Mathematical Model of Epidermal Structure

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Abstract Using a mathematical model of the epidermis, we investigate how the structure of the dermis affects the spatio-temporal pattern of the upper structure, especially the stratum corneum (SC). We find that, while large scale undulations greatly affects the upper structure, small scale undulations do not propagate into the upper structure, which is consistent with experimentally observed cross sections of the epidermis.

Keywords Off-lattice model · Calcium dynamics · Dermatology

1 Introduction

Skin is an important organ. It serves as barrier by blocking chemical and physical attacks from outside, and at the same time keeping body fluid inside. Skin is composed of two layers: the inner part is called *dermis*, where a network of blood vessels can be found; and the outer part is *epidermis*, where epidermal cells (keratinocytes) form a layered structure. The barrier function is maintained by the outermost layers in the epidermis, called the stratum corneum (SC). Several experiments have shown that, in healthy normal epidermis, there exists a layer of high concentration region of Ca^{2+} just beneath the SC. It is also known that the Ca^{2+} distribution in this layer is closely related to the status of the layered structure of the SC.

In order to fully understand the role of the barrier function, a model of the organized structure of the SC is required. In fact, cross sections of skin show that, while

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the dermis is highly undulated, the SC has a flat structure. Considering the fact that keratinocytes are supplied from the basal layer, which also has undulations matching the dermis beneath it, how a flat structure of the SC is created from the undulated basal layer is not clear.

We have recently proposed a mathematical model for epidermis, which is based on the Ca^{2+} localization phenomenon [1, 2]. This model could successfully reproduce the layered structure of the epidermis, namely the low-Ca^{2+} keratinocytes on the dermis, the SC on top, and the Ca^{2+} -localized monolayer between them. This model has also revealed that Ca^{2+} localization can reduce the spatio-temporal fluctuations of the SC. Using this model, in this paper, we investigate how the dermal structure influences the upper structure, especially the SC.

2 Particle Dynamics Model

Let us first briefly introduce our mathematical model of epidermis. Details about the model will be reported elsewhere [3].

Each epidermal cell is represented by a spherical particle, which is continuously supplied from the basal layer. Cells interact with each other through a short-range repulsive interaction: The cell at $\boldsymbol{x} = \boldsymbol{x}_i$ with the radius r_i feels the force $-\frac{\partial}{\partial \boldsymbol{x}_i} V(|\boldsymbol{x}_i - \boldsymbol{x}_j|)$ from the other cell at $\boldsymbol{x} = \boldsymbol{x}_j$ with the radius r_j, where we assume that V has a Lennard-Jones type interaction structure:

$$V(|\boldsymbol{x}_i - \boldsymbol{x}_j|) = 2\left(\frac{r_i + r_j}{|\boldsymbol{x}_i - \boldsymbol{x}_j|}\right)^6 - \left(\frac{r_i + r_j}{|\boldsymbol{x}_i - \boldsymbol{x}_j|}\right)^{12}. \tag{1}$$

The i-th cell is assigned a degree of differentiation, denoted by $S_i(t)$, which is a non-decreasing function of t. When $S_i(t) = S^*$, the cell is considered to be cornified, becoming a part of the SC. We assume that this cornification process is accelerated when Ca^{2+} inside the cell is high:

$$\dot{S}_i = \omega' + \alpha'(c_i - \bar{c})_+, \tag{2}$$

where $(x)_+$ equals x if x is positive and otherwise 0, c_i is the Ca^{2+} concentration of the i-th cell, and ω' and α' are constants.

The Ca^{2+} dynamics are modelled using our recently proposed mathematical model of intra-cellular Ca^{2+} in the epidermis [2]. This model is in essence a discretized version of a reaction-diffusion equation, with the source term coming from the cornified cell. Here it is assumed that, when a cell undergoes cornification, it releases a stimulant, which induces Ca^{2+} excitation in the neighbouring cells. There is thus an interdependence between the Ca^{2+} dynamics and the cell differentiation.

This model has successfully reproduced the experimentally observed Ca^{2+} localization phenomenon beneath the SC. Also it has been shown that when we neglect Ca^{2+} dynamics, the spatio-temporal structure of the Ca^{2+} localization is greatly affected, leading to instability in the SC layers [3].

3 Numerical Simulations

In this paper, new numerical results are presented about the effect of the dermal structure. We consider a three dimensional space $[0, L] \times [0, L] \times [f(x, y), L_z]$, where $f(x, y)$ determines the dermis. Here the following sinasoidal undulations, uniform in y, are assumed:

$$f(x, y) = \frac{A}{2} \sin\left(\frac{2\pi n x}{L}\right). \tag{3}$$

Periodic boundary conditions are assigned in the x and y directions. Particles on the dermis reproduce themselves at a constant rate, and thus supply new particles to the upper layers. Particles on the top layer disappear when a certain time elapses after cornification.

Figure 1 shows two examples of numerical simulations with different wavelengths of the dermal undulations. In both cases, we find that organized structures of epidermis are reproduced, where a localized layer of high-Ca^{2+} keratinocytes forms between the low-Ca^{2+} layers and the SC, which is in accordance with our previous results in the case of a flat dermis, as mentioned above [3]. However, in the case of undulated dermis, the upper structure shows significant differences depending on the wavelength of the dermis.

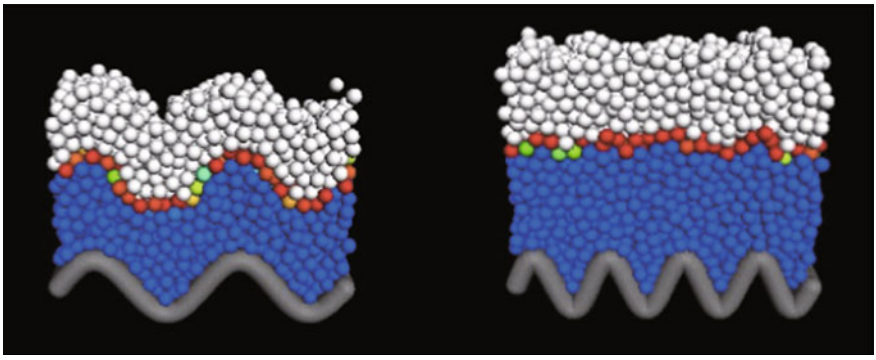

Fig. 1 Numerical simulation of the epidermis. *Left* $n = 2$, $A = 10$; *right* $n = 4$, $A = 10$. The dermal boundary is *colored gray*, and the SC is *colored white*. In the *middle* between the dermis and the SC, *colors* indicate the Ca^{2+} level: *blue* for *low* Ca^{2+}, *red* for high Ca^{2+}

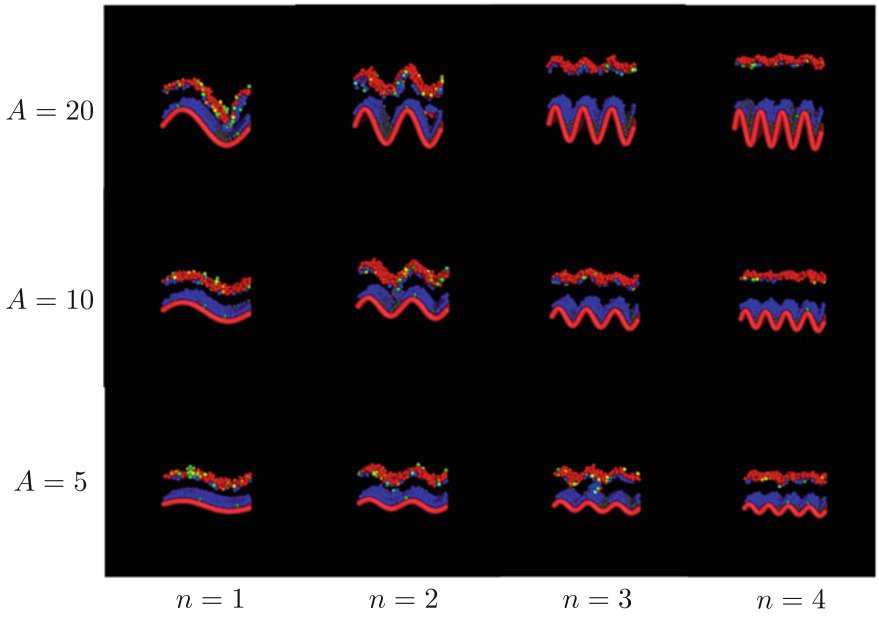

Fig. 2 Comparison of the spatial structure of Ca^{2+} localization layers for different values of n and A. For each panel, the *bottom red* represents the dermis. *Blue* and *gray* particles on the dermis represent the reproducible particles; *blue* ones are in the reproduction process. For the other particles, only the Ca^{2+} localization layer, the particles which are in contact with the SC, are shown

For different values of wavenumber n and amplitude A, we performed numerical simulations, as shown in Fig. 2. Here, apart from the dermis and the basal layer, we visualized only the cells which form Ca^{2+} localization layers: the cells which are in contact with the cornified cells. We found that, as n increases, which means the decreased wavelength of dermal undulations, the Ca^{2+} localization layer becomes flatter and flatter. In the case $n = 1$, for example, when the amplitude of the dermal undulation increases, the undulation of the Ca^{2+} localization layer becomes amplified. On the other hand, in the case $n = 5$, the undulation of the Ca^{2+} localization layer remains flat even for larger amplitudes.

To quantify these observations, we introduce the following evaluation function:

$$E(t) = \frac{1}{N_c(t)} \sum_{j \in \Omega} \frac{(z_j(t) - \bar{z}(t))^2}{D^2}, \tag{4}$$

where Ω is the set of particles which are in contact with the SC, $N_c(t)$ is the number of particles in Ω, $z_j(t)$ is the height of the j-th particle, D is the diameter of the particles, and $\bar{z}(t) \equiv \frac{1}{N_c(t)} \sum_{j \in \Omega} z_j(t)$. Note that all these values are time dependent. $E(t)$ can be used as a measure of deformation of the Ca^{2+} localization layer: $E(t) \geq 0$ by definition, and in particular $E(t) = 0$ if the layer is completely flat.

Figure 3 shows the time evolution of $E(t)$ for different values of n, with $A = 10$. It is clear that, when the wavelength of the dermal undulation is large (small n), the structure of the Ca^{2+} localization layer not only deforms in space, but also fluctuates in time. On the other hand, as the wavelength becomes shorter (larger n), this spatio-temporal flucation becomes reduced.

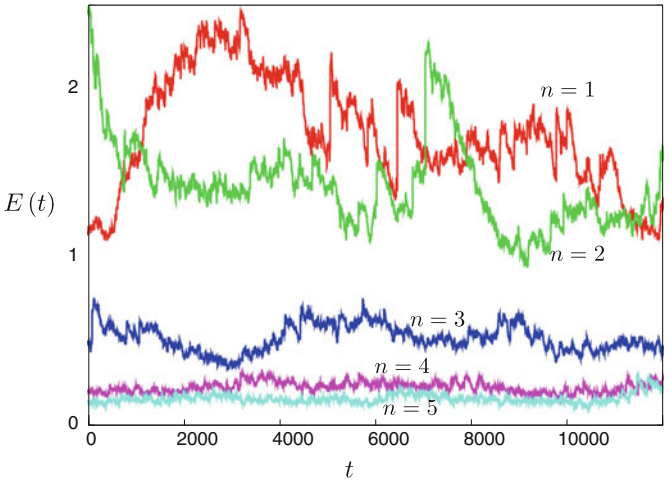

Fig. 3 Time evolution of $E(t)$ for different values of n, with $A = 10$

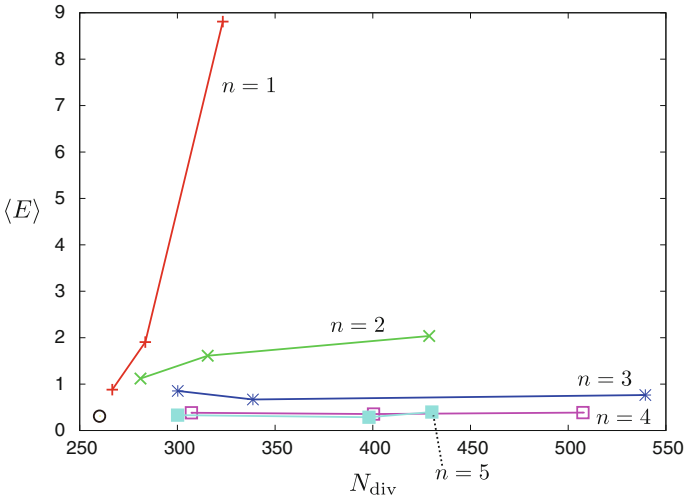

Fig. 4 Time average of $E(t)$ against the number of reproducible particles N_{div} for different values of n and A. For each n, three different values of A (5, 10, 20) are plotted, for each of which N_{div} is counted. The *open circle* near the *left bottom* corresponds to the case of the flat dermis ($n = 0$, $A = 0$)

Since different values n and A lead to different surface area of the dermis, the number of cells reproduced from the bottom layer, denoted by N_{div}, which is proportional to the surface area, also depends on n and A. In order to compare the deformation with the same supply rate of particles, we plotted the time-average of $E(t)$, $\langle E \rangle$, for different values of n and A, as a function of N_{div}, as shown in Fig. 4. This shows that the wavenumber dependence becomes larger as increasing the number of reproducible particles, i.e., as increasing the supply rate of particles. It is also indicated in Fig. 4 that there is a critical wavenumber between $n = 2$ and $n = 3$, above which the upper structure is not affected by the dermis.

4 Concluding Remarks

We have investigated the effect of dermal undulations on the epidermal structure, and found that, while large scale undulations are directly reflected in the upper structure, small scale undulations affect the upper structure in a limited way. This can be considered as a result of Ca^{2+} dynamics: since the stimulant of Ca^{2+} excitation diffuses into space, the high-stimulant-concentration surface tends to become flat, and particles which are about to undergo cornification also tends to follow this surface. Although a thorough analysis of our particle-based model beyond numerical investigation is difficult, a reduced model based on a reaction-diffusion system might be constructed, which can grasp the nature of reduced short-wavelength fluctuations observed here.

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