ANISOTROPIC CONDUCTIVITY AND UNCERTAINTY
QUANTIFICATION IN IRREVERSIBLE ELECTROPORATION
SIMULATIONS

A Dissertation in
Engineering Science and Mechanics
by
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Abstract

In the past few years, interest has drastically increased in using surgically inserted electrodes to ablate cancer cells. The treatment is referred to as irreversible electroporation (IRE) and has the advantage of being a minimally invasive procedure that can be used to treat tumors while inflicting minimal damage to surrounding tissue and preserving blood vessels. However, treatment planning is required to ensure the electrodes are placed in the correct location and at the proper voltages such that all cancer cells are killed while damaging as few healthy cells as possible. This treatment planning is accomplished through the use of computer simulations.

The accuracy of models to predict tissue ablation from IRE is an important component to IRE treatments. It has been well established that the conductivity of tissue increases as the electrical field increases, and a conductivity dependent on electrical field strength is often included in treatment planning models. However, previous work increases conductivity equally in all directions. This dissertation presents a novel formulation that increases the conductivity more in the direction of the electrical field. There is both theoretical and experimental evidence previously published to support this formulation. Results using this novel formulation are compared to previously published models.

The second part of the dissertation focuses on performing uncertainty quantification to determine how uncertainty in physical parameters affects the extent of ablation. There is a degree of uncertainty in the material properties of each specific person, as no two humans are identical. There is further uncertainty due to the incomplete knowledge of how the tissue’s properties vary during exposure to strong electrical fields. The goal of this research is to provide more knowledge that can be used for the continued development of treatment planning protocols for irreversible electroporation.

The third part of the dissertation presents a novel work-flow that will allow medical doctors to perform treatment planning in such a way that they can easily get feedback on how adjustments in electrode number and placement affects possible ablation shapes. The work-flow utilizes linear models to determine possible ablation
zones before using nonlinear models to determine voltages necessary to ablate the target zone. Enabling medical doctors to have a more active role in the treatment planning phase when compared to optimization algorithms, should improve the treatment planning process.
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\( \epsilon_0 \) The permittivity of a vacuum
\( \epsilon_r \) The relative permittivity
\( \sigma \) The conductivity tensor
\( \sigma_c \) The conductivity tensor for use with a Cartesian coordinate system
\( \sigma_f \) The conductivity tensor for use with a Frenat coordinate system
\( \sigma_t \) The conductivity in the direction tangent to the electric field
\( \sigma_n \) The conductivity in the direction normal to the electrical field
\( \sigma_b \) The conductivity in the bi-normal direction to the electrical field
\( \sigma_0 \) The baseline conductivity
\( \sigma_{\text{max}} \) The maximum conductivity reached by the tissue which is obtained after the tissue experiences electroporation.
\( \sigma_\Delta \) A measure of how anisotropic the conductivity tensor is.
\( \Delta_\sigma \) The difference of the max conductivity, \( \sigma_{\text{max}} \) and the baseline conductivity, \( \sigma_0 \).
\( \theta \) The angle between the tangent direction of the electrical field and the x-axis
\( U \) Electric potential
\( a(\cdot, \cdot) \) Bilinear form
\( A \) Coefficient used for curve fitting
B Coefficient used for curve fitting
T Coefficient used for curve fitting
W Coefficient used for curve fitting
n Unit normal vector
E The electrical field
$\| \cdot \|$ The $l^2$ norm of the electrical field
$\mathbf{R}(\theta)$ The rotation matrix for an angle $\theta$
$\mathbb{R}$ The Real numbers
$C^n$ The space of n-times differentiable functions
$H^n$ The Hilbert space of n-differentiable functions. Also a complete inner-product Sobolev space.
$p$ A p-order finite dimensional Lebesgue space.
$L^p$ A p-order infinite dimensional Lebesgue space.
$\mathcal{N}$ Normal distribution
UQ Uncertainty Quantification
TMP Transmembrane potential
IRE Irreversible electroporation
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Dedication

I would like to dedicate this dissertation to my friend, co-worker, and fellow river guide, Bill Roth. I was lucky enough to spend countless river trips with Bill. Bill’s good nature had a way of putting everyone in high spirits. He left this world due to pancreatic cancer, and although I miss him, the memory of his friendly smile and positive attitude remain. His life was a happy fun filled adventure that was well lived indeed.
Chapter 1
Introduction and Literature Review

To be conscious that you are ignorant is a great step to knowledge.

Sybil Benjamin Disraeli

1.1 Introduction

In 1971, President Richard Nixon “declared war” on cancer and initialized many research programs focused on treating and understanding the disease. Since that declaration, scientists and medical doctors have made huge advancements in both understanding cancer’s mechanisms and how to treat cancer. One such example is that life expectancy of a leukemia patient is roughly the same as someone without leukemia [2]. Even with these advancements, cancer remains a heavy social burden. In 2012 cancer was responsible for 8.2 million deaths or 14.6% of all human deaths [3]. In the US alone, $1.116 trillion dollars were spent on cancer in 2010 [3].

One new area of cancer research is irreversible electroporation (IRE). Irreversible electroporation is a minimally invasive procedure where needle electrodes are inserted into the body to ablate tumor cells with electricity. Application of an electrical field across a cell causes the cell membrane to become more permeable by developing nano-sized pores [4]. This process is called electroporation and comes
in two varieties. The first is called reversible electroporation and is characterized by the permeability of the cell membrane only being temporarily changed. At higher electric field strengths, the cell membrane permeability becomes permanently altered and causes the cell to die. If the electrical field is strong enough to cause cell death the process is called irreversible electroporation.

It was proposed in 2005 that irreversible electroporation can be used as a minimally invasive surgical procedure to ablate undesirable tissue [5]. Since then IRE’s applicability to treat tumors in a wide selections of organs has been researched. There are numerous advantages to IRE as an ablation technique that makes it a potentially beneficial procedure.

One of the key advantages of IRE is that the tissue ablation has well defined borders, and preserves important structures such as blood vessels and collagen [6]. The strong demarcation between living and ablated cells is one reason IRE shows potential to be used as a tumor ablation method for tumors adjacent to major blood vessels and other critical structures.

The lack of thermal effects also is a positive for IRE. Other minimally invasive techniques for tumor ablation rely on thermal energy to cause cell death. Thermal ablation techniques, such as radio frequency ablation, do not exhibit the strong demarcation between ablated and unablated cells due to the diffusive nature of thermal energy [6]. The lack of a well-defined line between living and dead cells makes thermal ablation techniques a less focused approach and can be problematic when being applied near sensitive structures such as major blood vessels. Finally, IRE patients also benefit by often being able to leave the hospital within 24 hours and experience shorter recovery times because the blood vessels and supporting structural are left unaffected.

When a doctor decides to use IRE, it is important to consider electrode positioning and required voltage to completely ablate the tumor while minimizing the damage to healthy tissue. Numerical simulations offer information to allow doctors to make informed decisions on how to best perform IRE procedures on an individual basis for patients. Thus, being able to use computer models to make accurate predictions of electrical fields during IRE treatment is essential to the successful application of IRE to ablate tumors.

The research in this dissertation is concerned with furthering knowledge of computer models for treatment planning. There are two main objectives. The first
is to investigate the role anisotropically changing conductivity plays in the final result from the simulation. Current simulations in the literature only consider isotropically changing conductivity. I wish to investigate the importance of including an anisotropically changing conductivity on the model’s output. The second objective is to investigate how uncertainty in the parameters propagates to uncertainty in the outcome, the end goal being to better inform medical doctors on the uncertainty in the simulation results during treatment planning. In keeping with the objective of furthering knowledge of IRE treatment planning, a novel workflow is presented that has the potential of better incorporating the experience of medical doctors in the treatment planning phase.

1.2 Literature Review

As far back as the late 1800’s, it was discovered that electricity has the ability to affect human tissue viability [7]. However, not until the 1980’s, nearly a 100 years later, did electricity begin to be utilized for medical applications. It was shown in 1982 that applying an electrical field across a cell causes the cell membrane to become more permeable by developing nano-sized pores [8]. This process is called electroporation and comes in two varieties, reversible and irreversible [9]. Reversible electroporation forms pores in the cell membrane that are small enough for the cell to reseal them after a time [10]. At higher electric field strengths, the formed pores become too large for the cell to reseal, and the permeability of the cell is permanently altered [5]. This process is referred to as irreversible electroporation (IRE). Irreversible electroporation eventually results in the cell dying because of the cell’s inability to maintain homeostasis. Figure 1.1 outlines the process of IRE [11].

The primary cause for pore formation in the cell membrane can be attributed to dielectric breakdown due to the induced membrane potential [12] and mechanical stress [13,14]. Molecule dynamics simulations in [15] have shown that pore formation occurs in two steps. Step one is water molecules organizing into a single file that penetrates the cell membrane. Step two is the widening of the once single file of water molecules [15]. It has also been shown that pore formation and growth continues after the pulses were finished [14]. This implies that pore formation and size is also dependent on secondary effects created by the movement of ions [14], and that larger diameter pores are most likely caused by osmotic pressure enlarging.
smaller pores. It has also been hypothesized by [14] that changes in membrane permeability can cause effects such as cell swelling and shrinking that can also play a role in affecting membrane pores.

Reversible electroporation was the first form of electroporation studied for modern medicine for its ability to temporarily increase the permeability of cell membranes for the purpose of delivering new DNA [8]. Since then, reversible electroporation has been used for numerous drug uptake procedures [16–19]. When increasing the permeability of the cell membrane for drug or gene uptake, causing irreversible damage that results in cell death is considered an unintended consequence that should be minimized.

In 2005, Davalos et al. showed that irreversible electroporation could theoretically ablate significant amounts of tissue without detrimental thermal effects [5]. This began the research of IRE as a minimally invasive ablation technique. The first report of using irreversible electroporation to ablate tumors in vivo was done in 2007 [20]. Since then, IRE has been applied to renal (kidney) tumors [21, 22], prostate tumors [23–25], pancreatic tumors [26, 27], liver tumors [28–32], brain tumors [33, 34], and lung tumors [35, 36].

Irreversible electroporation is considered a minimally invasive procedure. Performing an IRE procedure requires only small incisions to insert one to six needle electrodes. After the procedure, patients are often able to leave the hospital in less than 24 hours. Patients also experience shorter recovery times when compared to other minimally invasive tissue ablation techniques.

One of the key advantages of IRE is that the tissue ablation zone is well defined while preserving important structures within the ablation zone [37]. Examples of important structures that are preserved are blood vessels, bile ducts, nerves, and collagen [6, 38–42]. One hypothesis as to why these structures are spared is that their “higher collagenous connective tissue and elastic fiber content lacks a normal cellular membrane where IRE can create pores,” [43]. It has also been shown that nerves damaged during IRE have the potential for regeneration [40, 44]. In contrast, nerves damaged by thermal ablation are unable to regenerate [43].

This is not to say that there are no disadvantages to using IRE for tumor ablation. The strong electric fields used for tumor ablation can result in muscle contractions [45]. These muscle contractions can affect electrode needle implant location and require general anesthesia along with paralytic agents [46]. Irreversible
Electrical field produces nano-sized pores in the cell membrane. Cell loses the ability to maintain homeostasis. Apoptosis occurs leaving only cell debris.

Figure 1.1: Diagram outlining the theory behind irreversible electroporation for tissue ablation [1].

electroporation also is in need of improved mathematical models so that individual treatment plans can be determined that completely ablate the tumor [9]. The problem of electrode number and placement optimization for a given patient’s tumor is currently an open problem in irreversible electroporation research [47–49].

Irreversible electroporation is not the only minimally invasive technique for tumor ablation. One common minimally invasive tumor ablation technique is radio frequency ablation [50–52]. Radio frequency ablation is a procedure where a needle electrode is placed in the tissue to be ablated. High frequency current is applied to the electrode so that tissue is heated to the point of cell death [53].

There are also cryoablation methods that use cold to ablate tumors [54, 55]. Cryoablation is a minimally invasive procedure that inserts a cooled probe into the undesirable tissue [56]. Although easier to focus the treatment area than radio frequency ablation, cryoablation requires larger probes be inserted when compared
to IRE or radio frequency treatments [5,57].

Both radio frequency ablation and cryoablation techniques utilize thermal energy to ablate undesirable cells. However, due to the diffusive nature of thermal energy, thermal ablation techniques suffer from having a poorly defined treatment area. Thermal ablation techniques are also difficult to precisely control the ablation zone due to blood perfusion increasing the spread of thermal energy and consequently the ablation zone as well [5]. The result is healthy tissue being unintentionally killed in the process for both radio frequency ablation and cryoablation. Healthy tissue destruction can be problematic when there are sensitive structures nearby such as blood vessels, nerves, and the uretha [58].

Another disadvantage of thermal methods is that they cause cell death through necrosis (traumatic cell death) [59]. Irreversible electroporation ablates cells through apoptosis (programmed cell death) [43]. Apoptosis has a better outcome for patients because it results in less inflammation and scarring than necrosis [43].

To recap, the advantages of using IRE as an ablation techniques are:

1. IRE preserves vital structures such as major blood vessels, nerve fibers, and scaffolding structures.

2. IRE has a strong demarcation line between ablated cells and living cells.
3. IRE causes apoptosis cell death which results in quicker healing time.

4. IRE is a minimally invasive procedure with most patients leaving the hospital within 24 hours.

1.2.1 Clinical IRE System

Irreversible electroporation uses a direct current generator to induce electric fields strong enough to create nano-sized pores in cell membranes [38]. Although it varies by tissue type, it has been found that most cells experience IRE at an electric field strength around 800 V/cm [5]. There is some disagreement on the precise field strength required for IRE. There have even been different results for the same body part reported by different research groups. For example, [60] found prostate tumor ablation occurred at 700 V/cm while [61] found that IRE occurred at 1072 V/cm. Even with the disagreement on the precise value, irreversibly electroporating a volume of 50 to 70 cm$^3$ requires pulses of up to 3,000 V and currents up to 50 A [62].

Such strong electrical fields require the use of specialized medical equipment. The first IRE system approved for clinical use was first described by Bertacchini et al. in 2007 [62]. The IRE device they describe has become known as the NanoKnife by AngioDynamics and is pictured in Figure 1.3 and Figure 1.4 [11]. It is currently the only IRE device that is FDA approved for clinical study [63].

![Figure 1.3: Electrode probes used by the NanoKnife system](image)

The NanoKnife IRE system can deliver up to 3,000 V in a pulse. The electrodes are needle electrodes with a length of around 15 cm and are 16-19 gauge (0.0912-1.29mm) in diameter [43]. The NanoKnife IRE system supports up to 6 needle electrodes and can use monopolar or bipolar probes for tumor ablation [43]. These probes can be guided into position with assistance from either ultra-sound, computed tomography (CT), or magnetic resonance imaging (MRI) [64].
1.3 Clinical Studies

Irreversible electroporation for cell ablation is still a new medical procedure. As such it is still in the clinical study phase. A map of the hospitals in the United States that offers IRE as a treatment is displayed in Figure 1.5. Clinical studies of IRE as a treatment option for liver tumors shows promise [29]. IRE is a feasible treatment option for liver tumors because roughly 70% of liver tumors are unresectable (unable to be surgically removed) for various anatomic reasons [65]. Other focal ablation techniques such as thermal ablation can be used for the treatment of hepatic tumors, but IRE has the advantage of sparing vital structures [66]. Simulations and experiments have been performed on ablation zones for the liver [67,68]. A study conducted in 2015 on IRE as a treatment option for hepatic tumors found that major complications occurred in only 7.1% of patients [69]. Another multi-center study found favorable results for IRE as a treatment procedure for liver tumors [29].

Other organs also show potential as sites for IRE treatment. Pancreatic tumors are often aggressive and difficult to treat because of the close proximity to vital structures [63]. Studies have shown IRE can have a better outcome when compared
Irreversible electroporation is also being investigated as a treatment option for prostate cancer due to IRE’s ability to spare sensitive structures near the ablation zone. A single center pilot study of the IRE for prostate ablation had favorable results from following 25 patients for 6 months [25]. Other preliminary IRE prostate studies have shown positive results by having a low occurrence of complications [23, 72].

Studies have shown treating kidney tumors with IRE is a viable option with minimal complications [6, 73]. A Phase II clinical trial to investigate IRE as a treatment option for renal cancer is currently underway [22].

Although, IRE for treatments for liver, pancreatic, prostate and renal cancer is how the most promise, IRE for the treatment of other cancers is also being researched. In 2012, simulations were performed using COMSOL to evaluate the feasibility of using IRE as a treatment option for tumors located in the eye [74]. It was determined that the heat generated from IRE is at a sufficiently low level as to be safe for use for eye tumors [75]. Preliminary investigations into the feasibility of
using IRE for treating breast cancer is also underway [76]. Currently, using IRE for breast cancer, has been limited to animal studies and is yet to progress to the clinical stage. The results from animals studies are encouraging for the prospects of IRE as a breast cancer treatment [76].

However, IRE was found to not be appropriate for all organs. One study found IRE to be an ineffective treatment for lung tumors [36]. The precise reason as to the cause of IRE’s ineffectiveness to treat lung tumors is yet to be determined. Some of the difficulties with using IRE for lung cancer treatment is difficulty in placing electrodes due to the location of ribs, and close proximity of air to the tissue.

1.4 Mathematical Model

Electroporation produces nano-sized pores in the cell’s membrane. These pores are formed due to an induced transmembrane potential from an external electrical field. The transmembrane potential results in a rearrangement of the membrane’s lipid bilayer [77]. The rearrangement results in the formation of hydrophilic pores [77,78]. Pore formation size and frequency is directly correlated to the transmembrane potential. The hydrophilic pores are most likely to form at the poles of the cell that are aligned with the electrical field due to the transmembrane potential being highest there [14]. It is the formation of hydrophilic pores that is responsible for the increase in the cell’s conductivity and permeability. When the external electrical field has been removed, the cell’s membrane begins to reseal [79]. However, if the pore formation is too numerous, then the cell loses viability.

Therefore, a cell’s viability is directly related to the electrical field that it is exposed to. There is a critical value for a given cell above which it loses the ability to reseal the pores, and eventually dies. Any electrical field below this critical value, either does not form pores, or the pores are resealed when the electrical field is removed. This is part of the reason for the sharp demarcation between living and dead cells observed from IRE procedures.

When a doctor decides to use irreversible electroporation, it is important to consider electrode positioning and the voltage needed to completely ablate the tumor while minimizing the damage to healthy tissue. As discussed above, the main factor determining if a cell maintains viability is the electrical field strength.
it is exposed to. Therefore, in order to develop a specific patient’s treatment plan or general protocol, it is necessary to be able to accurately predict the electric field \[80\]. It is also for this reason that IRE simulations are often used to predict electrical field strength throughout the tissue.

The time required to charge the membrane of the cell is estimated on the order of nanoseconds while the pulse time for IRE treatments is on the order of microseconds \[81\]. Thus, when performing a numerical simulation, the electric field can be assumed to be at steady state because the capacitance of the tissue charges much faster than the time scale of the pulses \[82\]. From Gauss’ law of electrostatics, the electric field for an electrostatic problem is found by solving a Laplace-like equation,

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

(1.1)

where \(\sigma\) is the conductivity and \(U\) is the electric potential. The electric field, \(E\), is the negative gradient of the potential,

\[
E = -\nabla U.
\]

(1.2)

If \(\sigma\) is a constant, then equation 1.1 is linear. However, it has been shown that the conductivity of tissue increases during electroporation \[83\]. Modeling the conductivity as a function of the electric field,

\[
\sigma = \sigma(E),
\]

(1.3)

results in equation 1.1 becoming nonlinear, but also results in a more accurate model. Often a sigmoid curve for the conductivity is used \[67, 84, 85\]. A generic sigmoid function is plotted in 1.6. If the conductivity is isotropic, then \(\sigma\) is a scalar. However, for a material with an anisotropic conductivity, \(\sigma\) is represented by a rank-2 tensor.

Irreversible electroporation is considered a non-thermal treatment option. It is true that there is a small degree of heating from the resistance to the electrical flow called Joule heating. Some models do include thermal effects and changes in conductivity due to temperature change \[86–88\]. However, it was found that if IRE is administered with short pulses, then the amount of Joule heating is insignificant and for this reason will be left out of the model used for this research \[89\].
Figure 1.6: Plot of a generic sigmoid function. This is a commonly used function for the conductivity as a function of electrical field strength. In the plot $\sigma_0$ represents the conductivity before electroporation and $\sigma_{max}$ is the conductivity after electroporation.

The electrical fields also induce pH fronts in the tissue [90]. However, these effects are left unmodeled for IRE treatment planning simulations. This is partly due to the pH fronts having minimal amount of time to form during the quick pulses from IRE treatments. The other reason is that there presently is not a strong enough understanding of the biochemistry involved to include such physics into a model.

Boundary conditions need to be specified before equation 1.1 can be solved. It is common for boundaries of the electrode to be Dirchlet type and the remaining boundaries to be Neumann type [91]. Specifically, the boundary condition for a charged electrode would be

$$U = V_0$$  \hspace{1cm} (1.4)

where $V_0$ is the applied voltage of the electrode. For a grounded electrode, $V_0$ would be zero and the boundary condition would read

$$U = 0.$$  \hspace{1cm} (1.5)

The boundaries not in contact with an electrode, are often modeled as electrically
insulating,
\[ \frac{\partial U}{\partial n} = 0 \] (1.6)
where \( n \) is the outward pointing unit normal [91].

Almost all numerical studies use a time independent formulation for the electrical field. However, a very recent study used a time-dependent formulation to investigate the importance of including time in the numerical model [92]. The author’s of that research believe further work is needed before a definitive conclusion can be drawn [92].

1.4.1 Finite Elements

The mathematical formulation to predict the electrical field consists of solving Equation 1.1 on a given domain with boundary conditions. For many practical applications, this is too difficult to solve analytically and must be numerically approximated. There are several mathematical techniques that would provide a numerical approximate solution such as the method of lines, finite difference schemes, and the finite element method. In this dissertation, the finite element method will be used to numerically solve Equation 1.1.

The finite element method finds weak solutions to differential equations. This is in contrast to classical solutions which are referred to as strong solutions.

Linear polynomials will be used as basis vectors in the discretized form. These linear polynomials will be supported on discrete elements of the domain. Although higher polynomials elements could have been used, linear elements were used in all simulations for this dissertation.

1.4.2 Numerical Solvers

The finite element method always involves solving a system of linear equations in matrix form. Direct and iterative are the two classes of solvers that can be used to invert the stiffness matrix. Choice of which solver to use should be dependent on the problem and hardware involved with the simulation.

A direct solver is one that inverts a matrix in a method similar to Gaussian elimination. Gaussian elimination has a computational complexity of \( O(n^3) \) and is computationally inefficient to use on a matrix consisting of a lot of zeros such
as a sparse matrix. A more efficient approach of directly solving sparse linear systems, would be to use a frontal solver [93]. Frontal solvers avoid the unnecessary computations on the zeros by instead performing computations on the the dense elemental matrices instead. The matrix is solved in parts in a dense frontal matrix. The frontal is assembled on the transition between the solved and unsolved portion of the matrix K. The frontal matrix is assembled from elemental matrices, solved, and then updated using the next elemental matrix. The process is repeated until the entire matrix K is solved. By performing operations on a dense relatively small frontal matrix, the computation is more memory efficient and computationally efficient than performing Gauss elimination on the sparse matrix K directly.

The direct solver used in this dissertation is the MUMPS (MUltifrontal Massively Parallel Solver) [94]. It operates using the same principles as a frontal solver but by using multiple fronts at a time, the computation can be split amongst multiple processors which allows for parallel computing. The ability to utilize parallel computing is why MUMPS was the direct solver chosen for this dissertation. A direct solver was only used for the simulations performed in Chapters 2 and 6.

Iterative solvers can also be used to solved the system of linear algebraic equations of the form $Ku = f$. Unlike direct solvers, iterative solvers begin with an initial guess for $u_0$ and then improves the accuracy of $u$ with each iteration. The advantage of an iterative solver is a lower memory consumption when compared to direct solvers. The disadvantage of an iterative solver is that it is a less robust solution method when compared to direct solvers. The iterative solver used in this dissertation was the conjugate gradient solver implemented in COMSOL. The conjugate gradient method is way to solve a system of linear algebraic equations. An iterative solver was used for Chapters 3, 4, and 5.

1.4.3 Computer Hardware Used

All simulations in this dissertation were performed using Penn State’s ACI computational cluster. The PSU-ACI cluster has two sides. The first is ACI-i (where the ‘i’ stands for interactive). ACI-i is a cluster that supports graphical interfaces. However, jobs are limited to a walltime of 24 hours and the cluster is a shared resource amongst all users. This cluster was used to graphically make meshes and setup up cases in COMSOL.
Once the simulation was made on ACI-i. The file was then used on the other side of ACI, ACI-b where the ‘b’ stands for batch-submission. ACI-b does not support graphical interfaces. It does have the advantage of supporting batch job submission which allows the user to utilize far more computational power than is available on ACI-i. All simulations were performed on ACI-b.

ACI-b has nodes with 20 cores, 2.13 GHz processors with up to 1 Tb of memory. All simulations were run in a shared memory configuration. This means that all jobs were submitted to the cluster on a single node at a time, and therefore consumed less than a 1 Tb of memory.

1.5 State of the Art

Although IRE shows great potential and has come a long way, there are still hurdles to overcome before IRE moves out of the clinical research stage and into mainstream medicine. One such hurdle is that current mathematical models do not predict ablation zones with sufficient accuracy [95]. A study conducted in 2016, concluded that “ablation volumes were significantly less than predicted,” and that due to mathematical models performing poorly, “Physicians should consider carefully the limitations of mathematical models for IRE when planning ablations” [95]. Numerical models were also found to overestimate ablation zones during a comparison of simulations and experiments of swine kidneys which lead the authors to the conclusion that overestimation may lead to incomplete ablation of the tumor at the periphery [96]. Obviously, any incomplete tumor ablation is problematic for the patient.

To account for this overestimation, a factor of safety can be included in treatment planning by applying a voltage higher than what is numerically predicted to be necessary to ablate the target area. The question though is how high should this factor of safety be set? If the safety factor is too low, then the risk of incomplete tumor ablation exists. If the factor of safety is too high, then more healthy tissue is ablated than necessary. Currently, there is no agreement on what the factor of safety should be for treatment planning [97].

The factor-of-safety used in treatment planning should be a reflection of the level of uncertainty in the numerical results. To the best of my knowledge, no research has done an uncertainty quantification study for irreversible electroporation.
One goal of this research is to quantify how uncertainty in material properties propagate through the mathematical model and into the final solution. A greater understanding in the uncertainty of the final solution will provide physicians and researchers with more knowledge to make more informed decisions on what level the factor of safety should be set at.

1.6 Plan to Advance the State of the Art

This research consists of four research areas that are concerned with furthering the ability of numerical simulations to be used for treatment planning of IRE. The first area deals with investigating the importance of incorporating anisotropically changing conductivity into numerical models. The second area deals with studying how uncertainty in model parameters propagates through the model and into the final result. The third area deals with how to give medical doctors a more active role in the determination of electrode number and placement of treatment planning. The fourth area deals with ways to improve modelling electroporation on the cellular level. The from these research areas will contribute to helping physicians develop more reliable and safe treatment plans for their patients.

1.6.1 Anisotropic Changing Conductivity

When a strong enough electrical field is applied to a cell, hydrophillic pores form in the cell membrane. The hydrophillic pores result in an increasing the conductivity of the cell. It is the formation of pores in the cell membrane that causes the conductivity of tissue to increase during electroporation.

Pore formation is not distributed uniformly over the cell membrane [14]. The pore formation occurs more the larger the transmembrane potential (TMP). The transmembrane voltage for a spherical cell can be expressed by the equation

\[ \text{TMP} = 1.5rE_0 \cos(\theta) \]  

where \( r \) is the radius of the cell, \( E_0 \) is the electrical field, and \( \theta \) is the angle between the electrical field and the point on the cell [98]. The transmembrane potential drop is largest at the poles because \( \cos(\theta) \) is largest at the the poles. Therefore there is a bias towards pores forming in line with the electrical field. This bias has
been confirmed through scanning electron microscope images of liver cells after IRE [14]. Figure 1.7 illustrates the bias of pore formation.

Since pore formation occurs with a bias and pores are responsible for the increase in tissue conductivity, it follows that tissue conductivity would increase more in the direction of the electrical field than perpendicular to it. However, current IRE modeling solves Equation 1.1 with a conductance that increases isotropically as the magnitude of the electrical field increases. This dissertation proposes that the conductance increases anisotropically. Specifically, this research proposes solving Equation 1.1 with a conductance that increases more in the direction of the electrical field.

In 2012, electroporation experiments were done on chicken livers, and it was found that the conductivity of the liver changed anisotropically [99]. In particular, it was found that the conductivity increased more in the direction of the electrical field [99]. To the best of my knowledge, no researcher has performed simulations where the conductivity changes anisotropically during electroporation. I wish to investigate the effect a conductivity that depends on both electrical field magnitude and direction has on a simulation’s result.

As discussed above, there is both theoretical and experimental evidence to suggest that the conductivity changes in an anisotropic manner. Furthermore, it has been demonstrated experimentally that the conductivity of tissue is not always isotropic and that this anisotropic conductivity can effect the ablation shape during irreversible electroporation [100]. Researchers have performed IRE
numerical simulations with models that incorporate an anisotropic conductivity in their models and have found that anisotropy is an important characteristic to the accuracy of numerical models \[101,102\]. These previous works show the importance in correctly representing the anisotropic nature of the tissue in the mathematical model of IRE simulation.

The results of this investigation will be significant irregardless of the outcome. If it is found that including an anistropically changing conductivity has minimal difference from an isotropic changing conductivity than my research will have provided evidence for that simplification in models. Conversely, if it is found that an anistropically changing conductivity gives significantly different results from an isotropically changing conductivity than my research has provided evidence on the importance of including it in numerical models. Thus, the first research question I propose to investigate during my thesis research is

“Does an anisotropically changing conductivity play a significant role in the predicted electric field for an irreversible electroporation simulation?”

More details on this research plan and results can be found in Chapter 2.

1.6.2 Uncertainty Quantification

There is unavoidable uncertainty in parameters used for a numerical model. This uncertainty comes from experimental uncertainty in the determination of model parameters such as tissue conductivity and the field strength that irreversible electroporation begins. There is also added uncertainty due to the fact that a generic database of tissue properties do not perfectly represent an individual due to no two people being identical. These uncertainties in the model parameters are then propagated into uncertainties in the final solution.

Having uncertainty in results strongly indicates the need to incorporate statistics and probabilities into treatment planning protocols. It is important to consider the uncertainty of a prediction when being used for treatment planning so that a treatment plan with a sufficiently high chance of success is used.

Furthermore, most IRE simulations for treatment planning take a deterministic
Electrical field dependent Conductivity

This research

Anisotropic Conductivity

Corović, Selma, et al. "Modeling of electric field distribution in tissues during electroporation."


Gehl, Julie, et al. "In vivo electroporation of skeletal muscle: threshold, efficacy and relation to electric field distribution."

Figure 1.8: A Venn diagram that highlights how this research is a combination of previous works done, yet still novel.

approach towards cell death. Specifically, they assume cell death can be completely determined from the local electric field strength. Using a deterministic approach to determine cell death is only valid when the cell population is homogeneous [82]. In reality, tissue is comprised of different cells and orientations [82]. Cancerous tissue has particularly diverse cell population and therefore better suited to a statistical description than a deterministic one for the prediction of the ablation zone [82].

The second research question investigated dealt with how these uncertainties manifest themselves into the final predicted electrical field and can be phrased as:

"What role does uncertainty in conductivity play in the uncertainty in the predicted electric field for an irreversible electroporation simulation?"

It is the author’s belief that physicians should take a probabilistic and statistical approach to treatment planning due to unavoidable uncertainty in the accuracy of a simulation’s result. Medical doctors should consider the uncertainty in a simulation’s result when using that result for treatment planning. However, at this time there has not been a study on uncertainty quantification of the numerical
results for an IRE simulation to provide doctors with a level of uncertainty. The goal of this research is to provide a better understanding of how uncertainty in model input parameters propagate into uncertainty in the final predicted outcome so that physicians can make better informed decisions on how to set safety parameters for treatment planning.

1.6.3 Ablation Target Zone Work-flow

When performing treatment planning, physicians need to make decisions as to how many electrodes to use and where to place them. There are currently optimization algorithms that can decide the optimal position by minimizing a cost function. However, not all physicians will weigh each factor’s importance the same. It is the author’s belief that it would be better if physicians could determine electrode number and placement without having to assign values to a cost function.

To this end, this dissertation presents a novel work-flow that will allow medical doctors to perform treatment planning in such a way that they can easily get feedback on how adjustments in electrode number and placement affects possible ablation shapes. The work-flow utilizes linear models to determine possible ablation zones before using nonlinear models to determine voltages necessary to ablate the target zone. By allowing for medical doctors to have a more active role in the treatment planning phase when compared to optimization algorithms, the hope is to help improve the treatment planning process.

1.6.4 Nanochannel Electroporation Simulations

Research was also done on performing simulations of a nanochannel used for transfection of cells. The goal being to provide researchers with a model that they could use to improve future designs and select more optimal operation settings such as voltage. The goals of these devices are different from IRE as they are mostly interested in reversible electroporation. Simulations were done for both single cell and multi-cell setups as well as steady-state and transient simulations. Findings are presented in Chapter 6.
Chapter 2  
Anisotropic Conductivity Modelling

2.1 Introduction

It is well established in the literature that electroporation can affect the conductivity of tissue [83, 103–106]. The large increase in conductivity is a result of the pores formed during electroporation [107]. The research by Corovic et al., recommend that a conductivity that is dependent on electrical field strength should be incorporated into numerical simulations to increase accuracy [67].

Experiments performed by Mezeme et al. suggest that electroporation does not always isotropically increase the conductivity of the tissue, but conductivity is increased more in the direction tangent to the electric field [99]. Their experiments determined the conductivity of electroporated chicken livers by using magnetic resonance electrical impedance tomography (MREIT). The result of an anisotropic conductivity tensor can be explained by the pores forming in the cell membrane with a bias towards the direction of the electrical field [108]. This is because the voltage drop across the cell membrane is not equal around the entire cell, but is largest where the cell membrane is perpendicular to electrical field [108]. To the
best of my knowledge, there has not been an electroporation simulation with a conductivity tensor that is dependent on both electric field strength and electric field direction.

It has been stated in [109] that in certain situations it is important to consider the anisotropic conductivity of tissue during the electroporation treatment planning stage. That was for a constant conductivity. It is logical then to reason it would also be important to include anisotropic effects in how the conductivity tensor changes. Put differently, I propose that the electrical field direction should play a role in the change in conductivity. By performing simulations and comparing isotropic and anisotropic varying conductivities, this research will evaluate the importance of including anisotropically varying conductivity into a simulation during treatment planning.

Therefore, in this chapter, a mathematical model that incorporates a tissue’s conductivity increasing more in the direction of the electrical field is proposed. To do so, it was required for us to derive a formulation for the conductivity tensor such that conductivity increases by different amounts in the direction tangent and normal to the electrical field and can be easily implemented in numerical methods such as finite elements. Numerical simulations were performed for isotropic and anisotropic varying conductivities to evaluate the importance of including the electrical field’s direction in the formulation for conductivity.

2.2 Method

This section will discuss the details of the mathematical models used for comparing the well established isotropically increasing-conductivity formulation and this paper’s anisotropically increasing-conductivity formulation. The simulations used for comparison will be based off the irreversible electroporation experiments and simulations performed by Castellvi et al. [110]. This work will use their experimentally determined parameters to compare an isotropic formulation to an anisotropic formulation.
2.2.1 Governing Equations

In numerical simulations for treatment planning, it is assumed that the applied direct current electric field is at steady state [82]. The electrical potential, \( U \), satisfies the differential form of Gauss’s law at steady state:

\[
\nabla \cdot (\sigma \nabla U) = 0 \tag{2.1}
\]

where \( \sigma \) is the tissue’s conductivity. Then the electric field \( E \) is given by: \( E = -\nabla U \).

If \( \sigma \) is a constant, then equation (2.1) becomes the well-known Laplace equation. However, the conductivity of tissue is not in general constant but increases during electroporation [83], and therefore, we will model the conductivity as a function of the electric field, \( \sigma = \sigma(E) \).

We model the isotropic varying conductivity as a sigmoid Gompertz curve [67,84]:

\[
\sigma(\|E\|) = \sigma_0 + (\sigma_{\text{max}} - \sigma_0) \cdot \exp[-A \cdot \exp(-B \cdot \|E\|)] \tag{2.2}
\]

where \( A \) and \( B \) are unitless coefficients, \( \sigma_0 \) is the the base conductivity before electroporation, \( \sigma_{\text{max}} \) is the maximum conductivity a tissue can achieve after electroporation, and \( \|E\| \) is the \( l^2 \)- norm of the electrical field. By definition, the \( l^2 \)- norm of the electrical field is \( \|E\| = \sqrt{E_x^2 + E_y^2 + E_z^2} \) where \( E_x, E_y, E_z \) is the \( x, y, z \) component of the electrical field respectively. The values of \( A \) and \( B \) are found by fitting the curve for conductivity to experimental data.

If the conductivity is isotropic, then \( \sigma \) is a scalar. However, the conductivity is anisotropic when the conductivity increases more in the direction of the electrical field. This results in the conductivity, \( \sigma \), being represented by a rank-2 tensor.

We will compare two different cases. The first being when \( \sigma \) does not take into account the direction of the electrical field (isotropic-varying) and when \( \sigma \) does take into account the direction of the electrical field (anisotropic-varying). Both cases will solve Equation 2.1; the only difference will be in how \( \sigma \) is defined.

2.2.2 Isotropic-varying Formulation

This is the well established model that is often used for IRE simulation predictions. It will be used for comparison with our anisotropic-varying formulation. The isotropic-varying formulation has the conductivity increase equally in all directions.
Hence, it being refereed to as the isotropic formulation in this paper. The advantage of using an isotropic formulation is that the conductivity is represented by a single scalar, and the direction of the electrical field does not need to be considered. It is also less computationally intensive.

In the isotropic formulation, the changes in conductivity from electroporation can be taken into account with a sigmoid Gompertz curve for the conductivity [67,84,85]. The same expression for conductivity as was found in [110] which is

\[
\sigma(||E||) = 0.03 + 0.35 \times \exp(-\exp(-0.01(||E|| - 250)))
\]  

will be used for the isotropic formulation

### 2.2.3 Anisotropic-varying Tensor Derivation

In this paper, we propose a conductivity that takes into account the electrical field’s direction and magnitude. We wish to formulate the conductivity tensor such that the conductivity increases more in the direction of the electrical field. Since the electrical field does not increase equally in all directions, we will refer to this formulation as the anisotropic formulation in this paper.

We now wish to derive the matrix representation for the conductivity tensor for the anisotropic-varying case such that it can be implemented into a numerical scheme. This is the main contribution of the paper.

We begin by assuming the conductivity tensor is a real valued symmetric matrix. This is common assumption and is justified by assuming conductivity is independent of current flow being positive or negative. All symmetric matrices are diagnolizable. Therefore, the conductivity tensor is diagnolizable.

The anisotropic case can have a different conductivity in the direction of the electrical field than perpendicular to it. If we make the assumption that the conductivity in the direction of the electrical field is always equal or greater than any other direction, and that the conductivity in a direction perpendicular to the electrical field is always equal or less than any non-normal direction then the directions tangent and normal to the electrical field are principal directions. These assumptions are justified according to the experimental work found in [99].

Let \( \sigma_t \) be an arbitrary function representing the conductivity in the direction tangent to the electrical field. Also let \( \sigma_n \) and \( \sigma_b \) be arbitrary functions representing
conductivity in the direction normal and bi-normal to the electrical field respectively. By treating $\sigma_t$, $\sigma_n$, and $\sigma_b$ as arbitrary functions, we are providing a derivation that is valid for any expression for $\sigma_t$, $\sigma_n$, and $\sigma_b$ which may someday be ascertained through experiments.

A tensor is diagonal when the principal directions are chosen as the basis representation. We will therefore consider a coordinate system comprised of a unit vector tangent to the electrical field and two unit vectors perpendicular to the electrical field. A coordinate system consisting of a tangent vector, normal vector, and bi-normal vector, is sometimes referred to as a Frenet-Serret frame. These three vectors form an orthonormal basis in which the basis vectors point in the principal directions of the conductivity. Since the Frenet-Serret basis vectors are aligned with the principal directions then the conductivity tensor matrix representation is diagonal in the Frenet-Serret coordinate system and can be represented as

$$
\sigma_f = \begin{pmatrix}
\sigma_t & 0 & 0 \\
0 & \sigma_n & 0 \\
0 & 0 & \sigma_b
\end{pmatrix}
$$

(2.4)

where $\sigma_f$ is the matrix representation of the conductivity tensor in the Frenet-Serret coordinate system. It will be assumed that the conductivity is the same for any direction normal to the electrical field. This implies that both the normal and bi-normal direction conductivities are equal,

$$
\sigma_b = \sigma_n.
$$

(2.5)

Equation 2.5 simplifies Equation 2.4 to

$$
\sigma_f = \begin{pmatrix}
\sigma_t & 0 & 0 \\
0 & \sigma_n & 0 \\
0 & 0 & \sigma_n
\end{pmatrix}.
$$

(2.6)

where $\sigma_f$ represents a linear transformation that takes a vector from the Frenet-Serret frame and outputs a vector in the Frenet-Serret frame. This can be restated as

$$
\sigma_f : \mathbb{R}^3_f \rightarrow \mathbb{R}^3_f
$$

(2.7)
where $\mathbb{R}^3$ is the space of three dimensional vectors represented by the Frenet-Serret basis. However, for calculations, we would like to have the conductivity tensor in the Cartesian coordinate system as it is often impractical to implement the Frenet-Serret matrix representation into a numerical scheme such as finite elements. Thus, we wish to derive

$$\sigma_c : \mathbb{R}_c^3 \rightarrow \mathbb{R}_c^3 \quad (2.8)$$

where $\sigma_c$ is the matrix representation of the conductivity tensor in the Cartesian coordinate system, and $\mathbb{R}_c^3$ is the space of three dimensional vectors represented by the standard Cartesian basis. We will use the known form of the matrix representation of the conductivity tensor in the Frenet-Serret frame to derive the matrix representation of the conductivity tensor in the Cartesian frame.

Since the Frenet-Serret frame and the Cartesian coordinate system are both orthonormal, a change of basis between the two can be represented by a rotation through an angle $\theta$ about the z-axis and a rotation $\phi$ about the y-axis. Note only two rotations instead of three are necessary because the conductivity has been assumed to be equal in all normal directions.

The rotation tensor, $R(\theta, \phi)$, is a linear transformation such that

$$R : \mathbb{R}_c^3 \rightarrow \mathbb{R}_f^3 \quad (2.9)$$

A function diagram outlining the relationship between $\sigma_c$, $\sigma_f$, and $R$ can be found in Figure 2.1.

![Figure 2.1: Function Diagram for the conductivity tensor.](image)

We can decompose $R$ into two subsequent rotations. The first rotation will be about the z-axis, $R_z(\theta)$, and can be expressed by the matrix,

$$R_z(\theta) = \begin{pmatrix} \cos(\theta) & -\sin(\theta) & 0 \\ \sin(\theta) & \cos(\theta) & 0 \\ 0 & 0 & 1 \end{pmatrix} \quad (2.10)$$
where the angle $\theta$ is obtained through the relationship

$$\theta = \tan^{-1}\left(\frac{E_y}{E_x}\right). \quad (2.11)$$

The quantities $E_x$ and $E_y$ represent the x and y components of the electrical field respectively. Similarly, the second rotation will be about the y-axis, $R_y(\phi)$, and is expressed by the matrix,

$$R_y(\phi) = \begin{pmatrix} \cos(\phi) & 0 & -\sin(\phi) \\ 0 & 1 & 0 \\ \sin(\phi) & 0 & \cos(\phi) \end{pmatrix} \quad (2.12)$$

where $\phi$ is the angle described by the function

$$\phi = \tan^{-1}\left(\frac{E_z}{E_x}\right). \quad (2.13)$$

The quantity $E_z$ represents the z component of the electrical field. The rotation tensor can be then be expressed as

$$R(\theta, \phi) = R_y(\phi)R_z(\theta) \quad (2.14)$$

Using properties of rotation matrices, $R^{-1}$ is

$$R^{-1} = (R_y(\phi)R_z(\theta))^{-1} = R_z(-\theta)R_y(-\phi) \quad (2.15)$$

We are now able to express the conductivity tensor in matrix form with the domain and codomain being the Cartesian frame. This is accomplished by applying the rotation matrices in the following order:

$$\sigma_c = R^{-1}\sigma_f R \quad (2.16)$$

$$\sigma_c = R_z(-\theta)R_y(-\phi)\sigma_f R_y(\theta)R_z(\phi) \quad (2.17)$$

$$\sigma_c = \begin{pmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{12} & \sigma_{22} & \sigma_{23} \\ \sigma_{13} & \sigma_{23} & \sigma_{33} \end{pmatrix} \quad (2.18)$$
where
\begin{align*}
\sigma_{11} &= \cos^2(\theta) \left( \sigma_n \sin^2(\phi) + \sigma_t \cos^2(\phi) \right) + \sigma_n \sin^2(\theta) \quad (2.19) \\
\sigma_{22} &= \sin^2(\theta) \left( \sigma_n \sin^2(\phi) + \sigma_t \cos^2(\phi) \right) + \sigma_n \cos^2(\theta) \quad (2.20) \\
\sigma_{33} &= \sigma_n \cos^2(\phi) + \sigma_t \sin^2(\phi) \quad (2.21) \\
\sigma_{12} &= \sin(\theta) \cos(\theta)(\sigma_n - \sigma_t) \cos^2(\phi) \quad (2.22) \\
\sigma_{13} &= \cos(\theta)(\sigma_n - \sigma_t) \sin(\phi) \cos(\phi) \quad (2.23) \\
\sigma_{23} &= \sin(\theta)(\sigma_n - \sigma_t) \sin(\phi) \cos(\phi) \quad (2.24)
\end{align*}

The form of an anisotropic varying conductivity tensor has been derived with arbitrary functions for the conductivity in the tangent and normal directions. Therefore, this formulation is valid for any functions of conductivity for \( \sigma_t \) and \( \sigma_n \), including those dependent on electrical field strength. A derivation for the conductivity tensor in three dimensions is presented in Appendix B.

For the anisotropic case simulations, the conductivity used for the tangent direction, \( \sigma_t \), will have the same form as the conductivity for the isotropic case:
\begin{align*}
\sigma_t(\|E\|) = \sigma(\|E\|) &= 0.03 + 0.35 \times \exp(- \exp(-0.01(\|E\| - 250))) \quad (2.25)
\end{align*}

This was chosen because the measurements used to experimentally determine the form of the conductivity is often done using electrodes that are aligned with the electrical field.

As shown in [99], the conductivity tensor becomes more anisotropic as the electrical field strength increases. This ratio will be modelled using a sigmoid function, \( \sigma_\Delta \), where
\begin{align*}
\sigma_\Delta(\|E\|) &= 0.30 \times \exp(- \exp(-0.01 \times (\|E\| - 250))) \quad (2.26)
\end{align*}

is an adaptation of the data obtained in the experiments reported in [99]. Due to the limited amount of experimental data, this was the authors’ best guess as to the form for \( \sigma_\Delta \). But since the derivation was done in a general setting, it will be possible to plug in different formulations at a later time as they become available from experimental data. The approximation can be combined with the previous expression for \( \sigma_t \) to obtain the following expression for the conductivity in the
perpendicular direction:

\[ \sigma_n = (1 - \sigma_\Delta)\sigma_t. \]  

(2.27)

It is worth noting, that our form for \( \sigma_\Delta \) results in \( \sigma_t \) and \( \sigma_n \) being equal until the onset of electroporation. In other words, the conductivity is isotropic until the onset of electroporation. During electroporation, the conductivity tensor becomes more anisotropic with increasing electrical fields up until a value of \( \sigma_t \) being 30\% larger than \( \sigma_n \).

All simulations in this chapter will use boundary conditions as they were defined in Chapter 1. One of the electrodes will have a prescribed voltage of \( V_0 \), one electrode will be ground, and outer boundaries of the domain will be modeled as electrically insulating.

### 2.2.4 Monopolar Geometry

The geometry used for the monopolar simulations was the same as used by Castellvi et al. It consisted of two monopolar electrodes spaced 15 mm apart embedded in a 60 mm sphere. A schematic of the simulation geometry is shown in Figure 2.2. The outer surface and electrode sleeves were modeled as electrically insulating. The remaining boundary conditions is to set the active area of one electrode to ground and to enforce the condition that the active area of the other electrode is held at a constant voltage.

### 2.2.5 Bipolar Geometry

The domain used for the bipolar simulations was a 60 mm sphere. The electrode has a diameter of 1.5 mm and a length of 40.5 mm. The last 7 mm of the electrode are set to the positive voltage. The next 7 mm of the electrode is insulated, and then followed by 7 mm of the electrode set to ground. The remaining portion of the electrode is set to an insulating boundary condition as is the outer sphere. A schematic of the domain is shown in Figure 2.3.
2.3 Results

2.3.1 Monopolar Simulations

Both formulations were run with various voltages. For all simulations, a volume was considered irreversibly electroporated if the magnitude of the electrical field was 184 V/cm or greater. A comparison of the ablation volume can be found in Table 2.1. It can be seen that the anisotropic formulation predicts a slightly
smaller ablation zone than the isotropic formulation. This value was determined experimentally in [110] for the cases this work recreated for comparison.

Table 2.1: Results for 3D Monopolar Simulation

<table>
<thead>
<tr>
<th>Voltage</th>
<th>Isotropic IRE vol.(cm³)</th>
<th>Anisotropic IRE vol.(cm³)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 V</td>
<td>0.64</td>
<td>0.63</td>
<td>1.6 %</td>
</tr>
<tr>
<td>500 V</td>
<td>5.39</td>
<td>5.18</td>
<td>4.1 %</td>
</tr>
<tr>
<td>750 V</td>
<td>10.45</td>
<td>9.94</td>
<td>4.9 %</td>
</tr>
<tr>
<td>1000 V</td>
<td>15.81</td>
<td>14.87</td>
<td>5.9 %</td>
</tr>
<tr>
<td>1250 V</td>
<td>21.31</td>
<td>19.91</td>
<td>6.6 %</td>
</tr>
</tbody>
</table>

The shape between the anisotropic and the isotropic formulation are similar except for the anisotropic formulation resulting in a slightly less spherical ablation zone than the isotropic formulation. Similar results were seen for other voltages.
2.3.2 Bipolar Simulations

For the bipolar geometry, the volume predicted to be ablated is much lower for the anisotropic simulations than for the isotropic simulations. A summary of the results are displayed in Table 2.2. Notice that there is a larger percentage change between the isotropic and the anisotropic cases for the bipolar probe than for the monopolar probes. The anistotropic-varying formulation produces an ablation shape that is qualitatively similar, but quantitatively slightly smaller. Similar ablation shapes were seen for the other voltages as well.

<table>
<thead>
<tr>
<th>Voltage</th>
<th>Isotropic IRE vol. (cm$^3$)</th>
<th>Anistropic IRE vol. (cm$^3$)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 V</td>
<td>0.44</td>
<td>0.43</td>
<td>2.3 %</td>
</tr>
<tr>
<td>500 V</td>
<td>2.49</td>
<td>2.33</td>
<td>6.4 %</td>
</tr>
<tr>
<td>750 V</td>
<td>5.27</td>
<td>4.67</td>
<td>11.8 %</td>
</tr>
<tr>
<td>1000 V</td>
<td>7.89</td>
<td>7.06</td>
<td>12.8 %</td>
</tr>
<tr>
<td>1250 V</td>
<td>10.60</td>
<td>9.38</td>
<td>13.0 %</td>
</tr>
<tr>
<td>1500 V</td>
<td>13.30</td>
<td>11.71</td>
<td>12.0 %</td>
</tr>
<tr>
<td>1750 V</td>
<td>15.93</td>
<td>14.03</td>
<td>13.5 %</td>
</tr>
<tr>
<td>2000 V</td>
<td>18.59</td>
<td>16.30</td>
<td>14.0 %</td>
</tr>
</tbody>
</table>

2.4 Conclusion and Future Plans

In this chapter, we presented a derivation of a general formulation for an anistropic-varying tensor for implementation into IRE modeling software. The anistropic-varying tensor formulation allows the conductivity to take into consideration both electrical field direction and magnitude, as opposed to previous published works that only took into account electrical field magnitude. It was derived for arbitrary functions for $\sigma_t$ and $\sigma_n$, and is therefore applicable irregardless of the form chosen for $\sigma_t$ and $\sigma_n$. The formulation was compared to more commonly used isotropically varying formulations, and was found to decrease the predicted ablation zone for both monopolar and bipolar electrode setups.

In 2015, work was done by Wimmer et al. to investigate the accuracy of IRE simulations to predict ablation zone size [96]. By comparing experimental results performed on porcine kidneys, they observed that IRE simulations for
both monopolar and bipolar electrodes over-predict ablation zones when compared to experiments. Furthermore, Wimmer et al. found that constant conductivity formulation had a larger over prediction for bipolar simulations than for monopolar simulations when compared to experiments. The anistropic-varying formulation decreased the predicted ablation volume more for the bipolar case than for the monopolar case. Thus, an anisotropic formulation may be the solution to correcting the over-prediction seen in the current isotropic formulation.

Further experimental and numerical work is necessary before any definitive conclusions can be drawn on the importance of including an anisotropic-varying formulation in ablation zone predictions. One particular area would be how does a changing electrical field affect such as from multiple electrodes affect the formulation. Other areas would be further experimental investigation into how the pulse length and number affect the anisotropic nature of the conductivity tensor. However, the preliminary results for the anisotropic formulation for the conductivity tensor seem promising. They slightly decrease the predicted volume of ablated cells, and could be a possible explanation for the over-prediction seen by isotropic-varying formulations. The hope of this work is to encourage further research on how electrical fields can affect the conductivity tensor in different directions because more experimental data is necessary before any definitive conclusions can be drawn.
Chapter 3  |  Uncertainty Quantification of Conductivity

It is a truth very certain that when it is not in our power to determine what is true we ought to follow what is most probable.

Descartes, Discourse on Method

3.1 Introduction

Making individual IRE treatment plans depends on choosing an appropriate voltage for the electrodes. This is important because if too low a voltage is used then incomplete tumor ablation and tumor recurrence can occur. If too high a voltage is applied, healthy tissue is unnecessarily ablated. Treatment parameters can be chosen through the aid of numerical simulations. In an effort to increase the accuracy of these simulations, there have been numerous animal studies that compare experimental data with numerical predictions for various organs [21,96,111].

When performing IRE treatment planning, medical doctors will have a target ablation volume that includes the tumor and a margin-of-safety around the tumor [112]. This margin of safety should be as small as possible to minimize unnecessary healthy tissue ablation, but large enough to ensure a high probability of complete tumor ablation. We believe that the margin-of-safety size should be a reflection of the uncertainty in the numerical model used for the treatment planning.
Uncertainty is impossible to completely eliminate from the material properties used for an IRE simulation. There will always be uncertainty associated with the conductivity used for the model. This uncertainty will be different depending on how the parameter used was obtained. There are accuracy limitation if the values were obtained from an in vivo measurement due to the inherent difficulty of making in vivo tissue measurements. Likewise, there are uncertainties from in vitro measurements due to tissues changing properties as they are removed. The problem is further compounded by tissue properties not being static in time. They change according to factors such as hydration and activity level. Finally, there is uncertainty if the conductivity value used was obtained from a published database because no two people are exactly the same.

This chapter will be have two sections that both investigate how uncertainty in model parameters propagate into the ablation prediction. The first section will deal with UQ of homogeneous tissue with an effort taken to make the results as general as possible and would be applicable to studies used for IRE model validation. The second section investigate the uncertainty associated with a heterogeneous system consisting of healthy tissue and a tumor.

3.2 Homogeneous Tissue UQ

The research done for this section investigated how different model parameters affect the uncertainty in the predicted ablation zone. When matching experimental results to numerical predications, there is a range of electrical field strengths that best correspond to experimental ablations [113]. The goal was to see if uncertainty in electrical properties could explain the uncertainty in ablation threshold. It also had a goal of providing a possible reference that allows clinical IRE researchers to get estimates on predicted variability in ablation sizes for a given setup. Due to the multitude of tissues as well as individual procedure setups used for IRE, it would be nearly impossible to perform experiments for uncertainty quantification of all possible combinations.

This section aimed to provide uncertainty quantification for a large number of scenarios. In an effort to make this work applicable to as many scenarios as possible, all simulations were performed for a homogeneous material for various conductivity parameters.
3.2.1 Governing Equations

The model used for irreversible electroporation is again steady-state direct-current described by using the Laplace equation,

$$\nabla \cdot (\sigma \nabla U) = 0.$$  \hfill (3.1)

As a tissue becomes electroporated, the conductivity increases. This can be incorporated into the model by representing the conductivity as a function of electrical field strength [67,78,81,82]. This study followed the work done by [87], and modeled the conductivity as

$$\sigma(\|E\|) = \sigma_0 + (\sigma_{max} - \sigma_0) \cdot \exp[{-A \cdot \exp(-B \cdot \|E\|)}]$$  \hfill (3.2)

where $\|E\|$ is the electrical field strength, $\sigma_0$ is the base conductivity before electroporation, $\sigma_{max}$ is the maximum conductivity achieved due to electroporation, and $A$ and $B$ are both coefficients that affect the shape of the sigmoid curve. The coefficients $A$ and $B$ are determined from experimental data.

Electrical field strength is often used as the determining factor as to whether or not tissue is ablated. For a homogeneous material modeled using Equation 3.2, the electrical field is independent of the base conductivity, $\sigma_0$, and only a function of the change in conductivity, and the coefficients $A$ and $B$. Since the electrical field is the main quantity of interest to this research, we will define the change in conductivity, $\Delta_\sigma$, as

$$\Delta_\sigma = \sigma_{max} - \sigma_0.$$  \hfill (3.3)

Since electrical field strength is independent of base conductivity we can choose any value greater than 0. We chose a value of 1 S/m. Equation 3.3 simplifies Equation 3.2 to

$$\sigma(\|E\|) = 1 + \Delta_\sigma \cdot \exp[{-A \cdot \exp(-B \cdot \|E\|)}].$$  \hfill (3.4)

Equation 3.4 will be used as the governing equation for all simulations in the section for homogeneous tissue.
3.2.2 Geometry

The geometry used for homogeneous tissue simulations consisted of two monopolar electrodes inserted into a sphere with a diameter of 10 cm. The electrodes are modeled as a cylinder with diameter of 2 mm. The electrodes have an active area that is set to a prescribed voltage, and an insulated upper portion. A schematic of the geometry can be seen in Figure 3.1.

![Figure 3.1: Schematic of the geometry used for the homogenous simulations.](image)

The electrode exposure length and the space between electrodes was varied for different cases.

3.2.3 Boundary Conditions

The boundary conditions on the active electrode surfaces consisted of enforcing a prescribed voltage value. One electrode was set to ground and the other electrode was set to a voltage $V_0$. The voltage, $V_0$, was one of the parameters that was varied between setups. The other remaining surfaces, the insulated electrical sleeves on the electrodes and the outer domain surface, were treated as electrically insulated by enforcing on these boundaries, the condition.

3.2.4 Parameter Variation

To investigate how model parameters affect uncertainty, Monte Carlo simulations were run for different model setups.
Each setup consisted of 50 trials where four parameters, voltage, spacing, and exposure length were kept constant and the 3 stochastic variables, $A$, $B$, and $\Delta_\sigma$ in Equation 3.4 were randomly chosen from their probability distributions.

The parameter combinations were chosen from five different voltages, four different electrode exposures, four different electrodes spacings, and four different mean values of $\Delta_\sigma$. This resulted in 320 different parameter combinations (5 x 4 x 4 x 4). Table 3.1 lists the values used for each parameter.

The shape of the conductivity function was treated as stochastic by randomly varying the parameters $A$, $B$, and $\Delta_\sigma$. Three different probability distributions were used for the uncertainty in $\Delta_\sigma$ and three different probability distributions were used for uncertainty in $A$ and $B$. Therefore, 9 different combinations of probability distributions were used in total (3 x 3=9). Each of these stochastic variables was treated as normally distributed with a standard deviation of 1, 5, or 10 percent their mean. The mean values for $A$ and $B$ used are displayed in Table 3.1 and were taken as the values for 100 $\mu$s pulse from [87]. The mean for both $A$ and $B$ were kept the same between all trials. Although, this will not be the mean value for all tissue, it should be applicable to wide variety of tissues as many tissues have conductivities that follow sigmoid curves. Furthermore, for each set of trials, the percentage of uncertainty in $A$ was always set equal to the percentage of uncertainty in $B$.

The goal of this effort was to compute a database that would allow researchers to look up their configuration and have an estimate on the expected variation in ablation volume. Even if their specific configuration was not used, enough setups were simulated that the hope was researchers could interpolate the database to find approximations.

It is worth noting that the electrical field does not depend on the initial base conductivity, but only on how the conductivity changes due to electrical field strength. As most tissue follows a sigmoid curve [67, 87, 114], this work can be applied to numerous types of tissues by choosing a $\Delta_\sigma$ that corresponds to that tissue. For example, liver has a $\Delta_\sigma$ of approximately 6 [115] and approximately 3 for kidneys [87]. Since data was computed for range of $\Delta_\sigma$, interpolation can be utilized to apply the results to a wide range of tissue.

No effort was taken to incorporate pulse number or pulse duration into the model. Although both have been shown to have an effect on ablation size by affecting IRE
threshold [116]. Instead this work reported ablation volumes for multiple threshold values so that researchers could then utilize the electrical field data provided to make ablation predictions from their pulse parameters.

### 3.2.5 Results

Volumes of tissue experiencing electrical fields greater than 600 V/cm, 700 V/cm, and 800 V/cm were computed for all trials. A common ablation threshold is 700 V/cm [114]. but by providing a range of ablation thresholds, researchers can interpolate results to match their threshold.

Statistical data in the form of mean and standard deviations for each ablation threshold volume was calculated for each parameter combination and stored. Standard deviation in ablation volume ranged from approximately 1 to 10 percent of the ablation volume for a given threshold.

Due to the sheer number of simulations runs, I am unable to present all the results. I have selected a few cases to demonstrate the data that can be extracted from the database. However, I can be contacted if you would are interested in obtaining the database.

#### 3.2.5.1 Partial Derivatives

It was investigated to see how uncertainty in ablation volume and shape changes with respect to various parameters. Due to having data at discrete points, partial derivative have to be approximated using some method. We chose to use central

---

Table 3.1: Monte Carlo Simulation Parameters

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage (V)</td>
<td>2000, 2250, 2500, 2750, 3000</td>
</tr>
<tr>
<td>Space between electrodes (mm)</td>
<td>10, 15, 20, 25</td>
</tr>
<tr>
<td>Exposure length (mm)</td>
<td>10, 15, 20, 25</td>
</tr>
<tr>
<td>$\Delta \sigma$ (S)</td>
<td>3, 4, 5, 6</td>
</tr>
<tr>
<td>$A$ mean value</td>
<td>3.2166</td>
</tr>
<tr>
<td>$B$ mean value</td>
<td>0.002543</td>
</tr>
<tr>
<td>Standard Deviation of $A$ and $B$ (%)</td>
<td>1, 5, 10</td>
</tr>
<tr>
<td>Standard Deviation of $\Delta \sigma$ (%)</td>
<td>1, 5, 10</td>
</tr>
</tbody>
</table>
finite difference, however since the data will be made freely available, different numerical differentiation schemes can be implemented by future researchers.

Due to limitation of space, we have chosen to only present the case of 2500 V, 15 mm exposure, 15 mm spacing, $\Delta_\sigma$ is 4, and 5% standard deviation in both $\Delta_\sigma$, A, and B. These values were chosen for a rough comparison with previously published experimental work found in [113]. For this setup, a standard deviation of 105.5 mm$^3$ was found for an ablation threshold of 700 V/cm. The partial derivatives of the standard deviation are presented in Table 3.2.

Table 3.2: Partial Derivatives of Ablation Volume at 700 V/cm

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Change in volume std w.r.t. dependent variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage</td>
<td>0.141 mm$^3$/V</td>
</tr>
<tr>
<td>Exposure Length</td>
<td>3.69 mm$^3$/mm</td>
</tr>
<tr>
<td>Spacing</td>
<td>7.82 mm$^3$/mm</td>
</tr>
<tr>
<td>$\Delta_\sigma$</td>
<td>2.04 mm$^3$</td>
</tr>
<tr>
<td>Standard Deviation of $A$ and $B$</td>
<td>19.6 mm$^3$ per change in percent</td>
</tr>
<tr>
<td>Standard Deviation of $\Delta_\sigma$</td>
<td>0.45 mm$^3$ per change in percent</td>
</tr>
</tbody>
</table>

Table 3.2 show that changes in $A$, and $B$ have the greatest impact on the uncertainty in the ablation volume. It is therefore beneficial to know both the maximum conductivity as well as the actual shape of the conductivity curve. It is also important to estimate the shape of the electrical conductivity as a function of electrical field strength with as high an accuracy as possible.

3.2.5.2 Dimensional Changes

It was also investigated how the height, width, and depth of the ablation zone changes with respect to some of the variables. We will define the width as being the ablation volume’s largest measurement if you were looking down the electrodes and in the direction parallel to the line connecting the two electrodes. The height will be the direction perpendicular to the line connecting the electrodes if you were looking down them. The depth would be the direction parallel with the electrodes.

Since, we did not have access to experimental data that would allow us to better predict the probability distribution for the parameters of $\sigma(|E|)$, the parameters were assumed to be normally distributed with a standard deviation of 1, 5, and 10 percent.
It was found that the variability is more sensitive to changes in $A$ and $B$ than in $\Delta_\sigma$, but variability was still low from both. Some of the results are displayed in Table 3.3.

<table>
<thead>
<tr>
<th></th>
<th>st. dev. in $A$ and $B$</th>
<th>st. dev. in $\Delta_\sigma$</th>
<th>st. dev. in width</th>
<th>st. dev. in height</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 %</td>
<td>5 %</td>
<td>0.07 mm</td>
<td>0.02 mm</td>
<td></td>
</tr>
<tr>
<td>10 %</td>
<td>5 %</td>
<td>0.17 mm</td>
<td>0.21 mm</td>
<td></td>
</tr>
<tr>
<td>5 %</td>
<td>1 %</td>
<td>0.13 mm</td>
<td>0.17 mm</td>
<td></td>
</tr>
<tr>
<td>5 %</td>
<td>10%</td>
<td>0.14 mm</td>
<td>0.18 mm</td>
<td></td>
</tr>
</tbody>
</table>

### 3.2.5.3 Uncertainty Distribution

Work was also done to visualize how the uncertainty in ablation volume is distributed. A total of 50 cases were run for 15 mm spacing and exposure, a voltage of 3,000 V, a $\Delta_s$ of 4 and a 5% variability in both $\Delta_s$, $A$, and $B$.

We can treat the probability of ablation as a binary function, where for a given point, the tissue is ablated if the electrical field is greater than 700 V/cm. Letting $p$ be the true probability of ablation, we can estimate $p$ with $\hat{p}$ by

$$\hat{p} = \frac{\text{Number of trials above 700 V/cm}}{\text{Total number of trials}}.$$  

(3.5)

The estimator $\hat{p}$ is defined pointwise, and is therefore a function of the coordinates $x$, $y$, and $z$.

The probability of tissue being ablated is displayed in Figures 3.2 and 3.3. The zone where $\hat{p}$ was greater than 0 but less than 1 was approximately 0.25 cm in the width direction and approximately 0.5 cm in the height and depth directions.

One of the advantages of IRE is its ability to be used near sensitive structures; thus it is fortunate, that there is a sharp demarcation between $\hat{p}$ having a value of 1 (almost surely ablated) and a value of 0 (almost surely not ablated). This provides further evidence that IRE has the potential to be a precise and predictable ablation technique.
It has been suggested that cell death due to IRE is a stochastic process that is
dependent on electrical field strength experienced [82]. For this reason, it is more informative to be aware of the distribution throughout the volume for the standard deviation of the electrical field strength. Figures 3.4 and 3.5 shows slices of the volume colored by standard deviation of electrical field. These figures show that the greatest variation on the electrical field is around the electrodes as would be expected due the electrical field being highest there. A standard deviation value of 25 V/cm was near the ablation zone.

Figure 3.4: Plot of the standard deviation of \( \|E\| \) in the xy plane for \( z=0 \) to show the distribution throughout the volume.
3.2.5.4 Probabilistic cell death model

So far in this section, tissue has been assumed to be ablated if the tissue experienced an electrical field strength above a certain threshold. It has been shown that there is an associated probability of tissue ablation that is dependent on both electrical field strength and pulse parameters [116].

Although the model for statistical cell death will likely vary between tissue types, we choose to calculate the cell death distribution as an illustrative example. It is worth noting these results may not be applicable to other parameters, but are intended to provide preliminary information on how the probability of tissue ablation is distributed. We used the same case as was done in the preceding section for calculating the ablation probability estimator, \( \hat{p} \). In [82], a model for statistical cell death is developed and utilized in [116, 117]. The expression used for the fraction of cells killed is

\[
F = 1 - \frac{1}{1 + \exp \frac{E - E_c(n)}{A(n)}}
\]  

(3.6)

where \( F \) is the fraction of ablated cells, \( n \) is the number of pulse, \( E_c(n) \) is a function of pulse number that represents the electrical field strength which results in half
the cells being ablated, and $A(n)$ is a fitting parameter. For illustrative purposes, we choose values of $E_c(n)$ and $A(n)$ that correspond to 70 pulses with pulse length of 100 µs and inferred from [82].

We can then form an estimate of the probability of ablation as the mean value of $F$ from the trials. This gives us an estimate on ablation probability as

$$\hat{p}_F = \frac{F}{\text{Number of Trials}}.$$  \hspace{1cm} (3.7)

Next we plotted $\hat{p}_F$, as can be seen in Figures 3.6 and 3.7. The transition zones are similar but slightly larger than what is observed when ablation is treated as a binary operation. The similar sharpness can be explained due to electrical field having relatively low standard deviation of approximately 25 V/cm at the ablation zone perimeter.

![Figure 3.6: Plot of $\hat{p}_F$ in the xy plane for z=0 to show the distribution throughout the volume.](image)

Figure 3.6: Plot of $\hat{p}_F$ in the xy plane for $z=0$ to show the distribution throughout the volume.
3.3 Heterogeneous Tissue UQ

Next the effect uncertainty in conductivity of both a tumor and tissue have on ablation predictions of a heterogeneous system are investigated. The previous section was focused on a homogeneous system that is well suited to comparison of IRE experiments to refine numerical predictions of IRE treatments. However, IRE is being developed as a ablation technique for heterogeneous systems consisting of healthy tissue and tumors. The research presented in this section aims to contribute to the understanding of uncertainty of IRE procedures involving more than one tissue type.

3.3.1 Conductivity Formulation

In this section, the conductivity is modeled used a sigmoid Gompertz curve with the form

$$\sigma = \sigma_0 + \frac{\sigma_{\text{max}} - \sigma_0}{1 + \exp\left[\frac{E - T}{W}\right]}$$

(3.8)
where $T$ and $W$ are coefficients used for curve fitting to experimental data for the particular tissue being modelled. The values used for $T$ and $W$ used are 950 V/cm and 200 V/cm respectively which are the same values used in [114] for liver tissue.

It was stated in [118] that tissues increase conductivity between 3 to 6 times due to electroporation. A middle value of 4.5 was chosen to be used for these simulations. Therefore, for all simulations the maximum conductivity will be 4.5 times the base conductivity,

$$
\sigma_{\text{max}} = 4.5\sigma_0
$$

To account for uncertainty, $\sigma_0$, will be treated as a random variable. Consequently $\sigma_{max}$ will also be a random variable as it depends directly on $\sigma_0$. The distributions used will be a normal distribution.

A recap of the equations used can be found in Table 3.4.

Table 3.4: A recap of the governing equations used to implement the IRE model.

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation 1.1</td>
<td>$\nabla \cdot (\sigma \nabla U) = 0$</td>
</tr>
<tr>
<td>Equation 3.8</td>
<td>$\sigma = \sigma_0 + \frac{\sigma_{\text{max}} - \sigma_0}{1+\exp\left[\frac{E_1 - \sigma_0}{\frac{W}{2}}\right]}$</td>
</tr>
</tbody>
</table>

### 3.3.2 Geometry

A two-dimensional geometry was used for the numerical model. It consisted of two monopolar electrodes whose centers are spaced 9.2 mm apart. In between the two electrodes is a circular tumor with diameter of 7 mm. The tumor is centered in a circular domain with a diameter of 7 cm. The electrodes have a diameter of 1.2 mm [43]. This results in a distance of 0.5 mm between the tumor and the electrodes. A schematic of the geometry can be seen in Figure 3.8.
Figure 3.8: Schematic of the domain used for the heterogenous simulations.

3.3.3 Boundary Conditions

Boundary conditions were similar to those used for the UQ of homogeneous tissue in the previous section. Specifically, one electrode is set to a voltage $V_0$ while the other electrode is set to ground. The outer boundary of the domain is set to electrically insulating.

3.3.4 Monte Carlo Cases

Monte Carlo simulations were run for three different cases to evaluate how uncertainty in the conductivity propagates into predictions for the electrical field. The three different cases were:

1. Only the base conductivity of the tissue is a random variable
2. Only the base conductivity of the tumor is a random variable
3. Base conductivity of the tumor and tissue are both random variables

The Monte Carlo simulations performed here were based off the uncertainties in conductivity reported by Haemmerich et al. [119]. In their work, they reported liver tissue as having a base conductivity of 0.75 mS cm$^{-1}$ with a standard deviation of 0.28 mS cm$^{-1}$, and liver tumors with a base conductivity of 4.11 mS cm$^{-1}$ with a standard deviation of 2.56 mS cm$^{-1}$. The distributions for $\sigma_0$ for both tissue and the tumor will be normal distributions with mean and standard deviations as found in [119].
When using the mean values for all variables, it was found that a voltage of 1,725 V is the minimum voltage necessary to completely cover the entire tumor in an electrical field strength of 700 V/cm which is a common value used as the threshold for the onset of IRE [5, 80, 114]. However, in treatment planning, a higher voltage than the minimum is often used as factor-of-safety. For this reason, the three cases were also run at voltages of 1,800 V and 2,000 V. Different voltages were also used to examine the effect voltage has on uncertainty. Each case was run with 200 trials at the three voltages. This bring the total number of different setups to 9, which resulted in 9 different data sets each consisting of 200 trials.

### 3.3.5 Heterogeneous Results

#### 3.3.5.1 Case 1: Uncertainty in tissue base conductivity

The effect of modeling the base conductivity for the healthy tissue as a random variable was investigated. The base conductivity for the liver tissue was treated as a normally distributed random variable with mean 0.75 mS cm$^{-1}$ and standard deviation 0.28 mS cm$^{-1}$. The base conductivity of the tumor was kept constant at 4.11 mS cm$^{-1}$. Statistics concerning the electrical field strength experienced by the tumor were computed and are displayed in Table 3.5. Percentages of the tumor experiencing electrical field strengths above a given threshold are displayed in Table 3.6.

<table>
<thead>
<tr>
<th>V$_0$ = 1725</th>
<th>Avg E. Field (V/cm)</th>
<th>Min. E. Field (V/cm)</th>
<th>Max E. Field (V/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>954 ± 129</td>
<td>688 ± 100</td>
<td>1571 ± 294</td>
</tr>
<tr>
<td>V$_0$ = 1800</td>
<td>978 ± 133</td>
<td>706 ± 103</td>
<td>1641 ± 317</td>
</tr>
<tr>
<td>V$_0$ = 2000</td>
<td>1042 ± 146</td>
<td>754 ± 109</td>
<td>1844 ± 384</td>
</tr>
</tbody>
</table>

Table 3.6: Ablation zones percentage. Table shows percentage of tumor above a given electrical field strength from varying $\sigma_0$ for tissue.

<table>
<thead>
<tr>
<th>V$_0$ = 1725</th>
<th>&gt;1000 V/cm</th>
<th>&gt;800 V/cm</th>
<th>&gt;700 V/cm</th>
<th>&gt;600 V/cm</th>
<th>&gt;500 V/cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39 ± 24</td>
<td>82 ± 21</td>
<td>93 ± 18</td>
<td>97 ± 14</td>
<td>98 ± 11</td>
</tr>
<tr>
<td>V$_0$ = 1800</td>
<td>44 ± 25</td>
<td>85 ± 21</td>
<td>94 ± 18</td>
<td>97 ± 14</td>
<td>98 ± 10</td>
</tr>
<tr>
<td>V$_0$ = 2000</td>
<td>57 ± 25</td>
<td>90 ± 19</td>
<td>96 ± 16</td>
<td>98 ± 12</td>
<td>99 ± 9</td>
</tr>
</tbody>
</table>
Table 3.7: Ablation sizes for IRE threshold at >700 V/cm.

<table>
<thead>
<tr>
<th>Voltage (V)</th>
<th>Healthy Tissue (mm$^2$)</th>
<th>Tumor &amp; Healthy Tissue (mm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_0 = 1725$</td>
<td>90.5 ± 6.0</td>
<td>126.3 ± 12.9</td>
</tr>
<tr>
<td>$V_0 = 1800$</td>
<td>98.3 ± 6.2</td>
<td>134.5 ± 13.1</td>
</tr>
<tr>
<td>$V_0 = 2000$</td>
<td>118.1 ± 6.3</td>
<td>155.0 ± 12.5</td>
</tr>
</tbody>
</table>

A histogram for the average electrical field experienced by the tumor for 1725 V is displayed in Figure 3.9. The histogram shows the shape is roughly symmetrical. Similar results were found for the other voltages and other cases.

As we are most interested in preventing tumor recurrence, we looked at the first quartile for ablation percentage. It was found that only 75% of the trials had at least 65% of the tumor experiencing an electrical field of 700 V/cm or more. For 2,000 V, all the trials but 1 completely covered the tumor in a field at least 700 V/cm. This clearly shows the need for using a safety-factor in the form of a higher voltage. The effect of using a high voltage on the amount of healthy tissue and total tissue ablated is displayed in Table 3.7.

It was also investigated to get an estimate of how many trials exposed 90% of the tumor to an electrical field strength of 700 V/cm. This was done to get an idea of the chance of recurrence by not eliminating enough of the tumor. For 1,725 V, 29 out of 200 or 14.5% of the trials exposed less than 90% of the tumor to the ablating electrical field strength. This number drops to 9 out of 200 or 4.5% when a voltage of 2,000 V is applied. These numbers seem high for both the 1,725 V case and 2,000 V case when the goal is to ensure a high enough level of tumor ablation to prevent cancer recurrence and suggest using an even higher voltage for treatment. Histograms showing ablation percentage at 700 V/cm is displayed in Figure 3.10 and Figure 3.11.
Figure 3.9: Histogram of the average electrical field experienced by the tumor at 1725 V for case 1. Roughly follows a normal distribution.

Figure 3.10: Histogram for percentage of tumor above 700 V/cm for case 1 at 1,725 V.

Figure 3.11: Histogram for percentage of tumor above 700 V/cm for case 1 at 2,000 V.
### 3.3.5.2 Case 2: Uncertainty in tumor base conductivity

Next, the effect the tumor’s base conductivity had on the electrical field was investigated. This was done by modeling the conductivity in the tumor as a normally distributed random variable with mean 4.11 mS cm\(^{-1}\) and standard deviation 2.56 mS cm\(^{-1}\). The base conductivity of the tissue was kept constant at 0.75 mS cm\(^{-1}\). Results from the Monte Carlo simulations are displayed in Tables 3.8, 3.9 and 3.10.

Table 3.8: Electrical Field Statistics within the Tumor. Varying \(\sigma_0\) for the tumor.

<table>
<thead>
<tr>
<th>(V_0) (V/cm)</th>
<th>Avg E. Field (V/cm)</th>
<th>Min. E. Field (V/cm)</th>
<th>Max E. Field (V/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1725</td>
<td>1023 ± 231</td>
<td>737 ± 173</td>
<td>1734 ± 563</td>
</tr>
<tr>
<td>1800</td>
<td>1051 ± 244</td>
<td>758 ± 179</td>
<td>1814 ± 599</td>
</tr>
<tr>
<td>2000</td>
<td>1126 ± 278</td>
<td>812 ± 198</td>
<td>2033 ± 694</td>
</tr>
</tbody>
</table>

Table 3.9: Ablation zones percentage. Table shows percentage of tumor above a given electrical field strength from varying \(\sigma_0\) for the tumor.

<table>
<thead>
<tr>
<th>(V_0) (V/cm)</th>
<th>(&gt;1000) V/cm</th>
<th>(&gt;800) V/cm</th>
<th>(&gt;700) V/cm</th>
<th>(&gt;600) V/cm</th>
<th>(&gt;500) V/cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1725</td>
<td>44 ± 33</td>
<td>82 ± 20</td>
<td>94 ± 9</td>
<td>99 ± 2</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>1800</td>
<td>48 ± 33</td>
<td>85 ± 17</td>
<td>95 ± 8</td>
<td>99 ± 2</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>2000</td>
<td>59 ± 31</td>
<td>90 ± 13</td>
<td>98 ± 5</td>
<td>99 ± 1</td>
<td>100 ± 0</td>
</tr>
</tbody>
</table>

Interestingly, it was found that there was a lower standard deviation in the percentage of tumor above a given electrical field strength when the tumor was a random variable instead of the tissue. This result comes as a surprise since the variability of the conductivity is higher for the tumor than the tissue.

Again, the number of trials in which 10% or more of the tumor experienced an electrical field less than 700 V/cm was calculated. At 1,725 V, it was 55 out of 200 or 27.7%, and for 2,000 V it was 27 out of 200 or 13.5%. The histogram for the percentage of tumor above 700 V/cm can be found in Figure 3.12 for 1,725 V and in Figure 3.11 for 2,000 V.
Table 3.10: Ablation sizes for IRE threshold at >700 V/cm.

<table>
<thead>
<tr>
<th>Voltage (V)</th>
<th>Healthy Tissue (mm$^2$)</th>
<th>Tumor &amp; Healthy Tissue (mm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_0 = 1725$</td>
<td>$92.2 \pm 9.3$</td>
<td>$128.4 \pm 12.8$</td>
</tr>
<tr>
<td>$V_0 = 1800$</td>
<td>$100.0 \pm 9.3$</td>
<td>$136.56 \pm 12.4$</td>
</tr>
<tr>
<td>$V_0 = 2000$</td>
<td>$120.5 \pm 8.9$</td>
<td>$158.21 \pm 10.8$</td>
</tr>
</tbody>
</table>

Figure 3.12: Histogram for percentage of tumor above 700 V/cm for case 2 at 1,725 V.

Figure 3.13: Histogram for percentage of tumor above 700 V/cm for case 2 at 2,000 V.

3.3.5.3 Case 3: Uncertainty in tissue and tumor base conductivity

This case best represents the scenario of treatment planning. When planning for a specific patients there is a degree of uncertainty in both the conductivity of the tissue and the conductivity of the tumor. The conductivity for the tissue and for the tumor are both treated as independent random variables whose distributions are
the same as was used in cases 1 and 2. Statistics on the electrical field experience by the tumor are displayed in Tables 3.11, 3.12, and 3.13.

Table 3.11: Electrical Field Statistics within the Tumor. Varying $\sigma_0$ for both liver tissue and the tumor.

<table>
<thead>
<tr>
<th>$V_0$ (V)</th>
<th>Avg E. Field (V/cm)</th>
<th>Min. E. Field (V/cm)</th>
<th>Max E. Field (V/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1725</td>
<td>1034 ± 280</td>
<td>744 ± 211</td>
<td>1784 ± 654</td>
</tr>
<tr>
<td>1800</td>
<td>1064 ± 294</td>
<td>765 ± 218</td>
<td>1868 ± 694</td>
</tr>
<tr>
<td>2000</td>
<td>1142 ± 332</td>
<td>821 ± 240</td>
<td>2090 ± 805</td>
</tr>
</tbody>
</table>

Table 3.12: Ablation zones percentage. Table shows percentage of tumor above a given electrical field strength from varying $\sigma_0$ for both the liver tissue and the tumor.

<table>
<thead>
<tr>
<th>$V_0$ (V)</th>
<th>&gt;1000 V/cm</th>
<th>&gt;800 V/cm</th>
<th>&gt;700 V/cm</th>
<th>&gt;600 V/cm</th>
<th>&gt;500 V/cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1725</td>
<td>47 ± 37</td>
<td>78 ± 29</td>
<td>89 ± 21</td>
<td>96 ± 14</td>
<td>99 ± 7</td>
</tr>
<tr>
<td>1800</td>
<td>50 ± 37</td>
<td>80 ± 28</td>
<td>91 ± 20</td>
<td>96 ± 13</td>
<td>99 ± 6</td>
</tr>
<tr>
<td>2000</td>
<td>59 ± 36</td>
<td>85 ± 24</td>
<td>94 ± 16</td>
<td>98 ± 10</td>
<td>99 ± 4</td>
</tr>
</tbody>
</table>

Table 3.13: Ablation sizes for IRE threshold at >700 V/cm.

<table>
<thead>
<tr>
<th>$V_0$ (V)</th>
<th>Healthy Tissue (mm$^2$)</th>
<th>Tumor &amp; Healthy Tissue (mm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1725</td>
<td>92.6 ± 10.9</td>
<td>126.9 ± 19.0</td>
</tr>
<tr>
<td>1800</td>
<td>100.1 ± 11.3</td>
<td>135.1 ± 19.0</td>
</tr>
<tr>
<td>2000</td>
<td>120.2 ± 11.7</td>
<td>156.4 ± 17.9</td>
</tr>
</tbody>
</table>

For a voltage of 1725 V, it was found that 10% or more of the tumor was below an electrical field strength of 700 V/cm for 55 out of the 200 trials. This number drops to 36 out of the 200 trials for the 2,000 V case. This is a higher likelihood than when only the tissue was a random variable, and approximately the same as when only the tumor was a random variable.

If these simulations were used for treatment planning, it would surely be concluded that 2,000 V is insufficient because 90% of the tumor was ablated only 82% of the time. Therefore, a 15% increase in voltage is an insufficient amount for a factor of safety for this setup. However, if we lessen the threshold of ablation to 600 V/cm, then for every trial at least 90% of the tumor or more was ablated.

Contour plots of the mean value of the electrical field experienced by the tumor is displayed in Figure 3.16, and contour plots for the standard deviation of the
electrical field is in Figure 3.17. These figures show that there is higher standard deviation in the electrical field strength near the edges closest to the electrodes, and the least near the poles. This is similar to how the mean of the electrical field is greatest nearest the electrodes and least at the poles. To get a better sense of the percentage of change of the electrical field, the relative standard deviation was plotted in Figure 3.18. The relative standard deviation is defined to be the standard deviation divided by the mean and is expressed as a percentage. The tumor’s electrical field had a relative standard deviation of approximately 0.2-0.35. The relative standard error was similar for 1,800 V and 2,000 V.

Figure 3.14: Histogram for percentage of tumor above 700 V/cm for case 3 at 1,725 V.

Figure 3.15: Histogram for percentage of tumor above 700 V/cm for case 3 at 2,000 V.
Figure 3.16: Contour plot of the mean for the electrical field experienced by the Tumor

Figure 3.17: Contour plot of the standard deviation for the electrical field experienced by the tumor
3.3.6 Discussion and Conclusions

As the father of modern medicine, William Osler, once said, "Medicine is a science of uncertainty and an art of probability." Knowing the amount of uncertainty in a simulation for treatment planning is critical in predicting the probability of the treatment being a success. The result of this research will aid in the design of future treatment planning protocols by giving a mathematical basis to the safety factors chosen for treatment planning, and the research presented in this chapter will provide some of the information necessary to help predict a treatment’s probability of success.

In this chapter, Monte Carlo simulations were run for a wide range of IRE setups to examine the effect various parameters have on the variability of the ablation volume. Contributions of this chapter came from UQ of homogeneous and a heterogeneous system. The contributions were:

1. There was a sharp transition on the estimate of ablation probability and provided further evidence on the ability of IRE to be a precise treatment procedure.

2. There was reasonable agreement between the variability in dimensional sizes of the simulations and the experimental results found in [113] and [120]. Thus uncertainty in tissue conductivity could be a possible explanation for variation in dimensional sizes as opposed to variation in IRE threshold.
3. Small changes in uncertainty of the conductivity function fitting parameters $A$ and $B$ results in the largest change in ablation uncertainty. In contrast, changes in $\Delta\sigma$ played a minor role in affecting ablation uncertainty. This shows that overall shape of the conductivity function plays an important role in electrical field predictions.

4. Spacing between electrodes has a larger impact on ablation variability than the exposure length of the electrodes.

5. Even with a 10% standard deviation in the parameters $A$, $B$, and $\Delta\sigma$, ablation volume predictions varied by less than 10%.

6. The relative standard error for the electrical field of the tumor is 0.2-0.3 percent and its distribution throughout the tumor

Perhaps the largest contribution of this work is showing that uncertainty in the electrical field due to uncertainty in tissue conductivity properties at least partially explains the uncertainty in ablation volumes seen in experiments. To account for experimentally observed variability in ablation volumes, it has been suggested that there is a variability in tissue IRE threshold [61, 113]. It closely matched the experimental results seen in [61, 113, 120].

Another contribution of this work was finding that uncertainty in conductivity parameters can result in an expected uncertainty of 0.25 cm to 0.5 cm in ablation dimensions. This is an important consideration to keep in mind when treatment planning as this may be an intrinsic limitation to the accuracy of IRE procedures. The ablation variability will of course be dependent on the organ being treated as variability in observed tissue conductivity varies from organ to organ. Also these values may be different for heterogeneous systems such as when a tumor is present in the model.

Furthermore, this chapter contributed by displaying where in the tumor the greatest variability in the electrical field is. It was found that uncertainty in the tumor conductivity played a smaller role than the uncertainty in the liver tissue when it came to the percentage of the tumor covered by a given electrical field strength. This is potentially good news for treatment planning as tumors have a higher variability in conductivity. Conversely, variability in tissue conductivity
played a larger role than tumor conductivity in the minimum, maximum and average electrical field strength experienced by the tumor.

The goal of this work was not to provide a definitive answer to uncertainty quantification for IRE, but to encourage the application and research of uncertainty quantification in more aspects of treatment planning protocols in irreversible electroporation. IRE is still a relatively new field of study, and as such there is still growing amount of experimental data for conductivity of various tissues. As such there is many opportunities for future research. More specifically, experimental work is needed to better understand the uncertainties of various tissues. More mathematical and numerical work is needed to better understand how these uncertainties propagate into final ablation predictions.

The potential value of this research is to begin to provide expectations of uncertainty in treatment planning and experimental results for IRE. For all three homogeneous cases, the total area of ablated tissues had a relative standard deviation of \( \sim 10\% \). This amount of uncertainty helps with establishing expectations of accuracy for simulations used in treatment planning of IRE. It is would be reasonable to expect similar standard deviations when comparing experimental IRE procedures on livers to simulations.

The heterogeneous system used uncertainties for conductivity for the liver, but future work could use different organs. Uncertainties in the conductivity is not the same for all tissue, and these different uncertainties in conductivity could be used to develop different factor-of-safety guidelines for different tissues. Future work can also be done to see the effect tumor size has on uncertainty.
4.1 Introduction

Roughly one in ten IRE procedures have a local tumor recurrence due to incomplete ablation [121]. It was demonstrated by Golberg et al. that one possible explanation is due to blood vessels producing an electrical sink effect which results in islands of unablated cells [122]. Qasrawi et al. performed simulations on an anatomically accurate model of a liver that included blood vessels as small as 400 micrometers in diameter and concluded that blood vessels have a non-negligible effect on numerical ablation predictions [114].

Furthermore, it has been shown that blood vessels with diameters smaller than what was included in Qasrawi et al’s anatomically accurate model can have an electrical-field sink effect [122]. Unfortunately, tumors have a greater quantity of blood vessels due to angiogenesis [123], and a greater number of blood vessels would then result in a more prominent electrical sink effect in tumors.

Ideally, these smaller blood vessels would be mapped on an individual patient basis, and incorporated into a simulation’s geometry during the treatment planning
phase. However, this is impractical due to current imaging techniques being limited to structure sizes of approximately 200 micrometers [124]. Consequently, any structure smaller than 200 micrometers is left unaccounted for during the treatment planning phase.

Since it is currently not possible to image and include a patient’s blood vessels at these smaller scales, this is a source of uncertainty during the treatment planning process. The aim of this research is to better understand the degree at which these small scale vessels impact electrical field predictions for treatment planning.

To investigate the effect these small vessels have, simulations of a tumor surrounded by healthy tissue was simulated. The first set of simulations were done without including blood vessels as is typically done in IRE treatment planning. The second set of simulations consisted of four hundred Monte Carlo simulations with randomly distributed blood vessels within the tumor. Statistics were then determined for the unablated volumes and conclusions drawn.

The goal of this chapter was to provide physicians with more information on the potential area of unablated tissue that can be expected when performing treatment planning with models that do not include blood vessels with diameters smaller than 200 micrometers.

### 4.2 Methods

#### 4.2.1 Governing Equations

As was done in previous chapters and works, the problem will be treated as steady-state and modelled using Equation 1.1. The tissue conductivity was modelled using a sigmoid curve [67,84,114]. The conductivity is then expressed as

$$\sigma = \sigma_0 + \frac{\sigma_{\text{max}} - \sigma_0}{1 + \exp\left(\frac{T - \|E\|}{W}\right)}$$

(4.1)

where $T$ and $W$ are coefficients used for curve fitting, $\sigma_0$ is the the base conductivity before electroporation, $\sigma_{\text{max}}$ is the maximum conductivity a tissue can achieve after electroporation, and $\|E\|$ is the $l^2$-norm of the electrical field. In equation 4.1, $\sigma$ is only a function of the electrical field’s norm.

The values for $\sigma_0$, $\sigma_{\text{max}}$, $T$, and $W$ were those inferred from [115] and used
in [114] for both the healthy liver tissue and the tumor. The values used for both healthy tissue and tumorous tissue was 950 V/cm and 200 V/cm for T and W respectively [114,115]. Healthy tissue was modeled with conductivies for $\sigma_0$ and $\sigma_{\text{max}}$ of 0.05 S/m and 0.3 S/m respectively [114,115]. The tumorous tissue was modelled with conductivity values of 0.2 S/m and 0.5 S/m for $\sigma_0$ and $\sigma_{\text{max}}$ respectively [114,115]. The blood vessels were modeled as having a constant conductivity of 0.7 S/m [114].

4.2.2 Model Geometry

The geometry used for the numerical simulations was two dimensional. The entire domain was a 7 cm diameter circle. The two monopolar electrodes were modeled as 1 mm diameter circles. The tumor was located at the center of the domain and was represented by a circle with a diameter of 8 mm. To lessen the computational burden, only half of the geometry was modeled in the simulations through the use of a symmetry line. Figure 4.1 shows a detailed schematic of the geometry used.

![Figure 4.1: Schematic of geometry used for simulations. Dark inner circle is the tumor with the 0.5 cm margin of safety drawn around it.](image)
4.2.3 Boundary Conditions

The boundary conditions in this chapter will be defined the same as was done in Chapter 1. Also as was done in previous chapters, The voltage, $U$, will be prescribed on the electrodes and the boundary of the domain will be set to electrical insulating.

4.3 Results

Simulations were first performed to determine the minimum voltage necessary to completely ablate the tumor with no blood vessels in the model. By trial and error, it was found that the minimum voltage necessary to cause complete tumor ablation is approximately 1975 V. However, IRE treatments are often administered with a voltage higher than the bare minimum as a factor-of-safety. During tumor resection, a margin of safety of 0.5-1 cm is used in case of micro-metastasis [112]. For this reason, simulations were run to determine the voltage necessary to ablate the tumor with a safety margin of 0.5 cm. It was determined that a voltage of 2820 V was necessary to ablate the entire tumor and a factor of safety of 0.5 cm. These two voltages, 1975 V and 2820 V, were used for all subsequent simulations. Results for the simulations without blood vessels can be seen in Figures 4.2 and 4.3.
Figure 4.2: Electrical field strength (V/cm) for a geometry without blood vessels at 1975 V.

Figure 4.3: Electrical field strength (V/cm) for a geometry without blood vessels at 2820 V.
4.3.1 Monte Carlo Cases

Monte Carlo simulations were performed to quantify the effect these small scale blood vessels can have on ablation predictions. Twenty trials were performed for both voltages for a total of 50 simulations in all. For every trial, each blood vessel’s location was randomly chosen from a uniform distribution within the tumor.

The probability distributions for the size and number of blood vessels were taken from the experiments done by Ryscich et al. [125]. In their work they report distributions for both size and number of blood vessels found in a liver tumor (Table 3 and Figure 3 in [125]). For the simulations, the number of blood vessels was treated as a normally distributed random variable with a mean value of 49 and standard deviation of 13 blood vessel per $mm^2$. Each individual blood vessel’s size was treated as a random variable and follow the distribution found in Figure 3 of [125].

Each individual blood vessel location is chosen independently of every other blood vessel location and therefore allows for overlap between the blood vessels. This overlap was found to be small due to the blood vessels comprising a small percentage of the tumor’s area.

Mean and standard deviation data for electrical field properties as well as ablation results for both the tumor and the margin of safety can be found in Tables 4.1 and 4.2.

<table>
<thead>
<tr>
<th>Table 4.1: Monte Carlo Simulation Results</th>
<th>Tumor Avg. E. Field (V/cm)</th>
<th>Ablation Area (mm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_0 = 1975V$</td>
<td>841.9 ± 1.1</td>
<td>201.1 ± 2.6</td>
</tr>
<tr>
<td>$V_0 = 2820V$</td>
<td>1086 ± 0.8</td>
<td>343.1 ± 2.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4.2: Ablation Percentage Results</th>
<th>Tumor Ablation (%)</th>
<th>Safety Area Ablation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_0 = 1975V$</td>
<td>93.37 ± 1.29</td>
<td>Not calculated</td>
</tr>
<tr>
<td>$V_0 = 2820V$</td>
<td>99.41 ± 0.18</td>
<td>99.12 ± 0.11</td>
</tr>
</tbody>
</table>

As can be seen in Figures 4.4 and 4.5, the unablated tissue for the trials was localized to areas near blood vessels. As the blood vessels were of small diameters, the areas of unablated tissue near them was also small. Figures 4.6 and 4.7 show
a close up view of the electrical field distribution in the tumor for a case at 1975 V and 2820 V respectively. These figures further show the small ablations islands located near blood vessels. Some tissue was unablated at the edges of the margin of safety in the 2820 V case as well.

Both voltages exposed the tumor to average electrical field strengths significantly higher than the threshold for ablation. However, there were also areas significantly below the ablation threshold for ablation. These were small isolated islands of unablated tissue. The authors are not in a position to make predictions on if these unablated islands of tissue are large enough for significant chances of tumor recurrence.

For simulations at 1975 V, nearly 7% of the tumor was unablated on average. This number seems unacceptably high for treatment planning. However, for a voltage of 2820 V, the mean value of unablated tumor was approximately 1%; a much more reasonable number.

It is promising to see that the variability in the ablation percentage of the tumor is relatively small. The standard deviation was 1.29% for 1975 V, and less than 1% for 2820 V. Furthermore, the variability in the percentage of unablization in the tumor and margin of safety was even lower with a standard deviation of less than half a percent for 2820 V. Finally, the variability in the ablation in the total ablation area was also very low at approximately 1%.

Since the standard deviation was low for both voltages and various measures, we conclude that the effect small scale vessels have on ablation prediction is relatively consistent and fairly predictable. Therefore, if deemed necessary, the effect of small blood vessels can be reliably accounted for in modeling and treatment planning.
Figure 4.4: Example of results from a trial with a voltage of 1975 V that shows both the tumor and the margin of safety. The color red represents ablated tissue ($\geq 700$ V/cm). The blood vessels and electrodes are white.

Figure 4.5: Example of results from a trial with a voltage of 2820 V that shows both the tumor and the margin of safety. The color red represents ablated tissue ($\geq 700$ V/cm). The blood vessels and electrodes are white.
Figure 4.6: Example of results from a trial with a voltage of 1975 V. The color red represents ablated tissue ($\geq 700$ V/cm). The blood vessels and electrodes are colored white.

Figure 4.7: Example of results from a trial with a voltage of 2820 V. The color red represents ablated tissue ($\geq 700$ V/cm). The blood vessels and electrodes are colored white.
When treatment planning is done with a voltage corresponding to a 5 mm safety margin, the ablation of the tumor was nearly complete with low variability between trials. Furthermore, the variability seen in the ablation percentage, 1%, was lower than the variability that can be expected due to uncertainty in the electrical conductivity of the tumor [126]. It can then be concluded that the current practice of not taking into account small scale vessels for treatment planning is an acceptable practice.

4.4 Discussion

Some of the first steps taken towards understanding the impact of blood vessels on electrical field predictions was done in [114, 122]. This research built upon those previous works by focusing on the predicted effect small unmodelled blood vessels have on ablations. Generally accepted IRE governing equations were used to make numerical predictions and examine the variability in ablation area due to the presence of small diameter vessels in tumors.

The clinical relevance of this research is to provide researchers and physicians with more confidence in the current practice of not factoring in the effect small diameter vessels have on tumor ablation predictions. It also suggests that consideration must be taken when deciding to use a safety margin of less than 5 mm. Fortunately, 5 mm is often on the low end of safety margins as some physicians will even use 1 cm as a minimum for their safety margin [127]. For these cases, we conclude that even though tumors have more numerous blood vessels, the small scale vasculature of the tumor will still not have a prominent effect on the ablation size or shape at these voltages. Furthermore, the undertreatment area near a blood vessel is related to the size of the blood vessel. Since these simulations used small scale blood vessels, the resulting undertreatment areas consisted of small isolated areas of undertreatment. These small areas will be surrounded by ischemic tissue and may not result in new tumor growth.

It should be noted that this research is not saying that blood vessels should never be incorporated into the simulation geometry used for ablation zone predictions. Large scale vessels can and do have an important effect of ablation zones [114, 122].

This research was aimed at the effect caused by small diameter vessels that are currently too small to be captured by imaging techniques for incorporation into
numerical models.

One weakness of this study is that it was done in only two dimensions. Although it seems reasonable to assume that a similar conclusion would be reached if the simulations were performed in three dimensions, it should be verified. Future work should also include examining how changes in the tumor size affects the uncertainty. Other possible improvements to the study would be incorporating blood vessels in the healthy tissue and not just the tumor. This was done due to computational limitations and because the ablation of healthy tissue was only a secondary interest to this study. Finally this study used a uniform probability distribution to randomly choose each blood vessel’s location. It is possible that a different probability distribution better captures blood vessel distribution in a tumor.

4.5 Conclusions

It was determined that treatment planning with a margin of safety of 0.5 cm is enough to make the effect of small diameter blood vessels negligible and showed very little variability. However, it was found that when treatment planning was performed without a safety factor, percentages of unablated tumor were higher than what we would consider acceptable. This work then supports the current practice of not taking into account the effect of small diameter blood vessels in treatment planning when a margin of safety is included.
Chapter 5
IRE Treatment Planning Workflow

5.1 Introduction

It is possible to use numerical optimization algorithms to determine locations and voltages for electrodes. Optimization problems consist of minimizing a cost function where certain conditions are assigned a value. The assignment of these values is subjective and dependent on the individual surgeon due to medicine not being perfectly predictable. Just as not all doctors will take the same approach to a given medical problem, it can not be expected that all doctors will assign the same cost function. Furthermore, giving medical doctors the ability to adjust cost function parameters is not an optimal solution since medical doctors expertise doesn’t always translate easily into mathematical equations and algorithms. This can lead to optimization algorithms acting as a black box that determines treatment parameters.

Medical doctors should play as large a role as possible in treatment planning and the aim of this research was to develop a methodology that allows them take a more involved role. The end goal is better utilization of the wealth of knowledge and
experience held by the medical team. This will be accomplished by allowing medical doctors to instantly see how changing parameters (electrode position, number, and voltage) affects the ablation shape.

In this chapter, a work-flow is proposed in which a large amount of pre-computations enables the ability for medical doctors to change treatment parameters and see how it affects ablation zones without having to wait for the program to recompute after each change. Then once a an ablation zone had been determined, accurate nonlinear models are used to determine voltages that predict an ablation zone as close as possible to the targeted zone.

The idea behind this algorithm is that contour lines are similar for both the linear and nonlinear model.

5.2 Methods

This chapter will use the same governing equations and domain boundary conditions as was used in Chapter 4. Specifically a conductance described by Equation 4.1,

$$\sigma = \sigma_0 + \frac{\sigma_{max} - \sigma_0}{1 + \exp\left(\frac{T - ||E||}{W}\right)}.$$  

As was done in previous chapters, the values for $\sigma_0$, $\sigma_{max}$, T, and W were those inferred from [115] and used in [114] for both the healthy liver tissue and the tumor. The values used for both healthy tissue and tumorous tissue was 950 V/cm and 200 V/cm for T and W respectively [114,115]. Healthy tissue was modeled with conductivities for $\sigma_0$ and $\sigma_{max}$ of 0.05 S/m and 0.3 S/m respectively [114,115]. The tumorous tissue was modelled with conductivity values of 0.2 S/m and 0.5 S/m for $\sigma_0$ and $\sigma_{max}$ respectively [114,115].

5.2.1 Algorithm

The algorithm is built on the idea that electrical field contour lines have similar shapes for both the linear and nonlinear formulation. This is not saying that a given electrical field strength has the same contour or similar contours for both models. Instead, we are saying that for a given contour in the linear model, there is a corresponding contour that is similar in shape but at a possibly different electrical
field strength value. This is demonstrated in Figure 5.1 where contours have similar shapes for both linear and nonlinear models but different electrical field values.

Figure 5.1: Different electrical field contour lines that demonstrate the similar shape between the linear model (red) and the nonlinear model (blue). The contour lines do not have matching values as the contour lines for the linear model were at 250, 370, 550, 900 V/cm, and the contour lines for the nonlinear model were 300, 400, 550, and 800 V/cm.

This then allows the linear model to be used to determine possible ablation zone shapes before using the nonlinear model to determine voltages that produce the targeted ablation zone. The linear model is better suited to ablation zone determination due to solutions to linear differential equations being additive and because linear differential equations are faster to solve on computers.

Our proposed treatment planning process can be broken down into three separate phases.

1. Linear Model Computations

2. Electrode Configuration and Ablation Zone Determination
3. Electrode Voltage Determinations

**Step 1: Linear Model Computation**

The first step in the treatment planning algorithm is to run a large number of simulations of the linear model with two electrodes in a wide variety of positions. The results of these simulations will be utilized in step 2. Although this can require a large amount of computing resources, the problem is perfectly parallelizable due to each simulation being independent of the others. The problem is then well suited to being carried on a computer cluster.

It is important to note, that any voltage can be chosen for the linear models. Changing the voltage only changes the electrical field contour line values and not the shape of the contour lines themselves. Since the value of the contour lines are ignored in subsequent steps, we are free to chose any value for the voltages of the linear models.

**Step 2: Electrode Configuration and Ablation Zone Determination**

The second step in the process is using the results from Step 1 to help determine the electrode arrangement. It is at this step that the algorithm begins to show its advantage.

The process begins by allowing a doctor to choose a position for two electrodes. The doctor can move the electrode around on the screen as well as change the contour level and see how this influences the shape of the ablation zone. Since this is being done with precomputed linear models, the doctor doesn’t need to wait for the system to perform a calculation every time the voltage is changed or an electrode moves. The system will only have to read in the precomputed results and will therefore allow the doctor to easily and quickly experiment with ways of changing the ablation zone. Furthermore, the doctor can easily add multiple electrodes to the system and quickly see how changing the number and arrangement of electrodes affects the ablation zone.

We again would like to point out that the contour lines chosen for each electrode pair need not be the IRE threshold value, nor do they even need to be the same. The electrical contour lines of the linear model are used merely to show potential shapes that could be ablated by selecting the proper voltage such that the IRE threshold value contour matches as closely as possible.

Once a medical doctor has determined the number of electrodes, the arrangement of electrodes, and the targeted ablation zone, we move to step three of the algorithm.
Step 3: Electrode Voltage determination

Having determined where the electrodes will be placed and the area the medical doctors wish to ablate, the nonlinear model can be used to determine the value for the electrodes that will ablate the target zone from Step 2. It is important to use the more accurate nonlinear model for voltage determination due to the contour lines not having matching values.

This step consists of running several iterations of nonlinear model at various voltages to determine the voltage combination that most closely resembles the targeted ablation zone from Step 2. The process of choosing electrode voltages that most closely match the target area can be automated. Automating the process requires defining a metric function, and then minimizing it. Optimization should be a straightforward process since the ablation zone is continuously and smoothly dependent on the voltages, and thus allows the application of gradient based optimization algorithms.

There is some loss of accuracy due to non-active electrodes being left out of the linear model. However, this effect becomes more negligible farther away from the electrodes. Since the ablation zone edge is the area of interest and is far away from the actual electrodes themselves, the effect should be minor.

5.3 Results

The following subsections show results that compare the accuracy between the nonlinear model and a target zone determined from the linear model. The first subsections will look at homogeneous tissue and how various model parameters affect the accuracy of the linear model to be used for treatment planning. The final subsection will be a full example, consisting of multiple electrodes and a heterogeneous system.

5.3.1 Effect of Spacing

The effect of spacing between electrodes was investigated. Simulations were run with the nonlinear model for spacings of 10, 15, and 20 millimeters and a $\Delta_\sigma$ of 3. The voltage was set at 2500 V for all cases. After computing the nonlinear model, the linear model contour lines were compared to see how similar the results were.
Starting with the nonlinear model and moving to the linear model is in reverse from the algorithm but was done as a means to investigate the linear model’s accuracy with respect to spacing. The results are displayed below in Figures 5.2 - 5.4. The linear model shows more necking when compared to the nonlinear formulation.

Figure 5.2: Comparison of ablation zone between the linear (red) and nonlinear (blue) models for an electrode spacing of 10 mm.

Figure 5.3: Comparison of ablation zone between the linear (red) and nonlinear (blue) models for an electrode spacing of 15 mm.

Figure 5.4: Comparison of ablation zone between the linear (red) and nonlinear (blue) models for an electrode spacing of 20 mm.
5.3.2 Effect of $\Delta_\sigma$

Next, we investigated the effect $\Delta_\Sigma$ has on the accuracy of the model. As was done in the previous section, we will begin with a chosen nonlinear setup. We used an electrode spacing of 15 mm and a voltage 2,500 V. The change in conductivity, $\Delta_\sigma$, was varied from 2 to 5.

Figure 5.5: Comparison of ablation zone between the linear (red) and nonlinear (blue) models for $\Delta_\sigma = 2$.

Figure 5.6: Comparison of ablation zone between the linear (red) and nonlinear (blue) models for $\Delta_\sigma = 3$.

Figure 5.7: Comparison of ablation zone between the linear (red) and nonlinear (blue) models for $\Delta_\sigma = 4$.

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Figure 5.8: Comparison of ablation zone between the linear (red) and nonlinear (blue) models for $\Delta_\sigma = 5$.

As can been seen in Figures 5.5-5.8, the linear model is more accurate the smaller $\Delta_\sigma$ is. The result is to be expected as the governing equation becomes less linear the greater $\Delta_\sigma$ is. However, it can be seen that reasonable accuracy is still obtained even when $\Delta_\sigma$ is 5. This is because the boundary of ablation zone still has conductivity that behaves similar to the linear model due to the non-linearity being most concentrated in the center of the ablation zone; away from the ablation boundary.

5.3.3 Heterogeneous with Multiple Electrodes Example

As a final example, we have gone through the entire treatment planning algorithm as a demonstration of the typical work-flow. Although effort has been taken to make the case realistic, none of the authors are medical doctors and therefore this example’s purpose is solely for demonstrative purposes and not suggestive of IRE treatment protocols.

The example will be used to develop a treatment plan for an oval shaped tumor. The tumor is oblong. We will treat the problem as if there are no sensitive structures to take into consideration. Thus, our target area will be the entire tumor plus about 0.5 cm margin of safety around it. The electrodes are chosen to have a diameter of 1 mm. The same expression for the conductivity of the tumor and tissue as was used in Chapter 4, was used for this example.

Following the work-flow, we begin with Step 1 and run a large number of linear model simulations with electrode pairs in various arrangements. We choose our possible sites to be a box around the tumor that was multiple rows deep. The problem is perfectly parallelizable, and well suited to computation on a computer.
cluster. In practice, a larger number of simulations could have been run. But since this was for demonstrative purposes, we kept the number reasonable low.

Moving to Step 2, we experiment with different electrode configurations. Since the combinations have already been precomputed, we can move electrodes and change ablation size for a given setup and get instant ablation predictions. It is important to note that we ignore the electrical field value for a given contour used in target zone determination. In Step 3 we will choose voltage values that ensure the desired electrical field contour matches the IRE threshold value.

Step 2 should be handled by a medical doctor that would choose number of electrodes and ablation zones by considering factors such as the sensitivity of the surrounding tissue and how aggressive the treatment should be. This is the most important part of the algorithm because it allows doctors to see how varying electrode placement, number, and voltage can affect ablation size. By supplying medical doctors with more information, their knowledge, expertise, and judgment can play a more active role in determining a treatment plan that is best for their patient.

For demonstrative purposes, we chose an arrangement that is nonsymmetrical. Possible reasons to do this in practice would be physiological constraints that partially dictate electrode placement. This arrangement displays a potential strength of the algorithm to be applied to non-typical electrode arrangements such as for irregularly shaped tumors. The contour lines for the target ablation zone consists of electrical field strengths ranging from 425 V/cm to 675 V/cm. Notice how the contour lines are not the IRE threshold value, nor are they even all the same. An image of the target ablation zone can be seen in Figure 5.9.

Step 3 consisted of determining voltages to set the electrodes at to best ablate the targeted zone. Since there four electrodes in total, there are 6 different electrode pair combinations in which the voltage needs to be prescribed. To chose voltage settings for the electrode pairs, the nonlinear model was used as it provides a much more accurate ablation estimation than the linear model. The results of which are displayed in Figure 5.10 and show both the nonlinear model’s predicted ablations zone as well as the target area that was determined from the linear model. It can be seen that the nonlinear model was able to accurately capture the targeted ablation zone by never having a difference of 1 mm between the two formulations.
Figure 5.9: Side-by-side view of the target ablation zone on the left in red and the final predicted ablation zone on the right in blue. A non symmetric target zone was chosen for demonstrative purposes.

Figure 5.10: Overlay of ablation zone between the linear (red) target zone and the nonlinear (blue) model for the full example. Note the difference between the two was at no point more than a mm. The tumor is the inner oval and a 5 mm factor of safety is drawn around the tumor for reference.
5.4 Discussion

This chapter presented an algorithm and work-flow that has the potential to be used in treatment planning of IRE procedures. The crux of the algorithm was the idea that contour lines are similar for both the linear and nonlinear model. This is not saying that the results are the same for both models. For example, the contour line 700 V/cm in the linear model will most likely not directly correspond to the contour line at 700 V/cm for the nonlinear model. However, we have shown that there exists a contour line in the linear model whose shape is close to the contour line in the nonlinear model at the ablation threshold value.

This method has been shown to be accurate for a variety of situations. However, it was found to be more accurate as $\Delta_r$ and the spacing between electrodes decreased. It was also found to be more accurate as electrodes were added. This is beneficial as this method is best suited to helping to medical doctors decide on the number and arrangement of multiple electrode setups.

We would like emphasize that we are not saying this algorithm makes electrode placement algorithms obsolete. We envision this work-flow to be an enhancement to current treatment planning procedures. For example, an electrode placement algorithm can be used to get a preliminary arrangement, and then our work-flow can be used to let medical doctors fine-tune the electrode number and positions.

We acknowledge the algorithm took advantage of a computer cluster to carry out the necessary simulations, and that not all doctors have access to computer clusters. One possibility would be to purchase computing hours on a commercial cloud computing service. This might run into problems with patient confidentiality, but we believe a few thousand dollars would be able to purchase hardware that exceeds the computational needs of this work-flow. A few extra thousand dollars is small additional cost when compared to the hundreds of thousands of dollars an IRE machine costs [11].

The goal of this chapter’s research is to have doctors more involved in the treatment planning phase. To that end, one area of future work is the development of a graphical user interface (GUI). By utilizing a GUI, a medical team wouldn’t need to know how to use finite element software to follow our work-flow. Hence, the work-flow would be easier to learn, and more likely to be adopted by medical professionals. Other future work, would be the investigation of the work-flow in
3-dimensional space as well as developing a way to compensate for the necking experienced by the linear model.

5.5 Conclusions

Contour lines have similar shapes for both the linear and nonlinear models. This allows medical doctors to use the linear models to determine needle arrangements before using the nonlinear model to determine electrode voltages. This is a computationally efficient manner that can allow medical professionals to have a more interactive role in treatment planning.
Chapter 6  
Nano-channel Electroporation

More people each year die of cancer in the United States than all the Americans who lost their lives in World War II

Richard Nixon’s “Declaration of war on Cancer”

6.1 Introduction

The work in this chapter was done to help develop simulation models for the development of a nanochannel device for reversibly electroporating cells as a means of transfecting them for therapeutic applications [128–130]. These devices consist of using nanochannels to deliver a precise voltage to the cells [128, 130]. The advantage of using a device with a precise electroporation delivery configuration is a more uniform electroporation of cells resulting in fewer cells deaths and a higher transfection rate than bulk electroporation techniques [129]. One key advantage of using a nanochannel device is its ability to be used in-vivo as opposed to having to process cells ex-vivo [128]. It also has advantages over other in-vivo transfection methods such as viral transfection by being a much more precise method that allows for a more focused treatment approach [128]. And unlike viral transfection approaches, there are less safety concerns related to allergic reactions [129]. This makes it a more practical method for in-vivo applications [129].
Experimental evidence, has shown that the pulse width and voltage has an effect on the cell viability [130]. Voltages and duty cycles need to be carefully chosen to ensure a high transfection rate with a low cell mortality rate. The purpose of this chapter has been to develop computational tools necessary for future researchers to be able to input their model parameters so that they can simulate various voltages and help narrow down what the optimal voltage for their setup is. The goal was not to provide actual insight into the designing of transfection devices or results that necessarily are applicable to device design. The end goal of the research was to provide researchers with a tool to help in the designing more efficient transfection devices.

6.2 Simulation Parameters

A schematic of the initial simulation is based off the simulation shown in [128], and is shown in Figure 6.1, however it was found that due to the low conductivity of the cell membrane when compared to the rest of the materials in the simulation, the voltage was approximately constant from the active electrode to the top of the nanochannel. Therefore, simulations were performed using the schematic shown in Figure 6.2 and was found to have a less than .1% difference in the electric field experienced by the cell. Figure 6.3 shows a side-by-side comparison of the voltage from the two geometry setups. Thus all proceeding and presented simulations did not model the microchannel, and instead used the geometry shown in Figure 6.2 to further reduce the computational burden.
Figure 6.1: Initial Simulation Geometry

Figure 6.2: Simulation setup with the microchannel removed. By removing the microchannel and area above it, the computational expense can be greatly reduced with only a minor change in accuracy.
Figure 6.3: Comparison of the voltages in for the full and reduced geometries. The figure shows that the voltage stays approximately constant throughout the microchannel and can therefore be excluded from the simulation domains.

The governing equation for the steady-state simulations will again be the governing equation from all previous chapters,

$$ \nabla \cdot (\sigma \nabla U) = 0 \quad (6.1) $$

The conductivity of the external fluid is set to 0.5 S/m, the conductivity of the cytoplasm is set to 0.2 S/m and the conductivity of the membrane is set to $5 \times 10^{-7}$ S/m [129]. Previous simulations with a constant membrane conductivity predicted a lower electrode voltage necessary to induce electroporation than was observed experimentally. As a means of addressing this problem, a cell membrane conductivity that is dependent on electric field strength was implemented.

In the previous chapters, cells were considered infinitely small and therefore the conductivity due to electroporation could be treated as a pointwise quantity. This made it’s implementation into finite element weak form relatively straightforward. However, due to the small scale of these simulations, pore formation in this chapter was not treated as a pointwise change in conductivity. This is because the conductivity of a region of the cell only increased if a pore formed so that electricity could flow from the external fluid to the cytoplasm without traversing the membrane. If a pointwise conductivity condition was used then it would
have been possible for half a pore to form. In which case the model would have an increase in conductivity but physically there would not be a connection of the external fluid to the cytoplasm and no real increase in conductivity. Furthermore, molecular dynamic simulation have shown that pores in the membrane form by first completely forming through the membrane and then expanding laterally [15,131]. Figure 6.4 shows a pore forming halfway through the cell; a situation which is unrealistic according to [15, 131]. Figure 6.5 shows a pore forming all the way through the membrane as desired.

Figure 6.4: A demonstration how with a pointwise conductivity formulation. a pore can form halfway through the membrane if the threshold electric field is not constant through the membrane

![Figure 6.4](image)

Notice the conductivity is increased part of the way through the membrane but pores are either completely through or not at all.

Figure 6.5: An example of the desired response of the conductivity to only model pores that form completely through the membrane

![Figure 6.5](image)

Implementing a non-pointwise conductivity condition into a weak formulation is a much more difficult task. To overcome the half-pore formation conductivity
problem, the mesh of the membrane was chosen to ensure that only pores that formed all the way through were possible. This was done by carefully choosing the basis functions of the mesh. The mesh used linear elements. Since the voltage is modelled using linear basis functions, and the derivative of a linear function is a constant then the electric field will be a constant throughout a linear element. The mesh for the membrane was made such that the elements were only one thick and relatively skinny perpendicular to the membrane. In this way, the amount of electric field change was allowed to vary tangent to the membrane ie pore could form in different locations and widths, but by keeping the element depth one, a pore was guaranteed to only form completely through the element. This is shown in Figure 6.6. By utilizing the basis functions to help implement the conductivity formulation, the condition can still be defined pointwise in the membrane, and therefore easily implemented into a finite element weak form while also maintaining a non-pointwise modelling approach.

Figure 6.6: Close-up view of the mesh used for the membrane (highlighted in blue). Notice the mesh for the membrane is only one cell deep.
The function chosen for the non-constant conductivity of the cell membrane is

\[
\begin{align*}
\sigma_{\text{membrane}} &= 5 \times 10^{-7} \text{S/m} & \|E\| &\leq 10^8 \text{V/m} \\
\sigma_{\text{membrane}} &= 0.5 \text{S/m} & \|E\| &> 10^8 \text{V/m}
\end{align*}
\]

The electroporated value chosen is the conductivity of the external fluid because the increase in membrane conductivity is due to pore formation allowing the external fluid to conduct in the void left by the pore. A value of \(\|E\| = 10^8\) was chosen as the threshold value because an electric field of that strength in the cell membrane corresponds to a voltage drop of 1 V across the membrane, and it is believed that electroporation occurs when a 1 V drop across the membrane occurs [99]. Explicitly this can be written as

\[E \times \text{cell membrane width} = 10^8 \text{V/m} \times 0.01\mu\text{m} = 1\text{V}.
\]

Results will be presented for both constant and non-constant conductivity of the membrane. For all simulations, a mesh refinement study was done. Mesh refinement studies are done to ensure that the results are independent of mesh refinement level. For all cases, the parameters examined to ensure mesh independence were average, maximum and minimum electric field strength experienced by the membrane of the cell closest to the nanochannel. Mesh refinement was done until all parameters of interest changed less than 1% between refinement levels. It was found to occur at approximately 2 million elements. The mesh used for the membrane and nanochannel was structured while the mesh used for the remaining domains was unstructured.

Boundary conditions used for the simulations are similar to those used in previous chapter. The electrodes which in this case represent the top and bottom of the simulation domain, are strongly enforced Dirichlet conditions that were set by defining the voltage on them. The remaining boundaries are set to symmetry conditions.

### 6.3 Steady-State Results

Simulations were performed for multiple cells. The simulations consisted of a 5-by-5 cell block in which the cells butt up completely next to each other; thus forcing
them into rectangular shapes. Each cell was 20 by 5 µm with a membrane thickness of 0.01 µm. Figure 6.7 shows a zoomed in view of the geometry of the cells next to the nanochannel.

Figure 6.7: Close up of cell block and nanochannel.

Simulations were run at voltages of 75V to 250V in increments of 25V. Several attributes of the electric field of the membrane of the cell closest to the nanochannel were calculated and are displayed in Table 6.1 and Table 6.2 for both the constant and non-constant membrane conductivity models respectively. It was found that the non-constant membrane conductivity model resulted in the electric field experienced by the first cell being orders-of-magnitude less than the constant membrane conductivity model. This is a positive result, as the experimental results have shown that electroporation occurs at voltages higher than what the constant conductivity simulations have predicted. The electric field for the membrane closest to the nanochannel is shown in Figure 6.8 and Figure 6.9 for the constant and non-constant membrane conductivity models respectively. In those figures, it can be seen that the majority of the electric field strength is focused in the membrane. This is due to the conductivity of the membrane being several orders of magnitude lower than the cytoplasm and external fluid. It can also be seen by comparing the two figures that the non-constant conductivity formulation predicts a much lower electric field strength in the membrane and a higher electric field in the cytoplasm. In both figures, the electric field of the membrane is relatively uniform for the entire area abutting up against the nanochannel. It was also observed in all simulations
that only the cell closest to the nanochannel experienced electroporation.

Table 6.1: Results for Constant Membrane Conductivity

<table>
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<tr>
<th>Voltage</th>
<th>Average $\parallel E \parallel$ (V/m)</th>
<th>Max $\parallel E \parallel$ (V/m)</th>
<th>Min. $\parallel E \parallel$ (V/m)</th>
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<td>75</td>
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<td>1.8142 E10</td>
<td>615.05</td>
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</tr>
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<td>9.5528 E8</td>
<td>6.0472 E10</td>
<td>2050.2</td>
</tr>
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</table>

Table 6.2: Results for Non-constant Membrane Conductivity

<table>
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<tr>
<th>Voltage</th>
<th>Average $\parallel E \parallel$ (V/m)</th>
<th>Max $\parallel E \parallel$ (V/m)</th>
<th>Min. $\parallel E \parallel$ (V/m)</th>
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Figure 6.8: Closeup view of cell membrane for constant membrane conductivity at 250V

Figure 6.9: Closeup view of cell membrane for non-constant membrane conductivity at 250V. Notice the lower electric field than a constant membrane conductivity
6.4 Transient Results

Transient simulation were performed to investigate time effects on a cell and to provide a tool that can be used by future researchers in deciding which voltage pattern to apply. As these simulations are no longer steady-state, time must be incorporated into the governing equation. The governing equation used was

\[
\nabla \cdot (\sigma + \epsilon_0 \epsilon_r \frac{\partial}{\partial t}) E = 0
\]

(6.3)

where \( \epsilon_0 \) is the permittivity of a vacuum, and \( \epsilon_r \) is the relative permittivity of the cell. A value of 80 was chosen for the relative permittivity of all materials. This value was chosen because it is approximately the relative permittivity of water.

Transient simulations are more computationally demanding than steady-state simulations because they require solving a system of equations at each time step. To ease the computational burden of this investigation, only a single cell was modelled in the domain instead of the 5-by-5 block used in the steady-state simulations. The geometry used in the transient simulations is identical to the steady-state cases except the 19 cells not closest to the nanochannel have been removed.

The transient simulations were all performed with the constant conductivity for the cell membrane. This was done due to a lack of knowledge for the speed at which pores form in the cell membrane due to an induced electric field. However, as the previous sections already provided work demonstrating a way to implement a nonlinear conductivity model for the cell membrane, this section and the previous one can easily be combined by future researchers if desired. The simulation would take longer as Newton-Raphson subiterations would have to be performed to handle the now non-linear governing equation.

Simulations were performed with a square wave with a period of 20 ms and a 50% duty-cycle. Ten cycles in total were ran during the simulation for a total simulation time of 200 ms. Simulations were run with various peak voltages ranging from 100V to 200V in 25V increments. The square wave used for the voltage had first derivatives exist at all locations by smoothing the transitions. Figure 6.10 shows an example of one the voltages used in the simulations and the sharp transitions that were maintained even with the existence of first derivatives.
For all transient simulations, the voltage on the active electrode was never set to 0 V but instead is assigned a minimum of 0.01 V. This is because if during the off-cycle both electrodes are set to ground \((V = 0)\) then a numerical instability occurs. Thus a small voltage has to be maintained on the active electrode to avoid the numerical instability.

To ensure that a base voltage of 0.01 V did not have a significant impact on the solution, a technique similar to mesh refinement was utilized to ensure solution independence from voltage selection. Simulations were ran where the active electrode had a minimum voltage of 0.01 V and 0.001 V. Having ran the two cases, the solutions of both were compared and it was found that there was less than a 1% difference between the two simulation’s electric fields during the off part of the cycle. Due to the results being similar, it was therefore concluded that a base voltage of 0.01 V had a negligible effect on the simulation results.

The computation of the four different voltages took approximately 2,500 CPU hours running on a single node with 256 Gb of memory and 20 Xeon E7-4830 processors. The computations were all ran in a shared memory fashion using the direct solver algorithm MUMPS. The wall-time was approximately 5 days. This makes the time-dependent simulation significantly more time consuming to run than the steady-state simulations.
The results of the square wave simulation for a full cycle is shown in Figure 6.11. In Figure 6.11 it can be seen that the model predicts that the electric field in the membrane quickly reaches a near equilibrium state after a voltage change. Figure 6.12 shows a graph of the average electric field experienced by the cell membrane as a function of time over the course of a full cycle. This further demonstrates that the cell membrane reacts quickly to the change in voltage during the transition of the cycle. The quick response by the electric field in the membrane suggests that a steady-state simulation might be sufficient to determine optimal voltage parameters for transfection device designs. However, this should be reinvestigated if different $\epsilon_r$ values are used.

Figure 6.11: A cycle from the transient simulation showing the quick change in electric field for one cycle. Notice the quick reaction time of the electric field in response to a change in the applied voltage. Similar results were observed for all other cycles.
Figure 6.12: A cycle from the transient simulation showing the quick change in electric field for one cycle. Notice the quick reaction time of the electric field in response to a change in the applied voltage.

6.5 Summary of Work

The simulations in this chapter were different than previous chapters by operating on a much smaller length-scale. Previous chapters treated cells as points with zero-measure which was not the case in this chapter. The main objective of the research in this chapter was to provide a guide for performing simulations of cells being electroporated by nanochannels for future researchers. Four main contributions were made:

1. Propose and demonstrate the feasibility of using a cell membrane conductivity that is dependent on the electric field strength as a possible explanation for electroporation occurring at voltages higher than predicted by previous simulation models.

2. A method of implementing a cell membrane conductivity that is dependent on electric field strength and also avoid half-pore formation predictions.

3. Identification of the instability caused by setting both electrodes to the same value as well as a possible solution to handle it.
4. Provide evidence of using steady-state simulations instead of transient simulations due to the quick charge time of a cell membrane.

The goal of the research in this chapter was to develop computational models of nanochannel electroporation for use by future researchers. The author is not in a position to comment on the implications of this chapter’s results on the development of future transfection setups. It was observed for all simulations that electroporation only occurred in the cell closest to the nanochannel. This serves as further evidence that nanochannel electroporation devices can be used as a precise transfection technique. Also by the cell only experiencing electroporation on the surface near the nanochannel, damage to cell is minimized which is a positive thing.

One area of future work would be to combine the nonlinear conductivity model of the cell membrane with the transient simulation. This should be a relatively straightforward process for any researcher wishing to undertake it because the addition of the nonlinear model will only result in performing Newton-Raphson iterations at each timestep. Only a constant conductivity was used due to a lack of knowledge on the rate at which pores form in a cell membrane due to an induced electric field. The simulation parameters should be updated as more information on the cell’s electrical properties become available through experimentation.

Although a non-constant cell membrane conductivity is one possible explanation for the constant conductivity simulations under predicting the voltage necessary to induce electroporation; it is not the only one. Another possible explanation is that the voltage drop over the membrane that induces electroporation is lower than believed. It could also be a combination of the two explanations or possibly some other explanation. Further experimental work will be needed to better understand the mechanisms of pore formation so that more accurate models can be derived.

Future work can also be done to compare 2D and 3D model results to verify that 2D simulations are an accurate representation of the physics. The hope is that 2D models accurately capture the effects as they are much more computationally efficient, but this should be verified by a numerical study.

Finally, certain parameters used such as $\epsilon_r$ and the conductivity formula for the membrane were the author’s best guesses. This was due to the lack of available resources on the electric properties of the various components of cells due to the difficulty in measuring them. These simulations parameters should be updated with more accurate values as they become available in the literature and then used to
rerun the simulations. Along those same lines, sensitivity studies could be done to better understand how a change in the parameters affect the predicted electric field. The outcome of a sensitivity study would provide a better idea of the accuracy desired for the simulation parameters.
Chapter 7  |  Closing Remarks

In medicine, uncertainty is the water we swim in

Lisa Sanders

7.1 Introduction

Cancer is a disease that comes in many forms, and as such there will probably never be a cure-all that will work for all scenarios. That is why it is important to continue to develop new treatment options. Irreversible electroporation has shown potential to be yet another useful tool in the oncologist’s toolbox. Being able to successfully apply IRE treatments will require accurate numerical models for treatment planning [132]. This thesis will provide additional knowledge on how to successfully build and interpret these models as a step towards having IRE becoming a widespread treatment option.

This dissertation provides the first investigation into how a conductivity that depends on both electrical field strength and direction affects the predicted ablation zone. It is also provides some of the first steps towards understanding how uncertainties in the model parameters affect the final prediction zone. A work-flow that can be utilized by physicians to develop treatment plans was also presented. Finally, simulation models were made to further the development of nanochannel electroporation devices.

The research conducted in this dissertation aimed to make the following contributions to science:
1. A quantifiable understanding of how anisotropic conductivity changes affect the model

2. A quantifiable understanding of how uncertainty in conductivity propagates through a model for IRE treatment planning

3. A novel work-flow that can be utilized by physicians during IRE treatment planning.

4. Simulation methods to aid in the design of nanochannel electroporation design

### 7.2 Summary of Work Completed

The research on IRE modelling has three components to it. The first component, Chapter 2, dealt with incorporating anisotropic changes in the conductivity tensor. Effort was taken to keep the formulation as general as possible, and allows for any expression for the conductivity changes in the tangent and normal direction. This makes the work applicable to any tissue and makes the formulation useful as more experimental data becomes available. It was shown that incorporating anisotropic effects could be a possible explanation for the over predictions seem in IRE models.

The second component, Chapters 3 & 4, of the research dealt with furthering our knowledge of uncertainty in IRE models. In Chapter 3, the effect of uncertainty in the conductivity of both healthy tissue and tumorous tissue was investigated. The effect unmodelled small scale blood vessels can have on IRE predictions was researched in Chapter 4. This was done by performing Monte Carlo simulations that randomly varied the number, location, and size of small scale vessels.

The third component, Chapter 5, presented a novel work flow that utilized precomputed linear models to allow doctors to quickly determine target ablation zones. By using a large number of precomputed solutions, doctors would be able to adjust electrode position and voltage to get a better idea of possible target zones. The hope being that this method has medical doctors playing a more involved rule in the electrode placement and target zone determination. Simulations were run to examine how parameters such as spacing affect the correlation between the linear and nonlinear model. A full case example was done in 2D that demonstrated the feasibility of using this method as part of a treatment planning work flow.
The fourth component, Chapter 6, presented a method of modelling electroporation of individual cells in a nanochannel device. To the author's knowledge, it is the first time a non-constant cell membrane conductivity was utilized in this type of simulation. The non-constant membrane conductivity formulation is a potential solution to the current method under-predicting the voltage necessary to induce electroporation of the cells.

7.3 Future Work

The end goal of both this research and the possible future work would be to increase the reliability of treatment planning for irreversible electroporation of tumors. By increasing the reliability of treatment prediction, hopefully irreversible electroporation will someday be able to live up to its high potential as a safe and effective minimally invasive tumor ablation treatment.

Future work for each area of this dissertation is discussed at the end of each chapter. But I would like to outline some the future work for the research as a whole. One area of future work is that this research uses experimental data and setups performed by other researchers and reported in papers. This research would benefit from having a collaboration with an experimental group that would allow direct access to experimental data which could be used to further validate the anisotropic conductivity model. Another avenue of possible future work would be to explore the anisotropic conductivity model for setups involving more than 2 needle electrodes. Work could also be done for the precomputed linear model by talking to medical doctors to better understand the needs and wants they have when it comes to treatment planning so that at tool that is well suited to them is developed. This type of work is often to as 'customer discover stage' in the commercial innovation fields.

7.4 Conclusion

In conclusion, this dissertation presents a furthering in the knowledge of mathematical modelling used to develop IRE treatment plans. Although IRE still is in need of further development, it is the author’s hope that this research will be used to help bring IRE one step closer to becoming a standard procedure used by
oncologists around the globe.
Appendix A
Anisotropic Conductivity Tensor Formulation - 3D

The derivation for the anisotropic conductivity tensor will be presented for the 3-dimensional case. The 3-dimensional case will follow a similar procedure as was used to derive the 2-dimensional formulation presented in Chapter 2. The 3-dimensional derivation will make the same assumptions as was done in Chapter 2. Again we’ll start with the form of the conductivity tensor in the 3D Frenet-Serret frame.

\[
\sigma_f = \begin{pmatrix}
\sigma_t & 0 & 0 \\
0 & \sigma_n & 0 \\
0 & 0 & \sigma_b
\end{pmatrix}
\]  

(A.1)

where \( \sigma_b \) is the conductivity in the bi-normal direction. It will be assumed that the conductivity is the same in both the normal and bi-normal direction which is expressed as

\[
\sigma_b = \sigma_n.
\]  

(A.2)

Equation A.2 simplifies equation A.1 to

\[
\sigma_f = \begin{pmatrix}
\sigma_t & 0 & 0 \\
0 & \sigma_n & 0 \\
0 & 0 & \sigma_n
\end{pmatrix}
\]  

(A.3)

The 3D case will require two rotations to align the Frenet-Serret coordinate system with the Cartesian system. The first is a rotation about the z-axis, \( R_z(\theta) \), expressed
by the matrix,

\[
R_z(\theta) = \begin{pmatrix}
\cos(\theta) & -\sin(\theta) & 0 \\
\sin(\theta) & \cos(\theta) & 0 \\
0 & 0 & 1
\end{pmatrix}
\]  

(A.4)

where the angle \( \theta \) is obtained through the relationship

\[
\theta = \tan^{-1}\left(\frac{E_y}{E_x}\right).
\]  

(A.5)

Similarly, the second rotation is about the y-axis, \( R_y(\phi) \), and is expressed by the matrix,

\[
R_y(\phi) = \begin{pmatrix}
\cos(\phi) & 0 & -\sin(\phi) \\
0 & 1 & 0 \\
\sin(\phi) & 0 & \cos(\phi)
\end{pmatrix}
\]  

(A.6)

where \( \phi \) is the angle described by the function

\[
\phi = \tan^{-1}\left(\frac{E_z}{E_x}\right).
\]  

(A.7)

We are now able to express the conductivity tensor in matrix form with the domain and codomain being the Cartesian frame. This is accomplished by applying the rotation matrices in the following order:

\[
\sigma_c = R_y(-\phi)R_z(-\theta)\sigma_fR_z(\theta)R_y(\phi)
\]  

(A.8)

\[
= \begin{pmatrix}
c^2(\theta)(\sigma_n s^2(\phi) + \sigma_t c^2(\phi)) + \sigma_n s^2(\theta) & s(\theta)c(\theta)(\sigma_n - \sigma_t)c^2(\phi) & c(\theta)(\sigma_n - \sigma_t)s(\phi)c(\phi) \\
s(\theta)c(\theta)(\sigma_n - \sigma_t)c^2(\phi) & s^2(\theta)(\sigma_n s^2(\phi) + \sigma_t c^2(\phi)) + \sigma_n c^2(\theta) & s(\theta)(\sigma_n - \sigma_t)s(\phi)c(\phi) \\
c(\theta)((\sigma_n - \sigma_t)s(\phi)c(\phi) & s(\theta)(\sigma_n - \sigma_t)s(\phi)c(\phi) & \sigma_n c^2(\phi) + \sigma_t s^2(\phi)
\end{pmatrix}
\]

where \( c \) represents \( \cos \) and \( s \) represents \( \sin \).
Appendix B
Non-Technical Abstract

In the past few years, interest has drastically increased in using surgically inserted electrodes to ablate cancer cells. The treatment is referred to as irreversible electroporation (IRE) and has the advantage of being a minimally invasive procedure that can be used to treat tumors while minimizing damage to surrounding tissue.

The difficulty in the procedure is determining how many electrodes to use, where to place them, and what voltages should they operate at. Computer simulations are currently the tool of choice to plan a treatment for a specific patient. Therefore, it is desirable to have as accurate a model as possible for planning a treatment procedure that completely ablates the undesirable tissue while minimizing the amount of damage to healthy tissue.

Current treatment planning models, use a tissue conductivity that is isotropic and dependent on the magnitude of the electrical field. This dissertation proposes using a conductivity that is higher in the direction of the electrical field than the conductivity in the direction perpendicular to the electrical field. The result is a new formulation for the tissue conductivity that is dependent on both the magnitude and the direction of the electrical field. The goal of this being the development of more accurate models for treatment planning.

Simulations for treatment planning is made difficult by having no two people being perfectly identical. Therefore, there is a degree of uncertainty in the model parameters such as the precise conductivity of the tumor, the conductivity of the surrounding tissue, the electrical field strength required to kill cells, and the position of micro-structures such as small scale blood vessels.

Another goal of this research is to quantify the uncertainty in the simulation results. By providing medical doctors with knowledge of how uncertain the results
of the simulations are, they can choose treatment parameters that give a high probability of success.
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