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Phantom Studies of Fused-data TREIT using only Biopsy-probe electrodes

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Abstract

Transrectal electrical impedance tomography (TREIT) is a novel imaging modality being developed for prostate biopsy guidance and cancer characterization. We describe a novel fused-data TREIT (fd-TREIT) system and approach developed to improve imaging robustness and evaluate it on challenging clinically-representative phantoms. The new approach incorporates 8 electrodes (in 2 rows) on a biopsy probe (BP) and 12 electrodes on the face of a transrectal ultrasound (TRUS) probe and includes a biopsy gun, instrument tracking, 3D-printed needle guide, and EIT hardware and software. The approach was evaluated via simulation, a series of prostate-shaped gel phantoms, and an ex vivo bovine tissue sample using only absolute reconstructions. The simulations surprisingly found that using only biopsy-probe electrode measurements, i.e. omitting TRUS-probe electrode measurements, significantly improves robustness to noise thus leading to simpler modeling and significant decreases in computational times (~13x speed-up/reconstructions in ~27 minutes). The gel phantom experiments resulted in reconstructions with area under the curve (AUC) values extracted from receiver operator characteristic curves of > 0.85 for 4 out of the 5 tests, and when incorporating inclusion boundaries resulted in absolute reconstructions yielding 1.9% and 12.2% average percent errors for 3 consistent tests and all 5 tests, respectively. Ex vivo bovine tests revealed qualitatively that the fd-TREIT approach can largely discriminate a complex adipose and muscle interface in a realistic setting using data from 9 biopsy probe states (biopsy core locations). The algorithms developed here on challenging phantoms suggest strong promise for this technology to aid in imaging during routine 12-core biopsies.

Keywords

Data fusion; electrical impedance tomography; inverse problem; bioimpedance

I. Introduction

PROSTATE cancer represents the 2nd leading cause of cancer-related death in men and has a significant societal impact with 1 in 9 men being diagnosed with the disease [1]. The standard approach for diagnosing prostate cancer is through a 12-core transrectal ultrasound (TRUS)-guided biopsy procedure, during which small tissue cores are systematically extracted across the whole prostate. More recently, additional cores are being sampled from lesions detected during multi-parametric magnetic resonance imaging (mpMRI) using MR-TRUS fusions protocols [2]. The traditional gold-standard, TRUS-guided biopsies, miss 10%–30% of all cancers [3]. These low detection rates are largely a result of the small volume of tissue sampled during the biopsy procedures (typically <1% of the prostate volume) [4] and the limited malignant-to-benign tissue contrast present in gray-scale TRUS [5]. Imaging with a modality having better malignant-to-benign contrast than TRUS alone could provide enhanced biopsy guidance and enable significantly more tissue to be effectively sampled – *potentially reducing the number of missed cancers*.

In addition to these prostate cancer detection challenges, both TRUS and mpMRI struggle to accurately discriminate between aggressive and indolent disease [6], making it challenging for clinicians to determine the optimal treatment strategy for men with prostate cancer. Developing an imaging modality that is sensitive and specific to cancer grade may enable more accurate assessment of disease aggressiveness and ultimately help to reduce overtreatment in men with prostate cancer.

Numerous studies have found significant ($p < 0.001$) electrical property contrast between benign and malignant prostate tissues ([7–12]) and more importantly significant electrical property differences between high- and low-grade cancer ([13]). Expected tumor-to-benign conductivity contrasts are –10% and –21% at 10 kHz and permittivity contrasts are +54% and +159% at 100 kHz for glandular and stromal tissue, respectively, based on reported median values [12]. Grade discrimination with impedance was significantly better than standard of care TRUS-guided biopsy procedures, and similar to that reported for MRI-based alternatives (the most promising techniques) [14–17]. Leveraging electrical impedance tomography (EIT) approaches, a technique called transrectal EIT (TREIT) has been established ([18]) to image these high-contrast impedances in the prostate.

EIT aims to reconstruct 3D conductivity (and permittivity) distributions from sets of voltages measured from injected current patterns on electrodes that lie on the boundary of a domain. In the TREIT application, electrodes are placed both around and along the distal end of the biopsy needle (biopsy probe (BP) electrodes) and over the transducer surface of the TRUS probe. In particular, this study further develops fused data TREIT (fd-TREIT) from [19] in preparation for pre-clinical deployment by 1) adding a second row of 4 electrodes (8 total on the BP), 2) incorporating the biopsy gun using a clinically-standard 12-core protocol, and 3) utilizing a sensitivity-based approach to define an appropriate imaging

region (overcoming a significant limitation in [19]). Essentially, the fd-TREIT approach reconstructs over a region defined by the sensitivity of measurements from each core/state. Thus, although one state has limited sensitivity, the combination of 12-states effectively samples a large region (relative to the size of the prostate). Three sets of experiments were conducted: 1) simulations evaluating robustness to noise, 2) five gel prostate-mimicking phantom imaging studies with physiologically-equivalent conductivity contrasts, and 3) ex vivo bovine tissue imaging studies of a complex heterogeneous mixture of adipose and muscle tissues. Importantly, only absolute EIT reconstructions were performed in this study.

The gel phantom and ex vivo bovine experiments aimed to help assess how well TREIT can aid in detecting prostate cancer. In terms of TREIT's potential to aid in assessing aggressiveness, reconstructions were also performed assuming knowledge of lesion boundaries could be known *a priori*. Thus, accurate lesion conductivity reconstructions (or conductivity contrasts) indicate a strong potential to aid in assessing cancer aggressiveness. Clinically, lesion boundaries can be identified prior to biopsy through mpMRI (assuming they are sufficiently large, >5mm [20]) and can be used within the fd-TREIT algorithm via MR-TRUS fusion techniques that have been developed ([21], [22]), including via commercial solutions e.g. UroNav [23].

The paper is structured as follows: Section II describes the fd-TREIT system, the forward and inverse EIT problems, data collection, registration and segmentation, and the experiments. Section III describes the results of the simulation study, gel and ex vivo bovine phantoms, forward model accuracy, computational times, and registration errors. Section IV discusses the impact of these results and approaches for further improvement.

II. Methods

A. Fused-Data TREIT System

The TREIT system consists of 1) a 20-electrode array adhered to the transducer surface of a Phillips C9-EC TRUS probe (Philips Healthcare, Cambridge, MA, Fig. 1D) and an 8-electrode array wrapped around an 18-gauge BP (NAC-1820 ULTRA Biopsy Needle, Remington Medical, Alpharetta, GA, Fig. 1C), with both electrode arrays interfaced to a custom EIT system ([24]), 2) a TRUS probe (Fig. 1A–B) with a Pro-Mag Ultra (Argon Medical Devices, Frisco, TX) biopsy instrument (gun) mounted on its side, and 3) an Aurora V2 EM tracking system (Northern Digital Inc., Ontario, Canada, Fig. 1A) with 1×5 mm six degree-of-freedom EM trackers (Fig. 1A–B). The TRUS-array is sonolucent and all electrodes are goldplated on a flexible polyamide substrate. Further details of the BP electrodes are given in [25]. A needle guide (Fig. 1B) with an embedded EM tracker is attached to the end of the TRUS probe to ensure a consistent firing direction. The TRUS-probe holder, needle guide, and BP mounting bracket (Fig. 1E) were fabricated using a Form 2 3D printer (Formlabs, Somerville, MA).

The TRUS probe was registered to EM-space by recording the location of 5 known points on the TRUS probe (magenta dots in Fig. 1B&D) using a registered EM-tracked pointer (Fig. 1A). The BP electrodes were registered by pointing to the center of each electrode in each row to estimate the row center locations. Since the BP was fixed relative to the TRUS probe,

a tracker for the BP was unnecessary. All tracking data, i.e. tracker states, in the form of Cartesian 3D coordinates (translation) and quaternions (orientation) were acquired via serial communication with the Aurora system in MATLAB. The position accuracy of the EM tracker has a standard deviation of 0.39 mm ([19]). Errors in BP and TRUS registration should be smaller due to averaging over 8 and 5 points, respectively.

Voltage Measurements: The EIT system records sets of voltage data from the TRUS and BP electrodes at each biopsycore state. We refer to each measurement as an IIVV pattern where II represents the current injection electrode pair (I1,I2) and VV represents the differential voltage sensing pair of electrodes (V1,V2). Subsets of BP-only patterns and BP + TRUS patterns are investigated. The BP-only patterns consisted of 1) the four patterns of top-only (i.e. II and VV electrodes arranged as in Fig. 1F) and bottom-only electrodes ($n = 8$) and 2) patterns with the II (and VV) electrodes on different rows ($n = 584$) (see Fig. 1F). The TRUS + BP patterns included all BP-only patterns and patterns in which the II (and VV) electrode pairs consisted of one on the BP and one on the TRUS probe ($n = 3760$). Since our custom-built EIT system is currently only configured for 20 channels, the TRUS + BP patterns used only 12 of the 20 TRUS electrodes (see Fig. 1D) to allow recording on all 8 BP electrodes. The omission of some TRUS electrodes is simply an artifact of our hardware limitations and because the TRUS electrode array PCB was designed and manufactured prior to our investigations into the combined usage of BP electrodes. The specific 12 TRUS electrodes were selected to maximize the depth of sensitivity in both the long- and short-axes of the array. All acquired data was pre-filtered (see [19]) to remove noisy patterns prior to image reconstruction. Data was recorded at 4 frequencies, 10, 20, 40, and 80 kHz. The average injected current was ~ 0.6 mA across all frequencies.

B. 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 [26], based on a 3D finite element method (FEM) implementation [27]. The CEM realistically accounts for the contact impedance and shunting of electrodes. The US/EIT geometry is an open domain geometry. Based on our work from [28], we ensure the model is accurate by expanding the modeled domain so that effectively no current flows near the open boundaries. 3D FEM meshes were constructed in Gmsh ([29]) to model 1) the TRUS electrodes and BP electrodes (Fig. 2A, 1.0M nodes, 6.1M elements) and 2) the BP-electrodes only (Fig. 2B–C, 225k nodes, and 1M elements). The mesh was designed in [19]. The density of the mesh was controlled by h-values (a measure of tetrahedra size) of the elements at or very close to the electrodes (h_e), near the electrodes (h_{int}), and far from the electrodes (h_{bg}). The extent of the near-electrode sub-region (h_{int}) corresponds to the large darker/denser region in Fig. 2A–B. Ill-shaped elements were eliminated via Gmsh's element-shape optimization. The accuracy of the forward model is discussed in Section III.D along with a comparison to the precision error of the EIT system.

2) Inverse Problem: The inverse problem is solved with a Gauss-Newton algorithm that fuses data from N_S states (i.e. BP positions in this case of fd-TREIT) and employs Laplace-

smoothing Tikhonov regularization (initially described in [30]). After a linearization step ([31]) the error to be minimized, $E(\delta\sigma)$, is

$$E(\delta\sigma) = \sum_{n=1}^{NS} \|\mathbf{J}_n \delta\sigma - \Delta \mathbf{v}_n\|_2^2 + \lambda \|\mathbf{L}(\sigma_0 + \delta\sigma)\|_2^2, \quad (1)$$

where $\delta\sigma$ is the conductivity update, σ_0 is the initial estimate of the conductivity distribution, $\mathbf{J}_n$ is the Jacobian corresponding to the n th state, $\mathbf{v}_n$ is the voltage difference (between measured and simulated) of the n th state, $\mathbf{L}$ is the regularization matrix, and λ is the Tikhonov regularization factor. The Jacobian $\mathbf{J}_n$ is size $N_P \times N_{rN}$, where N_P is the number of measurement patterns and N_{rN} is the number of reconstruction nodes. The Jacobian is solved using lead field theory ([32], e.g. see [33]), which in a physics-based manner gives appropriate sensitivity to each electrode/impedance measurement due to its size and geometry. The least squares solution to (1) is

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

where $\mathbf{J}_{FD}$ and $\mathbf{v}_{FD}$ are concatenated matrices and vectors from all the states. 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 [34]. Note that at each iteration, the forward problem and Jacobian need to be computed for each of the N_S states. The process is iterated to obtain an absolute reconstruction of the conductivity distribution.

a) Dual Mesh: The algorithm performs 3D reconstructions utilizing the dual-mesh method [34], which allows one to solve the Jacobian on an *FEM* mesh while estimating the conductivity on a different *reconstruction* mesh. This permits the measurements from each state to be associated to one fixed region for reconstruction. The mapping for each state n is defined by a matrix $\mathbf{P}_n$ of size $N_{fN} \times N_{rN}$ where N_{fN} is the number of nodes in the FEM mesh. The following *non-standard* coarse-to-fine mapping algorithm is utilized to account for the varied nodal mesh densities of the FEM mesh relative to the uniformly-dense reconstruction mesh. Specifically, the FEM mesh has a higher density than the reconstruction mesh (for a particular state) near the electrodes, but a lower density compared to the reconstruction mesh far from the electrodes (but still within the ROI). This is a result of the open-domain and fused-data aspects of the problem. The mapping is constructed in three steps. The first step is to calculate the following

$$(\mathbf{P}_n)_{i,j} = \begin{cases} \frac{1}{\|X_i^{fN} - X_j^{rN}\|}, & \text{if } i = \arg \min_{k=1 \dots N_{fN}} \|X_k^{fN} - X_j^{rN}\|, \\ 0 & \text{otherwise.} \end{cases} \quad (3)$$

where X_i^{fN} and X_j^{rN} are the position of the i th and j th node from the FEM mesh and reconstruction mesh, respectively. In (3), $\mathbf{P}_n$ is a matrix that assigns the closest FEM node to each reconstruction node, weighted by the inverse distance (the closer the distance the higher the weight). Secondly, we scale each row that has associated reconstruction nodes to sum to one. Thirdly, any unassociated FEM nodes are associated to the closest reconstruction node. A particular advantage of this mapping strategy is that it enables the

combination of reconstruction meshes with FEM meshes that have highly variable node density. The mapping is illustrated in a 2D example with high node density near the needle at two states (Fig. 3A–D). The more-common case of multiple reconstruction nodes (magenta) associated with an FEM node (black) is shown in Fig. 3E, whereas the alternative where an FEM node was unassociated is shown in Fig. 3F.

b) Open Domain: The open domain/local regions of sensitivity are modeled with the aid of a mega-node (MN), which is a reconstruction node that is associated to all FEM nodes outside of a prescribed region of interest (ROI), see Fig. 5. That is, in the process of solving the inverse problem the reconstructed MN value is used to model the conductivity at every associated FEM node, i.e. a constant value outside the ROI. The ROI is designed to be 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 affecting the inner conductivity values. A sensitivity-based technique described in [28] is used to form a joint ROI from each individual state (Fig. 4). That is, for a given state, form a ROI by finding all nodes that have a sensitivity defined by,

$$s_j = \max_{i=1 \dots N_P} |(\mathbf{J}_0)_{ij} / (\mathbf{v}_{sim}(\sigma_0))_i| \quad (4)$$

which exceeds a tolerance threshold of S_0 . In (4), $\mathbf{J}_0$ is an untransformed Jacobian, $\mathbf{v}_{sim}(\sigma_0)$ is the simulated voltages, and the value s_j can be interpreted as the maximum boundary voltage percent change caused by a perturbation from the j th reconstruction node. Only the BP-patterns were used to form the ROI, which is why the red region is roughly an ellipsoid about the BP. The convex hull of all the individual ROIs is used as the full ROI. This is illustrated in a 3-state example (Fig. 4) for $S_0 = 1/1000$; here, the red region represents the ROI from a single state and the blue region shows the combined ROI. The TRUS and BP needle are cyan and the prostate is shown in green.

c) Soft-prior regularization: The soft-prior regularization is encoded within a Laplace smoothing regularization approach as was done in [35]. The Laplace regularization essentially connects adjacent nodes (Fig. 5), and the soft-prior information is encoded by removing connections that cross the boundaries. For example, in Fig. 5 the prostate and tumor boundaries are encoded within a 2D reconstruction mesh (red dots are nodes, black line segments are connections). Specifically, this study encodes the main boundary (gel prostate or ex vivo bovine) into the regularization, referred to as B-SR (Boundary-Soft-prior Regularization), or encodes both the boundary and inclusions (for gel prostate experiments), referred to as I+B-SR (see Fig. 5). A background/saline and prostate mega-node are used to model the conductivity outside the region of sensitivity (green region). Although not illustrated, the mega-nodes are connected via the Laplace smoothing to boundary nodes of the ROI.

C. Data Collection, Registration, and Segmentation

All experiments were performed in a saline-filled tank where the gel phantom or ex vivo bovine tissue sample was held fixed between two plastic brackets with thin thread (see Fig. 6A). For each state, the TREIT probe was held at a fixed height and translated horizontally

to a specified location wherein the BP was fired into the sample. After firing, 1) 3 sets of EIT data, 2) an US image, and 3) EM-tracker data were recorded. This process was performed 12 and 9 times for the gel and ex vivo bovine tissue phantoms, respectively.

After this data was recorded, EM-registration and validation was performed. Specifically, sixteen registration points were sampled by placing the tracked stylet into eight holes on the top bracket (used for thread, see Fig. 6A) and eight equally spaced points on the top of the bottom bracket. Additionally, each thread intersection (16 points) were recorded, and used to quantify the accuracy of the top surface.

Finally, the phantom and bracket assembly were removed from the large tank, placed into a small tank, and T2-weighted images were acquired with a Phillips 3T MRI (Fig. 6B). MR images were segmented to extract the 1) top and bottom bracket hole locations, 2) sample boundary, and 3) (if applicable) inclusion boundaries via a custom MATLAB GUI (Fig. 6B–C). The boundary segmentation was performed on a per-slice basis using a fast marching method, *imsegfmm* from MATLAB's Image Processing Toolbox, which required user-selected seed points. While TRUS images were not analyzed or segmented in this work, they could be used in a clinical setting when MR is not available, or when there are significant changes in prostate geometry that occur between the MR and TRUS imaging sessions.

We chose to perform image reconstruction in a particular coordinate frame, referred to as the inverse frame (IF), that was centered on the sample (calculated as the mean of the 16 registration bracket points) with x and y axes aligned with the vertical and horizontal registration points from Fig. 6A and the z-axis coming out of the page. Points in the EM frame, $\mathbf{p}_{EM}$ are transformed to the inverse frame through the following operation

$$\mathbf{p}_{IF} = \mathbf{R}_{EM}^{IF}(\mathbf{p}_{EM} - \mathbf{c}_{EM}) \quad (5)$$

where $\mathbf{R}_{EM}^{IF}$ is a rotation matrix from the EM to IF frame and $\mathbf{c}_{EM}$ is the center in the EM frame. MR-registration points are then aligned with the EM-registration points in the IF frame by aligning coordinate frames and matching centers. The coordinate frame alignment is performed by finding orthonormal vectors defining x-, and y-, and z-axes in the IF frame (Fig. 6A) and the MR frame and by constructing the following rotation matrix

$$\mathbf{R}_{MR}^{IF} = [\mathbf{u}_{x, IF} \ \mathbf{u}_{y, IF} \ \mathbf{u}_{z, IF}][\mathbf{u}_{x, MR} \ \mathbf{u}_{y, MR} \ \mathbf{u}_{z, MR}]^T \quad (6)$$

which transforms from the MR frame to the natural basis and then to the IF frame. At this point two metrics are calculated: 1) average difference between MR and EM bracket points in the IF frame, and 2) average error between the EM-top sample points and MR-sample boundary surface.

Mesh Transformations: Based on the TRUS registration, a mesh-to-TRUS mapping is constructed, $\mathbf{T}_{msh}^{TRUS}$, which is a 4×4 matrix that includes a rotation matrix and translation vector, assuming homogeneous points are applied to the mapping. Further the TRUS tracker

yields a transformation from the TRUS-tracker to the EM frame, $\mathbf{T}_{TRUS}^{EM}$. Thus, to transform the mesh points, $\mathbf{p}_{msh}$ to the IF frame the following relationship is used

$$\mathbf{p}_{IF} = \mathbf{R}_{EM}^{IF} \left(\mathbf{D} \mathbf{T}_{TRUS}^{EM} \mathbf{T}_{msh}^{TRUS} \begin{bmatrix} \mathbf{p}_{msh}^T & 1 \end{bmatrix}^T - \mathbf{c}_{EM} \right) \quad (7)$$

where $\mathbf{D}$ is a matrix that converts from homogeneous (4xn) to standard points (3xn).

D. Experiments

Three sets of experiments were performed that used simulation, gel phantoms, and ex vivo bovine tissue to evaluate the approach and determine its feasibility.

1) Simulation Study: Simulations were used to evaluate how sensitive the choice of ROI size and IIVV patterns were to variability and bias in the prostate position and variability in the voltage measurements. Study parameters explored are listed in Table I. For each error type and modeling choice, 10 random samples were drawn and 5-step absolute reconstructions were calculated assuming the two-inclusion scenario of the first gel prostate experiment (see Table II) using the B-SR approach. There were a total of 2,160 absolute reconstructions calculated. Evaluation metrics used include position and radius error of the reconstructed inclusions, background standard deviation, and number of reconstructed inclusions. A pixel was defined to be part of the reconstructed inclusion/s if its conductivity value was > 0.7 of the maximum conductivity. Each connected set of pixels was identified as a reconstructed inclusion. The background was defined as the group of pixels that were < 0.5 of the maximum conductivity. The radius of each inclusion was defined as the radius of a sphere with volume equal to the reconstructed inclusion volume.

2) Gel Prostate Phantom Study: This study included five gelatin prostates (Table II) each with two inclusions of various separation distances, volumes, and conductivities. The nominal maximum dimensions of the prostate were 4 cm x 5 cm x 3 cm. Samples of each gel (4 cm long block with 2 cm x 2 cm cross-section) were produced in a test cell with 2 cm x 2 cm electrodes on both ends and the conductivity computed from impedances recorded with an 4284A impedance analyzer (Keysight Technologies, Santa Rosa, CA).

The gelatin prostates (Fig. 6A) were constructed using a silicone prostate mold, saline of a specified conductivity, and 10% gelatin (Sigma Aldrich, gel strength 300). The inclusions were made prior to the prostate using the same saline/gelatin ratio but with different saline conductivity and with an addition of 1–5% graphite powder for MR contrast. The inclusions were suspended in the prostate mold with a thin thread. The prostate liquid-gelatin was added after cooling to approximately 30° C to minimize melting of the inclusions. Although the conductivity values exceed those reported in ex vivo human prostate tissue, the contrast for test 1 (26%) and 4 (22%) are similar, i.e. there is a reported 11% and 26% contrast between cancerous tissue and glandular or stromal tissue, respectively [12].

The 12-core biopsy TREIT experiments were conducted for each prostate. As the inclusions were visible, biopsy locations were chosen to ensure the inclusions and surrounding areas were sampled (this is similar to how a targeted biopsy would be performed clinically using

MR-TRUS fusion). Five-step absolute reconstructions were computed using both B-SR and I + B-SR approaches. The B-SR approach was evaluated by performing pixel-based thresholding of the images and then analyzing the resultant receiver operator characteristic (ROC) curves. Three different thresholds were compared: 1) optimal for each test (i.e. nearest 2-norm point to 100% sensitivity and 100% specificity), 2) best specificity with 100% sensitivity, and 3) a heuristic best threshold across all tests. Specifically, the average optimal tolerance fraction of consistent tests from ROC analysis (tests 1, 2, 3 & 5) were used, the fraction is in reference to the maximum conductivity of each reconstruction. This analysis assumes the inclusion pixels essentially correspond to a tumor. The I + B-SR images were analyzed quantitatively by investigating average values of the inclusion, benign prostate region, and the contrast (inclusion-to-benign contrast). ROC curve analysis was not performed on I + B-SR images because the inclusion boundary information is given to the inverse problem so an ability to detect it is extraneous.

3) Ex vivo Bovine Phantom Study: The experiment involved a 9-core biopsy TREIT experiment on a sample of ex vivo bovine tissue (never frozen) with a large adipose section crossing diagonally through the ROI (Fig. 7). While bovine tissue provides a muscle-to-adipose conductivity contrast ($\sim 14\times$ [36]) much higher than benign-to-cancer contrast expected in prostate tissue ($\sim 1.1\text{--}1.2\times$ [12]), the successful reconstructions on animal tissue represents a significant pre-clinical validation of this approach. The biopsy sites coincided with the centers of the grids formed by the threads holding the tissue sample. The sample was ~ 3 cm thick, which resulted in all 8 BP-electrodes falling within the tissue after firing. Only five-step, absolute B-SR reconstructions were performed. Results were analyzed similarly to the B-SR gel prostate experiments, i.e. pixel-based thresholding and ROC analysis. Quantitative thresholds were chosen as follows 1) optimal, 2) best specificity with 100% sensitivity, and 3) a heuristic-threshold chosen that qualitatively well-separates the adipose and muscle tissue. The sensitivity and specificity were calculated relating adipose tissue to a positive test, i.e. similar to the inclusion/tumor from the gel prostate experiments.

E. Additional Parameters

In all experiments the saline was approximately 0.1 S/m, and in all measured reconstructions a saline calibration step was performed after noise filtering ([37]). A Tikhonov value of 1×10^5 was heuristically determined through visual evaluation of reconstructions. All reconstructions only used the real-part of the data, producing conductivity-only images.

III. Results

A. Simulation Study

Selected results of the simulation study (Fig. 8) show box and whisker plots from the 10 samples (25–75% quantiles) of the position error and number of reconstructed inclusions (should be 2). Results are shown for position bias and variability errors using BP-only and TRUS + BP measurement patterns. ROI's for tolerances ranging from 1/50 to 1/1000 and for the whole prostate are displayed. All simulation results are given in S.I Fig. 1, i.e. Fig. 8 plus impedance variability results and radius and background standard deviation metrics. The most striking observation is that TRUS + BP patterns result in overall higher errors and a

wider spread in the number of reconstructed inclusions than when BP-only patterns are used. This suggests that BP-only patterns are substantially more robust to noise.

One can see that choosing the ROI as the whole prostate (red box in Fig. 8) results in higher errors compared to other ROI tolerances. Amongst the other ROIs, the choice of the best tolerance is less clear, with only moderate effects observed for the different tolerances explored. While not generalizable, in numerous cases an ROI tolerance of 1/1000 has either the lowest error or near lowest with smallest variations. Based on these simulation results and our practical observations that the TRUS + BP reconstructions were not successful on measured phantoms (i.e. large prostate surface artifacts and inclusion locations, when apparent, were inaccurate), the remaining reconstructions presented are based on the BP-only patterns and the ROI tolerances are analyzed further.

B. Gel Prostate Phantom Experiments

In order to determine a best ROI to use on the measured phantom experiments, 5-step absolute reconstructions were performed using the B-SR approach with ROI tolerances of 1/50 to 1/1000. Area under the curve (AUC) values were calculated for each experiment and ROI tolerance (Fig. 9). Results are similar to the simulation results, in that there is no clear-cut optimal ROI tolerance. Technically, 1/1000 is the maximum with an average AUC of 0.855 over the five gel samples, but 1/250 and 1/500 result in similarly high values of 0.847 and 0.849, respectively. Therefore, we considered these results to be roughly equivalent and present ROI tolerance results corresponding to 1/500, as these images qualitatively appeared best.

Three slices of absolute reconstructions using BP-only electrodes and an ROI tolerance of 1/500 for B-SR (Fig. 10) and I + B-SR (Fig. 11) for gel tests 3–5 illustrate the quality of the reconstructions at 40 kHz. Reconstructions of all gel tests using B-SR and I + B-SR with slices covering the whole prostate are shown in S.II (Figs 2–3). The two inclusions appear merged in tests 3 and 5 using B-SR (Fig. 10) likely due to the inclusions' separation distance. When the inclusions were further separated (test 4) the two inclusions are roughly differentiated (via the optimal threshold). Quantitative analysis of the B-SR reconstructions (Table III) reveal 1) high AUCs for tests 1–4 (> 0.85), 2) relatively low specificity (max of 59%) when sensitivity is fixed at 100%, and 3) comparable heuristic tolerance results except for test 4. The heuristic tolerance uses a fixed threshold chosen to be the average optimal tolerance fraction from tests 1, 2, 3 & 5, which is 0.86.

In the planned cancer detection application, the sensitivity gives the percent number of cancer pixels detected correctly, which ideally will be 100%. Corresponding to this, one can see from Table III (row 5) that the false positive rate (1-specificity) is high (62%, 41%, 49%, 52%, and 95%) - indicating that large percentages of the benign tissue would be misclassified.

The ROIs covered 66%, 58%, 56%, 58%, and 67% of the prostate volume for the 5 prostate tests, respectively, which have total prostate volumes (Table II) similar to human prostates. Although ideally 100% of the prostate is imaged, this approach (fd-TREIT with sensitivity-

based ROI) covers a substantial portion of the prostate (~60%) and is much larger than the tissue volume sampled with current biopsy protocols (< 1% prostate volume).

The I + B-SR results assume that the inclusion boundary is known. Consequently, the reconstructions in Fig. 11 should ideally have uniform yellow (high conductivity) within the inclusions and uniform blue/blue-green in the benign region. Gels 3 & 4 mostly follow this expectation, except for a small low conductivity artifact towards the top of Gel 3 and the top right of Gel 4. These are likely related to small errors in the segmentation of the prostate or state of the biopsy electrodes. The uniformity assumption in Gel 5 reveals a large error, i.e. a large high conductivity region outside of the inclusions. Similar segmentation/registration errors are suspected here as well.

Fig. 12A shows the average conductivities within the prostate (omitting inclusion) and inclusion corresponding to the I + B-SR EIT reconstructions and the test cell measurements for all five gel tests across the frequencies 10, 20, 40, and 80 kHz from left to right. Contrasts (Fig. 12B) were used to more clearly illustrate the quality of the reconstructions and account for small unintentional variabilities between the prostate gelatin conductivities. The contrast is defined as the inclusion conductivity divided by the prostate (excluding the inclusion) conductivity. Important to note, a single scaling factor (1.11) was applied to the EIT contrast ratio across all tests to produce Fig. 12B. This scaling factor provided an overall best fit for tests that had consistent inclusion-ratio accuracies (tests 1, 3, and 4). The average absolute percent errors in contrast were 10.0% and 19.9% for tests 1,3,4 and tests 1–5, respectively, without the scaling factor, and were 1.9% and 12.2% for tests 1,3,4 and tests 1–5, respectively, with the scaling factor. Errors were calculated between EIT and the test-cell (taken to be ground truth).

C. Ex Vivo Bovine Experiment

Four slices from the X/Y-, X/Z-, and Y/Z-planes of the absolute B-SR reconstruction using BP-only electrodes and an ROI based on 1/500 tolerance reveal the quality of the ex vivo bovine results (Fig. 13). A heuristically chosen threshold yields a contour that roughly separates large portions of adipose and muscle tissue. The AUCs from all ROI tolerances (Fig. 9) reveal a low sensitivity to the ROI choice, and Table III summarizes the AUC (0.67), sensitivity and specificity values for ROI tolerance of 1/500. The adipose tissue was equated with a positive test for AUC calculation. The interface between the adipose and muscle tissue is complex and given that the EIT algorithm was not provided information regarding its delineation (i.e. using an I + B-SR approach), these images represent a high quality EIT reconstruction.

D. Forward Model Accuracy

This section reports on the accuracy of the forward model relative to a highly refined FEM mesh and the measured precision for the BP-only mesh/patterns (see mesh in Fig 2B). The size of elements at or near the electrodes (h_{el} and h_{int}) were halved twice to produce two refined meshes (1-refined and 2-refined) relative to the used mesh; in practice, the 2-refined mesh represents the densest mesh on which we can calculate the forward solution. The background (h_{bg}) element size was set to 10 mm. The difference between the used and 1-

refined mesh voltages are compared to the 2-refined mesh to quantify the accuracy (Table IV). Both errors are small and comparable to the average precision errors of the measurement system, which are 0.38 mV or 0.078% based on 20 repeated measurements recorded from a homogeneously-filled saline tank of 0.1 S/m. Here we define the precision error to be

$$E_{Prec} = \frac{1}{N_P} \sum_{i=1}^{N_P} \left| v_{i,s} - \frac{1}{N_T} \sum_{s=1}^{N_T} v_{i,s} \right| \quad (8)$$

where s is the index of the N_T -repeated measurements, and the relative precision error is found by dividing each IIVV pattern by its mean voltage over the repeated measurements. The same h-value parameters were used for the TRUS + BP mesh.

E. Computational Cost

The mesh sizes and computational times show (Table V) that using the BP-only mesh allows for accurate modeling with 10x less nodes, yielding ~10x speed-up in the forward solution, and 13x speed-up in the overall inverse problem calculation (assuming 5-steps, 12 states and an ROI tolerance of 1/500). These computations utilized 1) a Linux-based server hosting 40, 2.4 GHz processors with 256 GB of RAM total, 2) an optimized EIT toolbox [27], and 3) *parfor* in MATLAB to run the forward and Jacobian calculations of the 9 or 12 states in parallel.

F. EM/MR Registration Errors

Registration between MR and EM space for the 8 top bracket points and between the sample (gel prostate or ex vivo bovine) and the thread intersection points (Table VI) show an average distance error of 1.0 mm. The average surface-to-EM error was also 1.0 mm. The errors ranged from 0.67 to 1.51 mm with averages of ~1 mm for both distance types.

IV. Discussion

In terms of EIT reconstructions, this study demonstrates that it is possible to reconstruct small-contrast inclusions in gel prostates and complex adipose/muscle interfaces in ex vivo bovine tissue samples using absolute reconstructions based on fd-TREIT with a B-SR approach. Despite errors associated with instrument tracking, numerical approximations in the fusion/inverse process (e.g. errors due to reconstruction mesh resolution and encoding soft priors), and potential off-axis biopsy needle trajectories, the approach appears to be quite robust. Further, while it may seem counterintuitive that adding measurements would be detrimental, we found that using BP-only patterns appears to be more robust to noise than using the larger TRUS + BP pattern set. The TRUS patterns have little sensitivity to the prostate interior, which is our primary interest, and high sensitivity to the prostate surface (see Fig. 3 from [19]); at this surface there will always be some segmentation error and a large step-change in true electrical properties between the prostate and periprostatic tissue. Based on this study, these two factors appear to be significant enough to omit the TRUS-patterns. Accurate inclusion/tumor boundary extraction using the B-SR approach is limited, but expected given the moderate resolution of EIT. However, if B-SR is only used to detect tumors, then the gel phantom results show good promise. While the Laplace smoothing

regularization technique used here generally produces smooth reconstructions, it is possible that more accurate inclusion boundaries could be achieved by using alternative regularization techniques, e.g. [38], [39]; exploration of these techniques were viewed as beyond the scope of this study.

The I + B-SR results show very accurate average contrast ratio errors (1.9% when excluding inconsistent cases and 12.2% over all tests) over the small set of gel tests. If similar results using this approach can be attained on real prostates (for example, given suspicious lesion information from mpMRI) then this approach could have significant impact on clinical care. Despite these promising results, there are confounding artifacts present in some of the images (e.g. gel 2 in Fig. 12 and gel 5 in Fig. 11). These artifacts are likely caused by inaccuracies in the prostate segmentation or modeled location of the biopsy electrodes. In ongoing research, we are exploring the use of commercial segmentation software (Mimics [40]) to more accurately define the needle trajectory based on information extracted from the ultrasound images. Alternatively, there are interesting EIT techniques that can improve estimates of imperfectly known boundaries, e.g. [41], [42] or solve for internal shapes [43]. A soft-prior EIT approach that solves for electrical properties and updates the prior-shape information may be considered in future studies.

Beyond investigating different regularization approaches and methods of reducing modeling errors, the other likely approaches to improve results are 1) speeding up the computational process and 2) adding more electrodes to the BP. The latter approach is straightforward to implement in software, but requires careful hardware design. More electrodes on the BP would likely increase the volume of the region of sensitivity (towards our goal of 100% coverage of the prostate), and it could increase the flexibility of the measurements. For example, in the current 8-electrode configuration if the electrodes are too close to the boundary they are removed entirely. Additional rows of electrodes would allow us to retain row separated patterns, while in the current two-row configuration all data from that state is removed when one row is near a prostate boundary.

The computational process for fusing data and reconstructing images is two-fold. First, all the data is compiled (EM, EIT, MR), data spaces are segmented and registered, the ROI is constructed, and mappings from reconstruction nodes to FEM nodes for all states are calculated. The second component is the actual computation of the inverse problem, which takes ~27 minutes (Table V). If reconstructions could be produced in near real-time, then feedback regarding percent prostate covered or quality of the reconstruction could be provided to the clinician. Part of this speed-up can be achieved through use of off-line computation and optimization of data handling that would help to streamline our approach; however, improving the computational time of the inverse problem remains challenging, and is part of ongoing investigations.

V. Conclusions

This study further developed the fd-TREIT approach, tested this approach on challenging phantoms, and now appears ready for ex vivo evaluation of the technique on prostate tissue. Importantly, based on simulation results and observations from measured reconstructions,

this study strongly suggests that BP-only measurements are more robust than when TRUS probe electrodes are also used – resulting in simpler modeling and consequently significant decreases in computational times. Additionally, the sensitivity-based ROI resulted in a robust method of determining the region to image. Specifically, the gel phantom experiments showed high AUCs (> 0.85 for 4 out of the 5 tests) and when incorporating inclusion boundaries resulted in absolute reconstructions yielding 1.9% and 12.2% in average absolute percent errors for 3 consistent tests and all 5 tests, respectively. Further, the ex vivo bovine test revealed that qualitatively the fd-TREIT approach can largely discriminate a complex heterogeneous tissue interfaces in a realistic setting using data from only 9 biopsy probe measurements. Overall, the methods developed here and image results presented suggest a strong promise for this technology to aid in imaging during routine 12-core prostate biopsies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

A. The Phillips C9-EC transrectal ultrasound probe in holder and stand with attached biopsy gun and EM generator and pointer, B. side view of the needle guide and tracker, C. BP electrodes, D. TRUS electrodes, E. the opened biopsy gun showing mounting assembly, and F. BP across- and intra-row electrode patterns.

Fig. 2.

A. TRUS + BP and B. BP-only meshes, which have high density of nodes near electrodes. C shows a zoom-in of the BP electrodes.

Fig. 3.

Illustration of FEM mesh, reconstruction grid (magenta circle and dots), and true conductivity distribution (three Gaussians) at two states (A and C) and the resulting discrete conductivity mapped from reconstruction grid to the FEM mesh (B and D). The FEM mesh has high density near the needle (red circle), which yields an accurate mapping in this high sensitivity region. Zoomed in views show multiple reconstruction nodes (magenta) associated with a FEM node (black) (E) and a case where a FEM node was unassociated and therefore mapped to the closest reconstruction node (F).

Fig. 4.

Illustration of a 3-state example of the fd-TREIT ROI (blue region) that results by combining the sensitivity-based ROI from each state (red region) via a convex hull assuming BP-only patterns. The sensitivity tolerance used was $S_0 = 1/1000$, the TRUS and needle are cyan, and the prostate is shown in green.

Fig. 5.
2D illustration of Laplace smoothing regularization and soft-priors encoding of a tumor (magenta) and prostate (cyan).

Fig. 6. Illustration of bracket (A), top-bracket registration points (red dots), and inverse (problem) frame (light blue) for a gel prostate phantom with corresponding MR image (B-C) showing the segmented prostate (green lines) and tumor boundaries (red lines) and the top-bracket registration points (blue). In practice, these would represent axial slices of the prostate.

Fig. 7.
Photo of the ex vivo bovine sample. The white is adipose tissue, pink is the muscle, and the 9 squares created by the crossing thread were used as the approximate BP insertion sites.

Fig. 8.

Box and whisker plots (25–75% quantiles) corresponding to 10 reconstructions of the position error and number of reconstructed inclusion (should be 2). Data shown for position bias and variability errors using BP-only and TRUS + BP measurement patterns. ROIs displayed for tolerances ranging from 1/50 to 1/1000 and for the whole prostate. The significantly larger noise using TRUS + BP patterns imply BP-only patterns are substantially more robust to noise – i.e. *the preferred patterns to use*.

Fig. 9.

Area under the ROC curves (AUC) for each gel test, the average gel test AUCs, and bovine test as a function of the ROI tolerances considered.

Fig. 10.

Absolute reconstructions (5-step) using B-SR with an ROI of 1/500 (cyan) for gel tests 3–5 at 40 kHz. The prostate (green) and inclusions (yellow or black) are clearly seen in the MR images (top row of each test) with overlaid biopsy positions and the EIT images (bottom rows) show contours of 85% max and optimal (ROC curve). In practice, these would represent axial slices of the prostate.

Fig. 11.

Absolute reconstructions (5-step) using I + B-SR with an ROI of 1/500 (cyan) for gel tests 3–5 at 40 kHz. The prostate (green) and inclusions (yellow or black) are clearly seen in the MR images (top row of each test) with overlaid biopsy positions and the EIT images (bottom rows). In practice, these would represent axial slices of the prostate.

Fig. 12.

A. Test cell and average EIT conductivity values for the (benign) prostate and inclusions for all five gel experiments where the 4 points for each test are results at 10, 20, 40, and 80 kHz, and B. scaled contrast (inclusion-to-prostate) ratios. A scaling factor of 1.11 was used, which was calculated as a best-fit for tests 1, 3, and 4.

Fig. 13.

Absolute reconstruction (5-step) using B-SR with an ROI of 1/500 (magenta) for the ex vivo bovine experiment. The bovine sample (green) and muscle/adipose tissue are clearly seen in the MR images (top row of each plane slices) with overlaid biopsy positions and EIT images (bottom rows); a contour at 25% of the maximum conductivity was heuristically chosen to best show the muscle/adipose boundary.

TABLE I

Simulation Study Parameters

Model Approach	Values (# of parameters explored)
ROI tolerances	1/50,1/100,1/250,1/500,1/1000, Whole prostate (6)
IIVV patterns	BP-only or BP+TRUS (2)
Error Type	Standard Deviations
Bias registration position	0.5 to 3.0 in 0.5 mm steps (6)
Noise in state position	0.5 to 3.0 in 0.5 mm steps (6)
Variability in voltage	0.2, 0.5,1.0,2.5, 5,10% (6)

TABLE II

Phantom Study Parameters

Test	1	2	3	4	5
Inc. Sep. (cm)	1.87	1.70	1.66	2.21	1.83
Inc. Vol. (cm ³)	1.1, 1.1	0.8, 0.9	1.4, 1.2	1.0, 1.1	1.3, 1.0
Prost. Vol. (cm ³)	45.2	48.9	47.8	44.8	48.8
Ine. Cond. (S/m)	0.40	0.38	0.41	0.34	0.59
Prost. Cond. (S/m)	0.32	0.23	0.28	0.28	0.27
Ine. Cond ratio	1.26	1.65	1.49	1.22	2.17

TABLE III

Phantom and Ex Vivo Bovine ROC Results, Showing Sensitivity (Sens.) and Specificity (Spec.) for Several Approaches

Test	1	2	3	4	5	Bovine
AUC	0.85	0.90	0.87	0.90	0.72	0.67
Opt. Sens.	0.77	0.87	0.80	0.88	0.67	0.59
Opt. Spec.	0.78	0.78	0.77	0.79	0.72	0.67
Opt. Tol. Frac.	0.87	0.85	0.86	0.98	0.89	0.33
Best Spec, with 100% Sens.	0.38	0.59	0.51	0.48	0.05	0.10
Heuristic Sens.	0.86	0.87	0.84	1.00	0.56	0.29
Heuristic Spec.	0.67	0.77	0.73	0.08	0.80	0.93

TABLE IV

Forward Solution Convergence Tests Between Used and 2 Refined Meshes Considering the BP-Only Mesh

Mesh	Used	1-Refine	2-Refine
h_{el} (mm)	0.40	0.20	0.1
h_{int} (mm)	1.00	0.50	0.25
Num. nodes	225k	585k	2.4M
Num. elements	1.0M	3.4k	14.5M
Ave. Volt Diff (mV)	0.29	0.36	-
Rel. Diff. (%)	0.112%	0.122%	-

TABLE V

Computational Times

Mesh	BP-only	TRUS+BP
Number nodes	225k	1M
Number elements	1.2M	6.2M
Forward calculation	55 sec	9.2 min
5-step abs. recon, 12 states	27.6 min	~6 hours

TABLE VI

Registration Average Distance Errors (mm)

Test	MR and EM top bracket	Surface to EM
Gel 1	0.93	0.78
Gel 2	0.67	0.70
Gel 3	0.86	0.90
Gel 4	1.51	1.16
Gel 5	0.98	0.96
Ex vivo	1.22	1.73