The 8th TSME International Conference on Mechanical Engineering
12-15 December 2017
Bangkok, Thailand

BME0004

Particle simulation on skin formation: − melanin transportation and formation of freckles −

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Abstract. Freckles appear on people owing to ultraviolet radiation and, as such, affect their appearance. The epidermis is the outermost layer of a human's skin, and epidermal conditions can be diagnosed from it in order to provide appropriate care. Recently, those interested in anti-aging treatments have been paying greater attention to the epidermal layer. The epidermis consists of four different layers. In particular, the basal layer, which is at the bottom of the epidermis, contains pigment cells called melanocytes. Melanocytes are associated with changes in flesh color including freckles: melanocytes become freckles when the epidermis is hit by ultraviolet rays. However, the interaction mechanisms between freckles and the basal layer have not yet been uncovered because it is difficult to directly observe the skin's basal layer. In order to investigate long-term skin formation, we created a model that simulates actual skin. Our model can analyze the basic epidermis model while constructing a model of melanin. In order to test this, we set conditions for the rate at which the basal layer's surface area increases and the rate at which its cells divide so as to simulate and show flesh color in aging and young epidermises. In the case of undulations in the structure of the basal layer, the rate at which the basal layer's surface area increases was changed. As a result of this analysis, the characteristics of the changes in the color depth of flesh according to undulations in the structure of the basal layer were found.

1. Introduction

Freckles appear on people owing to ultraviolet radiation and, as such, affect their appearance. The epidermis is the outermost layer of a human's skin, and epidermal conditions can be diagnosed from it in order to provide appropriate care [1]. Recently, those interested in anti-aging treatments have been paying greater attention to the epidermal layer.

The epidermis consists of four different layers. In particular, the basal layer, which is at the bottom of the epidermis, contains pigment cells called melanocytes. Melanocytes are associated with changes in flesh color including freckles: melanocytes become freckles when the epidermis is hit by ultraviolet rays. However, the interaction mechanisms between freckles and the basal layer have not yet been uncovered because it is difficult to directly observe the skin's basal layer.

Computational simulations can be useful to further understand the mechanisms underpinning the development of human skin, and several models have so far 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 our model represents a suitable method for simulating skin formation and, the actions of melanocytes.

In order to test this model, we developed an analytical method for the formation and turnover process of the skin; in addition, we introduced multiple cell division patterns [9-13]. Our model can

also be used to analyze the epidermis, melanin transportation, and the formation of freckles while taking stock of the change in the structure of the basal layer.

In this paper, we used our model to analyze a long-term skin formation process. Furthermore, we also set the rate at which the basal cells divide and the rate at which the basal layer's surface area increases to simulate the epidermis.

Our aim was to simulate how melanocytes are transported by the epidermis as it ages in order to contribute knowledge toward the development of medical skin treatments and cosmetics.

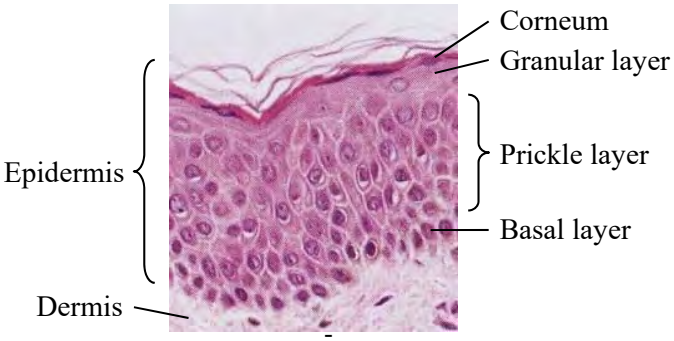
2. Analysis Object and Model Description

2.1. Analysis Object

Fig. 1 depicts a cross section of the skin [1]; the roles of each cell layer are annotated. The epidermis is the outermost layer of the skin and is primarily composed of cells called keratinocytes. The epidermis consists of four layers. The lowest-lying layer of the epidermis is the basal layer, which provides new cells each day via cell division. The dividing cells are called the prickle cell layer, and they are pushed and moved up toward the skin's surface. This layer transforms into the granular layer and then the stratum corneum, which detaches itself from the surface of the skin. This is called the turnover process and occurs approximately every four weeks. As a person ages, it becomes harder for the stratum corneum to detach from the surface, and as a result, skin becomes thicker [2].

During this turnover process, skin cells change not only in their shape but also in their physical properties. However, the cycle of turnover is longer in an aged epidermis [2].

The dermis is located under the epidermis, and the two are separated by the basal layer. Capillaries in the dermis supply nutrition and oxygen to the basal cells. Therefore, the epidermis is influenced by interactions with the dermis and nutritional effects from the capillaries.



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

2.2. Model Description

We introduced the particle model [8–10] into our analysis model to simulate the formation process of the epidermis [11–15]. The model considers the interaction between the particles and models the Lagrangian motion of the particles. This method is suitable for analyses with large deformations or for instances when the number of calculation points is varied, i.e., when the generation, division, and disappearance rates of the cells need to be varied.

The cellular particles move in response to inter-particle forces, such as the volume conservation force and the spring force. These relationships are shown in Eqs. (1)-(3) [14, 15].

The volume conservation force, F, in Eq. (1) maintains the distance between the particles. Owing to the repulsive force, particles eventually move to a stable distance. In this equation, k is a coefficient, ddr is the distance between two particles, dr0 is the standard distance (10.0 μm in this case), and dr1 is

the maximum distance for which the volume conservation force can act; it should be noted that dr1 is larger than dr0.

The basal layer maintains the shape of the monolayer, which includes its undulating structure. In order to introduce this monolayer into our model, we use the spring force shown in Eq. (2). Here k' is the coefficient of an elastic spring. The distance at which the spring force acts upon varies with the number density of the basal layer because it can fill the gaps generated by the basal layer. In addition, the spring force is also introduced to the stratum corneum and the granular layer in order to realize a strong cell junction.

By summing up the forces from the surrounding particles, the particles gradually move to positions in which the forces are balanced, as shown by Eq. (3). x and x' are the positions before and after the movements caused by these forces. α is a coefficient, and its value is 0.003.

Here, we state in detail the methodology to solve the equations with which the positions at which the forces are balanced can be found. As shown in Eq. (3), each particle moves according to the sum of the volume conservation force and the spring force. The particles are repulsed by each other and move toward positions where the effects of the forces are weakened. Therefore, each particle gradually moves and converges on a position in which the forces are balanced via repeated repulsion interactions. Our model determines the positions by calculating them 2,500 times per day.

$$\vec{F} = k \cdot \left(1 - \frac{ddr}{1.106 \times dr0}\right) \cdot \left(1 - \frac{ddr}{dr1}\right) \cdot \frac{dd\vec{r}}{ddr} \qquad (1)$$

$$\vec{f} = k' \cdot \left(1 - \frac{ddr}{1.106 \times dr0}\right) \cdot \frac{dd\vec{r}}{ddr} \qquad (2)$$

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

Although the volume conservation force acts on the particles in the dermis and the prickle layer, the spring force is also added to the particles of the other layers so as to increase the connections between the particles.

In addition, each basal cell is a stem cell and can divide into two daughter cells. This division has three patterns. Pattern 1 is where both cells become basal cells, and Pattern 2 is where one cell remains a basal cell while the other becomes a prickle cell. In Pattern 3, meanwhile, both cells change into prickle cells. Each basal cell follows one of these three patterns at random.

The basal layer is affected by a change in these cell division patterns; as a result, undulations form on the basal layer [14]. For example, when the number of basal cells increases, they press against other cells. Conversely, when the number of basal cells decreases, the surrounding basal cells fill the gaps and maintain the shape of the monolayer.

Here, we will explain the role of melanin pigment and melanocytes that we aim to analyze in this research with the aid of Fig. 2. Melanin pigment plays a role in preventing damage to the keratinocyte nucleus (DNA), and our skin color depends on the type and amount of melanin pigment. This melanin pigment is produced by pigment cells called melanocytes, which are present in the gaps between the basal cells. There is no transfer of melanin pigment between keratinocytes. Epidermal cells move and peel off on cell division while retaining the amount of melanin passed to it from the melanocytes. In this study, we analyzed an analytical model (melanin model) of light transmission through melanin pigment using the basic model of epidermal formation.

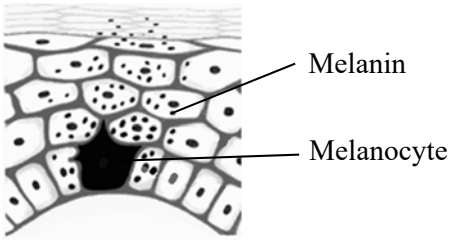


Fig. 2. Melanin and a melanocyte [1]

Subsequently, the absorbance, transmittance, and reflectance required for constructing the melanin model is described below. In this study, skin color is calculated using Lambert-Beer's law and Kubelka-Munk's law. In this study, we consider only the absorption and reflection of melanin pigment and analyze; we do not consider the light reflection of hemoglobin in the dermis.

First, Lambert-Beer's law is explained. This law is a combination of Lambert's law representing the relation between solute length and light absorption and Beer's law representing the relation between solution concentration and light absorption. It is the basic rule for utilizing the absorption of light for quantitative analysis; however, following conditions must be satisfied for this rule to be strictly established.

- The incident light must be monochromatic light.
- No reflection at the solution interface, no stray light inside the photometer.
- No scattering or irregular reflection should occur due to solute or solvent molecule (being a true solution).
- Even when the solution concentration changes, the dissolved state of the solute is constant, the dissociation of molecules, and the equilibrium of association do not move.

The following are the expressions depicting Lambert-Beer's law:

$$R = \frac{I}{I_0} = 10^{-\varepsilon c x} \qquad (4),$$

$$\varepsilon = \frac{A}{c \times x} \qquad (5), \text{ and}$$

$$A = \log\left(\frac{I}{I_0}\right) = \varepsilon c x \qquad (6).$$

Herein, I_0 is the intensity of the incident light velocity, I is the intensity of the transmitted light velocity, ε is the molar extinction coefficient, c is the molar concentration, x is the optical path distance, and A is the absorbance.

Next, Kubelka-Munk's law is explained using Fig. 3. It is assumed that the first layer having reflectance value r_1 and transmittance value t_1 and the second layer having reflectance and transmittance values of r_2 and t_2 are laminated. Then, the incident light passes through the first layer and the second layer and is affected by the reflectance and transmittance of each layer, as shown in Fig. 3. Therefore, the total reflectance R_{12} is given by the following Eq. (7).

$$R_{12} = r_1 + t_1^2 r_2 + t_1^2 r_1 r_2^2 + t_1^2 r_1^2 r_2^3 + \cdots = r_1 + \frac{t_1^2 r_2}{1 - r_1 r_2} \qquad (7).$$

Therefore, the total reflectance $R_{12\cdots n}$ in the n layer is as shown in the following Eq. (8).

$$R_{12\cdots n} = r_{12\cdots n-1} + \frac{t_{12\cdots n-1}^2 r_n}{1 - r_{12\cdots n-1} r_n} \quad (8).$$

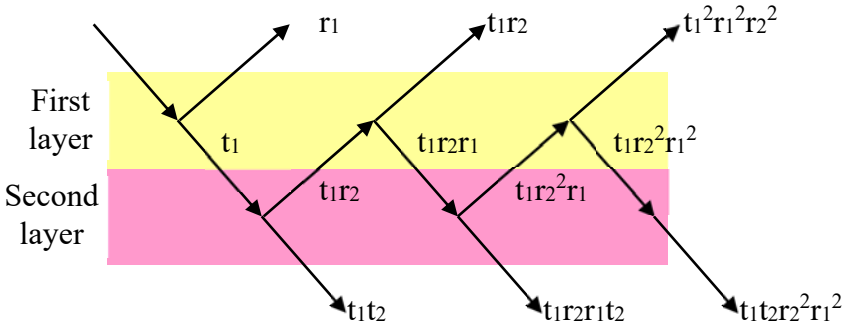


Fig. 3. Relation between reflectance and transmittance in two layers

3. Calculation Conditions

3.1. Base Model

In this study, analytical method is established using particle model and it is used for analysis. For the analytical method used and studied in this study, a method called particle method was used. It is a method in which a continuum is represented by a finite number of particles and the behavior of the continuum is calculated by the motion of the particles. Moving while keeping variables such as velocity and pressure of each particle. However, we do not use the lattices necessary for finite element method and finite element method. The initial configuration shown in Fig. 4 only consists of the dermis (light blue), capillaries (red), and basal layer (blue). The cell particles in this model are represented by spheres with a 10 μm diameter. However, the shape of the cell particles becomes thinner in the granular layer, changing with time, and adopts an elliptical shape that extends in the transverse direction by approximately 1 μm in thickness in the stratum corneum.

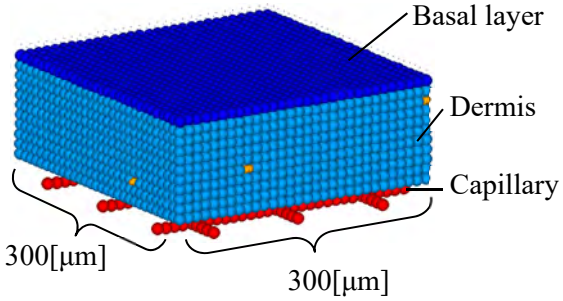


Fig. 4. Perspective view(initial shape)

Each basal cell divides once every five days (0.2 times per day), and the two daughter cells follow one of the three patterns at random as explained earlier. The divided prickle cells move freely under a force in order to keep the volume constant until they reach the granular layer. The spring force begins to gradually act, standing in the granular layer and extending into the stratum corneum, and connects each particle to form a continuum. Consequently, particle migration is reduced, and the structure becomes fixed.

Although initially there are no layers above the basal layer, a flat epidermis is formed in the analysis model after 45 days owing to basal cell division; the basal cells only divide through Pattern 2 in this period. The basal

layer initially has 900 cells (in a 30 by 30 particle block), and the number of basal cells increases to 1,080 after 45 days—this is an increase of 20%. The base model was analyzed under these conditions.

3.2. Melanin Model

This analysis focuses on the extinction coefficient, transmittance, and reflectance of the melanin pigment, and a simulation of the changes in the reflectance of a melanin pigment was also performed. Then, based on the changes in the reflectance, a skin color conversion was performed to display flesh color; the results were analyzed to determine whether or not the simulation can approximate actual skin color. In this analysis, melanocytes were placed between the basal layer cells, melanin is transferred, and the amount of melanin is calculated. Further, the absorbance, the permeability, and the reflectance are also calculated, and the skin color is calculated using the basic model. The initial particle arrangement of this analysis is shown below in Fig. 5. Melanocytes were placed between the keratinocytes of the basal layer, and one melanocyte was placed between five keratinocytes; additionally, one melanocyte was placed between three keratinocytes. Melanin is transferred from the melanocytes to the basal layer keratinocytes. The scale of the above-described model is shown in Fig. 5.

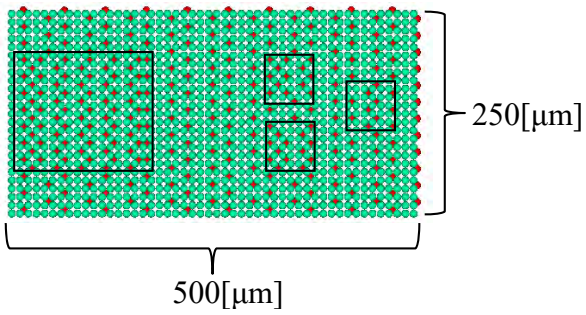


Fig. 5. Diagram of the distribution of the melanocytes

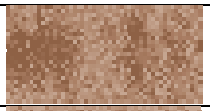
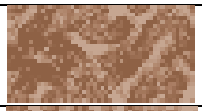
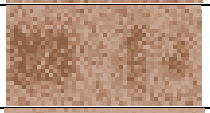
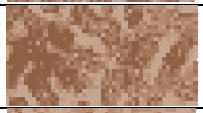
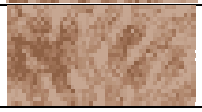
Furthermore, in addition to the initial arrangement shown in Fig. 5, in this study, an analysis was conducted focusing on the conditions of cell division of the skin cells, with regard to the presence or absence of irregularities of the basal layer, i.e., increases in the rate of basal layer cells dividing, a condition also known as keratolysis. Specific conditions are shown alongside the analysis results for comparison.

4. Results and Discussion

On the basis of the initial arrangement shown in Fig. 5, the conditions were varied, and the results were analyzed. The analyzed results are shown below. The scale is the same as in Fig. 5. The results in Table 1 display the flesh color when the cell division frequency is 0.15 [times/day], 0.2 [times/day], and 0.3 [times/day] in the basal layer without irregularities and with various irregularities, namely basal layer cell growth rates of 5%, 20%, and 40%.

100[μm]

Table 1. Skin color for different cell division rates and with and without irregularities

Cell division frequency [times/day]	No irregularities (Increase of basal layer 0%)	irregularities (Increase of basal layer 5%)	irregularities (Increase of basal layer 20%)	irregularities (Increase of basal layer 40%)
0.15				
0.2				
0.3				

On the basis of the skin color results shown in Table 1, it can be seen that, when the flesh color images are compared with the cell division frequency, the overall opacity of the skin decreases as cell division frequency increases. This is because skin ages when the frequency of cell division is low; thus, a lot of dark patches appear around the spots. Conversely, when the rate of cell division is high, the skin is younger, and thus, the overall proportion of high opacity skin decreases.

In addition, when comparing the flesh color images with the basal layer cell growth rate, it can be seen that the basal layer cell growth rate matches the unevenness of the basal layer. Therefore, as the rate of increase of the basal layer increases, the unevenness becomes clearly visible in the images of the skin color. However, compared with the case without concavities and convexities, the case with irregularities shows that a lot of melanocytes are deposited, and (in addition to spots) there are also skin areas with dark color. This is because the number of layers of the spinous layer cells of the epidermis changed owing to the unevenness of the basal layer; thus, an area of darker skin color appeared next to the spotted portion. Since epidermal cells retain at least 20% melanin in any layer of the basal layer, the spinous layer, the granular layer, and the stratum corneum, such skin coloring produces a dark area.

5. Conclusions

In this study, a numerical simulation of the melanin model was performed using the basic particle model of the epidermal formation process; skin color images were then formed from the analysis results. As a result of analyzing various skin conditions such as the frequency of cell division of skin cells, the presence or absence of unevenness of the basal layer, an increased rate of the basal layer cells dividing, or keratolysis, it was found that the skin's color became more opaque as the cell division frequency increased. In addition, we found that, by changing the basal layer cell growth rate, the degree of irregularity of the basal layer could be observed in the generated flesh color images. From these results, it became possible to analyze the melanin model for a wide range of conditions, and it was possible to obtain a significant amount of knowledge from the model.

In the future, we will further improve the melanin model to include differences in flesh color as displayed by various races, which was not considered in this research. Further, we will clarify the underlying mechanism of melanin formation and migration from the analysis model for a wider range

of conditions. This knowledge is expected to contribute to anti-aging agents [15]. As mentioned earlier, we will also examine the specific movement of melanin and decrease and mitigate errors.

References

[1] Saita, T. (2009). Introduction of Skin Histopathological Diagnostics, Nanko-do Co., Japan
[2] Kurihara, T. and Nagayama, K. (2016). Particle Simulation on Human Epidermal Aging – Effect of Basal Layer and Cell Division Rate –
[3] Kokura, S (Eds.) (2006). The front of anti-aging technology of skin, NTS Inc., Japan
[4] Querleux, B. (2014). Computational Biophysics of the Skin, by Pan Stanford Publishing, Print ISBN: 9789814463843, eBook ISBN: 9789814463850, DOI: 10.4032/9789814463850
[5] Sütterlin, T., Huber, S., Dickhaus, H. and Grabe, N. (2009). Modeling multi-cellular behavior in epidermal tissue homeostasis via finite state machines in multi-agent systems. Bioinformatics, 25, 2057-2063.
[6] Hirashima, T., Hosokawa, Y., Iino, T. and Nagayama, M. (2013). On Fundamental Cellular Processes for Emergence of Collective Epithelial Movement. Biology Open, 2, 600-666. doi: 10.1242/bio.20134523
[7] Adra, S., Sun, T., MacNeil, S., Holcombe, M. and Smallwood, R. (2010). Development of a Three Dimensional Multiscale Computational Model of the Human Epidermis. Open Journal PLoS ONE, 5, e8511.
[8] Nagayama, K., Nitta, J. and Miura, I. (2009). Numerical Analysis on Angiogenesis in Cancer Using a Particle Model. Theoretical and Applied Mechanics Japan, 58, 321-324.
[9] Hashiguchi, S. and Nagayama, K. (2011). Construction of a hair formation analysis method using the particle model, 2011 Bioengineering Conference, 23th Japan Society of Mechanical Engineers, 9D-01, Japan, 355-356.
[10] Nagayama K., Matsuoka S., Morisaki N. and Taguchi H. (2015). 3D Numerical Simulation of Hair Formation Process Using a Particle Model, Open Journal of Regenerative Medicine, February 6, 2015, http://file.scirp.org/Html/1-2390044_53849.htm
[11] Uehara, T., Nagayama, K., Amano, Y. and Tanahashi, M. (2013). Numerical simulation of epidermal skin formation using particle model. The Second BMIRC International Symposium on Frontiers in Computational Systems Biology and Bioengineering, January 30, 2013, Japan.
[12] Amano, Y., Uehara, T., Tanahashi, M. and Nagayama, K. (2012). An epidermal turnover model predicts uneven skin tone with aging. SY01.01 ICBS (World congress on the International Society for Biophysics and Imaging of the Skin), November 29, 2012, Copenhagen Denmark.
[13] Nagayama, K., Uehara, T., Amano, Y. and Tanahashi M. (2015). 3D Numerical Simulation of Epidermal Skin Turnover Process Using a Particle Model, Journal of Biosciences and Medicines http://dx.doi.org/10.4236/jbm.2015.33007
[14] Kurihara, T. and Nagayama, K. (2015). Particle Simulation on Epidermal Skin Formation-Mechanism of Basal Layer Formation, paper presented in The 6th TSME International Conference on Mechanical Engineering-BME 009, Hua-Hin, Thailand.
[15] Nagayama, K., Kurihara, T., Amano, Y. and Tanahashi, M. (2016). Particle Simulation of Skin Basal Layer Formation, Applied Journal of Biosciences and Medicines, vol.4, March 2016, pp. 33–37. doi: 10.4236/jbm.2016.43006.
[16] Fukuda, Y. and Nagayama, K. (2016). Particle Simulation on the Skin Formation - Melanin Transportation and Freckles Formation – in the Heisei 28 Graduation thesis summary, in Kyushu Institute of Technology.