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Short communication

Regional variations of in vivo surface stiffness of soft tissue layers of musculoskeletal extremities

Erica E. Neumann^{a,b}, Tammy M. Owings^a, Ahmet Erdemir^{a,b,*}^a Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA^b Computational Biomodeling (CoBi) Core, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

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ABSTRACT

Surface stiffness of bulk soft tissue in musculoskeletal extremities is important to consider in the design of prosthetics, exoskeletons, and protective gear. This knowledge is also foundational for surgical simulation and clinical interventions leveraging manipulation of the musculoskeletal surfaces. Injuries to musculoskeletal extremities are common and surgical and preventive interventions require interactions between various objects such as surgical tools and support surfaces with tissue boundaries. While a handful of investigations examined the variations in indentation mechanics due to pathology or injury specific sites, a comprehensive analysis across the surfaces of musculoskeletal extremities has not been completed. In this study we examine variations of surface stiffness across 8 sites of the upper and lower arms and legs for 95 subjects using an instrumented ultrasound device. Differences in surface stiffness were observed between gender, activity level, and indentation location groups. The lower arm posterior location had the highest average stiffness (3.89×10^{-3} MPa/mm), while the lowest stiffness was observed at the upper leg posterior location (0.98×10^{-3} MPa/mm). The differences between indentation sites were larger in magnitude when compared to differences due to demographics (gender and activity level). However the large ranges of the 95% confidence intervals suggest that an aggregated metric based on population or sub-group may not capture individual variations. This study implicates the motivation to explore tissue composition variations within the indentation sites as well as the potential importance to include variations in surface stiffness during surgical simulations.

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1. Introduction

A commonly used metric to specify interactions of soft tissue with their environment is surface stiffness, which can be easily measured through indentation of the tissue. Surface stiffness quantification may be beneficial in several application areas including device design, clinical, and surgical simulation. When designing external devices, such as protective gear (Shen et al., 2010), exoskeletons (Cherry et al., 2016), and prostheses (Petron et al., 2017; Sengeh et al., 2016), the surface stiffness of soft tissue layers dictates the nature of human-device mechanical interactions. Clinically, soft tissue layers of the extremities are exposed to support surfaces that are meant to distribute loads evenly across the contact surfaces (McInnes et al., 2015). Surface stiffness again plays a role in the design and optimization of these support surfaces to prevent loading to sensitive areas, which may result in pressure

ulcers (Oomens et al., 2013). Variations in surface stiffness may potentially be used to infer progression or presence of some diseases, such as spastic cerebral palsy (Kwon et al., 2012), or Parkinson's disease (Marusiak et al., 2010), that cause disruption to normal soft tissue composition or structure. Finally, with the growing desire to capture realism in surgical simulations, both physical and virtual, there is a need to capture soft tissue mechanics to accurately provide haptic feedback to the user. Without providing accurate haptic feedback, a simulation built for training or pre-surgical planning lacks or incorrectly portrays the tactile experience of the surgical procedure. This force feedback is captured experimentally using a variety of methods to collect force-displacement data, including elastography, aspiration, indentation and grasping techniques (Afshari et al., 2017).

For musculoskeletal soft tissue, indentation has been used throughout the literature to capture force-deformation behavior. Zheng and Mak investigated differences in the effective elastic properties of the lower limb at different postures, however there were only 8 subjects in the study (Zheng and Mak, 1999). Iivarinen et al. used a manual indentation device along with ultrasound

* Corresponding author at: Department of Biomedical Engineering (ND20), Lerner Research Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA.
E-mail address: erdemira@ccf.org (A. Erdemir).

imaging to examine stiffness in relation to the thickness of each tissue layer (skin, fat, and muscle) for different loading conditions of the forearm, however the study was limited by the number of participants (9 healthy individuals) (Iivarinen et al., 2011). Teoh et al. used a motorized indenter to extract stiffness of plantar soft tissue of the foot in 100 subjects and they did not find any differences between gender or correlations of stiffness to body mass or body mass index (Teoh et al., 2016). Silver-Thorn used a rate-controlled indenter to examine the difference of lower limb stiffness (10 sites) between amputees and non-amputees ($n = 5$ in each group) (Silver-Thorn, 1999). Overall, these studies focused on measuring force-displacement at a specific site or localized region of the body. In addition, the sample size is often small (<10 individuals) and therefore likely does not capture population variations. In addition, extensive research on the variations of skin mechanics with respect to age and site has been performed (Couturaud et al., 1995; Ryu et al., 2008). However, the mechanics of the bulk tissue that includes fat and muscle layers may also influence the indentation mechanics of extremities, which in turn leads to variations in haptic response.

While surface stiffness has been captured for several specific locations, a more general investigation, showing variations of the surface stiffness with regard to population demographic differences and physical changes across different locations of the extremities has not been completed. Therefore, in this study, our goal was to determine how demographics and extremity region may affect force feedback response of soft tissue in the extremities. To our knowledge, this is the first study to examine differences of indentation mechanics in the upper and lower segments of the arm and leg across a large population. Two hypotheses were investigated: (1) Demographics, including age, gender, activity level and BMI, would play a role in the surface stiffness trends of soft tissues in the extremities and (2) variations of surface stiffness response across different indentation sites would be observed.

2. Methods

2.1. Experiment overview

The data set used for analysis has already been provided in a publicly available database (Neumann et al., 2018). Complete data were available from 95 subjects (47 male, 48 female), the remaining 5 subjects (MULTIS001, MULTIS002, MULTIS004, MULTIS005, and MULTIS099) from the dataset were excluded due to errors in force data collection (see testing notes for details) (Neumann et al., 2018). Using an instrumented ultrasound (Schimmoeller et al., 2019), manual indentation was performed at posterior and anterior central regions of the upper and lower right arms and legs, for a total of 8 sites (Fig. 1). Additional details are included as supplementary material (Appendix A).

2.2. Soft tissue indentation assessment

Tissue behavior was characterized using a normalized surface stiffness of the bulk tissue response. First, pressure was calculated by dividing force magnitude values by the probe area. A linear fit to the pressure – probe displacement was calculated using *numpy.linalg.lstsq* in Python version 2.7 (<http://www.python.org>), where the slope of the line is equivalent to the tissue surface stiffness (y-intercept was set to zero). Displacement corresponds to the thickness change of the bulk soft tissue (superficial skin boundary to bone boundary) observed in the ultrasound images. Force channels were reset to zero at zero displacement and used to calculate force magnitude. The coefficient of determination (R^2) was used to assess the goodness of fit to the force-displacement data.

2.3. Statistical analysis

A linear mixed effect analysis was performed in R version 3.4.2 (R Core Team, 2017) using the 'lme4' and 'lmerTest' packages (Bates et al., 2015; Kuznetsova et al., 2017) to examine the relationship of demographics and indentation location to surface stiffness of the tissue. The subject ID was the only random effect, while the fixed effects were gender, age, activity level, BMI, and location. A Satterthwaite adjustment to the denominator degrees of freedom was used for fixed effects. The log-transformed surface stiffness was used for the response variable. The normality assumption was visually confirmed using a Q-Q plot of the model residuals. An overall significance level of 0.05 was used for tests of fixed effects and multiple comparisons were performed on factors that were significant overall utilizing the 'multcomp' package (Hothorn et al., 2008) with a Bonferroni correction to reported *p*-values. Mean (average) stiffness values and confidence intervals were calculated using the log-transformed data which were then back-transformed for results presentation.

3. Results

The average (\pm SD) loading rate across all trials was 6.9 ± 2.9 mm/s with a range of 1.0 to 24.8 mm/s. The average (\pm SD) coefficient of determination across all trials was 0.96 ± 0.04 , indicating goodness of fit (a comparison to a non-linear fit was also performed – see Appendix B). The average (\pm SD) indentation depth was $20.5 \pm 7.6\%$ of the initial tissue thickness. Across all subjects, indentation data for eight trials were missing the bone boundary, and therefore excluded from analysis.

Significant differences of stiffness between indentation location ($p < 0.001$), gender ($p = 0.005$), and activity level ($p = 0.017$) were observed (Figs. 2 and 3), however, there were no significant differences observed between age or BMI ($p = 0.470$ and $p = 0.745$, respectively). A summary of surface stiffness across the various categories within groups is included in Appendix C.

4. Discussion

This study examined the indentation mechanics of lumped soft tissue in musculoskeletal extremities to determine the influence of location, gender, age, activity level, and BMI on the surface stiffness. We found that gender, activity level, and indentation location effects are statistically significant. The results suggests that age and BMI do not significantly influence surface stiffness for the eight extremity regions examined in this study.

While our first hypothesis appears to be supported by gender and activity level differences, we expected to see larger differences between groups. Although the gender and activity level differences were statistically significant, the mean difference between male and female was only about 0.2×10^{-3} MPa/mm and between sedentary and moderately active, about 0.24×10^{-3} MPa/mm (Appendix C). These differences may not bear practical importance when compared to the differences seen between locations (Figs. 2 and 3). We therefore cannot conclude that demographics are responsible for a clinically relevant difference in surface stiffness. Demographic differences in soft tissue stiffness have been observed in several studies in the literature (Choi et al., 2015; Kwan et al., 2010; Zheng and Mak, 1999), however there are others that do not report differences (Makhsoos et al., 2008; Teoh et al., 2016). The variation in the literature is likely due to dissimilar testing methods or limited sample sizes. While the differences between groups are statistically significant, the confidence interval limits (95%) were large in both the gender and activity level categories. This may suggest the need to express surface stiffness as

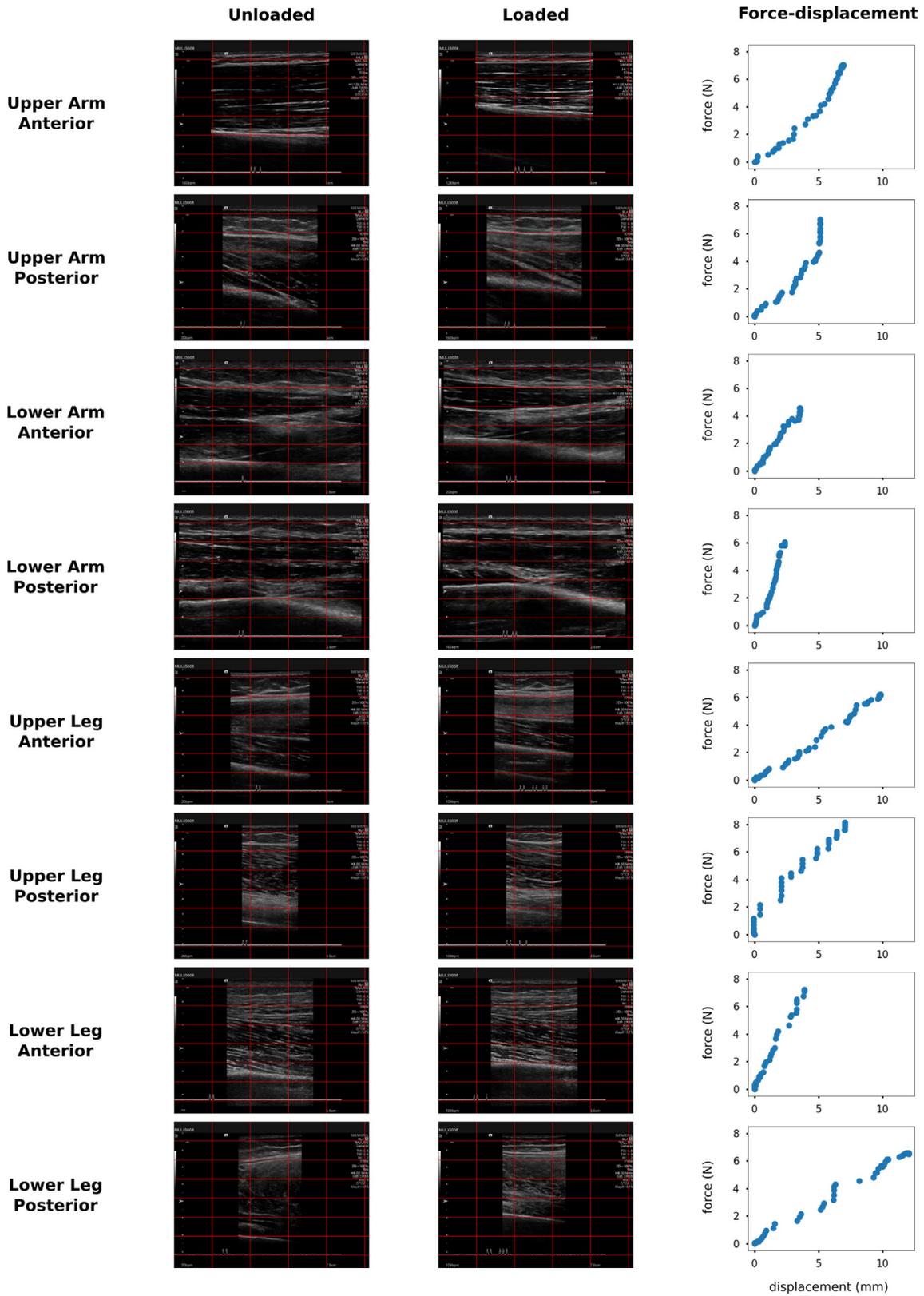


Fig. 1. Representative images for each of the eight indentation sites at unloaded and loaded (at maximum force) states, with corresponding force-displacement plot (MULTIS008-1). Note that displacement corresponds to tissue thickness change extracted from the ultrasound images.

an individualized metric, instead of a population or sub-population grouped variable, i.e., male vs. female, active vs. sedentary.

The surface stiffness of the soft tissue varied across locations of the body, fully supporting our second hypothesis. The upper seg-

ment of both extremities, in general, had a lower stiffness than the lower segment positions, with the exception of the lower leg posterior. This trend may be due to the thickness differences in the upper and lower segments of the extremities, however the

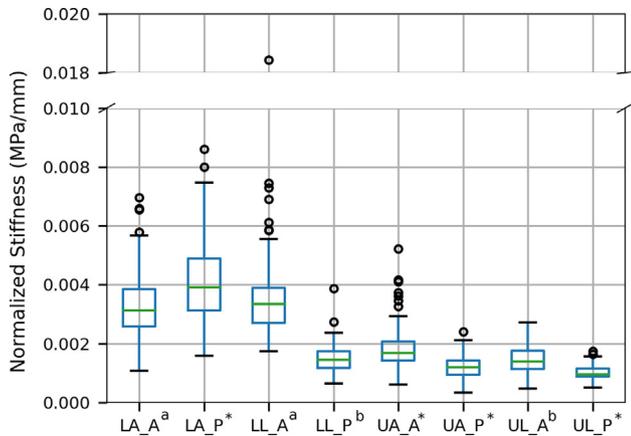


Fig. 2. Normalized soft tissue stiffness grouped by indentation site [*Significant difference when paired with all other categories within group ($p < 0.05$); ^a-Significant difference when paired with all other categories within group ($p < 0.05$), except between the lower arm anterior and lower leg anterior pair ($p = 1.0$); ^bSignificant difference when paired with all other categories within group ($p < 0.05$), except between the lower leg posterior and upper leg anterior pair ($p = 1.0$)]. Boxes extend from the first quartile (Q1) to the third quartile (Q3), with a green line representing the median (quartile 2). The whiskers extend to 1.5 * interquartile range (IQR). Outliers are represented by black circles. Data shown prior to log-transformation. Abbreviations: LA_A – lower arm anterior, LA_P – lower arm posterior, LL_A – lower leg anterior, LL_P – lower leg posterior, UA_A – upper arm anterior, UA_P – upper arm posterior, UL_A – upper leg anterior, UL_P – upper leg posterior. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

trends in thickness do not appear to follow the trends of stiffness (Figs. 2 and 4). In addition, we performed the same statistical analysis using the effective modulus [surface stiffness * initial thickness], which normalizes the surface stiffness using the initial lumped soft tissue thickness, and still observed differences across the locations (Fig. 4). This finding suggests that the variation in soft tissue mechanics across the extremities cannot be described by the lumped thickness alone. Details of the layer composition within the soft tissue, i.e. relative distribution of muscle and fat, may explain the trend differences observed between the lumped soft tissue thickness and surface stiffness, which will be explored in a future study. It is important to note which bone was targeted during each trial when examining the lower segment of each extremity. Specifically, the lower leg anterior indentation site was targeting the fibula bone. The interaction and structural integrity of the soft tissue interaction with the bone in this region is more complex than the single bone cases (upper leg and upper arm).

Location differences in soft tissue surface stiffness suggest that attention to location is important to consider when interacting with soft tissue. This study was the first to focus on a gross examination of surface stiffness across the length of the extremities, however other studies have also shown location dependent tissue stiffness in more focal areas of the lower limb (Silver-Thorn, 1999; Zheng and Mak, 1999). The lower leg posterior average surface stiffness of 1.42×10^{-3} MPa/mm is slightly larger than what was reported for eight subjects in Zheng and Mak (0.3×10^{-3} MPa/mm– 0.9×10^{-3} MPa/mm converted from effective Young’s modulus for comparison) (Zheng and Mak, 1999), however still within an acceptable range.

Our results indicate that in order to capture haptic realism, surface models of musculoskeletal extremities (including physical and computational) should include variations of force feedback depending on the desired area of interest. The surgeon must adapt to the stiffness that they feel to manipulate the tissue in a controlled manner. For example, three-dimensionally printed vertebrae bones have been developed for haptically and biomechanically accurate simulations of spinal surgery maneuvers (Burkhard et al., 2018). With the knowledge of region specific indentation stiffness, authenticity in haptics response of different areas of musculoskeletal extremities can be captured. In return, surgical simulations for training surgeons or practicing new surgical techniques can be enhanced, as done for patient-specific virtual simulations of reconstructive surgery due to head and neck defects (Olsson et al., 2015). In addition, when designing medical equipment or devices that interact with soft tissue, design specifications should consider the tissue stiffness in the area of interest, including its population variability.

As far as we know, this is the first study to quantify and compare surface stiffness across the extremities. We found that soft tissue surface stiffness varies across locations of the extremities (see Appendix D for discussion of limitations) and that location is more influential to surface stiffness variation than subject demographics. This knowledge is crucial to improving medical simulations, simulators, and equipment as well as understanding the importance of person- and application-specific treatment or diagnosis related to manipulation of musculoskeletal extremity surfaces. While the lack of an apparent correlation between total tissue thickness and surface stiffness indicates that haptic response of musculoskeletal regions cannot be inferred solely by the knowledge of lumped soft tissue thickness, composition of the underlying soft tissue layers may ultimately define the surface stiffness interactions. Future work will examine the role of tissue composition, i.e. skin, fat, and muscle layer thicknesses, to determine a potential model for prediction of the haptic response at the surface of the

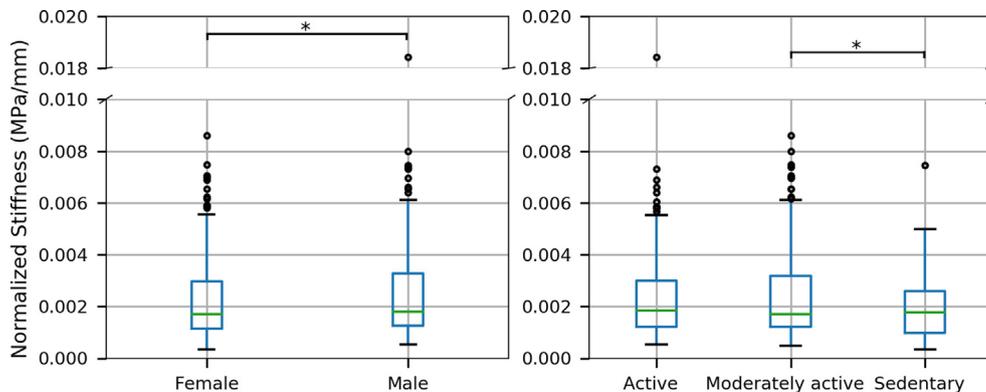


Fig. 3. Normalized soft tissue stiffness grouped by gender (left) and activity level (right) [*Significant difference between groups $p < 0.05$]. Boxes extend from Q1 to Q3, with a green line representing the median. The whiskers extend to 1.5 * IQR. Outliers are represented by black circles. Data shown prior to log-transformation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

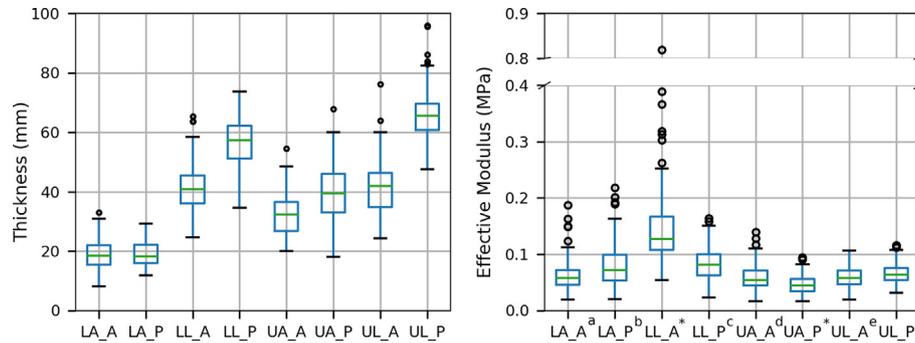


Fig. 4. Soft tissue thickness at the unloaded state grouped by indentation site (left) and effective modulus grouped by indentation site (right). Boxes extend from Q1 to Q3, with a green line representing the median. The whiskers extend to $1.5 \times \text{IQR}$. Outliers are represented by black circles. Abbreviations: LA_A – lower arm anterior, LA_P – lower arm posterior, LL_A – lower leg anterior, LL_P – lower leg posterior, UA_A – upper arm anterior, UA_P – upper arm posterior, UL_A – upper leg anterior, UL_P – upper leg posterior. For effective modulus data only: ^aSignificant difference when paired with all other categories within group ($p < 0.05$); Significant difference when paired with all other categories within group ($p < 0.05$), ^bexcept when LA_A is paired with UL_A ($p = 1.0$), UL_P ($p = 0.87$) and UA_A ($p = 1.0$), ^cexcept when LA_P is paired with UL_P ($p = 0.55$) and LL_P ($p = 1.0$), ^dexcept when LL_P is paired with LA_P ($p = 1.0$), ^eexcept when UA_A is paired with LA_A ($p = 1.0$) and UL_A ($p = 1.0$), ^fexcept when UL_A is paired with UA_A ($p = 1.0$), LA_A ($p = 1.0$), and UL_P ($p = 0.26$), ^gexcept when UL_P is paired with UL_A ($p = 0.26$), LA_A ($p = 0.87$), and LA_P ($p = 0.55$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tissue using only the layer thicknesses. If successful, this model will allow us to define the haptic response in any area of the extremities using solely the major soft tissue thicknesses (including skin, fat, and muscle layer thickness). This simplified approach will provide a more accessible description of surface stiffness, without the need for precision data collection devices or finite element analysis. To conclude, this study motivates the exploration of tissue composition variations within the indentation sites as well as the importance of surface stiffness variation awareness during surgical simulations.

5. Dissemination

Aggregated data for this study can be found in downloads section of the project website (<https://simtk.org/projects/multis>) or directly at https://simtk.org/frs/?group_id=1032.

Declaration of Competing Interest

The authors declare they have no conflict-of-interest in relation to this publication.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jbiomech.2019.08.001>.

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