A Patient-specific Irreversible Electroporation Treatment Planning Model Based on Human Tissue Properties

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Academic Abstract: Irreversible electroporation (IRE) is a focal ablation technique that has been shown in recent clinical trials to be effective in treating pancreatic cancer. The technique uses short, high voltage pulses to induce nanoscale pores in the target cell membranes, leading to cell death. Due to its non-thermal mechanism, IRE is particularly well suited for treating a tumor that is unresectable due to its close location to crucial structures such as blood vessels and nerves. Predicting the region of treatment is critical for optimal treatment of the tumor. The only predictive tools clinicians currently rely on for IRE treatment planning are computer tomography (CT), ultrasound (US) imaging, and real-time resistance measurement is used to monitor treatment progress. However, there is currently no method to plan optimal pulse parameters such as voltage, pulse duration, pulse number, and electrode spacing prior to treatment. Computational treatment planning models aim to perform this prediction in 3D, however, the electric field region relies on the electrical response of human tissue during IRE. This work quantifies this response for the first time and implements human tissue properties in a patient-specific, 3D treatment planning model.

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**General Audience Abstract:** Pancreatic cancer results in 40,000 deaths every year in the U.S, making it one of the most challenging diseases to treat. The current treatments for this disease fall short and have failed to significantly extend patient life expectancy. A technique called irreversible electroporation (IRE) has been shown in recent clinical trials to be effective in treating pancreatic cancer. IRE excels at treating tumors that are located near important blood vessels, nerves, and other important structures. However, clinicians do not have a way to visualize the region of treatment before surgery. In the research setting, 3D computational models aim to predict this area, but so far these models have been based on animal tissue, often of the incorrect organ type. This work applies IRE to human tissue samples, quantifies its electrical behavior, and implements that information in a personalized, predictive 3D model.
Dedication

This work is dedicated to the memory of my dad, Gregg Beitel, who motivated me at an early age to get my hands dirty in the garage and on the benchtop, which ultimately led me to pursue an engineering career. The attention to detail and excitement he had for engineering will impact me for the rest of my life.
Acknowledgments

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Chapter 1

Introduction

Pancreatic cancer is a particularly deadly malignancy that results in 40,000 deaths every year in the U.S. [2]. One major challenge in the treatment of pancreatic cancer is that diagnoses often occur in late stages of the disease, when the tumor has already metastasized. Little to no side effects are present up to this point, making the disease difficult to detect in its early stages. Because of its location within the body, the pancreas is surrounded by critical vasculature, making tumors unresectable in many cases [3]. Current treatments such as chemotherapy and resection have had little efficacy on patient survival, therefore new treatment methods are needed. Additionally, cutting edge immunotherapies are having little effect on overall patient survival due to the immunosuppressive environment surrounding pancreatic tumors [4]. Focal ablation techniques such as radio frequency (RF) and microwave ablation have shown promise in treating pancreatic cancer, but induce damage to critical structures due to their thermal mechanism of cell death [5]. Another focal ablation therapy
known as irreversible electroporation (IRE) uses high voltage pulses to treat tumors. IRE is a minimally invasive cancer therapy that has been shown to be an effective treatment of kidney, pancreatic, and liver tumors \cite{3,6,7}. During the procedure, two or more needle electrodes are inserted directly into a target area and used to deliver short, high voltage pulses. These pulses are purported to create small pores (Fig. 1.1) within the cell membranes, termed electroporation (EP). If the voltage is above a certain threshold, the cell is irreversibly electroporated and dies \cite{6}. The therapy has demonstrated efficacy especially in tumors which are difficult to resect due to being located close to surrounding critical structures such as nerves, major arteries and blood vessels \cite{3}. In a recent clinical trial, IRE was shown to extend the median survival of pancreatic cancer patients from 6-13 months to 24.9 months \cite{3}. In contrast with other ablation techniques such as microwave and radio frequency ablation, IRE takes advantage of a non-thermal mechanism in order to induce cell death in a target region \cite{8}.

The region of cell death depends directly on IRE parameters such as the voltage, electrode...
spacing, and properties of the target tissue. Taking these parameters into account is essential for clinicians to avoid under- and over-treatment of the tumor, which could result in recurrence or unnecessary damage to healthy tissue (Fig. 2.1). This work presents the first predictive IRE model based on the dynamic electrical behavior of human pancreatic tissue, and reports the changes in properties of human liver and pancreatic tissue for use in pre-treatment planning models.
Chapter 2

Background

2.1 Electroporation

Electroporation was first observed in the 1950s, and has since been utilized in two major regimes: reversible and irreversible. When the voltage applied to a cell is below a certain threshold, nanoscale pores form on the membrane which subsequently reseal. Techniques involving gene or molecular transfer take advantage of this reversible electroporation regime to deliver molecules into the cell through the pores. In the early 2000s, Davalos et al. proposed the use of voltages above this reversible threshold in order to purposefully induce cell death in a targeted manner [9]. Subsequent studies evaluated irreversible electroporation effects in vitro [10,11] as well as in vivo [6,12,13].

Clinicians aiming to optimize IRE treatments currently rely only on pre-operative CT and
ultrasound imaging for treatment planning [14]. Clinicians also monitor real-time resistance feedback from the IRE instrument to gauge treatment progress [15]. Despite these techniques, clinicians still need a method to visualize the region of ablation prior to treatment, especially within a complicated anatomical geometry, as is the case especially in pancreatic tumors [16]. One method of visualization is numerical treatment planning models, which have been developed in the research setting. A vital component of these models is the definition of electrical and thermal properties of the tissue. Until now, these preliminary models have relied on animal tissue properties [1, 14]. Additionally, a different organ type than the target tissue is used. However, tissue properties have been shown to differ between organs as well as species [17, 18]. In the case of human tissue, samples are especially hard to obtain, particularly regarding tumor tissue. Gabriel et al. have explored electrical properties of tissue extensively, yet the work did not focus particularly on lower frequency effects as is expected with IRE. Because of the duration of the pulse (approximately 100
\( \mu s \), the waveform is approximated as direct current (DC). Another problem is that IRE induces dynamic changes in the tissue conductivity; as electroporation occurs, more current paths form through the cell membranes, leading to higher conductivity. This change follows a non-linear, sigmoidal relationship [19].

2.2 Quantifying Change in Conductivity due to Electroporation

Due to the complex three-dimensional geometry of IRE procedures and the inhomogeneity of tissue, these dynamic properties are difficult to calculate from real-time current \textit{in vivo}. One method of determining the dynamic conductivity induced by electroporation is by performing a parametric sweep on a function to best fit experimental data [19,20]. A model is constructed in a finite element software package, then the parameters of the model are fit to measured current. Another method of measuring the dynamic conductivity of tissue \textit{ex vivo} is to apply electric fields using a parallel plate configuration, which induces a macroscopically homogeneous field distribution [21]. When applying a known voltage, the resulting current can be used to calculate conductivity from equation (2.1).

\[
R = \frac{l}{\sigma A}
\]  

(2.1)

In this equation, \( R \) is the resistance which is calculated from the measured current and
applied IRE voltage, \( l \) is the length or distance between the flat plate electrodes, and \( A \) is the cross sectional area of the cylindrical sample. A pre-pulse with a voltage well below the threshold for reversible electroporation can be delivered to the tissue to determine initial conductivity for each sample [19].

The electrical conductivity of biological tissue varies non-linearly with electric field strength, and follows a sigmoidal relationship. Prior studies have shown that the tissue conductivity versus electric field behavior can be approximated with the function given by (2.2). A symmetric sigmoid function was used because of the simple relation of the fitted parameters to the reversible and irreversible thresholds [19]. This further informs models by providing estimated electric field magnitudes for these thresholds. Additionally, the function fit the data more accurately than a modified Gompertz function.

\[
\sigma(E) = \sigma_0 + \frac{\sigma_1 - \sigma_0}{1 + De^{E/A}} \tag{2.2}
\]

### 2.3 Modelling Tissue as an Electrical Circuit

Biological tissue can be modeled as an electrical circuit (Fig. 2.2), with various discrete components representing physical properties of the cells that make up the tissue. The Cole-Cole model consisting of discrete resistances and capacitances is often used to represent tissue [22].

Together, these components form a model of electrical current through a cell. In the case
of electroporation, this network is dynamic, and the change in electrical properties within the tissue are reflected in changing component values. The lipid bilayer membrane behaves electrically similarly to a discrete capacitor. When the frequency of an applied voltage signal approaches zero, this capacitance becomes an open circuit, leaving the extracellular resistance as the dominant circuit element. This parameter reflects the DC resistance of the tissue. After the application of IRE, new current paths are formed in the cellular membrane, which decreases the overall DC resistance. With increasing voltage magnitude, this electroporation resistance $R_p$ also decreases. We hypothesize that various types of tissue are expected to have differing reactions to electroporation due to physiological differences such as water and bile content, cell structure, and density.
2.4 Change in conductivity due to temperature

Studies indicate that electroporation occurs within the first few microseconds of an applied pulse above the electroporation threshold [23]. The resulting change in conductivity is therefore due solely to the generation of extracellular current paths. If multiple pulses are applied, any subsequent increases in conductivity are due to the increase in temperature caused by Joule heating in the tissue 2.3. The temperature-dependent conductivity $\sigma(T)$ is related to the conductivity at the onset of IRE pulsing ($\sigma_0$), the temperature coefficient $\alpha$ [S/m*°C], and the change in temperature in °C.

$$\sigma(T) = \sigma_0 \times [1 + \alpha(T - T_0)]$$  \hspace{1cm} (2.3)

By determining the initial conductivity prior to electroporation, the change in conductivity due to electroporation, and the final conductivity after the application of IRE, the thermal effects on tissue conductivity can be calculated.
Chapter 3

Methods

3.1 Sample Preparation

Freshly resected pancreatic and liver tissue biopsies were obtained with Institutional Review Board (IRB) approval from ten de-identified patients in collaboration with the University of Louisville Department of Surgical Oncology (Fig. 3.1). The amount of tissue acquired varied from patient to patient, as well as the tissue type (tumor versus normal). The size of the biopsy allowed for approximately two or three cylindrical samples per patient. Since electrical properties of tissue begin to change over time, experiments were performed within one hour of biopsy.

Upon receipt, samples were immediately placed into a room temperature phosphate buffered solution (PBS). This step served two purposes: breaking up blood clots for similar conductiv-
Figure 3.1: Pancreatic tumor biopsies from a de-identified human patient (obtained with IRB approval)

ities between samples, and mimicking the *in vivo* conductivity of blood. The PBS consisted of 13.7 mM sodium chloride, 2.7 mM potassium chloride, 10 mM sodium phosphate, and 1.8 mM potassium phosphate in deionized water. This formulation has been used previously in our group, primarily for organ preservation [24]. Before each set of experiments, the electrical conductivity of the PBS was ensured to be 0.85 S/m with a pH of 7.5. Soaking the tissues in PBS before measurement also helped to cut down on tissue variability by washing blood clots which could affect the conductivity. The extra PBS solution remaining on the surface of the tissue was dried to keep the samples consistent, as the amount of PBS transferred to the molds along with the tissue might have varied as well. Tissue samples were further sectioned using a scalpel for placement into the PDMS molds. The molds were then placed between two stainless steel, flat plate electrodes (Harvard Apparatus, Holliston, Massachusetts).
3.2 Flat Plate Electrode Experimental Setup

Custom-made polydimethylsiloxane (PDMS) molds were made using the Sylgard 184 Silicone Elastomer kit. The base and curing agent were mixed at a ratio of 10:1, poured into a flat dish, and cured on a hot plate for 1 hour at 95 °C. After curing, the PDMS was sectioned into 2 cm by 2 cm squares. Next, a biopsy punch with a diameter either 6 or 8 mm was used to punch a vertical cylindrical hole through the mold, and a punch with a 1 mm diameter was used to create a lateral hole through the mold, creating a port for the fiber optic temperature probe (Fig. 3.2, 3.3).
A relay controlled by a 12 V DC power supply was used to switch electrode connections between a square wave pulse generator (BTX 830, Harvard Apparatus, Holliston, Massachusetts) and a commercial potentiostat (Gamry Reference 600). A fiber optic temperature probe (Luxtron m600, Lumasense Technologies, Santa Clara, California) was inserted through the side of the PDMS mold and into the sample. The probe was placed approximately at the center of the tissue sample. A 1000x attenuation high voltage probe (P5210A, Tektronix Inc., Beaverton, Oregon) and current probe (TCPA300, Tektronix Inc., Beaverton, Oregon) were connected between the output and a digital oscilloscope (DPO2012, Tektronix, Inc., Beaverton, Oregon). Voltage and current waveforms were collected in real time using Matlab vR2016a (Mathworks Inc., Natick, MA, US).

By performing impedance spectroscopy before and after the application of IRE, software can be used to fit the resulting data to the circuit shown in Fig. 2.2. After positioning the tissue
sample between the parallel plates, an impedance sweep was performed from 1 Hz to 1 MHz at 10 points per decade with a voltage amplitude of 10 mV. Next, a single 25 V, 100 µs pulse was delivered prior to IRE pulses in order to provide a second metric to determine initial conductivity. A series of 100 pulses with a width of 100 µs was delivered at a frequency of 1 Hz with an electric field strength of either 45 V/cm, 900 V/cm, 1400 V/cm, or 2500 V/cm. A sketch of a representative waveform is shown in Fig. 3.4. Finally, a post-IRE impedance sweep was performed in order to determine changes in the tissue due to electroporation and thermal effects.
3.3 3D Model Construction

There are three major steps in the construction of a patient-specific 3D model: CT scan segmentation, mesh generation and refinement, and physics model construction in finite element software (Fig. 3.5).

The CT scan of a human patient was provided by Dr. Robert Martin, University of Louisville. The Digital Imaging and Communications in Medicine (DICOM) data were loaded into 3D Slicer Software. Next, the pancreatic tissue and vasculature were segmented individually to create a 3D volumetric model. A Gaussian smoothing function with a size of 1 mm was applied to both geometries, while holes and extrusions were filled or removed with a kernel size of 4 mm. Both geometries were imported to GMSH software as .STL surface mesh files for optimization and refinement, then imported into COMSOL Multiphysics (5.3a,
COMSOL Inc., Burlington, Massachusetts). The surface meshes were then converted into geometries. A tumor mimic of 2 cm in diameter and two electrodes each 1 mm in diameter were constructed in COMSOL and placed 1 cm apart. Next, a final 3D mesh was generated and optimized (Fig. 3.6). The resulting mesh contained a total of 28180 elements of varying sizes. Beginning with a course element size, the mesh was refined until the electric potential on the surface of the pancreas differed by less than or equal to 1 %.
3.4 COMSOL Simulation of Electric Field

Two separate sets of material properties were assigned to normal and tumor tissue, respectively. The percent change conductivity curves determined earlier in the study were implemented for pancreatic normal and tumor regions, using the average initial conductivities of 0.158 and 0.169 S/m, respectively.

First, a stationary simulation was performed to calculate the electric potential within the geometry. One electrode was assigned a Dirichlet boundary condition, while the other was similarly assigned to ground (0 V). The governing equation (3.1) was then solved for electric potential \( \phi \) [25].

\[
\nabla \cdot (\sigma \cdot \nabla \phi) = 0
\]

(3.1)

3.5 Sigmoidal Conductivity Curve Fitting

Current at the end of the first pulse was used to determine the change in conductivity due to electroporation at each electric field magnitude based on the known geometry of the PDMS molds using equation (2.1). Initial conductivity was determined from the low voltage pre-pulse of 25 V and calculated in a similar fashion. For each sample, percent change in conductivity due to electroporation was calculated and plotted (Fig. 4.5a-d), then values for each electric field magnitude were calculated and plotted (Fig. 4.5e). Using the solver
in Excel 2016 (Microsoft Corporation, Redmond, Washington), the values were fit to the sigmoidal function in equation (2.2).

3.6 Statistical Analyses

All statistical tests were performed in JMP® Pro (version 13, SAS Institute Inc., Cary, NC). The least squares means Student’s t-test was used to assess differences in means across all four tissue types for change in conductivity. This test accounts for unbalance in the design. Individual contrast tests were also performed to determine statistical differences between tissue types. For all tests, a significance value of $p < 0.05$ was used.
Chapter 4

Results

4.1 Initial Conductivity

Initial conductivity was determined from the low voltage pre-pulse of 25 V and calculated using equation (2.1). The initial conductivity of both liver and pancreatic normal tissue is lower than tumor tissue. Additionally, a greater discrepancy exists between normal and tumor tissue in liver compared with pancreatic 4.1.
Table 4.1: Initial Conductivity Values

<table>
<thead>
<tr>
<th>Organ</th>
<th>Type</th>
<th>Mean Initial Conductivity (S/m)</th>
<th>Sample Size</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Normal</td>
<td>0.083</td>
<td>8</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
<td>0.265</td>
<td>3</td>
<td>0.049</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Normal</td>
<td>0.158</td>
<td>11</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
<td>0.169</td>
<td>5</td>
<td>0.070</td>
</tr>
</tbody>
</table>

4.2 Percent Change in Conductivity

Current at the end of the first pulse was used to calculate conductivity at each electric field magnitude based on the known geometry of the PDMS molds using equation (2.1). For each sample, percent change in conductivity was calculated and plotted (Fig. 4.5a-d), then values for each electric field magnitude were calculated and plotted (Fig. 4.5e).

4.3 Conductivity Curve Fitting

Using the solver in Excel 2016 (Microsoft Corporation, Redmond, Washington), the values were fit to the sigmoidal function in equation 2.2.
Figure 4.1: Percent change in conductivity is plotted versus electric field magnitude for normal liver (n=8)
Figure 4.2: Percent change in conductivity is plotted versus electric field magnitude for normal pancreas (n=11)
Figure 4.3: Percent change in conductivity is plotted versus electric field magnitude for tumor pancreas (n=5)
Figure 4.4: Percent change in conductivity is plotted versus electric field magnitude for tumor liver (n=3)
Figure 4.5: Mean percent change in conductivity at each point was fit to a symmetric sigmoidal function.
Table 4.2: Sigmoid Fit Parameters

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Type</th>
<th>A</th>
<th>B</th>
<th>D</th>
<th>$\sigma_1$</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Normal</td>
<td>211.0</td>
<td>3.338</td>
<td>109.9</td>
<td>76.54</td>
<td>1414</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
<td>173.3</td>
<td>6.610</td>
<td>138.0</td>
<td>28.58</td>
<td>19.00</td>
</tr>
<tr>
<td>Liver</td>
<td>Normal</td>
<td>747.0</td>
<td>51.30</td>
<td>20.54</td>
<td>125.9</td>
<td>160.7</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
<td>652.6</td>
<td>38.78</td>
<td>7872</td>
<td>26.00</td>
<td>1.488E-10</td>
</tr>
</tbody>
</table>

Table 4.3: Student’s t-test Results

<table>
<thead>
<tr>
<th>Organ</th>
<th>Type</th>
<th>Least Squared Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Normal</td>
<td>A</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Normal</td>
<td>A, B</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Tumor</td>
<td>B</td>
</tr>
<tr>
<td>Liver</td>
<td>Tumor</td>
<td>B</td>
</tr>
</tbody>
</table>

4.4 Change in Temperature

Temperature monitored during the IRE treatments using the fiber optic temperature probe was plotted for all ten patients (Fig. 4.6-4.14).
Figure 4.6: Change in temperature during IRE treatment of samples from patient 1.

Figure 4.7: Change in temperature during IRE treatment of samples from patient 2.
Figure 4.8: Change in temperature during IRE treatment of samples from patient 4.
Figure 4.9: Change in temperature during IRE treatment of samples from patient 5.

Figure 4.10: Change in temperature during IRE treatment of samples from patient 6.
Figure 4.11: Change in temperature during IRE treatment of samples from patient 7.

Figure 4.12: Change in temperature during IRE treatment of samples from patient 8.
Figure 4.13: Change in temperature during IRE treatment of samples from patient 9.

Figure 4.14: Change in temperature during IRE treatment of samples from patient 10.
4.5 Model Simulation

From the patient CT scan (Fig. 4.15), the finalized vasculature and pancreas volumes were visualized in 3D slicer (Fig. 4.16). The pancreas geometry was exported, then meshed together with the tumor mimic and electrodes in COMSOL (Fig. 4.17). A parametric sweep was performed using voltages of 500 V, 1000 V, 2000 V, 3000 V, and 5000 V. The electric field region was plotted for each parameter. A representative electric field distribution resulting from the application of 3000 V is shown in (Fig. 4.18).

Next, based on preliminary hydrogel experiments, a threshold of death for pancreatic cancer cells was set at 479 V/cm [26]. Using the simulation results, the expected region of tissue death was plotted in red for any tissue exposed to a electric field strength above 479 V/cm (Fig. 4.19).
Figure 4.16: 3D view of final reconstructed volumes

Figure 4.17: Finalized mesh in COMSOL
Figure 4.18: Electric field distribution for $V = 3000$ V

Figure 4.19: Region of treatment highlighted in red for $V = 3000$ V. Threshold of ablation based on 479 V/cm value determined by previous in vitro cell experiments.
Chapter 5

Discussion

5.1 Comparison of tissue types

Tumor tissue of both types were found to have a lower initial conductivity than normal tissue (4.1), which is consistent with trends found in the literature [27]. The Student’s t-test of multiple comparisons (also known as Fisher’s test) was used to assess differences between change in conductivity across all tissue types 4.3. Groups not connected by the same letter are significantly different. With regards to percent change in conductivity, the test showed that normal liver and pancreas are statistically different from tumor tissue of those types. Also, tumor tissue was found to be statistically the same between liver and pancreas.

Histologic sub-types were assessed but the results are beyond the scope of this work. The conductivity curves presented include results from all tested sub-types of liver and pancreatic
tissue. The percent change in conductivity followed a sigmoidal curve and was fit to a biologically relevant function. The fit parameter 'A' for normal liver tissue is significantly lower than the other tissue types. The smaller value for A is the best fit parameter for this function, and places the transition zone for normal liver tissue at a higher electric field magnitude.

Previous work from our group found an approximately $3.8 \times$ increase in conductivity during similar pulsing conditions in porcine kidney tissue [1]. The values reported here are significantly lower for human liver and pancreatic tissue ($0.8 \times$ and $1.30 \times$, respectively). This discrepancy could be due to natural differences between human and animal tissues, as well as differences across tissue types. Our results also indicate a discrepancy in the location of the inflection point. In sigmoid functions describing absolute conductivity, this inflection point may be indicative of the reversible threshold for electroporation [1,28]. Therefore, the results imply that human liver tissue (both tumor and normal) may possess a higher reversible, and subsequently irreversible, threshold than human pancreatic tissue. The inflection points of the sigmoidal curves are at a lower electric field magnitude than initially hypothesized, and more experiments done at intermediate voltages would better define the transition region of the curves.

In addition, liver tissue undergoes a significantly greater percent change in conductivity at high electric field magnitudes as compared with pancreatic tissue. This suggests that at the same electric field magnitude, larger ablation regions will form in liver than in pancreas. In addition, the discrepancy between tumor and normal tissue is heightened in liver
as compared with pancreas. Therefore, in liver treatment planning models, it is advised that the cancerous and healthy regions within the patient anatomy are assigned the correct conductivity functions.

We expected tumor tissue to undergo a larger change than normal tissue with increasing electric field, however, in both the liver and pancreas, tumor tissue conductivity does not increase as drastically as normal tissue with the electric field magnitude. This may be due to existing necrotic tissue within the tumor sample, leading to a low change in conductivity for high electric fields. When comparing the two tumor types, the mean change in conductivity between the two groups is statistically insignificant ($p = 0.3216$). This can be seen in Fig. 4.5 in the closer convergence of the two types at higher electric field magnitude. While conductivities of additional tumor types should be examined in order to confirm this trend, this finding may indicate the similar properties of tumors across organ types. In summary, experiments still need to be performed to verify computational models based on these curves, but this data provides a closer prediction of expected treatment areas in human patients.

### 5.1.1 Limitations

The limitations of these conductivity curves is they represent the mean change in conductivity for a sample of patients. In practice, a patient’s tissue may differ from these values due to natural variability between patients, but are expected to fall within the range observed in this study. Another limitation is the conditions under which the conductivity measurements
were performed. Though the modified PBS solution the tissues were soaked in is formulated to mimic the conductivity and pH of blood, it may have introduced some variability from the raw conductivity values expected \textit{in vivo}. However, this variation is not expected to affect the percent change due to electroporation as this effect is hypothesized to be due to new current paths forming in the cell membranes.

Additionally, while all tissue experiments were performed within one hour of excision, there may have been minor differences between tissue tested immediately after receipt and those tested towards the end of the hour.
Chapter 6

Conclusions

This work examines the dynamic electrical changes due to IRE in human pancreatic and liver tissue for the first time. The conductivity curves resulting from this study can be used to improve ablation region predictions for future studies. The result that both tumor tissue types undergo a similar change in conductivity also provides insight to the potentially comparable electrical properties of varying types of tumors. In conclusion, clinicians should expect lower dynamic conductivity changes in human pancreatic and liver tissue than previously predicted by porcine kidney tissue. Special care should be taken to ensure treatment planning models incorporate human tissue properties for the target organ in order to better predict the ablation region.

This work also implemented the resulting conductivity curves in a patient-specific, 3D model. These curves are intended to serve as generic input for a personalized treatment plan.
cians could then visualize the resulting electric field based on known human tissue properties within a patient’s specific anatomy. In addition, pulse parameters and electrode positioning could be optimized for that patient’s particular tumor.

6.1 Future Work

Following treatment, samples were fixed in formalin for histological analysis. While factors such as tissue sub-type were quantified for each sample, a correlation between these and conductivity was not established as part of this work. An investigation of how factors such inflammation and presence of additional disease, such as pancreatitis, affect the tissue conductivity would afford even greater personalization of IRE treatment planning models. Additionally, a second set of parameters could be quantified for inflamed tissue.

Incorporation of IRE death thresholds would also boast improvements to the treatment planning model presented. One method of determining these thresholds in vitro is through the use of a 3D tumor mimic, which better represents the structure of cells in vivo. Immortalized cell lines such as PANC-1 or Bx-PC3 have been used recently to quantify these thresholds by applying IRE at various magnitudes and performing fluorescence microscopy to determine regions of cell death. A numerical simulation can then be overlaid with the region to quantify the electric field strength. By inputting these thresholds into a 3D treatment planning model, the region of ablation can be predicted.

Furthermore, at this time, IRE has been applied to several types of porcine, murine, and
human tissue *ex vivo*. This information is currently spread over numerous publications and records. In order to make these curves more available to researchers and clinicians, a graphical user interface (GUI) could be constructed. This GUI could be hosted on a website, where users could input pulse parameters and receive an estimated region of ablation. While this solution may not be as personalized as a full treatment planning model reconstructed from patient scan, it would provide a closer prediction than what is currently available.
Chapter 7

Bibliography


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