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Particle Simulation on Epidermal Skin Formation - Mechanism of Basal Layer Formation -

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Abstract

Skin is the largest organ of the human body. The bottom of the epidermis is called the basal layer and is very uneven. However, the mechanism of uneven formation of the basal layer has not yet been elucidated. Computational simulation can be useful in further understanding the mechanisms of skin formation. We propose a particle model that can handle complex biological phenomena, including cell interactions and is a suitable method for the simulation of skin formation. In this study, we created a model similar to the actual skin using three-dimensional analysis and elucidated the formation mechanism of the basal layer. Particularly, each basal cell of this model is subjected to three patterns of cell division, which can simulate skin formation with an increase and decrease of basal cells and the consequent generation of upper cell layers. Therefore, we analyzed the association between these cell division patterns and the uneven formation of the cell layer.

Keywords: Numerical Simulation, Skin Formation, Particle Model, Basal Layer

1. Introduction

Skin is the largest organ of the human body. We can diagnose epidermal conditions and provide appropriate care particularly because the epidermis is the most external part of the skin [1]. In recent years, there has been an increasing concern regarding the cosmetic aspects of skin care in both men and women, prompting research studies on anti-ageing therapy and cosmetics.

The epidermis consists of four differentiated layers. In particular, the basal layer, which is at the bottom of epidermis, is unevenly formed. This unevenness is considered to be associated with spots and ageing. Therefore, it is important to elucidate the mechanism of the formation of an uneven basal layer. However, there are many unexplained phenomena in skin metabolism and the formation of uneven layers because the *in situ* observation of basal layer formation is difficult.

Computational simulation can be useful in further understanding the mechanisms of skin development, and several models have been proposed [2-5]. In this study, we propose a particle model that can handle complex biological phenomena, including cell interactions such as cell division, motion, deformation, and transition [6-8]. Furthermore, we believe that it is a suitable method for simulating skin formation. We developed an analytical method for studying the formation and turnover process of the skin using the particle model [9-11].

This study clarified the mechanism of cutification, which includes basal layer unevenness, using the particle method. The particle method can simulate three-dimensional skin formation with cornification and by changing physical properties, whereas also being able to increase and decrease basal cell production. We analyzed a process of long term skin formation and elucidated the mechanism of uneven basal layer formation using this model. Our aim was to elucidate the phenomena of epidermal skin formation using this model to contribute to medical skin treatment and the development of cosmetics.

2. Analysis Object and Model Description

2.1 Analysis Object

Figure 1 depicts a cross-section of the skin [1], and the roles of each cell layer are described. The epidermis is the outermost layer of the skin and is primarily composed of cells called keratinocytes. The epidermis consists of four layers. A basal layer, which is the lowest layer of the epidermis, provides new cells by dividing each day. The dividing cells are called the prickle layer, which are pushed and moved up toward the skin surface, transforming into the granular layer and stratum corneum, which finally detaches from the skin surface. Skin cells change not only in their shape but also in their physical properties during this process. This process is referred to as turnover and occurs at approximately 4-week intervals. Dermis is located under the epidermis, and is divided by the basal layer. Furthermore, capillaries in the dermis supply nutrition and oxygen for basal cells.

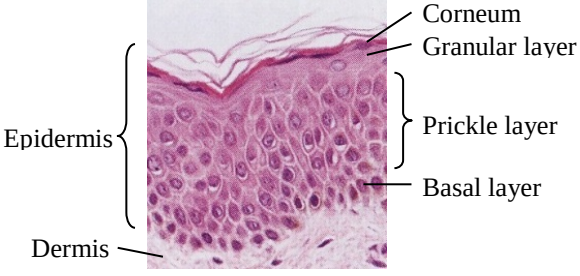


Fig. 1 Cross-section of the skin [1]

2.2 Model Description

The particle model [6-8] is introduced to simulate the epidermal skin formation process [9-11]. The model considers the interaction between the particles and pursues motions of the particles in a Lagrangian way. This method is suitable for analysis with large deformations, or when the numbers of calculation points are changing. The cellular particles move in response to inter-particle forces, such as volume conservation force and spring force. The volume conservation force, F, in Equation (1) works to keep the distance between the particles. Because of the repulsive force, particles eventually move to a stable distance. Here k, is a coefficient, ddr is the distance between two particles, $dr0$ is the standard distance (10.0 μm in this case), $dr1$ is the maximum distance which volume conservation force works to; $dr1$ is larger than $dr0$. The spring force f in Equation (2) works to make the continuum of the cellular particles structural. Here, k' is the coefficient of elastic spring. Spring force has already introduced cornification into our model [9-11]. In this paper, we describe the application of spring force to the basal layer. The actual basal layer maintains a layer with film shape, which includes unevenness. To introduce this film shape to our model, we use spring force shown in Equation (2) to produce intervals in basal cells. Moreover, the distance which spring force works to is variable because it can fill the gaps generated by the basal layer. In Equation (3), by summing up these forces from the surrounding particles, the particles gradually move to the position of the force balance. x and x' are the positions before and after movement by these forces. α is a coefficient, and its value is 0.003.

$$\vec{F} = k \cdot \left(1 - \frac{ddr}{1.106 \times dr0}\right) \cdot \left(1 - \frac{ddr}{dr1}\right) \cdot \frac{d\vec{dr}}{ddr} \quad (1)$$

$$\vec{f} = k' \cdot \left(1 - \frac{ddr}{1.106 \times dr0}\right) \cdot \frac{d\vec{dr}}{ddr} \quad (2)$$

$$\vec{x}' = \vec{x} + \alpha \cdot \left(\sum \vec{F} + \sum \vec{f}\right) \quad (3)$$

In addition, each basal cell is a stem cell and can divide into two daughter cells. This division has three patterns as shown in Figure 2. Pattern.1 is where both cells become basal cells, and Pattern.2 is where one cell remains as a basal cell and another cell becomes a prickle cell, while in Pattern.3, both cells change into prickle cells. Each basal cell follows a pattern among these three patterns at random. We modeled the basal layer using function of film shape and stem cells having abilities to follow three patterns. When basal cells increase, the film shape suffers a change, because the increase in basal cells presses them against other cells. Besides, when basal cells decrease, surrounding basal cells fill the gap and keep the film shape.

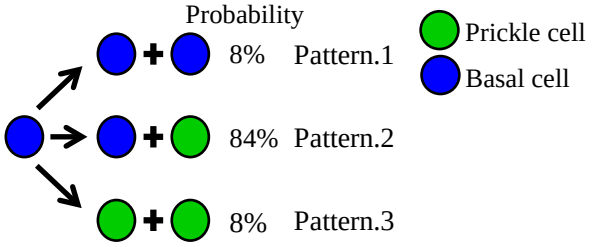
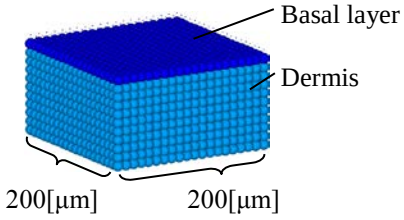


Fig. 2 Cell division of basal layer cell [12, 13]

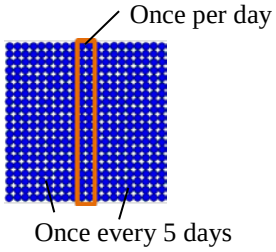
3. Calculation Conditions

The initial placement shown in Figure 3 (a) can be configured only for the dermis (light blue) and basal layer (blue). The model of initial cell particles presents a spherical shape with a 10 μm diameter. The shape becomes thinner in the granular layer, changing with time, and adopts an elliptical shape that extends to the transverse direction of approximately 1 μm in thickness in the stratum corneum. Each basal cell divides once every 5 days of analysis time, and the two daughter cells take a pattern among the three division patterns at random. The divided prickle cells freely move under a force to keep the volume constant until it reaches the granular layer. Spring force begins to gradually occur from the granular layer to the corneum layer and connects to each particle. Consequently, migrations reduce, and finally, the structure is fixed. In addition, only volume conservation force works on particles of dermis and prickle layer. By contrast, spring force is also added to particles of other layers to increase connection between the particles.

To elucidate the mechanism of unevenness in the basal layer, we analyzed the case setting condition for division pattern of basal cells. At the central area shown in Figure 3 (b), basal cells are set to divide once per day of analysis time only through Pattern.1 in Figure.2. In the same manner, we also analyzed the division processes for Pattern.2 and Pattern.3. We analyzed this skin model for 200 days of analysis time.



(a) Perspective view



(b) Top view

Fig. 3 Initial shapes

4. Results and Discussion

Figures 4 and Figure 5 show the results of the 200th day of basal layer growth in the case of fixing stem cell division patterns at the center. We consider the mechanism of uneven basal layer formation using results of epidermal formation analysis as shown in Figure 4. At first, the result for pattern.1 division (a) shows that unevenness is formed only around the center where cell division is active. This result indicates that unevenness is formed at the location where new basal cells are generated. When a new basal cell is generated, the cells surrounding this are partly packed. Therefore, we consider unevenness is generated by these clusters of basal cells being extruded. Secondly, in the case of Pattern.2 (b), the whole of the central region is indented towards the dermis. This result means that basal cells are forced into the dermis. The upper part above the basal layer is more elastic than the lower part because of the spring force of the cell junction in corneum and granular layers. Therefore, when a basal cell generates a prickle cell in the upper part, the basal cell suffers a depressed reaction. For this reason, there is strong force into the dermis where Pattern.2 is active. Third, in Pattern.3 (c), unevenness is not formed at the center of the domain. It can be said that Pattern.3 does not take part in uneven layer formation. This is because, in the case of a basal cell evolving into two prickle cells, the presence of basal cells around the original cell fills the gaps. Finally, when all patterns are collated in the analysis (d), unevenness is formed toward the dermis. This result includes two functions of Pattern.1 and Pattern.2; unevenness is generates by a function of Pattern.1, and then the unevenness suffers force towards the dermis by Pattern.2. As a result, formation of unevenness has a relationship with generation of basal cells and direction of force acting on basal cells.

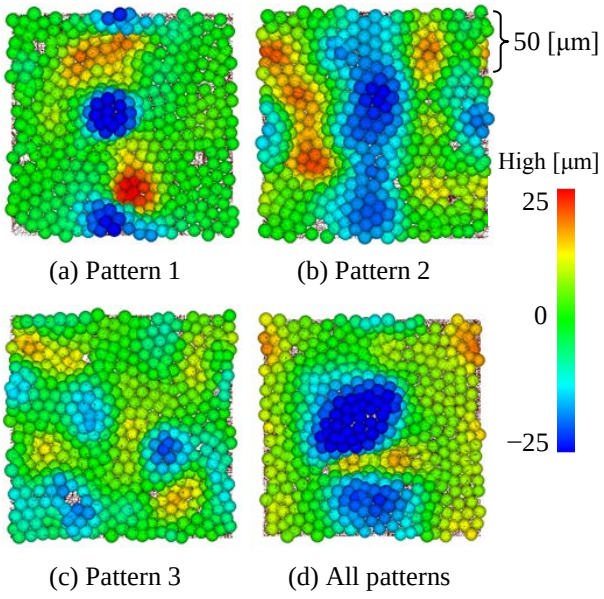


Fig. 4 Results of different patterns with epidermal skin at 200 days (Bottom view)

Furthermore, we examined the result which only included basal layer as shown in Figure 5. First, when assessing the result of Pattern.1, unevenness was formed as shown in Figure 4 (a). From this result, we found that the unevenness of the basal layer was formed as a result of its own proliferation. Next, the result for Pattern.2 was different from Figure 4 (b) because there was no hollow aspect. This is because that model does not include prickle cells that are in the upper layer because of the calculation only being used for the basal layer. Therefore, it can be concluded that force toward dermis is by the force of repulsion from the prickle layer. Lastly, the result from Pattern.3 indicates that these cells processes in Pattern.3 do not have relationship with uneven layer formation as with Figure 4 (c). Finally, both concavity and convexity are formed in results including all patterns (d). This cause is likely to be due to basal cells, which can move freely toward the vertical direction because there is no downward force from the prickle layer. Thus, the cause of hollow formation is force of repulsion from the prickle layer.

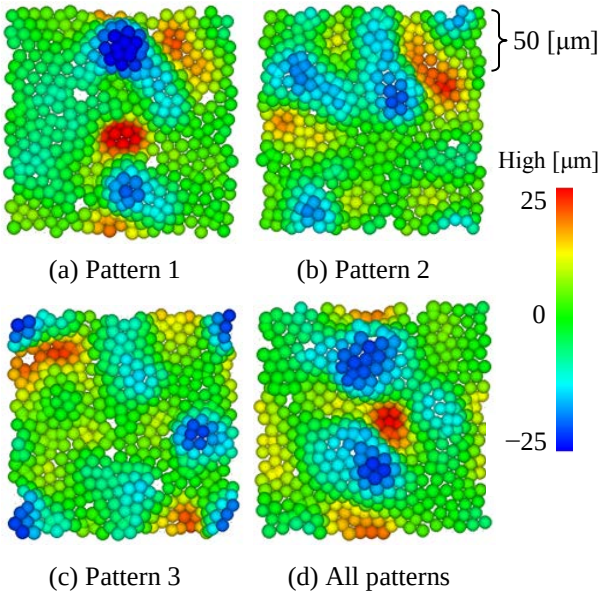


Fig. 5 Results of different patterns without epidermal skin at 200 days (Bottom view)

5. Conclusions

In this study, we analyzed the relationships between division patterns of basal cells and unevenness formation, and elucidated the mechanism of unevenness formation of the basal layer by 3D numerical simulation of epidermal formation using the particle model. If a basal cell generates a new basal cell, either concavity or convexity is newly formed. In the case where a basal cell generates a prickle cell, the function of concavity becomes stronger because the new cell is pressed down by the upper epidermis. However, there is no effect on unevenness formation when the existing basal cell disappears. For the simulation including these three patterns with high cell

division frequency at 1.0 per day, though both concavity and convexity were formed at the location where cell division is active, the overall unevenness resulted in a hollow shape. Thus, we elucidated the mechanism of basal layer formation by focusing on cell division, and highlighted that the contribution to unevenness formation varies by cell division pattern. We would next examine numerical simulation by considering capillaries in the dermis, because it is assumed that nutrition supplied from the capillary influences division of basal cells.

6. References

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