Published in final edited form as:

IEEE Trans Med Imaging. 2019 June ; 38(6): 1409–1419. doi:10.1109/TMI.2018.2886152.

Towards Electrical Impedance Tomography Coupled Ultrasound Imaging for Assessing Muscle Health

Ethan K. Murphy*,

Thayer School of Engineering, Dartmouth College, Hanover, NH 03755, USA.

Joseph Skinner,

Thayer School of Engineering, Dartmouth College, Hanover, NH, USA

Maria Martucci,

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Seward B. Rutkove,

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Ryan J. Halter

Thayer School of Engineering and Geisel School of Medicine at Dartmouth College, Hanover, NH 03755 USA.

Abstract

This study establishes for the first time that a coupled Ultrasound (US) and Electrical Impedance Tomography (EIT) system can serve as a non-invasive, spatially-localized approach to extract clinically-relevant muscle properties. The US/EIT system represents a potential enhancement to Electrical Impedance Myography (EIM), which has shown promise as a non-invasive technology that may have important clinical use in indicating neuromuscular disease status and as a diagnostic tool. A 2.5D EIT algorithm evaluated on simulation, measured phantoms, and measured patient data was studied to evaluate US/EIT's ability to distinguish different aspects of muscle tissue. Simulated and phantom experiments revealed depths of distinguishability of 3.2 and 4.2 mm in simulation for 10% and 20% changes in muscle properties, respectively, and 3.6 mm in measured phantom experiments assuming a 12% muscle conductivity change. Reconstructions from patient data established that there were consistent differences 1) between longitudinal (along) and transverse (across) muscle conductivity reconstructions at frequencies of 40 and 80 kHz, and 2) side-by-side comparison between healthy and diseased tissue in terms of conductivity, permittivity, and phase at 40 and 80 kHz. Comparisons were made between the EIT reconstructed values and electrical impedance spectroscopy (EIS) measurements (an available surrogate in place of standard EIM measurements) made with the US/EIT system, wherein 1) EIS and EIT show similar sensitivity to longitudinal and transverse differences and 2) EIT showed a more consistent ability

to differentiate healthy and diseased tissue. These results suggest that US/EIT appears very promising for non-invasive and spatially localized diagnosis of muscle health.

Keywords

Data fusion; electrical impedance tomography; electrical impedance myography; inverse problem

I. Introduction

ELECTRICAL impedance myography (EIM) is a noninvasive, painless method that assesses muscle health through measurement of broadband electrical impedance signatures. EIM studies using four-electrode linear arrays have noninvasively quantified healthy muscle anisotropy below the skin and adipose-tissue layer [1], and demonstrated significant impedance phase differences between healthy and diseased muscle for amyotrophic lateral sclerosis, myopathies, and radiculopathy [2]. Its noninvasive nature makes EIM attractive especially in comparison to conventional needle electromyography techniques. However, there are a number of potential limitations to EIM, such as: dependence on skin/adipose-tissue thickness, an inability to distinguish closely spaced muscle groups, and an inability to assess heterogeneity of muscle [3].

Here we describe a novel approach that couples electrical impedance tomography (EIT) with co-registered ultrasound (US) imaging with the intent of addressing and overcoming these limitations. In comparison to EIM, EIT relies on an array of electrodes, usually ranging from 16–32, to record a series of impedance measurements from numerous sets of current patterns (each current pattern is composed of a selected source and sink electrode). A reconstruction algorithm uses these measured impedances to create a complex conductivity image of the region under study. Conventional EIT reconstruction algorithms require solving a non-linear ill-posed inverse problem to estimate the spatial distribution of electrical properties within a domain partially bounded by the set of electrodes. The challenge with these problems is that the noisy and limited boundary measurements can significantly influence the estimation of the internal complex conductivity distribution. The coupled US/EIT system developed here leverages segmented US data to constrain the EIT image reconstruction algorithm and provide a more accurate estimate of the internal electrical properties. Since EIT spatially reconstructs electrical properties it implicitly accounts for the skin/adipose-tissue layers, can potentially separate contributions from individual muscles, and provides a map of tissue heterogeneity, overcoming several of EIM's limitations.

The simulation, phantom, and pre-clinical human studies conducted here demonstrate that complex conductivity images reconstructed through use of a coupled US/EIT system can successfully capture different physiological and pathological muscle characteristics. The simulated and phantom experiments characterize the *depth of distinguishability* assuming changes in a muscle's electrical properties, i.e. the maximum depth at which muscle of two different electrical properties can be distinguished. Specifically, simulations suggest that muscle conductivity changes of 10% and 20% can be detected at depths of 3.2 and 4.2 mm, respectively, and phantom experiments demonstrate that a 12% change in conductivity can

be detected at a depth of 3.6 mm. US/EIT reconstructions evaluated on 46 data sets recorded bilaterally from the legs of 3 patients with radiculopathy established that there were consistent differences between 1) longitudinal (along) and transverse (across) muscle conductivity at frequencies of 40 and 80 kHz, and 2) in side-by-side comparisons conductivity, permittivity, and phase at 40 and 80 kHz for healthy and diseased muscle tissues. To the best of our knowledge, this appears to be the first reported study demonstrating these relationships using EIT. In comparison to EIT reconstructions without using US data, this coupled approach revealed substantial improvements in image accuracy and clearly demonstrates the benefit of incorporating US data. These results suggest that EIT may represent a promising approach for non-invasive, spatially localized assessment of muscle health.

A comparison between electrical impedance spectroscopy (EIS) and US/EIT is also performed, which revealed 1) EIS and EIT show similar sensitivity to longitudinal and transverse differences and 2) EIT showed a more consistent ability to differentiate healthy and diseased tissue. We do not refer to the EIS measurements as EIM measurements, because our US/EIT probe does not provide adequate electrode spacing required for standard EIM measurements. Specifically, the current-drive and voltage-measurement electrode spacing for the EIS patterns in this study were 2.1 cm and 0.7 cm, respectively, whereas the spacing for standard EIM is 6 cm and 3 cm, respectively [4]. Thus the EIS results presented here are likely less sensitive to muscle and more sensitive to skin/adipose-tissue variability than standard EIM measurements.

The paper is structured as follows. Section 2 describes the coupled US/EIT system, EIS measurements, the forward and inverse problems required for EIT image reconstruction, data collection approaches, data processing steps, metrics and additional parameters. Section 3 describes the results of the simulation, phantom, and initial in vivo human experiments. Section 4 discusses the comparisons of EIS and EIT results to EIM results from literature, and future approaches for refining the US/EIT system. We note all usages of impedance in this manuscript refer to *electrical* impedance and not *acoustic* impedance.

II. Methods

A. Coupled US/EIT System

The coupled US/EIT system consisted of a Terason t3000 ultrasound imaging system (Burlington, MA, USA) and custom-designed EIT data acquisition system [5] with a 5 to 12 MHz (12L5V) US probe and sonolucent electrode array wrapped around the active face of the US probe (Fig. 1). The electrode array included thirty $2\text{ mm} \times 5\text{ mm}$ gold-plated electrodes printed on a 1 mil polyamide substrate with 1 mm and 2 mm spacing between electrodes. Due to limitations in the EIT system hardware, only 20 of the electrodes were used for data acquisition. The US probe was placed in a custom-designed 3D printed housing that secured the electrode array and cable in place and provided an electrode array to skin gap of 2 mm. During data acquisition, this gap was filled with US gel to ensure a uniform electrical contact between the electrodes and the skin; specifically, this limited the variation in pressure and contact area between the skin and the different electrodes since the

only patient contacting point was the rim of the 3D printed housing. Minimal degradation in US image quality was observed with this additional 2 mm layer of US gel.

Electrical impedance data was recorded at 10, 20, 40, and 80 kHz using exhaustive, non-flip tetrapolar impedance patterns associated with the 20 electrodes. Each tetrapolar pattern, denoted as an IIVV pattern, is defined by the 4 electrodes involved in the impedance measurement, i.e. II represents the current injection electrode pair (I1,I2) and VV represents the differential voltage sensing pair of electrodes (V1,V2). Flip patterns consist of an IIVV pattern in which the current drive or voltage sense electrodes are interchanged, e.g. for an IIVV = [1 2 3 4], the flip patterns would include [1 2 4 3], [2 1 3 4], and [2 1 4 3]. A total of 29,070 IIVV impedance patterns were recorded for each frequency: 4-electrode combinations from 20 possible $(20 \text{ choose } 4) \times 6$ IIVV electrode orderings per combination = 29,070 patterns. All patterns were recorded in ~5.4 second per image frame with each impedance measurement based on an average of 64 wavelengths. The number of patterns actually used for image reconstruction were reduced by removing bad patterns (based on the noise filter described in [6]) and bad electrodes. Bad electrodes are defined as those electrodes in which the histogram of the difference between measured and simulated impedances for a specific electrode were qualitatively different from the expected distribution, where a 'good' distribution is represented as a single mode near zero, and a 'bad' histogram is bimodal with one mode centered away from zero. This histogram metric uncovered a consistent connection issue with electrodes 16–20. Thus only electrodes 1–15 were used (green electrodes in Fig 1D). Electrical impedance data recorded from this system can be reported as discrete EIS measurements or as complex conductivity images based on EIT reconstruction approaches.

B. EIS Measurements

All EIS measurements were collected using the same custom-designed system used for EIT-data acquisition [5]. These EIS measurements are defined as a specific set of IIVV impedances recorded at the 4 signal frequencies. The average of the following IIVV patterns were used to define a discrete or bulk EIS measurement: [1 13 5 8], [2 12 6 9], [3 11 7 10] (see Fig 1D). These patterns should provide consistent impedance values based on their similar geometry and based on our EIM experience should be minimally effected by variations of the skin/adipose-tissue layer thickness ([7]).

C. EIT Image Reconstruction

1) Forward Problem: The forward problem computes the electric potential within the domain and the electrode voltages on the boundary given a specified injected current on boundary electrodes. The complete electrode model (CEM) is used [8], based on a 3D finite element method (FEM) implementation [9]. The CEM realistically accounts for the contact impedance and shunting of electrodes. The US/EIT geometry is an open domain geometry, which is accurately modeled by expanding the modeled domain so that effectively no current flows near the open boundaries. Gmsh [10] is used to construct the 3D FEM mesh (~200k nodes and 1M elements).

2) *Inverse Problem*: The inverse problem is based on a standard Gauss-Newton algorithm that employs a generalized Tikhonov regularization scheme. After a linearization step ([11]) about an initial estimate of the conductivity, σ_0 , the error to be minimized, $E(\delta\sigma)$, is

$$E(\delta\sigma) = \left\| \mathbf{J}\delta\sigma - \Delta\mathbf{v} \right\|_2^2 + \lambda \left\| \mathbf{L}(\sigma_0 + \delta\sigma - \sigma_{REF}) \right\|_2^2 \quad (1)$$

where $\delta\sigma$ is the conductivity update, $\mathbf{J}$ is the Jacobian, $\mathbf{L}$ is the regularization matrix, λ is the Tikhonov regularization factor, σ_{REF} is a reference conductivity, and $\mathbf{v}$ is the vector difference between measured, $\mathbf{v}_{Meas}$, and simulated voltages, $\mathbf{v}_{Sim}(\sigma_0)$. The least squares solution to (1) is

$$\delta\tilde{\sigma} = (\mathbf{J}^T \mathbf{J} + \lambda \mathbf{L}^T \mathbf{L})^{-1} (\mathbf{J}^T \Delta\mathbf{v} - \lambda \mathbf{L}^T \mathbf{L}(\sigma_0 - \sigma_{REF})). \quad (2)$$

The updated estimate of the conductivity is $\tilde{\sigma}_1 = \sigma_0 + \beta\delta\tilde{\sigma}$, where β is chosen using a parabolic line-search algorithm [12]. The process is iterated to obtain an absolute reconstruction of the conductivity distribution.

The algorithm performs 2.5D reconstructions utilizing the dual-mesh method [12], which allows one to solve the Jacobian on a fine FEM mesh while estimating the conductivity on a much coarser inverse mesh. 2D reconstructions were chosen to match the dimension of the US data; this assumption is reasonable considering the minimal depth of sensitivity expected in the short axis due to the small electrode spacing along this axis (Fig. 1). The coarse mesh was 2D in the depth(z) and long axes (x) plane of the US probe (see Fig. 1A), and this was associated with a 3D fine FEM mesh that had constant conductivity values defined along the short-US probe axis (y).

The open domain is modeled in the inverse problem by constructing a mega-node (MN) consisting of all fine nodes outside of a prescribed region of interest (ROI). This ROI includes the region that heuristically has sufficient sensitivity to produce spatially varying conductivity images and a transition zone to allow for transition to the MN without effecting the inner conductivity values; see [13] for more details.

Soft Regularization: Standard Tikhonov (SR-ST).—Spatial information from US imaging can be incorporated into the inverse problem through augmentation of the $\mathbf{L}$ matrix ([14]–[16]) or through incorporation into the reference conductivity, σ_{REF} ([17]). Here we leverage the latter approach and refer to it as Soft Regularization: Standard Tikhonov. The reference conductivity, σ_{REF} , is assigned a single frequency-dependent complex conductivity value from literature ([18]) for each segmented region. The regularization matrix, $\mathbf{L}$, is defined to be a diagonal matrix with components equal to the relative maximum Jacobian value for each coarse node. Similar approaches have been used in EIT ([19], [20]) and in geophysical applications [21]. Specifically, a vector, $\mathbf{s}$, of maximum Jacobian values across all measurement patterns, N_M , for each coarse node, j , was assembled (i.e.

$s_j = \max_{1 \leq i \leq N_M} (J_{i,j})$). The relative sensitivity, $s_{Rel} = s/\max(s)$ is then used as the diagonal of

L. This scaling penalizes large conductivity changes in high sensitivity regions, while allowing for larger conductivity changes in regions of low sensitivity. Heuristically, this approach produced images with similar spatial variation in the high sensitivity areas near to the probe surface (US gel and skin/adipose-tissue regions) to that of regions of lower sensitivity far from the probe surface (muscle) while biasing the overall reconstructed value from each region towards the values from literature.

A standard approach for EIT reconstruction (i.e. with no US data) is also considered as a means for demonstrating the benefits of US-coupled EIT. Specifically, this approach referred to as the *standard approach* uses a σ_{REF} vector that is identically zero and the same sensitivity-based regularization matrix used in the SR-ST approach.

D. Data Collection Approaches

Three experiments using simulated, measured phantom, and measured patient data were conducted to evaluate the potential of using US/EIT imaging for assessing muscle health.

Simulated Patient Data.—Simulated data was generated from 50 segmented profiles of the US gel, skin, adipose tissue, and muscle regions extracted from patient US images. These profiles (x/z-plane) were extended in the y-axis and meshed using Gmsh to produce a 3D volumetric representation of the anatomy (assuming no spatial variation in the y-axis). Boundary voltages were simulated on this mesh by solving the 3D FEM forward problem assuming injection currents of 0.3 mA and conductivity profiles that varied only in the US imaging plane. The simulated conductivities were 0.10 S/m, 0.022 S/m, 0.024 S/m for the US gel, skin, and adipose-tissue layers, respectively. The muscle conductivities were 0.35 S/m, 0.385 S/m, and 0.42 S/m, which correspond to healthy muscle at 40 kHz [18], and a 10% and 20% increase to simulate muscle disease, respectively. The skin and adipose-tissue conductivities also corresponded to values reported at 40 kHz [18]. No noise was added to the simulated voltages, but different FEM meshes were used for simulating the voltages and performing image reconstruction to ensure no inverse crime was committed.

Measured Phantom Data.—Multiple heterogeneous phantoms, consisting of stacked layers of tissue-simulating gelatin slabs, were used to evaluate the impact of skin/-adipose-tissue thickness and varying electrical properties of muscle (see Fig. 1E and Fig. 2). Phantom data consisted of 54 sets of measurements recorded from 9 skin/adipose-tissue gels ranging from 1.6 to 5.6 mm thick, 2 muscle gels, and 3 repeated measurements per gel configuration. Each repeated measurement involved removing the US/EIT probe, reapplying US gel, and placing it back on the gel phantom. The conductivities were 0.183 S/m, 0.191 S/m, 1.15 S/m and 1.02 S/m for the US gel (Sonigel), skin/adipose-tissue layer, muscle 1, and muscle 2, respectively. These conductivity values were assigned to the reference conductivity vector for SR-ST-based inversion. Drops of 0.1 S/m saline were used to remove air bubbles between gel layers. The gels were produced using a 7:1 saline to gelatin mixture (Sigma-Aldrich, 175 g Bloom strength). The thin gel layers were set in petri dishes to ensure uniform thickness. The larger conductivity values used in these experiments were chosen to

maintain a large ratio between the skin/adipose-tissue layer and muscle. The conductivity ratios were smaller in this phantom work than in the simulation and patient experiments due to the minimum achievable conductivity for gel-based tissue phantoms (gel phantoms have a minimum conductivity of ~ 0.1 S/m even when deionized water is used as the solvent).

Measured Patient Data.—US/EIT data was recorded from the leg muscles on both sides of three patients with unilateral radiculopathy. The data was collected at Beth Israel Deaconess Medical Center, Boston, MA and was conducted under an IRB-approved protocol from consenting individuals. For each patient, US gel (Gamma Pharmaceutical Innovations Inc, Newark, NJ, ~ 0.1 S/m) was applied directly to the US probe, the electrode array was then taped down over the probe face, the US housing was installed around the US/EIT probe, and more US gel was applied in the 2 mm gap. Data acquisition was performed by Drs. Rutkove and/or Martucci. Three repeated longitudinal (in the direction of muscle fibers) and transverse measurements (across muscle fibers) were made at multiple sites on these individuals. Each repetition involved removing the US/EIT probe, reapplying US gel, and placing it back on the patient. The data was analyzed in terms of longitudinal versus transverse (similar to the analysis from [1]) and healthy versus diseased sides from each site of each individual.

E. Image and Data Processing

The US gel/skin and adipose-tissue/muscle interfaces in US images were segmented using a custom-built Matlab (MathWorks, Natick, MA) graphical user interface (Fig 3A). All segmentations were reviewed by Dr. Martucci for accuracy. The skin/adipose-tissue interface was not reliably distinguishable due to artifacts near the surface. Because skin and adipose tissue have similar conductivities (e.g. 0.22 S/m vs 0.24 S/m at 40 kHz [13]) these tissues were grouped into a single layer. The adipose-tissue/muscle interface is then linearly extended on both ends (i.e. past the left and right side of the yellow box in Fig. 3B) and encoded into a FEM mesh to account for current flowing outside the region directly below the probe face. A single coarse mesh is used (see Fig. 3B) that has increased nodal spacing as a function of distance from the electrode array (a common design for open domain geometries [22]). The coarse nodes are separated into the US gel, skin/adipose-tissue layer, and muscle regions (Fig. 3B). Further, the coarse nodes are mapped only to FEM nodes in the same region, e.g. notice the smooth top and bottom boundaries of the fine FEM mesh elements (red tetrahedra) that are associated to the skin/adipose-tissue region in Fig. 3B. To analyze the muscle properties, we computed the average nodal complex conductivity values in a region extending to a maximum depth of 10 mm and spanning the width of the US image (purple box in Fig. 3), which is a conservative estimate of where we expect to be able to produce accurate, spatially-varying reconstructions. This is based on the heuristic of estimating depth of sensitivity as half of the maximum extent of electrodes, which is 28 mm in this study (the span of electrodes 2 to 15, see Fig 1D).

F. Metrics

The average reconstructed complex conductivities were calculated for each region including the US gel layer, skin/adipose-tissue layer, and muscle region. For the patient data the repeated measurements were averaged together to improve noise characteristics. Descriptive

statistics, review of example images, and comparison of individual patient imaging studies are used to evaluate the clinical potential of this imaging modality.

Within the simulation and phantom experiments, a *depth of distinguishability* was defined to evaluate how far below the surface different muscle conductivities could be detected with US/EIT. The depth of distinguishability was calculated by determining the depth at which the ± 1 SD (standard deviation) envelope of the linear fits to the different muscle reconstructions intersect. An illustration depicting the depth of distinguishability from simulation results of a 20% change in muscle conductivity shows the ± 1 SD regions (cyan and green regions) intersect at 4.6 mm (Fig. 4).

G. Additional Measurement Parameters

In all measured reconstructions a data calibration step was performed after noise filtering using a homogenous gel phantom (~ 0.1 S/m) [23]. A Tikhonov value of 1×10^5 was heuristically determined through visual evaluation of patient data reconstructions. The injected current in EIT and EIS measurements was approximately 0.23 mA, 0.26 mA, 0.30 mA, 0.33 mA for the 10 kHz, 20 kHz, 40 kHz, and 80 kHz measurements, respectively. To give a practical measure of the EIT system signal quality (incorporating noise from cables, electrode array, holding the probe, etc.) Signal-to-Noise Ratio (SNR) values for the EIS patterns considered in this study were computed using repeated EIT measurements recorded from a phantom (0.1 S/m saline with 10% gelatin and 20% graphite as in [24]) with a complex conductivity of $\sim 0.25 + 0.07i$ S/m (15° phase); yielding SNR values of 30 dB, 35 dB, and 27 dB for the real, imaginary, and phase components, respectively.

III. Results

All results were evaluated using the soft-regularization (SRST) and standard approaches. Unless explicitly stated otherwise all results shown use the SR-ST technique.

A. Simulated and Phantom Experiments

SR-ST reconstructions from the different layers of simulated and phantom experiments (Figs. 5A & 6A, respectively) show the expected conductivity relationships (i.e. $\sigma_{\text{muscle}} > \sigma_{\text{skin}} & \sigma_{\text{adipose}}$) and a generally downward trend in muscle conductivity as a function of skin/adipose-tissue thickness. The depth to muscle was defined as the average distance between the skin surface and start of muscle tissue. In simulation, muscle depth varied along the long-axis of the US probe, whereas in phantom experiments all gels were flat (Figs. 1E & 2). Magnified views (Figs. 5B & 6B) reveal that the different muscle conductivities (simulated and measured) are clearly distinguishable at shallow depths and appear to intersect at deeper depths. The variability in the muscle conductivities from simulation are attributed to the differently shaped skin/adipose-tissue/muscle interfaces. The depths of distinguishability (Figs. 5B & 6B) for the simulated data were 3.2 and 4.6 mm for the 10% and 20% muscle conductivity change, respectively, and for the measured phantom experiment was 3.4 mm, where the two muscles varied by $\sim 12\%$ in conductivity. Differencing the muscles reconstructions (Figs. 5C & 6C) reveals that although the differences reduce as depth increases, the order is almost always correct (50 out of 50 for

simulation, and 45 out of 54 for phantoms), i.e. the higher conductivity muscle is consistently reconstructed as being more conductive.

Standard-approach reconstructions (without soft regularization) were markedly different. The muscle reconstructions from the simulated patient data decreased in value till approximately 6 mm then increased, and the reconstructed muscle in phantom data increased. In both simulated and phantom reconstructions the depth of distinguishability was negative (implying that the different muscle properties could not be reliably distinguished at any depth). Additionally, 30 out of 50 and 45 out of 54 cases for the simulated and phantom experiments had muscle changes in the correct direction, respectively.

Three examples of measured phantom SR-ST reconstructions (Figs. 7A – C) from three muscle depths highlight the clear separation between skin/adipose-tissue and muscle layers and show minimal change in estimated muscle conductivity down to ~10 mm (2.8% change in σ_{muscle} between 2.01 mm and 4.82 mm skin/adipose-tissue layer thicknesses). There is a slight decrease in conductivity values as muscle depth increases, and one can observe an increase in artifacts as the depth increases (bottom portions of Figs. 7B – C). In comparison, the standard reconstructions on the same phantom examples (Figs 8A – C) show profiles that resemble the true layered structure, but there is significant blurring across layers. Further, the estimated muscle conductivity changes much more than the SR-ST reconstructions (+14.6% between 2.01 mm and 4.82 mm skin/adipose-tissue layer thicknesses). Based on the quantitative and qualitative analysis, the SR-ST approach appears to produce far superior reconstructions compared to the standard approach.

B. Patient Data: US/EIT-based muscle imaging

A total of 8 sites were measured across the three patients, resulting in 46 EIT reconstructions (3 EIT per site) at each frequency. Two datasets could not be reconstructed because the US images were missing, and one additional reconstruction at 10 kHz was not included because no inverse step was taken (β from the parabolic line-search was found to be zero). Table I shows the patient information (age, sex, depth to muscle, location of measurement site/s). Each site had measurements taken in the longitudinal and transverse direction. The minimum and maximum depths to muscle in Table I plus US image cross sections from Figs. 9, 12, and 14 reveal the variability within patients and across patients of the depth to muscle. Since each patient was only affected on one side, the healthy side was used for the side-by-side healthy versus diseased comparison. In all cases, the US image was not corrupted by the presence of the electrode array and was sufficient for segmenting the adipose-tissue/muscle interface (Fig. 9).

The conductivity, permittivity, and phase SR-ST EIT reconstructions of the US gel, skin/adipose tissue, and muscle tissue of all 8 patient cases across all frequencies (Fig. 10) are compared against the (true) literature values. The EIT and literature values are in good agreement for conductivity (all regions), permittivity and phase for muscle. Specifically, the muscle conductivity (mean $\pm$ SD = 0.36 $\pm$ 0.018 S/m) is significantly different from the skin/adipose-tissue conductivity (mean $\pm$ SD = 0.071 $\pm$ 0.027 S/m), $p < 0.01$. The coupled skin/adipose-tissue EIT values differ from literature values due to the largely different permittivity ($Im(\sigma_{skin}) = 0.016\text{--}0.078$ S/m, $Im(\sigma_{adipose}) = 0.005\text{--}0.006$ S/m) and

phase ($Ph(\sigma_{skin}) = 56.4\text{--}79.8^\circ$, $Ph(\sigma_{adipose}) = 1.1\text{--}1.5^\circ$) for skin and adipose. Thus the EIT algorithm is forced to effectively split the difference. Further the US gel is expected to have nearly zero permittivity/phase, but the EIT values are much higher, similar to skin, which implies that skin is likely pushed into the US gel gap. All of these observations are consistent with our expectations of the tissue properties when considering our current segmentation limitations (see Section IV for more details).

C. Patient Data: Longitudinal versus Transverse

Comparisons between the longitudinal and transverse muscle conductivities on the healthy (unaffected) side (Fig. 11) reveal that: 1) EIS measurements show consistent differences between longitudinal and transverse measurements (in the correct direction; i.e. $R_{long} < R_{trans}$) for 10 and 20 kHz with small change at 40 and 80 kHz in the wrong direction, and 2) EIT shows mostly consistent muscle differences (in the correct direction; i.e. $\sigma_{long} > \sigma_{trans}$) at 40 and 80 kHz. Although, the differences are small, the EIT values result in σ_{long} greater than σ_{trans} in all 40 and 80 kHz cases. Note that the higher conductivity longitudinal values (σ) should correspond to lower resistance values (R) observed in EIS. The muscle fibers should appear more anisotropic at lower frequencies (see Fig. 2 in [25]), which is consistent with the trends shown in the EIS data (Fig. 11A). It is unexpected that the EIT reconstructions show less directional differentiation at lower frequencies. However, we hypothesize this is due to anisotropy not being modeled in the inverse problem. Although in this small set of samples there is no threshold that can be used to discriminate longitudinal and transverse electrical impedances or conductivities (see Fig. 11), it is observed that the EIT differences at 40 and 80 kHz vary less than the EIS differences at 10 and 20 kHz; specifically, the coefficient of variation were 0.34 and 0.95 for the EIT and EIS differences, respectively. Standard approach reconstructions (no soft regularization) could not definitively discriminate longitudinal from transverse cases, i.e. only 1, 2, and 1 cases were in the correct direction at 20, 40, and 80 kHz, respectively – *no inverse steps were taken for reconstructions at 10 kHz so no comparison was possible there*. Overall, this analysis reveals that EIT coupled with US can image the muscle under the skin/adipose-tissue layer with less variability than EIS (when using this US-coupled electrode array).

Example longitudinal and transverse EIT (real) conductivity reconstructions (Fig. 12) overlaid on the US image, which correspond to P1 at 80 kHz, show the expected results of 1) low conductivity US gel and skin/adipose-tissue layers with higher conductivity muscle layers and 2) a higher conductivity in the muscle layer in the longitudinal compared to the transverse images.

D. Patient Data: Healthy versus Diseased side

Healthy-side versus diseased-side EIS and EIT muscle values are presented in Fig. 13 separated by longitudinal and transverse measurements, and their differences (healthy minus diseased sides) are presented in Fig. 14. Only 10 and 20 kHz are shown for EIS and 40 and 80 kHz for EIT because these were found to yield consistent differences in the correct direction in the longitudinal versus transverse analysis. There are several trends in the EIT data. In the longitudinal measurements, conductivity is generally lower in healthy muscle as compared to diseased tissue, while the permittivity and phase of healthy sides are higher

than in diseased sides. The opposite trend is observed in the transverse EIT cases. In the longitudinal measurements, the average phase reduction between healthy and diseased muscle was 26% and 38% for 40 and 80 kHz, respectively; in the transverse case, there was an increase of 29% and 37% for 40 and 80 kHz, respectively. In terms of standard approach reconstructions, no clear trends were found between healthy and diseased sides. Examples of healthy and diseased EIT phase reconstructions of longitudinal cases, corresponding to P3B, overlaid on the US image are shown in Fig. 15. The blocky discontinuities near the electrodes appear to be common near-electrode artifacts, and as these do not appear in Fig. 12 may indicate that the phase data has a higher sensitivity to model-mismatch than conductivity, especially near the electrode array.

Trends are less clear in the EIS data. It appears that the healthy sides tend to have larger resistance and smaller phase than diseased sides. Based on literature, one would expect the resistance and phase of the healthy side to be larger than the diseased side ([26]). Our hypothesis for the less clear trends and inconsistency with literature of the EIS results are discussed.

IV. Discussion

This study suggests that US/EIT has the potential to consistently detect differences between longitudinal and transverse muscle and healthy and diseased muscle tissue in an in vivo setting and that incorporation of US data into the EIT reconstruction is necessary to achieve this. These findings represent an important step in establishing EIT as an extension of EIM. In addition to these results there are two important points of discussion: 1) Comparisons between past EIM and our current EIS results to the US/EIT results. 2) Methods to improve the performance of the US/EIT system.

Comparison between EIM, EIS and US/EIT.

It is important to note that the EIS results reported here are based on electrodes more closely spaced than normally considered in EIM (distances are noted in Section I). Since current does not flow as deeply into the muscle for closely spaced electrodes, EIS's sensitivity to differences in skin/adipose-tissue thickness is amplified in this system, resulting in a less accurate assessment of muscle. Use of US/EIT, however, can account for the skin/adipose-tissue layer thickness and suggests trends similar to those found with standard EIM [2]. Specifically, the 26%–38% decrease in diseased muscle phase observed for US/EIT trends in the same direction as the 15% phase decrease observed for EIM when comparing healthy patients to those with radiculopathy [27]. Although this study could not find fixed thresholds to discriminate longitudinal from transverse cases and to discriminate healthy from diseased cases, smaller variations were found in EIT compared to EIS. This is viewed as an important step toward showing that EIT has the potential to provide more reliable tissue classification than EIM.

Methods to improve the performance of the US/EIT system.

Two aspects of the system that could enhance imaging accuracy would be to increase the depth of sensitivity and to improve segmentation quality. **Sensitivity.** A wider electrode

spacing could be adopted to sense deeper muscle. This could be implemented by using a larger on-probe electrode array (i.e. having the electrode array extend beyond the probe face or ensuring that all channels on the current system are functional). **Segmentation.** The surface reflection artifacts of the US images left the top skin surface and the skin/adipose-tissue interface challenging to segment, which appear to cause the discrepancies observed between reconstructions and literature (Fig. 10). The top skin surface could be accurately constrained by introducing a semi-solid gel layer in the US housing so that the 2 mm gap is maintained and US segmentation of this layer is not needed. Alternatively, a larger gap could be considered, in which the optimal gap thickness is one that produces US images with negligible reflection artifacts at the skin interface while providing maximum sensitivity to the muscle's electrical properties.

Algorithmic Improvements.

In addition to system changes, algorithm modifications may improve sensitivity and mitigate segmentation errors. Incorporation of anisotropy and adding full 3D reconstructions into the inverse problem could improve EIT results. The lack of anisotropic modeling could explain the poor performance at the low frequencies (10 and 20 kHz) for the longitudinal and transverse comparison (Fig. 11). We could extract estimates of the anisotropic direction based on the probed region's anatomy and recorded US images. This directional information coupled with literature-based estimates of in-fiber and across-fiber properties can be incorporated into the EIT reconstruction framework using methods developed for anisotropic brain imaging ([28], [29]). Because healthy muscle is highly anisotropic, this approach could significantly improve model accuracy and overall sensitivity to changes in muscle. Further, investigating the depth variation in the short axis could be important for determining the need for 3D reconstructions; transitioning to a full 3D reconstruction framework would likely require 3D US information be acquired and more widely spaced electrodes in the short-axis direction. In terms of segmentation, alternative strategies such as a fuzzy soft-regularization techniques could help to reduce uncertainty in the segmentation of the skin/adipose-tissue interface [30], and improve model accuracy and overall quality of EIT images. Other regularization approaches could also be considered, such as using $(\mathbf{L}^T \mathbf{L})^p$ in (2) with an optimally chosen p value [19].

V. Conclusions

This study establishes for the first time that a coupled Ultra-sound/Electrical Impedance Tomography system can be used to spatially map the electrical properties of subsurface skin and adipose tissue and the underlying musculature. In addition, this system provides consistent differences between 1) longitudinal and transverse muscle conductivity reconstructions, and 2) healthy and diseased muscle tissue (in terms of conductivity, permittivity, and phase). After minor system and algorithm upgrades, a larger in vivo patient study is needed to more definitively determine 1) optimal algorithmic approaches, 2) improvements offered by EIT over EIM, and 3) the clinical potential of this technology.

Acknowledgements

This work was supported in part by the U.S. National Institutes of Health under Grants K24 NS060951 and 1R01CA143020-01A1 and DoD CDMRP Grant W81XWH-15-1-0102. We would also like to thank Xiaotian Wu for his design and 3D printing of the US housing and mock US probe.

This work was supported in part by the U.S. National Institutes of Health under Grant 1R01CA143020-01A1 and DoD Congressionally Directed Medical Research Program under Grant W81XWH-15-1-0102.

References

- [1]. Aaron R, Huang M, and Shiffman CA, "Anisotropy of human muscle via non-invasive impedance measurements," *Phys. Med. Biol.*, vol. 42, no. 7, pp. 1245–1262, 1997. [PubMed: 9253037]
- [2]. Rutkove SB, Fogerson PM, Garmirian LP, and Tarulli AW, "Reference values for 50-kHz electrical impedance myography," *Muscle and Nerve*, vol. 38, no. 3, pp. 1128–1132, 2008. [PubMed: 18642375]
- [3]. Rutkove SB, "Electrical impedance myography: Background, current state, and future directions," *Muscle and Nerve*, vol. 40, no. 6, pp. 936–946, 2009. [PubMed: 19768754]
- [4]. Narayanaswami P, Spieker AJ, Mongiovi P, Keel JC, Muzin SC, and Rutkove SB, "Utilizing a handheld electrode array for localized muscle impedance measurements," *Muscle and Nerve*, vol. 46, no. 2, pp. 257–263, 2012. [PubMed: 22806375]
- [5]. Khan S, Manwaring P, Borsic A, and Halter R, "FPGA-Based Voltage and Current Dual Drive System for High Frame Rate Electrical Impedance Tomography," *IEEE Trans. Med. Imaging*, vol. 34, no. 4, pp. 888–901, 2015. [PubMed: 25376037]
- [6]. Murphy EK, Wu X, and Halter RJ, "Fused-data transrectal EIT for prostate cancer imaging," *Physiol. Meas.*, 2018.
- [7]. Jafarpour M, Li J, White JK, and Rutkove SB, "Optimizing electrode configuration for electrical impedance measurements of muscle via the finite element method," *IEEE Trans. Biomed. Eng.*, vol. 60, no. 5, pp. 1446–1452, 2013. [PubMed: 23314763]
- [8]. Somersalo E, Cheney M, and Isaacson D, "Existence and Uniqueness for Electrode Models for Electric Current Computed Tomography," *SIAM J. Appl. Math.*, vol. 52, no. 4, pp. 1023–1040, 1992.
- [9]. Borsic A, Hartov A, Paulsen KD, and Manwaring P, "3D electric impedance tomography reconstruction on multi-core computing platforms," *Conf. Proc. Int. Conf. IEEE Eng. Med. Biol. Soc.*, vol. 2008, no. 1557–170X (Print), pp. 1175–1177, 2008.
- [10]. Lee T, Leok M, and McClamroch NH, "Geometric numerical integration for complex dynamics of tethered spacecraft," *Proc. 2011 Am. Control Conf.*, no. 5, pp. 1885–1891, 2011.
- [11]. Lionheart WRB, "EIT reconstruction algorithms: pitfalls, challenges and recent developments," *Physiol. Meas.*, vol. 25, no. 1, pp. 125–142, 2004. [PubMed: 15005311]
- [12]. Borsic A, Halter R, Wan Y, Hartov A, and Paulsen KD, "Electrical impedance tomography reconstruction for three-dimensional imaging of the prostate," *Physiol. Meas.*, vol. 31, no. 8, pp. S1–S16, 2010. [PubMed: 20647619]
- [13]. Murphy E, Mahara A, and Halter R, "A Novel Regularization Technique for Microendoscopic Electrical Impedance Tomography," *IEEE Trans. Med. Imaging*, vol. 35, no. 7, pp. 1593–1603, 2016. [PubMed: 26812707]
- [14]. Steiner G, Soleimani M, and Watzenig D, "A bio-electromechanical imaging technique with combined electrical impedance and ultrasound tomography," *Physiol. Meas.*, vol. 29, no. 6, pp. S63–S75, 2008. [PubMed: 18544806]
- [15]. Meaney PM, Golnabi AH, Epstein NR, Geimer SD, Fanning MW, Weaver JB, and Paulsen KD, "Integration of microwave tomography with magnetic resonance for improved breast imaging," *Med. Phys.*, vol. 40, no. 10, p. 103101, 2013. [PubMed: 24089930]
- [16]. Murphy EK, Mahara A, Wu X, and Halter RJ, "Phantom Experiments using Soft-Prior Regularization EIT for Breast Cancer Imaging," *Physiol. Meas.*, vol. 38, pp. 1262–1277, 2017. [PubMed: 28530205]

- [17]. Brooksby BA, Dehghani H, Poque BW, and Paulsen KD, "Near-infrared (NIR) tomography breast image reconstruction with a priori structural information from MRI: Algorithm development for reconstructing heterogeneities," *IEEE J. Sel. Top. Quantum Electron*, vol. 9, no. 2, pp. 199–209, 2003.
- [18]. Andreuccetti D, Fossi R, and Petrucci C, "Dielectric Properties of Body Tissues: HTML clients." [Online]. Available: <http://niremf.ifac.cnr.it/tissprop/htmlclie/htmlclie.php>. [Accessed: 09-Nov-2017].
- [19]. Adler A, Dai T, and Lionheart WRB, "Temporal image reconstruction in electrical impedance tomography," *Physiol. Meas*, vol. 28, no. 7, 2007.
- [20]. Cheney M, Isaacson D, Newell JC, Simske S, and Goble J, "NOSER: An algorithm for solving the inverse conductivity problem," *Int. J. Imaging Syst. Technol*, vol. 2, no. 2, pp. 66–75, 1990.
- [21]. Loke MH and Barker RD, "Practical techniques for 3D resistivity surveys and data inversion," *Geophys. Prospect*, vol. 44, pp. 499–523, 1996.
- [22]. Loke MH, "Tutorial?: 2-D and 3-D electrical imaging surveys," *Geotomo Softw. Malaysia*, no. 7, p. 127, 2013.
- [23]. Soni NK, Dehghani H, Hartov A, and Paulsen KD, "A novel data calibration scheme for electrical impedance tomography," *Physiol. Meas*, vol. 24, no. 2, pp. 421–435, 2003. [PubMed: 12812427]
- [24]. Kao TJ, Saulnier GJ, Isaacson D, Szabo TL, and Newell JC, "A versatile high-permittivity phantom for EIT," *IEEE Trans. Biomed. Eng*, vol. 55, no. 11, pp. 2601–2607, 2008. [PubMed: 18990630]
- [25]. Epstein BR and Foster KR, "Anisotropy in the dielectric properties of skeletal muscle," *Med. Biol. Eng. Comput*, vol. 21, no. 1, pp. 51–55, 1983. [PubMed: 6865513]
- [26]. Spieker AJ, Narayanaswami P, Fleming L, Keel JC, Muzin SC, and Rutkove SB, "Electrical impedance myography in the diagnosis of radiculopathy," *Muscle and Nerve*, vol. 48, no. 5, pp. 800–805, 2013. [PubMed: 23483460]
- [27]. Rutkove SB, Esper GJ, Lee KS, Aaron R, and Shiffman CA, "Electrical impedance myography in the detection of radiculopathy," *Muscle and Nerve*, vol. 32, no. 3, pp. 335–341, 2005. [PubMed: 15948202]
- [28]. Abascal J-FPJ, Arridge SR, Lionheart WRB, Bayford RH, and Holder DS, "Validation of a finite-element solution for electrical impedance tomography in an anisotropic medium," *Physiol. Meas*, vol. 28, no. 7, pp. S129–40, 2007. [PubMed: 17664630]
- [29]. Abascal JF, Arridge SR, Atkinson D, Horesh R, Fabrizi L, De Lucia M, Horesh L, Bayford RH, and Holder DS, "Use of anisotropic modelling in electrical impedance tomography: description of method and preliminary assessment of utility in imaging brain function in the adult human head," *Neuroimage*, vol. 43, no. 2, pp. 258–268, 2008. [PubMed: 18694835]
- [30]. Deng B, Brooks DH, Boas DA, Lundqvist M, and Fang Q, "Characterization of structural-prior guided optical tomography using realistic breast models derived from dual-energy x-ray mammography," *Biomed. Opt. Express*, vol. 6, no. 7, p. 2366, 2015. [PubMed: 26203367]

Fig. 1.

A. The Ultrasound (US) probe (Terason, Inc, Burlington, MA), B. sonolucent electrode array, C. the US housing used in data collection, which provides a 2 mm gap between skin and electrodes, D. diagram showing the electrodes used, and E. US/EIT system in use for a gel phantom experiment. A mock, 3D printed, US probe was used during gel experiments.

Fig. 2.

Phantom experimental setup showing the US housing that has a 2 mm thick US gel (0.183 S/m) that is placed on top of skin/adipose tissue (0.191 S/m with thickness of 1.6–5.6 mm) and muscle tissue (1.15 S/m or 1.02 S/m with thickness > 3 cm).

Fig. 3.

A. The segmented US image where the skin/adipose-tissue layer is colored red and the muscle region is colored green, and B. the coarse nodes illustrating the reconstructed points and the separate region (US gel is cyan circles, skin/adipose tissue is red x's and muscle are green diamonds). A cross section of the segmented FEM mesh in the skin/adipose-tissue layer is shown. The yellow box shows the US image extent and the purple box is the region used for analysis of the muscle.

Fig. 4.

Illustration of how the depth of distinguishability is calculated. The cyan and green boxes represent ± 1 SD regions about linear fits to two different types of muscle (+0% and +20% change). The intersection of these regions represents a depth where these two muscle property differences could be distinguished.

Fig. 5.

A. Reconstructions of the US gel, skin, adipose-tissue, and muscle layers for 50 simulated cases, B. a zoomed in view of the muscle results, and C. conductivity differences of muscle reconstructions. The muscle conductivity was increased from a standard literature value (0.35 S/m) by 0%, 10%, and 20%. The colored regions in B represent ± 1 SD bounds, which are used to calculate the depth of distinguishability between 0% and 10% and 0% and 20% muscle changes, respectively.

Fig. 6.

A. Reconstructions of the US gel, skin/adipose gel, and muscle gel layers for 54 measured datasets (18 gel combinations and 3 repetitions per combination), and B. a zoomed in view of the muscle results, and C. conductivity difference of the two muscle reconstructions. The colored regions in B represent ± 1 SD bounds, which are used to calculate the depth of distinguishability between the two muscles.

Fig. 7.

Example phantom gel reconstructions of where the adipose-gel layer (depth to muscle) was A. 2.01 mm, B. 3.65 mm, and 4.82 mm where the true US gel, skin/adipose-gel, and muscle conductivities were 0.183 S/m, 0.191 S/m, and 1.15 S/m, respectively.

Fig. 8.

Example phantom gel reconstructions using the standard approach (no soft regularization). The adipose-gel layer (depth to muscle) was A. 2.01 mm, B. 3.65 mm, and 4.82 mm where the true US gel, skin/adipose-gel, and muscle conductivities were 0.183 S/m, 0.191 S/m, and 1.15 S/m, respectively.

Fig. 9.

A) Ultrasound image acquired with US/EIT probe, B) Segmented US image, C) overlaid conductivity image.

Fig. 10.

All patient A. Conductivity, B. Permittivity, and C. Phase EIT reconstructions of the US gel, skin/adipose tissue, and muscle tissue considered in this study with (True) literature curves included for comparison at the 4 frequencies (10, 20, 40, and 80 kHz) plotted versus muscle depth.

Fig. 11.

Comparisons between longitudinal and transverse muscle impedances (A) and reconstructed conductivities (B) across all healthy patient sides. The left-side plots show measurement/reconstruction values ordered left to right from P1 to P3B, whereas the right-side plots show differences.

Fig. 12.

Example EIT reconstructions of the longitudinal and transverse directions from 80 kHz images of P1 overlaid on their respective US images. The average value of the muscle conductivities (averaged within the purple boxes) are noted in the image titles, which show as expected the longitudinal direction is higher than the transverse.

Fig. 13.

Comparison between the healthy versus diseased sides in terms of EIS A. resistance and B. phase measurements and the average muscle C. conductivity, D. permittivity, and E. phase from the EIT reconstructions. The two best EIS and EIT frequencies were selected based on the longitudinal versus transverse analysis. The bar plots are ordered left to right from P1 to P3B.

Fig. 14.

Differences between the healthy and diseased sides in terms of EIS A. resistance and B. phase measurements and the average muscle C. conductivity, D. permittivity, and E. phase from the EIT reconstructions. The two best EIS and EIT frequencies were selected based on the longitudinal versus transverse analysis.

Fig. 15.

Example EIT phase reconstructions of healthy and diseased sides corresponding to P3B, overlaid on the associated US image. The muscle average phase values (averaged within the purple boxes) are noted in the image titles.

TABLE I

Patient Information

Patients	Age	Sex	Ave. Depth to Muscle (min/max) mm		Probed Site/s	
1	67	M	3.18 (2.06/3.83)		Tibialis Anterior	
2	65	M	5.02 (3.93/5.82)		Tibialis Anterior	
3	47	M	A.	4.19(3.45/4.88)	A.	Lateral Gastrocnemius
			B.	4.46 (3.91/5.65)	B.	Medial Gastrocnemius