Program Digest, 2019 IEEE International Ultrasonics Symposium (IUS)
Glasgow, Scotland, October 6-9, 2019

Analysis of Factors Affecting Shear Wave Speed in *in vivo* Skin

Anna E. Knight, M.S.
Department of Biomedical Engineering
Duke University
Durham, NC, USA
anna.knight@duke.edu

Adam B. Pely, M.S.
Department of Biomedical Engineering
Duke University
Durham, NC, USA
a.pely76@gmail.com

Felix Q. Jin
Department of Biomedical Engineering
Duke University
Durham, NC, USA
felix.jin@duke.edu

Adela R. Cardones, M.D.
Associate Professor of Dermatology
Duke University Medical Center
Durham, NC, USA
adela.cardones@duke.edu

Mark L. Palmeri M.D., Ph.D.
Associate Prof of the Practice, BME
Duke University
Durham, NC, UA
mark.palmeri@duke.edu

Kathryn R. Nightingale, Ph.D.
Professor of Biomedical Engineering
Duke University
Durham, NC, USA
kathy.nightingale@duke.edu

***Abstract*—In 10 patients with cutaneous sclerotic skin conditions, shear wave elasticity imaging (SWEI) was used to measure shear wave speed in the skin *in vivo*. The dermis was segmented using an thresholding-based algorithm and group speeds were found in both the dermis and the subcutaneous tissue. Phase velocities were calculated in the layer, and a linear regression was fit to obtain a dispersion slope. A statistically significant non-zero dispersion was found in the skin *in vivo*. An ordinary least squares multiple linear regression was performed to assess what factors affected the dispersion slope. Thickness did not have a statistical effect on the dispersion slope in each model, and subcutaneous speed was only found to have a statistical effect at one of two investigated frequency-thickness products. This work shows SWEI based dispersion in the skin *in vivo* and demonstrates the importance of subcutaneous speed in future models.**

***Index Terms*—skin, SWEI, dispersion, elastography, SWS**

I. Introduction

Cutaneous sclerotic skin diseases such as morphea and graft-versus-host disease have irreversible effects, can greatly limit patient motion, and are treated with very harsh immunosuppressive therapies [1]–[3]. These diseases occur when there is increased collagen deposition in the skin, leading to increased stiffness [4], [5], however they cannot be identified on B-mode alone as changes in thickness are not sufficient for diagnosis [6], [7]. As such, many efforts have been made to come up with a quantitative way to measure skin stiffness.

Shear wave elastography imaging (SWEI) measurement of stiffness in the skin is of clinical interest as a quantitative measure of sclerotic skin disease progression. Skin thickness can be on the same order as shearwave wavelength, and so the structured geometry of the dermis is hypothesized to induce dispersion of the shear waves within the dermis. Studies to date have demonstrated an overall difference in group shear wave speed (SWS) in sclerotic skin compared to healthy [6], [8], [9], but for longitudinal monitoring of disease progression a better understanding of what factors affect the shear wave speed in the skin is clinically necessary. Previous works have accounted for the thickness of the skin with techniques like normalization of group SWS by the skin thickness or generating a normalization metric using the diseased location and matched contralateral healthy location thickness [6], [8], [9], but did not account for the Lamb wave or Rayleigh wave like behavior potentially present in the skin based on its thickness relative to shear wave length, although efforts have been to account for this in modeling and in phantoms [10], [11]. Dispersion, a frequency dependence of the phase velocity [12], can result from both viscoelasticity of the material itself or from the plate like structure of the material [13]. Dispersion has been previously demonstrated in the skin using mechanical vibrometry [14], [15].

One of the primary objectives of this work was to investigate if SWEI can be used to assess dispersion in the skin *in vivo*. Previous simulation work [10] also indicated that the stiffness of the material in the subcutaneous layer beneath the dermal layer could have a significant effect on the phase speeds and dispersion measured in the skin itself. This study aims to evaluate the impact of subcutaneous tissue stiffness, dermal layer thickness, and group SWS on dispersion measures in the dermal layer *in vivo*.

II. Methods

A. SWEI Methods

A custom multi track location (MTL) supersonic imagine (SSI) SWEI sequence was created on a Siemens SC2000 scanner using a 14L5 transducer at 6 MHz. 10 patients with sclerotic skin conditions were recruited in compliance with Duke University's IRB protocol. SWEI measurements were taken in both diseased sclerotic plaques and matched contralateral healthy locations in a total of 55 locations across the 10 subjects. If multiple acquisitions were taken at a given location, these were processed separately and averaged together.

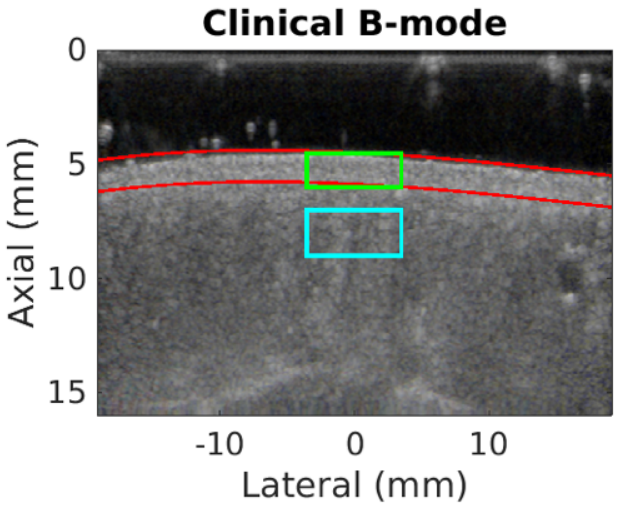

Fig. 1. B-mode of skin image. The red outline shows the dermis as identified using thresholding-based segmentation methods. The green box shows the region of acoustic radiation force excitation region of interest selected from the dermis, while the light blue box shows the region of acoustic radiation force excitation region in the subcutaneous layer, which begins 1 mm deep to the bottom of the dermis and extends 2 mm axially.

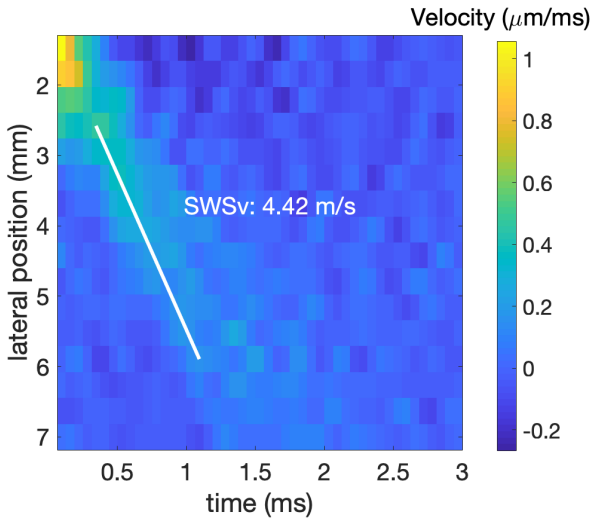

Fig. 2. Velocity space time data from inside the dermal layer. Displacement data was differentiated through time to calculate velocity data at each lateral position, then a Radon Sum approach [17] was used to identify the velocity based group speed in the dermal layer. In this example, the speed is 4.42 m/s.

B. Thresholding-Based Segmentation

A two-step thresholding approach based on Otsu's method was used to segment and identify the dermal layer on the skin images. Otsu's method [16] finds the binary threshold level that minimizes the variances within classes. First, Otsu's threshold was applied to each image to generate a binary mask. The skin's top edge was then detected by starting at a pre-defined depth and searching for the first bright pixel. To remove outliers, we fit a cubic polynomial to the top boundary and removed points more than a standard deviation away from the regression. The bottom boundary was then detected similarly, starting a set distance from the top boundary. A linear regression was applied to the difference between top and bottom positions (i.e. the thickness) and was used to remove outliers for the bottom boundary. An example segmentation produced using this thresholding method is shown in Figure 1. The subcutaneous region was defined as the axial region extending from 1 mm deep to the bottom boundary to 3 mm deep to the bottom boundary.

C. SWEI Processing

Only 27 out of 55 locations across 10 patients, with varied disease states, had data of high enough quality to segment the dermal layer and measure reliable shearwave speeds in both the dermis and subcutaneous layer. Acquisition inclusion was decided based visual assessment of both Otsu segmentations and shear wave speed trajectories in the dermis and subcutaneous layer. After Otsu based segmentation was used to find the dermal layer, we applied both a Radon Sum based approach [17] to find the velocity group speed (SWSv) as seen in Figure 2, and a 2DFT approach [18] to calculate the phase velocities at discrete frequencies from 0.02 to 3 kHz within the dermis as seen in Figure 3. The discrete

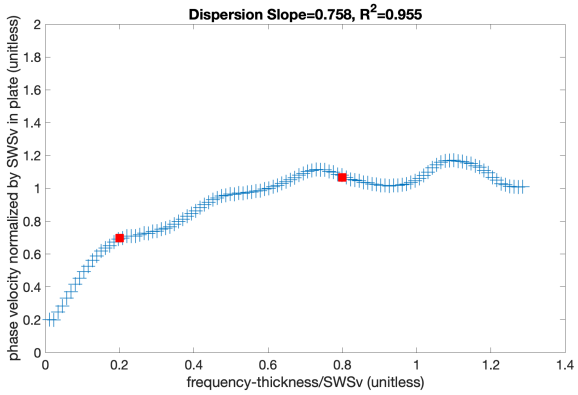

Fig. 3. Phase Velocities in the dermal layer. Blue marks indicate the phase velocity normalized by group shear wave speed (SWSv) (unitless) calculated at each discrete temporal frequency (kHz), then multiplied by thickness of the dermal layer (2.43 mm), and also normalized by SWSv (4.42 m/s), resulting in a unitless x-axis. The red marks show the bandwidth from 0.2 to 0.8 over which a linear regression was fit. The dispersion slope in this example is 0.758.

frequencies were then multiplied by the thickness of the dermis to obtain a frequency-thickness product as is standard for plate like materials [19]. Then both phase velocity and frequency-thickness product (fd) were normalized by the velocity group speed in the dermal layer (SWSv). The dispersion slope was linear regressed in the 0.2 to 0.8 frequency-thickness normalized by SWSv ($fd/SWSv$, unitless) and a slope was calculated based on fitting to the normalized phase speeds in this region. This slope, which is also unitless, was used as a measure of dispersion in the dermal layer. Additionally, the displacement based group speed in the subcutaneous layer was calculated using a time of arrival based approach, as seen in Figure 4.

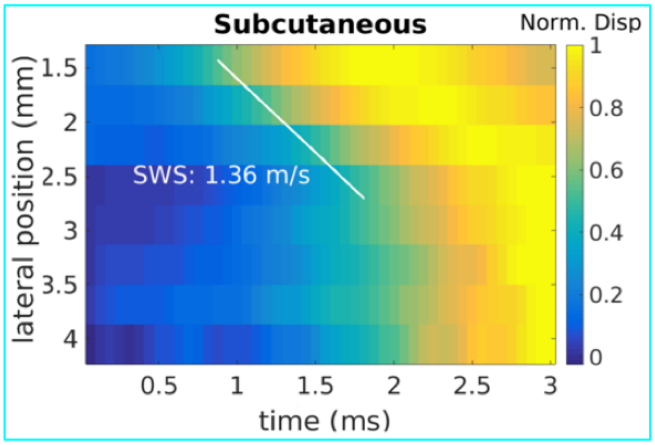

Fig. 4. Speed in the Subcutaneous Layer. A time of arrival based approach was used to find the displacement based group speed in the subcutaneous region. At each lateral position, the displacement through time was normalized to the maximum displacement, then the time of arrival of 50% of this maximum was used as wave arrival time. This was chosen due to the notably slower shear wave speeds in the subcutaneous layer, such that the maximum displacement had not occurred during the tracking time window (3 ms).

D. Multiple Linear Regression and Statistical Analysis

The statsmodel and scipy packages in Python were used for all statistical analysis, both using an $\alpha = 0.05$. An ordinary least squares regression using the statsmodel package in Python was used to investigate how the following variables affected the dispersion slope: 1) phase velocity at a specific $fd/SWSv$, 2) displacement based group speed in the subcutaneous layer, and 3) thickness of the dermal plate itself. This analysis was repeated at two different $fd/SWSv$ values: $0.2fd/SWSv$ and $0.75fd/SWSv$, the lower and upper end of the linear region respectively.

III. Results and Discussion

The thickness adjusted dispersion slope in the dermal layer (0.77 ± 0.39 $unitless$) was found to be statistically significantly different from 0 using a two-tailed one sample t-test ($F = 10.33$, $p < 0.001$). This shows that dispersion, as represented by the thickness and group speed adjusted linear slope of the phase velocity curve, is present in the dermis.

An ordinary least squares multiple linear regression was calculated to predict thickness adjusted dispersion slope (Slope) based on 1) normalized phase velocity at 0.2 (PhVel0.2) 2) displacement based group speed in the subcutaneous layer (Subcut), and 3) thickness of the dermal layer (d). A significant regression equation was found ($F = 4.09$, $p = 0.018$, with an R^2 of 0.348, representing a poor fit. The predicted regression equation was:

$$Slope = 0.13 * Subcut - 1.6 * PhVel0.2 + 0.07 * d + 1.48$$

As seen in Table 1, each of the independent variables was found to be statistically significant, except thickness. Velocity based group speed in the dermal layer was 3.7 ± 1.7 m/s, subcutaneous speed was 1.90 ± 1.07 m/s, thickness was 2.65 ± 1.03 mm, and the dispersion slope was 0.78 ± 0.39.

TABLE I
OLS REGRESSION RESULTS FOR $fd/SWSv = 0.2$, SUBCUTANEOUS SPEED, AND THICKNESS EFFECT ON DISPERSION SLOPE

Overall Results	**R-squared** = 0.348			
	F-statistic = 4.09			
	Prob(F-statistic = 0.018			
Dependent Variable: Dispersion Slope	**No. Observations** = 27			
	Df Residuals = 23			
	Df Model = 3			
	Covariance Type: non robust			
	Independent Variables			
Variable	**Coefficient**	**Std Error**	**t**	$P > \|t\|$
Subcut	0.13	0.06	2.16	0.042
NormPhaseVel at 0.2	-1.6002	0.60	-2.647	0.014
Thickness	0.074	0.064	1.16	0.260
Constant	0.55	0.15	3.7	0.001

Another ordinary least squares multiple linear regression was calculated to predict thickness adjusted dispersion slope (Slope) based on 1) normalized phase velocity at 0.75 (PhVel0.75) 2) displacement based group speed in the subcutaneous layer (Subcut), and 3) thickness of the dermal layer (d). A significant regression equation was found ($F = 30.26$, $p < 0.001$), with an R^2 of 0.798. The predicted regression equation was:

$$Slope = 0.05 * Subcut + 1.62 * PhVel0.75 - 0.02 * d - 1.22$$

As seen in Table 2, only the normalized phase velocity at 0.75 was significant, thickness and subcutaneous speed were not statistically significant.

TABLE II
OLS REGRESSION RESULTS FOR $fd/SWSv = 0.75$, SUBCUTANEOUS SPEED, AND THICKNESS EFFECT ON DISPERSION SLOPE

Overall Results	**R-squared** = 0.798			
	F-statistic = 30.26			
	Prob(F-statistic = 3.69e-08			
Dependent Variable: Dispersion Slope	**No. Observations** = 27			
	Df Residuals = 23			
	Df Model = 3			
	Covariance Type: non robust			
	Independent Variables			
Variable	**Coefficient**	**Std Error**	**t**	$P > \|t\|$
Subcut	0.0515	0.035	1.469	0.1555
NormPhaseVel at 0.75	1.6235	0.189	8.5901	0.000
Thickness	-0.0176	0.037	-0.474	0.640
Constant	-1.22	0.218	-5.62	0.000

These results show overall that statistically significantly dispersion present in the dermis, and that it can be measured using ultrasound based SWEI. These results are concordant with mechanical vibrometry results from other groups [15], that demonstrate that dispersion is present in the dermis. It is interesting to note that in neither of the OLS regression model results (Table 1 and 2), was the thickness of the dermal plate itself found to be statistically significant. This is likely due to the fact that the analysis already accounted for thickness by calculating slope based on the frequency-thickness product normalized by the group SWS. In the OLS

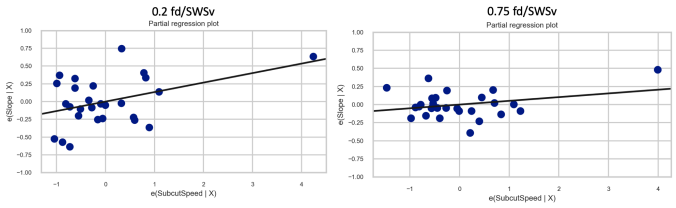

Fig. 5. Partial Regression Plots. These partial regression plots show the effect of subcutaneous speed on the dispersion slope, after taking thickness and phase velocity into account as part of the OLS multiple regression models described in Table 1 and 2. On the left is the partial regression plot for when taking phase velocity at $0.2fd/SWSv$ into account, and on the right $0.8fd/SWSv$)

regression model looking at the lower frequency phase velocity (0.2), the subcutaneous speed was significant, while it was not at the higher frequency phase velocity (0.75). This can be seen in the slopes of the partial regression plots seen in Figure 5: there is less slope to the regression at higher frequency phase velocity. This may be explained by the fact that, the dermis appears more plate like, and so the presence of a shear supporting substrate is a greater violation of the standard Lamb-wave assumptions [19]. It is important to note that while dispersion is present in the skin, it cannot be concluded from this analysis what portion of this dispersion can be attributed to the plate like structure of the dermal layer, and what can be attributed to viscoelasticity of the material itself.

IV. Conclusions

This work demonstrates dispersion is present in the dermis *in vivo*, and shows that this dispersion can be measured with shear wave elastography. We also show that the dispersion, as characterized by a linear slope of the phase velocity curve after normalization for dermal layer thickness and group SWS, is statistically significantly influenced by the group speed in the subcutaneous layer, depending on the exact frequency.

Acknowledgment

The authors would like to thank the Duke Medical Imaging Training Program Grant T32 EB001040, as well as the Duke MSTP Program T32 GM007171. We would also like to thank Courtney Trutna, Cody Morris, Ned Rouze, and Gabriela Torres Garate for productive discussion and feedback.

References

[1] S. Arai, M. Jagasia, B. Storer, X. Chai, J. Pidala, C. Cutler, M. Arora, D. J. Weisdorf, M. E. D. Flowers, P. J. Martin, J. Palmer, D. Jacobsohn, S. Z. Pavletic, G. B. Vogelsang, and S. J. Lee, "Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH Consensus Criteria," *Blood*, vol. 118, no. 15, pp. 4242–4249, oct 2011. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3204740/

[2] N. Fett and V. P. Werth, "Update on morphea: Part II. Outcome measures and treatment," *Journal of the American Academy of Dermatology*, vol. 64, no. 2, pp. 231–242, 2011. [Online]. Available: http://dx.doi.org/10.1016/j.jaad.2010.05.046

[3] ——, "Update on morphea: Part I. Epidemiology, clinical presentation, and pathogenesis," *Journal of the American Academy of Dermatology*, vol. 64, no. 2, pp. 217–228, 2011.

[4] T. Krieg and K. Takehara, "Skin disease: a cardinal feature of systemic sclerosis," *Rheumatology*, vol. 48, no. suppl_3, pp. iii14–iii18, 2006. [Online]. Available: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/kep108

[5] D. Khanna, D. E. Furst, P. J. Clements, Y. Allanore, M. Baron, L. Czirjak, O. Distler, I. Foeldvari, M. Kuwana, M. Matucci-cerinic, M. Mayes, T. M. Jr, P. A. Merkel, J. E. Pope, and R. James, "Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis," vol. 2, no. 1, pp. 11–18, 2017.

[6] S. Y. Lee, A. Cardones, K. Nightingale, and M. Palmeri, "Assessment Of Cutaneous Sclerotic Disorders Using ARFI/SWEI," *Ultrasound in Medicine & Biology*, vol. 41, no. 4, p. S82, 2015. [Online]. Available: http://linkinghub.elsevier.com/retrieve/pii/S0301562914011600

[7] S. Y. Lee, A. R. Cardones, J. Doherty, K. Nightingale, and M. Palmeri, "Preliminary Results on the Feasibility of Using ARFI/SWEI to Assess Cutaneous Sclerotic Diseases," *Ultrasound in Medicine and Biology*, vol. 41, no. 11, pp. 2806–2819, oct 2016. [Online]. Available: http://dx.doi.org/10.1016/j.ultrasmedbio.2015.06.007

[8] Y. Yang, L. Qiu, L. Wang, X. Xiang, Y. Tang, H. Li, and F. Yan, "Quantitative Assessment of Skin Stiffness Using Ultrasound Shear Wave Elastography in Systemic Sclerosis," *Ultrasound in Medicine & Biology*, vol. 45, no. 4, pp. 902–912, 2019.

[9] L. Wang, F. Yan, Y. Yang, X. Xiang, and L. Qiu, "Quantitative Assussment of Skin Stiffness in Localized Scleroderma Using Ultrarsound Shear-Wave Elastography," *Ultrasound in Medicine & Biology*, vol. 43, no. 7, pp. 1339–1347, 2017.

[10] A. Pely, K. Nightingale, and M. Palmeri, "Towards a more accurate model for shear wave propagation in skin: characterizing the effects of the lower boundary material on the propagation of Lamb waves," *Ieee Ius*, pp. 8–11, 2016.

[11] T.-M. Nguyen, J.-L. Gennisson, M. Couade, D. Touboul, P. Humbert, J. Bercoff, M. Fink, and M. Tanter, "Shear wave propagation in complex sub wavelength tissue geometries: Theoretical and experimental implications in the framework of cornea and skin shear wave imaging," *2010 IEEE International Ultrasonics Symposium*, pp. 1145–1148, oct 2010. [Online]. Available: http://ieeexplore.ieee.org/lpdocs/epic03/wrapper.htm?arnumber=5935698

[12] N. Rouze, Y. Deng, C. Trutna, M. Palmeri, and K. Nightingale, "Characterization of Viscoelastic Materials using Group Shear Wave Speeds," *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 3010, no. c, pp. 1–15, 2018.

[13] M. W. Urban, S. Chen, and M. Fatemi, "A Review of Shearwave Dispersion Ultrasound Vibrometry (SDUV) and its Applications." *Current medical imaging reviews*, vol. 8, no. 1, pp. 27–36, 2012.

[14] X. Zhang, T. G. Osborn, M. R. Pittelkow, B. Qiang, R. R. Kinnick, and J. F. Greenleaf, "Quantitative assessment of scleroderma by surface wave technique," *Medical Engineering and Physics*, vol. 33, no. 1, pp. 31–37, 2011. [Online]. Available: http://dx.doi.org/10.1016/j.medengphy.2010.08.016

[15] X. Zhang, B. Zhou, S. Kalra, B. Bartholmai, J. Greenleaf, and T. Osborn, "An Ultrasound Surface Wave Technique for Assessing Skin and Lung Diseases," *Ultrasound in Medicine and Biology*, vol. 44, no. 2, pp. 321–331, 2018. [Online]. Available: https://doi.org/10.1016/j.ultrasmedbio.2017.10.010

[16] N. Otsu, P. Smith, D. B. Reid, C. Environment, L. Palo, P. Alto, and P. L. Smith, "Otsu_1979_otsu_method," vol. C, no. 1, pp. 62–66, 1979.

[17] N. C. Rouze, Y. Deng, M. L. Palmeri, and K. R. Nightingale, "Robust characterization of viscoelastic materials from measurements of group shear wave speeds," *IEEE International Ultrasonics Symposium, IUS*, vol. 2016-Novem, no. 8, pp. 3–6, 2016.

[18] I. Z. Nenadic, B. Qiang, M. W. Urban, H. Zhao, W. Sanchez, J. F. Greenleaf, and S. Chen, "Attenuation measuring ultrasound shearwave elastography and in vivo application in post-transplant liver patients," *Physics in Medicine and Biology*, vol. 62, no. 2, pp. 484–500, 2017.

[19] J. L. Rose, *Ultrasonic Guided Waves in Solid Media*, 2014.