\|\widetilde{k}_i\right\|_{L^1\left(0,a_i^+;C^1[0,L]\right)}. \tag{45}$$

The main result is given by the following theorem. Let $\mathcal{K}$ and $\mathcal{L}$ be two positive constants that depend on the parameters of the problem. This dependence is described by some very complicated expressions what will be determined during the demonstration of Teorem 4.1. From this reason we do not indicate them in the theorem.

Theorem 4.1. Let u_0,.C_α and R so that (43) takes place and let $\mathcal{K}$ so

that $\mathcal{K}$ <R. Then the problem (22)-(26) has at least one solution
$p = (p_1, p_2, p_3, p_4, p_5)$ so that

$$p_i \in C^1\left(\left[0, a_i^+\right]; L^2(0, L)\right) \cap C\left(\left[0, a_i^+\right]; H^1(0, L)\right), i = \overline{1, 5}, \tag{46}$$

$$\|p_i\|_{C([0,a^+];H^1(0,L))} < R, i = \overline{1, 5}, \tag{47}$$

$$0 \le p_i(a, x) \le C_N + \frac{u_0}{C_\alpha}, \quad (a, x) \in \left[0, a_i^+\right] \times [0, L], i = \overline{1, 5}. \tag{48}$$

In addition, for $\mathcal{L}$ <1 , the solution is unique.

We fix $z \in \mathcal{M}$ and we define

$$U(x, z) = u_0 + \frac{1}{\Phi^*}\sum_{i=1}^{5}\int_0^x \int_0^{a_i^+} \widetilde{k}_i(a, \xi) z_i(a, \xi)\, da d\xi. \tag{49}$$

4.2. The demonstration of the existence and unicity of the solution of the system

We remark that the solution of the system in σ depends on p_i and we note it σ^p. We take $z = (z_1, z_2, z_3, z_4, z_5) \in \mathcal{M}$. We fix this z in (22)-(27) in all the nonlinear terms (respectively in $U(x,z)$), in the right member of equation (22), in the right member of the boundary condition in $a = 0$ from (22) and in the right member of equation (27).

Thus we obtain the system:

$$\begin{cases} \frac{\partial p_1}{\partial a} + \frac{\partial}{\partial x}\left(U(x,z)\,p_1\right) + \left(\mu_1(a,x) + \lambda_1(\sigma)\right)p_1 - \lambda_5(\sigma)\,z_5\frac{M_5(a)}{M_1(a)} = 0, \\ p_1(0,x) = \chi(x)\int_0^{a_1^+}\beta_p(a)\,z_1(a,x)\,M_1(a)\,da, \\ p_1(a,0) = \widetilde{N}_1(a), \end{cases} \tag{50}$$

$$\begin{cases} \frac{\partial p_2}{\partial a} + \frac{\partial}{\partial x}\left(U(x,z)\,p_2\right) + \mu_2(a,x)\,p_2 = 0, \\ p_2(0,x) = r(x)\int_0^{a_1^+}\beta_1(a)\,p_1(a,x)\,M_1(a)\,da, \\ p_2(a,0) = \widetilde{N}_2(a), \end{cases} \tag{51}$$

$$\begin{cases} \frac{\partial p_3}{\partial a} + \frac{\partial}{\partial x}\left(U(x,z)\,p_3\right) = 0, \\ p_3(0,x) = \int_0^{a_2^+}\beta_2(a)\,p_2(a,x)\,M_2(a)\,da, \\ p_3(a,0) = 0, \end{cases} \tag{52}$$

$$\begin{cases} \frac{\partial p_4}{\partial a} + \frac{\partial}{\partial x}\left(U(x,z)\,p_4\right) = 0, \\ p_4(0,x) = \sum_{i=1}^{2}\int_0^{a_i^+}\mu_i(a)\,p_i(a,x)\,M_i(a)\,da \\ \quad + \left(2 - r(x)\right)\int_0^{a_1^+}\beta_1(a)\,M_1(a)\,p_1(a,x)\,da, \\ p_4(a,0) = 0, \end{cases} \tag{53}$$

$$\begin{cases} \frac{\partial p_5}{\partial a} + \frac{\partial}{\partial x}\left(U(x,z)\,p_5\right) + \left(\mu_5(a,x) + \lambda_5(\sigma)\right)p_5 - \lambda_1(\sigma)\,p_1 = 0, \\ p_5(0,x) = 0, \\ p_5(a,0) = 0, \end{cases} \tag{54}$$

$$\begin{cases} -\frac{d^2\sigma}{dx^2} = d_1(\sigma)\int_0^{a_1^+}M_1(a)\,v_1(a)\,z_1(a,x)\,da \\ \quad + d_2(\sigma)\int_0^{a_2^+}M_2(a)\,v_2(a)\,z_2(a,x)\,da \\ \quad + d_5(\sigma)\int_0^{a_5^+}M_5(a)\,v_5(a)\,z_5(a,x)\,da + f(x), \\ \sigma(0) = \sigma_0,\ \frac{d\sigma}{dx}(L) + \widetilde{\alpha}\sigma(L) = \sigma_L. \end{cases} \tag{55}$$

Let σ be the solution of the problem (55) and $p = (p_1, p_2, p_3, p_4, p_5)$ the solution of the problem (50)-(54)

Let the mapping

$$\psi : \mathcal{M} \to \mathcal{M},\ \psi(z) = p, \tag{56}$$

that associates to the element $z = (z_1, z_2, z_3, z_4, z_5) \in \mathcal{M}$ the element $p = (p_1, p_2, p_3, p_4, p_5)$. We demonstrate that the mapping ψ is well defined and that it satisfies the conditions from Schauder's theorem, and so it has a fixed point. After that we show that the mapping ψ is a contraction, so the solution of the system (22)-(26) is unique.

We consider the problem (55)

Proposition 4.1. If

$$v_{1M} a_1^+ L_1 + v_{2M} a_2^+ L_2 + v_{5M} a_5^+ L_5 < \frac{2}{L^2 \left(C_N + \sqrt{L} R \right)}, \tag{57}$$

then the problem (55) has an unique solution $\sigma \in H^2(0, L)$.

Proposition 4.2. Let $z, \overline{z} \in \mathcal{M}$ and $\sigma, \overline{\sigma}$ the solutions of the problem (55) corresponding to z and $\overline{z}$, respectively. If (57) takes place then it exists $C_\sigma > 0$ so that:

$$\|\sigma - \overline{\sigma}\| \le C_\sigma \|z - \overline{z}\|_Y \tag{58}$$

For the calculations that follow we remark that the problems (50)-(54) have the form

$$\begin{cases} \frac{\partial p_i}{\partial a} + \frac{\partial}{\partial x}(g(x) p_i) + h_i(a, x) p_i = f_i(a, x), (a, x) \in \left(0, a_i^+\right) \times (0, L) \\ p_i(0, x) = F_i(x), x \in (0, L) \\ p_i(a, 0) = G_i(a), a \in \left(0, a_i^+\right). \end{cases} \tag{59}$$

Proposition 4.3. For $\mathcal{K} < R$ the mapping (56) is well defined, i.e. $\psi(z) \in \mathcal{M}, (\forall)\ z \in \mathcal{M}$.

Proposition 4.4. The mapping $\psi : \mathcal{M} \to \mathcal{M}$ given by (56) is continuous with respect to the norm induced on $\mathcal{M}$ by the norm from Y.

Proposition 4.5. $\psi(\mathcal{M})$ is relatively compact in Y.

By using Schauder's theorem we obtain thar the mapping ψ has a fixed point.

5. Numerical solution of the problem

5.1. Numerical scheme

In order to obtain a numerical solution of the problem (22)-(27) we will use a finite difference scheme. In order to build the finite difference scheme we will follow the ideas presented in [28]. We will write $U(x)$ instead of $U(x,p)$. We obtain a system equivalent to (22)-(27). We multiply (22)-(27) by $U(x)$ and we introduce the functions:

$$\overline{p_i}(a,x) = U(x)\, p_i(a,x), i = \overline{1,5}. \tag{60}$$

$$n_i(a,x) = M_i(a)\, p_i(a,x) = M_i(a)\frac{\overline{p_i}(a,x)}{U(x)}, i = \overline{1,5}. \tag{61}$$

The system (22)-(27) becomes:

$$\begin{cases} \frac{\partial \overline{p_1}}{\partial a} + U(x)\frac{\partial \overline{p}_1}{\partial x} + (\mu_1(a,x) + \lambda_1(\sigma))\,\overline{p}_1 - \lambda_5(\sigma)\,\overline{p}_5\frac{M_5(a)}{M_1(a)} = 0, \\ \overline{p}_1(0,x) = F_1(x), \\ \overline{p}_1(a,0) = G_1(a), \end{cases} \tag{62}$$

$$\begin{cases} \frac{\partial \overline{p}_2}{\partial a} + U(x)\frac{\partial \overline{p}_2}{\partial x} + \mu_2(a,x)\,\overline{p}_2 = 0, \\ \overline{p}_2(0,x) = F_2(x), \\ \overline{p}_2(a,0) = G_2(a), \end{cases} \tag{63}$$

$$\begin{cases} \frac{\partial \overline{p}_3}{\partial a} + U(x)\frac{\partial \overline{p}_3}{\partial x} = 0, \\ \overline{p}_3(0,x) = F_3(x), \\ \overline{p}_3(a,0) = G_3(a), \end{cases} \tag{64}$$

$$\begin{cases} \frac{\partial \overline{p}_4}{\partial a_4} + U(x)\frac{\partial \overline{p}_4}{\partial x} = 0, \\ \overline{p}_4(0,x) = F_4(x), \\ \overline{p}_4(a_4,0) = G_4(a_4), \end{cases} \tag{65}$$

$$\begin{cases} \frac{\partial \overline{p}_5}{\partial a_5} + U(x)\frac{\partial \overline{p}_5}{\partial x} + (\mu_5(a_5,x) + \lambda_5(\sigma))\,\overline{p}_5 - \lambda_1\overline{p}_1 = 0, \\ \overline{p}_5(0,x) = F_5(x), \\ \overline{p}_5(a_5,0) = G_5(a_5), \end{cases} \tag{66}$$

$$\begin{cases} -U(x)\frac{d^2\sigma}{dx^2} = d_1\int_0^{a_1^+} M_1(a)\,v_1(a)\,\overline{p}_1 da \\ +d_2\int_0^{a_2^+} M_2(a)\,v_2(a)\,\overline{p}_2 da \\ +d_5\int_0^{a_5^+} M_5(a)\,v_5(a)\,\overline{p}_5 da + U(x)\,f(x), \\ \sigma(0) = \sigma_0, \\ \frac{d\sigma}{dx}(L) + \widetilde{\alpha}\sigma(L) = \sigma_L, \end{cases} \tag{67}$$

We obtain the following equations by discretization

$$P_1^{i+1,j+1} = \frac{\lambda_5\left(\sigma^{j+1}\right)\frac{M_5^i}{M_1^i}P_5^{i,j}h + P_1^{i,j}}{1+h\left(\mu_1^{i,j}+\lambda_1\left(\sigma^{j+1}\right)\right)}, i=\overline{0,n_{a_1^+}-1}, \tag{68}$$

$$P_2^{i+1,j+1} = \frac{P_2^{i,j}}{1+\mu_2^{i,j}h}, i=\overline{0,n_{a_2^+}-1}, \tag{69}$$

$$P_3^{i+1,j+1} = P_3^{i,j}, i=\overline{0,n_{a_3^+}-1}, \tag{70}$$

$$P_4^{i+1,j+1} = P_4^{i,j}, i=\overline{0,n_{a_4^+}-1}, \tag{71}$$

$$P_5^{i+1,j+1} = \frac{h\lambda_1\left(\sigma^{j+1}\right)P_1^{i,j} + P_5^{i,j}}{1+h\left(\mu_5^{i,j}+\lambda_5\left(\sigma^{j+1}\right)\right)}, i=\overline{0,n_{a_5^+}-1}. \tag{72}$$

$$\begin{aligned} U^{j+1} \quad = \quad & \frac{h}{\Phi^*}\left[\sum_{i=0}^{n_{a_1^+}-1} v_1^i M_1^i P_1^{i,j+1} + \sum_{i=0}^{n_{a_2^+}-1} v_2^i M_2^i P_2^{i,j+1}\right. \\ & + \sum_{i=0}^{n_{a_3^+}-1} v_3^i M_3^i P_3^{i,j+1} + \sum_{i=0}^{n_{a_4^+}-1} v_4^i M_4^i P_4^{i,j+1} \\ & \left. + \sum_{i=0}^{n_{a_5^+}-1} v_5^i M_5^i P_5^{i,j+1}\right], \end{aligned} \tag{73}$$

The numerical error estiomation for $p_i, i=\overline{1,5}$ is of the same order as h.

5.2. Numerical algorithm

Step 0. Data initialization: $a_i^+, a_i^-, ..., n_{a_i^+}, h, \sigma_0, \sigma_L, \alpha, \widetilde{\alpha}$, functions $\beta_i, M_i, v_i, \mu_i, \chi, r$, all the parameters from the basal layer.

Step 1. Computations of the functions $G_l\left(a\right), F_l\left(x\right), l=1,...,5$ for $j=0$ and for $i=0$.

Step 2. Verification of the conditions of campability.

Step 3. Computation of $U^0 = u_0$.

Step 4. Initialization of $j=0, k^0=u_0 h$ and $L^0=0$.

Step 5. Computation of L^{j+1} and of the following values in this order: $\overline{p}_1^{i+1,j+1}$, $\overline{p}_1^{0,j+1}$, $\overline{p}_2^{0,j+1}$, $\overline{p}_2^{i+1,j+1}$, $\overline{p}_3^{0,j+1}$, $\overline{p}_3^{i+1,j+1}$, $\overline{p}_4^{0,j+1}$, $\overline{p}_4^{i+1,j+1}$, $\overline{p}_5^{0,j+1}$, $\overline{p}_5^{i+1,j+1}$, U^{j+1}, for $i=0,...,n_{a_l^+}-1\left(l=1,...,5\right)$ and $j=0,...,N_x-1$.

Step 6. Solve with a finite difference scheme the boundary value problem

$$\begin{cases} -U(x)\frac{d^2\sigma}{dx^2} = d_1\int_0^{a_1^+} M_1(a)\, v_1(a)\,\overline{p_1}da \\ +d_2\int_0^{a_2^+} M_2(a)\, v_2(a)\,\overline{p_2}da \\ +d_5\int_0^{a_5^+} M_5(a)\, v_5(a)\,\overline{p_5}da + U(x)\, f(x), \\ \sigma(0) = \sigma_0 \\ \frac{d\sigma}{dx}\left(L^{j+1}\right) + \widetilde{\alpha}\sigma\left(L^{j+1}\right) = \sigma_L \end{cases} \tag{74}$$

and compute $\sigma^{j+1} = \sigma\left(L^{j+1}\right)$.

Step 7. Computation of the real values

$$n_l^{i,j} = M_l^i \frac{\overline{p}_l^{i,j}}{U^j}, i = \overline{0, n_{a_1^+}}, j = \overline{0, N_x}, l = \overline{1,5},$$

Step 8. Transformation of the vectors of discrete values into functions of a and x.

Step 9. Computation of the integrals of n_l, with respect to a and computation of the function Φ.

Step 10. Computation of the function $\Gamma(x)$ and of Λ^*.

5.5. Numerical results

Based on the numerical algorithm presented above we wrote a Matlab programme in order to obtain a numerical solution of the problem we dealt with in this thesis. We fixed certain numerical values for some of the problem parameters and we let others vary between certain limits in order to put into evidence the influence of the medicinal treatment on the epidermis. The conclusions of the numerical analysis we made on the problem we dealt with in this thesis are presented in the final part of the thesis. The figures below represent one of the cases studied in this thesis and contain the variation of the concentration of the treatment σ, the variations of the functions λ_i that represent the rate of transformation of the cells of type i as a result of the medicinal treatment, $i \in \{1,5\}$, the variation of the density of the number of cells related to x (measured in cells/μm^3) which is defined by the formula

$$\int_0^{a_i^+} n_i(a,x)\, da, i = \overline{1,5},$$

and the variation of the cohesion function Γ.

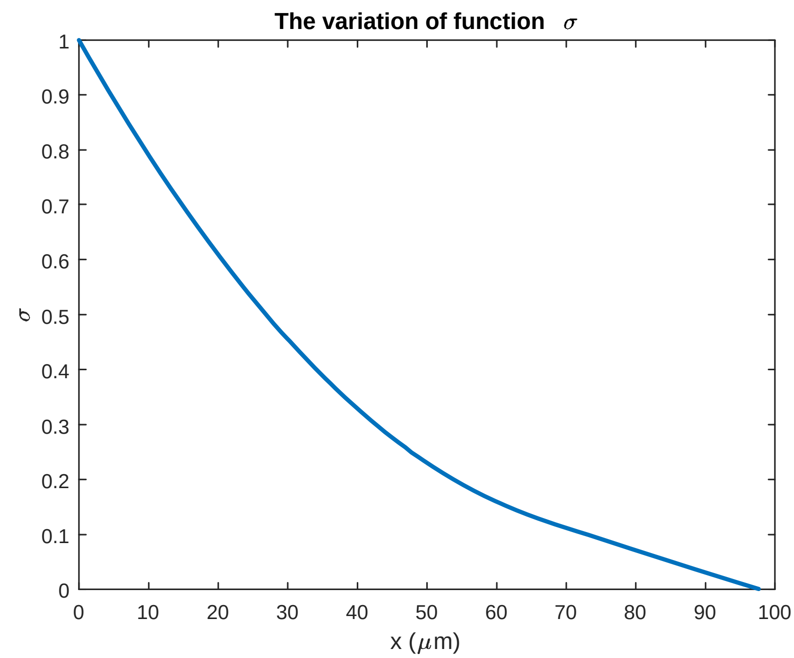

Figure 3a. Variation of function σ, $\lambda_{1,\max} = 1$ (case 2)

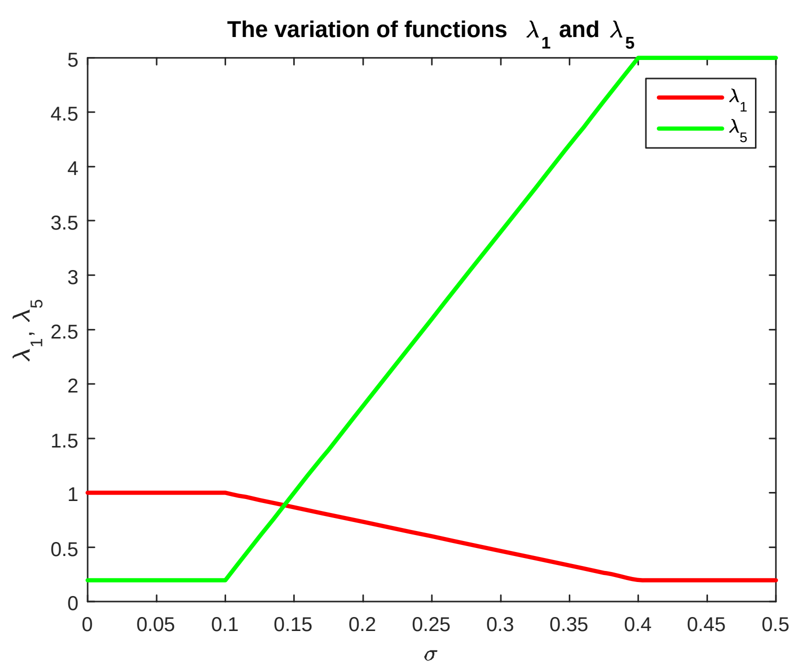

Figure 3b. Variation of functions λ_1, λ_5 (case 2)

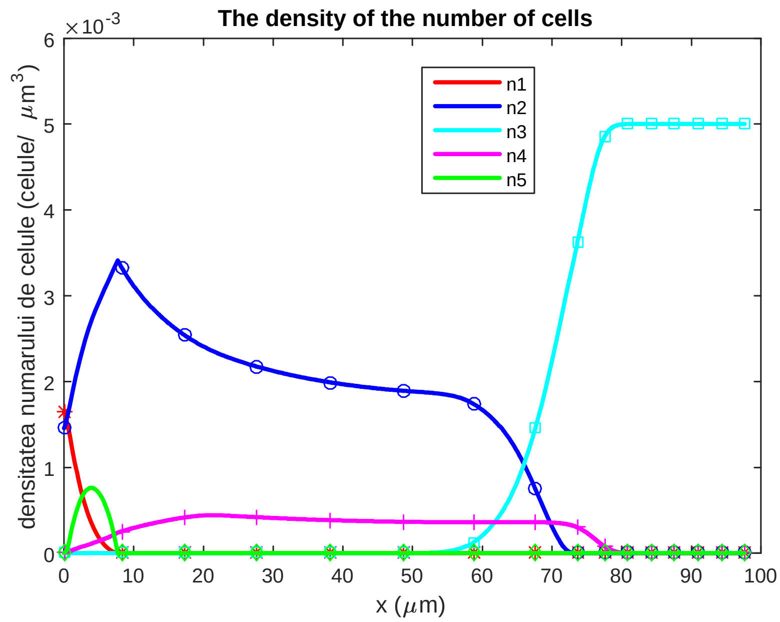

Figure 3c. The density of the number of cells, $\lambda_{1,\max} = 1$ (case 2)

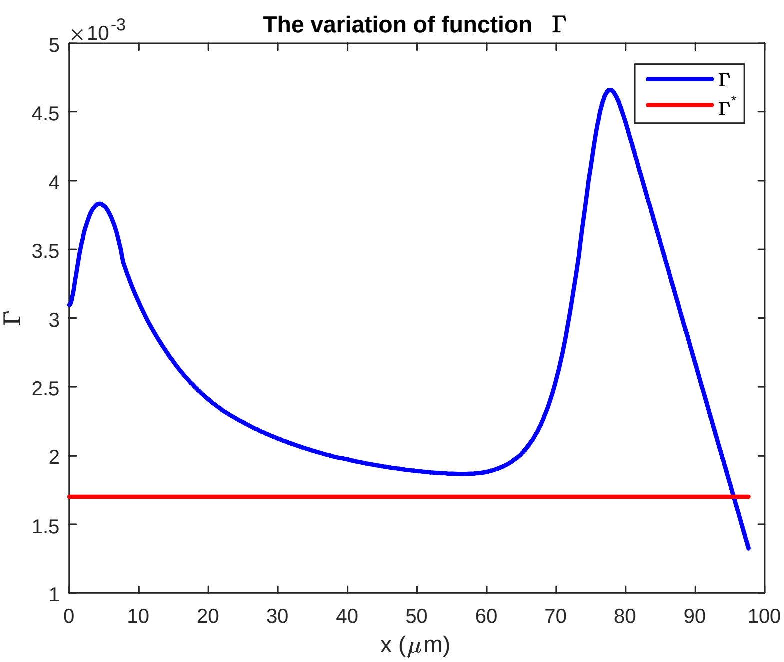

Figure 3d. Variation of function Γ, $\lambda_{1,\max} = 1$ (case 2)

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