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Comparative Study of Separation between Ex-Vivo Prostatic Malignant and Benign Tissue using Electrical Impedance Spectroscopy and Electrical Impedance Tomography

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Abstract

Currently no efficient and reliable technique exists to routinely assess surgical margins during a radical prostatectomy. Electrical impedance spectroscopy (EIS) has been reported as a potential technique to provide surgeons with real-time intraoperative margin assessment. In addition to providing a quantified measure of margin status, a co-registered electrical impedance tomography (EIT) image presented on a surgeon's workstation could add value to the margin assessment process. To investigate this, we conducted a comparative study between EIS and EIT to evaluate the potential these technologies might have for margin assessment. EIS and EIT data was acquired from ex-vivo human prostates using a multi-electrode endoscopic impedance acquisition probe. EIS and EIT show good predictive performance with a 0.76 and 0.80 area-under-curve (AUC), respectively, when considering discrete frequencies only. A machine learning (ML) algorithm is implemented to combine features, which improves the AUCs of EIS and EIT to 0.84 and 0.85, respectively. Single-step EIT takes significantly less time to reconstruct than multi-step EIT, yet provides similarly accurate classification results, making the single-step approach a potential candidate for real-time margin assessment. While the ML-based approach clearly exhibits benefits as compared to the single feature assessment, the decision to use EIS vs. EIT is unclear since each approach performs better for different subsets of tissue classifications. The results presented in this paper corroborate our previous studies and present the strongest evidence yet that an intraoperative-capable impedance probe can be used to distinguish benign from malignant prostate tissues. An in-vivo study with a large cohort will be necessary to definitively determine the preferred approach and to show the clinical effectiveness of using this technology for margin assessment.

1. Introduction

Prostate cancer is currently one of the most common cancers and second most fatal cancer in men in the United States (US). In 2016, approximately 180,890 men were diagnosed with prostate cancer, and 26,120 men were expected to die of the disease (Siegel *et al* 2016). Surgical removal of the prostate through a radical prostatectomy (RP) represents a potential treatment strategy for men with organ-confined prostate cancer. The Center for Disease Control has reported that over 100,000 RPs are performed annually in the US (CDC 2010). To ensure surgical efficacy, it is important to verify that no cancer cells extend beyond the margins of the excised prostate. Cancer found on this margin suggests that additional cancer cells might remain within the peri-prostatic tissue of the pelvic cavity. No clinical protocols are routinely used to intraoperatively assess these surgical margins. Instead, margins are evaluated through pathological assessment of the prostate *following* RP, when it is too late to provide additional surgical intervention. Positive surgical margins (PSMs) are associated with disease recurrence and are often treated with toxic adjuvant therapies. Average PSM rates in contemporary robot-assisted laparoscopic prostatectomy (RALP) procedures range from 6.5% to 32% (Yossepowitch *et al* 2014), and around 80% of the RPs are performed robotically (NCI 2015). Incidence of PSMs decrease disease-free survival rates; 10 years after RP, the disease-free survival rate for patients without PSM is 73 – 90%, while for patients with PSMs the rate is 49 - 60% (Orviato *et al* 2006, Rouanne *et al* 2014). Reducing the number of PSMs will: 1) reduce the morbidity associated with adjuvant and salvage therapies in patients who would have had PSMs, 2) reduce the financial burdens associated with treatment of recurrent cancer on the patient and healthcare providers, and 3) reduce the mortality rate associated with prostate cancer recurrence.

This study explores electrical impedance spectroscopy (EIS) and electrical impedance tomography (EIT) as the basis for a surgical margin assessment (SMA) tool. It has the potential to be a low-cost, radiation free, real-time technique, which could significantly impact clinical outcomes thereby leading to enhanced quality of life for patients following RP. Based on previous findings, EIS has been successfully shown to distinguish between malignant and benign prostate tissue (Halter *et al* 2008a, 2007, 2008b). Cancerous prostatic tissue has a significantly lower conductivity than benign stroma and glandular prostatic tissues at frequencies ranging from 0.1 to 100 kHz and a permittivity that is significantly higher than all benign tissues at 100 kHz (Halter *et al* 2009). Based on these studies we have been recently developing SMA EIS/EIT probes. Khan *et al.* reported preliminary results from this effort where a technique called the Composite Impedance Metric (CIM) was used to establish separation between benign and malignant prostatic tissue that had a predictive accuracy of 90.3% using the Support Vector Machine (SVM) algorithm and a best area-under-curve (AUC) from receiver operator characteristic (ROC) analysis of 0.86 (Khan *et al* 2016). However, there were several limitations to this study that should be addressed. First, the labelling procedure was inexact, probe measurement locations were only known to within a quadrant of a prostatic slice, where the quadrant is roughly 6 times the area of the probe. Second, the resolution of the probed sites for the 9-electrode probe used is limited to a diameter of 7.5 mm. Third, the high frequency phase data used to conduct SVM

classification may be affected by the presence of stray capacitance in the system, which is nearly 300 pF at each channel (Khan *et al* 2016).

Other approaches have been investigated for SMA during RP, including several optical-based approaches, e.g. (Yadav *et al* 2009, Gao *et al* 2011), and intraoperative frozen section (IFS) analysis (Fromont *et al* 2003, Von Bodman *et al* 2013). IFS analysis has been the most-studied SMA approach, but its use is still controversial (Von Bodman *et al* 2013), as the IFS procedure adds significant surgical time (20-30 minutes) and co-registration is challenging.

This report presents an ex-vivo study of 19 human prostates in which a radially distributed 17-electrode endoscopic probe and Dartmouth's Electrical Impedance Acquisition (EIA) System (figure 1) were used to record impedances. Here we overcome the shortcomings of the previous study (Khan *et al* 2016); 1) probe locations are accurately co-registered to histology, 2) the 17-electrode probe yields higher resolution measurements (the 17-electrode probe provides twice the resolution as the 9-electrode probe used in (Khan *et al* 2016)), and 3) a multi-frequency SVM approach is used that is not solely reliant on high frequency reactance/permittivity data. EIS and EIT show good predictive performance with the best AUCs being 0.76 and 0.80, respectively, when considering discrete frequencies, and the SVM improves the AUCs of EIS and EIT to 0.84 and 0.85, respectively (the corresponding sensitivity and specificities are (0.81, 0.73) for EIS and (0.73, 0.90) for EIT, respectively).

The paper is structured as follows. After describing the probe and acquisition system in Section 2, the dataset and clinical protocol are described in Section 3. Following this, the EIT algorithm is described and data analysis is detailed in terms of features used and the machine learning algorithm leveraged. Benefits and challenges of both techniques and their potential clinical impacts are discussed.

2. Methods

2.1 Data Acquisition: Dartmouth Electrical Impedance Acquisition (EIA) System and Probe

The Dartmouth EIA system is a broadband (100 Hz-10 MHz) 32-channel data acquisition (DAQ) system with a SNR >90 dB and possesses high speed capabilities (up to 80 frames/second) (Khan *et al* 2013). The system is flexible and has a modular hardware and software design that allows for performance upgrades such as DAQ frame rate and SNR. The EIA uses National Instruments (NI) hardware and software modules, which offer inherent compatibility over generations of hardware and software revisions.

A radially distributed 17-electrode microendoscopic probe is used for data collection (Mahara *et al* 2015); the probe is 11 mm in diameter with 1 mm diameter gold-plated electrodes (205089-4-ND, DigiKey) that protrude 1 mm from the probe face and have rounded hemispherical ends (see figures 1B and 2A). The probe tip housing is constructed using electrical-grade G-9 type garolite (McMaster Carr, Elmhurst, Illinois), a continuous-woven glass fabric laminated with an epoxy resin. The water absorption of G-9 garolite is 0.69 – 0.074%, compressive strength is 15,000 - 35,000 psi, dielectric strength is 370-450 volts/mil, and thermal stability ranges up to 137.8 °C (Anon 2014). These characteristics

provide for a robust probe design that is strong, nonabsorbent, and capable of undergoing repeated steam sterilization processing (probe exposed to 125 °C for 25 minutes) as is required prior to intraoperative use.

Multiple four-electrode (tetrapolar) measurement combinations can be used to gauge impedance. We specifically focus on 3 types: 1) All tetrapolar patterns, 2) Outer ring patterns, and 3) Inner ring patterns. Impedance measurements from a total of 14,280 electrode combinations are recorded during each impedance acquisition (All patterns). For outer or inner ring tetrapolar impedance patterns, a small current ($<1 \text{ mA}_{\text{rms}}$ as specified by the IEC 60601-1 standard (IEC 60601-1:2005)) is driven between two electrodes spaced 3 electrodes apart (e.g. 10 & 13 figure 2B), and the voltage difference between the pair of adjacent electrodes located between the driving electrodes (e.g. 11 & 12 figure 2B) is measured. Using this approach, inner ring impedances were recorded with 8 current drive electrode pairs (6/9, 7/2, 8/3, 9/4, 2/5, 3/6, 4/7, and 5/8) and outer ring impedances were recorded with pairs (14/17, 15/10, 16/11, 17/12, 10/13, 11/14, 12/15, and 13/16). Since these inner and outer patterns are rotationally symmetric, the effects due to unused electrodes (i.e. current shunting) for each measurement pattern should be consistent across all inner and outer measurements, respectively. The reciprocal of each of these drive pairs was also used (i.e. 6/9 and 9/6) to give a total of 16 impedance measurements per ring. A noise filter applied to the data removes patterns whose 1) voltage difference is too small ($< 50 \text{ mV}$), 2) voltage or current noise power is too large ($> 2 \text{ V}$ and $> 3/(499 \Omega) \text{ A}$ for voltage and current, respectively; see (Khan *et al* 2016) for description of noise power measurements in this system and note that 499Ω is the resistor used on the current sense electrode), and/or 3) if the sensed current magnitude is too small ($< 0.1 \text{ mA}$, in voltage drive mode). These thresholds were empirically determined and were conservatively chosen to keep higher quality measurements.

Prior to making tissue measurements, the probe is placed in a 0.1 S/m saline bath and impedances are recorded. Using the forward model of EIT (see Section 2.3.1) simulated resistances and reactances are calculated. The ratio between the measured and simulated impedances defines a complex, frequency-dependent calibration factor that is used to adjust every tetrapolar impedance measurement. This is a standard approach used to minimize instrumentation errors associated with channel-to-channel variations and electrode imperfections (Wan *et al* 2013).

2.2 Clinical Data Collection Procedure: Probing and Histology

The probe was used to gauge the electrical properties of 19 ex-vivo prostates removed during RALP procedures performed by a single surgeon at Dartmouth-Hitchcock Medical Center, which was conducted under an IRB approved protocol and includes data from consenting individuals. Immediately following RALP, the resected prostate was transferred to the Anatomic Pathology Laboratory. The prostate was sectioned into 2-5 mm thick slices and intraprostatic measurements were acquired from the cut tissue surfaces (figure 3) at 11 discrete frequencies (5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 kHz). The measurements were performed approximately 30 minutes post-resection, at which time the prostate cooled to room temperature ($\sim 25^\circ \text{ C}$). The probe was pressed against the cut surface of 3-4 slices per

case. Since the applied pressure can impact impedance measurements (González-Correa *et al* 2005), a single individual (AM) performed all EIS measurements while attempting to apply a consistent pressure across all cases. The intraprostatic probed locations included both benign and grossly identifiable cancer regions. Immediately after recording the impedance data, three pins were inserted next to electrode 10, 12, and 16 (figure 2B) in order to mark the location and orientation that was probed (figure 3b). Specimens were fixed and stained with H&E for microscopic evaluation (figure 3c-d), maps were created to specify the cancerous regions within the slice and to determine each probed location and orientation (figure 3e). Image processing was used to calculate the percent benign and cancer for each probed site (figure 3f). The slices are either fully benign (Bn) or have some distribution of prostatic cancer (PCa). The PCa distributions are presented in Table 1.

Impedance data were recorded from 135 intraprostatic tissue sites from 19 patients which were divided into 5 groups defined by cancer content (Table 1). It has been suggested that the prognosis for men with PSMs < 3mm is statistically better than that of men with PSMs > 3mm (Ochiai *et al* 2008). Given that the area sensed by the probe is 38.5 mm² (diameter of 7 mm), a 3 mm diameter (7.1 mm²) tumor region is equivalent to 18% of the probed area. Thus this 18% cutoff was used to define two of the groups (G2 & G3), which allows for additional clinically relevant analysis of the data.

2.3. Electrical Impedance Tomography

2.3.1 Forward Problem—The forward problem relies on the Laplace equation,

$$\nabla \cdot \sigma \nabla u = 0, \quad (1)$$

to calculate the electric potential, u , over the entire domain, where σ is the conductivity. In order to realistically account for discrete electrodes and obtain accurate boundary electrode voltage data, the complete electrode model (CEM) is used (Somersalo *et al* 1992), which has been found to be the most accurate electrode model (Cheng *et al* 1989). The CEM-based boundary conditions specify the current and contact impedance at each electrode and assume that no current flows in or out of the system except through the electrodes. The finite element method (FEM) in 3D with linear basis functions is used to calculate the forward problem.

2.3.2. Inverse Problem—The inverse problem aims to recover the conductivity distribution within the domain from the boundary voltage measurements due to different sets of applied currents. At each frequency, the EIS measurements are used as the input to the EIT inverse problem. A Gauss-Newton algorithm employing a Tikhonov regularization scheme is used. This inverse algorithm attempts to minimize the following

$$E(\sigma) = \frac{1}{2} \| \mathbf{F}(\sigma) - \mathbf{V}_{Meas} \|_2^2 + \frac{\alpha}{2} \| \mathbf{L}(\sigma - \sigma_0) \|_2^2, \quad (2)$$

with respect to the conductivity, σ . $\mathbf{F}(\sigma)$ and $\mathbf{V}_{Meas}$ are concatenated vectors of all the simulated and measured voltage patterns, respectively, α is the Tikhonov factor, $\mathbf{L}$ is a regularization matrix, and σ_0 is the initial or previous estimate of the conductivity. This is a standard approach to EIT reconstructions that after linearizing the problem results in an iterative algorithm to recover the conductivity, see (Lionheart 2004) for a detailed discussion.

We solve the EIT problem in two ways; 1) assuming the conductivity is a constant throughout the whole domain (constant EIT), and 2) assuming that the conductivity varies spatially below the probe site (3D EIT). In the first approach, the regularization term can be ignored because the problem is no longer ill-conditioned when there is only one unknown. The second approach utilizes a technique (Murphy *et al* 2016) that was purposely developed for open-domain probes, such as this SMA device. The technique separates the domain into a local region where we expect sufficient sensitivity to accurately estimate spatially dependent conductivity values and an outer region that is assumed constant (referred to as a mega node (MN)). The local sensitive region is connected to the MN through the regularization matrix, which reduces boundary artifacts. The same parameters that yielded the best reconstructions from (Murphy *et al* 2016) are used, i.e. a $20 \times 20 \times 8$ rectilinear grid was used for the inverse dual mesh (Borsic *et al* 2010) where the tolerance for the region of sensitivity was chosen to be $1/400$ and the MN constrained Laplace smoothing technique was used with a Tikhonov factor of 1×10^5 . The 8 discrete z-values, from the rectilinear grid, correspond to reconstructions at 8 distinct depths, which are 0.2, 0.5, 0.8, 1.1, 1.5, 2.2, 3.2, 4.3 mm. Although some prostate slices were likely thinner than the reconstruction mesh, all reconstructions used this single mesh (extending down to 4.3 mm) for consistency and because slice thickness was not measured.

Only absolute reconstructions were produced in this study, and reconstructions using 1 and 3 steps (iterations) were considered. One would expect that more iterations would provide more accurate reconstructions. However, there is an additional computational cost of using multiple iterations. Thus the EIT results are evaluated in terms of their quality and computational cost.

2.4. Data Analysis

Benign tissues (Group 1) were compared to cancerous tissues (Groups 2-5) by identifying significant differences and the predictive properties of the impedance features individually and jointly using an SVM. Details of these group comparisons are given in Table 2. The predictive measures are the AUC, sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACCU). The optimal threshold was calculated as the closest point on the ROC curve to (0, 1), i.e. the closest point to 100% sensitivity and 100% specificity.

2.4.1. Features—In this study, EIS, constant EIT, and 3D EIT features are explored. Their descriptions are summarized in Table 3 and the feature characteristics are described here.

EIS features include the 11 resistances (R), 11 reactances (X), 11 magnitudes ($\sqrt{R^2 + X^2}$), and 11 phases ($\tan^{-1}(X/R)$) of an inner or outer ring impedance pattern corresponding to the

11 frequencies. Samples were considered to be each of the inner or outer patterns (8), standard and reciprocal patterns (2), and all intraprostatic tissue sites (135). Thus the overall size of the EIS feature set for inner and outer patterns was $2160 \text{ samples} \times 44 \text{ features}$, where $2160 = 8 \cdot 2 \cdot 135$ and $44 = 11 \cdot 4$. The 16 patterns (with reciprocals) were separated into different samples because they represent (physically) different measurements of the prostate tissue and it provided a means to increase the number of samples.

Constant EIT features included the reconstructed conductivity and permittivity values (2) using either inner, outer, or all tetrapolar patterns (3) at the 11 discrete frequencies. 3D EIT features included the average reconstructed conductivity and permittivity values (2) using all the tetrapolar measurements at each of the 8 depths, plus an overall average, at each of the 11 frequencies. The overall feature set size was 135×66 and 135×198 , where $66 = 2 \cdot 3 \cdot 11$ and $198 = 2 \cdot (8+1) \cdot 11$ for the constant and 3D EIT features, respectively. Samples for the EIT reconstructions corresponded 1-to-1 with the probe sites, as one could not separate reconstructions like the EIS measurements recorded for each pattern.

2.4.1.1. Discrete Feature Analysis: For each group comparison, significance tests were performed between each group and for each feature the predictive scores were calculated. A two-sample t-test was used to determine significance with a p value of 0.05. A total of 44, 66, and 198 ROC analyses were performed and all performance metrics including AUC, ACCU, SN, SP, PPV, and NPV are computed for the EIS, constant EIT, and 3D EIT feature sets, respectively.

2.4.1.2 Multi-Feature Evaluation: SVM: A binary SVM classifier is used for the group comparisons presented in Table 2. Functions from the Statistics and Machine Learning Toolbox in MATLAB r2016b are used to implement, train, and test the SVM classifier. For every comparison, we train a SVM model using a leave-one-patient-out (LOPO) approach and a Gaussian kernel function. The LOPO approach is used to ensure that the training is fair, i.e. if data is very consistent on individual patients then this advantage is removed using this training approach. After numerous manual searches for optimal parameters, the kernel scale was set to 5 and the box constraint was set to 1. For the comparisons, the SVM is trained by selecting a randomized subset of Bn datasets equaling the total number of PCa datasets to limit any potential training model biases due to imbalanced datasets (Kotsiantis et al 2006). This process is repeated 200 times to minimize effects of variability in results due to randomized datasets. The SVM model outputs predicted labels (classification result) and posterior probabilities (probability that the classifier is correct, (Platt 1999)) from all the random draws; these are used to create ROC curves for each run. An average AUC is calculated across all runs.

An iterative feature extraction algorithm is used to select the optimal subset of features that maximizes the AUC. First, the features that yielded significant differences are sorted in descending order of AUCs from the discrete feature analysis. Next, the SVM classification algorithm is performed using the best feature. Each subsequent feature is tested one at a time where each candidate feature is retained into the optimal set of features if it improves the overall AUC of the SVM. If the AUC of the SVM algorithm decreases then that feature is disregarded. This feature extraction processes iteratively and in a greedy fashion selects the

best feature sets that maximizes the AUC of the SVM algorithm. We report results on the final best feature set for each of the group comparisons and approaches.

3. Results

3.1 Discrete Feature Analysis

Discrete features analyzed include the inner and outer pattern EIS data, constant EIT using 1 and 3 iterations, and 3D EIT using 1 and 3 iterations. As an example, figure 4 shows the outer ring EIS measurements and outer ring constant EIT data using 3 iterations. The data is separated between groups, and an asterisk (*) denotes when there are significant differences between groups. The boxes represent 25-75% quantiles, the whiskers extend from the minimum to the maximum data points, black dots show all points outside the quantiles, and the red line represents the median of the data. The longer whiskers indicate that there are some apparent outliers, although these data points were not determined to be bad in terms of measurement quality. The impedance and conductivity/permittivity appear related and follow expected trends across frequencies. It is expected that if impedances for cancerous tissues are higher than benign tissues, the conductivities of cancerous tissues would be lower than benign tissues. A similar relationship is observed between the absolute value of the reactance and permittivity. In general, these trends hold as shown in figure 4a and 4c. No perfect separation exists between any two groups. However, the boxes, representing 25%–75% quantiles, are distinctly separate between G1 and G5 for the three lowest frequencies for the EIS resistance and the constant EIT conductivity and permittivity.

ROC analyses were performed using only features that exhibit significant differences for all four group comparisons. The AUCs for these significantly different features for all EIS and EIT methods are reported in figure 5. The majority of the G1 vs. G5 comparison features were significantly different, and yielded the highest AUCs (majority between 0.70-0.85 AUC) among any other group comparisons. This is because G5 (100% PCa) has the highest presence of PCa among any groups, and therefore provides the largest distinction from G1 (Bn) data. The best AUC for the G1 vs. G5 comparison was 0.85, which corresponds to permittivity using 3D EIT at a frequency of 90 kHz and depth of 0.5 mm.

On the contrary, only 3 features for outer ring EIS, and 1 feature for inner ring EIS were significantly different for G1 vs. G2 and none for any of the EIT based methods. Among the few features that were significantly different, the AUCs were relatively low (close to 0.6). The G2 (<18%) PCa has the least amount of PCa among any PCa groups which we expect to be the most challenging to distinguish from benign prostate. Further, the significant feature differences and AUC performances for the other two comparisons (G1 vs. G3) and (G1 vs. G4) were better than G1 vs. G2, but worse than G1 vs. G5. Formal comparison between G1 and G2 was omitted due to lack of significantly different features and minimal separation in terms of impedance (figure 4).

The features with best AUCs for each of the methods (EIS: outer, EIS: inner, constant EIT, and 3D EIT) are plotted in figure 6 and their predictive properties specified in Table 4. The AUCs for EIS outer and EIS inner are less than AUCs for constant EIT and 3D EIT in all three comparisons (G1 vs. G3; G1 vs. G4; G1 vs. G5). This implies that a discrete feature

group for EIT is better able to separate Bn from various groupings of PCa than EIS. A striking observation is the very poor positive predictive value (PPV ~0.21-0.45) for all features and group comparisons. This can be primarily attributed to the imbalance between benign and cancer samples. That is, when there are many more cancer cases than benign, the optimal choice from the ROC analysis is insensitive to the large percent of false positives.

The AUC for inner ring EIS is better than outer ring by 9% for G1 vs. G5 comparison, although both are relatively low at 0.76 and 0.67, respectively. However, the outer ring AUC is better than inner ring by 5% and 3% for G1 vs. G4 and G1 vs. G3, respectively, but the overall AUC performance remain in the mid-60s. Due to the low AUC performance metrics for EIS based analysis, nothing significant can be concluded from the trends between the inner and outer rings at various groupings. In general, the AUCs are better for EIT results.

For the EIT results, the 1-step constant EIT is nearly the same as the 3-step constant EIT reconstructions, but the 1-step 3D reconstructions are consistently worse than the 3-step 3D reconstructions. Specifically, for the G1 vs. G5 comparison, the constant EIT AUCs are identical for 1 step and 3 step estimations for both conductivity and permittivity (i.e. AUCs = 0.80 and 0.82, respectively). For 3D EIT reconstructions, the 3-step permittivity estimation is enhanced 5% to 0.85 as compared to same reconstruction using a single step. These trends generally persist for G1 vs. G3 and G1 vs. G4, although they are not as prominent as that observed for G1 vs. G5.

3.2 Multi-Feature Evaluation

A ROC analysis was performed for an optimal subset of features selected using the greedy, iterative feature extraction algorithm and the SVM binary classification. This analysis uses multi-feature information and can combine useful information from many distinct frequencies. As expected, the AUCs of separation for all comparison are higher than when only using 1 best discrete feature as presented in Section 3.1. The ROCs for EIS outer, EIS inner, constant EIT and 3D EIT are presented in figure 7 and Table 5.

Although the AUCs for EIT performed better when only 1 best feature set was used compared to EIS, it can be observed that when using a multi-frequency SVM approach, the AUCs for both EIS and EIT based techniques are similar. In fact, the AUC for G1 vs. G3 and for G1 vs. G4 is higher for both inner and outer EIS methods compared to any corresponding EIT methods. The AUC for G1 vs. G5 using EIS methods is also only 1-2% less than AUCs obtained from EIT based methods. Overall, it seems that when using a multi-feature based SVM approach, the EIS based technique has better performance - in terms of AUC - in separating Bn (G1) from presence of PCa > 18% (G3) and PCa > 0% (G4); however EIT has better performance in separating Bn (G1) from presence of 100% PCa (G5). The predictive accuracy of EIT is consistently higher than EIS by 2-3% as well.

3.3 Computational Cost of EIT Reconstructions & SVM Analysis

The computational steps ultimately required for surgical margin assessment include: 1) data acquisition from the EIA system, 2) data extraction, 3) EIT inverse solution (if applicable), and 4) evaluation of trained SVM models. Data extraction and evaluating a trained SVM model requires negligible computational time (after being optimized) (<< 1 second). The

current data acquisition time required to sample an exhaustive pattern set from the 17-electrode probe and the Dartmouth EIA system (Khan *et al* 2015) using 32 averages and a 10 kHz frequency is 1.1 seconds and the total time required to sample all 11 discrete frequencies from 5-100 kHz is 6.99 seconds. The computational times for the constant and 3D EIT reconstructions assuming 1 and 3 iterations are shown in Table 6. These times are reported for a computer with a 2.7 GHz Intel CPU with 16 cores and 94 GB of RAM. The constant EIT with 1 iteration has an essentially negligible computational cost ($\ll 1$ second). The 3D EIT technique with 1 iteration for 1 frequency is 2.9 seconds. If EIT reconstruction at multiple frequencies are necessary, the computation time can be parallelized using multiple cores so the overall time would not be affected. The time required to compute a 3-iteration, single discrete frequency reconstruction for both constant and 3D EIT are significant at ~1.3 and 12.3 minutes, respectively. At present, these times are too costly for multi-iteration EIT to be used clinically. However, the multi-iteration 3D EIT can be significantly improved. For instance, if we pre-compute certain data/matrices, use the GPU Jacobian implementation (50 $\times$ speedup) from (Borsic *et al* 2012), and omit a parabolic-line search step, then given our present mesh and inverse approach we expect a 3-step reconstruction to take approximately 24.8 seconds – which is ~48 $\times$ faster than IFS-based assessment (25 sec vs. 1200 sec) and approaches a clinically acceptable time. Regardless, the results from this study do not, at present, imply that additional gains would be provided by performing multiple EIT iterations.

4. Discussion

This study reports the predictive ability of EIS and EIT to distinguish cancerous from benign prostate tissue. The SVM applied to both EIS and EIT data has similar results that illustrate the promise of this technology especially in differentiating between benign and 100% cancerous measurements.

Limitations of the Dataset

While these findings are encouraging, the dataset was small with 3.5 $\times$ to 8.8 $\times$ as many benign cases as cancerous cases (Table 2). One might naturally be concerned with the accuracy of the SVM training and testing given such a small database. To partially mitigate this, we have used best practices (e.g. repeated sampling of the benign dataset to train on balanced datasets) and have used leave-one-patient-out training to ensure fair data modeling. One can see the effect of balancing the datasets by comparing the NPV and PPV values from the discrete feature (imbalanced – Table 4) and multi-feature SVM results (balanced – Table 5). That is, the optimal point in the imbalanced sets appear to perform much better in correctly identifying benign cases (NPV ~0.9+) and poorly for cancerous cases (PPV ~0.3), and when the dataset is balanced we see a more realistic/representative results of the data (PPV and NPV ~0.7-0.8).

An additional limitation of the study is that all measurements were recorded from ex vivo tissue samples at room temperature. While in vivo tissues probed at normal body temperatures will be different in an absolute sense from the ex vivo tissues probed here

(Haemmerich *et al* 2002), we expect the relationships between the different tissue types (i.e. cancer and benign prostate) to be similar.

EIT versus EIS

It is compelling to use the EIS data based on its simplicity, but there are two practical reasons that (constant, 1-iteration) EIT may be the preferred method/feature type. First, the conductivity and permittivity reconstructed from EIT are intrinsic properties of the tissue as opposed to probe specific resistance and reactance measurements. Thus the EIT reconstructions can be more easily compared to other studies, e.g. (Halter *et al* 2008b, 2009). As an example, we compare the discrete conductivity at 10 kHz and 100 kHz described here to results from (Halter *et al* 2009) in figure 8. The benign and stroma conductivity are consistently larger than cancerous tissue and the general trend of conductivity values are very similar across the two studies. Although the permittivity results provided very good predictive results, we omit this comparison as there is less consistency compared to other studies (Halter *et al* 2008b, 2009) in terms of the benign to cancer relationship and the permittivity magnitudes. We believe this lack of consistency may be due to resistive-only-load calibration and/or phase changes caused by capacitive coupling through the long, tightly-spaced wires of the probe. The second reason EIT may be preferred is that the 17-electrode probe can produce many measurements (14,280), while the EIS features rely only on the few geometrically identical measurements (16 measurements on the outer or inner ring). Admittedly, one could consider additional non-geometrically identical EIS measurements to produce a more robust EIS/SVM-approach; however, that would likely require a more complex feature selection algorithm and/or SVM model and has not been explored here. Despite these benefits, given the similar results of EIS and EIT and the small sample size, we cannot definitively conclude the best approach. While not explored here, one might also consider combining the EIS and EIT data together to form a more complex classification model. The benefit of this approach might be that the resistance and reactance data associated with EIS can be used to describe different tissue characteristics than the conductivity and permittivity parameters estimated in EIT (Martinsen and Grimnes 2011).

Single-Step versus Multi-Step EIT

In the presented results the single-step EIT reconstructions appear essentially as good as the multi-step EIT reconstructions. This suggests that the single-step EIT reconstructions are the preferred approach as it yields clinically feasible computational times and does not significantly reduce the quality. However, it is surprising that multiple iterations do not improve the results. This implies that the model cannot better fit the data through multiple iterations. We believe this is either an indication of the limits of the approach based on the frequency-dependent SNR of the probe and system or due to practical issues of the data collection process. First, if the noise in the data is too high, then this could clearly limit the ability to discriminate finer detail that multiple iterations could uncover. Second, during the data collection process there was variability in probe pressure applied and in the prostate slice thickness (2-5 mm). Pressure has been found to potentially produce significant differences in impedance measurements (González-Correa *et al* 2005), and simulations have revealed that impedance measurements can be significantly affected if the prostate slices are thinner than average (2-3 mm). If these factors are significant enough, then they may be

removing the potential improvements the multi-step EIT results can yield. Although it was not possible to remove these confounding effects, the positive findings reported here indicate the potential robustness of the EIS/EIT data to practical issues that can arise in data collection.

Technology Promise and Comparison

A study that combined laser-induced autofluorescence, white-light remission, and high-frequency impedance spectroscopic measurements reported a highly accurate ability to identify benign and malignant prostate tissue *ex vivo* (Salomon *et al* 2009). Ninety-five tissue samples from 32 patients were stored in liquid nitrogen immediately following a prostatectomy procedure and were later thawed for their experimentation. The statistical analysis of their combined technique demonstrated a differentiation of benign and malignant prostate tissue with a sensitivity of 87.5% and a specificity of 87.3%, and by adding the acquired high frequency impedance data to the statistical analysis, sensitivity and specificity were increased to 93.8% and 92.4%, respectively. Despite the promising results in an *ex-vivo* setting, this technology has not been investigated in an *in vivo* setting and many limitations for clinical translation persist, such as – 1) statistical analysis of spectral data was not performed in blinded fashion; 2) it is well established that the freezing then thawing process will significantly impact tissue impedance (Yu *et al* 2004); 3) a limited cancer set was explored (n=16), 4) the pathway for miniaturization of the instrument for use in RALP remains unclear.

Another technology currently being explored for intraoperative pathological characterization of tissue for surgical margin assessment is the intelligent knife (iKnife). The iKnife uses mass spectrometry to evaluate the plume of smoke emitted as an electrosurgical knife dissects tissue. The plume contains sufficient biological material, enabling the device to discriminate between cancer and benign tissues (Balog *et al* 2013). Many studies have reported the promise of using iKnife and suggest a possibility for potential clinical translation in organs such as stomach, colon, liver, lung, breast, brain (Takats *et al* 2012, Schäfer *et al* 2009, Balog and Takats 2010, Balog *et al* 2013); however, no study has been conducted for prostate. Despite promising results of iKnife in these organ systems, there is a lack of suitability in RALP procedures for several reasons: 1) much of the RALP procedure involves separating the functioning tissue (e.g. nerve, muscle, blood vessels) from the prostate instead of cutting through these structures. These critical structures should not be damaged during the procedure so electrosurgical approaches are not typically recommended near this anatomy; 2) a RALP procedure usually includes carbon dioxide (CO₂) insufflation of the abdominal cavity and the potential interaction effects of CO₂ in context of RALP procedure with other gases used during iKnife mass spectrometry have not been studied; 3) the current dimension and design of iKnife is not compatible to fit within a laparoscopic da Vinci surgical port.

In comparison to our prior study (Khan *et al* 2016), the clinical parameters are quite similar, but here we have significantly improved registration between impedance measurements, yielding a more nuanced analysis on accuracy as a function of percent cancer. Overall, the results presented in this paper corroborate our previous studies and present the strongest

evidence yet that an intraoperative-capable impedance probe can be used to distinguish benign from malignant prostate tissues.

5. Conclusion

This study has compared EIS and EIT measurements in discrete- and multi-feature approaches on a set of ex-vivo prostate tissue data. We have found that multi-feature based SVM classification is the preferred approach to distinguish Bn from PCa, which provides significant improvement compared to the best discrete features (up to 16% improvement). Further, the EIS based technique has better performance - in terms of AUC - in separating Bn (G1) from either PCa > 18% (G3) or PCa > 0% (G4); however, EIT has better performance in separating Bn (G1) from presence of 100% PCa (G5) and EIT is at least 2% better in terms of ACCU over all group comparisons. An in-vivo study with a large cohort will be necessary to definitively determine the preferred approach and to show the clinical effectiveness of the best-technique for margin assessment.

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Figure 1.

A) 17-electrode probe showing connector interface to the electrical impedance data acquisition system, B) The probe surface, and C) Dartmouth EIA system.

Figure 2.

The 17-electrode probe face showing A) top view of contact surface, B) electrode numbering scheme, and C) the inside ring (green) and outside ring (red) of electrodes used for EIS analysis (modified from (Mahara *et al* 2015)).

Figure 3.

Ex vivo data acquisition and labeling procedure. a) An example of a probed measurement, b) 3 pins used to localize the probed location, c) & d) micrograph (L) and (R) examples showing pin locations in red, e) cancer islands enclosed in black, and f) image processing of the probed location is used to determine the percent cancer of the measurement (modified from (Mahara *et al* 2015)).

Figure 4.

Outer ring EIS impedance (a-b) and constant EIT conductivity and permittivity data corresponding to all 5 groups and all 11 frequencies. EIS is visualized in terms of the average impedance of the 8 standard patterns from each probe site. The boxes represent 25-75% quantiles, the whiskers extend to the minimum and maximum data point, black dots show all points outside the quantiles, the red line represents the median of the data, and the asterisks (*) denote when there is a significant difference ($p < 0.05$) between the given group and G1.

Figure 5.

AUC values calculated from performing ROC analysis on features that yielded significant differences from G1 for each of the EIS and EIT methods considered (EIT methods used 3 steps). All frequencies are plotted for each method.

Figure 6. ROC curves of the features with the highest AUCs for the EIS: outer, EIS: inner, constant EIT (3-step), and 3D EIT (3-step). The feature details along with predictive metrics are listed in Table 4.

Figure 7.
ROC curves of the best multi-feature SVM results for the EIS: outer, EIS: inner, constant EIT, and 3D EIT.

Figure 8.

Comparison between the conductivity results using all the methods from the present study (narrow vertical boxes) to the results from (Halter *et al* 2009) (wide horizontal boxes). The boxes represent 25-75% quantiles (both studies), the whiskers extend to the minimum and maximum data point, black dots show all points outside the quantiles, the black horizontal line represents the median of the data (both studies), and the asterisks (*) denote when there is a significant difference ($p < 0.05$) between the benign and cancerous tissue. Results from (Halter *et al* 2009) are significantly different ($p < 0.05$) at both frequencies.

Table 1

Grouping of Ex-Vivo Data

Groups	% Cancer	Cases
1	0%	105
2	1–18%	7
3	19–100%	23
4	1–100%	30
5	100%	12
Total	0–100%	135

Table 2

Benign (Bn) to Cancer (PCa) Comparisons

Group Comparison	% Cancer Type		Tissue Sites		Ratio (Bn to PCa)
	Bn	PCa	Bn	Ca	
1 vs. 2	0%	1–18%	105	7	15.0
1 vs. 3	0%	19–100%	105	23	4.6
1 vs. 4	0%	1–100%	105	30	3.5
1 vs. 5	0%	100%	105	12	8.8

Table 3

Description of Features

Type	Total Set Size (samples $\times$ features)	Sample Description	Feature Description
EIS (inner or outer)	2160 $\times$ 44	From each probe site the 8 patterns, standard or reciprocal	Resistance, reactance, magnitude and phase at each frequency (11)
Constant EIT	135 $\times$ 66	Each probe site	Conductivity and permittivity values using inner, outer, and all patterns at each frequency (11)
3D EIT	135 $\times$ 198	Each probe site	Conductivity and permittivity values using all patterns at each depth and an overall average (9) at each frequency (11)

Table 4

Prediction metrics for the best discrete features: sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), accuracy (ACCU), and area-under-curve (AUC).

Comp.	Method	Freq. (kHz)	Type/Depth	SENS	SPEC	PPV	NPV	ACCU	AUC
G1 vs. G3	EIS: Outer	20	Resistance	0.56	0.73	0.32	0.88	0.70	0.67
	EIS: Inner	40	Magnitude	0.60	0.62	0.27	0.88	0.62	0.64
	Cons. EIT: Cond., 1-step	40	Outer	0.58	0.81	0.39	0.90	0.77	0.72
	Cons. EIT: Perm., 1-step	40	Outer	0.71	0.66	0.31	0.92	0.67	0.74
	Cons. EIT: Cond., 3-step	40	Outer	0.58	0.78	0.37	0.90	0.75	0.71
	Cons. EIT: Perm., 3-step	40	Outer	0.67	0.71	0.33	0.91	0.70	0.73
	3D EIT: Conductivity, 1-step	40	1.5 mm	0.76	0.66	0.33	0.93	0.68	0.71
	3D EIT: Permittivity, 1-step	10	1.5 mm	0.65	0.79	0.41	0.91	0.77	0.76
	3D EIT: Conductivity, 3-step	90	3.2 mm	0.69	0.74	0.31	0.93	0.74	0.74
	3D EIT: Permittivity, 3-step	5	2.2 mm	0.68	0.82	0.44	0.92	0.79	0.77
G1 vs. G4	EIS: Outer	20	Resistance	0.56	0.73	0.32	0.88	0.70	0.67
	EIS: Inner	30	Reactance	0.66	0.51	0.27	0.84	0.54	0.62
	Cons. EIT: Cond., 1-step	30	Outer	0.73	0.64	0.37	0.89	0.66	0.73
	Cons. EIT: Perm., 1-step	30	Outer	1.00	0.53	0.38	1.00	0.63	0.70
	Cons. EIT: Cond., 3-step	30	Outer	0.80	0.58	0.35	0.91	0.63	0.72
	Cons. EIT: Perm., 3-step	30	Outer	0.87	0.60	0.38	0.94	0.66	0.72
	3D EIT: Conductivity, 1-step	30	3.2 mm	0.64	0.64	0.31	0.87	0.64	0.68
	3D EIT: Permittivity, 1-step	10	1.5 mm	0.60	0.79	0.45	0.87	0.75	0.71
	3D EIT: Conductivity, 3-step	30	3.2 mm	0.64	0.64	0.31	0.87	0.64	0.68
	3D EIT: Permittivity, 3-step	90	0.5 mm	0.78	0.66	0.36	0.93	0.68	0.74
G1 vs. G5	EIS: Outer	40	Magnitude	0.56	0.73	0.32	0.88	0.70	0.67
	EIS: Inner	40	Resistance	0.75	0.65	0.21	0.96	0.66	0.76

Comp.	Method	Freq. (kHz)	Type/Depth	SENS	SPEC	PPV	NPV	ACCU	AUC
	Cons. EIT: Cond., 1-step	10	Outer	0.83	0.81	0.34	0.98	0.81	0.80
	Cons. EIT: Perm., 1-step	10	Outer	0.83	0.75	0.29	0.97	0.76	0.82
	Cons. EIT: Cond., 3-step	40	Outer	0.82	0.78	0.30	0.97	0.79	0.80
	Cons. EIT: Perm., 3-step	40	Outer	0.83	0.76	0.29	0.97	0.77	0.82
	3D EIT: Conductivity, 1-step	90	0.5 mm	0.78	0.81	0.28	0.97	0.81	0.79
	3D EIT: Permittivity, 1-step	5	All depths	0.67	0.87	0.38	0.96	0.85	0.80
	3D EIT: Conductivity, 3-step	40	All depths	0.73	0.82	0.32	0.96	0.81	0.79
	3D EIT: Permittivity, 3-step	90	0.5 mm	0.89	0.80	0.30	0.99	0.81	0.85

Table 5

Prediction Metrics for the multi-feature SVMs: sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), accuracy (ACCU), and area-under-curve (AUC).

Comp.	Method	No. Features	SENS	SPEC	PPV	NPV	ACCU	AUC
G1 vs. G3	EIS: Outer	20	0.75	0.73	0.73	0.74	0.74	0.83
	EIS: Inner	15	0.74	0.73	0.73	0.74	0.74	0.82
	Constant EIT, 1-step	6	0.84	0.70	0.74	0.82	0.77	0.80
	3D EIT, 1-step	12	0.84	0.70	0.74	0.82	0.77	0.80
	Constant EIT, 3-step	6	0.84	0.70	0.74	0.81	0.77	0.80
	3D EIT, 3-step	8	0.83	0.71	0.74	0.81	0.77	0.80
	EIS: Outer	20	0.73	0.70	0.71	0.72	0.71	0.80
	EIS: Inner	19	0.72	0.71	0.71	0.71	0.71	0.80
	Constant EIT, 1-step	1	0.74	0.73	0.73	0.73	0.73	0.78
	3D EIT, 1-step	12	0.70	0.77	0.76	0.72	0.74	0.79
G1 vs. G4	Constant EIT, 3-step	1	0.71	0.75	0.74	0.72	0.73	0.79
	3D EIT, 3-step	4	0.82	0.66	0.71	0.79	0.74	0.77
	EIS: Outer	18	0.81	0.73	0.75	0.80	0.77	0.84
	EIS: Inner	15	0.81	0.72	0.74	0.79	0.76	0.83
	Constant EIT, 1-step	6	0.73	0.90	0.88	0.77	0.81	0.85
	3D EIT, 1-step	6	0.72	0.88	0.86	0.76	0.80	0.84
	Constant EIT, 3-step	5	0.72	0.91	0.88	0.76	0.81	0.85
	3D EIT, 3-step	4	0.72	0.89	0.87	0.76	0.81	0.84
	EIS: Outer	18	0.81	0.73	0.75	0.80	0.77	0.84
	EIS: Inner	15	0.81	0.72	0.74	0.79	0.76	0.83
G1 vs. G5	Constant EIT, 1-step	6	0.73	0.90	0.88	0.77	0.81	0.85
	3D EIT, 1-step	6	0.72	0.88	0.86	0.76	0.80	0.84
	Constant EIT, 3-step	5	0.72	0.91	0.88	0.76	0.81	0.85
	3D EIT, 3-step	4	0.72	0.89	0.87	0.76	0.81	0.84
	EIS: Outer	18	0.81	0.73	0.75	0.80	0.77	0.84
	EIS: Inner	15	0.81	0.72	0.74	0.79	0.76	0.83
	Constant EIT, 1-step	6	0.73	0.90	0.88	0.77	0.81	0.85
	3D EIT, 1-step	6	0.72	0.88	0.86	0.76	0.80	0.84
	Constant EIT, 3-step	5	0.72	0.91	0.88	0.76	0.81	0.85
	3D EIT, 3-step	4	0.72	0.89	0.87	0.76	0.81	0.84

Table 6

Computation Time for EIT methods

Method	Iterations	Time one frequency (sec)
Constant EIT	1	8e-4
3D EIT	1	2.9
Constant EIT	3	79.0
3D EIT	3	737.3 (12.3 min)