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Kinetics of the maintenance of the epidermis

Research Article

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Abstract: The epidermis is the outermost layer of skin. It is comprised of keratin-containing cells called keratinocytes. Functionally, the epidermis serves as a physical barrier that can prevent infection and regulate body hydration. Maintenance and repair of the epidermis are important for human health. Mechanistically, these processes occur primarily via proliferation and differentiation of stem cells located in the basal monolayer. These processes are believed to depend on cell-cell communication and spatial constraints but existing kinetic models focus mainly on proliferation and differentiation. To address this issue, we present a mean-field kinetic model that takes these additional factors into account and describes the epidermis at a biosystem level. The corresponding equations operate with the populations of stem cells and differentiated cells in the basal layer. The keratinocytes located above the basal layer are treated at a more coarse-grained level by considering the thickness of the epidermis. The model clarifies the likely role of various negative feedbacks that may control the epidermis and, accordingly, provides insight into the cellular mechanisms underlying complex biological phenomena such as wound healing.

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1. Introduction

Biological systems are complex. As a rule, a system can be divided into subsystems which may be hierarchical or operate in parallel, and this process of division can often be continued downwards or upwards. Operation of biosystems is typically based on various feedbacks, but the corresponding mechanistic information is usually incomplete and remains to be elucidated further. Increasing understanding about the function of such systems is a prerogative of systems biology [1–3]. Currently, with a rapid expansion of our knowledge about biological subsystems, this interdisciplinary science is becoming more widely studied. One of the general concepts in this field is that the maintenance and stability of biological systems is often based on negative feedback loops.

In order to clarify the principles that govern the function of a biological system, generic kinetic models offer

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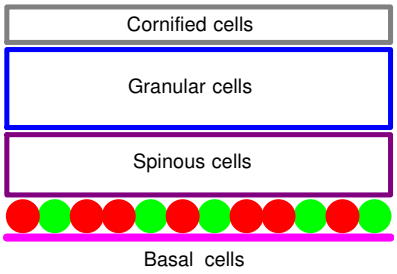

Figure 1. Schematic structure of the epidermis. Stem and differentiated cells located in the basal layer are shown explicitly. Stem cells are also found in the hair follicles (not shown), but while they have the potential to generate epidermis in circumstances such as wounding, they do not appear to contribute to maintaining normal epidermis [4].

a method to describe the interplay between corresponding subsystems. Such models should not only reflect the available knowledge about a biosystem, but also be sound with regards to biophysical chemistry. From these general perspectives, we focus our present work on the skin epidermis.

The epidermis is a self-renewing tissue between 0.05 and 1.5 mm thick that helps living organisms to avoid infection by pathogens, repel chemical and physical assaults, and prevent unregulated loss of water and solutes [4]. Structurally, the epidermis can be divided into four layers including, in respective order: (i) the basal monolayer containing stem and partially differentiated cells; [(ii) and (iii)] the spinous and granular layers composed of differentiated cells; and (iv) the cornified layer of dead cells (Fig. 1). The maintenance of the epidermis depends primarily on proliferation and differentiation of stem cells in the basal layer. Stem cells are also available in hair follicles. Under normal physiological conditions, the former and latter stem cell populations seem to function independently [4]. During cutaneous wound healing, follicular stem cells appear to play an important role in skin regeneration [5]. (Various stem cells are also indispensable for development of the epidermis [6]. However, this subject is beyond the scope of this article.)

Experimental studies of the epidermis are numerous [4]. Understanding the mechanisms that govern the maintenance of the epidermis is, however, still limited. Concerning the key processes occurring in the basal layer, there are contrasting lines of scientific evidence [7]. Morphological and cell proliferation studies [8] in mice have indicated that slow-cycling stem cells operate together with amplifying cell progeny, which are then converted into differentiated cells [Fig. 2(a)]. In contrast, lineage tracing

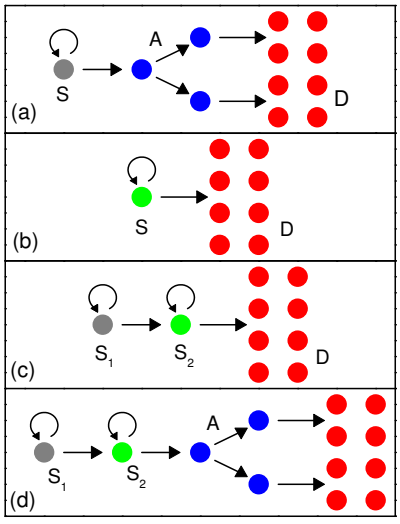

Figure 2. Kinetic schemes of proliferation and differentiation of stem cells in the basal layer according to Refs. [8] (a), [9] (b), [10] (c), and [7] (d). S, S_1 and S_2, A, and D represent stem, amplifying, and differentiated cells, respectively. Curly arrows indicate self-renewing ability of stem cells. (Adapted from Ref. [7].)

studies based on inducible genetic labeling [9] suggest the existence of a single population of stem cells that directly generates differentiated cells [Fig. 2(b)]. More recently, comparative analysis of two different transgenic mouse models [10] has provided evidence of two different stem cell populations, including slowly dividing and actively cycling ones [Fig. 2(c)]. Both of these populations share a similar pattern of asymmetric self-renewal in which the balance between proliferation and differentiation is achieved via stochastic fate choice (presumably on the level of interconnected functional gene networks [11]). This mechanism appears to reconcile seemingly contradictory earlier results. Taken together, these findings in combination with knowledge about stem cell proliferation and differentiation in other tissues [7] suggest that, in general, slowly dividing stem cells generate activated stem cells, which give rise to transient amplifying progenitors that eventually produce differentiated cells [Fig. 2(d)].

In terms of regulating these pathways, the proliferation and differentiation of stem cells (especially *in vivo*) are generally believed to depend on cell-cell communication, adhesion, and spatial constraints [12–14] (the corresponding kinetic models are reviewed in Ref. [15]). Since the epidermis is a heterogeneous mixture of different layers,

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cell-cell communication in this milieu is likely to be complex. Despite numerous related experimental studies [16]-[20], understanding of the role and mechanisms of the function of different signals is still far from complete (see the discussion below in Sec. 2). In light of this complexity, existing kinetic models related to the epidermis are focused primarily on proliferation and differentiation of stem cells in the basal layer (Refs. [9–11] and [21]-[30]). There is limited consideration of cell-cell communication, and as a rule neither feedback between the basal layer and the upper layers nor spatial constraints are taken into account. The goal of this work is to build a more comprehensive generic kinetic model that incorporates these variables in order to clarify the role these factors may play in maintaining and repairing the epidermis. Relying on the general principles of systems biology [1–3], we assume that maintenance and stability of the epidermis are based on negative feedback and systematically analyze the likely role of the corresponding factors.

2. Model

In our analysis, we adopt the simplest scheme to describe proliferation and differentiation of stem cells in the basal layer [Fig. 2(b)]. Specifically, the layer is assumed to contain stem cells, S, and differentiated cells, D. The division of stem cells occurs symmetrically or asymmetrically as

$$\mathrm{S} \rightarrow 2\mathrm{S}, \tag{1}$$

$$\mathrm{S} \rightarrow \mathrm{S} + \mathrm{D}, \tag{2}$$

$$\mathrm{S} \rightarrow 2\mathrm{D}. \tag{3}$$

The differentiated cells located in the basal layer may migrate to the upper layer of the epidermis,

$$\mathrm{D} \rightarrow \mathrm{E}, \tag{4}$$

where E designates the cell in the latter state. The top layer of the epidermis consists of dead, flat cells that are removed from this layer approximately every two weeks. This process is represented as

$$\mathrm{E} \rightarrow \emptyset. \tag{5}$$

To describe steps (1)-(4), we use the S and D populations (per unit area), N_s and N_d, respectively. The keratinocytes located above the basal layer are described at a more coarse-grained level based on the thickness of the epidermis, h. The mean-field kinetic equations for these variables are read as

$$dN_s/dt = (k_1 - k_3)N_s, \tag{6}$$

$$dN_d/dt = (k_2 + 2k_3)N_s - \kappa N_d, \tag{7}$$

$$dh/dt = as(\kappa N_d - rN_t), \tag{8}$$

where a is the cell size, s is the area per cell in the basal layer under saturation, N_t is the number of cells in the top layer, and k_1, k_2, k_3, κ and r are the rate constants of steps (1)-(5), respectively.

To account for the physics behind the steady state, we introduce the dependence of the rate constants in Eqs. (6)-(8) on N_s, N_d, and h. This dependence is assumed to result from signal-mediated cell-cell communication and spatial constraints. Following this line, it is convenient to operate with the S and D coverages defined as $\theta_s = N_s/N_*$ and $\theta_d = N_d/N_*$, where $N_* \equiv 1/s$ is the population of the basal layer at saturation. To also account for the spatial constraints, we further consider that the rate constants k_1, k_2 and k_3 are proportional to $1 - (\theta_s + \theta_d)^n$, where $n \geq 1$ is the corresponding exponent. This simple approach is widely employed in biological models that are focused on population kinetics as well as in various physicochemical kinetic models. In particular, $n = 1$ corresponds to the so-called logistic growth, while $n > 1$ is associated with generalized logistic growth [31]. With $n = 1$, the kinetics are sensitive to saturation already at $\theta_s + \theta_d \simeq 0.5$. In physiological situations, the saturation is expected to influence the kinetic at larger coverages. For this reason, we use $n > 1$ below.

The signal-mediated regulation of cell populations in general and the epidermis in particular is typically mediated via negative feedbacks. As already noted in the Introduction, this principle is common in nature [3] (the corresponding kinetic models focused on stem cells can be found, e.g., in Refs. [32]-[36]). Concerning the epidermis, experimental studies indicate that the keratinocyte population is controlled by Ca^{2+} [17, 18], ephrin [19] (a membrane-linked protein serving as a ligand for Eph receptors), a family of epidermal growth factors (such as factor-α, amphiregulin, heparin binding-EGF, and epiregulin) acting in an autocrine or paracrine manner [16], and Rho family proteins related to cell-cell adhesion [20]. With increasing environmental Ca^{2+} concentration, the proliferation of keratinocytes is retarded while differentiation is enhanced [18]. Proliferation is also negatively regulated by the Eph/ephrin signaling complexes [19]. The inclusion of this information into our model is, however, not straightforward. For example, Ca^{2+} is supplied into the epidermis from underlying layers [37]. The Ca^{2+} gradient depends on

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the epidermal permeability barrier and endogenous Ca^{2+} stores contained in the endoplasmic reticulum and Golgi [17]. Whether and how this gradient is influenced by the stem cells is now not clear (in recent experimental studies [17, 18] and review [38], this aspect is not mentioned; according to the most recent model [39], the Ca^{2+} concentration in the basal layer is considered to be constant, and accordingly the Ca^{2+}-mediated regulation can hardly be described in terms of feedbacks). Eph/ephrin signaling complexes are, in turn, inherent to various keratinocytes, and it is not clear either how this factor can be incorporated into the model. The situation with other epidermal growth factors is similar. For these reasons, we focus our analysis on general aspects of the regulation of proliferation and differentiation of keratinocytes.

The signal-mediated regulation depends on the concentration of the corresponding species (for examples, we refer to the models described in Refs. [40, 41]). In our treatment, the concentrations are assumed to depend monotonously on θ_s, θ_d, and/or h and accordingly the rate constants k_i ($i = 1$, 2 or 3) and κ are also considered to depend monotonously on these variables. Specifically, we use the conventional Hill expressions in order to describe these dependences (in the context of stem cells, these expressions were employed, e.g., in Refs. [33, 34]). For example, the dependence of the rate constants k_i on θ_s and θ_d are represented as

$$k_i \propto \lambda_i^m/(\lambda_i^m + \theta_s^m + \theta_d^m) \tag{9}$$

in the case when step (1) or (2) is regulated by S and D competitively, or as

$$k_i \propto \lambda_i^m/(\lambda_i^m + \theta_s^m) \tag{10}$$

or

$$k_i \propto \lambda_i^m/(\lambda_i^m + \theta_d^m) \tag{11}$$

when the regulation is related, respectively, to S or D (λ_i and m are the Hill parameters). The feedback between the differentiated cells in the basal layer and the cells located in the upper layers is in turn described as

$$\kappa \propto \mu^l/(\mu^l + h^l), \tag{12}$$

where μ and l are the parameters.

Using e.g. expressions (9), (11) and (12) for k_1, k_2 and κ and setting $N_t = N_*$, we have

$$\frac{d\theta_s}{dt} = \left(\frac{k_1^\circ \lambda_1^m}{\lambda_1^m + \theta_s^m + \theta_d^m} - k_3^\circ\right)[1 - (\theta_s + \theta_d)^n]\theta_s, \tag{13}$$

$$\frac{d\theta_d}{dt} = \left(\frac{k_2^\circ \lambda_2^m}{\lambda_2^m + \theta_d^m} + 2k_3^\circ\right)[1 - (\theta_s + \theta_d)^n]\theta_s - \frac{\kappa_\circ \mu^l \theta_d}{\mu^l + h^l}, \tag{14}$$

$$\frac{dh}{dt} = a\left(\frac{\kappa_\circ \mu^l \theta_d}{\mu^l + h^l} - r\right), \tag{15}$$

where k_i° and $\kappa_\circ$ are the rate constants in the absence of spatial constraints and feedback.

If alternatively k_1 is described by employing expression (10), Eq. (13) should be rewritten as

$$\frac{d\theta_s}{dt} = \left(\frac{k_1^\circ \lambda_1^m}{\lambda_1^m + \theta_s^m} - k_3^\circ\right)[1 - (\theta_s + \theta_d)^n]\theta_s. \tag{16}$$

Eqs. (13)-(16) allow us to illustrate the key predictions of the model. Basically, our model can be classified as a minimal model describing the epidermis, because we use the simplest scheme of proliferation and differentiation of stem cells in the basal layer, the simplest equation for the other layers, and operate on the mean-field level (to describe spatial effects related, e.g., to cell-cell adhesion, the lattice Monte Carlo simulations are preferable [36]). It contains five rate constants, k_1, k_2, k_3, κ, and r. The last rate constant, r, which characterizes dead cells is not regulated, and its value is fixed. Each of the other four rate constants can, in principle, be regulated in different ways. Although full classification of the corresponding kinetics is beyond our goal, our analysis of different situations has drawn out general conclusions that can be illustrated by using specific examples of the different types of regulation.

Concerning the relation between our model and the other kinetic models, we repeat (cf. the Introduction) that the earlier studies are primarily focused on the cells in the basal layer. In particular, Eqs. (6) and (7) have been employed in Refs. [9, 23–26, 28] in order to describe this layer. In our analysis, we complement Eqs. (6) and (7) by Eq. (8) for the other layers and focus on the feedbacks mediated by cell-cell communication.

If the parameters in Eqs. (6)-(8) are chosen arbitrarily and are fixed, the model does not predict a steady state, i.e., there will be either uncontrolled growth or shrinkage of the epidermis. To reach a steady state at least in the basal layer, there must be the condition that $k_1 = k_3$ in Eq. (6) (this condition makes the model close to the Moran class [33, 42]). Under steady-state conditions, Eq. (7) then yields $N_d = [(k_2 + 2k_3)/\kappa]N_s$. These prescriptions were employed in Refs. [9, 23, 24]. In our analysis, such constraints are not imposed.

After the completion of our work, a three-variable model operating with the population of stem cells in the basal layer, the population of differentiated cells in other layers, and the concentration of a growth factor controlling the division of stem cells was recently proposed in Ref. [30]

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(Eqs. (3.3)). In that study, the growth factor formation rate is assumed to depend on its concentration and to be independent of the cell populations, while the degradation rate is determined by the cell populations. Compared to our model, this alternative scheme does not include feedback mediated directly between stem cells and differentiated cells. Thus, the two models are complementary and consistent.

3. Results of calculations

To illustrate our findings, let us consider, for example, that the transition of the differentiated cells from the basal layer to the upper layers is regulated by the cells located in the upper layers and the corresponding rate constant is described by Eq. (12). In addition, let us consider that the asymmetric division resulting in differentiation [step (2)] is regulated by D as described by Eq. (11), while the symmetric division resulting in differentiation [step (3)] is not regulated. For the symmetric division resulting in proliferation [step (1)], we will choose the regulations described by Eq. (9), (10) or (11).

Taking into account that the processes under consideration occur on an one-week time scale, biologically reasonable values of the rate constants are expected to be in the range from 0.2 to 2 w^{-1} (w = week) or higher (because the rates are reduced due to negative feedback and spatial constraints). Under steady-state conditions, the model should predict $\theta_1 \simeq 0.2$ and $\theta_2 \simeq 0.7$ (see the experiment and earlier simulations [9]). Following this line, rate constants can be selected to obtain $\theta_2 \simeq 0.7$. However, the situation with θ_1 is found to depend strongly on the type of regulation that governs the symmetric division resulting in proliferation [step (1)].

If we (i) assume that regulation of symmetric division resulting in proliferation is related to S and D and described by Eq. (9) or related to D and described by Eq. (11) and (ii) choose the parameter such that $\theta_2 \simeq 0.7$ under steady-state conditions, the model typically predicts that θ_1 is smaller than 0.2. The natural way to increase θ_1 is to increase k_1°. With increasing k_1°, θ_1 and θ_2 first increase slightly but then the system is rapidly trapped into the state where the basal layer contains only stem cells, as illustrated e.g. in Fig. 3 showing the kinetics calculated by using Eqs. (13)-(15). Physically, this occurrence is related to the decrease of the rate of steps (2) and (3) with increasing coverage due to the spatial constraints. These steps become less favourable compared to step (4), and the D population diminishes. Practically, this means that the results are too sensitive with respect to model parameters.

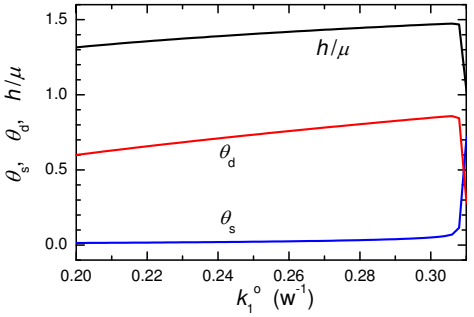

Figure 3. Coverages of stem and differentiated cells in the basal layer and thickness of the upper layers as a function of k_1° under steady-state conditions according to Eqs. (13)-(15) with $k_2^\circ = 50\ w^{-1}$, $k_3 = 0.1\ w^{-1}$, $\kappa_\circ = 2\ w^{-1}$, $r = 0.3\ w^{-1}$, $\lambda_1 = \lambda_2 = 0.6$, $l = 4$, $m = 2$, $n = 4$, and $\mu/a = 100$.

If we assume that regulation of the symmetric division resulting in proliferation is related to S as described by Eq. (10) and choose the parameters so that $\theta_2 \simeq 0.7$ under steady-state conditions, the condition $\theta_1 \simeq 0.2$ can easily be met, and the steady-state kinetics are not too sensitive with respect to the parameters, as illustrated in Fig. 4 showing the results obtained by employing Eqs. (14)-(16).

To illustrate some predictions of the model (with the same type of regulation and parameters as those chosen to construct Fig. 4), we show (Fig. 5, thick lines) what happens if initially (at $t = 0$) two variables correspond to the steady state while one of the variables is lower than that calculated for the steady state. With the parameters selected, we have $\theta_s = 0.2$, $\theta_d = 0.69$, and $h/\mu = 1.38$ at the steady state.

If the coverage of stem cells is initially decreased down to 0.1 [Fig. 5(a)], it then slowly increases up to the steady-state value while the coverage of differentiated cells in the basal layer and the thickness of the upper layers remains close to those corresponding to the steady state.

If the coverage of differentiated cells in the basal layer is initially decreased down to 0.3 [Fig. 5(b)], it rapidly returns to the steady-state value while the coverage of stem cells and the thickness of the upper layers remain close to those corresponding to the steady state.

If the thickness of the upper layers is initially reduced down to $h/\mu = 0.5$ [Fig. 5(c)], the population of stem cells remains close to the steady-state value while the population of differentiated cells in the basal layer first rapidly drops (because the transit of these cells to the upper layers becomes facilitated) and then the population of these cells as well as the population of differentiated cells in the upper layers slowly increase up to the steady-state level.

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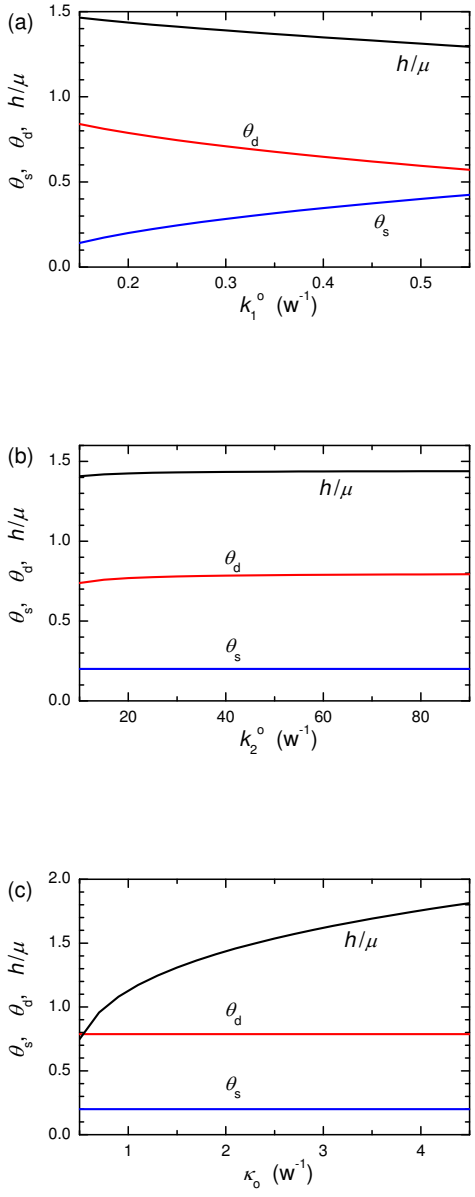

Figure 4. Coverages of stem and differentiated cells in the basal layer and thickness of the upper layers under steady-state conditions according to Eqs. (14)-(16): (a) as a function of k_1° for $k_2^\circ = 50$ w^{-1} and $\kappa_\circ = 2$ w^{-1}, (b) as a function of k_2° for $k_1^\circ = 0.2$ w^{-1} and $\kappa_\circ = 2$ w^{-1}, and (c) as a function of $\kappa_\circ$ for $k_1^\circ = 0.2$ w^{-1} and $k_2^\circ = 50$ w^{-1}. The other parameters are $k_3 = 0.1$ w^{-1}, $r = 0.3$ w^{-1}, $\lambda_1 = 0.2$, $\lambda_2 = 1$, $l = 4$, $m = 2$, $n = 4$, and $\mu/a = 100$.

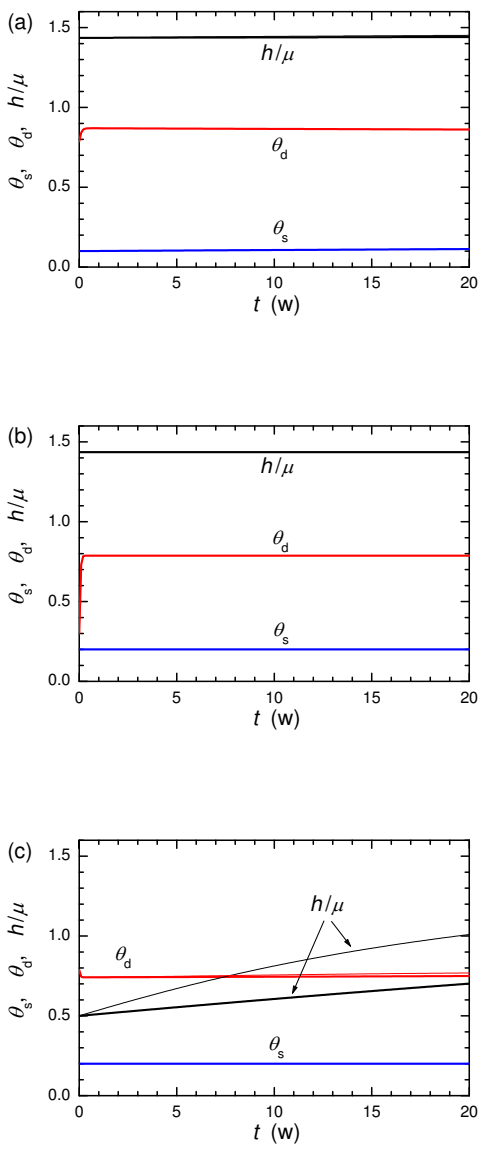

Figure 5. Coverages of stem and differentiated cells in the basal layer and thickness of the upper layers as a function of time for (a) $\theta_s(0) = 0.1$, $\theta_d(0) = 0.69$, $h(0)/\mu = 1.38$, (b) $\theta_s(0) = 0.2$, $\theta_d(0) = 0.3$, $h(0)/\mu = 1.38$, and (c) $\theta_s(0) = 0.2$, $\theta_d(0) = 0.69$, $h(0)/\mu = 0.5$. The kinetics shown by thick and thin lines have been calculated with $\mu/a = 100$ and $\mu/a = 30$, respectively (the other parameters are similar to those used to construct Fig. 4: $k_1^\circ = 0.2$ w^{-1}, $k_2^\circ = 50$ w^{-1}, $k_3 = 0.1$ w^{-1}, $\kappa_\circ = 2$ w^{-1}, $r = 0.3$ w^{-1}, $\lambda_1 = 0.2$, $\lambda_2 = 1$, $l = 4$, $m = 2$, and $n = 4$). Note that variation of μ/a influences the time scale of the transient regime but does not change the steady-state values of the variables ($\theta_s = 0.2$, $\theta_d = 0.69$, and $h/\mu = 1.38$). In particular, the kinetics shown in panel (c) indicate that the transition to the steady-state regime becomes faster with decreasing μ/a from 100 to 30. The kinetics exhibited in panels (a) and (b) are nearly independent of μ/a (the thick and thin lines almost coincide and are not distinguishable).

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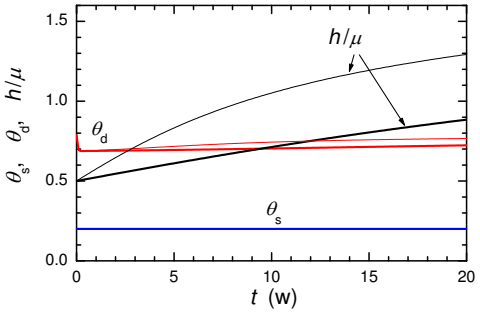

Figure 6. As Fig. 5(c) for $\kappa_\circ = 4\ w^{-1}$. In this case, the steady-state values of the variables are: $\theta_s = 0.2$, $\theta_d = 0.788$, and $h/\mu = 1.76$.

If the thickness of the upper layers is initially reduced, the time scale of the subsequent transient kinetics depends first of all on μ/a and $\kappa_\circ$. With decreasing μ/a (Fig. 5, thin lines) or increasing $\kappa_\circ$ (Fig. 6), the transient period becomes shorter.

From a biological perspective, the situation described in Fig. 5(c) and 6 may resemble the repair of the epidermis after damage. Specifically, the proliferation and differentiation of stem cells in the basal layer is modulated in response to an event that initially reduced the thickness of the upper layer - e.g., a wound that requires healing. Interestingly, the time scale of the initial phase of this process is predicted in this case to be about one or two months while the timescale of the whole process is on the order of several months. The former and latter timescales are, respectively, comparable with and longer than that (a few weeks) typically observed during wound healing. The longer period of time that is predicted by the model appears to indicate that amplifying cells [Fig. 2(d)] and/or follicular stem cells [5] may actually participate in repair, although they were not represented in the model. Additionally, it is worth considering that the healing time may be related to the depth of the wound. Looking forward, this general kinetic model now provides an avenue to understand the dynamics of wound healing and the relationship between the process time and spatial constraints. For example, this model may find utility in comparing the repair of deep wounds versus superficial wounds.

4. Conclusion

We have presented and analyzed a generic mean-field kinetic model to understand the maintenance and repair of the epidermis. It operates with the populations of stem cells and differentiated cells in the basal layer and the thickness of the layers located above the basal layer. It also takes cell-cell communication and spatial constraints into account. The underlying general idea behind this approach is that the maintenance of epidermis is controlled by negative feedback. Although this idea is central within systems biology [1–3], the corresponding models clarifying the likely role of various feedbacks in the maintenance and repair of the epidermis have so far remained to be elucidated further. In this work, we have presented the first model to describe this behaviour. The key predictions of our model are illustrated in Figs. 3-6. The corresponding kinetics have been calculated numerically by using specific values for the different parameters. One of the aims of this method was to show general trends predicted by the model (this means that we have performed many more calculations than we present).

Our general conclusions are as follows:

(i) Not every type of negative feedback is suitable for maintenance of the epidermis. For example, the model is too sensitive to the choice of parameters if we assume that proliferation of stem cells is controlled simultaneously by stem cells and differentiated cells, or by differentiated cells. Self-inhibition of stem cells seems to be preferable.

(ii) The time scale of transient regimes is sometimes predicted to be longer than one may expect in light of biological responses in nature. This might indicate that the model should be complemented by terms describing amplifying cells and/or follicular stem cells. Another consideration is that deeper wounds require longer healing times than superficial wounds. Further analysis of the spatial constraints may be warranted.

At present, experimental reports concerning the regulation of stem cell proliferation and differentiation in the epidermis are lacking, particularly at the level of communication between stem cells and differentiated cells. Our kinetic model provides insights into the maintenance and repair of epidermis that may guide future experiments.

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