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AN AGE-STRUCTURED MODEL OF EPIDERMIS GROWTH

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Abstract We propose a model with age and space structure for the evolution of the supra-basal epidermis. The model includes different types of cells: proliferating cells, differentiated cells, corneous cells, and apoptotic cells. We assume that all cells move with the same velocity and that the local volume fraction, occupied by the cells is constant in space and time. This hypothesis, based on experimental evidence, allows us to determine a constitutive equation for the cell velocity. We focus on the stationary case of the problem, that takes the form of a quasi-linear evolution problem of first order, and we investigate conditions under which there is a solution.

Keywords Nonlinear PDE · Population theory · Age structure · Cell populations · Stratified epithelium

Mathematics Subject Classification (2000) 92B05 · 92C17 · 92C37 · 35F61

1 Introduction

At the surface of the body, the epidermis (the outermost part of the skin) provides a barrier that prevents the penetration of microbes and retains the body fluids. The epidermis is formed by a multilayer arrangement of epithelial cells (keratinocytes) that undergo a continuous renewal process. Proliferative cells in the innermost layer (basal cell layer) detach from the underlying basement membrane, stop proliferating and move

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outward forming the suprabasal layers [21, 29, 10] (see Fig. 1). Suprabasal cells undergo a progressive maturation, called keratinization, during which the fibrous protein keratin accumulates in the cells. At the end of this process, cells filled of keratin die, and the dead cells (corneocytes) form the stratum corneum [13]. The deepest cells of stratum corneum retain their bonds but, when they are slowly pushed to the surface by newly forming cells, the corneous cells gradually lose their bonds and are eventually shed from the surface, through a process named desquamation.

The proliferative activity in the basal layer of epidermis has been extensively studied by means of computational models and comparison with experimental labelling data [16, 22, 17]. A comprehensive agent-based computational model for the simulation of cell proliferation, cell migration and multi-layer formation in epithelia was developed in [25]. Simulation models for the particular cellular and spatial organization of intestinal crypts have been presented in [20, 19]. More recently, a multi-scale modelling approach for the study of crypts dynamics has been proposed in [26].

After the pioneering study of the age structure in a stratified epithelium proposed in [3], an age-structured mathematical model of the hierarchical cell population of epidermis was presented in [24]. This model considers the steady-state of the subpopulations of stem cells, transiently proliferating cells, and post-mitotic cells committed to terminal differentiation, but disregards their spatial organization. An age-structured model has also been introduced to describe the cell populations in the epithelial crypts of the colon and their homeostasis [14]. In the general field of population dynamics, since the papers by Gurtin [11] and Gurtin and MacCamy [12], a number of investigations have been devoted to propose and study models with age and spatial structure (see [28] for a recent survey). Here we mention only some models developed to describe the diffusion of populations in a multilayer environment [7], and the growth of cell populations in tumours [4, 27, 8, 9].

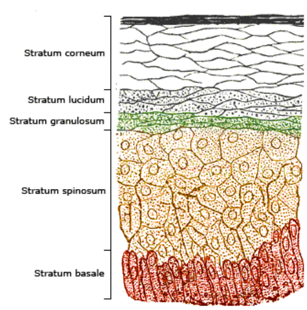

Fig. 1 Diagram of the cell layers of epidermis. http://en.wikipedia.org/wiki/File:Skinlayers.png

In the present work, we propose a model with age and space structure for the evolution of the suprabasal epidermis. The age structure of the model is motivated by the need of representing the following three phenomena: (1) the variability of the duration of the cell cycle of proliferating cells; (2) the maturation process of non-proliferating, differentiated cells that leads to their transformation into corneous cells; (3) the progressive loss of bonds among the corneous cells that leads to their ultimate shedding. Although the cell activity in the basal cell layer is of fundamental importance for the homeostasis of the epidermis, a precise description of the basal cell population is beyond the scope of this work. As we shall see, the basal layer activity will be simply summarized by a boundary condition in our model.

Concerning the analysis of the model, we will focus on the stationary problem as a first step in the analysis that will be further developed, in a future work, with the study of the dynamical case. Actually, the stationary problem is a model in itself and has an interest of its own, since it possibly describes the spatial organization of the normal, unperturbed epidermis, or the new state that might be reached in the response to a long-lasting and time-invariant external injuring action. On the other hand the mathematical techniques that we set up to study the stationary problem are somewhat preliminary to the study of the dynamical case.

The paper has the following structure: the mathematical model is presented in Sect. 2, and the stationary-state problem, related to the normal state of epidermis or to long lasting time-invariant pathological states, is formulated in Sect. 3. The proof of existence and uniqueness of a stationary solution begins in Sect. 4 through the proof of a preliminary result and is completed in Sect. 5 for the case of assigned outer boundary of the spatial domain. A discussion of the determination of this boundary at the stationary state is given in Sect. 6.

2 The mathematical model

As previously mentioned, we shall study the growth of the epidermis, focusing on the description of the suprabasal region. We assume a planar idealized geometry, so that the Cartesian coordinate x, perpendicular to the epidermis plane, is the only spatial variable. We denote the time by $t \in (0, T)$. The variable x will range from $x = 0$, the interface with the basal cell layer, to $x = \Lambda(t)$, 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.

In normal skin cell proliferation occurs almost exclusively in the basal layer (see [29], [17]) where stem cells generate transiently proliferating cells that after few (4-5) rounds of proliferation cease to divide, thus producing non-proliferating (quiescent), differentiated cells. In pathological situations, however, the proliferation extends also to the suprabasal layers, [18]. In order to account for (moderate) hyper-proliferative disorders we will assume 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, and we assume that the final transition to the corneous state occurs at a rate dependent on this age.

The model will include different classes of cells: proliferating cells, differentiated cells, corneous cells, and apoptotic cells. These classes will be respectively indexed by $i = 1, \ldots, 4$. The last class, apoptotic cells, includes all the dead cells produced by pathological mitosis of proliferating cells, as well as by the death of proliferating and differentiated cells due to external causes.

Adopting a continuous approach to describe these cell subpopulations, we denote by $n_i(a_i, x, t)$ the density with respect to 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, $n_i(a_i, x, t)da_i dx$ gives the number of cells with age between a_i and $a_i + da_i$ in a cylinder of unit base and height from x and $x + dx$.

All cells at a given position are assumed to move with the same velocity, and $u(x, t)$ denotes the velocity field, positive in the outward direction. Moreover, we assume that the local volume fraction (i.e. the ratio between the volume of all cells in an elementary reference region around a given position and the volume of that region, see Eq. (7) below) is constant in space and time. As we will see, thanks to our one-dimensional geometry, this hypothesis will enable us to determine the cell velocity (see for instance [2]). This assumption appears quite adequate for the viable layers [15] as well as for most of the stratum corneum in the case of normal epidermis [1], since cells are closely packed there, with a very small extracellular space. In the presence of external damaging agents, when it cannot be excluded that variations of the extracellular space may occur, the above assumption must be considered as a simplifying approximation. In [4], [8], [27], the cell velocity field was derived in a similar way by assuming that the number of cells per unit volume is constant, which is equivalent to assuming, when all cell classes have the same volume, that cells have constant local volume fraction. In our case, however, different cell types have significantly different cell volumes, thus it is necessary to explicitly consider the local volume fraction occupied by the cells. Without such phenomenological hypothesis, determining the constitutive equation for the velocity field, would require a complete mechanical model describing the forces involved in the interactions among individual cells and between the cells and the extracellular matrix (see [2], [6]). This would lead to far more complex models relying on additional assumptions and parameters.

According to the above assumptions, we can write the following system of balance equations, one for each cell subpopulation, in the domains $(0, a_i^+) \times (0, \Lambda(t)) \times (0, T)$, $i = 1, ..., 4$, with their respective boundary and initial conditions:

$$\begin{aligned}
&\frac{\partial n_1}{\partial t} + \frac{\partial n_1}{\partial a_1} + \frac{\partial}{\partial x}(un_1) = -\beta_1(a_1)n_1 - \mu_1(a_1, x, t)n_1, \\
&n_1(0, x, t) = 0, \\
&u(0, t)n_1(a_1, 0, t) = S_1(a_1, t), \\
&n_1(a_1, x, 0) = n_{10}(a_1, x),
\end{aligned} \tag{1}$$

$$\begin{aligned}
&\frac{\partial n_2}{\partial t} + \frac{\partial n_2}{\partial a_2} + \frac{\partial}{\partial x}(un_2) = -\beta_2(a_2)n_2 - \mu_2(a_2, x, t)n_2, \\
&n_2(0, x, t) = r(x, t) \int_0^{a_1^+} \beta_1(a_1)n_1(a_1, x, t)da_1, \\
&u(0, t)n_2(a_2, 0, t) = S_2(a_2, t), \\
&n_2(a_2, x, 0) = n_{20}(a_2, x),
\end{aligned} \tag{2}$$

$$\begin{aligned}
&\frac{\partial n_3}{\partial t} + \frac{\partial n_3}{\partial a_3} + \frac{\partial}{\partial x}(un_3) = -\beta_3(a_3)n_3, \\
&n_3(0, x, t) = \int_0^{a_2^+} \beta_2(a_2)n_2(a_2, x, t)da_2, \\
&u(0, t)n_3(a_3, 0, t) = 0, \\
&n_3(a_3, x, 0) = n_{30}(a_3, x),
\end{aligned} \tag{3}$$

$$\begin{aligned}
&\frac{\partial n_4}{\partial t} + \frac{\partial n_4}{\partial a_4} + \frac{\partial}{\partial x}(un_4) = -\beta_4(a_4)n_4, \\
&n_4(0, x, t) = \sum_{i=1}^{2} \int_0^{a_i^+} \mu_i(a_i, x, t)n_i(a_i, x, t)da_i \\
&\qquad\qquad + (2 - r(x, t)) \int_0^{a_1^+} \beta_1(a_1)n_1(a_1, x, t)da_1, \\
&u(0, t)n_4(a_4, 0, t) = 0, \\
&n_4(a_4, x, 0) = n_{40}(a_4, x).
\end{aligned} \tag{4}$$

In the above equations, $\beta_1(a_1)$ denotes the rate of division of proliferating cells, $\beta_2(a_2)$ is the rate of transition of differentiated cells to the corneous state, $\beta_3(a_3)$ represents the rate of a possible degradation of corneocytes, $\beta_4(a_4)$ the rate of degradation of apoptotic cells to a liquid waste. 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, each age a_i will be limited by the finite upper bound a_i^+ and the respective cell density will vanish at $a_i = a_i^+$. The loss rate $\beta_3(a_3)$ is introduced mainly for the technical reason of guaranteeing *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 $\bar{a}_3 > a_i^+$, $i = 1, 2, 4$, 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, as it will be made clear later.

The function $r(x,t)$ is the mean number of viable cells originated at the division of a proliferating cell. Under normal, non pathologic conditions $r(x,t) \equiv 2$. Otherwise, $r(x,t) \in [0,2)$. The functions $\mu_1(a_1,x,t)$ and $\mu_2(a_2,x,t)$ are the mortality rates of proliferating and differentiated cells induced by external causes. The explicit dependence on x and t of these functions reflects the possible dependence of the effects of physical agents like radiation or chemicals on space and time. The functions $S_1(a_1,t)$ and $S_2(a_2,t)$ represent the flow of proliferating and, respectively, differentiated cells from the basal layer, and are the physical inputs of the system. We actually suppose that at the basal layer we have no input of cells of type 3 and 4 (thus we set $S_3(a_3,t) = S_4(a_4,t) = 0$). Alternatively, the boundary conditions at $x = 0$ can be directly assigned as

$$n_i(a_i, 0, t) = N_i(a_i, t), \quad i = 1, \ldots, 4 \tag{5}$$

where $N_i(a_i,t)$ is related to $S_i(a_i,t)$ by

$$N_i(a_i, t) = \frac{S_i(a_i, t)}{u(0, t)}, \tag{6}$$

as long as $u(0,t) > 0$. Some compatibility conditions will have to be specified, as we will discuss later.

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

$$\Phi(x,t) = \sum_{i=1}^{4} \int_0^{a_i^+} v_i(a_i) n_i(a_i, x, t) da_i. \tag{7}$$

where $v_i(a_i)$, $i = 1, \ldots, 4$, is the mean volume of a cell of type i at age a_i. The cell volumes $v_i(a_i)$ do not vanish in $[0, a_i^+]$, and we disregard the possibility that these volumes depend on x and t. Obviously, from its definition, $\Phi(x,t)$ is meaningful if $0 \leq \Phi(x,t) \leq 1$ (notice that $n_i(a_i,x,t)da_i$ is a number of cells per unit volume).

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

$$\Gamma(x,t) = \sum_{i=1}^{3} \int_0^{a_i^+} \gamma_i(a_i) n_i(a_i, x, t) da_i, \tag{8}$$

where $\gamma_i(a_i) \geq 0$, $i = 1, \ldots, 3$, is the coefficient that expresses the specific contribution of a cell of type i at age a_i (we disregard cells of type $i = 4$ because unlikely they contribute significantly to cohesion). In the following, we will suppose γ_1 and γ_2 constant, whereas, to represent the progressive loss of bonds among the corneocytes, we assume γ_3 continuously differentiable and such that

$$\gamma_3'(a_3) < 0, \quad \gamma_3(a_3) = 0 \ \text{ for } \ a_3 \in [\hat{a}_3, a_3^+], \tag{9}$$

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

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

and

$$\Gamma(\Lambda(t), t) \geq \Gamma^*. \tag{10}$$

By taking into account that the constraint

$$u(\Lambda(t), t) \geq \frac{d\Lambda}{dt}(t) \tag{11}$$

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

$$\frac{d\Lambda}{dt}(t) < u(\Lambda(t), t), \quad \Gamma(\Lambda(t), t) = \Gamma^*, \tag{12}$$

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

$$\frac{d\Lambda}{dt}(t) = u(\Lambda(t), t), \quad \Gamma(\Lambda(t), t) \geq \Gamma^*, \tag{13}$$

and the boundary $\Lambda(t)$ is a "material boundary"(as it moves solidly with the cells), and obeys to the first equation in (13). Note that in (12) the strict inequality $\Gamma(\Lambda(t), t) > \Gamma^*$ cannot hold because, if it is $\Gamma(\Lambda(t), t) > \Gamma^*$, the boundary will necessarily move with the cells and then $d\Lambda/dt = u(\Lambda(t), t)$.

In a different biological context, the role of constraints like (10)-(11) on determining the nature of a free boundary has been considered in [5]. As we will see in the following, the first case (12) will hold for the epidermis at the stationary state.

Next, we shall deduce a conservation equation for Φ which will provide the determination of the velocity u under the hypothesis that the local volume fraction occupied by the cells is constant. Indeed we assume

$$\Phi(x,t) = \Phi^*, \quad (x,t) \in [0, \Lambda(t)] \times [0, T], \tag{14}$$

where, strictly speaking, $\Phi^* < 1$ since extracellular fluids are present in the tissue. However $\Phi^* = 1$ can be a good approximation, because the volume fraction of the extracellular space appears very small in normal epidermis [15]. To deduce such an equation, first we multiply each equation in (1)-(4) by $v_i(a_i)$, integrate it over $(0, a_i^+)$, and sum up over $i = 1, ..., 4$. We obtain

$$\begin{aligned} \frac{\partial \Phi}{\partial t} + \sum_{i=1}^{4} \int_0^{a_i^+} v_i(a_i) \frac{\partial n_i}{\partial a_i}(a_i, x, t) da_i + \frac{\partial}{\partial x}(u\Phi) \\ + \sum_{i=1}^{4} \int_0^{a_i^+} v_i(a_i) \beta_i(a_i) n_i(a_i, x, t) da_i \\ + \sum_{i=1}^{2} \int_0^{a_i^+} v_i(a_i) \mu_i(a_i, x, t) n_i(a_i, x, t) da_i = 0. \end{aligned} \tag{15}$$

Performing the integrations by parts, and taking into account the boundary conditions at $a_i = 0$, as well as that $n_i(a_i^+, x, t) = 0$ and that $\beta_i(a_i)n_i(a_i)$ must be integrable (as we expect for a solution), after some algebra we get the equation

$$\frac{\partial \Phi}{\partial t} + \frac{\partial}{\partial x}(u\Phi) = \sum_{i=1}^{4} \int_0^{a_i^+} k_i(a_i, x, t) n_i(a_i, x, t) da_i, \tag{16}$$

where

$$\begin{aligned} k_1(a_1, x, t) = \frac{\partial v_1}{\partial a_1} + \beta_1(a_1) \left(v_2(0) r(x, t) - v_1(a_1) \right) \\ + \mu_1(a_1, x, t)(v_4(0) - v_1(a_1)) \\ + \beta_1(a_1)(2 - r(x, t)) v_4(0), \end{aligned} \tag{17}$$

$$\begin{aligned} k_2(a_2, x, t) = \frac{\partial v_2}{\partial a_2} + \beta_2(a_2)(v_3(0) - v_2(a_2)) \\ + \mu_2(a_2, x, t)(v_4(0) - v_2(a_2)), \end{aligned} \tag{18}$$

$$k_3(a_3, x, t) = \frac{\partial v_3}{\partial a_3} - \beta_3(a_3) v_3(a_3), \tag{19}$$

$$k_4(a_4, x, t) = \frac{\partial v_4}{\partial a_4} - \beta_4(a_4) v_4(a_4). \tag{20}$$

We note that the k_3 and k_4 are actually functions of age, only.

Taking into account assumption (14), we can deduce from (16) the following equation that must be satisfied by u

$$\frac{\partial u}{\partial x} = \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^{a_i^+} k_i(a_i, x, t) n_i(a_i, x, t) da_i, \quad u(0, t) = u_0(t), \tag{21}$$

and therefore we get

$$u(x, t) = u_0(t) + \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^{x} \int_0^{a_i^+} k_i(a_i, \xi, t) n_i(a_i, \xi, t) da_i d\xi, \tag{22}$$

where the function $u_0(t)$ can be determined from the boundary conditions at $x = 0$ in (1)-(4), multiplying by $v_i(a_i)$, integrating over $(0, a_i^+)$, summing up over $i = 1, ..., 4$, and imposing (14). We deduce that it does not depend on n_i and is given by

$$u_0(t) = \frac{1}{\Phi^*} \sum_{i=1}^{2} \int_0^{a_i^+} v_i(a_i) S_i(a_i, t) da_i, \tag{23}$$

so that $u_0(t) > 0$ as far as S_1 and S_2 do not vanish simultaneously. Alternatively, $u_0(t)$ must be prescribed if the boundary conditions at $x = 0$ are given in the form (5).

We see that $u(x,t)$ depends in fact on all the functions n_i, and we have obtained a constitutive form based on the assumption that the local volume fraction occupied by the cells is constant.

On the other hand, we easily see that, with the constitutive form (22), a solution of system (1)-(4) with boundary conditions satisfying

$$\Phi(0,t) = \sum_{i=1}^{2} \int_0^{a_i^+} v_i(a_i) N_i(a_i,t) da_i = \Phi^*, \tag{24}$$

and

$$\Phi(x,0) = \sum_{i=1}^{4} \int_0^{a_i^+} v_i(a_i) n_{i0}(a_i,x) da_i = \Phi^*, \tag{25}$$

actually satisfies (14). In fact, by direct calculation from (7), using (1)-(4) and (17)-(21), we get

$$\frac{\partial \Phi}{\partial t} + u \frac{\partial}{\partial x} \Phi = 0$$

and, integrating along the characteristic lines, by (24) and (25) we have (14). Therefore the regime we are dealing with is characterized by the fulfillment of this assumption.

Simplified expressions of the terms k_i's can be obtained taking, as a first approximation, v_i constant. We obtain in this case

$$\begin{aligned} k_1(a_1,x,t) = \beta_1(a_1)\,(r(x,t)v_2 - v_1)) \\ +\mu_1(a_1,x,t)(v_4 - v_1) + \beta_1(a_1)(2 - r(x,t))v_4, \end{aligned} \tag{26}$$

$$k_2(a_2,x,t) = \beta_2(a_2)\,(v_3 - v_2) + \mu_2(a_2,x,t)(v_4 - v_2), \tag{27}$$

$$k_3(a_3,x,t) = -\beta_3(a_3) v_3, \tag{28}$$

$$k_4(a_4,x,t) = -\beta_4(a_4) v_4. \tag{29}$$

Biological evidence [23] suggests that $v_2 > v_1$ and $v_3 < v_2$. The value of v_4 could be different for different modalities of cell damage.

3 The stationary case

In this work we will focus on the stationary state of the model, proving its existence and uniqueness. The analysis of the stability properties will be the object of a future study. As we already noticed in Section 1, the stationary state possibly describes the spatial organization of the normal, unperturbed epidermis, or the new state that might be reached in the response to a long-lasting and time-invariant external injuring action. Thus, we assume that the source terms S_1 and S_2, the coefficient r and the exogenous mortality rates μ_1 and μ_2 are not influenced by time. Moreover, in order to have a meaningful solution we suppose that S_1 and S_2 are not both equal to zero.

Introducing now the survival probability functions

$$M_i(a_i) = \exp\left(-\int_0^{a_i} \beta_i(\xi) d\xi\right), \; i = 1, ..., 4$$

we will change the state variables $n_i(a_i, x)$ into the normalized densities

$$p_i(a_i, x) = \frac{n_i(a_i, x)}{M_i(a_i)} \tag{30}$$

and adopt the following constitutive form for the velocity (see (22)), as a function of the solution $p \equiv (p_1, \dots, p_4)$,

$$U(x; p) = u_0 + \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^x \int_0^{a_i^+} k_i(a_i, \xi) M_i(a_i) p_i(a_i, \xi) da_i d\xi, \tag{31}$$

where $u_0 > 0$ is assigned and is related to the flux at the basal layer by

$$u_0 = \frac{1}{\Phi^*} \sum_{i=1}^{2} \int_0^{a_i^+} v_i(a_i) S_i(a_i) da_i. \tag{32}$$

Then, considering the age-densities (6) of the number of cells per unit volume at the basal layer, rather than the cell fluxes, as input data of the problem, we get the following system of equations for p_i in the respective domains $(0, a_i^+) \times (0, \Lambda^*)$,

$$\begin{aligned} &\frac{\partial p_1}{\partial a_1} + \frac{\partial}{\partial x}(U(x;p)p_1) + \mu_1(a_1, x) p_1 = 0 \\ &p_1(0, x) = 0, \\ &M_1(a_1) p_1(a_1, 0) = N_1(a_1); \end{aligned} \tag{33}$$

$$\begin{aligned} &\frac{\partial p_2}{\partial a_2} + \frac{\partial}{\partial x}(U(x;p)p_2) + \mu_2(a_2, x) p_2 = 0 \\ &p_2(0, x) = r(x) \int_0^{a_1^+} \beta_1(a_1) M_1(a_1) p_1(a_1, x) da_1, \\ &M_2(a_2) p_2(a_2, 0) = N_2(a_2); \end{aligned} \tag{34}$$

$$\begin{aligned} &\frac{\partial p_3}{\partial a_3} + \frac{\partial}{\partial x}(U(x;p)p_3) = 0, \\ &p_3(0, x) = \int_0^{a_2^+} \beta_2(a_2) M_2(a_2) p_2(a_2, x) da_2, \\ &p_3(a_3, 0) = 0; \end{aligned} \tag{35}$$

$$\begin{aligned} &\frac{\partial p_4}{\partial a_4} + \frac{\partial}{\partial x}(U(x;p)p_4) = 0, \\ &p_4(0, x) = \sum_{i=1}^{2} \int_0^{a_i^+} \mu_i(a_i, x) M_i(a_i) p_i(a_i, x) da_i \\ &\qquad + (2 - r(x)) \int_0^{a_1^+} \beta_1(a_1) M_1(a_1) p_1(a_1, x) da_1, \\ &p_4(a_4, 0) = 0; \end{aligned} \tag{36}$$

where the functions N_1, N_2 satisfy (24), and Λ^* represents the (free) border to be determined by the condition

$$\Gamma(\Lambda^*) = \sum_{i=1}^{3} \int_0^{a_i^+} \gamma_i(a_i) M_i(a_i) p_i(a_i, \Lambda^*) da_i = \Gamma^*. \tag{37}$$

Concerning condition (37), we remark that, since at the stationary state it is $\frac{d\Lambda}{dt}(t) = 0$, the constraint (11) implies $U(\Lambda^*; p) \geq 0$. Then, in principle, two cases would be possible: either

$$U(\Lambda^*; p) > 0, \quad \Gamma(x) > \Gamma^*, \; x \in [0, \Lambda^*), \quad \Gamma(\Lambda^*) = \Gamma^*, \tag{38}$$

or

$$U(\Lambda^*; p) = 0, \quad \Gamma(x) > \Gamma^*, \; x \in [0, \Lambda^*), \quad \Gamma(\Lambda^*) \geq \Gamma^*. \tag{39}$$

However, as we will show in Sect. 6, only the case (38) is compatible with the existence of a stationary state. Thus Λ^* will be determined from condition (37). Moreover, it will be also shown in Sect. 6 that a solution such that (38) holds is necessarily characterized by $U(x; p) > 0$ in $[0, \Lambda^*]$.

We also note that, for the stationary problem, condition (14) provides the following constraint

$$\sum_{i=1}^{4} \int_0^{a_i^+} v_i(a_i) M_i(a_i) p_i(a_i, x) da_i = \Phi^*, \tag{40}$$

which is necessarily satisfied by the solution of (33)-(36), with $U(x; p)$ given by (31).

We append to the system compatibility conditions that ensure the continuity of the solution in age and space and express the continuity of the biological processes between the basal and the suprabasal layers. Namely we assume first that

$$\widetilde{N}_i(a_i) = \frac{N_i(a_i)}{M_i(a_i)}, \quad a_i \in [0, a_i^+], \quad i = 1, 2 \tag{41}$$

belong to $C^2[0, a_i]$, then we require

$$\widetilde{N}_1(0) = 0, \qquad \widetilde{N}_1(a_1^+) = 0, \tag{42}$$

$$\widetilde{N}_2(0) = r(0) \int_0^{a_1^+} \beta_1(a_1) M_1(a_1) \widetilde{N}_1(a_1) da_1, \tag{43}$$

$$\int_0^{a_2^+} \beta_2(a_2) M_2(a_2) \widetilde{N}_2(a_2) da_2 = 0, \tag{44}$$

$$\begin{aligned} \sum_{i=1}^{2} \int_0^{a_i^+} & \mu_i(a_i, 0) M_i(a_i) \widetilde{N}_i(a_i) da_i \\ & + (2 - r(0)) \int_0^{a_1^+} \beta_1(a_1) M_1(a_1) \widetilde{N}_1(a_1) da_1 = 0. \end{aligned} \tag{45}$$

The first condition is equivalent to supposing that no proliferating cell of zero age or of maximal age can be released from the basal layer. The second condition corresponds to assuming that the last round of cell division is characterized by the same mitotic rate function β_1 and the same value of r, independently of the fact that it occurs in the basal or in the suprabasal layer. The third and the fourth conditions are guaranteed by assuming:

$$\text{supp}(\widetilde{N}_2) \subseteq [0, a_2^*), \quad \text{supp}(\beta_2) \subseteq (a_2^{**}, a_2^+), \quad a_2^* < a_2^{**} < a_2^+, \tag{46}$$

where $\text{supp}(f) = \{a; f(a) \neq 0\}$, and

$$\mu_1(a_1, 0) = \mu_2(a_2, 0) = 0, \quad r(0) = 2. \tag{47}$$

Assumption (46) means that the differentiated cells coming from the basal layer are far from the maturation level at which they begin to transform into corneous cells. Assumptions (47) says that the exogenous causes of cell death and of abortive mitosis are taken mild enough to not affect the basal layer.

The mathematical approach to problem (31)-(36) will be split in two parts. In the first step, which will be developed in Sect. 5, we shall consider the problem in a fixed interval $[0, L]$ proving the existence of a solution under some conditions, independently of L being equal to Λ^* or not, i.e. condition (37) being satisfied or not. In the second step, performed in Sect. 6, we will determine Λ^* by condition (37). The next section is instead devoted to some preliminary results.

It is easy to see that model (31)-(37), using arbitrary reference length and time, can be made non-dimensional without changing the form of the equations. In the following, we will consider the model in the non-dimensional form maintaining, for simplicity, the same symbols. The mathematical hypotheses assumed to the study this model are:

$$\beta_i \in L^1_{\text{loc}}(0, a_i^+), \int_0^{a_i^+} \beta_i(a_i)da_i = +\infty, \quad \beta_i \geq 0 \;\text{ a.e. } a_i \in (0, a_i^+), \tag{48}$$

$$\mu_i \in C^2([0, a_i^+] \times [0, +\infty)), \quad \mu_i \geq 0 \;\text{ a.e. } (a_i, x) \in [0, a_i^+] \times [0, +\infty), \tag{49}$$

$$r \in C^1[0, +\infty), \quad 0 \leq r(x) \leq 2 \quad x \in [0, +\infty) \tag{50}$$

$$N_i \in C^2[0, a_i^+], \quad N_i \geq 0 \quad a_i \in [0, a_i^+], \tag{51}$$

$$v_i \in C^1[0, a_i^+], \quad v_i > 0 \quad a_i \in [0, a_i^+], \tag{52}$$

$$\gamma_i \in C^1[0, a_i^+], \quad \gamma_i \geq 0 \quad a_i \in [0, a_i^+]. \tag{53}$$

Note that we have

$$\beta_i M_i \in L^1(0, a_i^+), \tag{54}$$

and, defining

$$\widetilde{k}_i(a_i, x) = k_i(a_i, x) M_i(a_i), \tag{55}$$

recalling (17)-(20) we have

$$\widetilde{k}_i \in L^1(0, a_i^+; C^1[0, L]), \quad \text{for any} \quad L < +\infty. \tag{56}$$

4 Preliminary results

We shall begin by proving an intermediate result that will be used in the main existence theorem in the next section. This result refers to the well-posedness of the generic problem

$$\begin{array}{ll} \dfrac{\partial v}{\partial a} + \dfrac{\partial}{\partial x}(\alpha(x)v) + \pi(a, x)v = 0 & \text{in } (0, a^+) \times (0, L), \\ v(a, 0) = G(a) & \text{in } (0, a^+), \\ v(0, x) = F(x) & \text{in } (0, L), \end{array} \tag{57}$$

under the hypotheses

$$\alpha \in H^2(0, L), \;\alpha(x) > 0 \;\text{ for } \quad x \in [0, L], \tag{58}$$

$$G \in C^2[0, a^+], \quad F \in H^1(0, L), \quad F(0) = G(0), \tag{59}$$

$$\pi \in C^2([0,a^+] \times [0,L]). \tag{60}$$

We look for a *strict solution* v to (57), which means that

$$v \in C^1([0,a^+];L^2(0,L)) \cap C([0,a^+];H^1(0,L)) \tag{61}$$

and satisfies (57).

Since we will embed our problem in the space $L^2(0,L)$, we will denote the scalar product and norm in this space, respectively by $((\cdot,\cdot))$ and $\|\cdot\|$. When dealing with other spaces we will indicate the space itself by a subscript.

Our preliminary result is an existence theorem for problem (57) with some estimates depending on the constant

$$\omega = \frac{3}{2}\|\alpha_x\|_\infty + \sqrt{L}\,\|\alpha_{xx}\| + \pi_+ L, \tag{62}$$

where

$$\pi_+ = \|\pi\|_{C^1([0,a^+]\times[0,L])}\,.$$

We have

Theorem 1 *Let (58)-(60) hold. Then, problem (57) has a unique strict solution which satisfies the estimate*

$$\|v\|_{C([0,a^+];H^1(0,L))} \le e^{\omega a^+}\left\{\|F\|_{H^1(0,L)} + \sqrt{a^+}\sqrt{\alpha(0)}\,\|G\|_{C[0,a^+]}\right\}. \tag{63}$$

If moreover

$$F(x) \ge 0 \;\; \textit{for} \;\;\; x \in [0,L], \quad G(a) \ge 0 \;\; \textit{for} \;\;\; a \in [0,a^+], \tag{64}$$

then the solution of problem (57) satisfies

$$v(a,x) \ge 0 \;\; \textit{for} \;\;\; (a,x) \in [0,a^+] \times [0,L]. \tag{65}$$

Proof We first perform a function transformation by denoting

$$q(a,x) = v(a,x) - G(a) \tag{66}$$

and replace it in (57), obtaining the system

$$\begin{array}{ll} \dfrac{\partial q}{\partial a} + \dfrac{\partial}{\partial x}(\alpha(x)q) + \pi(a,x)q = f(a,x) & \text{in } (0,a^+)\times(0,L), \\ q(a,0) = 0 & \text{in } (0,a^+), \\ q(0,x) = q_0(x) & \text{in } (0,L), \end{array} \tag{67}$$

where

$$f(a,x) = -G_a(a) - \alpha_x(x)G(a) - \pi(a,x)G(a), \tag{68}$$

$$q_0(x) = F(x) - G(0). \tag{69}$$

From the above assumptions we get

$$f \in C^1([0,a^+];H^1[0,L]), \;\; q_0 \in H^1(0,L), \;\; q_0(0) = 0. \tag{70}$$

We define the linear operator $B : D(B) \subset L^2(0,L) \to L^2(0,L)$ by

$$B\theta = (\alpha\theta)_x, \quad D(B) = \{\theta \in H^1(0,L); \theta(0) = 0\}.$$

We notice that B is well defined because $(\alpha\theta)_x \in L^2(\Omega)$ for any $\theta \in D(B)$ and that $\overline{D(B)} = L^2(0,L)$. Moreover, the operator B is quasi m-accretive on $L^2(0,L)$. Indeed, we have

$$((B\theta,\theta)) = \int_0^L (\alpha\theta)_x \theta dx = \frac{1}{2}\alpha(L)\theta^2(L) + \frac{1}{2}\int_0^L \alpha_x(x)\theta^2(x)dx$$
$$\geq -\frac{1}{2}\|\alpha_x\|_\infty \|\theta\|^2 \text{ for any } \theta \in D(B).$$

Then, by setting

$$\omega_0 = \frac{1}{2}\|\alpha_x\|_\infty, \tag{71}$$

we get

$$(((\lambda I + B)\theta,\theta)) \geq (\lambda - \omega_0)\|\theta\|^2,$$

for $\lambda > \omega_0$, proving that B is quasi-accretive.

Next, we prove the quasi m-accretivity of B, i.e., that

$$Range(\lambda I + B) = L^2(0,L) \quad \text{for } \lambda \text{ large enough.}$$

Let $\eta \in L^2(0,L)$. We must prove that the equation

$$\lambda\theta + (\alpha\theta)' = \eta$$

has a solution in $D(B)$. We multiply the equation by α, denote $\tilde{\theta} = \alpha\theta$ and get

$$\lambda\tilde{\theta} + \alpha\tilde{\theta}\,' = \alpha\eta.$$

Its solution

$$\tilde{\theta}(x) = \int_0^x e^{-\lambda\int_\sigma^x \frac{1}{\alpha(\xi)}d\xi}\eta(\sigma)d\sigma$$

implies that

$$\theta(x) = \frac{1}{\alpha(x)}\int_0^x e^{-\lambda\int_\sigma^x \frac{1}{\alpha(\xi)}d\xi}\eta(\sigma)d\sigma, \tag{72}$$

and it is easy to see that it belongs to $D(B)$.

Since B is quasi m-accretive, the operator $(-B)$ is the generator of a linear C_0 -semigroup e^{-Ba} such that

$$\left\|e^{-Ba}\right\|_{\mathcal{L}(L^2(0,L),L^2(0,L))} \leq e^{\omega_0 a} \quad \text{for any } a \in [0,a^+].$$

Thus, we can consider the Cauchy problem

$$\begin{aligned} &\frac{dq}{da}(a) + Bq(a) + \mathcal{T}(a)q(a) = f(a),\\ &q(0) = q_0, \end{aligned} \tag{73}$$

where

$$\mathcal{T}(a)q(a,\cdot) = \pi(a,\cdot)q(a,\cdot). \tag{74}$$

Since

$$q_0 \in D(B), \quad \mathcal{T} \in C^2([0,a^+];\mathcal{L}(L^2(0,L);L^2(0,L))), \tag{75}$$

we get that (73) has a unique strong solution

$$q \in C^1([0,a^+]; L^2(0,L)) \cap C([0,a^+]; D(B)), \tag{76}$$

whence, going back to $v(a,x) = q(a,x) + G(a)$, we obtain that it is a strict solution to (57). In order to establish the estimate we multiply directly (57) by v and integrate over $[0,L]$ and over $[0,a]$ obtaining

$$\begin{aligned} &\frac{1}{2}\|v(a)\|^2 + \frac{1}{2}\int_0^a \alpha(L)v^2(s,L)ds - \frac{1}{2}\int_0^a \alpha(0)v^2(s,0)ds \\ &+\frac{1}{2}\int_0^a\int_0^L \alpha_x(x)v^2(s,x)dxds + \int_0^a\int_0^L \pi(s,x)v^2(s,x)dxds = \frac{1}{2}\|v_0\|^2, \end{aligned}$$

so that

$$\begin{aligned} \|v(a)\|^2 \le \|F\|^2 + a^+\alpha(0)\|G\|^2_{C[0,a^+]} \\ + (\|\alpha_x\|_\infty + \pi_+)\int_0^a \|v(s)\|^2 ds \end{aligned}$$

and, via Gronwall's lemma, we get

$$\|v(a)\|^2 \le e^{2\omega a}\left(\|F\|^2 + a^+\alpha(0)\|G\|^2_{C[0,a^+]}\right), \quad a \in [0,a^+],$$

with ω given by (62). Finally we can write

$$\|v(a)\| \le e^{\omega a}\left(\|F\| + \sqrt{a^+}\sqrt{\alpha(0)}\,\|G\|_{C[0,a^+]}\right), \quad a \in [0,a^+]. \tag{77}$$

In order to estimate the derivative v_x, we first gain some regularity considering the sequences $F^n \in H^2(0,L)$ and $G^n \in C^3[0,a^+]$ such that

$$G^n \longrightarrow G, \quad \text{in} \quad C[0,a^+]$$

$$F^n \longrightarrow F, \quad \text{in} \quad H^1(0,L), \quad F^n_x(0) = 0, \quad F^n(0) = G^n(0).$$

Then, the corresponding problems (73), with q_0 and f respectively replaced by

$$q_0^n(x) = F^n(x) - G^n(0)$$

and

$$f^n(a,x) = -G^n_a(a) - \alpha_x(x)G^n(a) - \pi(a,x)G^n(a),$$

have solutions $q^n \in C^2([0,a^+]; L^2(0,L)) \cap C([0,a^+]; D(B^2))$, because $q_0^n \in D(B^2)$ and $f^n \in C^2([0,a^+]; L^2(0,L))$. Thus the corresponding solution v^n to problem (57) satisfies

$$v^n \in C^2([0,a^+]; L^2(0,L)) \cap C([0,a^+]; D(B^2)), \quad v^n_x(a,0) = 0 \tag{78}$$

and, since the problem is linear, estimate (77) yields

$$v^n \longrightarrow v, \quad \text{in} \quad C([0,a^+], L^2(0,L)).$$

We also get an estimate for $w^n = v^n_x$ starting from the problem

$$\begin{aligned} &\frac{\partial w^n}{\partial a} + \frac{\partial}{\partial x}(\alpha(x)w^n) + (\alpha_x(x) + \pi(a,x))w^n(a) \\ &\qquad\qquad +(\alpha_{xx}(x) + \pi_x(a,x))v^n = 0, \\ &w^n(a,0) = 0, \\ &w^n(0,x) = F^n_x(x), \end{aligned} \tag{79}$$

accounting for the derivative of (57) based on (78). In fact, multiplying by w^n and integrating we get

$$\frac{1}{2}\left\|w^n(a)\right\|^2+\frac{1}{2}\int_0^a\int_0^L \alpha_x(x)(w^n(s,x))^2dxds$$
$$+\int_0^a\int_0^L(\alpha_x(x)+\pi(s,x))(w^n(s,x))^2dxds$$
$$\le\frac{1}{2}\left\|F_x^n\right\|^2-\int_0^a\int_0^L(\alpha_{xx}+\pi_x)v^n(s,x)w^n(s,x)dxds.$$

Then, noticing that

$$\left\|(\alpha_{xx}+\pi_x)\,v^n(a)\right\|\le\left(\sqrt{L}\left\|\alpha_{xx}\right\|+\pi_+L\right)\left\|v_x^n(a)\right\|_{L^2(0,L)},$$

where we took into account that

$$\|\theta\|_{C[0,L]}\le\sqrt{L}\,\|\theta_x\|\,,\qquad\text{for any}\quad\theta\in D(B),\tag{80}$$

finally we get

$$\left\|w^n(a)\right\|^2\le 2\omega\int_0^a\left\|w^n(s)\right\|^2ds+\left\|F_x^n\right\|^2,$$

and consequently

$$\left\|w^n(a)\right\|=\left\|v_x^n(a)\right\|\le e^{\omega a}\left\|F_x^n\right\|.\tag{81}$$

Since problem (79) is linear, this estimate implies that w^n is a Cauchy sequence and we conclude

$$v^n\longrightarrow v\qquad\text{in}\quad C([0,a^+],H^1(0,L)),$$

so that, going to the limit in (81) and adding to (77), we have (63).

Finally, to prove (65), we consider the negative part of v

$$v^-(a,x)=\max_{(a,x)\in[0,a^+]\times[0,L]}\{-v(a,x),0\}\,,$$

and, multiplying the equation by v^- and integrating, by the Stampacchia lemma we get

$$\frac{1}{2}\int_0^{a_i}\int_0^L\frac{\partial}{\partial\xi}(v^-(\xi,x))^2dxd\xi+\frac{1}{2}\int_0^{a_i}\int_0^L\frac{\partial}{\partial x}\left(\alpha(x)(v^-(\xi,x))^2\right)dxd\xi$$
$$+\frac{1}{2}\int_0^{a_i}\int_0^L\alpha_x(x)\frac{\partial}{\partial x}(v^-(\xi,x))^2dxd\xi-\int_0^{a_i}\int_0^L\pi(a,x)(v^-(\xi,x))^2dxd\xi=0.$$

Then

$$\|v^-(a)\|^2-\|F^-\|^2+\alpha(L)\int_0^a(v^-(\xi,L))^2d\xi$$
$$-\alpha(0)\int_0^a(G^-(\xi))^2d\xi\le(\|\alpha_x\|_\infty+2\pi_+)\int_0^a\|v^-(\xi)\|^2d\xi,$$

so that, since (64) implies $F^-\equiv 0$, $G^-\equiv 0$ and $\alpha(L)>0$, we get

$$\|v^-(a)\|^2\le(\|\alpha_x\|_\infty+2\pi_+)\int_0^a\|v^-(\xi)\|^2d\xi,$$

which means $v^-\equiv 0$ and (65) is proved.

∎

5 Existence results in a given interval [0, L]

In this section, we fix a space interval $[0,L]$ and consider problem (33)-(36) in this interval, with the definitions (31)-(32), under the assumptions (48)-(53), and the compatibility conditions (42)-(45).

We stress that, at this stage, we do not include condition (37) which instead will be used later to determine the physical boundary of the cell tissue. Actually, we note that the problem is local in space, and a solution in an interval $[0,L]$, if restricted to an interval $[0,L_1]$, with $L_1 < L$, is still a solution to the problem in the smaller interval. Thus we will determine a solution in $[0,L]$ with the purpose of subsequently finding $\Lambda^* < L$ fulfilling condition (37).

We preliminarily note that, in order to have a positive velocity $U(x;p)$, for all $x \in [0,L]$, we need to put some a priori restrictions on the solution. Namely, we look for a solution $p_i(a,x)$ satisfying the bound

$$\|p_i\|_{C([0,a_i^+];H^1(0,L))} < \frac{u_0}{\sqrt{L}C_\alpha} \tag{82}$$

where (see (56))

$$C_\alpha = \frac{1}{\Phi^*}\sum_{i=1}^4 \left\|\widetilde{k}_i\right\|_{L^1(0,a_i^+;C^1[0,L])}. \tag{83}$$

This is just a sufficient a priori condition in order to guarantee a positive velocity as we expect to occur in the biological process, at the stationary state.

Our purpose is to obtain the solution of (33)-(36) via a fixed point procedure in a suitable space. To this aim we define

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

with the norms

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

and consider the space

$$\mathcal{Y} = \prod_{i=1}^4 C([0,a_i^+];L^2(0,L)),$$

endowed with the norm

$$\|z\|_{\mathcal{Y}} = \left(\sum_{i=1}^4 \|z_i\|_{H_i}^2\right)^{\frac{1}{2}},$$

where $z \equiv (z_1,z_2,z_3,z_4) \in \mathcal{Y}$.

Then we consider the set

$$\mathcal{M} = \left\{z \in \mathcal{Y};\ z_i \in V_i,\ \|z_i\|_{V_i} \le R,\ z_i(a,x) \ge 0,\ z_i(a_i,0) = \widetilde{N}_i(a_i)\right\}, \tag{84}$$

where $\widetilde{N}_i(\cdot)$ are defined in (41) for $i=1,2$ and $\widetilde{N}_i(\cdot) \equiv 0$ for $i=3,4$. Moreover, in (84) $R>0$ is a fixed constant that, in order to fulfill (82) is chosen such that

$$R < \frac{u_0}{\sqrt{L}C_\alpha}. \tag{85}$$

We easily note that $\mathcal{M}$ is a closed subset of $\mathcal{Y}$. Our purpose is to build a mapping $\Psi : \mathcal{M} \to \mathcal{M}$ by fixing $z \equiv (z_1, z_2, z_3, z_4) \in \mathcal{M}$ and replacing $U(x;p)$ by

$$U(x;z) = u_0 + \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^x \int_0^{a_i^+} \widetilde{k}_i(a_i,\xi) z_i(a_i,\xi) da_i d\xi. \tag{86}$$

in problem (33)-(36).

Concerning the function $U(x;z)$, since $z_i \in \mathcal{M}$, we have

$$U(\cdot;z) \in H^2(0,L), \tag{87}$$

and

$$|U(x;z) - u_0| \le \frac{\sqrt{L}}{\Phi^*} \sum_{i=1}^{4} \left\| \widetilde{k}_i \right\|_{L^1(0,a_i^+;C^1[0,L])} \|z_i\|_{H_i} \le \sqrt{L} C_\alpha R, \tag{88}$$

hence

$$-\sqrt{L} C_\alpha R \le U(x;z) - u_0 \le \sqrt{L} C_\alpha R.$$

Therefore, by the choice (85) for R, we ensure

$$0 < U(x;z) < 2u_0, \text{ for any } x \in [0,L]. \tag{89}$$

From the equality

$$z_i(a_i,x) = z_i(a_i,0) + \int_0^x (z_i)_x(a_i,\xi) d\xi$$

we get

$$\begin{aligned} |z_i(a_i,x)| &\le \left| \widetilde{N}_i(a_i) \right| + \sqrt{L} \, \|(z_i)_x\|_{H_i} \\ &\le \left\| \widetilde{N}_i \right\|_{C[0,a_i^+]} + \sqrt{L} \, \|z_i\|_{V_i} \le C_N + \sqrt{L} R, \end{aligned} \tag{90}$$

where

$$C_N = \max_{i=1,2} \left\| \widetilde{N}_i \right\|_{C^1[0,a_i^+]}, \tag{91}$$

so that, respectively denoting by $U'(x,z)$ and $U''(x,z)$ the first and second derivatives of $U(x,z)$ with respect to the variable x, we have (see (86))

$$\begin{aligned} \left| U'(x;z) \right| &\le \frac{1}{\Phi^*} \sum_{i=1}^{4} \int_0^{a_i^+} \left| \widetilde{k}_i(a_i,x) \right| |z_i(a_i,x)| \, da_i \\ &\le \left(C_N + \sqrt{L} R \right) C_\alpha < C_N C_\alpha + u_0. \end{aligned} \tag{92}$$

In addition we have

$$\left\| U'(\cdot;z) \right\| \le \frac{1}{\Phi^*} \sum_{i=1}^{4} \left\| \widetilde{k}_i \right\|_{L^1(0,a_i^+;C^1[0,L])} \|z_i\|_{H_i} \le C_\alpha R < \frac{u_0}{\sqrt{L}}, \tag{93}$$

$$\left\| U''(\cdot\,;z) \right\| \le \frac{1}{\Phi^*} \sum_{i=1}^{4} \left\| \widetilde{k}_i \right\|_{L^1(0,a_i^+;C^1[0,L])} \|z_i\|_{V_i} \le C_\alpha R < \frac{u_0}{\sqrt{L}}. \tag{94}$$

Now we are ready to build the mapping $y = \Psi(z)$ solving in a sequence the problems (33)-(36) with $U(x;p)$ replaced by $U(x;z)$ given in (86). Namely we start considering the problem

$$\begin{aligned}
&\frac{\partial y_1}{\partial a_1} + \frac{\partial}{\partial x}(U(x;z)y_1) + \mu_1(a_1,x)y_1 = 0 && \text{in } (0,a_1^+) \times (0,L),\\
&y_1(a_1,0) = \widetilde{N}_1(a_1) && \text{in } (0,a_1^+),\\
&y_1(0,x) = 0 && \text{in } (0,L).
\end{aligned} \tag{95}$$

and apply Theorem 1 to have existence of a unique solution $y_1 \geq 0$ which satisfies the estimate

$$\|y_1\|_{V_1} \leq \sqrt{a^+ u_0}\; C_N \;\mathcal{K}_0\left(a^+, \mu_+, C_N, C_\alpha, u_0, L\right)$$

where

$$a^+ = \max_{i=1,\dots,4}\{a_i\}, \quad \mu_+ = \max_{i=1,2} \|\mu_i\|_{C^1([0,a_i^+]\times[0,L])} \tag{96}$$

and

$$\mathcal{K}_0\left(a^+, \mu_+, C_N, C_\alpha, u_0, L\right) = \exp\left(\frac{3}{2}a^+ C_N C_\alpha + \frac{5}{2}a^+ u_0 + a^+\mu_+ L\right), \tag{97}$$

where we have plugged estimates (92)-(94) into (62).

Once we have computed y_1 we pass to the problem

$$\begin{aligned}
&\frac{\partial y_2}{\partial a_2} + \frac{\partial}{\partial x}(U(x;z)y_2) + \mu_2(a_2,x)y_2 = 0 && \text{in } (0,a_2^+) \times (0,L),\\
&y_2(a_2,0) = \widetilde{N}_2(a_2) && \text{in } (0,a_2^+),\\
&y_2(0,x) = F_2(x) && \text{in } (0,L),
\end{aligned} \tag{98}$$

with

$$F_2(x) = r(x)\int_0^{a_1^+} \beta_1(a_1)M_1(a_1)y_1(a_1,x)da_1 \geq 0. \tag{99}$$

Then, applying again Theorem 1 we find a solution $y_2 \geq 0$ satisfying

$$\|y_2\|_{V_2} \leq (1+r_+)\;\sqrt{a^+u_0}\; C_N \mathcal{K}_0^2\left(a^+, \mu_+, C_N, C_\alpha, u_0, L\right) \tag{100}$$

with

$$r_+ = \|r\|_{C^1[0,L]}\,. \tag{101}$$

Going further in the same way we solve the problems for y_3 and y_4 respectively with

$$F_3(x) = \int_0^{a_2^+} \beta_2(a_2)M_2(a_2)y_2(a_2,x)da_2 \geq 0, \tag{102}$$

$$\begin{aligned}
F_4(x) = \sum_{i=1}^{2}\int_0^{a_i^+} &\mu_i(a_i)M_i(a_i)y_i(a_i,x)da_i\\
&+(2-r(x))\int_0^{a_1^+} \beta_1(a_1)M_1(a_1)y_1(a_1,x)da_1 \geq 0,
\end{aligned} \tag{103}$$

and we find $y_3 \geq 0$, $y_4 \geq 0$, satisfying the estimates

$$\|y_3\|_{V_3} \leq (1+r_+)\sqrt{a^+u_0}\; C_N\; \mathcal{K}_0^3\left(a^+, \mu_+, C_N, C_\alpha, u_0, L\right),$$

$$\|y_4\|_{V_4} \leq (2+r_+)(1+\mu_+a^+)\sqrt{a^+u_0}\; C_N\; \mathcal{K}_0^3\left(a^+, \mu_+, C_N, C_\alpha, u_0, L\right).$$

In conclusion, defining (see (97))

$$\begin{aligned}&\mathcal{K}\left(r_+, a^+, \mu_+, C_N, C_\alpha, u_0, L\right)\\&\quad= (2+r_+)(1+\mu_+ a^+)\sqrt{a^+ u_0}\; C_N\; \mathcal{K}_0^3\left(a^+, \mu_+, C_N, C_\alpha, u_0, L\right),\end{aligned} \tag{104}$$

we have, for $i = 1, \ldots, 4$,

$$\|y_i\|_{V_i} \le \mathcal{K}\left(r_+, a^+, \mu_+, C_N, C_\alpha, u_0, L\right),$$

and, using this inequality in each equation for y_i, we also get

$$\left\|\frac{\partial y_i}{\partial a_i}\right\|_{C\left([0,a_i^+];L^2(0,L)\right)} \le \delta, \tag{105}$$

where δ is a constant depending on all the parameters.

Now, assuming the following condition in addition to (85),

$$\mathcal{K}\left(r_+, a^+, \mu_+, C_N, C_\alpha, u_0, L\right) < R, \tag{106}$$

the above procedure gives

$$y \equiv (y_1, y_2, y_3, y_4) \in \mathcal{M}$$

and we can define the mapping $\Psi : \mathcal{M} \to \mathcal{M}$, by

$$\Psi(z) = y.$$

Thanks to (105) we also have that $\Psi(\mathcal{M})$ is compact in $\mathcal{Y}$.

Next, we assume (106), and estimate the difference between $y = \Psi(z)$ and $\overline{y} = \Psi(\overline{z})$. To this purpose, for each $i = 1, \ldots, 4$ we write the systems for y_i and $\overline{y}_i$, respectively corresponding to $U(x; z)$ and $U(x; \overline{z}_i)$, make the difference, multiply it by $(y_i - \overline{y}_i)$ and integrate over $(0, a_i) \times (0, L)$, obtaining

$$\begin{aligned}\|y_i(a_i) - \overline{y}_i(a_i)\|^2 &\le \|y_i(0) - \overline{y}_i(0)\|^2\\&\quad+ \int_0^{a_i}\int_0^L \left|U'(x;z)\right| |y_i - \overline{y}_i|^2\, dx d\xi\\&\quad+2\int_0^{a_i}\int_0^L \left|U'(x;z) - U'(x;\overline{z})\right| |\overline{y}_i|\, |y_i - \overline{y}_i|\, dx d\xi\\&\quad+2\int_0^{a_i}\int_0^L |U(x;z) - U(x;\overline{z})|\, |\overline{y}_{ix}|\, |y_i - \overline{y}_i|\, dx d\xi\end{aligned} \tag{107}$$

where we have taken into account that $y_i(a_i, 0) - \overline{y}_i(a_i, 0) = 0$.

Each term of (107) may indeed be evaluated as follows. First we have

$$\begin{aligned}&\int_0^{a_i}\int_0^L \left|U'(x;z)\right| |y_i - \overline{y}_i|^2\, dx d\xi\\&\qquad\le (C_N C_\alpha + u_0)\int_0^{a_i} \|y_i(\xi) - \overline{y}_i(\xi)\|^2\, d\xi,\end{aligned}$$

where we have used (92). Then

$$\begin{aligned}&2\int_0^{a_i}\int_0^L \left|U'(x;z) - U'(x;\overline{z})\right| |\overline{y}_i|\, |y_i - \overline{y}_i|\, dx d\xi\\&\quad< 2\left(C_N + R\sqrt{L}\right)\int_0^{a_i} \left\|U'(\cdot;z) - U'(\cdot;\overline{z})\right\| \|y_i(\xi) - \overline{y}_i(\xi)\|\, d\xi\\&\quad< 4a^+ \left(C_N C_\alpha + u_0\right)^2 \|z - \overline{z}\|_{\mathcal{Y}}^2 + \int_0^{a_i} \|y_i(\xi) - \overline{y}_i(\xi)\|^2\, d\xi,\end{aligned}$$

and

$$2\int_0^{a_i}\int_0^L |U(x;z)-U(x;\overline{z})|\,|\overline{y}_{ix}|\,|y_i-\overline{y}_i|\,dxd\xi$$
$$\leq 4\sqrt{L}C_\alpha \|z-\overline{z}\|_{\mathcal{Y}}\int_0^{a_i}\|\overline{y}_{ix}(\xi)\|\,\|y_i(\xi)-\overline{y}_i(\xi)\|\,d\xi$$
$$\leq 4a^+u_0^2\|z-\overline{z}\|_{\mathcal{Y}}^2+\int_0^{a_i}\|y_i(\xi)-\overline{y}_i(\xi)\|^2\,d\xi,$$

where we have used the estimates (compare with (88) and (93))

$$|U(x;z)-U(x;\overline{z})|\leq \sqrt{L}C_\alpha\sum_{i=1}^4\|z_i-\overline{z}_i\|_{H_i}\leq 2\sqrt{L}C_\alpha\|z-\overline{z}\|_{\mathcal{Y}},$$

$$\left\|U'(\cdot;z)-U'(\cdot;\overline{z})\right\|\leq 2C_\alpha\|z-\overline{z}\|_{\mathcal{Y}},$$

and, since $\overline{y}$ belongs to $\mathcal{M}$ (compare with (90)),

$$|\overline{y}_i(a_i,x)|\leq\left(\frac{C_N}{u_0}+R\sqrt{L}\right),\quad \|\overline{y}_{ix}(a_i)\|\leq\|y_i\|_{V_i}\leq R.$$

Placing these estimates in (107) we get

$$\|y_i(a_i)-\overline{y}_i(a_i)\|^2\leq(2+u_0+C_NC_\alpha)\int_0^{a_i}\|y_i(\xi)-\overline{y}_i(\xi)\|^2\,d\xi$$
$$+4a^+\,(2u_0+C_NC_\alpha)^2\,\|z-\overline{z}\|_{\mathcal{Y}}^2+\|y_i(0)-\overline{y}_i(0)\|^2. \tag{108}$$

Now, taking into account that $y_1(0,x)\equiv 0$ and that for $i=2,3,4$ the values of $y_i(0,x)$ are respectively assigned in (99), (102), (103), we apply Gronwall lemma in a sequence to the inequalities (108) and finally end with the following estimate

$$\|y-\overline{y}\|_{\mathcal{Y}}\leq\mathcal{L}\left(r_+,a^+,\mu_+,C_N,C_\alpha,u_0\right)\|z-\overline{z}\|_{\mathcal{Y}} \tag{109}$$

where

$$\mathcal{L}\left(r_+,a^+,\mu_+,C_N,C_\alpha,u_0\right)$$
$$=2\sqrt{a^+}\left(2+r_++a^+\mu_+\right)(2u_0+C_NC_\alpha)\,e^{(2+u_0+C_NC_\alpha)a^+}.$$

We conclude that the mapping $\Psi:\mathcal{M}\to\mathcal{M}$ is continuous in $\mathcal{Y}$, so that, since $\Psi(\mathcal{M})$ is compact, by Schauder fixed point theorem we have an existence result for our original problem (33)-(36), in the set $\mathcal{M}$. Moreover, under the following additional condition

$$\mathcal{L}\left(r_+,a^+,\mu_+,C_N,C_\alpha,u_0\right)<1, \tag{110}$$

the mapping $\Psi:\mathcal{M}\to\mathcal{M}$ is a contraction in $\mathcal{Y}$, and we have also uniqueness of the solution.

The key tool for the previous construction is the fulfillment of conditions (85), (106) and (110) that, of course, will depend on the many parameters occurring in the process. While a discussion of such conditions will be provided in the next section, here we summarize the result stating the following theorem:

Theorem 2 *Let L, u_0, $N_1(a_1)$, $N_2(a_2)$, C_α and R be given such that (85) and (106) are satisfied. Then, (31)-(36) has a solution*

$$p_i \in C^1([0,a_i^+];L^2(0,L)) \cap C([0,a_i^+];H^1(0,L)), \tag{111}$$

for $i = 1,\dots,4$, satisfying

$$\|p_i\|_{C([0,a_i^+];H^1(0,L))} < R, \tag{112}$$

$$0 \le p_i(a_i,x) \le C_N + \frac{u_0}{C_\alpha}, \qquad in \quad [0,a_i^+] \times [0,L], \tag{113}$$

$$0 < U(x;p) < 2u_0, \qquad in \quad [0,L]. \tag{114}$$

If, in addition, (110) is satisfied, then the solution is unique.

We note that, in view of (92), $U(x;p)$ is Lipschitz continuous on $[0,L]$.

6 Existence of the free boundary Λ^* in the stationary case

In the previous sections we have seen that existence (and uniqueness) of a solution to problem (31)-(36) can be established under the sufficient conditions (85), (106), (110) which involve all the parameters that in the model give a shape to the biological process. The length L of the interval on which the existence of a solution is guaranteed, is actually conditioned by the parameters and the fulfillment of the sufficient conditions occurs for parameter combinations somehow reflecting the nature of the process and the possibility of epidermis formation. Summarizing the relevant constants involved in the conditions, we have to consider (see (91), (32), (83), (96), (101)) C_N, depending on the density of the number of cells at $x = 0$; u_0, which is their velocity; C_α, a structural parameter depending on how cell volume changes with age, on the division rate of proliferating cells and on the loss of cells of any type; μ_+ and r_+, which depend on a possible exogenous death process. We also note that due to (24), C_N satisfies the lower bound

$$C_N \ge \frac{\Phi^*}{\displaystyle\sum_{i=1}^{2} \int_0^{a_i^+} v_i(a_i) M_i(a_i) da_i}.$$

We remark that conditions (85) and (106) are both fulfilled if and only if

$$C_\alpha \sqrt{L}\, \mathcal{K}\left(r_+, a^+, \mu_+, C_N, C_\alpha, u_0, L\right) \; < \; u_0, \tag{115}$$

and then, for a given set of parameters, we obtain a range of values for L (namely L must be sufficiently small) such that (115) is satisfied. Thus, the results we state in Theorem 2 are local with respect to x. In particular, we note that when u_0 decreases to zero, (115) is satisfied only if L is going to zero as well.

On the other hand, condition (110), which is sufficient to guarantee uniqueness, is not necessarily satisfied for L small enough, because the function $\mathcal{L}$ which depends on L through the constants C_α and C_N, does not vanish as L tends to zero. However, since (110) forces u_0 to be sufficiently small, it also implies a small enough length L.

Since the left hand side of (115) is an increasing function of L, for any given set of parameters we may define L^+ as the unique value of L satisfying the equality

$$C_\alpha \sqrt{L}\, \mathcal{K}\left(r_+, a^+, \mu_+, C_N, C_\alpha, u_0, L\right) \; = \; u_0 \tag{116}$$

so that Theorem 2 provides a solution in any interval $[0, L]$ such that $L < L^+$.

Furthermore, since (115) is actually a sufficient condition for existence, any solution existing on the basis of this condition may actually exist on an interval larger than $[0, L^+)$. By the standard application of the Zorn's Lemma, we may consider the set of maximal solutions and, for any such maximal solution $p \equiv (p_1, p_2, p_3, p_4)$, let $L_{max}(p)$ denote the maximal length of the interval where the solution exists in the sense that all p_i are non-negative, and satisfy (111), (31)-(36) for any $L < L_{max}(p)$. Note that in correspondence with a solution p, the velocity $U(x; p)$ is Lipschitz continuous in any interval $[0, L]$ with $L < L_{max}(p)$. Of course $L^+ \le L_{max}(p)$.

It is important to note that along the whole interval $[0, L_{max}(p))$ the velocity $U(x; p)$ remains positive. In fact we have

Proposition 1 *Let* $p \equiv (p_1, p_2, p_3, p_4)$ *be a solution in the maximal interval* $[0, L_{max}(p))$, *then*

$$U(x; p) > 0 \quad for \quad x \in [0, L_{max}(p)).$$

Proof Suppose that $U(x; p) = 0$ for some $x \in [0, L_{max}(p))$. Since $U(0; p) = u_0 > 0$, then

$$x^* = \inf \{x \in [0, L_{max}(p)) | U(x; p) = 0\} > 0$$

and

$$U(x; p) > 0 \quad for \quad x \in [0, x^*), \quad U(x^*; p) = 0.$$

Let $x = \eta(a, x_0)$ denote the characteristic curve through $(0, x_0)$. Namely $\eta(a, x_0)$ is defined by

$$\begin{cases} \eta'(a) = U(\eta(a); p), & a > 0, \\ \eta(0, x_0) = x_0, & x_0 \in [0, x^*]. \end{cases}$$

The characteristics defined above pertain to each single problem (33)-(36). Since $U(x; p)$ is positive in $[0, x^*)$ and Lipschitz continuous in $[0, x^*]$, the characteristic lines are increasing and are also uniquely determined. Since $U(x^*; p) = 0$, the line $x = x^*$ cannot be crossed, thus the characteristics lay in the strip $(a, x) \in [0, \infty] \times [0, x^*]$ and the following points can be defined

$$x_1 = \eta(a_1^+, 0), \quad x_2 = \eta(a_2^+, x_1), \quad x_3 = \eta(a_3^+, x_2).$$

Of course $x_1 < x_2 < x_3 < x^*$, and it easy to see that

$$\begin{array}{l} p_1(a_1, x) = 0 \text{ for } \quad x > \eta(a_1, 0), \quad a_1 \in [0, a_1^+], \\ p_2(a_2, x) = 0 \text{ for } \quad x > \eta(a_2, x_1), \; a_2 \in [0, a_2^+], \\ p_i(a_i, x) = 0 \text{ for } \quad x > \eta(a_i, x_2), \; a_i \in [0, a_i^+], \quad i = 3, 4. \end{array} \tag{117}$$

Consequently, recalling that $a_3^+ > a_i^+$, $i = 1, 2, 4$, we have

$$p_i(a_i, x) \equiv 0, \quad a_i \in [0, a_i^+], \quad x \in (x_3, x^*] \quad i = 1, 2, 3, 4,$$

which is impossible because the constraint (40) would not be fulfilled for $x \in (x_3, x^*]$. ∎

The previous Proposition explains why we have disregarded (39). In fact such a condition is not feasible because it violates constraint (40). From the proof it also turns out that $L_{max}(p) < \infty$ and that there is no $L < L_{max}(p)$ such that the characteristic $x = \eta(a, x_2)$ can be defined for a in the whole interval $[0, a_3^+]$.

Now we are ready to complete the solution of our stationary problem, looking for the boundary Λ^*. For a given solution $p \equiv (p_1, p_2, p_3, p_4)$ of (31)-(36), we have the corresponding cohesion function

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

defined for $x \in [0, L_{max}(p))$. The cohesion function $\Gamma(x)$ turns out to be continuous, and differentiable a.e. on $[0, L]$, with $L < L_{max}(p)$. As mentioned in Sect. 2, we impose that Γ is greater than Γ^* at $x = 0$, i.e., taking into account (32) and (24):

$$\Gamma(0) = \sum_{\iota=1}^{2} \gamma_i \int_0^{a_i^+} N_i(a_i) da_i > \Gamma^*. \tag{118}$$

Then, recalling that a solution to problem (31)-(36) in the interval $[0, L]$, if restricted to an interval $[0, L_1]$ with $L_1 < L$, is still a solution to the same problem in the smaller interval, we look for $\Lambda^* < L_{max}(p)$ satisfying condition (37). We note that in principle this condition may not be satisfied because the parameters in the phenomenological function $\Gamma(x)$ are independent of the parameters that regulate the cellular process. Indeed we could try to impose a cohesion so strong that desquamation never occurs within the interval where the solution exists. Since, however, we assume that cohesion does not occur for cells of type 4 and is lost by corneocytes with age greater than $\hat{a}_3$ (see (9)), a sufficient condition for finding Λ^* is that the characteristic $x = \eta(a, x_2)$ is defined for $a \in [0, \hat{a}_3]$, namely

$$\hat{x}_3 = \eta(\hat{a}_3, x_2) < L_{max}(p). \tag{119}$$

In fact, if (119) is satisfied, we have

$$x_1 < x_2 < \eta(a, x_2) < \eta(\hat{a}_3, x_2) = \hat{x}_3 < x_3, \quad \text{for} \quad a \in [0, \hat{a}_3)$$

and, from (117),

$$\begin{aligned} p_1(a_1, \hat{x}_3) &= 0, \quad \textit{for} \quad a_1 \in [0, a_1^+] \\ p_2(a_2, \hat{x}_3) &= 0, \quad \textit{for} \quad a_2 \in [0, a_2^+] \\ p_3(a_3, \hat{x}_3) &= 0, \quad \textit{for} \quad a_3 \in [0, \hat{a}_3), \end{aligned}$$

so that

$$\Gamma(\hat{x}_3) = 0$$

and, in view of (118) we find roots of the equation

$$\Gamma(x) = \Gamma^*$$

in the interval $[0, \hat{x}_3]$. We can summarize our results in the following

Theorem 3 *Let* $p \equiv (p_1, p_2, p_3, p_4)$ *be a solution of (31)-(36), in the maximal interval* $[0, L_{max}(p))$*. Suppose that (118) and (119) are satisfied. Then problem (31)-(37) has a solution.*

Through the previous theorem, the model we have analyzed provides a general framework to describe the structure of a stratified epithelium. From the analysis of the characteristic lines given in the proof of Proposition 1 we may also see how the model predicts that proliferating and differentiated cells dwell in the inner layers while the outer stratum is made of corneous cells that stick together and move until they lose their cohesion. In fact, if $\Lambda^* > x_2$, only corneous cells will be present for $x \in [x_2, \Lambda^*]$. Our aim is now to test the model quantitatively, numerical simulations will be presented and discussed in a future paper together with some comparison with experimental situations.

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References

1. Allen, T.D., Potten, C.S.: Ultrastructural site variation in mouse epidermal organization. J. Cell Sci. **21**, 341-359 (1976)
2. Ambrosi, D., Preziosi, L.: On the closure of mass balance models for tumor growth. Math. Models Meth. Appl. Sci. **12**, 737-754 (2002)
3. Appleton, D.R., Wright, N.A., Dyson, P.: The age distribution of cells in stratified squamous epithelium. J. Theor. Biol. **65**, 769-779 (1977)
4. Bertuzzi, A., Gandolfi, A.: Cell kinetics in a tumour cord. J. Theor. Biol. **204**, 587-599 (2000)
5. Bertuzzi, A., Fasano, A., Gandolfi, A.: A free boundary problem with unilateral constraints describing the evolution of a tumor cord under the influence of cell killing agents. SIAM J. Math. Anal. **36**, 882-915 (2004)
6. Byrne, H.M., Preziosi, L.: Modelling solid tumor growth using the theory of mixture. Math. Med. Biol. **20**, 341-366 (2003)
7. Cusulin, C., Iannelli, M., Marinoschi, G.: Age-structured diffusion in a multi-layer environment. Nonlinear Analysis Real World Applications **6** (1), 207-223 (2005)
8. Dyson, J., Villella-Bressan, R., Webb, G.: The evolution of a tumor cord cell population, Comm. Pure Appl. Anal. **3**, 331-352 (2004)
9. Friedman, A., Hu, B.: The role of oxigen in tissue maintenance: mathematical modeling and qualitative analysis, Math. Mod. Meth. Appl. Sci. **18**, 1409-1441 (2008)
10. Fuchs, E., Raghavan, S.: Getting under the skin morphogenesis. Nature Rev. Genet. **3**, 199-209 (2002)
11. Gurtin, M.E.: A system of equations for age-dependent population diffusion. J. Theor. Biol. **40**, 389-392 (1973)
12. Gurtin, M.E., MacCamy, R.C.: On the diffusion of biological populations, Math. Biosci. **33**, 35-49 (1977)
13. Hadgraft, J.: Skin, the final frontier. Int. J. Pharm. **224**, 1-18 (2001)
14. Johnston, M.D., Edwards, C.M., Bodmer, W.F., Maini, P.K., Chapman, S.J.: Mathematical modeling of cell population dynamics in the colonic crypt and in colorectal cancer. Proc. Natl. Acad. Sci. USA **104**, 4008-4013 (2007)
15. Klein-Szanto, A.J.P.: Stereological baseline data of normal human epidermis. J. Invest. Dermatol. **68**, 73-78 (1977)
16. Loeffler, M., Potten, C.S., Ditchfield, A., Wichmann, H.E.: Analysis of the changes in the proportions of clustered labelled cells in epidermis. Cell Tissue Kinet. **19**, 377-389 (1986)
17. Loeffler, M., Potten, C.S., Wichmann, H.E.: Epidermal cell proliferation: II. A comprehensive mathematical model of cell proliferation and migration in the basal layer predicts some unusual properties of epidermal stem cells. Virchows Arch. (B) **53**, 286-300 (1987)
18. Lowes, M.A., Bowcock, A.M., Krueger, J.G.: Pathogenesis and therapy of psoriasis. Nature **445**, 866-873 (2007)
19. Meineke, F.A., Potten C.S., Loeffler, M.: Cell migration and organization in the intestinal crypts using a lattice-free model. Cell Prolif. **34**, 253-266 (2001)

20. Paulus, U., Potten, C.S., Loeffler, M.: A model of the control of cellular regeneration in the intestinal crypt after perturbation based solely on local stem cell regulation. Cell Prolif. **25**, 559-578 (1992)
21. Potten, C.S.: The epidermal proliferative unit: the possible role of central basal cellcell proliferation. Cell Prolif. **7**, 77-88 (1974)
22. Potten, C.S., Loeffler, M.: Epidermal cell proliferation: I. Changes with time in the proportions of isolated, paired and clustered labelled cells in sheets of murine epidermis, Virchows Arch. (B) **53**, 279-285 (1987)
23. Rowden, G.: Ultrastructural studies of keratinized epithelia of the mouse. III. Determination of the volume of nuclei and cytoplasm of cells in murine epidermis. J. Invest. Dermatol. **64**, 1-3 (1975)
24. Savill, N.J.: Mathematical models of hierarchically structured cell populations under equilibrium with application to the epidermis. Cell Prolif. **36**, 1-26 (2003)
25. Stekel, D., Rashbass, J., Williams, E.D.: A computer graphic simulation of squamous epithelium. J. Theor. Biol. **175**, 283-293 (1995)
26. van Leeuwen, I.M., Byrne, H.M., Jensen, O.E., King, J.R.: Crypt dynamics and colorectal cancer: advances in mathematical modelling. Cell Prolif. **39**, 157-181 (2006)
27. Webb, G.: The steady state of a tumor cord cell population. J. Evol. Eqs **2**, 425-438 (2002)
28. Webb, G.: Population models structured by age, size, and spatial position. In: Structured population models in Biology and Epidemiology. Auger, P., Magal, P., Ruan, S. (eds.), Springer Verlag, 2008, 1-49
29. Weinstein, G.D., McCoullog,J.L., Ross, P.: Cell proliferation in normal epidermis. J. Invest. Dermatol. **82**, 623- (1984)