Numerical simulation of skin formation: epidermal stem cells and undulation of the basal layer

Shu Oba and Katsuya Nagayama

1Graduate School of Computer Science and Systems Engineering, Kyushu Institute of Technology, 680-4 Kawazu, Fizuka, Fukuoka, 820-8502, Japan

*Corresponding Author: nagayama.katsuya304@mail.kyutech.jp, +81-948-29-7778

Abstract

The basal layer at the base of the epidermis produces new epidermal cells once a week and plays an important role in skin formation. Interestingly, the basal layer undulates, and the amplitude of this undulation is dependent on age or disease. However, the mechanisms driving this phenomenon have not been well studied. This work simulated the skin formation process using an original method to understand the mechanism of the undulation formation in the basal layer. The basal layer has cells with both short and long cell cycles, but only the former has been examined in previous studies. Accordingly, we more accurately simulated the skin formation process by including cells with a long cell cycle and observed undulation of the basal layer. Based on our findings, we propose that the basal layer undulates due to the interaction between two types of basal layer cells.

Keywords: Basal Layer, Undulation, Epidermal Stem Cell, Skin

1. Introduction

The skin is the largest organ in the body and plays roles in water retention and protection from external threats. However, it is extremely difficult to observe the interior layers of the epidermis, as epidermal cells spend about a month before they reach the skin surface. This work simulated the inside of the skin to understand the mechanism of its formation and is expected to contribute to product development in the beauty industry.

This study focuses on the basal layer, which is located at the base of the epidermis. The basal layer consists of progenitor epidermal cells and plays an important role in skin formation. Interestingly, the basal layer undulates, and the amplitude of this undulation is dependent on age or disease [1]. The undulation amplitude in our simulation results does not correspond with that described in the literature because the phenomenon has not previously been studied [2–8]. A goal of this work is to understand the mechanism of the basal layer undulation so that this characteristic may be applied to simulations in the future.

The basal layer contains cells with short and long cell cycles, but only the former has been considered in previous studies [2–8]. We hypothesized that differences in the behavior of these two types of cells could influence undulation formation in the basal layer. Accordingly, we chose to include cells with a long cell cycle in our simulation of the skin formation process.
2. Analysis target
As shown in Figure 1, the skin is mainly composed of three layers: the epidermis, dermis, and subcutaneous tissue. The topmost of these layers, the epidermis, is itself composed of four layers, the bottom most of which is the basal layer. The basal layer plays a role in producing new epidermal cells.

3. Analysis method
3.1 Particle method
The particle method represents a continuum using a finite number of particles and calculates the behavior of the continuum through the movement of the particles. Each moving particle has a characteristic set of variables associated with it. This method does not use the mesh required by the finite difference method or the finite-element method. For this study, the particle method was used because each particle can be regarded as a cell, and the particles can move freely.

3.2 Cell dynamics
Skin cells move by exerting forces on each other. In the case of epidermal cells, the division of basal cells pushes neighboring cells upward. Therefore, for this study, cell-to-cell interactions were represented using a body force and a spring force so that the particles could move by the equilibrium of the forces [2, 3]. Equation (1) shows the body force, and Equation (2) shows the spring force. Since the body force mainly works to push the cells up, the repulsive force is larger than the attractive force. The spring force works to strengthen the binding force. Each cell moves according to Equation (3),

\[ F = k \left( 1 - \frac{r}{1.106 \times r_1} \right) \left( 1 - \frac{r}{1.4 \times r_1} \right) \]  
\[ f = k' \left( 1 - \frac{r}{1.106 \times r_1} \right) \]  
\[ \Delta x = \alpha \left( \sum F + \sum f \right) \]

where \( r \) is the inter-particle distance; \( r_1 \) is the cell diameter; \( k \) and \( k' \) are inter-particle coefficients; \( \alpha \) is the movement coefficient.
3.3 Maintenance of basal layer
The basal layer is composed of one cell layer. However, it is difficult to maintain this layer in a simulation by relying only on the force between cells. Therefore, for this study, a method for maintaining the layer is proposed. As shown in Figure 2, it is possible to maintain the layer by placing virtual particles above and below the basal cell particles and exerting a spring force on them.

Figure 2. Particle placement for the maintenance of the basal layer.

3.4 Cell division
The basal layer has two types of cells: epidermal stem cells and transit-amplifying (TA) cells. Epidermal stem cells divide about 4–6 times a year [10]. On the other hand, TA cells divide about once a week [10]. As shown in Figure 3, both epidermal stem cells and TA cells have three division patterns. There is about a 10% chance of duplication, an 80% chance of asymmetric division, and a 10% chance of differentiation [10]. For this study, these profiles are applied to two types of cells.

Figure 3. Division of two types of cells.
4. Analysis flow
The analysis flow is shown in Figure 4. The analysis frequency is 2500 times a day, and the analysis period is 300 days.

![Analysis flow diagram](image)

Figure 4. Analysis flow. For cell deformation, the epidermal cells change to thinner as they grow into prickle cells, granule cells, and corneum cells. For cell type changing, after a certain period, the epidermal cells change from prickle cells to granule cells or from granule cells to corneum cells. For peeling calculation, dead corneum cells peel off [4, 5].

5. Analysis conditions
The overall initial placement is shown in Figure 5. Each particle diameter is 10 μm. The analysis area is 300 × 300 × 300 μm³. A periodic boundary condition was adopted in the horizontal direction. In the vertical direction, particles outside the analysis area were removed.

![Overall initial placement](image)

Figure 5. Overall initial placement.
The placement of basal cells is shown in Figure 6. For 100 days after the start of the analysis, the basal layer was simulated using only TA cells and was restrained, which allowed the simulation to reach equilibrium. Then, as shown in Figure 6(a)–(c), three patterns of cell placement were simulated from 100 days to 300 days. In addition, only the basal layer is displayed.

![Figure 6](image)

**Figure 6.** Placement of basal cells. Epidermal stem cells are red, whereas TA cells are blue.

6. Analysis results

The analysis results are shown in Figure 7(a)–(c). The basal layer for each pattern undulated over time. In addition, we noted that epidermal stem cells tended to be distributed more in the convex regions of the basal layers.

The distribution ratio for epidermal stem cells in the convex regions is shown in Figure 8. Over 90% of epidermal stem cells were distributed in the convex regions from 100 days to 150 days. After this point, the distribution ratio for epidermal stem cells in the convex regions generally showed a downward trend, but rose again at around 300 days. From these results, it was shown that epidermal stem cells tended to be distributed in the convex regions of the undulating basal layer, which corresponded with the literature [1].
Figure 7. Analysis results. Epidermal stem cells are red, whereas TA cells are blue.

Figure 8. Distribution ratio for epidermal stem cells in convex regions.
7. Discussion
We hypothesized that the reason the basal layer undulates is related to the interaction of two types of basal cell divisions. As shown in Figure 3, epidermal stem cells only divide horizontally. Therefore, epidermal stem cell numbers increase horizontally, which could cause buckling of the basal layer. On the other hand, TA cells divide either horizontally or vertically. Therefore, TA cells may temporarily be pushed down by the generation of prickle cells. In addition, TA cells could frequently be pushed down because these cells divide more often than epidermal stem cells. From these findings, we suggest that basal cells caused the buckling of its layer and that epidermal stem cells and TA cells moved to the convex and the concave regions of the basal layer, respectively, leading to the undulation formation.

8. Conclusions
In this study, we succeeded in simulating the basal layer using epidermal stem cells. We demonstrated that the differences in the cell cycle and the division direction between epidermal stem cells and TA cells contribute to the undulation formation in the basal layer. In addition, we also showed that epidermal stem cells tend to be distributed in the convex regions of the basal layer.

In the future, we will simulate how the undulation amplitude of the basal layer changes with age or disease.

References
[1] Yamada T Hasegawa S Miyachi K Date Y Inoue Y Yagami A Arima M Iwata Y Yamamoto N Nakata S Matsunaga K Sugiura K and Akamatsu H 2018 Mech. Ageing dev. 171 37-46
[2] Kurihara T and Nagayama K 2015 Proc. 6th TSME Int. Conf. Mech. Eng. (Petchburi: Mahidol University)
[3] Kurihara T and Nagayama K 2016 Proc. 7th TSME Int. Conf. Mech. Eng. (Chiang Mai: Chulalongkorn University)
[4] Shobuda K and Nagayama K 2019 IOP Conf. Ser.: Mater. Sci. Eng. 501 012032
[5] Oba S and Nagayama K 2020 IOP Conf. Ser.: Mater. Sci. Eng. 886 012019
[6] Nagayama K Uehara T Amano Y and Tanahashi M 2015 3D J. Biosci. Med. 3 45-49
[7] Nagayama K Kurihara T Amano Y and Tanahashi M 2016 J. Biosci. Med. 4 33-77
[8] Nagayama K and Kurihara T 2018 J. Appl. Math. Phy. 6 1757-1762
[9] Saita T 2009 Introduction to Dermatopathology Diagnosis 2nd ed (Tokyo: Nankodo) pp 2-13
[10] Mascré G Dekoninck S Drogat B Youssef K K Brohée S Sotiropoulou P A Simons B D and Blanpain C 2012 Nature 489 257-262