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TIME EVOLUTION FOR A MODEL OF EPIDERMIS GROWTH

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Abstract

In this paper we study a system of nonlinear hyperbolic equations, with nonlocal boundary conditions and a free boundary, arising in the modelling of epidermis growth. The model was introduced in a previous paper [9] where conditions for the existence of a steady state were investigated. The present paper is 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. The proof of the theorem is based on the integration along characteristic curves in order to obtain suitable estimates allowing to set up a fixed point procedure. The modellistic aim of the paper is a description of the structure of the epidermis as a layered aggregate of different type of cells.

Key words: Nonlinear hyperbolic PDE; nonlocal conditions; free boundary; population dynamics; epidermis growth.

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Abstract. In this paper we study a system of nonlinear hyperbolic equations, with nonlocal boundary conditions and a free boundary, arising in the modelling of epidermis growth. The model was introduced in a previous paper [9] where conditions for the existence of a steady state were investigated. The present paper is 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. The proof of the theorem is based on the integration along characteristic curves in order to obtain suitable estimates allowing to set up a fixed point procedure. The modellistic aim of the paper is a description of the structure of the epidermis as a layered aggregate of different type of cells.

MSC: 92B05, 92C17, 92C37, 35F61
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1 Introduction

In this paper we study a problem arising in the modelling of epidermis growth, namely a system of nonlinear hyperbolic equations, with nonlocal boundary conditions and a free boundary.

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The model we consider aims to describe the epidermis as an aggregate of different cells. In fact, the epidermis is formed by epithelial cells, arranged in multiple layers, undergoing a continuous renewal process. Cells in the innermost layer (basal cell layer) detach after proliferation from the underlying basement membrane and move outward forming the suprabasal layers [13, 19]. Suprabasal cells progressively mature, by a process during which the fibrous protein keratin accumulates in the cells. At the end of such a process, cells filled of keratin die, and the dead cells (corneous cells or corneocytes) form the stratum corneum [10]. Although the deepest cells of stratum corneum retain their intercellular bonds, corneocytes gradually lose their adhesion when are slowly pushed to the surface by newly born cells, and are eventually shed from the surface through a process named desquamation.

Whereas many mathematical models have been proposed for cell aggregates, including age structure [4, 7, 17, 18] and biophysical properties [3, 5, 6, 8, 14], few models have been devoted to the spatial organization of stratified epithelia [1, 15, 16]. We recently proposed a model with age and spatial structure to describe the evolution of suprabasal epidermis [9]. In this model, which briefly will be illustrated in the following, the cell proliferation in the basal layer is simply summarized by the boundary conditions. In [9] the existence of a stationary solution was studied.

In our model, we assumed a planar idealized geometry, so that the Cartesian coordinate x, perpendicular to the epidermis plane, is the only spatial variable. The boundary $x = 0$ represents the interface with the basal cell layer, whereas $x = \Lambda(t)$ (t denoting time) defines the *epidermis outer boundary* which coincides with the end of the stratum corneum in most conditions. The boundary $\Lambda(t)$ is not known a priori.

Although in normal skin cell proliferation occurs almost exclusively in the basal layer [19]), where stem cells generate transiently proliferating cells that after 4-5 rounds of proliferation become (quiescent) differentiated cells, in pathological cases the proliferation can even extend to the suprabasal layers, [12]. In order to account for moderate hyper-proliferation, we assumed that the last round of division may occur in the suprabasal region. The maturation process of the differentiated cells is supposed to evolve with their age, as well as the final transition to the corneous state.

The model includes proliferating cells, differentiated cells, corneous cells, and apoptotic cells. These classes are respectively indexed by $i = 1, \ldots, 4$. The class of apoptotic cells includes all the dead cells caused by pathological mitosis and/or by external damaging agents (e.g chemicals or UV radiations). We denote by $n_i(t, a_i, x,)$ the density with respect to the age $a_i \in [0, a_i^+]$ of the number of cells of type i per unit volume, at position x and time t. Thus, $n_i(t, a_i, x)da_i dx$ gives the number of cells with age between a_i and $a_i + da_i$ in a cylinder of unit base that extends from x and $x + dx$.

All cells at a given position are assumed to move with the same velocity $u(t, x)$, positive in the outward direction.

The local fraction of volume occupied by cells at time t around the point x, denoted by $\Phi(t, x)$, can be expressed by

$$\Phi(t,x) = \sum_{i=1}^{4} \int_0^{a_i^+} v_i(a_i) n_i(t, a_i, x) da_i. \tag{1}$$

where $v_i(a_i) > 0$, $i = 1, \ldots, 4$, is the mean volume of a cell of type i at age a_i. From its definition, $\Phi(t, x)$ is obviously meaningful if $0 \leq \Phi(t, x) \leq 1$. The function $\Phi(t, x)$ is supposed to be *constant*

$$\Phi(t, x) = \Phi^*, \quad (t, x) \in [0, T] \times [0, \Lambda(t)], \tag{2}$$

with $0 < \Phi^* < 1$. This assumption appears quite adequate for the viable layers as well as for most of the stratum corneum [2, 11], where cells are closely packed with very small extracellular space.

We also consider a phenomenological quantity, $\Gamma(t, x)$, that represents (in arbitrary unit) the degree of cohesion of the tissue at position x and time t. We assume that cells differently contribute to the tissue cohesion by means of their adhesion bonds, according to their type and, possibly, according to their age. Thus, we define the cohesion function $\Gamma(t, x)$ as:

$$\Gamma(t,x) = \sum_{i=1}^{3} \int_0^{a_i^+} \gamma_i(a_i) n_i(t, a_i, x) da_i, \tag{3}$$

where $\gamma_i(a_i) \geq 0$, $i = 1, 2, 3$, is the adhesiveness of cells of type i at age a_i (apoptotic cells do not contribute significantly to the cohesion). We suppose γ_1 and γ_2 constant, whereas, to represent the progressive loss of adhesion among the corneocytes, we take γ_3 continuously differentiable and such that

$$\gamma_3'(a_3) < 0, \quad \gamma_3(a_3) = 0 \text{ for } a_3 \in [\hat{a}_3, a_3^+], \tag{4}$$

with $\hat{a}_3 > 0$. We assume that the epidermis maintains its cohesion as long as Γ is greater than a critical value Γ^*. Thus, the outer boundary $\Lambda(t)$ will be such that

$$\Gamma(t,x) > \Gamma^* \quad \text{for } x \in [0, \Lambda(t)),$$

and

$$\Gamma(t, \Lambda(t)) \geq \Gamma^*. \tag{5}$$

By taking into account that the constraint

$$u(t, \Lambda(t)) \geq \frac{d\Lambda}{dt}(t) \tag{6}$$

must be satisfied to avoid the nonsense of an epidermis boundary that "detaches"from the cells, two regimes are possible. In the first case it is

$$\frac{d\Lambda}{dt}(t) < u(t, \Lambda(t)), \quad \Gamma(t, \Lambda(t)) = \Gamma^*, \tag{7}$$

and the equation $\Gamma(t, \Lambda(t)) = \Gamma^*$ defines the boundary $\Lambda(t)$. In the second case

$$\frac{d\Lambda}{dt}(t) = u(t, \Lambda(t)), \quad \Gamma(t, \Lambda(t)) \geq \Gamma^*, \tag{8}$$

the boundary $\Lambda(t)$ moves solidly with the cells (it is a "material boundary"). Note that in (7) the strict inequality $\Gamma(t, \Lambda(t)) > \Gamma^*$ cannot hold because, if $\Gamma(t, \Lambda(t)) > \Gamma^*$, the boundary necessarily should move together with the cells and $d\Lambda/dt = u(t, \Lambda(t))$.

The system proposed in [9] to describe the nonstationary growth of the epidermis reads

$$\begin{aligned}
\frac{\partial n_1}{\partial t} + \frac{\partial n_1}{\partial a_1} + \frac{\partial}{\partial x}(u(t,x)n_1) &= -\beta_1(a_1)n_1 - \mu_1(t, a_1, x)n_1, \\
n_1(t, 0, x) &= 0, \\
n_1(t, a_1, 0) &= N_1(t, a_1), \\
n_1(0, a_1, x) &= n_{10}(a_1, x),
\end{aligned} \tag{9}$$

$$\begin{aligned}
\frac{\partial n_2}{\partial t} + \frac{\partial n_2}{\partial a_2} + \frac{\partial}{\partial x}(u(t,x)n_2) &= -\beta_2(a_2)n_2 - \mu_2(t, a_2, x)n_2, \\
n_2(t, 0, x) &= r(t,x) \int_0^{a_1^+} \beta_1(a_1) n_1(t, a_1, x) da_1, \\
n_2(t, a_2, 0) &= N_2(t, a_2), \\
n_2(0, a_2, x) &= n_{20}(a_2, x),
\end{aligned} \tag{10}$$

$$\begin{aligned}
\frac{\partial n_3}{\partial t} + \frac{\partial n_3}{\partial a_3} + \frac{\partial}{\partial x}(u(t,x)n_3) &= -\beta_3(a_3)n_3, \\
n_3(t, 0, x) &= \int_0^{a_2^+} \beta_2(a_2) n_2(t, a_2, x) da_2, \\
n_3(t, a_3, 0) &= 0, \\
n_3(0, a_3, x) &= n_{30}(a_3, x),
\end{aligned} \tag{11}$$

$$
\begin{aligned}
\frac{\partial n_4}{\partial t} + \frac{\partial n_4}{\partial a_4} + \frac{\partial}{\partial x}(u(t,x) n_4) &= -\beta_4(a_4) n_4, \\
n_4(t,0,x) &= \sum_{i=1}^{2} \int_0^{a_i^+} \mu_i(a_i,x) n_i(t,a_i,x) da_i \\
&\quad + (2 - r(t,x)) \int_0^{a_1^+} \beta_1(a_1) n_1(t,a_1,x) da_1, \\
n_4(t,a_4,0) &= 0, \\
n_4(0,a_4,x) &= n_{40}(a_4,x),
\end{aligned}
\tag{12}
$$

for $t \in [0,T]$, $x \in [0,\Lambda(t)]$, $a_i \in [0,a_i^+]$, $i = 1,...,4$.

In the above equations, β_1 denotes the rate of division of proliferating cells, β_2 the rate of transition of differentiated cells to corneous cells, β_3 represents the rate of degradation of corneocytes, β_4 the rate of degradation of apoptotic cells. All these (per cell) rates are age dependent and are assumed to blow up at $a_i = a_i^+ < +\infty$, $i = 1,...,4$, in such a way that $\int_0^{a_i^+} \beta_i(a_i) da_i = +\infty$. Thus, the respective cell density n_i will vanish at $a_i = a_i^+$. The loss rate β_3 is introduced only to guarantee *a priori* the above property also for the density of corneous cells. We suppose, however, that the support of the function β_3 is confined to an interval $(\bar{a}_3, a_3^+)$ with $\bar{a}_3 > \hat{a}_3$, i.e with $\bar{a}_3$ sufficiently large so that the loss β_3 does not actually influence the evolution of the outer boundary Λ. The function $r(t,x)$ is the mean number of viable cells originated at the division of one proliferating cell. Under normal, non pathological conditions $r(t,x) \equiv 2$, otherwise, $r(t,x) \in [0,2)$. Finally, $\mu_1(t,a_1,x)$ and $\mu_2(t,a_2,x)$ are the mortality rates, induced by external causes, of proliferating and, respectively, differentiated cells.

Thanks to the one-dimensional geometry, the hypothesis (2) allows us to determine the velocity field $u(t,x)$ that has the following expression depending on the cell densities (see for the derivation [9]),

$$
u(t,x) = u_0(t) + \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^x \int_0^{a_i^+} k_i(t,a_i,\xi) n_i(t,a_i,\xi) da_i d\xi, \tag{13}
$$

where $u_0(t)$ is given. The function $u_0(t)$ is the velocity by which cells leave the basal layer. The expressions of the coefficients k_i are given in [9] and depend on the cell volumes v_i, and the vital parameters β_i, μ_i and r.

The age densities $N_i(t,a_i)$, $i = 1,2$, prescribe the boundary conditions at $x = 0$, and must be such that $\Phi(t,0) = \Phi^*$. Since there is no input of cells of type 3 and 4 from the basal layer, the corresponding boundary conditions are zero. Finally, the initial conditions n_{i0} must satisfy $\Phi(0,x) = \Phi^*$ in the interval $[0,\Lambda_0]$, where $\Lambda_0 = \Lambda(0)$.

The purpose of this work is to prove the existence of a solution to (9)-(13) and to interpret the conditions under which this result is possible. To this end, in Sections 2 and 3 we shall give some intermediate results, considering that the space variable x is in $[0,L]$, with L finite and fixed. Theorem 3.1 relies on the Banach fixed point theorem and provides the arguments that will be used in Section 4, where we shall prove the final result of existence to (9)-(13).

2 Preliminary results: the linear problem

In this section we deal with the following problem written for a scalar function, generically denoted $w(t,a,x)$,

$$
w_t + w_a + \alpha w_x + (\alpha_x + \pi) w = f \text{ in } (0,T) \times (0,a^+) \times (0,L), \tag{14}
$$

$$
w(0,a,x) = w_0(a,x) \text{ in } (0,a^+) \times (0,L), \tag{15}
$$

$$
w(t,0,x) = F(t,x) \text{ in } (0,T) \times (0,L), \tag{16}
$$

$$
w(t,a,0) = G(t,a) \text{ in } (0,T) \times (0,a^+), \tag{17}
$$

where α depends on t and x and π and f are functions of t, a, x. For simplicity, the partial derivatives of a function are indicated by a subscript.

We shall study the existence and uniqueness of a solution to this problem and establish some estimates for a later use.

To solve the above system we use the method of characteristics and, due to the special structure of the equation, we may consider only the spatial characteristic, namely the function $\varphi(t,\sigma,x)$ which is the solution to the problem

$$\begin{aligned} \varphi_t(t,\sigma,x) &= \alpha(t,\varphi(t,\sigma,x)), \\ \varphi(\sigma,\sigma,x) &= x. \end{aligned} \tag{18}$$

As it is known, φ has the evolution property

$$\varphi(t,\sigma_1,\varphi(\sigma_1,\sigma,x)) = \varphi(t,\sigma,x). \tag{19}$$

We have

Lemma 2.1. *Let* $\alpha \in C([0,T];C^1[0,L])$,

$$\alpha(t,0) > 0, \text{ for any } t \in [0,T]. \tag{20}$$

Then, the solution to (18) *exists, it is unique and*

$$\varphi_x(t,\sigma,x) = \exp\left(\int_\sigma^t \alpha_x(s,\varphi(s,\sigma,x))ds\right). \tag{21}$$

The function $\sigma \to \varphi(t,\sigma,0)$ *is decreasing and*

$$\varphi_\sigma(t,\sigma,0) = -\frac{\alpha(\sigma,0)}{\varphi_x(\sigma,t,\varphi(t,\sigma,0))}. \tag{22}$$

Proof. Since $\alpha \in C([0,T];C^1[0,L])$ the solution to (18) exists on a maximum time interval $[0,T_{\max}(\sigma,x)]$. Actually, $T_{\max}(\sigma,x)$ is either T or such that $\varphi(T_{\max}(\sigma,x),\sigma,x) = L$. Differentiating the equations in (18) with respect to x we have

$$\begin{aligned} \varphi_{xt}(t,\sigma,x) &= \varphi_x(t,\sigma,x)\alpha_x(t,\varphi(t,\sigma,x)), \\ \varphi_x(\sigma,\sigma,x) &= 1, \end{aligned}$$

whence we get (21) by integration with respect to t.

For obtaining (22) we start from the equality

$$\varphi(\sigma,t,\varphi(t,\sigma,0)) = 0$$

and differentiate it with respect to σ,

$$\varphi_t(\sigma,t,\varphi(t,\sigma,0)) + \varphi_x(\sigma,t,\varphi(t,\sigma,0))\varphi_\sigma(t,\sigma,0) = 0.$$

Therefore, using (18) and (19) we get (22) and note that $\varphi_\sigma(t,\sigma,0) < 0$. □

Since for a fixed t the function $\sigma \to \varphi(t,\sigma,0)$ is decreasing it follows that, for $x < \varphi(t,0,0)$, the equation

$$\varphi(t,\sigma,0) = x$$

can be uniquely solved in terms of σ, and provides a solution $\sigma = C(t,x) < t$, such that

$$\varphi(t,C(t,x),0) = x. \tag{23}$$

Note that by writing $\varphi(t',t,x) = \varphi(t',t,\varphi(t,C(t,x),0)$ we get

$$\varphi(t',t,x) = \varphi(t',C(t,x),0), \ \forall t' \in [0,T]. \tag{24}$$

Moreover, by differentiating (23) with respect to x,

$$\varphi_\sigma(t, C(t,x), 0) C_x(t,x) = 1,$$

whence, using (22) and (21) we obtain

$$\begin{aligned} C_x(t,x) &= \frac{1}{\varphi_\sigma(t, C(t,x), 0)} = -\frac{\varphi_x(C(t,x), t, \varphi(t, C(t,x), 0)}{\alpha(C(t,x), 0)} \\ &= -\frac{1}{\alpha(C(t,x),0)} \exp\left(\int_t^{C(t,x)} \alpha_x(s, \varphi(s, t, \varphi(t, C(t,x), 0) ds \right) \\ &= -\frac{1}{\alpha(C(t,x),0)} \exp\left(\int_t^{C(t,x)} \alpha_x(s, \varphi(s, C(t,x), 0) ds \right). \end{aligned} \tag{25}$$

For generic functions $f(t,a,x)$, $g(a,x)$, $g(t,x)$ or $g(t,a)$ we shall denote

$$\begin{aligned} |f|_\infty &= \|f\|_{C([0,T]\times[0,a^+]\times[0,L])}, \quad |f|_{\infty,1,\infty} = \|f\|_{C([0,T];L^1(0,a^+;C[0,L]))}, \\ |g|_\infty &= \|g\|_{C([0,B^*]\times[0,C^*])}, \end{aligned} \tag{26}$$

where B^*, C^* can be the pairs (a^+, L), (T, L) or (T, a^+).

The next result provides the existence of the solution to (14)-(17) and the estimates $|w(t)|_\infty$ and $|w_x(t)|_\infty$ that will be necessary in Theorem 3.1. Since only $|w(t)|_\infty$ will be useful in the case with a nonvanishing f, the estimate $|w_x(t)|_\infty$ will be computed for $f \equiv 0$.

For simplicity, we shall use the following notations:

$$E(t,a,x) = e^{-\int_{C(t,x)}^t [\alpha_x(s,\varphi(s,C(t,x),0)) + \pi(s,a-t+s,0))]ds},$$

$$E_+(t,a,x) = e^{-\int_{t-a}^t [\alpha_x(s,\varphi(s,t,x)) + \pi(s,s+a-t,\varphi(s,t,x))]ds},$$

$$E_-(t,a,x) = e^{-\int_0^t [\alpha_x(s,\varphi(s,t,x)) + \pi(s,a-t+s,\varphi(s,t,x))]ds},$$

$$f_I(t,a,x) = \int_0^a f(t-\sigma, a-\sigma, \varphi(t-\sigma,t,x)) e^{-\int_0^\sigma [\alpha_x(t-\tau,\varphi(t-\tau,t,x)) + \pi(t-\tau,a-\tau,\varphi(t-\tau,t,x))]d\tau} d\sigma,$$

$$\begin{aligned} f_{II}(t,a,x) &= \int_0^{t-C(t,x)} \{ f(t-\sigma, a-\sigma, \varphi(t-\sigma, C(t,x), 0)) \\ &\quad \times e^{-\int_0^\sigma [\alpha_x(t-\tau,\varphi(t-\tau,C(t,x),0)) + \pi(t-\tau,a-\tau,\varphi(t-\tau,C(t,x),0))]d\tau} \} d\sigma \end{aligned}$$

$$f_{III}(t,a,x) = \int_0^t f(t-\sigma, a-\sigma, \varphi(t-\tau,t,x) e^{-\int_0^\sigma [\alpha_x(t-\tau,\varphi(t-\tau,t,x)) + \pi(t-\tau,a-\tau,\varphi(t-\tau,t,x))]d\tau} d\sigma,$$

$$f_{IV}(t,a,x) = f_{II}(t,a,x).$$

Then we have

Proposition 2.2. *Assume*

$$\begin{aligned} w_0 &\in C^1([0,a^+]\times[0,L]),\ F \in C^1([0,T]\times[0,L]),\ f \in C^1([0,T]\times[0,a^+]\times[0,L]), \\ G &\in C^1([0,T]\times[0,a^+]),\ \pi \in C^1([0,T]\times[0,a^+]\times[0,L])), \end{aligned}$$

$$\pi(t,a,x) \geq 0 \text{ for any } (t,a,x) \in [0,T]\times[0,a^+]\times[0,L],$$

$$\alpha \in C^1([0,T];C^2[0,L]),\ \alpha(t,0) > 0 \text{ for any } t \in [0,T],$$

with the compatibility conditions

$$F(t,0) = G(t,0),\ w_0(0,x) = F(0,x),\ w_0(a,0) = G(0,a), \tag{27}$$

$$F_x(t,0) = G_a(t,0),\ \ w_{0a}(0,x) = F_t(0,x),\ \ w_{0x}(a,0) = G_t(0,a). \tag{28}$$

Then, system (14)-(17) *has a unique solution* $w \in C^1([0,T]\times[0,a^+]\times[0,L])$ *given by*

$$w(t,a,x) = \begin{cases} F(t-a,\varphi(t-a,t,x))E_+(t,a,x) + f_I(t,a,x), \\ \qquad\qquad \textit{if } t>a,\ x>\varphi(t,t-a,0) \\ \\ G(C(t,x),a-t+C(t,x))E(t,a,x) + f_{II}(t,a,x), \\ \qquad\qquad \textit{if } t>a,\ x<\varphi(t,t-a,0) \\ \\ w_0(a-t,\varphi(0,t,x))E_-(t,a,x) + f_{III}(t,a,x), \\ \qquad\qquad \textit{if } t<a,\ x>\varphi(t,0,0) \\ \\ G(C(t,x),a-t+C(t,x))E(t,a,x) + f_{IV}(t,a,x), \\ \qquad\qquad \textit{if } t<a,\ x<\varphi(t,0,0) \end{cases} \tag{29}$$

which satisfies

$$|w(t)|_\infty \le \left(|w_0|_\infty + |F|_\infty + |G|_\infty + \int_0^t |f(s)|_\infty\, ds\right)\exp(T\,|\alpha_x|_\infty), \tag{30}$$

and

$$\begin{aligned} &|w_x(t)|_\infty \le e^{2T|\alpha_x|_\infty} \times (1 + |\alpha_x|_\infty + |\pi|_\infty + T(|\alpha_{xx}|_\infty + |\pi_x|_\infty)) \\ &\left\{|w_{0x}|_\infty + |F_x|_\infty + |w_0|_\infty + |F|_\infty + |G|_\infty + \left|\frac{G_t}{\alpha(\cdot,0)}\right|_\infty + \left|\frac{G_a}{\alpha(\cdot,0)}\right|_\infty + \left|\frac{G}{\alpha(\cdot,0)}\right|_\infty\right\} \end{aligned} \tag{31}$$

for any $t \in [0,T]$.

Proof. We consider a solution $w \in C^1([0,T]\times[0,a^+]\times[0,L])$ to problem (14)-(17) and use the characteristics (18) to derive its necessary form. To this purpose we define the function

$$V(s) = w(t_0+s, a_0+s, \varphi(t_0+s,t_0,x_0)). \tag{32}$$

It can be easily verified that it satisfies the problem

$$\begin{aligned} V'(s) &= -\left[\alpha_x(t_0+s,\varphi(t_0+s,t_0,x_0)) + \pi(t_0+s,a_0+s,\varphi(t_0+s,t_0,x_0))\right]V(s) \\ &\quad + f(t,a,x), \\ V(0) &= w(t_0,a_0,x_0). \end{aligned}$$

Therefore

$$\begin{aligned} &V(s) = w(t_0,a_0,x_0)e^{-\int_0^s[\alpha_x(t_0+\tau,\varphi(t_0+\tau,t_0,x_0))+\pi(t_0+\tau,a_0+\tau,\varphi(t_0+\tau,t_0,x_0))]d\tau} \\ &+ \int_0^s \{f(t_0+\sigma,a_0+\sigma,\varphi(t_0+\sigma,t_0,x_0)) \\ &\times e^{-\int_\sigma^s[\alpha_x(t_0+\tau,\varphi(t_0+\tau,t_0,x_0))+\pi(t_0+\tau,a_0+\tau,\varphi(t_0+\tau,t_0,x_0))]d\tau}\}d\sigma. \end{aligned} \tag{33}$$

In order to compute $w(t,a,x)$ we have four cases depending on the central characteristics.

First we consider the case $t>a$, illustrated in Fig. 1, where the central characteristic $\varphi(t,t-a,0)$ is shown. We have two situations.

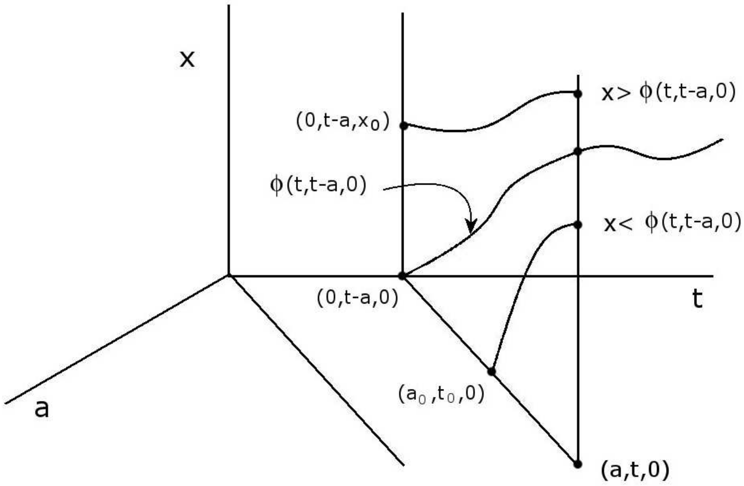

Fig. 1 Characteristics scenario for $t > a$ (cases I and II)

I. If $t > a$ and $x > \varphi(t, t-a, 0)$ then we choose

$$a_0 = 0,\ s = a,\ t_0 = t-a,\ x_0 = \varphi(t-a, t, x)$$

which are replaced in the above expression of $V(s)$, to get

$$\begin{aligned} &w(t,a,x) = w(t-a, 0, \varphi(t-a,t,x)) \times \\ &e^{-\int_0^a \alpha_x(t-a+\tau, \varphi(t-a+\tau, t-a, \varphi(t-a,t,x)))d\tau} \times e^{-\int_0^a \pi(t-a+\tau,\tau,\varphi(t-a+\tau,t-a,\varphi(t-a,t,x)))d\tau} \\ &+ \int_0^a \{f(t-a+\sigma, \sigma, \varphi(t-a+\sigma, t-a, \varphi(t-a,t,x))) \\ &\times e^{-\int_\sigma^a [\alpha_x(t-a+\tau,\varphi(t-a+\tau,t-a,\varphi(t-a,t,x)))+\pi(t-a+\tau,\tau,\varphi(t-a+\tau,t-a,\varphi(t-a,t,x)))]d\tau}\} d\sigma. \end{aligned} \tag{34}$$

Then, taking into account the initial and boundary data in (14)-(17) and the relations in Lemma 2.1 we compute the integrals by changing the variables. In fact, taking into account (19) we get

$$w(t-a, 0, \varphi(t-a,t,x)) = F(t-a, \varphi(t-a,t,x)),$$

$$\begin{aligned} & e^{-\int_0^a \alpha_x(t-a+\tau,\varphi(t-a+\tau,t-a,\varphi(t-a,t,x))d\tau} \\ = \ & e^{-\int_0^a \alpha_x(t-a+\tau,\varphi(t-a+\tau,t,x))d\tau} = e^{-\int_{t-a}^t \alpha_x(\sigma,\varphi(\sigma,t,x)d\sigma}, \end{aligned}$$

and

$$\begin{aligned} & e^{-\int_0^a \pi(t-a+\tau,\tau,\varphi(t-a+\tau,t-a,\varphi(t-a,t,x))d\tau} \\ = \ & e^{-\int_0^a \pi(t-a+\tau,\tau,\varphi(t-a+\tau,t,x))d\tau} = e^{-\int_{t-a}^t \pi(\sigma,\sigma+a-t,\varphi(\sigma,t,x))d\sigma}. \end{aligned}$$

For the second term in the sum (34) we have

$$\begin{aligned} = \ & \int_0^a f(t-a+\sigma,\sigma,\varphi(t-a+\sigma,t,x)) e^{-\int_\sigma^a [\alpha_x(t-a+\tau,\varphi(t-a+\tau,t,x))+\pi(t-a+\tau,\tau,\varphi(t-a+\tau,t,x))]d\tau} d\sigma \\ & = \int_0^a f(t-a+\sigma,\sigma,\varphi(t-a+\sigma,t,x)) e^{-\int_0^{a-\sigma} \left[\alpha_x(t-\tau',\varphi(t-\tau',t,x))+\pi(t-\tau',a-\tau',\varphi(t-\tau',t,x))\right]d\tau} d\sigma \\ & = \int_0^a f(t-\sigma',a-\sigma',\varphi(t-\sigma',t,x)) e^{-\int_0^{\sigma'} \left[\alpha_x(t-\tau',\varphi(t-\tau',t,x))+\pi(t-\tau',a-\tau',\varphi(t-\tau',t,x))\right]d\tau'} d\sigma' \\ = \ & f_I(t,a,x). \end{aligned}$$

In conclusion we obtain the first line in (29).

II. If $t > a$ and $x < \varphi(t, t-a, 0)$ we choose

$$x_0 = 0,\ t_0 = C(t, x),\ a_0 = a - t + C(t, x),\ s = t - C(t, x),$$

because by setting $x_0 = 0$ then t_0 should be necessarily determined from the equation $\varphi(t, t_0, 0) = x$, according to (23), see again Fig. 1. Then, proceeding by similar computations we get the second expression in (29).

When $t < a$, the central characteristic is $\varphi(t, 0, 0)$, as seen in Fig. 2, and we have the following two situations:

III. If $t < a$ and $x > \varphi(t, 0, 0)$ then we choose

$$t_0 = 0,\ s = t,\ a_0 = a - t,\ x_0 = \varphi(0, t, x).$$

IV. If $t < a$ and $x < \varphi(t, 0, 0)$ the choice is exactly as in the case II,

$$x_0 = 0,\ t_0 = C(t, x),\ a_0 = a - t + C(t, x),\ s = t - C(t, x).$$

In these cases performing a few changes of variables in the integrals we obtain the third and fourth lines in (29).

Finally, the explicit form (29) for $w(t, a, x)$ is the necessary form of the solution to problem (14)-(17). In turn we can check that (29) provides a solution to (14)-(17). Thus we have proved existence and uniqueness for (14)-(17) in the form (29). Actually, (29) also allows to deduce directly the estimates. Actually, since $\pi \geq 0$, we have

$$|E_+|_\infty \leq e^{-\int_{t-a}^t \alpha_x(s,\varphi(s,t,x))ds} \leq e^{\int_{t-a}^t |\alpha_x|_\infty ds} \leq e^{|\alpha_x|_\infty a^+} \leq e^{|\alpha_x|_\infty T},$$

and similarly

$$|E_-|_\infty \leq e^{T|\alpha_x|_\infty}, \quad |E|_\infty \leq e^{T|\alpha_x|_\infty}.$$

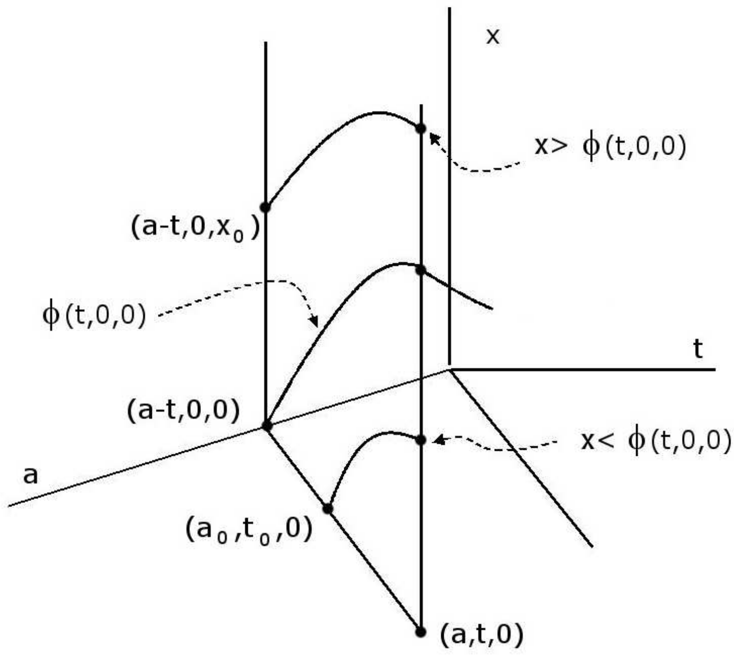

Fig. 1 Characteristics scenario for $t < a$ (cases III and IV)

Moreover,

$$\begin{aligned} |f_I(t)|_\infty &\leq e^{T|\alpha_x|_\infty} \int_0^a |f(t-\sigma')|_\infty \, d\sigma' = e^{T|\alpha_x|_\infty} \int_{t-a}^t |f(\sigma)|_\infty \, d\sigma \\ &\leq e^{T|\alpha_x|_\infty} \int_0^t |f(\sigma)|_\infty \, d\sigma \end{aligned}$$

and for $f_{II} = f_{IV}$ and f_{III} we get the same estimates. Thus,

$$|w(t)|_\infty \le e^{T|\alpha_x|_\infty} \left(\int_0^t |f(s)|_\infty \, ds + \begin{cases} |F|_\infty \text{ in case I} \\ |G|_\infty \text{ in case II or IV} \\ |w_0|_\infty \text{ in case III} \end{cases} \right)$$

which leads to (30).

In order to obtain (31) we need to differentiate with respect to x in (29) where we set $f = 0$. In the first case, when $t > a$ and $x > \varphi(t, t-a, 0)$, we get

$$w_x(t, a, x) = L_1(t, a, x) + L_2(t, a, x),$$

where

$$L_1(t, a, x) = F_x(t-a, \varphi(t-a, t, x))\varphi_x(t-a, t, x)E_+(t, a, x),$$

$$\begin{aligned} L_2(t, a, x) &= -F(t-a, \varphi(t-a, t, x))E_+(t, a, x) \\ &\quad \times \int_{t-a}^t [\alpha_{xx}(s, \varphi(s, t, x)) + \pi_x(s, a, \varphi(s, t, x))] \, \varphi_x(s, t, x) ds. \end{aligned}$$

Then, since $t > a$, we have

$$|L_1(t)|_\infty \le |F_x|_\infty \, e^{|\alpha_x|_\infty \int_{t-a}^t ds} \le |F_x| \, e^{|\alpha_x|_\infty a} \le |F_x| \, e^{|\alpha_x|_\infty T},$$

$$\begin{aligned} |L_2(t)|_\infty &\le |F|_\infty \, e^{2|\alpha_x|_\infty T} \int_{t-a}^t (|\alpha_{xx}|_\infty + |\pi_x|_\infty) ds \\ &\le T(|\alpha_{xx}|_\infty + |\pi_x|_\infty) \, |F|_\infty \, e^{2|\alpha_x|_\infty T}. \end{aligned}$$

The other cases are similar and can be evaluated using the relations (21)-(25) to obtain (31). □

We note that the explicit form (29) is also meaningful if the data satisfy weaker conditions, namely if we only assume

$$\begin{aligned} w_0 &\in C([0, a^+] \times [0, L]), \; F \in C([0, T] \times [0, L]), \; f \in C([0, T] \times [0, L]), \\ G &\in C([0, T] \times [0, a^+]), \; \pi \in C([0, T] \times [0, a^+] \times [0, L]), \end{aligned}$$

$$\pi(t, a, x) \ge 0 \text{ for any } (t, a, x) \in [0, T] \times [0, a^+] \times [0, L],$$

$$\alpha \in C([0, T]; C^1[0, L]), \; \alpha(t, 0) > 0 \text{ for any } t \in [0, T]$$

with the compatibility conditions (27).

Thus, (29) provides a generalized solution to problem (14)-(17) satisfying (30). We will refer to this kind of solution when dealing with the nonlinear problem in the next section.

3 Preliminary results: the nonlinear problem

In this section we provide the basic result that will be used to discuss the epidermis evolution theory. Namely, using the results of the previous section, we prove the existence of a solution to the following auxiliary problem, in the domains $[0, T] \times [0, a_i^+] \times [0, L]$, $i = 1, ..., 4$, with L fixed:

$$\begin{aligned} \frac{\partial p_1}{\partial t} + \frac{\partial p_1}{\partial a_1} + \frac{\partial}{\partial x}(U(t, x; p)p_1) &= -\mu_1(t, a_1, x)p_1, \qquad (35) \\ p_1(t, 0, x) &= 0, \\ p_1(t, a_1, 0) &= P_1(t, a_1), \\ p_1(0, a_1, x) &= p_{10}(a_1, x), \end{aligned}$$

$$
\begin{aligned}
\frac{\partial p_2}{\partial t}+\frac{\partial p_2}{\partial a_2}+\frac{\partial}{\partial x}(U(t,x;p)p_2) &= -\mu_2(t,a_2,x)p_2, \\
p_2(t,0,x) &= r(t,x)\int_0^{a_1^+}\beta_1(a_1)M_1(a_1)p_1(t,a_1,x)da_1, \\
p_2(t,a_2,0) &= P_2(t,a_2), \\
p_2(0,a_2,x) &= p_{20}(a_2,x),
\end{aligned} \tag{36}
$$

$$
\begin{aligned}
\frac{\partial p_3}{\partial t}+\frac{\partial p_3}{\partial a_3}+\frac{\partial}{\partial x}(U(t,x;p)p_3) &= 0, \\
p_3(t,0,x) &= \int_0^{a_2^+}\beta_2(a_2)M_2(a_2)p_2(t,a_2,x)da_2, \\
p_3(t,a_3,0) &= 0, \\
p_3(0,a_3,x) &= p_{30}(a_3,x),
\end{aligned} \tag{37}
$$

$$
\begin{aligned}
\frac{\partial p_4}{\partial t}+\frac{\partial p_4}{\partial a_4}+\frac{\partial}{\partial x}(U(t,x;p)p_4) &= 0, \\
p_4(t,0,x) &= \sum_{i=1}^{2}\int_0^{a_i^+}\mu_i(t,a_i,x)M_i(a_i)p_i(t,a_i,x)da_i \\
&\quad +(2-r(t,x))\int_0^{a_1^+}\beta_1(a_1)M_1(a_1)p_1(t,a_1,x)da_1, \\
p_4(t,a_4,0) &= 0, \\
p_4(0,a_4,x) &= p_{40}(a_4,x),
\end{aligned} \tag{38}
$$

where $p=(p_1,p_2,p_3,p_4)$ and

$$
U(t,x;p)=u_0(t)+\frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^x\int_0^{a_i^+}\widetilde{k}_i(t,a_i,\xi)p_i(t,a_i,\xi)da_i d\xi. \tag{39}
$$

We note that this system is related to (14)-(13) being obtained through the variable transformation

$$
p_i(t,a_i,x)=\frac{n_i(t,a_i,x)}{M_i(a_i)}, \tag{40}
$$

$$
\widetilde{k}_i(t,a_i,x)=k_i(t,a_i,x)M_i(a_i),
$$

where

$$
M_i(a_i)=\exp\left(-\int_0^{a_i}\beta_i(s)ds\right).
$$

Let us assume

$$
\begin{aligned}
p_{i0} &\in C([0,a_i^+];C^1[0,L]),\ P_i\in C^1([0,T]\times[0,a_i^+]),\ u_0\in C[0,T], \\
\mu_i &\in C([0,T];C([0,a_i^+];C^1[0,L])),\ r\in C^1([0,T]\times[0,L]), \\
\widetilde{k}_i &\in C([0,T];L^1(0,a_i^+;C^1[0,L])),
\end{aligned} \tag{41}
$$

and

$$
\begin{aligned}
\mu_i(t,a_i,x) &\geq 0,\ r(t,x)\in[0,2],\ u_0(t)>0, \\
\text{for any } (t,a_i,x) &\in [0,T]\times[0,a_i^+]\times[0,L].
\end{aligned} \tag{42}
$$

We make the following notations that will be used in the sequel:

$$
C_\alpha=\frac{1}{\Phi^*}\sum_{i=1}^{4}\left(\left|\widetilde{k}_i\right|_{\infty,1,\infty}+\left|\widetilde{k}_{ix}\right|_{\infty,1,\infty}\right), \tag{43}
$$

$$C_d = C^+ \left(1 + |\mu|_\infty + T\,|\mu_x|_\infty\right) \times \left\{ \sum_{i=1}^{4} \left(|p_{i0}|_\infty + |p_{i0x}|_\infty\right) + \sum_{i=1}^{2} \left(|P_i|_\infty + \left|\frac{P_i}{u_0}\right|_\infty + \left|\frac{P_{it}}{u_0}\right|_\infty + \left|\frac{P_{ia}}{u_0}\right|_\infty \right) \right\}, \tag{44}$$

where

$$a^+ = \max_{i=1,\dots,4}\{a_i\},\ r^+ = \max_{(t,x)\in[0,T]\times[0,L]} \{|r|_\infty, |r_x|_\infty\},\ \mu^+ = \max_{(t,x)\in[0,T]\times[0,L]} \{|\mu|_\infty, |\mu_x|_\infty\}, \tag{45}$$

$$C^+ = 4(1+a^+)(1+r^+)^3(1+\mu^+ a^+), \tag{46}$$

and $p_{i0x} = \frac{\partial p_{i0}}{\partial x}$, $P_{it} = \frac{\partial P_i}{\partial t}$, $P_{ia} = \frac{\partial P_i}{\partial a_i}$, $i = 1, \dots, 4$. We have

Theorem 3.1. *Let $R_1 > 0$, $R_2 > 0$ be fixed and assume that C_d, C_α and T are such that the following inequalities*

$$\begin{aligned} C_d e^{3TC_\alpha R_1} &\le R_1, \\ R_1(1 + C_\alpha R_1 + TC_\alpha(R_1+R_2)) &\le R_2 \end{aligned} \tag{47}$$

hold. Then, system (35)-(38) *under the hypotheses* (41)-(42) *has a unique solution*

$$p_i \in C([0,T]\times[0,a_i^+]\times[0,L]). \tag{48}$$

Proof. We consider the spaces

$$Y = \prod_{i=1}^{4} C([0,a_i^+]\times[0,L]),\ X = C([0,T];Y),$$

respectively endowed with the norms

$$\begin{aligned} \|h\|_Y &= \sum_{i=1}^{4} |h_i|_\infty,\ h = (h_1,\dots,h_4)\in Y, \\ \|z\|_X &= \sup_{t\in[0,T]} \|z(t)\|_Y,\ \text{for } z\in X. \end{aligned}$$

We define the subsets of X,

$$\begin{aligned} M_0 = &\left\{ z = (z_1,z_2,z_3,z_4)\in X;\ z_i \in C([0,T];C([0,a_i^+];C^1[0,L])),\right. \\ &\left. |z_i|_\infty \le R_1,\ z_i(t,a_i,0) = P_i(t,a_i),\ |z_{ix}|_\infty \le R_2 \right\} \end{aligned}$$

and

$$\begin{aligned} M = &\{ z = (z_1,z_2,z_3,z_4)\in X;\ z_i \in C([0,T];C([0,a_i^+];W^{1,\infty}(0,L))), \\ &|z_i|_\infty \le R_1,\ z_i(t,a_i,0) = P_i(t,a_i),\ |z_{ix}|_{L^\infty} \le R_2 \}. \end{aligned}$$

We note that M is closed and $M = \overline{M_0}$.

Let $z\in X$ and fix $p = z$ in the expression of $U(t,x;p)$ in (35)-(38), getting

$$\alpha(t,x) := U(t,x;z) = u_0(t) + \frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^x \int_0^{a_i^+} \widetilde{k}_i(t,a_i,\xi) z_i(t,a_i,\xi)\, da_i d\xi. \tag{49}$$

We note that $\alpha(t,0) = u_0(t)$.

We obtain the following problem with the solution denoted $Z_i(t)$,

$$\begin{aligned} \frac{\partial Z_1}{\partial t} + \frac{\partial Z_1}{\partial a_1} + \frac{\partial}{\partial x}(U(t,x;z)Z_1) &= -\mu_1(t,a_1,x)Z_1, \\ Z_1(t,0,x) &= 0, \\ Z_1(t,a_1,0) &= P_1(a_1,t), \\ Z_1(0,a_1,x) &= p_{10}(a_1,x), \end{aligned} \tag{50}$$

$$\begin{aligned} \frac{\partial Z_2}{\partial t}+\frac{\partial Z_2}{\partial a_2}+\frac{\partial}{\partial x}(U(t,x;z)Z_2) &= -\mu_2(t,a_2,x)Z_2, \\ Z_2(t,0,x) &= r(t,x)\int_0^{a_1^+}\beta_1(a_1)M_1(a_1)Z_1(t,a_1,x)da_1, \\ Z_2(t,a_2,0) &= P_2(t,a_2), \\ Z_2(0,a_2,x) &= p_{20}(a_2,x), \end{aligned} \tag{51}$$

$$\begin{aligned} \frac{\partial Z_3}{\partial t}+\frac{\partial Z_3}{\partial a_3}+\frac{\partial}{\partial x}(U(t,x;z))Z_3) &= 0, \\ Z_3(t,0,x) &= \int_0^{a_2^+}\beta_2(a_2)M_2(a_2)Z_2(t,a_2,x)da_2, \\ Z_3(t,a_3,0) &= 0, \\ Z_3(0,a_3,x) &= p_{30}(a_3,x), \end{aligned} \tag{52}$$

$$\begin{aligned} &\frac{\partial Z_4}{\partial t}+\frac{\partial Z_4}{\partial a_4}+\frac{\partial}{\partial x}(U(t,x;z)Z_4) = 0, \\ &Z_4(t,0,x) = \sum_{i=1}^{2}\int_0^{a_i^+}\mu_i(a_i,x)M_i(a_i)Z_i(t,a_i,x)da_i \\ &\qquad + (2-r(t,x))\int_0^{a_1^+}\beta_1(a_1)M_1(a_1)Z_1(t,a_1,x)da_1, \\ &Z_4(t,a_4,0) = 0, \\ &Z_4(0,a_4,x) = p_{40}(a_4,x). \end{aligned} \tag{53}$$

Since $U(t,x;z)$ is continuous in $[0,T]\times[0,L]$ and continuously differentiable with respect to x, we can apply Proposition 2.3 to produce a solution to (50)-(53), allowing us to define the mapping

$$\Psi : X \to X,\ \ \Psi(z) = Z.$$

Indeed, according to Proposition 2.3, problem (50) with

$$p_0 = p_{10},\ F = 0,\ G = P_1,\ f = 0,\ \pi = \mu_1$$

has a unique solution Z_1 given by (29). By (30) we have

$$|Z_1|_\infty \le e^{T|\alpha_x|_\infty}\left(|p_{10}|_\infty + |P_1|_\infty\right).$$

Stepping forward, problem (51) is (14)-(17) in which

$$p_0 = p_{20},\ G = P_2,\ f = 0,\ \pi = \mu_2$$

and

$$F(t,x) = r(t,x)\int_0^{a_1^+}\beta_1(a_1)M_1(a_1)Z_1(t,a_1,x)da_1. \tag{54}$$

Of course, F is known on the basis of the previously determined function Z_1. This problem has a solution satisfying

$$\begin{aligned} |Z_2|_\infty &\le e^{T|\alpha_x|_\infty}\left(|p_{20}|_\infty + r^+|Z_1|_\infty + |P_2|_\infty\right) \\ &\le e^{2T|\alpha_x|_\infty}(1+r^+)\sum_{i=1}^{2}(|p_{i0}|_\infty + |P_i|_\infty). \end{aligned}$$

Finally, the subsequent two systems are still (14)-(17) in which

$$p_0 = p_{i0},\ G = 0,\ f = 0,\ \pi = \mu_3$$

$$F(t,x) = \int_0^{a_2^+} \beta_2(a_2)M_2(a_2)Z_2(t,a_2,x)da_2,$$

and respectively, $\pi = \mu_4$,

$$\begin{aligned} F(t,x) &= \sum_{i=1}^{2} \int_0^{a_i^+} \mu_i(a_i,x)M_i(a_i)Z_i(t,a_i,x)da_i \\ &\quad +(2-r(t,x)) \int_0^{a_1^+} \beta_1(a_1)M_1(a_1)Z_1(t,a_1,x)da_1. \end{aligned}$$

In both cases F is again known because Z_1 and Z_2 have been previously determined. We have

$$\begin{aligned} |Z_3|_\infty &\leq e^{T|\alpha_x|_\infty} \left(|p_{30}|_\infty + r^+ |Z_2|_\infty\right) \\ &\leq e^{3T|\alpha_x|_\infty}(1+r^+)^2 \left(\sum_{i=1}^{3} |p_{i0}|_\infty + \sum_{i=1}^{2} |P_i|_\infty \right), \end{aligned}$$

$$|Z_4|_\infty \leq e^{T|\alpha_x|_\infty} \left(|p_{40}|_\infty + a^+\mu^+ \sum_{i=1}^{2} |Z_i|_\infty + 2\,|Z_1|_\infty \right),$$

whence we can write

$$|Z_i|_\infty \leq e^{3T|\alpha_x|_\infty} C^+ \left(\sum_{j=1}^{4} |p_{j0}|_\infty + \sum_{j=1}^{2} |P_j|_\infty \right), \tag{55}$$

for any $i = 1, ..., 4$.

Once we have defined the mapping $\Psi : X \to X$ we show that

$$\Psi : X \to X \text{ is continuous,} \tag{56}$$

$$\Psi(M_0) \subset M_0, \tag{57}$$

$$\|\Psi(z(t)) - \Psi(\overline{z}(t))\|_Y \leq C \int_0^t \|z(s) - \overline{z}(s)\|_Y \, ds, \ \forall z, \overline{z} \in M_0, \tag{58}$$

with C a constant that will be specified.

The property (56) is a consequence of the continuity of the characteristics (18) with respect to $\alpha(t,x)$. Namely, if

$$z_n \in X, \ z_n \to z \text{ strongly in } X, \text{ as } n \to \infty$$

then

$$U(t,x;z_n) \to U(t,x;z) \text{ strongly in } C([0,T]\times[0,L]), \text{ as } n \to \infty.$$

Denoting $\varphi_n(t,\sigma,x)$ the characteristics relative to $\alpha_n(t,x) = U(t,x;z_n)$ we have

$$\varphi_n(t,\sigma,x) \to \varphi(t,\sigma,x) \text{ as } n \to \infty.$$

This convergence plugged into the solution to (50)-(53), according to (29), shows that

$$\Psi(z_n) \to \Psi(z) \text{ strongly in } X, \text{ as } n \to \infty.$$

In order to prove (57) we note that if z_i is continuously differentiable with respect to x (as it is if $z \in M_0$), then

$$\alpha(t,x) = U(t,x;z) \in C([0,T];C^2[0,L])$$

and we have that $Z_1 \in C^1([0,T];C([0,a_1^+];C^1[0,L]))$, by Proposition 2.3. Therefore, when considering problem (51) the term (54) also belongs to $C^1([0,T];C^1[0,L])$ and we have $Z_2 \in C^1([0,T];C([0,a_1^+];C^1[0,L]))$. Going farther we get the same regularity for Z_3 and Z_4.

Finally, following the computations of $|Z_{ix}|_\infty$ in each equation (50)-(53), on the basis of the estimate (31), we get after some algebra

$$|Z_{ix}(t)|_\infty \le e^{2T|\alpha_x|_\infty} (1 + |\mu|_\infty + T|\mu_x|_\infty + |\alpha_x|_\infty + T|\alpha_{xx}|_\infty) \times \left\{ \sum_{i=1}^{4} (|p_{i0}|_\infty + |p_{i0x}|_\infty) + \sum_{i=1}^{2} \left(|P_i|_\infty + \left|\frac{P_i}{u_0}\right|_\infty + \left|\frac{P_{it}}{u_0}\right|_\infty + \left|\frac{P_{ia}}{u_0}\right|_\infty \right) \right\},$$

for any $t \in [0, T]$. Thus, by the notations (45)-(44) we have

$$|Z_i|_\infty \le C_d e^{3T|\alpha_x|_\infty}, \tag{59}$$

$$|Z_{ix}|_\infty \le C_d(1 + |\alpha_x|_\infty + T|\alpha_{xx}|_\infty) e^{2T|\alpha_x|_\infty}. \tag{60}$$

On the other hand, since $z \in M_0$, we have $|z_i|_\infty \le R_1$ and $|z_{ix}|_\infty \le R_2$ and we can evaluate α_x and α_{xx}. In fact

$$|\alpha_x(t, x)| \le \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^{a_i^+} \left|\widetilde{k}_i(t, a_i, x)\right| |z_i(t, a_i, x)|\, da_i$$

$$\le \frac{1}{\Phi^*} \sum_{i=1}^{4} \left|\widetilde{k}_i(t, \cdot, x)\right|_1 |z_i(t, \cdot, x)|_\infty \le \frac{1}{\Phi^*} \sum_{i=1}^{4} \left|\widetilde{k}_i\right|_{\infty,1,\infty} |z_i|_\infty \le C_\alpha R_1,$$

for any $(t, x) \in [0, T] \times [0, L]$, hence

$$|\alpha_x|_\infty \le C_\alpha R_1. \tag{61}$$

We also have

$$\begin{aligned}
|\alpha_{xx}(t, x)|_\infty &\le \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^{a_i^+} \left|\widetilde{k}_{ix}(t, a_i, x)\right| |z_i(t, a_i, x)|\, da_i \\
&\quad + \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^{a_i^+} \left|\widetilde{k}_i(t, a_i, x)\right| |z_{ix}(t, a_i, x)|\, da_i \\
&\le \frac{1}{\Phi^*} \sum_{i=1}^{4} \left(\left|\widetilde{k}_{ix}(t, \cdot, x)\right|_1 |z_i|_\infty + \left|\widetilde{k}_i(t, \cdot, x)\right|_1 |z_{ix}|_\infty \right) \\
&\le \frac{1}{\Phi^*} \sum_{i=1}^{4} \left(\left|\widetilde{k}_{ix}\right|_{\infty,1,\infty} |z_i|_\infty + \left|\widetilde{k}_i\right|_{\infty,1,\infty} |z_{ix}|_\infty \right) \\
&\le C_\alpha (|z_i|_\infty + |z_{ix}|_\infty), \text{ for } (t, x) \in [0, T] \times [0, L],
\end{aligned}$$

hence

$$|\alpha_{xx}|_\infty \le C_\alpha(R_1 + R_2). \tag{62}$$

By (59), (60), (61), (62) and (47) we finally have

$$|Z_i|_\infty \le C_d e^{3TC_\alpha R_1} \le R_1, \tag{63}$$

$$\begin{aligned}
|Z_{ix}|_\infty &\le C_d e^{2TC_\alpha R_1}(1 + C_\alpha R_1 + TC_\alpha(R_1 + R_2)) \\
&\le C_d e^{3TC_\alpha R_1}(1 + C_\alpha R_1 + TC_\alpha(R_1 + R_2) \\
&\le R_1(1 + C_\alpha R_1 + TC_\alpha(R_1 + R_2) \le R_2,
\end{aligned} \tag{64}$$

hence $Z = (Z_1, Z_2, Z_3, Z_4) \in M_0$ and we have got (ii).

To prove (58), let $z, \overline{z} \in M_0$ and $Z = \Psi(z)$, $\overline{Z} = \Psi(\overline{z})$ be the corresponding solutions to (50)-(53). Denoting $W = Z - \overline{Z}$ and $w = z - \overline{z}$, we get the system

$$\begin{aligned}
W_{it} + W_{ia} + \pi_i W_i + U(t, x; z)W_{ix} + U_x(t, x; z)W_i &= f_i(t, a, x), \\
W_i(t, 0, x) &= F_i(t, x) - \overline{F_i}(t, x), \\
W_i(t, a, 0) &= 0, \\
W_i(0, a, x) &= 0,
\end{aligned} \tag{65}$$

where

$$f_i(t,a_i,x) = -\left\{U(t,x;w)\overline{Z_{ix}} + U_x(t,x;w)\overline{Z_i}\right\},\ i=1,...,4. \quad (66)$$

Then using estimate (30) we get for $i = 1$,

$$|W_1(t)|_\infty \le e^{T|\alpha_x|_\infty} \int_0^t |f_1(s)|_\infty \, ds.$$

Using this estimate we obtain for $i = 2$,

$$\begin{aligned} & |W_2(t)|_\infty \\ \le \quad & e^{T|\alpha_x|_\infty}\left(r^+ \int_0^{a_1^+} \beta_1(a_1)M_1(a_1)\,|W_1(t)|_\infty\, da_1 + \int_0^t |f_2(s)|_\infty\, ds\right) \\ \le \quad & (1+r^+)e^{2T|\alpha_x|_\infty} \sum_{i=1}^{2} \int_0^t |f_i(s)|_\infty\, ds. \end{aligned}$$

Proceeding further we finally get for any $i = 1,...,4$,

$$|W_i(t)|_\infty \le C^+ e^{4T|\alpha_x|_\infty} \sum_{j=1}^{i} \int_0^t |f_j(s)|_\infty\, ds. \quad (67)$$

Then, taking into account (49) and (43), we have

$$\begin{aligned} |U(t,x;w)| &\le \frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^x \int_0^{a_i^+} \left|\widetilde{k}_i(t,a_i,\xi)\right| |w_i(t,a_i,\xi)|\, da_i d\xi \\ \le \quad & \frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^L \left|\widetilde{k}_i(t,\cdot,\xi)\right|_1 |w_i(t)|_\infty\, d\xi \\ \le \quad & \|w(t)\|_Y \frac{L}{\Phi^*}\sum_{i=1}^{4}\left|\widetilde{k}_i\right|_{\infty,1,\infty} \le LC_\alpha \|w(t)\|_Y\,, \end{aligned} \quad (68)$$

and

$$\begin{aligned} |U_x(t,x;w)| &= \frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^{a_i^+} \left|\widetilde{k}_i(t,a_i,x)\right| |w_i(t,a_i,x)|\, da_i \\ \le \quad & \frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^{a_i^+} \left|\widetilde{k}_i(t,\cdot,x)\right|_1 |w_i(t)|_\infty\, da_i \le C_\alpha \|w(t)\|_Y\,. \end{aligned} \quad (69)$$

Concerning the norms of f_i we write

$$\begin{aligned} & |f_i(t,a,x)| \le |U(t,x;w)|\left|\overline{Z_{ix}}\right| + |U_x(t,x;w)|\left|\overline{Z_i}\right| \\ \le \quad & C_\alpha(L\left|\overline{Z_{ix}}\right|_\infty + \left|\overline{Z_i}\right|_\infty)\,\|w(t)\|_Y\,. \end{aligned} \quad (70)$$

Thus, by (67), (63) and (64) it follows that

$$\begin{aligned} |W_i(t)|_\infty &\le C_\alpha C^+ e^{4T|\alpha_x|_\infty}\sum_{j=1}^{i}\int_0^t \left(L\left|\overline{Z_{ix}}\right|_\infty + \left|\overline{Z_i}\right|_\infty\right)\|w(s)\|_Y\, ds \quad (71) \\ \le \quad & 4C_\alpha C^+ e^{4TC_\alpha R_1}(LR_2 + R_1)\int_0^t \|w(s)\|_Y\, ds. \end{aligned}$$

Therefore, we obtain (58), i.e.,

$$\|\Psi(z(t)) - \Psi(\overline{z}(t))\|_Y \le C(R_1,R_2)\int_0^t \|z(s) - \overline{z}(s)\|_Y\, ds, \quad (72)$$

where

$$C(R_1, R_2) = 16C_\alpha C^+ e^{4C_\alpha R_1}(R_1 + LR_2).$$

Once (56)-(58) are established we proceed to prove the existence of a fixed point of Ψ. Actually we change to norm in X by defining the equivalent norm $\|\cdot\|_{X_B}$ by

$$\|v\|_{X_B} = \sup_{t\in[0,T]} \left\{ e^{-\eta t} \|v(t)\|_Y \right\}, \ \forall v \in X.$$

Then, for $z, \overline{z} \in M_0$, by (72), we get

$$e^{-\eta t} \|\Psi(z(t)) - \Psi(\overline{z}(t))\|_Y \leq C(R_1, R_2)e^{-\eta t} \int_0^t e^{\eta s} \|z - \overline{z}\|_{X_B} ds \tag{73}$$

$$\leq \ C(R_1, R_2)\frac{1 - e^{-\eta t}}{\eta} \|z - \overline{z}\|_{X_B}$$

and so

$$\|\Psi(z) - \Psi(\overline{z})\|_{X_B} \leq \rho \|z - \overline{z}\|_{X_B}, \ \text{for } z, \overline{z} \in M_0,$$

with $\rho = \frac{C(R_1,R_2)}{\eta} < 1$ for η chosen sufficiently large.

By continuity and (57) it follows that

$$\Psi(M) \subset M$$

and

$$\|\Psi(z) - \Psi(\overline{z})\|_{X_B} \leq \rho \|z - \overline{z}\|_{X_B}, \ \forall z, \overline{z} \in M.$$

In conclusion, we have proved that Ψ is a contraction on M and so its fixed point is the unique solution to (50)-(53). □

4 Back to the problem of epidermis evolution

We now go back to the original problem (9)-(13) to discuss how the model may represent epidermis evolution.

The model parameters described in Introduction reflect the intrinsic structure of the epidermis. In particular, the cohesion functions $\gamma_i(a_i)$ are constitutive parameters of the cohesivity $\Gamma(t, x)$ defined in (3). Moreover, the average volume of cells is given by $v_i(a_i)$, $i = 1, ..., 4$ and these volumes enter the total volume fraction $\Phi(t, x)$ which is taken constant according to (2).

The distributions $N_i(t, a_i)$ $i = 1, 2$, are data of the model, accounting for the boundary condition at $x = 0$, i.e., at the upper boundary of the basal layer. At this boundary the cells leave the layer with the velocity $u_0(t)$ which is another datum of the problem. In the standard case in which cell production at the basal layer is not externally influenced, N_i and u_0 can be independent of t.

The value of the cell volume fraction Φ^*, is also a parameter of the model and the condition

$$\sum_{i=1}^{2} \int_0^{a_i^+} v_i(a_i)N_i(t, a_i)da_i = \Phi^* \tag{74}$$

must be fulfilled.

At time $t = 0$ we consider an initial distribution of cells, concentrated in a space interval $[0, \Lambda_0]$, i.e., $n_{i0}(a_i, x)$, $a_i \in [0, a_i^+]$, $x \in [0, \Lambda_0]$, assuming that the volume fraction condition is satisfied

$$\sum_{i=1}^{4} \int_0^{a_i^+} v_i(a_i)n_{i0}(a_i, x)da_i = \Phi^*, \ x \in [0, \Lambda_0]. \tag{75}$$

Moreover, we assume that the initial cell distribution is such that

$$\Gamma(0, x) = \sum_{i=1}^{3} \int_0^{a_i^+} \gamma_i(a_i)n_{i0}(a_i, x)da_i \geq \Gamma^*, \ x \in [0, \Lambda_0], \tag{76}$$

with $\Gamma(0,0) > \Gamma^*$, i.e., we suppose that the cohesion condition is satisfied by the initial datum. We consider all data and parameters of the problem as defined for $t \in [0,\infty)$ and $x \in [0,\infty)$, though we expect to have a solutions on finite intervals.

Proposition 4.1. *Assume that*

$$\begin{aligned} n_{i0} &\in C([0,a_i^+];C^1[0,\Lambda_0]),\ \frac{n_{i0}}{M_i} \in C([0,a_i^+];C^1[0,\Lambda_0]), \\ N_i &\in C^1([0,\infty)\times[0,a_i^+]),\ u_0 \in C([0,\infty)),\ u_0(t) > 0, \\ \mu_i &\in C([0,\infty);C([0,a^+];C^1[0,\infty))),\ \mu_i(t,a_i,x) \geq 0 \\ r &\in C^1([0,\infty)\times[0,\infty)),\ r(t,x) \in [0,2], \\ k_i &\in C([0,\infty);L^1(0,a_i^+;C^1[0,\infty))), \end{aligned}$$

with the proper compatibility conditions corresponding to (27)-(28).

Then problem (9)-(13) *has a unique solution, local in time,* $n_i \in C([0,T_{\max}]\times[0,a_i^+]\times[0,\Lambda(t)])$*, where the free boundary* $\Lambda(t)$ *is defined by*

$$\Lambda(t) = \sup\left\{x \in [0,\widetilde{\Lambda}(t)];\ \Gamma(t,x) > \Gamma^*\right\} \tag{77}$$

and $\widetilde{\Lambda}(t)$ *is the solution to*

$$\widetilde{\Lambda}'(t) = u(t,\widetilde{\Lambda}(t)),\ \widetilde{\Lambda}(0) = \Lambda_0. \tag{78}$$

Proof. In order to apply Theorem 3.1, we fix $L > \Lambda_0$. We set p_{i0} as the C^1-extension of the function $\frac{n_{i0}(a_i,x)}{M_i(a_i)}$, defined for $x \in [0,\Lambda_0]$, to the whole interval $[0,L]$ and $P_i(t,a_i) = \frac{N_i(t,a_i)}{M_i(a_i)}$.

For such an initial distribution, the constants C_d and C_α (recall (43) and (44)) are determined and we can choose R_1 and R_2 such that

$$R_1 > C_d,\ R_2 > C_d(1 + C_\alpha C_d). \tag{79}$$

Then, (47) if fulfilled for T small.

Consequently, problem (35)-(39) has a unique solution $p_i \in C([0,T];C([0,a_i^+];C^1[0,L])$ satisfying

$$|p_i|_\infty \leq R_1,\ \ |p_{ix}|_\infty \leq R_2. \tag{80}$$

The solution we have found provides the velocity $U(t,x;p)$ and the set of characteristic curves $\varphi(t,\sigma,x)$ satisfying

$$\begin{aligned} \varphi_t &= U(t,\varphi;p), \\ \varphi(\sigma,\sigma,x) &= x. \end{aligned}$$

Let us consider the spatial characteristic originating at $x = \Lambda_0$, i.e., $\widetilde{\Lambda}(t) = \varphi(t,0,\Lambda_0)$., and define

$$T_{\max} = \sup\left\{t \in [0,T] : \tilde{\Lambda}(t) < L\right\}.$$

The other characteristics $\varphi(t,0,x)$ with $x > \Lambda_0$ are not related to the physical data n_{i0}, but only to its mathematical extension, so that we are only interested in the solution $p_i(t,a_i,x)$ for $a_i \in [0,a_i^+]$, and $(t,x) \in \Omega$, where

$$\Omega = \{(t,x); t \in [0,T_{\max}], x \in [0,\widetilde{\Lambda}(t)]\}.$$

Setting

$$n_i(t,a_i,x) = M_i(a_i)p_i(t,a_i,x)$$

we get a solution to (9)-(13) in the space domain $[0,\widetilde{\Lambda}(t)]$.

We are left with determining the physical moving boundary $\Lambda(t)$ satisfying (7) or (8). Now, the function $\Gamma(t,x)$ is well defined in Ω and we can identify the boundary $\Lambda(t)$ as

$$\Lambda(t) = \sup\left\{x \in [0,\widetilde{\Lambda}(t)];\ \Gamma(t,x) > \Gamma^*\right\},$$

as claimed. □

Remark. We observe that $0 < \Lambda(t) \leq \widetilde{\Lambda}(t)$ and note that

$$\Phi(t,x) = \Phi^*$$

in the domain $\{(t,x);\ t \in [0,T_{\max}],\ x \in [0,\Lambda(t)]\}$. This property is guaranteed by the form of the constitutive equation for $u(t,x)$, whenever (74),(75) are satisfied (see [9]).

As an example of boundary evolution we can choose Λ_0 and the initial distribution n_{i0} such that

$$\Gamma(0,x) = \sum_{i=1}^{3} \int_0^{a_i^+} \gamma_i(a_i) n_{i0}(a_i,x) da_i > \Gamma^*,\ x \in [0,\Lambda_0],$$

setting all the parameters to be time invariant. Then, equation (78) provides a solution $\widetilde{\Lambda}(t)$ having the same property

$$\Gamma(t,\widetilde{\Lambda}(t)) > \Gamma^*$$

at least for t in a small interval $[0,t^*]$, with

$$t^* = \inf\{t; \Gamma(t,\widetilde{\Lambda}(t)) \leq \Gamma^*\}.$$

Then, by (8) we have

$$\Lambda(t) = \widetilde{\Lambda}(t) \text{ for } t \in [0,t^*]$$

and the boundary $\Lambda(t)$ moves.

If $\Gamma(t,\widetilde{\Lambda}(t)) \leq \Gamma^*$ then the boundary Λ is defined by

$$\Gamma(t,\Lambda(t)) = \Gamma^*.$$

Thus, the boundary $\Lambda(t)$ is different from $\widetilde{\Lambda}(t)$ and proceeds at a speed

$$\Lambda'(t) < u(t,\Lambda(t)),$$

according to (7).

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