Epidermis growth from biology to mathematics and vice versa

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Presentation Outline

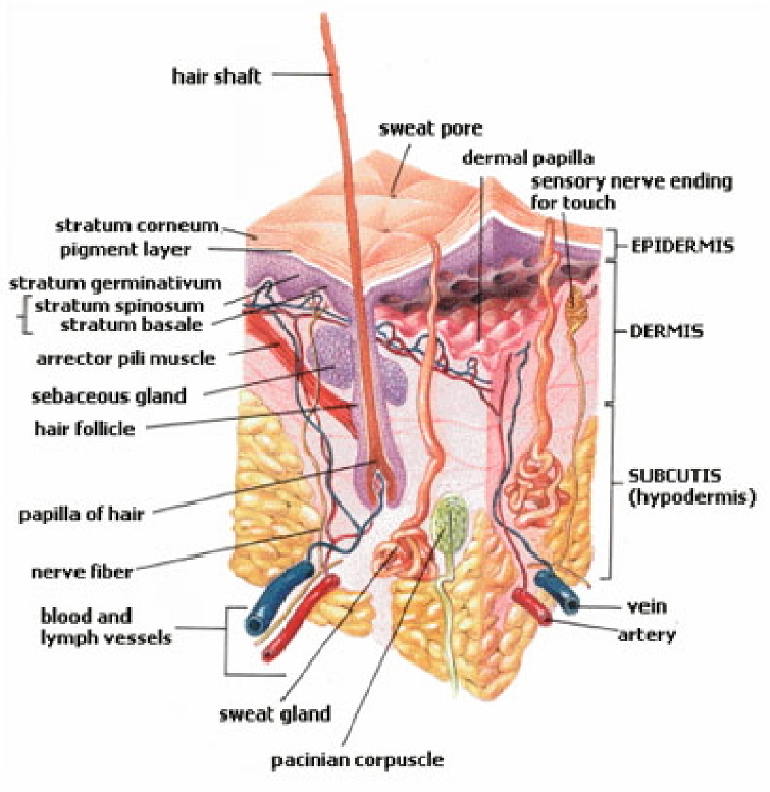
- *From biology to mathematics: biological overview and mathematical modelling*
- *Functional treatment of the mathematical model (stationary case)*
- *Numerical treatment of the mathematical model*
- *From mathematics to biology: utility in diagnosis and treatment*

Some results from a common work with

- Alberto Gandolfi, IASI, CNR, Rome
- Mimmo Iannelli, University of Trento, Italy

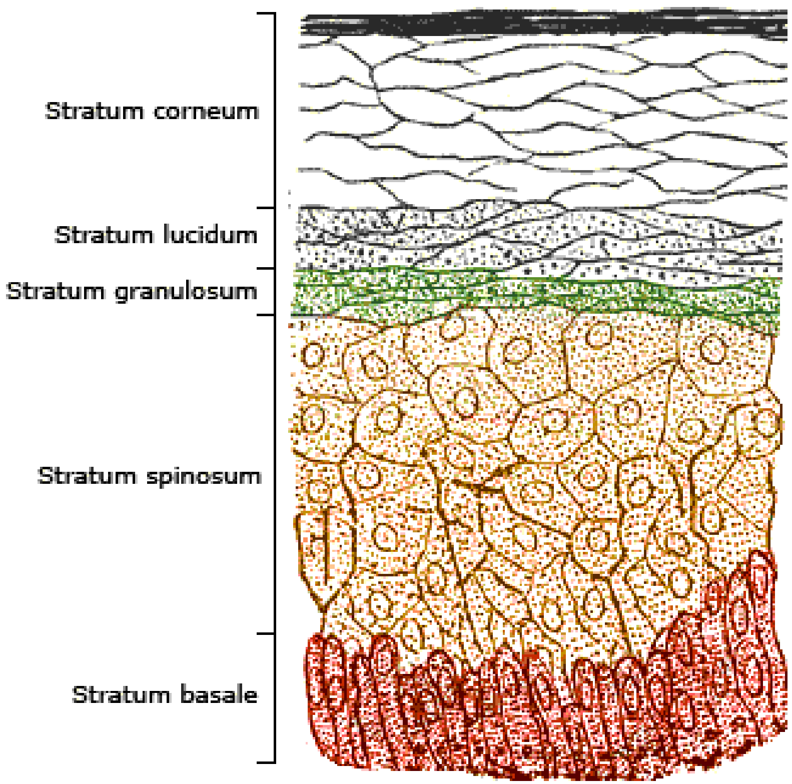
An age-structured model of epidermis growth, J. Math. Biol., Springer, in press

1 From biology to mathematics



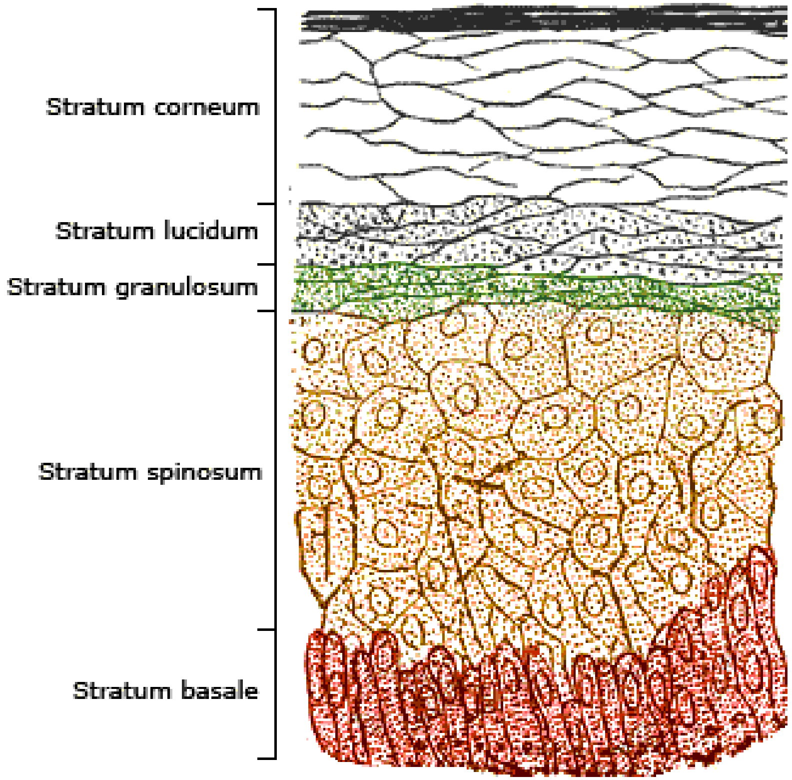
http://en.wikipedia.org/wiki/File:Skin.png

Epidermis: a multilayer arrangement of epithelial cells (*keratinocytes*) subject to a continuous renewal process.



http://en.wikipedia.org/wiki/File:Skinlayers.png

- In *stratum basale*, the cells divide and push already formed cells into higher layers.
- As cells move into the higher layers (suprabasal layer), they flatten and eventually die.



$n_3(a_3, x, t)$ corneous cells

$n_4(a_2, x, t)$ apoptotic cells

$n_2(a_2, x, t)$ differentated cells

$n_1(a_1, x, t)$ proliferant cells

♦ $n_j(a_j, x, t)$ denotes the density of cells n_j, $j = 1, ..., 4$.

– $a_j \in [0, a_j^+]$ is the age in the phase "i"

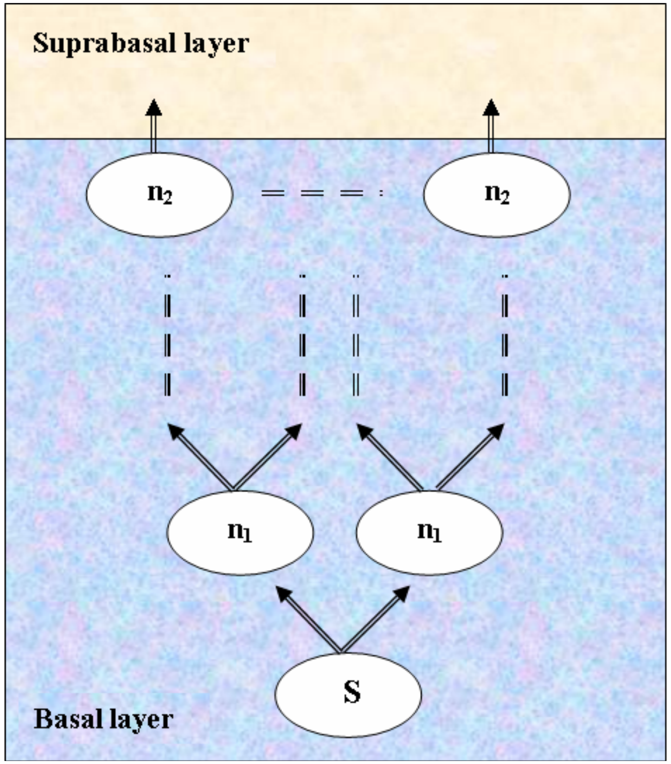
– $x \in [0, L(t)]$ (from the interface with the basal cell layer, to the end of the stratum corneum)

– $t \in [0, T]$.

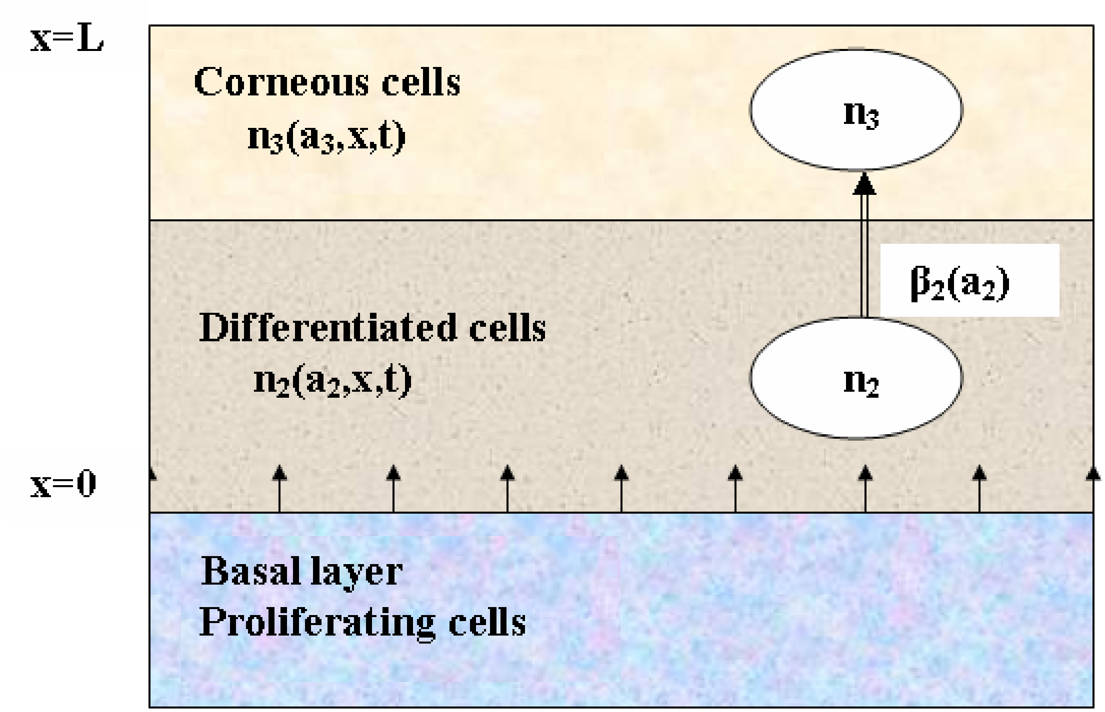
1.1 Basic aspects for the mathematical modelling

1.1.1 Normal growth

► Cell proliferation occurs almost exclusively in the basal layer (see Weinstein et al., 1984; Loeffler et al., 1987), where stem cells generate transiently proliferating cells (n_1) that after few (4-5) rounds of proliferation cease to divide producing non-proliferating (quiescent), differentiated cells (n_2).



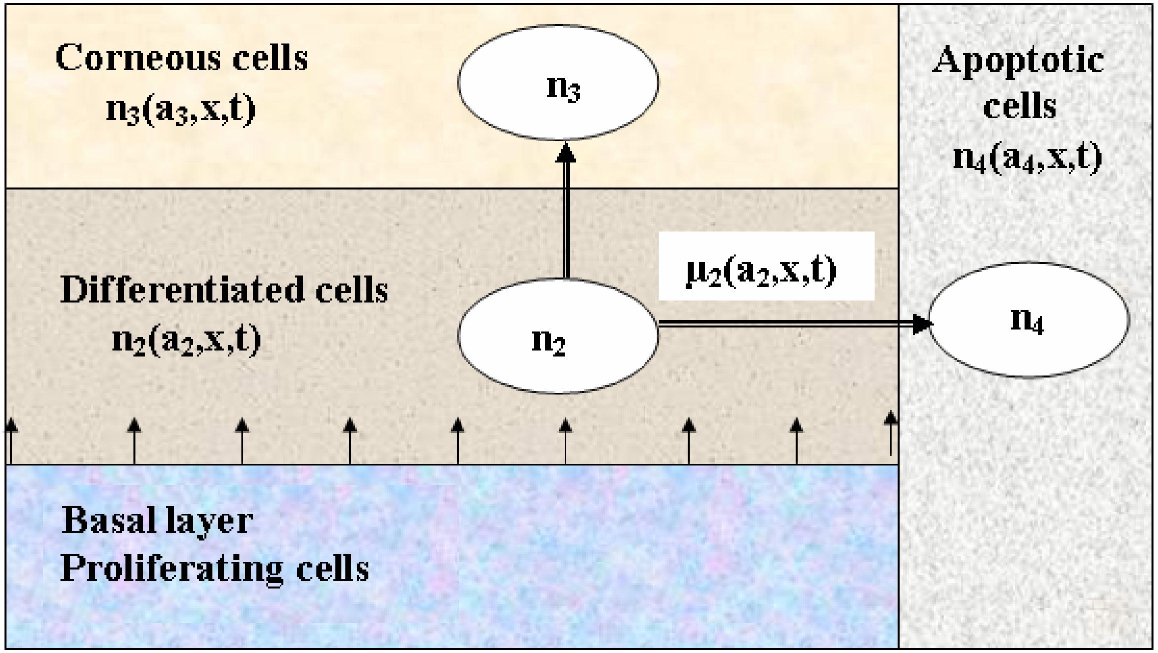
♦ Suprabasal differentiated cells (n_2) undergo a progressive maturation, called keratinization, during which the fibrous protein keratin accumulates in the cells, transforming them in corneous cells (n_3).



Normal growth and apoptosis

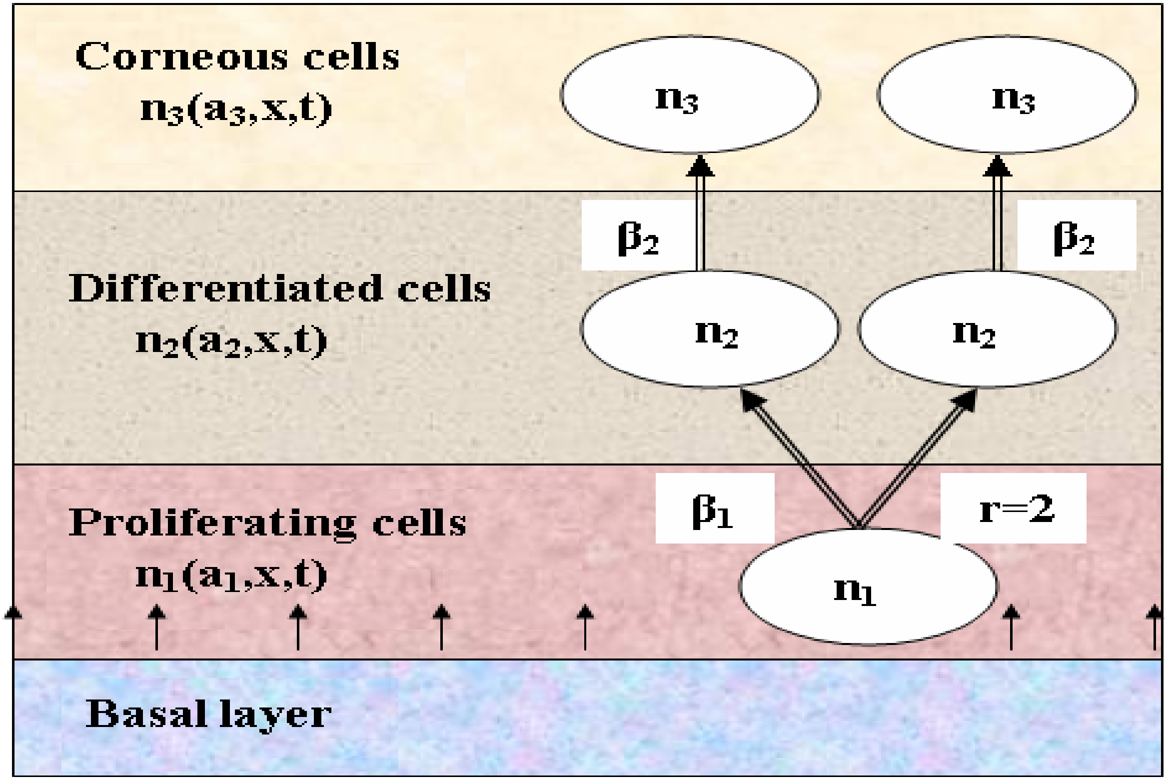
► natural death

► external (accidental) causes: radiation, exposure to certain chemicals, mechanical injuries.



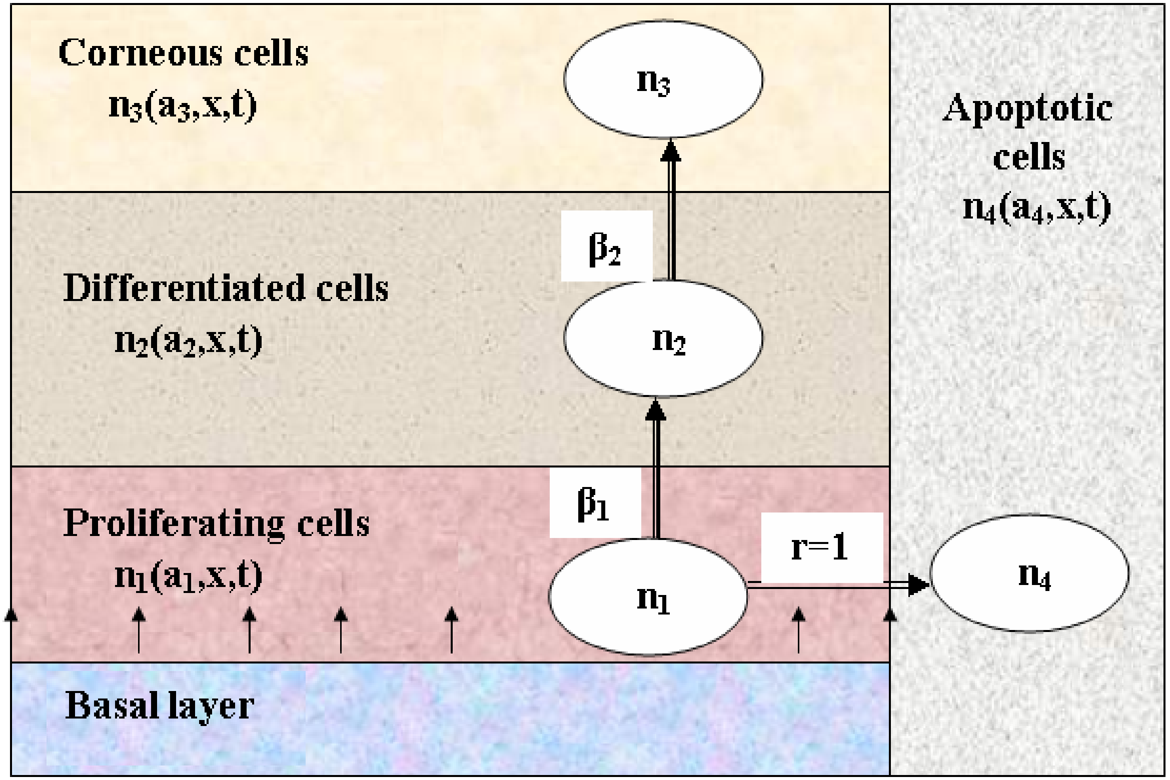
1.1.2 Pathological growth: (moderate) hyperproliferative disorders

Proliferation extends also to the suprabasal layers (Lowes, 2007). Assume that the last round of division may occur in the suprabasal region.



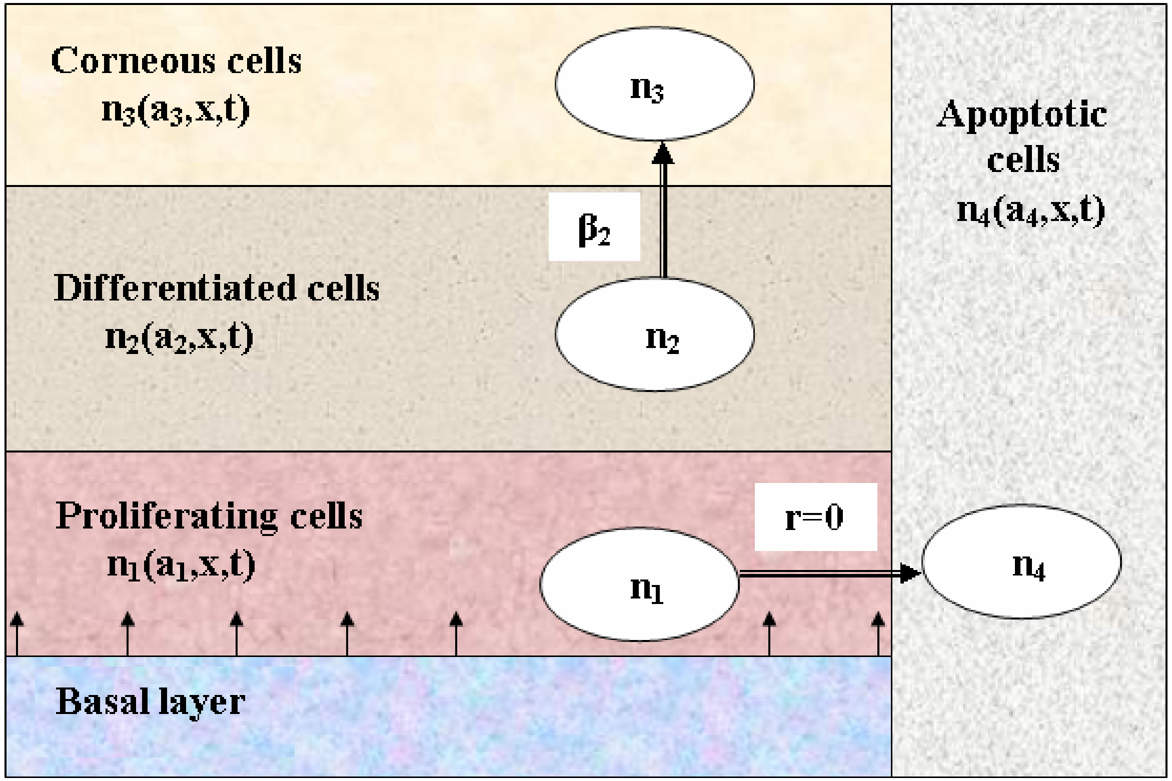
Incomplete mitosis

► a pathologic mitosis of proliferating cells



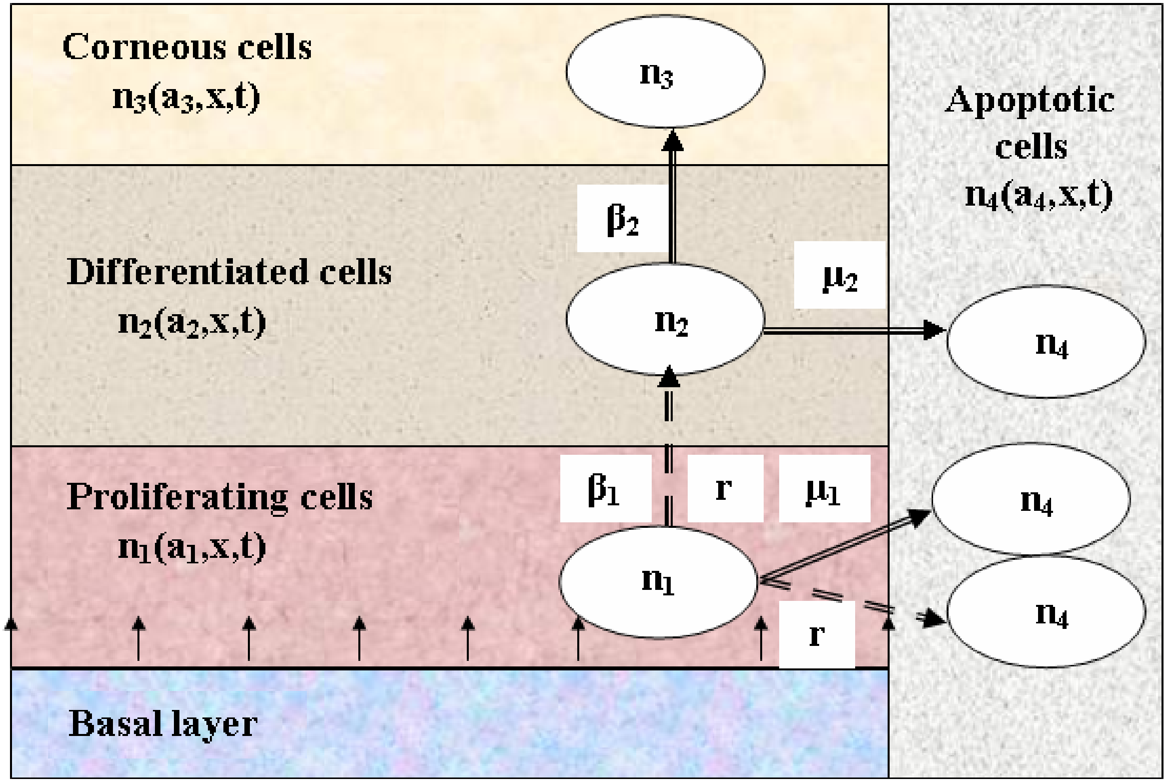
Absence of mitosis

► a pathologic mitosis of proliferating cells



Pathological growth and external influences

► a pathologic mitosis of proliferating cells and apoptosis of proliferating and differentiated cells



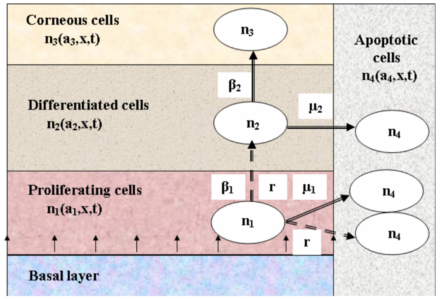
1.2 Mathematical model

- A continuous approach for $n_j(a_j, x, t)$ in $\Omega_j(t) \times [0, T]$,

$$\Omega_j(t) = [0, a_j^+] \times [0, L(t)], \quad j = 1, ..., 4.$$

Proliferating cells

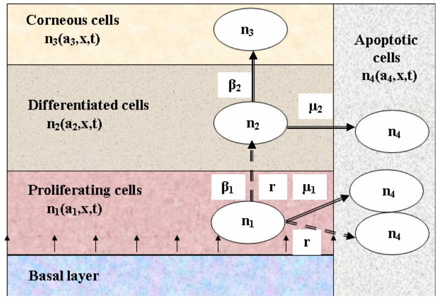
$\frac{\partial n_1}{\partial t} + \frac{\partial n_1}{\partial a_1} + \frac{\partial}{\partial x}(un_1) = -\beta_1(a_1)n_1 - \mu_1(a_1, x, t)n_1$	in $\Omega_1(t)$	conservation of n_1
$n_1(a, x, t) = 0$	at $a_1 = 0$	no birth of n_1 in $[0, L(t)] \times [0, T]$
$u(x, t)n_1(a_1, x, t) = S_1(a_1, t)$	at $x = 0$	flux of n_1 from the basal layer
$n_1(a_1, x, t) = n_{10}(a_1, x)$	at $t = 0$	initial distribution of n_1 in $\Omega_1(0)$



$\beta_1(a_1)$ denotes the rate of division of proliferating cells
$S_1(a_1, t)$ represents the flow of proliferating cells from the basal layer
$u(x, t)$ denotes the velocity field, positive in the outward direction
$\mu_1(a_1, x, t)$ is the mortality rate of proliferating cells induced by external causes.

Differentiated cells

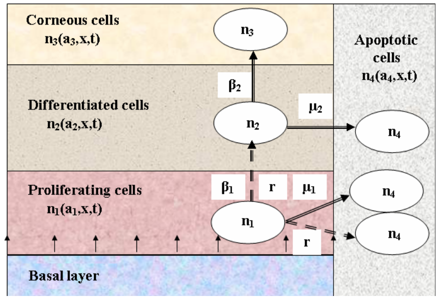
$\frac{\partial n_2}{\partial t} + \frac{\partial n_2}{\partial a_2} + \frac{\partial}{\partial x}(un_2) = -\beta_2(a_2)n_2 - \mu_2(a_2,x,t)n_2$	in $\Omega_2(t)$	conservation of n_2
$n_2(a_2,x,t) = r(x,t)\int_0^{a_1^+} \beta_1(a_1)n_1(a_1,x,t)da_1$	at $a_2 = 0$	birth of n_2 in $[0, L(t)] \times [0, T]$
$u(x,t)n_2(a_2,x,t) = S_2(a_2,t)$	at $x = 0$	flux of n_2 from the basal layer
$n_2(a_2,x,t) = n_{20}(a_2,x)$	at $t = 0$	initial distribution of n_2 in $\Omega_2(0)$



$\beta_2(a_2)$ the rate of transition of differentiated (quiescent) cells to the corneous state
$S_2(a_2,t)$ represents the flow of differentiated cells from the basal layer
$r(x,t)$ is the mitosis rate for n_1
$\mu_2(a_2,x,t)$ is the mortality rate of differentiated cells induced by external causes.

Corneous cells

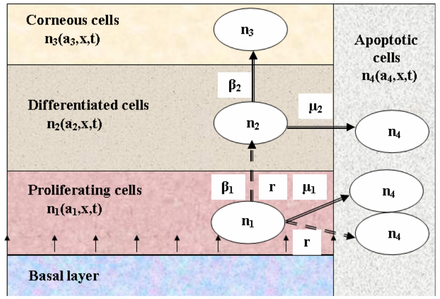
$\frac{\partial n_3}{\partial t} + \frac{\partial n_3}{\partial a_3} + \frac{\partial}{\partial x}(un_3) = -\beta_3(a_3)n_3$	in $\Omega_3(t)$	conservation of n_3
$n_3(a_3,x,t) = \int_0^{a_2^+} \beta_2(a_2)n_2(a_2,x,t)da$	at $a_3 = 0$	birth of n_3 in $[0,L(t)] \times [0,T]$
$n_3(a_3,x,t) = 0$	at $x = 0$	no flux of n_3 from the basal layer
$n_3(a_3,x,t) = n_{30}(a_3,x)$	at $t = 0$	initial distribution of n_3 in $\Omega_3(0)$



$\beta_3(a_3)$ represents the rate of a possible degradation of corneocytes.

Apoptotic cells

$\frac{\partial n_4}{\partial t} + \frac{\partial n_4}{\partial a_4} + \frac{\partial}{\partial x}(un_4) = -\beta_4(a_4)n_4$	in $\Omega_4(t)$	conservation of n_4
$n_4(a_4,x,t) = \sum_{i=1}^{2} \int_0^{a_i^+} \mu_i(a_i,x)n_i(a_i,x,t)da_i + (2 - r(x,t)) \int_0^{a_1^+} \beta_1(a_1)n_1(a_1,x,t)da_1$	at $a_4 = 0$	birth of n_4 in $[0, L(t)] \times [0, T]$
$n_4(a_4,x,t) = 0$	at $x = 0$	no flux of n_4 from the basal layer
$n_4(a_2,x,t) = n_{40}(a_4,x)$	at $t = 0$	initial distribution of n_4 in $\Omega_4(0)$



$\beta_4(a_4)$ the rate of degradation of apoptotic cells to a liquid waste.

1.3 Model assumptions

Cohesivity function

$$\Gamma(x,t) = \sum_{i=1}^{4} \int_0^{a_i^+} \gamma_i(a_i) n_i(a_i,x,t)\,da_i, \quad \gamma_i(a_i) \geq 0,\ i = 1,\ldots,4,$$

represents the level of cohesion of the tissue at position x and time and γ_i expresses the specific contribute of a cell of type i at age a_i.

Cohesive epidermis : $\Gamma(x,t) > \Gamma^*$ for $x \in [0, L(t))$,

$$\Gamma(L(t),t) \geq \Gamma^*.$$

Cell velocity

Impose the constraint

$$u(L(t),t) \geq \dot{L}(t)$$

which avoids the nonsense of the epidermis boundary that “detaches” from the cellular material.

Epidermis end condition

$$\Gamma(L(t), t) = \Gamma^*,$$

$$u(L(t), t) > \dot{L}(t).$$

Local fraction of volume

Volume occupied by all cells at time t around the point x

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

is constant

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

$v_i(a_i)$, $i = 1, \ldots, 4$, is the mean volume of a cell of type i at age a_i, position x, and time t.

Rates of division

$$\beta_i \in L^1_{\text{loc}}(0, a_i^+)$$

$$\int_0^{a_i^+} \beta_i(a_i)da_i = +\infty.$$

The *survival probability function*

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

Denote

$$\widetilde{n}_i(a_i, x, t) = \frac{n_i(a_i, x, t)}{M_i(a_i)}, \ \widetilde{S}_i(a_i, t) = \frac{S_i(a_i, t)}{M_i(a_i)}, \ \widetilde{n}_{i0}(a_i, x) = \frac{n_{i0}(a_i, x)}{M_i(a_i)}.$$

Final system

$$\frac{\partial \widetilde{n}_i}{\partial t} + \frac{\partial \widetilde{n}_i}{\partial a_i} + \frac{\partial}{\partial x}(u\widetilde{n}_i) + \mu_i(a_i, x, t)\widetilde{n}_i = 0 \quad \text{in } (0, a_i^+) \times (0, L(t)) \times (0, T),$$

$$\begin{aligned} \widetilde{n}_i(0, x, t) &= \sum_{j=1}^{4} r_{ij}(x, t) \int_0^{a_j^+} \beta_j(a_j) M_j(a_j) \widetilde{n}_j(a_j, x, t) da_j \\ &+ \sum_{j=1}^{4} r_{0ij} \int_0^{a_j^+} \mu_j(a_j) M_j(a_j) \widetilde{n}_j(a_j, x, t) da_j \\ &\qquad \text{in } (0, L(t)) \times (0, T), \end{aligned}$$

$$u(0, t)\widetilde{n}_i(a_i, 0, t) = \widetilde{S}_i(a_i, t) \quad \text{in } (0, a_i^+) \times (0, T),$$

$$\widetilde{n}_i(a_i, x, 0) = \widetilde{n}_{i0}(a_i, x) \quad \text{in } (0, a_i^+) \times (0, L(t)).$$

1.4 Determination of the velocity

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

$$\Downarrow$$

$$u(x,t;\widetilde{n}_i) = \frac{1}{\Phi^*}\int_0^x K(\xi,t;\widetilde{n}_i(\cdot,\xi,t))d\xi + u_0(t),$$

$$u_0(t) = \frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^{a_i^+} v_i(a_i)M_i(a_i)\widetilde{S}_i(a_i,t)da_i.$$

$$K(x,t;\widetilde{n}_i(\cdot,x,t)) = \sum_{i=1}^{4}\int_0^{a_i^+} k_i(a_i,x,t)\widetilde{n}_i(a_i,x,t)da_i.$$

Simplified expressions of the terms k_i can be obtained taking, as a first approximation, v_i constant.

$$k_1(a_1,x,t) = [\beta_1(a_1)\,(r(x,t)v_2 - v_1))$$

$$+\mu_1(a_1,x,t)(v_4 - v_1) + (2 - r(x,t))\beta_1(a_1)v_4]\,M_1(a_1),$$

$$k_2(a_2,x,t) = [\beta_2(a_2)\,(v_3 - v_2) + \mu_2(a_2,x,t)(v_4 - v_2)]\,M_2(a_2),$$

$$k_3(a_3,x,t) = -\beta_3(a_3)v_3M_3(a_3),$$

$$k_4(a_4,x,t) = -\beta_4(a_4)v_4M_4(a_4).$$

1.5 The stationary case

The stationary state describes the spatial organization of the normal, unperturbed epidermis, or the possible new state reached in the response to a long-lasting and time-invariant external injuring action.

$$\frac{\partial \widetilde{n}_i}{\partial a_i} + \frac{\partial}{\partial x}(\widetilde{u}\widetilde{n}_i) + \mu_i(a_i, x)M_i(a_i)\widetilde{n}_i = 0 \text{ in } (0, a_i^+) \times (0, L),$$

$$u_0\widetilde{n}_i(a_i, 0) = \widetilde{S}_i(a_i) \text{ in } (0, a_i^+), \qquad \text{(stationary)}$$

$$\widetilde{n}_i(0, x) = \sum_{j=1}^{4} \int_0^{a_j^+} A_{ij}(a_j, x)\widetilde{n}_j(a_j, x)da_j \text{ in } (0, L).$$

The model is completed with the conditions for the determination of L

$$u(L) > 0, \quad \Gamma(L) = \Gamma^*,$$

and with certain compatibility conditions

$$\frac{\widetilde{S}_i(0)}{u_0} = \sum_{j=1}^{4} \int_0^{a_j^+} A_{ij}(a_j, 0)\widetilde{n}_j(a_j, 0)da, \ i = 1, ..., 4.$$

2 Mathematics: Functional treatment of the stationary case

- Assume L fixed and prove the existence of a unique solution by the Schauder fixed point theorem.
- Determination of L using the condition $\Gamma(L) = \Gamma^*$.

2.1 Existence and uniqueness for L fixed

Functional framework

Define

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

with the norms

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

Let R be a nonengative number, $R < \frac{u_0}{\sqrt{L} C_\alpha}$ and introduce the set

$$M = \left\{ (z_1, z_2, z_3, z_4); \;\; z_i \in V_i, \;\; \|z_i\|_{V_i} \leq R, \;\; z_i(a_i, 0) = \frac{\widetilde{S}_i(a_i)}{u_0} \right\}.$$

Note that M is a closed subset of

$$Y = \prod_{i=1}^{4} H_i.$$

M is a complete metric space with the metric $d(y_1, y_2) = \|y_1 - y_2\|_Y$, for any $y_1, \, y_2 \in M$.

Fixed point theorem

$$u(x;\widetilde{n}_i) = \frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^x\int_0^{a_i^+} k_i(a_i,x)\widetilde{n}_i(a_i,x)da_i d\xi + u_0,$$

Fix

$$(z_1, z_2, z_3, z_4) \in M$$

$$\alpha(x;z_i) = \frac{1}{\Phi^*}\sum_{i=1}^{4}\int_0^x\int_0^{a_i^+} k_i(a_i,x)z_i(a_i,x)da_i d\xi + u_0.$$

Replace z_i and α in the system:

$$\frac{\partial \widetilde{n}_i}{\partial a_i} + \frac{\partial}{\partial x}(\widetilde{u}(x;\widetilde{n}_i)\widetilde{n}_i) + \mu_i(a_i,x)M_i(a_i)\widetilde{n}_i = 0 \text{ in } (0,a_i^+)\times(0,L),$$

$$u_0\widetilde{n}_i(a_i,0) = \widetilde{S}_i(a_i) \text{ in } (0,a_i^+),$$

$$\widetilde{n}_i(0,x) = \sum_{j=1}^{4}\int_0^{a_j^+} A_{ij}(a_j,x)\widetilde{n}_j(a_j,x)da_j \text{ in } (0,L).$$

Fixed point theorem

$$\frac{\partial \widetilde{v}_i}{\partial a_i} + \frac{\partial}{\partial x}(\alpha(x)\widetilde{v}_i) + \pi_i(a_i, x)\widetilde{v}_i = 0 \text{ in } (0, a_i^+) \times (0, L),$$

$$u_0 \widetilde{v}_i(a_i, 0) = \widetilde{S}_i(a_i) \text{ in } (0, a_i^+), \qquad \text{(intermediate)}$$

$$\widetilde{v}_i(0, x) = \sum_{j=1}^{4} \int_0^{a_j^+} A_{ij}(a_j, x) z_j(a_j, x) da_j = F(x) \text{ in } (0, L).$$

Fixed point theorem

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$$\widetilde{v}_i(0, x) = \sum_{j=1}^{4} \int_0^{a_j^+} A_{ij}(a_j, x) z_j(a_j, x) da_j = F(x) \text{ in } (0, L).$$

Define $\Psi : M \to Y$,

$$(z_1, z_2, z_3, z_4) \xrightarrow{\Psi} (\widetilde{v}_1, \widetilde{v}_2, \widetilde{v}_3, \widetilde{v}_4)$$

Prove that

Ψ is a contraction on Y.

Intermediate problem

$$\frac{dv}{da}(a) + Bv(a) + \mathcal{T}(a)v(a) = f(a), \text{ a.e. } a \in (0, a^+), \qquad (*)$$

$$v(0) = v_0$$

$$B : D(B) \subset L^2(0,L) \to L^2(0,L),\ D(B) = \{v \in H^1(0,L); v(0) = 0\},\ Bv = (\alpha v)_x$$

$$\mathcal{T} \in C^2([0,a^+]; \mathcal{L}(L^2(0,L); L^2(0,L))),\ \ \mathcal{T}(a)v(a,\cdot) = \pi(a,\cdot)v(a,\cdot)$$

Intermediate problem

$$\frac{dv}{da}(a) + Bv(a) + \mathcal{T}(a)v(a) = f(a), \text{ a.e. } a \in (0, a^+), \qquad (*)$$

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$$\mathcal{T} \in C^2([0, a^+]; \mathcal{L}(L^2(0, L); L^2(0, L))), \;\; \mathcal{T}(a)v(a, \cdot) = \pi(a, \cdot)v(a, \cdot)$$

Proposition. *Problem* $(*)$ *has a unique solution*

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

$$\|v\|_{C([0,a^+];H^1(0,L))} \leq \mathcal{F}(\textit{problem parameters})$$

Proof. Based on the quasi m-accretiveness of B with the constant $\omega = \frac{3}{2} \|\alpha_x\|_\infty + \sqrt{L} \|\alpha_{xx}\| + \pi_1 L.$

Fixed point theorem

Prove that Ψ is continuous on M, $\Psi(M) \subset M$, $\Psi(M)$ is compact

$$(z_1, z_2, z_3, z_4) \xrightarrow{\Psi} (\widetilde{v}_1, \widetilde{v}_2, \widetilde{v}_3, \widetilde{v}_4)$$

Ψ is a contraction on Y

$\Longrightarrow$ Ψ has a fixed point and replace in (intermediate) $z_i = \widetilde{v}_i$.

Theorem. *Let L be fixed. Under certain conditions satisfied by the parameters problem* (stationary) *has a unique nonnegative bounded solution*

$$\widetilde{n}_i \in C^1([0, a_i^+]; L^2(0, L)) \cap C([0, a_i^+]; H^1(0, L)),\ i = 1, ..., 4,$$

satisfying

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

$$\widetilde{n}_i \in \left[0, \frac{C_S}{u_0} + \frac{u_0}{C_\alpha}\right] \ \mathit{for\ any}\ (a_i, x) \in [0, a_i^+] \times [0, L],\ \ i = 1..., 4,$$

$$0 < \widetilde{u}(x; \widetilde{n}_i) \leq 2u_0.$$

$+$ conditions for problem parameters in good agreement with the biological facts

$$\mathcal{K}_0(\textit{problem parameters}) < R < \frac{u_0}{\sqrt{L}C_\alpha}$$

$$\mathcal{K}_1(\textit{problem parameters}) < 1$$

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
- the division rate of proliferating cells β_1 and the transformation rate of differentiated cells β_2
- the loss of cells of any type, μ_i and r, which depend on a possible exogenous death process

2.2 Determination of L

$$\Gamma(L) = \Gamma^*.$$

- $\Gamma \in C[0, L]$
- $\Gamma(x) > 0$
- $\Gamma(0) > \Gamma^*$
- Prove

$$\Gamma(x) \underset{x\to\infty}{\longrightarrow} 0.$$

$$\Uparrow$$

$$\|n_i(\cdot, x)\|_{L^2(0,a_i^+)} \underset{x\to\infty}{\longrightarrow} 0.$$

3 Mathematics: Numerical treatment of the mathematical model

3.1 Theoretical approach

$$\frac{\partial \widetilde{n}_i}{\partial a_i} + \frac{\partial}{\partial x}(\widetilde{u}(x;\widetilde{n}_i)\widetilde{n}_i) + \mu_i(a_i,x)M_i(a_i)\widetilde{n}_i = 0 \text{ in } (0,a_i^+)\times(0,L),$$

$$u_0\widetilde{n}_i(a_i,0) = \widetilde{S}_i(a_i) \text{ in } (0,a_i^+),$$

$$\widetilde{n}_i(0,x) = \sum_{j=1}^{4}\int_0^{a_j^+} A_{ij}(a_j,x)\widetilde{n}_j(a_j,x)da_j \text{ in } (0,L),$$

$+$ compatibility conditions.

Theoretical approach

$$\frac{\partial \widetilde{n}_i^k}{\partial a_i} + \frac{\partial}{\partial x}(\widetilde{u}(x;\widetilde{n}_i^{k-1})\widetilde{n}_i^k) + \mu_i(a_i,x)M_i(a_i)\widetilde{n}_i^k = 0 \text{ in } (0,a_i^+)\times(0,L),$$

$$u_0\widetilde{n}_i^k(a_i,0) = \widetilde{S}_i(a_i) \text{ in } (0,a_i^+),$$

$$\widetilde{n}_i^k(0,x) = \sum_{j=1}^{4}\int_0^{a_j^+} A_{ij}(a_j,x)\widetilde{n}_j^{k-1}(a_j,x)da_j \text{ in } (0,L),$$

$+$ compatibility conditions.

Theoretical approach

$$\frac{\partial v}{\partial a} + \frac{\partial}{\partial x}(\alpha(x)v) + \pi(a,x)v = 0 \text{ in } (0,a^+) \times (0,L),$$

$$u_0 v(a,0) = S(a) \text{ in } (0,a^+), \qquad \text{(intermediate)}$$

$$v(0,x) = F(x) \text{ in } (0,L),$$

$+$ compatibility conditions.

Theoretical approach

$$\alpha(x)\frac{\partial v}{\partial x} - \varepsilon\frac{\partial^2 v}{\partial a^2} + \frac{\partial v}{\partial a} + \left(\pi(a,x) + \frac{\partial \alpha}{\partial x}\right) v = 0 \text{ in } (0,a^+) \times (0,L),$$

$$u_0 v(a,0) = S(a) \text{ in } (0,a^+), \qquad \text{(approximate)}$$

$$v(0,x) - \varepsilon\frac{\partial v}{\partial a}(0,x) = F(x) \text{ in } (0,L),$$

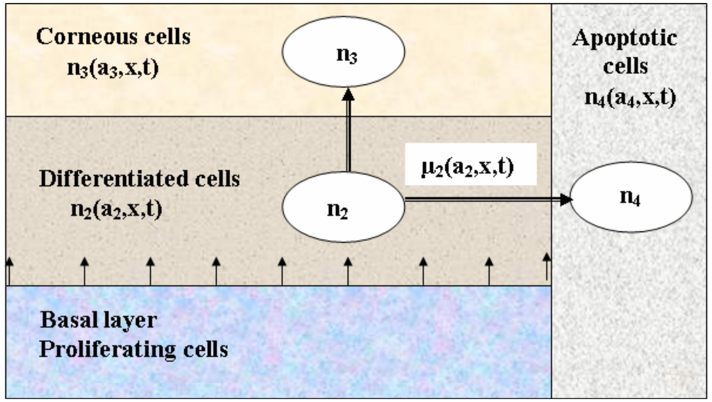
$$\frac{\partial v}{\partial a}(a^+,x) = 0$$

Theoretical approach

Theorem. *Problem* (approximate) *has a unique strong solution. The sequence of the solutions to (approximate) tends to a unique weak solution to* (intermediate).

3.2 Numerical simulations

Normal growth with apoptosis of differentiated cells



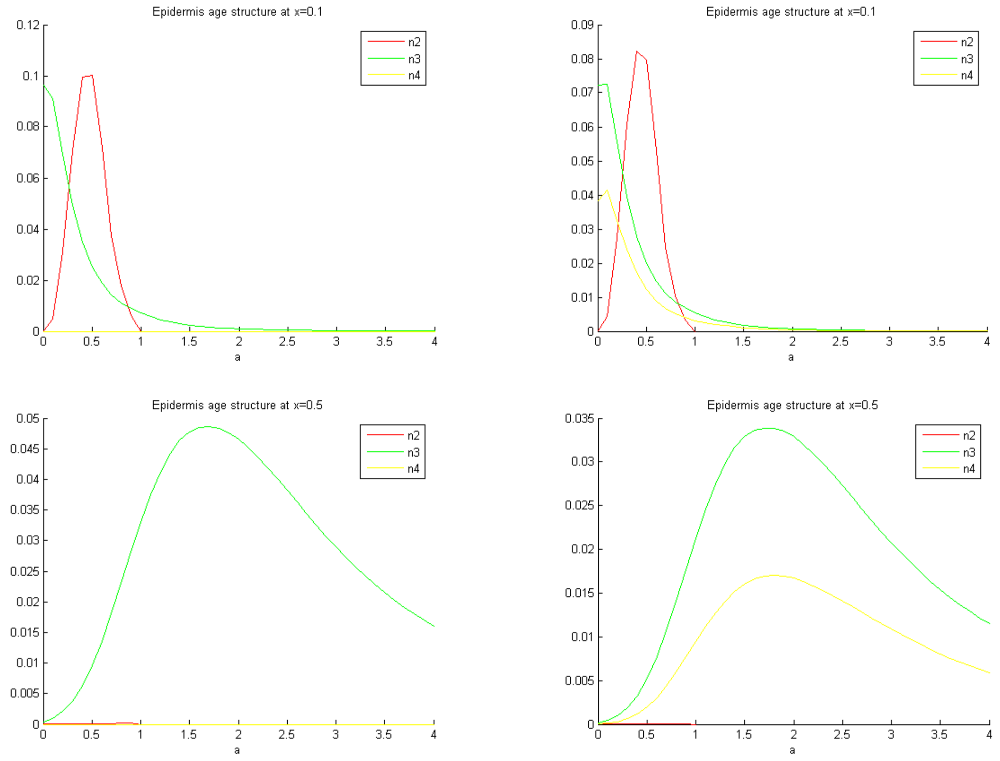
$$\beta_2, S_2, \mu_2;\ \beta_3 \Longrightarrow n_2, n_3$$

$$S_2(a) = \begin{cases} a(0.5-a), & a \in [0, 0.5) \\ 0, & a \in [0.5, 1] \end{cases} \qquad \beta_2(a) = \frac{1}{1-a},\ \ a \in [0,1)$$

$\mu_2(x) = 0$ compared with $\mu_2(x) = \exp(x)$

Normal growth with apoptosis of differentiated cells

Normal growth with $\mu_2 = 0$ Normal growth with $\mu_2 = \exp(x)$



Normal growth, no apoptosis ($\mu_2 = 0$) and a different interval of transformation of n_2 into n_3

Case I (slow transformation)

$$S_2(a) = \begin{cases} a(0.5-a), & a \in [0, 0.5) \\ 0, & a \in [0.5, 1] \end{cases}$$

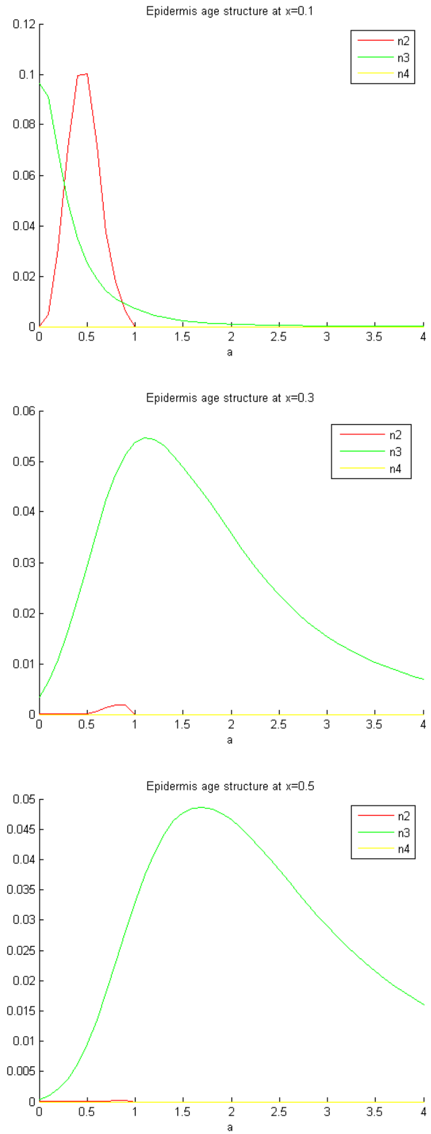
$$\beta_2(a) = \frac{1}{1-a}, \qquad a \in [0, 1)$$

Case II (fast transformation)

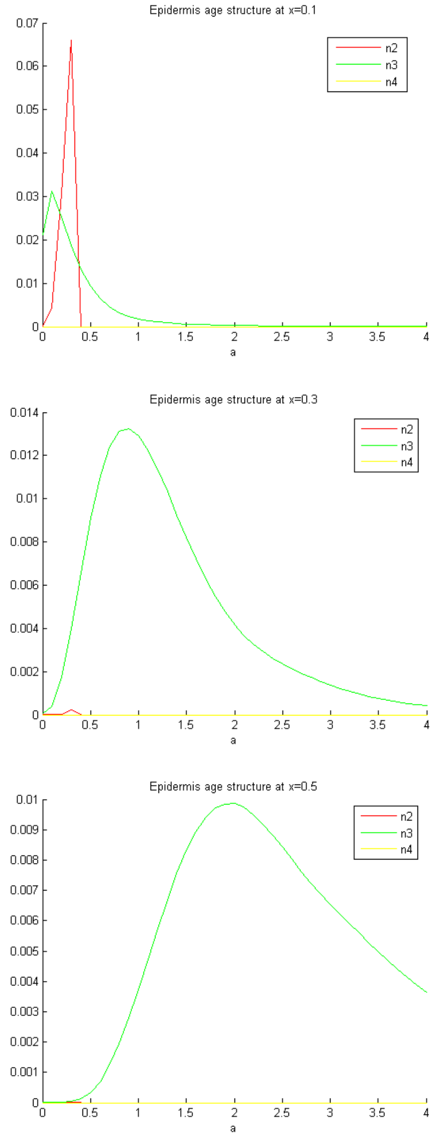
$$S_2(a) = a(0.5-a), \quad a \in [0, 0.4)$$

$$\beta_2(a) = \frac{1}{4}\frac{1}{0.4-a}, \qquad a \in [0, 0.4)$$

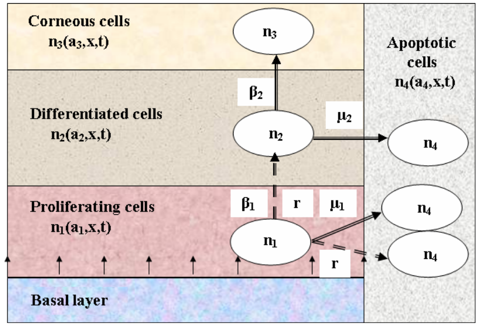
Case I: Slow transformation



Case II: Fast transformation



Pathological growth: proliferative disorder



$$S_1, \beta_1, \mu_1; S_2, \beta_2, \mu_2; \beta_3; r \Longrightarrow n_1, n_2, n_3, n_4$$

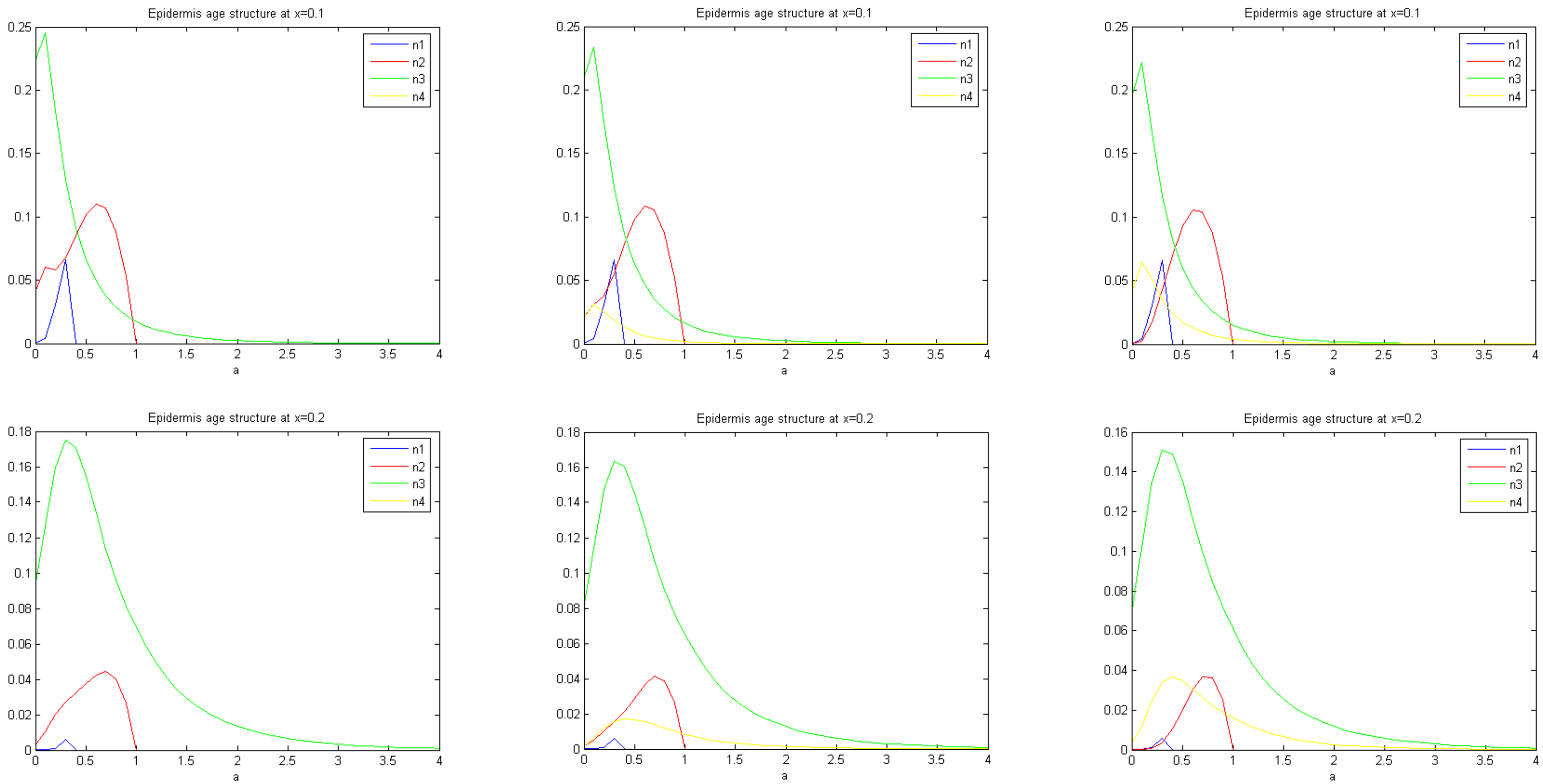
$$\mu_1 = \mu_2 = \beta_3 = \beta_4 = 0.$$

$$S_1(a) = a(0.5 - a), \quad a \in [0, 0.4] \quad \beta_1(a) = \frac{1}{4}\frac{1}{0.4 - a}, \quad a \in [0, 0.4)$$

$$S_2(a) = \frac{1}{4}a(1 - a), \quad a \in [0, 1] \quad \beta_2(a) = \frac{1}{1 - a}, \quad a \in [0, 1)$$

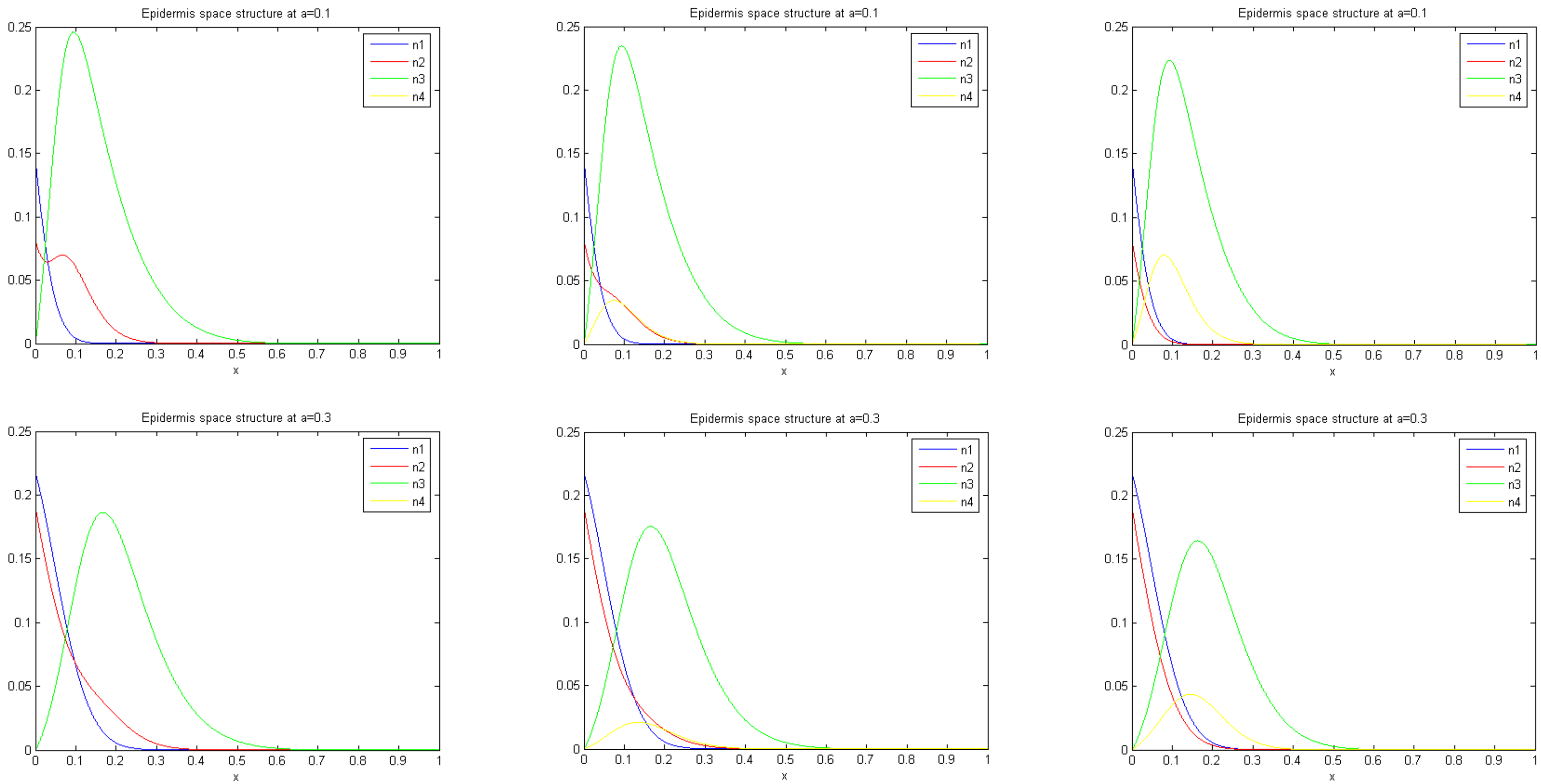
Epidermis age structure at various space positions

Complete mitosis, $r = 2$ **Incomplete mitosis, $r = 1$** **No mitosis, $r = 0$**



Epidermis space structure at various cell ages

Complete mitosis, $r = 2$ **Incomplete mitosis,** $r = 1$ **No mitosis,** $r = 0$



4 From mathematics to biology

- Identification problems of the parameters $(\beta_i, S_i, u_0, ...)$ on the basis of experimental data $\Longrightarrow$ diagnostic

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- Control problems $\Longrightarrow$ information for the biological research and medical therapies

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.... *in progress and future studies*

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Thank you for your attention !