

Effect of changes in Skin Thickness on pain-relief Transcutaneous Electrical Nerve Stimulation (TENS)

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Abstract— Transcutaneous Electrical Nerve Stimulation (TENS) suppresses chronic pain by stimulating deep nerves near the fascia from electrodes on the skin's surface. TENS has different effects on patients of different ages due to the variation of the thickness of skin layers when one becomes older.

In this paper, we aim to optimize the stimulation effectiveness of TENS for patients of different ages through investigation of TENS stimulations of three different skin types categorized by age, Young, Old, and Older. In this investigation, the skin layer (stratum corneum, epidermis layer, dermis layer) in each model was created, and the thickness was varied. The effect of sin wave stimulation at 1 Hz, 100 Hz, and 10 kHz on the nerve stimulation effect near the fascia was examined.

It is found that besides the well-known effect of stratum corneum, the thickness of the dermis layer significantly affects the stimulating effect. In addition, by using a lumped circuit model, it is showed that the change in the current path causes a mitigation in the stimulation effect in the dermis layer.

I. INTRODUCTION

Transcutaneous Electrical Nerve Stimulation (TENS) suppresses chronic pain by applying electrical stimulation from electrodes on the skin's surface to nerves near the fascia. This is because the excitement of the afferent nerves A δ and C, is transmitted to the central nervous system and acts, which releases a substance called an endogenous opioid, that is block transmit pain signals [1],[2].

The skin layer and fat layer are factors that have a particularly strong influence when performing TENS. In previous studies, the stratum corneum, which is one of the skin layers, has the property of being difficult to pass through electrical stimulation [3]. It is known that increasing the thickness of the fat layer reduces the stimulating effect and changes the electrode area for obtaining the optimum stimulating effect [4]. On the other hand, although the epidermis layer and the dermis layer, which are the skin layers excluding the stratum corneum, exist in the surface layer shallower than the fat layer, none of them has quantitatively clarified their effects on TENS. One of the reasons is that it is difficult to evaluate the skin layer anatomically because the electrical properties such as thickness and conductivity change

depending on the location, the age of the individual, and environmental factors such as temperature and humidity [5]. In the related study of the electrical properties of the skin layers, to derive the impedance of the skin layers, various circuit models representing each layer with resistors and capacitors were created, and methods for quantitatively expressing these factors were discussed [5]. These factors affect the electrical properties of the epidermis and dermis layers, which can have a significant impact on TENS stimulation. Therefore, to optimize TENS, it is necessary to understand the effect of changes in the electrical characteristics of the skin layer in addition to the size of the stimulation electrode area that has been studied so far. In the verification of the stimulation effect by the electrode area conducted in the previous research, it was clarified by the biometric experiment that the applied voltage value that the subject perceives the stimulation becomes smaller by stimulating with the electrode having a large area. This result is the basis for using relatively large electrodes in today's TENS [6]. Also, increasing the electrode area for inter-electrode distances over 3 cm increases the range of effect of the stimulus while weakening the stimulus transmission in the depth direction [7]. As a factor that causes changes in the electrical characteristics of the skin layer, changes in skin thickness with age are significant. Although the degree of change in thickness is different, it is a phenomenon that occurs in common to all people, and even if this phenomenon is the same stimulus, the effect becomes weaker with age, or on the contrary, the stimulus becomes too strong.

Thus, understanding the effect of age-related changes in skin thickness on stimulation intensity increases the possibility of more effective stimulation than at present. This research aims to prepare three models in which the thickness of each layer is changed due to age change using a 3D finite element method simulation model to realize the optimum stimulus that brings about an analgesic effect TENS. We searched for the tendency of changes in the nerve stimulation effect near the fascia concerning changes in the thickness of the stratum corneum, epidermis, and dermis in the model and considered the causes of the results.

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II. METHODS

To confirm the effect of the change in the thickness of the skin layer, a Finite Element Method (FEM) simulation model was created using COMSOL Multiphysics, the voltage in the model was monitored, and the stimulation intensity was derived from it. In addition, in order to confirm whether the tendency derived by the FEM simulation model is correct, a lumped circuit model was constructed, the current of each layer were calculated, and the results were used for a comparison.

A. Finite Element Method (FEM) simulation model

The potential distribution inside the living body generated by electrical stimulation is derived using Laplace's equation. The Laplace equation in the frequency domain is as shown in (1) below,

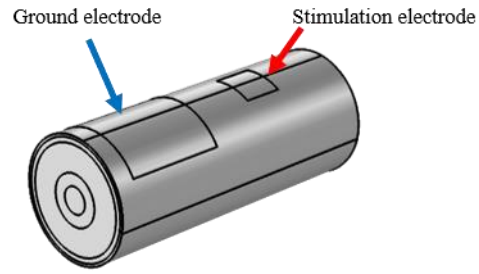
$$\nabla \cdot [\sigma(\omega) + j\omega\epsilon_0\epsilon_r(\omega)] \nabla V_e = 0 \quad (1)$$

where ω is the angular frequency, σ is the conductivity, ϵ_r is the relative permittivity, ϵ_0 is the permittivity of air, and both are dispersive. FEM in COMSOL Multiphysics® (Sweden, COMSOL AB / COMSOL, Inc.) [8] was used to solve the partial differential equations in (1).

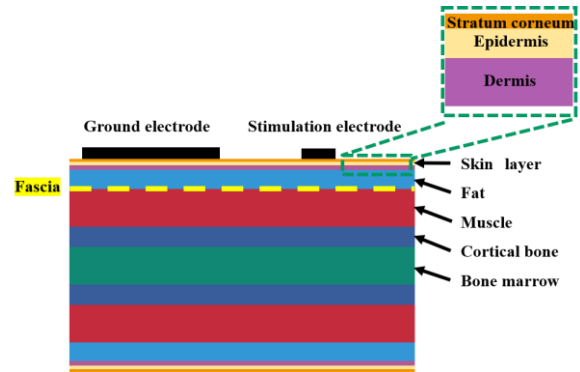
In this study, a 3D cylindrical multi-layer model (Fig. 1) was created with a length of 150 mm that imitated a living body arm. Three groups of tissue properties based on age (Young, Old, and Older) were studied. Their frequency-dependent electrical properties were set as reported in literature, and tabulated in Table I, Table II. The thickness of each layer was also varied. The thickness of the stratum corneum, the epidermis layer, and the dermis layer was set to variable in order to investigate the influence of the change in the thickness of the skin layer on the stimulating effect. The variation of thickness was estimated from the results reported in the related studies. (See Table III, IV, V)

Although the size of the electrode is preferred to adjust according to the depth of the target nerve, etc. [4], in this study, the ground electrode is $5 \text{ cm} \times 5 \text{ cm}$ (25 cm^2), the stimulation electrode is $2 \text{ cm} \times 2 \text{ cm}$ (4 cm^2), constantly. The distance between the electrodes also is constant at 30 mm. For the stimulation waveform, the electrical stimulation of a sine wave that vibrates by 1 V positive and negative with reference to -50 V was used as an input. In addition, as an initial condition, the charge in the model was set to 0 C, and the surface of the model was set to have insulation performance so that electrical effects other than input stimulation were ignored.

The potential distribution generated near the fascia was used in Activation function (AF) to evaluate the nerve stimulation intensity [16]. By this AF, the magnitude of nerve stimulation intensity was derived for each skin layer thickness, and by comparing these values, the effect of skin layer thickness on TENS stimulation was examined.



(a)



(b)

Figure1. (a) FEM simulation model, (b) cross-sectional view of the model

TABLE I. Conductivity of 3D model

| Tissue | | Conductivity, σ (S/m) | | |
|-----------------|--------|------------------------------|-------------------------|-------------------------|
| | | 1 Hz | 100 Hz | 10 kHz |
| Stratum corneum | | 1.00E-05 ^[3] | 1.82E-05 ^[3] | 1.18E-04 ^[3] |
| Epidermis | Axial | 0.95 ^[9] | 0.95 ^[9] | 0.95 ^[9] |
| | Radial | 0.15 ^[9] | 0.15 ^[9] | 0.15 ^[9] |
| Dermis | Axial | 2.57 ^[9] | 2.57 ^[9] | 2.57 ^[9] |
| | Radial | 1.62 ^[9] | 1.62 ^[9] | 1.62 ^[9] |
| Fat | | 0.035 ^[10] | 0.041 ^[10] | 0.043 ^[10] |
| Muscle | Axial | 0.2 ^[10] | 0.27 ^[10] | 0.34 ^[10] |
| | Radial | 0.067 ^[10] | 0.089 ^[10] | 0.11 ^[10] |
| Cortical bone | | 0.02 ^[10] | 0.02 ^[10] | 0.02 ^[10] |
| Bone marrow | | 0.1 ^[10] | 0.101 ^[10] | 0.102 ^[10] |
| Electrode | | 8.9E6 ^[8] | 8.9E6 ^[8] | 8.9E6 ^[8] |

TABLE II. Relative permittivity of 3D model

| Tissue | | Relative permittivity, ϵ_r | | |
|-----------------|--------|-------------------------------------|---------------|---------------|
| | | 1 Hz | 100 Hz | 10 kHz |
| Stratum corneum | | 1.00E+04 [3] | 2.00E+03 [3] | 1.11E+03 [3] |
| Epidermis | Axial | 8.97E+08 [9] | 5.05E+06 [9] | 6.07E+4 [9] |
| | Radial | 2.31E+07 [9] | 4.60E+05 [9] | 2.64E+04 [9] |
| Dermis | Axial | 7.13E+08 [9] | 5.41E+06 [9] | 2.42E+05 [9] |
| | Radial | 1.13E+09 [9] | 1.03E+07 [9] | 9.62E+04 [9] |
| Fat | | 9.91E+06 [10] | 1.52E+05 [10] | 9.12E+02 [10] |
| Muscle | Axial | 2.62E+07 [10] | 9.33E+06 [10] | 2.59E+04 [10] |
| | Radial | 2.62E+07 [10] | 9.33E+06 [10] | 2.59E+04 [10] |
| Cortical bone | | 1.04E+05 [10] | 5.85E+03 [10] | 5.22E+02 [10] |
| Bone marrow | | 1.94E+06 [10] | 7.25E+04 [10] | 7.50E+02 [10] |
| Electrode | | 1.00 [8] | 1.00 [8] | 1.00 [8] |

TABLE III. Width of change in stratum corneum thickness in 3D model

| Tissue | Thickness (mm) | | |
|-----------------|----------------|---------------|---------------|
| | Young | Old | Older |
| Stratum corneum | 0.024~0.029 | 0.024~0.029 | 0.024~0.029 |
| Epidermis | 0.0600 [8] | 0.068 [11] | 0.078 [11] |
| Dermis | 1.41 [8] | 0.60 [12][13] | 0.50 [12][13] |
| Fat | 2.50 [8] | 3.54 [14] | 4.40 [14] |
| Muscle | 13.50 [8] | 11.10 [14] | 9.17 [14] |
| Cortical bone | 6.00 [8] | 6.00 [8] | 6.00 [8] |
| Bone marrow | 6.50 [8] | 6.50 [8] | 6.50 [8] |
| Electrode | 0.01 [8] | 0.01 [8] | 0.01 [8] |

TABLE IV. Width of change in epidermis thickness in 3D model

| Tissue | Thickness (mm) | | |
|-----------------|----------------|---------------|---------------|
| | Young | Old | Older |
| Stratum corneum | 0.029 [8] | 0.024 [15] | 0.029 [15] |
| Epidermis | 0.0600~0.0784 | 0.0600~0.0784 | 0.0600~0.0784 |
| Dermis | 1.41 [8] | 0.60 [12][13] | 0.50 [12][13] |
| Fat | 2.50 [8] | 3.54 [14] | 4.40 [14] |
| Muscle | 13.50 [8] | 11.10 [14] | 9.17 [14] |
| Cortical bone | 6.00 [8] | 6.00 [8] | 6.00 [8] |
| Bone marrow | 6.50 [8] | 6.50 [8] | 6.50 [8] |
| Electrode | 0.01 [8] | 0.01 [8] | 0.01 [8] |

TABLE V. Width of change in dermis thickness in 3D model

| Tissue | Thickness (mm) | | |
|-----------------|----------------|-------------|-------------|
| | Young | Old | Older |
| Stratum corneum | 0.029 [8] | 0.024 [15] | 0.029 [15] |
| Epidermis | 0.0600 [8] | 0.068 [11] | 0.078 [11] |
| Dermis | 0.500~1.411 | 0.500~1.411 | 0.500~1.411 |
| Fat | 2.50 [8] | 3.54 [14] | 4.40 [14] |
| Muscle | 13.50 [8] | 11.10 [14] | 9.17 [14] |
| Cortical bone | 6.00 [8] | 6.00 [8] | 6.00 [8] |
| Bone marrow | 6.50 [8] | 6.50 [8] | 6.50 [8] |
| Electrode | 0.01 [8] | 0.01 [8] | 0.01 [8] |

B. Lumped circuit model

Fig. 2 shows the lumped circuit model proposed for this study. Each layer shown in Fig. 2 represents by a parallel circuit of a resistor and a capacitor. Also, a separate parallel circuit is created to reproduce each layer's electrical characteristics in the cylindrical radial direction (depth direction) and the cylindrical axial direction [17]. The circuit simulation software LTspice (Analog Devices) was used for implementation.

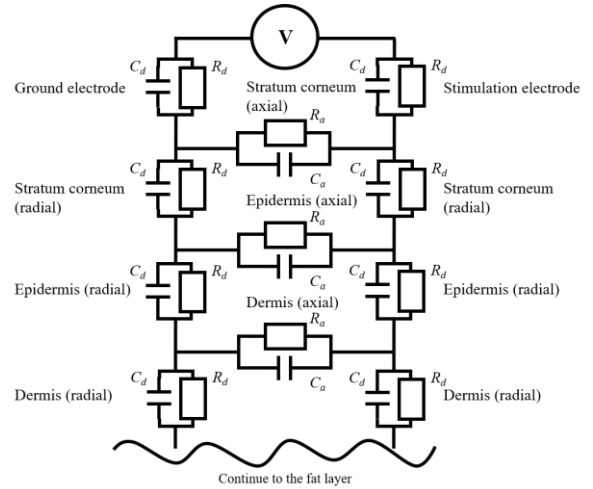


Figure 2. Lumped circuit model

The resistivity and permittivity used in the lumped circuit model was derived from the conductivity and relative permittivity used in the cylindrical models in Tables I and II. The resistance value R_d and capacitance value C_d in the cylindrical radial direction (depth direction) calculate, regarded them as rectangular parallelepiped objects, from (2) and (3) below.

$$R_d = \rho \frac{l}{A_d} \quad (2)$$

$$C_d = \epsilon_0 \epsilon_r \frac{A_d}{l} \quad (3)$$

$$l_1 = \frac{\theta}{360} \times 2 \pi r_1 \quad (4)$$

Where l_1 is the shorter arc-length of each layer boundary, derived by (4) using the angle θ that can be derived from the size of the electrode and the distance (radius) between the stimulating electrode and the center of the cylinder, as shown in Fig. 3(a). A_d is the area of arc $l_1 \times$ axial length (the length of the side of the electrode) d , ρ is resistivity, ϵ_0 is the permittivity of air, l is the thickness of the layer, and ϵ_r is the relative permittivity.

In deriving the resistance value R_a and the capacitance value C_a in the direction of the cylinder axis, also regarded them as rectangular parallelepiped objects, as in (5) and (6)

$$R_a = \rho \frac{l}{A} \quad (5)$$

$$C_a = \epsilon_0 \epsilon_r \frac{A}{l} \quad (6)$$

ρ is resistivity, ϵ_0 is the permittivity of air, ϵ_r is the relative permittivity, l is the length in the axial direction of the cylinder (distance between electrodes), and A is the cross-sectional area of the cylinder.

The cross-sectional area A was derived by (7) and (8) using the angle θ that can be derived from the size of the stimulating electrode and the distance (radius) between the stimulating electrode and the center of the cylinder, as shown in Fig. 3(b).

$$A_a = \frac{\theta}{360} \times \pi(r_2^2 - r_1^2) \quad (7)$$

$$A = 4 \times A_a \quad (8)$$

r_2 is the radius of the outer circle of cross-sectional area A_a , r_1 is the radius of the inner circle of cross-sectional area A_a . These lengths are calculated by each layer thickness.

In the FEM simulation model, the voltage in the axial direction of the cylinder appeared to spread beyond the size of the stimulating electrode, so the cross-sectional area A_a was set to four times. Regarding the electrodes, both the thickness and the electrode area are the same as the finite element method simulation model.

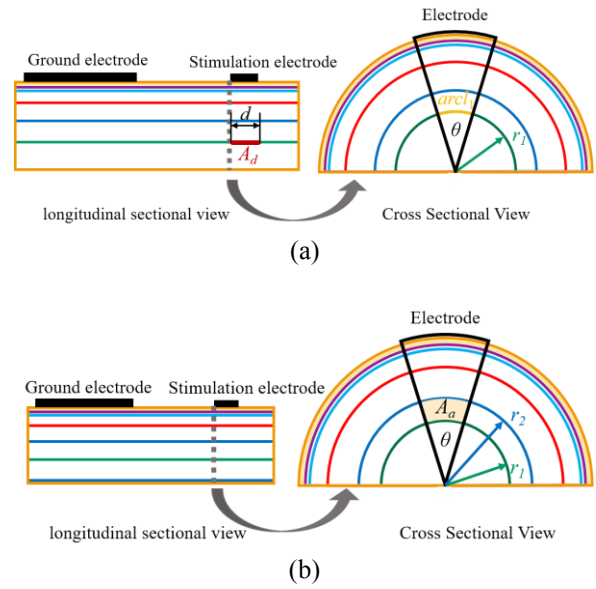


Figure3. (a) Derivation method of arc-length (Semicircle omitted)

(b) Derivation method of cross-sectional area (Semicircle omitted)

III. RESULT & DISCUSSIONS

A. The trends of stimulation intensity at different frequencies

At 1 Hz, the change in stimulation intensity due to the change in thickness of the stratum corneum, epidermis layer, and dermis layer is shown in Fig. 4. As shown in Fig. 4, the increase in the stratum corneum in all age group models showed a decrease in the stimulation intensity near the fascia. Meanwhile, no change in the stimulation intensity near the fascia due to the increase in epidermis thickness was observed in any age group model. A decrease in the stimulation intensity near the fascia due to the increase in dermis thickness was observed in all age group models.

When the frequency is changed to 100 Hz, the change in stimulation intensity due to the change in thickness of each of the stratum corneum, epidermis layer, and dermis layer is shown in Fig. 5. Comparing to the trends at 1 Hz in Fig. 4, the stimulation intensity is generally increased. However, it is noticed that there was no significant difference in the tendency of the stimulation intensity near the concerning the

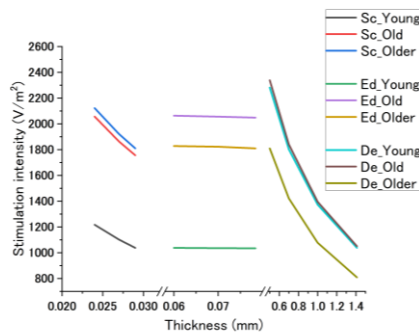


Figure 4. Changes in stimulation intensity due to the thickness of the Stratum corneum (Sc), Epidermis (Ed), and Dermis (De) at 1 Hz stimulation

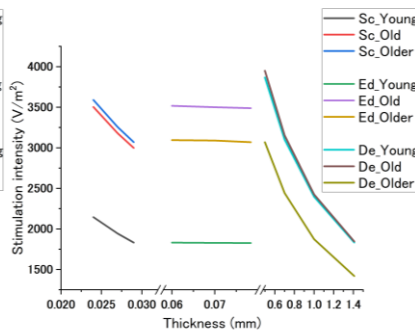


Figure 5. Changes in stimulation intensity due to the thickness of the Stratum corneum (Sc), Epidermis (Ed), and Dermis (De) at 100 Hz stimulation

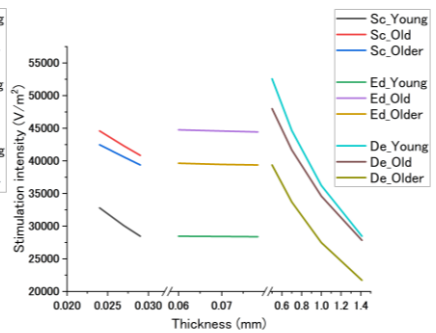


Figure 6. Changes in stimulation intensity due to the thickness of the Stratum corneum (Sc), Epidermis (Ed), and Dermis (De) at 10 kHz stimulation

changes in the thickness of the stratum corneum, epidermis layer, and dermis layer.

When the frequency is increased further to 10 kHz, the change in stimulation intensity due to the change in thickness of the stratum corneum, epidermis layer, and dermis layer is shown in Fig. 6. The stimulation intensity increased overall compared to the results at frequencies of 1 Hz and 100 Hz. There was no significant difference in the tendency of the stimulation intensity near the fascia concerning the changes in the thickness of the stratum corneum, epidermis layer, and dermis layer. However, in terms of the relationship between the increase in the thickness of the stratum corneum and the stimulation intensity, the Old model showed the highest stimulation intensity, unlike the previous frequencies. Also, in the relationship between the increase in the thickness of the dermis layer and the stimulation intensity, the Young model showed the highest stimulation intensity, unlike the previous frequencies.

B. Stimulation intensity decrease rate by each age model

For each of the three age models, the rate of decrease in stimulation intensity due to the increase in thickness of the stratum corneum, epidermis layer, and dermis layer is shown in Table VI, VII, VIII.

TABLE VI. Stimulation intensities decrease rate for each frequency when the Stratum corneum changes from 0.024 mm to 0.029 mm

| Age model | Decrease rate (%) | | |
|-----------|-------------------|--------|--------|
| | 1 Hz | 100 Hz | 10 kHz |
| Young | 14.8 | 14.7 | 13.2 |
| Old | 14.7 | 14.5 | 8.4 |
| Older | 14.7 | 14.5 | 7.3 |

TABLE VII. Stimulation intensities decrease rate for each frequency when the Epidermis thickness changes from 0.0600 mm to 0.0784 mm

| Age model | Decrease rate (%) | | |
|-----------|-------------------|--------|--------|
| | 1 Hz | 100 Hz | 10 kHz |
| Young | 0.3 | 0.3 | 0.3 |
| Old | 0.7 | 0.8 | 0.7 |
| Older | 1.0 | 0.8 | 0.7 |

TABLE VIII. Stimulation intensities decrease rate for each frequency when the Dermis thickness changes from 0.500 mm to 1.411 mm

| Age model | Decrease rate (%) | | |
|-----------|-------------------|--------|--------|
| | 1 Hz | 100 Hz | 10 kHz |
| Young | 54.5 | 52.7 | 45.9 |
| Old | 55.1 | 53.3 | 42.1 |
| Older | 55.3 | 53.8 | 44.9 |

It is shown that in all three age models, the decrease rate of stimulation intensity due to the increase in thickness of the stratum corneum, epidermis layer, and dermis layer did not change significantly even if the stimulation frequency changes from 1 Hz to 100 Hz, but, under 10kHz stimulation, in the stratum corneum, the rate of decrease was about 6% higher only in the Young model, and in the dermis layer, the rate of decline was about 9 ~ 13% lower in all age models than under 1Hz stimulation. In the epidermis layer, the rate of decrease did not change significantly even under stimulation at 10 kHz.

In this study, using three age-specific models and different stimulation frequencies of 1Hz, 100 Hz, and 10 kHz, the

effects of the skin layers made up of the stratum corneum, epidermis, and dermis on electrical stimulation by TENS were investigated.

First, we discuss the effect of the skin layer on the stimulation frequency. When the stimulation frequency changed to high frequency, the stimulation intensity increased in all age group models. This is because, as shown in Table I and Table II, the conductivity of each layer increases, and the relative permittivity decreases as the frequency increases, so the impedance decreases, and the stimulation is more likely to be transmitted to the deep fascia. It is considered that this reduced the rate of decrease in stimulation intensity in spite of the increase in dermis layer thickness when the stimulation frequency was 10 kHz. It was also shown that in all three age models, the decrease rate of stimulation intensity due to the increase in thickness of the stratum corneum, epidermis layer, and dermis layer does not change significantly even if the stimulation frequency changes from 1 Hz to 100 Hz.

When the increase in the thickness of the stratum corneum, the decrease rate tended to be high only in the Young model, which is considered to be related to the fact that the dermis layer was thicker in the young model than in the other model (See Table III). For an effect of the stratum corneum, as has been said from studies so far [3][18], it was possible to show a tendency that the stimulation intensity decreases as the thickness increases. From this result, it is considered that the finite element method simulation model used in this study is a model close to an actual living body.

For the effects of the epidermis layer, unlike the stratum corneum, there was no significant decrease in stimulation intensity due to changes in thickness. The reasons for this phenomenon are as follows: As shown in Tables I and II, the epidermis layer has relatively high conductivity and a low relative permittivity, so the impedance is small, and the function of hindering stimulation is small. Also, the change in thickness width was minimal, about 0.002 mm.

For the effect of the dermis layer, the stimulation intensity decreased due to the increase in thickness. In the literature, this result was reported qualitatively, but it has never been shown quantitatively [19]. It is a little difficult to consider the reason why this phenomenon occurred. Because it is well-known that the dermis layer has a higher conductivity and relative permittivity than the stratum corneum and the epidermis layer, and therefore has a small impedance. So, we focused on the current flowing through dermis layer. To see the current of each layer, we measured the change in the current value due to the change in thickness using a lumped circuit model that expressed the FEM simulation model as an electric circuit and used it for the study. And we were able to get interesting results by the measurement using the circuit model.

Fig. 7 and Fig. 8 show the magnitude of the current according to the thickness of the resistor and capacitor parallel circuit part that resembles the dermis layer when stimulus of 1 Hz and 10 kHz are applied, respectively. From the results of the FEM model, the effect of decreasing in stimulation intensity due to the increase in the thickness of the dermis layer weakened for higher stimulation frequencies, but it

showed a tendency like 1 Hz at 100 Hz. Therefore, the measurement was performed at 1 Hz and 10 kHz.

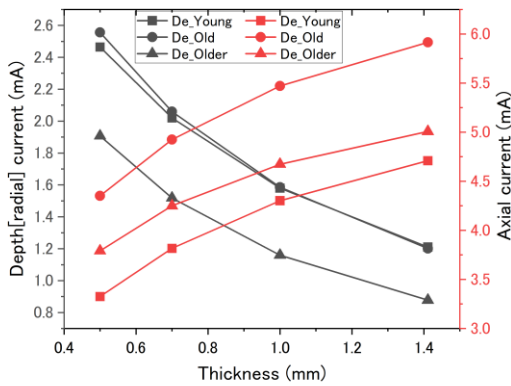


Figure 7. Relationship between depth [radial] current and axial current of dermis layer and dermis layer thickness in each model at 1 Hz stimulation

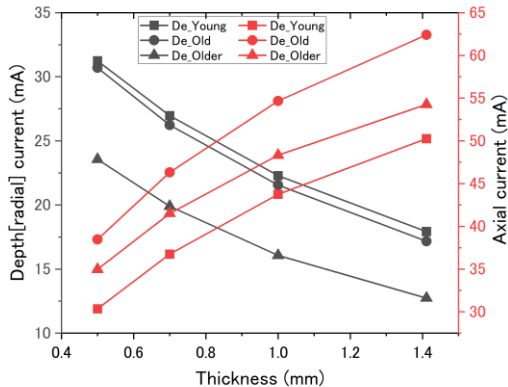


Figure 8. Relationship between depth [radial] current and axial current of dermis layer and dermis layer thickness in each model at 10 kHz stimulation

In Fig. 7, for the current in the depth direction, the 1 Hz stimulation showed almost the same value in the Young model and the Old model. However, at 10 kHz as shown in Fig. 8, stimulation showed a higher value in the Young model than in the Older model. From this result, it can be inferred that at 10 kHz, the voltage under the dermis layer is also higher in the Young model by Ohm's law than the Older model. In fact, the fascia stimulation intensity values at 10 kHz measured by the FEM simulation model (Fig. 6) were higher in the Young model. From the above, it is clearly seen that the lumped circuit model grasped the tendency of the electrical change of the FEM model.

For the thickness of the dermis layer, it was shown that as the thickness increases, the current flowing in the depth direction tends to decrease, while the current flowing in the axial direction tends to increase. This phenomenon is considered to be related to the fact that the dermis layer is anisotropic, and the flow is easier in the axial direction than in the depth direction.

Therefore, when the thickness of the dermis layer increases, instead of hindering the stimulation by increasing the impedance as in the stratum corneum, the stimulation intensity decreases near the fascia by changing the current path from the depth direction to the axial direction. The function of this dermis layer may be an important factor in determining the stimulation parameters in TENS in the future.

There are restrictions on this study. The model used in this study only responds to changes in estimated thickness with age, cannot respond to changes due to other factors such as temperature and humidity or electrode area ratio. In addition, regarding changes in the current path of the dermis layer, it is necessary to look at trends due to stimulation frequencies and relationships with other layers that were not examined this time. In future research, we would like to conduct further quantification by measuring with different electrode area ratios and frequencies and measuring the stimulation intensity due to the difference in the amount of water content in the skin layer (i.e., dry or wet skin).

In near future, this conduction model will be combined with computational models of afferent nerves A δ and C responding to stimulation waves [20], for investigating the effect of chronic pain suppression from the viewpoint action potential generation. Moreover, more direct pain relief effect could be confirmed by pain-related EEG measurement [21], [22].

IV. CONCLUSION

This study reveals that when stimulating nerves near the fascia with TENS, the thickness of the dermis layer in addition to the stratum corneum decreases stimulation intensity. It was also showed that the rate of decrease due to the thickness of the skin layer did not change when the stimulation frequency was between 1 Hz and 100 Hz. These results are important for achieving optimal stimulation for the individual to enhance the effectiveness of TENS.

REFERENCES

- [1] Fields, Howard. "State-dependent opioid control of pain." *Nature Reviews Neuroscience* 5.7 (2004): 565-575.
- [2] Radhakrishnan, Rajan, and Kathleen A. Sluka. "Deep tissue afferents, but not cutaneous afferents, mediate transcutaneous electrical nerve Stimulation-Induced antihyperalgesia." *The Journal of Pain* 6.10 (2005): 673-680.
- [3] Yamamoto, Tatsuma, and Yoshitake Yamamoto. "Electrical properties of the epidermal stratum corneum." *Medical and biological engineering* 14.2 (1976): 151-158.
- [4] Kuhn, Andreas, et al. "The influence of electrode size on selectivity and comfort in transcutaneous electrical stimulation of the forearm." *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 18.3 (2010): 255-262.
- [5] Bora, Dhruva Jyoti, and Rajdeep Dasgupta. "Various skin impedance models based on physiological stratification." *IET systems biology* 14.3 (2020): 147-159.
- [6] Alon, Gad, Gideon Kantor, and Henry S. Ho. "Effects of electrode size on basic excitatory responses and on selected stimulus parameters." *Journal of Orthopaedic & Sports Physical Therapy* 20.1 (1994): 29-35.
- [7] Jose D. Gomez-Tames, Jose. Gonzalez, and Wenwei Yu, A Simulation Study: Effect of the Inter-Electrode Distance, Electrode Size and Shape in Transcutaneous Electrical Stimulation, 34th Annual International Conference of the IEEE EMBS, San Diego, California USA, 28 August - 1 September, 2012

- [8] Zhu, Kaihua, et al. "A 3D Computational Model of Transcutaneous Electrical Nerve Stimulation for Estimating A β Tactile Nerve Fiber Excitability." *Frontiers in Neuroscience* 11 (2017): 250.
- [9] Tavernier, André, Marcel Dierickx, and Maurice Hinsenkamp. "Tensors of dielectric permittivity and conductivity of in vitro human dermis and epidermis." *Bioelectrochemistry and bioenergetics* 30 (1993): 65-72.
- [10] Gabriel, Sami, R. W. Lau, and Camelia Gabriel. "The dielectric properties of biological tissues: III. Parametric models for the dielectric spectrum of tissues." *Physics in medicine & biology* 41.11 (1996): 2271.
- [11] Trojahn, Carina, et al. "Measuring skin aging using optical coherence tomography in vivo: a validation study." *Journal of biomedical optics* 20.4 (2015): 045003.
- [12] Branchet, M. C., et al. "Skin thickness changes in normal aging skin." *Gerontology* 36.1 (1990): 28-35.
- [13] Tsai, B., et al. "Dielectrical properties of living epidermis and dermis in the frequency range from 1 kHz to 1 MHz." *Journal of Electrical Bioimpedance* 10.1 (2019): 14-23.
- [14] Mayrovitz, Harvey N., et al. "Age-related changes in male forearm skin-to-fat tissue dielectric constant at 300 MHz." *Clinical physiology and functional imaging* 37.2 (2017): 198-204.
- [15] Egawa, M., and H. Tagami. "Comparison of the depth profiles of water and water-binding substances in the stratum corneum determined in vivo by Raman spectroscopy between the cheek and volar forearm skin: effects of age, seasonal changes and artificial forced hydration." *British Journal of Dermatology* 158.2 (2008): 251-260.
- [16] Rattay, Frank. "The basic mechanism for the electrical stimulation of the nervous system." *Neuroscience* 89.2 (1999): 335-346.
- [17] Gómez, F., et al. "Modeling and simulation of equivalent circuits in description of biological systems-a fractional calculus approach." *Journal of Electrical Bioimpedance* 3.1 (2012): 2-11.
- [18] Kalia, Yogeshvar N., Fabrice Pirot, and Richard H. Guy. "Homogeneous transport in a heterogeneous membrane: water diffusion across human stratum corneum in vivo." *Biophysical journal* 71.5 (1996): 2692-2700.
- [19] Kruglikov, Ilja L. "Influence of the dermis thickness on the results of the skin treatment with monopolar and bipolar radiofrequency currents." *BioMed research international* 2016 (2016).
- [20] He, Siyu, et al. "A simulation study on selective stimulation of C-fiber nerves for chronic pain relief." *IEEE Access* 8 (2020): 101648-101661.
- [21] Tripanpitak, Kornkanok, et al. "Granger Causality-Based Pain Classification Using EEG Evoked by Electrical Stimulation Targeting Nociceptive A δ and C Fibers." *IEEE Access* 9 (2021): 10089-10106.
- [22] Tripanpitak, Kornkanok, et al. "Classification of Pain Event Related Potential for Evaluation of Pain Perception Induced by Electrical Stimulation." *Sensors* 20.5 (2020): 1491.