Visualization of viscoelastic behavior in vivo skin using optical coherence tomography-based straingraphy combined with suction device

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Abstract
Although various apparatuses have been developed to assess the skin mechanical function, the spatial viscoelastic behavior of each skin layer including the epidermis and dermis is yet unclear. To resolve that lack of clarity, we built a handmade system combining a suction device with optical coherence tomography (OCT). OCT can visualize the vertical section of the skin with high spatial resolution and high acquisition speed. In addition, we developed a novel algorithm for time-dependent strain tomography, named Dynamic Optical Coherence Strainography (D-OCSA), which can analyze the changes in strain distributions over time in sequential OCT images. Using the system, successive OCT images of volar forearm skin were obtained after the suction release, followed by calculation of spatial distribution of creep recovery time as an index of viscoelastic behavior. As a result, we revealed that the creep recovery time in the dermis was significantly larger than that of the epidermis. This is the first report to provide evidence that there is a spatial difference in the viscoelastic behavior in the skin. Future application of our method would be beneficial to the diagnosis of skin mechanical function and the validation of cosmetic and medical applications.

Keywords: Elastography, Dynamic optical coherence straingraphy, Optical coherence tomography, Suction device, Creep recovery time, Viscoelastic behavior

1. Introduction
Skin mechanical properties are of great importance for skin health, tactile impressions, barrier function from external disturbances, and so on. To assess the mechanical function of the skin, various apparatuses have been developed, most of which measure the deformation or mechanical stress reaction of the whole skin during or after the application of physical stress or displacement. One of the representative commercially available instruments is the Cutometer® (Courage & Khazaka Electronic GmbH, Köln, Germany) which measures the vertical deformation of the skin surface during and after application of a vacuum (Barel et al., 1995). There are many studies using a Cutometer® which indicated the relationship between skin mechanical properties and age (Krueger et al., 2011), wrinkle formation (Luebberding et al., 2014), sagging (Fujimura et al., 2007), the effects of applied skincare products (Dobrev, 2000) and the quality of reconstructed skin cover (Sin et al., 2010). Although the advantage of a Cutometer® is its high reproducibility and reliability, the measurement results reflect the whole skin’s mechanical character and cannot specify the mechanical behavior of each layer of skin including the epidermis and dermis. However, it is well known that each layer has a different function in the skin (Agache et al., 2017). To evaluate these functions, spatial distribution is thought to be important to assess the skin’s mechanical properties.

Recently, as a method for estimating the mechanical properties of living body components, elastography has been developed (Doyley and Parker, 2014). An elastography system consists of a mechanical load device and a noninvasive tomography such as an ultrasonic diagnostic apparatus, optical coherence tomography (OCT), and so on. The basic principle of elastography is to track speckle patterns in the two tomographic images before and after mechanical
loading, followed by visualizing the spatio-temporal mechanical behavior under the calculation of the local deformation or deformation speed. For diagnosis of diseases accompanied by alterations in mechanical properties, several elastography systems combined with ultrasonic diagnostic apparatuses have been commercial available; For example, ACUSON NX3 (Siemens AG, Munich, Germany), HI VISION Ascendus (Hitachi, Ltd., Tokyo, Japan) and so on. However, the resolution of these ultrasonic apparatuses is several hundred micrometers. The resolution is too low to analyze the spatial distribution of the skin’s mechanical properties, because the thickness of each skin layer involved in the epidermis and dermis is an order of ten to hundreds of micrometers. On the other hand, the resolution of OCT is approximately several micrometers (Bouma et al., 2001), and thus, the tomographic technique is thought to be suitable using for elastography targeted skin (Wang and Larin, 2015). Previous studies of OCT elastography have investigated the mechanical properties of the skin applying several mechanical load methods to the skin; For example, dynamic uni-axial compressive stress (Kennedy et al., 2011) and surface waves induced by short impulses (Larin and Sampson, 2017). These studies estimated the elastic response in the stratum corneum in hydration conditions (Kennedy et al., 2011) and the Young’s modulus of the dermis and subcutaneous fat (Larin and Sampson, 2017). However, the difference of mechanical behavior between epidermis and dermis, which are the main layers in the skin, still remain unclear. To investigate this point, in this study, we built an elastography system combined with a suction device like as Cutometer® with OCT, and investigated the mechanical behavior, especially the viscoelastic behavior, after application of a vacuum in forearm skin in vivo.

2. Material and Methods

2.1 Elastography system combined with suction device and OCT

We built a handmade elastography system which combined an air suction device with OCT (IVS-2000, Santec Inc., Aichi, Japan) (Figure 1(a)). The chamber has a suction hole of 4 mm diameter and the suction pressure was adjusted by the regulator (ITV2090-312S5, SMC Inc., Tokyo, Japan) with the system connecting the vacuum pump (G-5, Ulbako Inc., Miyazaki, Japan) and the air tank. Figure 1(b) shows the curve of suction pressure against time. Suction pressure setting at 2 kPa was applied to subjected skin at a constant pressure for 5 seconds, followed by a 5-second relaxation period just after releasing to atmospheric pressure by opening an electromagnetic valve (VT307W-5H1-02, SMC Inc., Tokyo, Japan). In all periods, successive OCT images were acquired while synchronizing with the signal of the suction pressure. The acquired image size of OCT was set as 128 pixel (depth) × 192 pixel (width), and the pixel resolution was 7.81 μm per pixel for both image depth and width. These acquiring conditions made the frame rate of OCT images 79.05 frames per second.

![Fig.1 Elastography system combined a handmade suction device with OCT. (a) Illustration of the experimental apparatus. (b) Time course of the suction pressure.](image-url)
2.2 Dynamic Optical Coherence Strainography

We developed Dynamic Optical Coherence Strainography (D-OCSA) as a two-dimensional tomographic technique for obtaining time-dependent strain distributions, i.e. strain rate. A flowchart of the algorithm for D-OCSA is shown in Fig. 2. In the D-OCSA algorithm, the spatio-temporal distributions of deformation speed vectors are calculated from successive OCT images, and then the spatial distribution of creep recovery time is outputted.

Fig.2 Algorithm flowchart of Dynamic Optical Coherence Strainography (D-OCSA).

In the D-OCSA algorithm shown in Fig. 2, two OCT images which were taken after releasing to atmospheric pressure in Fig. 1(a). The similarity between the selected OCT images was calculated as a correlation coefficient map \( R_{i,j}(\Delta X, \Delta Z) \) for every subsets based on cross-correlation analysis shown in Fig. 2(b), as follows:

\[
R_{i,j}(\Delta X, \Delta Z) = \sum_{x=1}^{N_x} \sum_{z=1}^{N_z} \left[ f(X_i Z_j) - f \right] [g(\Delta X Z_j + \Delta Z) - g] \sqrt{\sum_{x=1}^{N_x} \sum_{z=1}^{N_z} [f(X_i Z_j) - f]^2 \sum_{x=1}^{N_x} \sum_{z=1}^{N_z} [g(\Delta X Z_j + \Delta Z) - g]^2}
\]

where \( f(X_i Z_j) \) and \( g(X_i Z_j) \) are the speckle patterns of selected OCT images in the subset regions before and after the time series, respectively. The subset size and its central coordinates are \( (N_x, N_z) \) and \( (X_i, Z_j) \), respectively. The displacement vector, defined as \( \hat{U}_{i,j} \), is outputted in Fig. 2(b) as the maximum correlation value by calculated from:

\[
\hat{U}_{i,j} = \frac{\Delta X_{\text{max}}}{\Delta Z_{\text{max}}} = \arg \max R_{i,j}(\Delta X, \Delta Z)
\]

The D-OCSA algorithm shown in Fig. 2(c) to (f) applies speckle cross-correlation analysis recursively to synthetic OCT images with a quarter reduction of subset size. OCT images have speckle noise and contain less valid information than other images commonly used in digital image correlation (DIC) analysis (Yoneyama and Murasawa, 2009). Furthermore, the available pixel number of OCT image is typically quite less than that of normal DIC image, because an example depth dynamic rage for skin diagnosis is less than 1 millimeter with about 5 micrometer resolutions. Such low quality and quantity information causes erroneous vectors in cross-correlation analysis. To correct vectors as well as to enhance the vector resolution with suppressing the erroneous vectors, the recursive cross-correlation method is incorporated into the D-OCSA algorithm. Error propagation is prevented by the erroneous vector removal and the spatial interpolation of removal vectors shown in Fig. 2(d) and (e), respectively. In addition, in Fig. 2(c), adjacent cross-correlation multiplication (ACM) was applied for the robustness improvement of calculating the displacement vector. In the ACM, the maximum correlation value is detected by multiplying the correlation value of the subset region and overlapping adjacent subset regions. Since these subset regions have a unique correlative relationship in their displacement vectors, the peak of maximum correlation value is more sharpened by applying the ACM.
Furthermore, for high-accuracy subpixel analysis, D-OCSA uses the upwind gradient method (Yamamoto and Uemura., 2009) followed by the image deformation method (Kim and Sung, 2006). Since the gradient method is generally advantageous detecting displacement vector even in the high resolution, it is used as a local sub-pixel analysis under the conditions of a small sized subset. In the upwind gradient algorithm in Fig. 2(g), tempo-spatial infinitesimal changes between the intensity distribution of \( f(x, z, t) \) and \( f(x + \Delta x, z + \Delta z, t + \Delta t) \) are the variation in background intensity, i.e. the error. They are given by the following Lagrangian derivative equation based on a Taylor series expansion:

\[
\Delta f(x + \Delta x, z + \Delta z, t + \Delta t) - \Delta f(x, z, t) = \frac{\partial f}{\partial x} \Delta x + \frac{\partial f}{\partial z} \Delta z + \frac{\partial f}{\partial t} \Delta t + O(\Delta^2)
\]

where \( \Delta x \) and \( \Delta z \) represent the subpixel movement amount. Here, the left side of Equation (3) can be assumed to converge to zero, that is white noise, if the intensity of OCT light source and the frame rate of OCT images are constant. In the optimization problem to minimize the white noise error of the left side, the least squares method can determine the sub-pixel shift \( (\Delta x, \Delta z) \) from substituting the intensity gradient and the intensity change calculated inside the subset. The intensity gradients are given by the average of the upwind and downwind differences for both corresponding subsets between two synthetic OCT images. The intensity gradient is approximated using the first-order upwind difference scheme because the application of high-order difference requiring a lot of spatial data is affected strongly by the speckle noise error.

In the image deformation algorithm in Fig. 2(h), the sub-pixel movement amount is optimized by convergent calculation as a maximum correlation coefficient between two synthetic OCT images, which takes expanding, contracting and shearing deformation into account. Allowing for the central coordinates in the subset before deformation to be \( \vec{r} = (x, z) \), the position vector in the local coordinate system inside the subset is defined as \( \vec{r} = (\Delta x, \Delta z) \). Assuming linear deformation, it could be presumed that the corresponding coordinates after deformation, \( \vec{r}^* = (x^*, z^*) \), could be approximated using the sub-pixel movement vector \( \vec{u} = (u, v) \) as the following equations:

\[
x^* = x + \Delta x + u \frac{\partial x}{\partial x} + \frac{\partial u}{\partial x} \Delta z \\
z^* = z + \Delta z + v \frac{\partial z}{\partial x} + \frac{\partial v}{\partial x} \Delta z
\]

The intensity distribution within a linear deformed subset is interpolated by the tricubic function based on deconvolution of point spread function determined by OCT specifications, e.g. light source and objective lens (Kim and Sung, 2006). Deformation parameters of subset are iteratively calculated by the Newton-Raphson method (Bruck et al., 1989), as the upwind gradient method can give the initial displacement in subpixel order (Sugii et al, 2000).

Here, \( U_{OCSA} \) is the tempo-spatial data in the deformation field calculated after sub-pixel analysis. Excluding the region where the correlation value is less than 0.7 in Fig. 2(i), the spatial distribution of the vector of deformation speed was outputted by the time-space weight moving least squares method in Fig. 2(j), as follows:

\[
J = \sum_{n=1}^{N} \sum_{m=1}^{M} \sum_{l=1}^{L} [U_{OCSA}(x_l, z_m, t_n) - U_{app}(x_l, z_m, t_n)]^2
\]

where \( L, M \) and \( N \) are defined as arbitrary numbers of data in the tempo-spatial radius of influence ellipsoid, \( U_{app} \) which is defined as a three-variable quadratic polynomial and a tempo-spatial approximate function in the deformation field is calculated as the minimum evaluation value \( J \). The spatial distribution of the two-dimensional strain rate tensor is calculated as the differential coefficient of \( U_{app} \). A numerical validation study of D-OCSA was executed using phantom OCT images based on the FEM deformation simulation and the Monte Carlo scattering simulation. D-OCSA can provide approximately the displacement vector resolution 0.03 pixel and RMS of strain error 250 \( \mu \)e, even though superposition of speckle patterns and OCT signal noise can be simulated in phantom images.

Furthermore, after applied logarithmic transformation to deformation vector in Fig. 2(k), we calculated the
distribution of creep recovery time as an index of viscoelastic behavior in Fig. 2(l). Generally, in the Kelvin–Voigt model represented by a viscous damper and elastic spring connected in parallel, the strain rate \( \dot{\varepsilon}(t) \) after unloading is calculated from the following equation:

\[
\dot{\varepsilon}(t) = A \exp \left\{ -\frac{t}{\tau(k,c)} \right\} \tag{7}
\]

where \( A, k \) and \( c \) are constant value, the elastic modulus and viscosity coefficient, respectively. Creep recovery time, defined as \( \tau(k,c) \), is calculated as the ratio of viscosity coefficient to elastic modulus (Lakes, 2014). Here, relaxation time of strain rate after unloading is equal to that of deformation speed. Thus, the left side of the equation (7) holds not only at the strain rate but also at the deformation speed. To analyze the spatial distribution of creep recovery time defined as \( T(x,z) \), the natural logarithm was taken with respect to the deformation speed at arbitrary coordinates and approximated to the following expression using the least squares method:

\[
\ln\{w(x,z,t)\} \cong -\frac{t}{T(x,z)} + b(x,z) \tag{8}
\]

where \( w(x,z,t) \) and \( b(x,z) \) are deformation speed and constant value at arbitrary coordinates, respectively. \( T(x,z) \) was calculated as the linear slope that fitted the time-dependent change in the natural logarithmic deformation speed. Considering the signal-to-noise ratio of the vector of deformation speed, the range to be approximated by equation (8) was set to 0.38 seconds after the suction release.

To analyze the site-specific creep recovery time, the regions of epidermis and dermis were defined as follows: the border between epidermis and dermis was detected from the OCT signal intensities averaged horizontally using the second band of bright reflecting layer caused by dermal collagen (Neerken et al., 2004). The ranges within \( \pm 90 \mu m \) from the border in the depth direction was defined as epidermis and dermis, respectively.

### 2.3 Human experiment

This study enrolled 6 Japanese subjects (3 men and 3 women) aged 19–24 years, who gave their informed consent. Elastography measurement was performed on their volar forearm skin at position of 6 cm from the elbow to wrist side. The protocol of this study was approved by the ethics committees in our institution (No.17-04). Comparison of averaged creep recovery time between epidermis and dermis was conducted unpaired \( t \)-test.

### 3. Results

The subset size \((N_x,N_z)\) in the D-OCSA algorithm was set from (33, 33) to (9, 9) by recursively applying speckle cross-correlation analysis shown in Fig. 2(c) to (f). Figure 3 shows the typical result of the spatial distribution of deformation speed vector in which the region indicated by dark triangles around 650 \( \mu m \) in \( z \) coordinate is the border between the dermis and epidermis, calculated by the intensity profile of the OCT image.

![Fig. 3. The vector distribution of deformation speed of a 22-year-old subject. Intensity image obtained by OCT is shown in (a). Distribution of deformation speed at 0.19 and 0.38 seconds after the suction release is shown in (b) and (c), respectively. The region pointed by dark triangles is indicated the dermal-epidermal junction.](image-url)
Figure 4 shows the distribution of creep recovery time calculating the above representative example in which the dark area shows the region with a correlation value of less than 0.7. The averaged creep recovery time in the dermis was significantly larger than that in the epidermis (Fig. 5).

Fig. 4. Spatial distribution of creep recovery time. The region pointed by dark triangles is indicated the dermal-epidermal junction.

Fig. 5. Comparison of averaged creep recovery time between epidermis and dermis. Values are presented as mean ± standard deviation of 6 measurements. *, P < 0.01 (Student’s t-test for unpaired samples).

4. Discussion

This is the first report to provide evidence that there is a significant difference of the viscoelastic behavior between the epidermis and dermis in vivo. To disclose that, we built an elastography system combined with a suction device with OCT, followed by a calculation of a spatio-temporal distribution of deformation speed vectors and creep recovery time using our D-OCSA algorithm.

For estimating the mechanical properties of the skin, various methods such as air suction have been developed. However, most of these methods could not specify the distribution of mechanical properties in the skin. To solve the problem, we previously investigated a reverse engineering approach using the Cutometer® and Dermal Torque Meter® (Dia-Stron, Hampshire, UK) to calculate the elastic modulus of the stratum corneum and dermis (Hara et al., 2013). However, the skin has not only elasticity but also viscosity (Agache and Varchon, 2017). Past computer simulation approaches have shown it is difficult to make clear the distribution of viscoelastic behavior because heterogeneous skin structure might cause a complex viscoelastic behavior against external force.

To clear the distribution of the viscoelastic behavior, this study applied an elastography technique to the skin in vivo. Elastography is a method for analyzing the dynamic mechanical behavior distribution inside a living body such as skin (Kennedy et al., 2011), breasts (Gara et al., 1997) and so on, by combining with a dynamic loading device and noninvasive measurement. In this study, we built a system combined with a suction device with OCT which could visualize the vertical section in the skin non-invasively (Fig. 1). While our system is the same as Cutometer® in terms of applying air suction to the skin, it can investigate the viscoelastic behavior in the skin after suction release using successive OCT images with D-OCSA algorithm (Fig. 2). Figure 3 shows the result of temporal change of deformation speed vectors after the suction release. Comparing Fig. 3(b) and (c), it is suggested that the magnitude of the vector in the epidermis decayed faster than that in the dermis. To analyze this result more quantitatively, we calculated the spatial distribution of creep recovery time (Figs. 4 and 5). To avoid the noise of body movement which cannot ignored in large time scale, the range of 0.38 seconds after the suction release was set for the approximation of the creep recovery time. Fig. 5 shows that the creep recovery time in the dermis was significantly larger than that in the epidermis. In the viscoelastic model, creep recovery time reflects its viscoelastic property. The greater the creep recovery time of the viscoelastic model becomes, the larger the property of the viscosity to elastic property, suggesting that the dermis in the skin was more viscous than the epidermis. The result in Fig. 5 is thought to reflect that the dermis has high moisture content and the viscous nature is retained higher by the glycosaminoglycan holding water. It is known that, with photo-aging, dermal collagen fibers decrease (Yasui et al., 2013) while glycosaminoglycan increases (Oh et al., 2011).
These structural changes may lead to larger creep recovery time, and there is a possibility that our elastography system can evaluate the dermal photo-aging. Focusing on the spatial distribution of creep recovery time in the dermis shown in Fig. 4, high creep recovery time is observed around the dark area. The dark area shown in Fig. 4 may indicate the blood vessels because low correlation region in successive OCT images is known to indicate dermal vasculature (Enfield et al., 2011). The result inferred is that blood vessels may play a role in determining the viscoelastic properties of the dermis.

5. Conclusion

This study applied the technique of elastography to in vivo skin using a suction method, and detected the spatial distribution of viscoelastic behavior in the skin. Future application of our method would be beneficial to the diagnosis of skin’s mechanical function and the validation of cosmetic and medical applications.

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